KDDW 2019

Korea Digestive Disease Week

A New Frontier for Convergence in Gastroenterology and Hepatology

PROCEEDINGS

Organized by

Member Societies : 대한소화기학회, 대한간학회, 대한소화기기능성질환·운동학회, 대한췌장담도학회, 대한상부위장관·헬리코박터학회, 대한장연구학회, 대한소화기암학회

Associated Societies : 대한위암학회, 한국간담췌외과학회, 대한대장항문학회, 대한비만대사외과학회, 대한소아소화기영양학회

KDDW2019
Korea Digestive Disease Week

www.kddw.org

Welcome Message

KDDW2019
Korea Digestive Disease Week

Dear colleagues,

Welcome to the third Korea Digestive Disease Week (KDDW 2019)!
On behalf of the organizing committee, it is my great pleasure to invite you to KDDW 2019 to be held at the Grand Hilton Hotel, Seoul, Korea from November 28 to 30, 2019.

This is a truly meaningful meeting since seven member societies—The Korean Society of Gastroenterology, Korean Association for the Study of the Liver, The Korean Society of Neurogastroenterology and Mobility, Korean Pancreatobiliary Association, Korean College of Helicobacter and Upper Gastrointestinal Research, Korean Association for the Study of Intestinal Diseases, and Korean Society of Gastrointestinal Cancer—and five associated societies—The Korean Gastric Cancer Association, Korean Association of Hepato-Biliary-Pancreatic Surgery, The Korean Society of Coloproctology, Korean Society for Metabolic and Bariatric Surgery, and The Korean Society of Pediatric Gastroenterology, Hepatology and Nutrition—have joined together to host KDDW 2019.

Under the theme of A New Frontier for Convergence in Gastroenterology and Hepatology, many high quality scientific programs will be held for professionals coming together from around the world to share knowledge and new perspectives. I believe that KDDW 2019 will play a significant role for the large gathering of professors, doctors, and distinguished leaders to exchange valuable ideas, socialize, and interact with one another. I hope that you may get the most out of KDDW 2019, and return home with your expectations met.

I also hope that you will get the best of your time here in Seoul, a city of both rich culture and traditions and many modern resources.

I thank all of you for joining me and being a part of this wonderful event, and sincerely wish that the 2019 meeting will contribute to the further growth and advancement of KDDW and our field. Once again, welcome to KDDW 2019.

Sincerely yours,

Dong Ki Lee, M.D., Ph.D.
President
Organizing Committee of KDDW 2019
The Korean Society of Gastroenterology

Committees

KDDW2019 Korea Digestive Disease Week

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Program at a Glance

KDDW2019 Korea Digestive Disease Week

November 28 (Thu) / Day 1

Time/Place	4F, Convention Center			3F, Convention Center		
	Convention Hall A	Convention Hall B	Convention Hall C	Emerald Hall A	Emerald Hall B	Diamond Hall
07:30-	Registration					
09:00-10:30	**Symposium 01** (KASL1) Korean		**In-depth Symposium 01** (KSG) English	**PG Course 01** (KSNM) Korean	**Plenary Session 01** (UGI-LGI-Motility) English	**Big Data Research** (KSG) English
10:30-11:00	Coffee Break					
11:00-11:30	**Chung Yong Kim Memorial Lecture** (KASL) Korean		**In-depth Symposium 02** (KSG) English	**PG Course 02** (KSGC) Korean	**Symposium 02** (KSNM1) English	**Multidisci-plinary Session 01** (KCHUGR) Korean
11:30-12:30	**General Meeting** (KASL)					
12:30-13:30	**Luncheon Symposium 01** (GILEAD) English		Lunch			
13:30-14:00	Break					
14:00-15:30	**Symposium 03** (KASL2) Korean		**In-depth Symposium 03** (KSG) English	**PG Course 03** (KASID) Korean	**Presidential Lecture** (KSNM) Korean	**Presidential Lecture** (KCHUGR) Korean
					Special Lecture (KSNM) English	**Special Lecture** (KCHUGR) English
15:30-16:00	Coffee Break					
16:00-17:30	**Symposium 04** (KASL3) Korean		**In-depth Symposium 04** (KSG) English	**PG Course 04** (KCHUGR) Korean	**Multidisci-plinary Session 02** (KSNM-KASID-KSCP) Korean	
18:30-20:00						

Member Societies :

- The Korean Society of Gastroenterology
- Korean Association for the Study of the Liver
- The Korean Society of Neurogastroenterology and Motility
- Korean Pancreatobiliary Association
- Korean College of Helicobacter and Upper Gastrointestinal Research
- Korean Association for the Study of Intestinal Diseases
- Korean Society of Gastrointestinal Cancer

2F, Main Hotel					
Grand Ballroom A	Grand Ballroom B	Grand Ballroom C	Flamingo	Skylark	White Heron
	Special Lecture (KSGC) English				
Topic Forum 01 (GI Cancer1) English	**Gender Specific Medicine in Gastroenterology** (KSG) English		**E-poster Oral 01-1** (PB1) English	**E-poster Oral 02-1** (LGI1) English	**E-poster Oral 03-1** (UGI1) Korean
			E-poster Oral 01-2 (PB1) Korean	**E-poster Oral 02-2** (LGI1) English	**E-poster Oral 03-2** (UGI1) English
Topic Forum 02 (GI Cancer2) English			**E-poster Oral 04-1** (PB2) English	**E-poster Oral 05-1** (LGI2) English	**E-poster Oral 06-1** (UGI2) English
			E-poster Oral 04-2 (PB2) English	**E-poster Oral 05-2** (LGI2) English	**E-poster Oral 06-2** (UGI2) English
Free Paper 01-1 (UGI1) English					
Free Paper 01-2 (UGI1) English					
Presidential Dinner (Invited Only)					

Associated Societies :

- The Korean Gastric Cancer Association
- Korean Association of Hepato-Biliary-Pancreatic Surgery
- The Korean Society of Coloproctology
- Korean Society for Metabolic and Bariatric Surgery
- The Korean Society of Pediatric Gastroenterology, Hepatology and Nutrition

Program at a Glance

KDDW2019 Korea Digestive Disease Week

November 29 (Fri) / Day 2

Time/Place	4F, Convention Center			3F, Convention Center		
	Convention Hall A	Convention Hall B	Convention Hall C	Emerald Hall A	Emerald Hall B	Diamond Hall
07:30-08:30						
08:30-09:00						
09:00-10:30	**Symposium 05** (KCHUGR1) English	**Symposium 06** (KASID1) Korean	**Joint Symposium** (ANMA-KSNM) English	**Combined Symposium 01** (KPBA-KAHBPS1) Korean	**Plenary Session 02** (LV-PB-GI Cancer-others) English	**Symposium 07** (KSGC1) Korean
10:30-11:00	Coffee Break					
11:00-12:30	**Presidential Lecture** (KSG) Korean **Special Lecture** (KSG) Korean **General Meeting** (KSG)		**Symposium 08** (KSNM2) Korean	**Combined Symposium 02** (KPBA-KAHBPS2) Korean	**Topic Forum 03** (UGI2) English	**Symposium 09** (KASID2) English
12:30-13:30	**Luncheon Symposium 02** (OLYMPUS) Korean	**Luncheon Symposium 03** (CJ HealthCare) English	Lunch			
13:30-14:00	Break					
14:00-15:30	**Combined Symposium 03** (KSPGHAN-KSG) Korean	**Combined Symposium 04** (KASL-KAHBPS) Korean	**Symposium 10** (KSNM3) Korean	**PG Course 05** (KPBA) Korean	**Symposium 11** (KSGC2) English	**Basic/ Translational Symposium 01** (KPBA) English
15:30-16:00	Coffee Break					
16:00-17:30	**Combined Symposium 05** (KCHUGR-KGCA) Korean	**Combined Symposium 06** (KASID-KSPGHAN) Korean	**Multidisciplinary Session 03** (KPBA-KAHBPS) English	**PG Course 06** (KASL) Korean	**Topic Forum 04** (PB1) English	**Basic/ Translational Symposium 02** (KSGC) English

2F, Main Hotel

Grand Ballroom A	Grand Ballroom B	Grand Ballroom C	Flamingo	Skylark	White Heron
				MTP 01 (KASID) Korean	**MTP 02** (KSGC) English
Free Paper 02-1 (LV1) English	**Presidential Lecture** (KSGC) Korean		**E-poster Oral 07-1** (PB3) English	**E-poster Oral 08-1** (LGI3) English	**E-poster Oral 09** (Motility1) English
Free Paper 02-2 (LV1) English			**E-poster Oral 07-2** (PB3) Korean	**E-poster Oral 08-2** (LGI3) Korean	
Free Paper 03-1 (LGI1) Korean	**Abdominal US 지도인증의교육 01** (KSG)	**Abdominal US 지도인증의 Hands-on Session (전문의) 01** (KSG)	**E-poster Oral 10-1** (PB4) Korean		**E-poster Oral 11-1** (UGI3) English
Free Paper 03-2 (LGI1) English			**E-poster Oral 10-2** (PB4) English		**E-poster Oral 11-2** (UGI3) English
Free Paper 04-1 (LV2) English	**Abdominal US 지도인증의교육 02** (KSG)	**Abdominal US 지도인증의 Hands-on (전문의) 02** (KSG)			
Free Paper 04-2 (LV2) English					

Program at a Glance

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November 30 (Sat) / Day 3

Time/Place	4F, Convention Center			3F, Convention Center		
	Convention Hall A	Convention Hall B	Convention Hall C	Emerald Hall A	Emerald Hall B	Diamond Hall
07:30-08:30			**Breakfast Symposium** (SYSMEX KOREA) English			
08:30-09:00			**Joint Symposium** (IASL1) English			
09:00-10:30	**Combined Symposium 07** (KASID-KSCP) Korean	**Video Session 01** (KSG-UGI) English		**Editor Session** Korean	**Metabolism & Obesity 01** (KSG-KSMBS-KSPGHAN) English	**Multidisciplinary Session 04** (KSGC-KGCA) Korean
10:30-11:00	Coffee Break					
11:00-12:30	**Korean GI Frontiers** (KSG) Korean	**Video Session 02** (KSG-LGI) English	**Joint Symposium** (IASL2) English	**Basic/ Translational Symposium 03** (KASID) English	**Metabolism & Obesity 02** (KSG-KSMBS-KASL) Korean	**Presidential Lecture** (KPBA) Korean **Special Lecture** (KPBA) English
12:30-13:30	Lunch					
13:30-14:00	Break		**Joint Symposium** (IASL3) English	Break		
14:00-15:30	**Presidential Lecture** (KASID) Korean **Special Lecture** (KASID) English			**Video Session 03** (KPBA1) English	**Metabolism & Obesity 03** (KSG-KSMBS) Korean	**Multidisciplinary Session 05** (KSGC-KSCP) Korean
15:30-16:00	Coffee Break					
16:00-17:30	**Symposium 12** (KPBA1) English	**Free Paper 07-1** (LGI2) English **Free Paper 07-2** (LGI2) English	**Joint Symposium** (IASL4) English	**Video Session 04** (KPBA2) English	**Metabolism & Obesity 04** (KCHUGR-KSMBS) English	**Primary Care Session** (KSNM) Korean

2F, Main Hotel

Grand Ballroom A	Grand Ballroom B	Grand Ballroom C	Flamingo	Skylark	White Heron
			MTP 03 (KCHUGR) English	**MTP 04** (KPBA) English	
Free Paper 05-1 (Motility1) English	**Abdominal US Hands-on Session (전임의) 01** (KSG)		**Nursing Session 01** (KASID) Korean		
Free Paper 05-2 (Motility1) English					**ERCP Hands-on Session 01** (KPBA)
Topic Forum 05 (PB2) English	**Abdominal US Hands-on Session (전임의) 02** (KSG)		**E-poster Oral 12-1** (GI Cancer1) English	**Nursing Session 02** (KPBA) Korean	**ERCP Hands-on Session 02** (KPBA)
			E-poster Oral 12-2 (GI Cancer1) English		
Luncheon Meeting					
Free Paper 06 (Motility2) Korean	**Abdominal US Hands-on Session (전임의&전공의) 03** (KSG)			**Nursing Session 03** (KSGC) Korean	**ERCP Hands-on Session 03** (KPBA)
Free Paper 08 (GI Cancer3) English	**Abdominal US Hands-on Session (전임의&전공의) 04** (KSG)				**ERCP Hands-on Session 04** (KPBA)

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November 28 (Thu)_Day 1

Big Data Research (KSG)
Beyond big data to artificial intelligence (AI) in colon cancer

09:00-10:30 (Diamond Hall)
English

Chairs: Ming-Shiang Wu (Taiwan), Hyun-Soo Kim (Korea)

Special Lecture (KSGC)

09:40-10:20 (Grand Ballroom B+C)
English

Chair: Hyun Yong Jeong (Korea)

Presidential Lecture (KASL)
Chung Yong Kim Memorial Lecture

11:00-11:30 (Convention Hall A+B)
Korean

Chair: Kwan Sik Lee (Korea)

In-depth Symposium 02 (KSG)
Current status and perspective for early diagnosis of pancreatic cancer

11:00-12:30 (Convention Hall C)
English

Chairs: Laufey Amundadottir (United States), Yong Tae Kim (Korea)

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Gender Specific Medicine in Gastroenterology (KSG) -01
Clinical application of gender medicine: from research to bedside

11:00-12:00 (Grand Ballroom B+C)
English

Chairs: Etsuko Hashimoto (Japan), Seun Ja Park (Korea)

Gender Specific Medicine in Gastroenterology (KSG) - 02
Development of career promotion program for women and young doctors

12:00-12:30 (Grand Ballroom B+C)
English

Chairs: Hidekazu Suzuki (Japan), Nayoung Kim (Korea)

Symposium 03 (KASL2)
Modulation of gut-liver axis in liver diseases: How far have we come?

14:00-15:30 (Convention Hall A+B)
Korean

Chairs: Jin Mo Yang (Korea), Kwang Cheol Koh (Korea)

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Presidential Lecture (KCHUGR)

14:00-14:40 (Diamond Hall)
Korean

Chair: Jong-Jae Park (Korea)

Extracellular vesicle in gastrointestinal disease and microbiome in gastric carcinogenesis
Jae Gyu Kim 153
(Chung-Ang University Hospital, Korea)

Special Lecture (KCHUGR)

14:40-15:20 (Diamond Hall)
English

Chair: Jae Gyu Kim (Korea)

Personalized nutrition and gut microbiota
Ming-Shiang Wu 157
(National Taiwan University, Taiwan)

Symposium 04 (KASL3)
Recent updates in management of liver diseases

16:00-17:30 (Convention Hall A+B)
Korean

Chairs: Kwang-Hyub Han (Korea), Han Chu Lee (Korea)

Clinical development of new HBV therapies
Sang Hoon Ahn..... 161
(Yonsei University College of Medicine, Korea)

Management of diabetes and dyslipidemia in patients with nonalcoholic steatohepatitis
Seung-Hyun Ko..... 162
(The Catholic University of Korea St. Vincent's Hospital, Korea)

Autoimmune hepatitis in real practice
Kang Mo Kim..... 164
(Asan Medical Center, Korea)

Local ablation therapy of hepatocellular carcinoma
Seung Kak Shin 165
(Gachon University Gil Medical Center, Korea)

In-depth Symposium 04 (KSG)
New hope for treating pancreatic cancer

16:00-17:30 (Convention Hall C)
English

Chairs: Volker Ellenrieder (Germany), Ho Soon Choi (Korea)

Direct targeting oncogenic Ras mutants by IgG-format cytosol-penetrating antibody
Yong-Sung Kim..... 169
(Ajou University, Korea)

Extracelluar vesicles (EVs): exosomes and microvesicles
Yong Song Gho 170
(POSTECH, Korea)

Targeting altered metabolism in pancreatic cancer
Soo-Youl Kim..... 171
(National Cancer Center, Korea)

Establishment of PDAC organoids model using EUS-guided tissue biopsy: a new window into understanding PDAC and drug discovery
Jookyung Park Park 172
(Samsung Medical Center, Korea)

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November 29 (Fri)_Day 2

MTP 01 (KASID)
Meet the Professor

07:30-08:30 (Skylark)
Korean

Chair: Yoon Tae Jeen (Korea)

MTP 02 (KSGC)
Meet the Professor

07:30-08:30 (White Heron)
English

Chair: Moo-In Park (Korea)

Symposium 05 (KCHUGR1)
Limits and prospects of acid inhibitors

09:00-10:30 (Convention Hall A)
English

Chairs: Yong Chan Lee (Korea), Shin Maeda (Japan)

Symposium 06 (KASID1)
Optimal strategies of colonoscopy in LGI disease

09:00-10:30 (Convention Hall B)
Korean

Chairs: Suk-Kyun Yang (Korea), Sung-Ae Jung (Korea)

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Presidential Lecture (KSG)

11:00-11:30 (Convention Hall A+B)
Korean

Chair: Jin Hong Kim (Korea)

Special Lecture (KSG)

11:30-12:00 (Convention Hall A+B)
Korean

Chair: Dong Ki Lee (Korea)

Symposium 08 (KSNM2)
Recent updates of esophageal motility disorder

11:00-12:30 (Convention Hall C)
Korean

Chairs: Kwang Jae Lee (Korea), Moo-In Park (Korea)

Combined Symposium 02 (KPBA-KAHBPS2)
Best treatment opinion for advanced hilar malignancy

11:00-12:30 (Emerald Hall A)
Korean

Chairs: Dong Wook Choi (Korea), Sang-Soo Lee (Korea)

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Symposium 10 (KSNM3)
Gut microbiota and diet in IBS

14:00-15:30 (Convention Hall C)
Korean

Chairs: Myung-Gyu Choi (Korea), Kyu Chan Huh (Korea)

PG Course 05 (KPBA)
Improve your ERCP skill for CBD stone removal

14:00-15:30 (Emerald Hall A)
Korean

Chairs: Seok-ho Dong (Korea), Sang-Woo Cha (Korea)

Symposium 11 (KSGC2)
Colorectal cancer: new topic and issue

14:00-15:30 (Emerald Hall B)
English

Chairs: Seun Ja Park (Korea), Yoon Tae Jeen (Korea)

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Multidisciplinary Session 03 (KPBA-KAHBPS)
Effective multidisciplinary approaches to IHD stone

16:00-17:30 (Convention Hall C)
English

Chairs: Jin Hong Kim (Korea), Kyo-Sang Yoo (Korea)

PG Course 06 (KASL)
Updated KASL guidelines: HBV, Cirrhosis

16:00-17:30 (Emerald Hall A)
Korean

Chairs: Soonkoo Baik (Korea), Jin-Woo Lee (Korea)

Basic/Translational Symposium 02 (KSGC)
Toward the precision medicine

16:00-17:30 (Diamond Hall)
English

Chairs: Laufey Amundadottir (United States), Tae Il Kim (Korea), Sun Young Rha (Korea)

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November 30 (Sat)_Day 3

Joint Symposium (IASL1)
Global unsolved issues in viral hepatitis

08:30-10:30 (Convention Hall C)
English

Chairs: Kwang-Hyub Han (Korea), Myungken Lee (Korea), Markus Peck (Austria)

Editor Session
Tips to become a good journal

09:00-10:30 (Emerald Hall A)
Korean

Chairs: Young S. Kim (United States), Sang Woo Lee (Korea)

Metabolism & Obesity 01 (KSG-KSMBS-KSPGHAN)
Obsetiy and metabolic syndrome: where are we now and where are we going?: pathophysiology, epidemiology, diagnosis, classification etc.

09:00-10:30 (Emerald Hall B)
English

Chairs: David Wang (United States), Hyun Wook Baik (Korea), Joo-Ho Lee (Korea)

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Video Session 02 (KSG-LGI)

11:00-12:30 (Convention Hall B)
English

Chairs: Han-Mo Chiu (Taiwan), Bo-In Lee (Korea)

Joint Symposium (IASL2)
Opening ceremony / Special lectures

11:00-11:30 (Convention Hall C)
English

Chair: Kwang-Hyub Han (Korea)

Joint Symposium (IASL2)
Professional platform: how to start and build-up academic career - I

11:30-12:30 (Convention Hall C)
English

Chairs: Samuel Lee (Canada), Jacob George (Australia)

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Nursing Session 02 (KPBA)
For the Best Care of Pancreaticobiliary Cancers

11:00-12:30 (Skylark)
Korean

Chairs: Jun Kyu Lee (Korea), Hee Hyuk Im (Korea)

Presidential Lecture (KASID)

14:00-14:40 (Convention Hall A+B)
Korean

Chair: Dong Soo Han (Korea)

Special Lecture (KASID)

14:40-15:20 (Convention Hall A+B)
English

Chair: Joo Sung Kim (Korea)

Joint Symposium (IASL3)
Controversial issues in liver diseases

13:30-14:30 (Convention Hall C)
English

Chairs: Kwan Soo Byun (Korea), Han Chu Lee (Korea)

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Multidisciplinary Session 05 (KSGC-KSCP)
Controversial issues for management of advanced rectal cancer

14:00-15:30 (Diamond Hall)
Korean

Chairs: Jonghoon Lee (Korea), Jun Won Um (Korea)

Preoperative stenting for left-sided obstructive disease: Should it be reserved for high risk group alone?	Jae Jun Park (Severance Hospital, Korea)	501
Optimal use of rectal radiation therapy for potentially resectable metastatic disease	Jiho Nam (Pusan National University Hospital, Korea)	502
Timing of curative surgery for metastatic disease: when should we consult to surgeon?	Jin Yong Shin (Inje University Haeundae Paik Hospital, Korea)	503
Recent advance of preoperative/postoperative systemic therapy	Suk Young Lee (Wonkwang University Sanbon Hospital, Korea)	504

Nursing Session 03 (KSGC)
Advanced nursing in GI cancer

14:00-15:30 (Skylark)
Korean

Chairs: Chan-Guk Park (Korea), Jun Kyu Lee (Korea)

Oncology emergencies in GI cancer	Chung Eun Lee (Severance Hospital, Korea)	509
Pain and nursing of GI cancer patients on chemotherapy	Boyoung Byun (National Cancer Center, Korea)	510
Patient safety and nursing of GI cancer patient on chemotherapy	Geunsook Lee (Yonsei University Wonju College of Medicine, Korea)	512
Social and emotional health and nursing of GI cancer patients on chemotherapy	Eunju Park (CHA Gangnam Medical Center, Cha University, Korea)	513

Symposium 12 (KPBA1)
Treating acute pancreatitis; what's next?

16:00-17:30 (Convention Hall A)
English

Chairs: Yong-Tae Kim (Korea), Young Deok Cho (Korea)

Etiology and diagnosis, severity classification	Jun Kyu Lee (Dongguk University Ilsan Hospital, Korea)	517
Optimal medical management	Rungsun Rerknimitr (Chulalongkorn University, Thailand)	518
Optimal endoscopic management	Ji Young Bang (AdventHealth Orlando, United States)	519
Surveillence	Se Woo Park (Dongtan Sacred Heart Hospital, Korea)	520

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Primary Care Session (KSNM) 16:00-17:30 (Diamond Hall)
Solving 10 most frequently asked questions from FGID patients in the clinic Korean

Chairs: Soo Teik Lee (Korea), Poong-Lyul Rhee (Korea)

KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

[09:00-10:30, Convention Hall A+B]

Symposium 01 (KASL1) Korean

Noticeable research of liver disease in year 2019

Chairs: **Jung-Hwan Yoon** (Seoul National University Hospital, Korea)

Kwan Soo Byun (Korea University Guro Hospital, Korea)

Viral hepatitis

Hyung Joon Yim, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology,Korea University Ansan Hospital, Ansan, Korea

New publications in 2019 regarding viral hepatitis have been reviewed. We classified the clinical papers into 3 categories including hepatitis A, hepatitis B, and hepatitis C. Articles worth paying attention are introduced in this section.

Acute hepatitis A is a self-limiting disease, but rarely causes acute liver failure leading to liver transplantation or death. To predict the risk for transplant or death in hepatitis A-related acute liver failure (ALFA), a model was derived in Korea and validated in several countries.(1) Using a multivariate proportional hazard model, a risk-prediction model (ALFA score) consisting of age, international normalized ratio, bilirubin, ammonia, creatinine, and hemoglobin levels acquired on the day of ALF diagnosis was developed. The score showed the higher discrimination in prediction of liver failure and death compared with existing criteria for determining prognosis of liver failure. It is expected that the new scoring system help making early decision for performing liver transplantation to prevent death in patients with ALFA.

Chronic hepatitis B virus (HBV) infection is a global health burden. Spontaneous loss of hepatitis B surface antigen (HBsAg) is a rare event in patients with chronic HBV infection.(2) The incidence and the clinical scenario after the HBsAg loss were meta-analyzed.(2,3)

To enhance the chance of HBsAg in patients receiving entecavir, adding peg-interferon may be an option. However, the candidate should be carefully selected, as the patients with low HBsAg and HBV DNA levels are only likely to be benefited by this strategy.(4)

At this time, the routine practice is the maintaining the nucleos(t)ide analogues (NA). Recently, ten-year efficacy and safety of tenofovir disoproxil fumarate (TDF) was reported, and the virologic response rates approached 100% without any incidence of antiviral resistance.(5) However, after stopping TDF which was continued 8 years or more, almost a third of patients experienced a grade 3 or higher laboratory abnormality including viral rebound and ALT flare.(6) Hence life-long therapy until loss of the HBsAg would be a safer way, although quantified HBsAg level < 2 log IU/mL could be an alternative cut-off under careful monitoring.(7)

Long-term NA therapy may be associated with antiviral resistance although newly developed resistance was rarely observed in patients with TDF for multiple treatment failures during 5 years.(8) Nevertheless, recently tenofovir resistance was reportedly in two CHB patients.(9) Five mutations (rtS106C [C], rtH126Y [Y], rtD134E [E], rtM204I/V, and rtL269I [I]) were commonly found in viral isolates from the patients. The novel mutations C, Y, and E were associated with drug resistance. Hence, newer treatments with different therapeutic targets are necessary to overcome NA resistance. Currently, efficacy and safety of therapeutic vaccines (e.g. GS-4774),(10) capsid assembly modulator NVR 3-778,(11) immune check point inhibitor (nivolumab),(12) and liver-targeted antisense oligonucleotide (GSK3389404) were reported although those are still under early phase of clinical development.(13)

The goal of NA therapy is prevention of clinical events, especially, development of hepatocellular carcinoma (HCC) to prolong survival of the patients with chronic HBV infection.(14) Interestingly, there were reports that TDF is associated with lower risk of HCC than entecavir (ETV) in CHB patients in Korea and China.(15,16) Further Korean multicenter and international consortium studies showed the contradictory results that the overall prognosis in terms of HCC and death or OLT was not different between the ETV and TDF groups.(17-20) Further pooled data analyses may be needed.

Besifovir, which was developed in Korea, is a new NA. The 2 year phase 3 trial data showed non-inferior antiviral effect and improved safety of besifovir compared to TDF.(21) Long term outcome of besifovir treatment are warranted in terms of reduction of clinical events such as HCCs. However, we should keep in mind that occurrence of HCC is multifactorial, therefore multi-disciplinary approach is necessary. Recent clinical data reported the risk of HCC increases with high HBsAg and hepatitis B core-related antigen levels,(22,23) accompanying fatty liver disease,(17) smoking,(24) and alteration of gut microbiota.(25) However, statin use and daily aspirin therapy were preventive for HCC occurrence.(26,27) Indeed, the choice of NA itself should not be the sole factor in prevention of HCC.(28,29) Considering early initiation of therapy with expanded treatment indication would be needed, especially for high viral load and no significant ALT elevation.(30)

Chronic hepatitis C treatment encountered a new era with directly acting antiviral agents (DAAs). Korean real-life data of the first generation DAA with daclatasvir+ asunaprevir for genotype 1b and

sofosbuvir + ribavirin for genotyope 2 were published.(31,32) The clinical trial data and real world data of second generation DAA, glecaprevir + pibrentasvir for 8 week are available.(33,34)

Currently, treatment duration became shortened; the newer agent, JNJ-4178 (AL-335, odalasvir, and simeprevir) achieved SVR by 6 or 8 weeks of treatment.(35)

It is now certain that DAA therapy reduces risk of developing HCC and not associated with recurrence of HCC.(36,37) Although DAA therapies are highly effective, a small proportion of patients fail to achieve sustained virologic responses (SVR). Fortunately, a triple combination therapy with sofosbuvir/velpatasvir/voxilaprevir were highly effective for patients with previously failed with DAAs.(38) By achieving SVR in this population, a moving forward step toward the elimination of hepatitis C infection would be expected.

In conclusion, new data from the recent studies on viral hepatitis are emerging, and will support practicing an evidence based medicine.

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Alcohol-related and non-alcoholic fatty liver diseases

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The prevalence of non-alcoholic fatty liver disease (NAFLD) and Alcoholic liver disease (ALD) is increasing. Alcoholic steatohepatitis (ASH) and subtypes of NAFLD such as Non-alcoholic steatohepatitis (NASH) / NASH-fibrosis are a potentially progressive liver disease that can lead to cirrhosis, hepatocellular carcinoma and death. Despite this important burden, we are only beginning to understand its mechanisms of pathogenesis and the contribution of environmental, immunological and genetic factors to the risk of developing a progressive course of disease. Research is underway to identify appropriate non-invasive diagnostic methods, prognostic biomarkers and effective treatments. To develop effective future therapies for NAFLD and ALD, a precise understanding of its molecular mechanisms is required. This Review focuses on summarize the meaningful clinical studies of NAFLD and ALD in 2019 can helpful in future reseaches.

Liver cirrhosis and complications

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In 2019, a variety of interesting studies on cirrhosis and related complications were published.

Recently, multicenter organ failure caused by advanced cirrhosis has been attracting much attention, and among them, deterioration of renal function has been a major research subject. However, objective evaluation of changes in renal function in patients with cirrhosis is very difficult. Overestimation of renal function frequently occurs in patients with liver cirrhosis when using serum creatinine. Decreased muscle mass has a great impact on overestimation of kidney function especially in male patients with cirrhosis. Compared with creatinine, cystatin C was more closely correlated with measured glomerular filtration rate and had a higher predictive ability for renal complications and survival than creatinine.[1] Since the accuracy of estimated glomerular filtration rate (eGFR) measurement is low, efforts are being made to develop better new functional prediction models. One of recent proposal is GFR assessment in liver disease (GRAIL) model. GRAIL was superior in assessing low GFR before and after transplantation compared to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Modification of diet in renal disease (MDRD)-4, and MDRD-6.[2] A study on the clinical use of GRAIL was followed, a comparative evaluation of Model for End-stage Liver Disease (MELD)-GRAIL-Na using GRAIL and existing MELD-Na was performed. Incorporation of MELD-GRAIL-Na instead of MELD-Na showed it may impact outcomes for 12-17% awaiting transplant and affect organ allocation.[3] However, there is a limitation that the evaluation of renal function by GRAIL does not take into account the amount of muscles that significantly affects renal function evaluation in patients with cirrhosis. Many discussions and verification studies on GRAIL are expected in the future.

Kidney biomarkers appear to be useful in differential diagnosis between acute tubular necrosis (ATN) and other types of acute kidney injury (AKI) in cirrhosis, particularly hepatorenal syndrome (HRS-AKI). Distinction is important because treatment is different. However, kidney biomarkers are still not used in clinical practice. In a recent stuy,[4] urinary NGAL measured at day 3 had the greatest accuracy for differential diagnosis between ATN and other types of AKI (area under the receiver operating characteristic curve, 0.87; 95% confidence interval, 0.78-0.95). Progression of AKI during hospitalization was associated with persistently high NGAL levels, and NGAL was an independent predictive factor of AKI progression and 28-day mortality. These results support the use of NGAL in clinical practice within the context of a diagnostic algorithm for differential diagnosis of AKI and outcome prediction in cirrhosis.

The transition from acute renal injury to chronic renal disease is clinically not uncommon. This is also can be common in cirrhosis, because this condition is related with sustained low basal effective circulatory flow. Maiwall R et al studied the incidence and risk factors of the development of chronic kidney disease in cirrhosis.[5] In this study, almost two-thirds of patients with cirrhosis develop episodes of AKI and reduction in GFR; one-third progress to CKD, resulting in adverse outcomes. Higher MELD and CysC levels and number of AKI episodes predict development of CKD in patients with cirrhosis. Then what is the impact of CKD on Outcomes in Cirrhosis? A Recent study performed by The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) showed that CKD patients had significantly higher rates of superimposed acute kidney injury (AKI; 68% versus 21%; $P < 0.001$) and eventual need for dialysis (11% versus 2%; $P < 0.001$) than non-CKD patients. CKD patients also had more cases of acute-on-chronic liver failure as defined by the NACSELD group, which was associated with reduced 30- and 90-day overall survival ($P < 0.001$ for both). A 10 mL/minute drop in eGFR was associated with a 13.1% increase in the risk of 30-day mortality. So, this study suggested patients with CKD should be treated as a high-risk group among hospitalized patients with cirrhosis.[6]

In the point of treatment, the evaluation for the usefulness of non-selective beta blocker (NSBB) for compensated cirrhotic patients was done as multicenter prospective randomized controlled trial.[7] In this study, long-term treatment with NSBB increased decompensation-free survival in patients with compensated cirrhosis combined with clinically significant portal hypertension (hepatic venous pressure ≥ 10 mmHg), mainly by reducing the incidence of ascites. Albumin treatment had already shown good effect for cirrhosis and its related complications through the long term interventional treatment.[8] Not only oncotic effect but also non-oncotic effects of albumin are proposed as main mechanism of beneficial effect. However, the studies for the basic mechanisms of the beneficial effects of albumin is not enough. Fernández J and his colleagues evaluated the effect of albumin treatment (20% solution) on hypoalbuminemia,

cardiocirculatory dysfunction, portal hypertension, and systemic inflammation in patients with decompensated cirrhosis with and without bacterial infections. In this study, albumin treatment reduced systemic inflammation and cardiocirculatory dysfunction in patients with decompensated cirrhosis and these effects might be responsible for the beneficial effects of albumin therapy on outcomes of patients with decompensated cirrhosis.

In addition to the papers presented above, there are many excellent domestic and international studies not mentioned in this article, but they cannot be introduced due to lack of space.

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Hepatocellular carcinoma

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The systemic management of hepatocellular carcinoma (HCC) has evolved considerably over the last decade. Sorafenib is the first agent ever to show a survival benefit in patients with advanced HCC and has now become the standard first-line treatment for patients with BCLC-C stage HCC. Lenvatinib has recently shown to be non-inferior to sorafenib, and accordingly represents an alternative to sorafenib in the first-line setting. For the patients who intolerable or progressed on sorafenib, regorafenib and next cabozantinib exhibited a survival improvement as rescue therapy in order. A subset of sorafenib-failed patients with serum alpha-fetoprotein of ≥400 ng/mL also would benefit from second-line ramucirumab. Since phase II clinical trials of immune-checkpoint inhibitors including nivolumab and pembrolizumab had demonstrated relatively safe and durable antitumor activity in advanced HCC patients, global phase III efficacy data for nivolumab versus sorafenib as first-line therapy were presented at the ESMO meeting in October 2019. Unfortunately, the overall survival did not meet the predefined threshold for statistical significance (Hazard ratio [HR] 0.84, *P*=0.04419). However, nivolumab showed clinically meaningful improvements in objective and complete response rates in that study. Another spotlighted randomized, placebo controlled study of pembrolizumab in HCC patients with sorafenib failure did not meet significance per the pre-specified statistical criteria for successful overall and progression-free survival data (HR 0.78, one-sided *P*=0.0238; and HR 0.72, one-side *P*=00022, respectively), although the drug achieved a significantly greater objective response rate compared to placebo (18.3% *vs.* 4.4%, one-side *P*=0.00007).

At present, various clinical II or III trials evaluating the efficacy and safety of targeted agents combined with immune-checkpoint inhibitors are on the current investigation based on preclinical evidence for synergistic combinations as follows, in addition to ongoing trials of monotherapy (Table 1). Progress in this area would help to shed light on real clinical practice for hard-to-treat HCCs in the near future.

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Table 1. Ongoing clinical trials of mono- and combo-treatments in advanced HCC

Agent	Clinical trial number	Phase	Design
BGB-A317 (anti-PD1) vs. sorafenib	NCT03412773	III	First-line
Avelumab (anti-PD-L1) vs. placebo	NCT03389126	II	After sorafenib
Donafenib (Raf, ERK) vs. sorafenib	NCT02645981	II/III	First-line
Atezolizumab + bevacizumab vs. sorafenib	NCT03434379	III	First-line
Durvalumab + tremelimumab vs. sorafenib	NCT03298451	III	First-line
Nivolumab + galunisertib (TGF-beta inhibitor)	NCT02423343	I/II	Second-line
Nivolumab + CC-122 (pleiotrophic modifier)	NCT02859324	I/II	First or Second-line
Nivolumab + bevacizumab	NCT03382886	I	Second-line
Nivolumab + lenvatinib	NCT03418922	I/II	Second/First-line
Nivolumab + sorafenib	NCT03439891	I/II	First-line
Pembrolizumab + lenvatinib	NCT03006926	I/II	Second/First-line
Pembrolizumab + regorafenib	NCT03347292	I	First-line
SHR-1210 (anti-PD1) + apatinib (VEGFR)	NCT03463876	II	Second-line
Avelumab + axitinib	NCT03289533	I	First-line
Durvalumab + bevacizumabv vs. placebo	NCT03847428	III	Second-line
Durvalumab + ramucirumab	NCT02572687	I	Second-line
PDR001 (anti-PD1) + sorafenib	NCT02988440	I	First-line
Nivolumab + ipilimumab	NCT01658878	I/II	First or Second-line

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KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

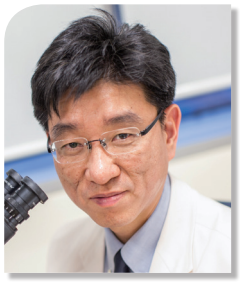
[08:45-10:30, Convention Hall C]

In-depth Symposium 01 (KSG) English

Unveiling the road to early diagnosis of pancreatic cancer

Chairs: **Dong Ki Lee** (Gangnam Severance Hospital, Korea)

Tooru Shimosega (South-Miyagi Medical Center, Japan)



Gene evolution from PanIN to pancreatic cancer

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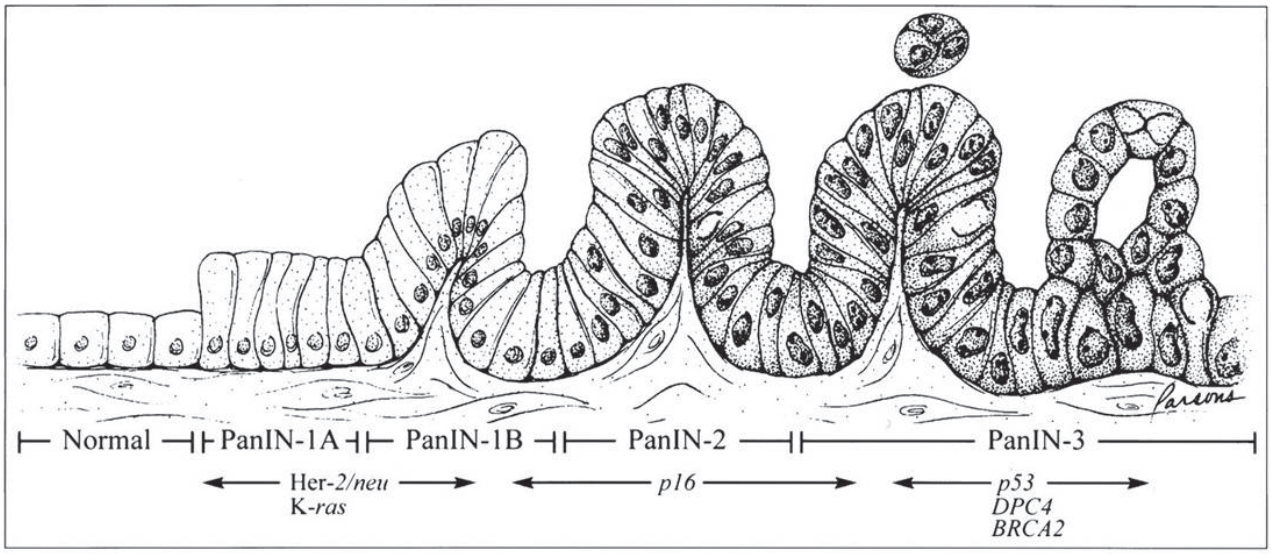
A large number of molecular alteration have been described in pancreatic ductal adenocarcinoma. The most commonly mutated genes include KRAS, CDKN2A (p16), TP53, SMAD4/DPC4, and MKK4. Mutations of the KRAS oncogene are found in over 90% of the cases and represent an early genetic alteration. Mutations of CDKN2A (p16), TP53, SMAD4/DPC4, occur in more than half of cases as well. These molecular alterations are typical of pancreatic ductal adenocarcinoma and distinguish them at a molecular level from other pancreatic neoplasm. It is worth mentioning that the search for genetic molecular alterations in the invasive component of pancreatic ductal adenocarcinoma and in precursor intraepithelial lesions of the same specimen have provided key information on the genetic progression of pancreatic carcinoma. It is important to point out that patients with chronic pancreatitis, but lacking microscopic features of invasive or in situ adenocarcinoma or ductal atypia, often have KRAS mutations in the non-neoplastic epithelium, indicating that this s genetic alteration is not specific for malignancy or even premalignant conditions. Obviously, this limits greatly the diagnostic utility of this marker in histologic or cytologic material. Since DPC4 is inactivated in approximately half of pancreatic ductal carcinomas but practically never in benign conditions, the immunohistochemical absence of the protein product in the ductal epithelium of a pancreatic biopsy specimen is strongly suggestive of carcinoma, while positive staining does not rule out this possibility. Although Lynch syndrome patients have a seven- to eightfold increase in pancreatic ductal adenocarcinoma, MSI does not appear to play a significant role in sporadic ductal adenocarcinomas; the rare cases of pancreatic carcinoma that ate MSI-high tend to have the medullary phenotype. These tumors typically do not have KRAS mutations but commonly exhibit mutations in the BRAF gene, a downstream component of the KRAS pathway.



Challenge to screen early pancreatic cancer in general population

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Recently, Japan Pancreas Society (JPS) revised the clinical guidelines for PC in 2019. As for the early diagnosis of PC with a long-term prognosis, a long-term prognosis is expected in the case of PC < 1cm. the dilatation of the pancreatic duct and cystic lesion are important as indirect findings. When the direct depiction of the tumor is difficult by US and dynamic MDCT, EUS, or MRCP should be performed. EUS-FNA should be performed when a mass lesion is detected by EUS. When localized stenosis of the pancreatic duct, caliber change, and dilatation of the branch duct are found, ERCP followed by serial pancreatic juice aspiration cytologic examination (SPACE) should be performed.

The Japan Study Group on the Early Detection of PC (JEDPAC) reported 200 cases with Stage 0 and I, which accounted for 0.7% and 3% of all PC. Overall, 20% of the early-stage PC cases were symptomatic. Image findings such as dilatation or irregular stenosis of the main pancreatic duct (MPD) detected by CT, MRCP, or EUS were useful to detect early-stage PC. Preoperatively, SPACE followed by ERCP was commonly applied than EUS-FNA.As for image diagnosis of PCIS, abnormal findings in the MPD, such as localized stenosis with distal MPD dilatation, irregularity, non-continuous narrowing and granular defects were frequently observed by ERCP, MRCP or EUS. Focal ductal branch dilatations and cystic lesions around the MPD were also observed. The JEDPAC data from 200 early-stage cases reported that local fatty changes may be specific to early-stage PC. Localized pancreatitis with infiltration of inflammatory cells, fibrosis, and fatty infiltration were frequently observed in the parenchyma around PCIS and atypical epithelium. In addition, there were some PCIS cases with intraductal spread, and mismatch of cancer and MPD stenosis. EUS could detect localized pancreatitis, fibrosis, andfatty infiltration around PCIS as a slightly low echoic lesion.

It has been reported that regional networks between specialists in PC (SPC) and general practitioners (GP) should play an important role for early diagnosis of PC. Onomichi city is a rural city located in Hiroshima Prefecture in western Japan, and its total population is approximately 150 000. Onomichi Medical Association established a social program for early diagnosis of PC in 2007. From January 2007 to June 2017, a total of 12307 cases consulted SPC after starting this program. After carrying out CT, MRI, and EUS to detect suspicious findings of PC, such as mass lesions, dilatation of MPD or cystic regions, ERCP or EUS-FNA was carried out. If irregular stenosis of the MPD was observed on ERCP, SPACE was additionally done. As a result, 555 out of 12307 cases were histologically diagnosed as PC. Of these cases, 24 were diagnosed as stage 0 and 21 were diagnosed as stage I histologically. As the concept of the Onomichi project spreads, some Japanese medical associations have tried to establish the regional network for early diagnosis of PC. In the future, regional networks between SPC and GP in medical associations for early diagnosis of PC should be established in other areas in Japan.

Genetic predisposition to pancreatic cancer, results from genome-wide association studies (GWAS)

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Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related deaths in the United States and the seventh world-wide. This seminar will discuss results from genome-wide association studies (GWAS), conducted within the NCI-led Pancreatic Cancer Cohort Consortium. This collaborative effort has identified over 20 common pancreatic cancer risk loci. Additional approaches including a Transcriptome Wide Association Analysis (TWAS) using GWAS data in conjunction with transcriptome datasets have identified multiple additional risk loci/genes. Functional characterization of a subset of these loci will be presented highlighting different molecular mechanisms underlying pancreatic cancer risk.

How to diagnose early pancreatic cancer: from Japanese experiences

Tooru Shimosegawa, M.D.

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Pancreatic cancer (PDAC) remains most malicious tumor with poor prognosis. There is no clear definition of early PDAC due to invasive nature and high malignant potential of even small tumor. According to the data of Japan Pancreatic Cancer Registry (JPCR), the 5-year survival rates of Stage 0, Ia and Ib were 85.8%, 68.7% and 59.7%, respectively. Considering the relatively fair survival rates, Stage 0 and I PDAC can be considered as early stage, tentatively. We performed re-evaluation of the JPCR data according to the tumor size. The results demonstrated that even small tumors like T1a (tumor size 5 mm or less), T1b (5-10 mm) and T1c (10-20 mm) showed regional lymph node metastasis with frequencies of 18.8%, 17.5% and 27.9 %, respectively, and they also had distant metastasis with frequencies of 12.5 %, 8.7 % and 14.3%, respectively. Therefore, to improve prognosis of patients, it is ideal to detect PDAC in Stage 0 that means in carcinoma *in situ*. The Study Group for the Early Detection of Pancreatic Cancer of Japan (JEDPAC) collected the data of 200 cases of Stage 0 (51) and I (149) from 14 high volume centers and studied how to diagnose PDAC in early stage. According to the analysis, picking up stenosis and upstream dilatation of MPD and fatty tissue deposition of the pancreas are important clues to detect PDAC in early stage. Cytology of pancreatic juice obtained by brushing or ENPD collection on ERCP is important for confirmation of Stage 0 PDAC, whereas EUS-FNA plays major role for confirmation of Stage I tumor. Finally, we studied the findings useful to differentiate the MPD stenosis by PDAC (malignant stenosis) and by inflammation (benign stenosis). The results demonstrated that both fatty tissue deposition in pancreatic parenchyma and ENPD cytology had sensitivity and specificity of 50% and 100%, respectively, and combination of them raised the sensitivity. In conclusion, detection of stenosis and upstream dilatation of MPD and deposition of fatty tissues at or around MPD stenosis in combination with histological confirmation by pancreatic juice cytology or EUS-FNA are important procedures to diagnose early PDAC.

KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

[09:00-10:30, Emerald Hall A]

PG Course 01 (KSNM) Korean

A to Z of Functional Dyspepsia

Chairs: **Sei Jin Youn** (Chungbuk National University Hospital, Korea)

Oh Young Lee (Hanyang University Medical Center, Korea)

Pathophysiology

Chung Hyun Tae, M.D., Ph.D.

Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul Hospital, Seoul, Korea

Functional dyspepsia defines clinical syndrome comprising chronic bothersome postprandial fullness, early satiety, epigastric pain, and epigastric burning. The pathophysiology of functional dyspepsia is not well understood. However, several potential mechanisms have been suggested. Delayed gastric emptying was thought to be one of the main players in the pathophysiology of functional dyspepsia. Visceral hypersensitivity in is characterized by a lowered threshold for induction of pain in the presence of normal gastric compliance. It is associated with postprandial epigastric pain, epigastric pain, belching, and weight loss. Gastric accommodation is mediated by a vasovagal reflex initiated by food ingestion and generated via the upper body of the stomach. Impaired relaxation of gastric fundus in response to antral distention also contributes to accommodation. This has been linked to early satiety. Recent studies has focused that duodenal eosinophilia has associated with functional dyspepsia. The presence of duodenal eosinophilia has also been associated with allergy and the post prandial syndrome subtype of functional dyspepsia, suggesting that a hypersensitivity to luminal contents may be involved. It has long been assumed that H pylori–related gastritis could cause dyspeptic symptoms via a variety of disturbances in acid secretion, motility, and neuroendocrine pathway. It has been recognized for decades that functional dyspepsia is commonly linked with psychological comorbidities, such as anxiety and depression. Post-infectious functional dyspepsia following *Salmonella, Escherichia coli, Campylobacter*, giardiasis or norovirus, and possibly other upper intestinal infec¬tions is a newly-recognized syndrome. Even though limited data, genetic factors are associated with functional dyspepsia. GNbeta3, which alters G-protein activation and multiple other pathways, was the first single nucleotide polymor¬phism associated with functional dyspepsia. The nitric oxide synthase gene has also been linked to functional dyspepsia.

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Assessment

Jong Kyu Park, M.D., Ph.D.

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Functional dyspepsia (FD) is one of the most common gastrointestinal (GI) disorders that significantly impacts on the usual activities of patients. According to the recently revised Rome IV criteria,[1] FD is defined as a syndrome with one or more of the following symptoms which includes bothersome postprandial fullness, early satiation, epigastric pain and epigastric burning with no evidence of structural disease including at upper endoscopy that is likely to explain the symptoms. These criteria should be fulfilled for at least three months with symptom onset at least six months before diagnosis. Rome IV committee proposed more detailed descriptive definitions of symptoms, because symptom definition remained somewhat vague and potentially difficult to interpret in Rome III. Post prandial distress syndrome (PDS), which is characterized by meal-induced dyspeptic symptoms, was slightly modified that postprandial fullness and early satiety as well as epigastric pain and burning can be perceived by the patients as being induced or worsened by a meal. Epigastric pain syndrome (EPS), which refers to epigastric pain or epigastric burning that does not arise exclusively postprandial, can occur during fasting, and can be relieved by ingestion of a meal. The frequency of symptoms was specifically stated as that the bothersome symptom should be at least 3 days per week in PDS, and at least 1 day a week in EPS. Bothersome was clinically defined as a symptom which is severe enough to usual activities and semi-quantitatively as ≥2 in a 5-point adjectival scale linked to the effect exerted by symptoms on usual activities. If a remission of dyspeptic symptom is sustained more than 6 month after *helicobacter pylori* (*H. pylori*) eradication, which was classified into *H. pylori*-associated dyspepsia, not FD.

In the diagnosis of FD, symptoms alone cannot exclude the organic cause of dyspepsia and there are no clinically useful biomarkers at present. If an alarm symptom (weight loss, dysphagia, GI bleeding, iron-deficient anemia, abdominal mass or persistent vomiting) is noted, organic disease should be suspected. However, alarm signs had a limited value to predict the upper GI malignancy in meta-analysis.[2] Several studies have showed that there were no differences in controlling global dyspeptic symptoms between *H. pylori* test and treat and prompt upper GI endoscopy in undiagnosed dyspeptic patients, and *H. pylori* test and treat was more cost-effective. Western guidelines recommend *H. pylori* test and treat or empirical PPI therapy rather than prompt upper endoscopy for initial approach of FD. In Asia, the incidence of gastric cancer is very high, and the age of onset is younger than Western country, especially the incidence in Korea is the highest in the world. Therefore, if *H. pylori* test and teat strategy were applied in dyspeptic patients, upper GI malignancy such as gastric cancer can be missed. A recent systematic review with meta-analysis was conducted to evaluate the appropriateness of prompt endoscopy as an initial strategy for uninvestigated dyspepsia in Asia.[3] They concluded that the optimal age threshold for endoscopy screening in patients with uninvestigated dyspepsia in Asia might be 35 years. According to annual report of cancer statistics in Korea in 2014, the proportion of gastric cancer was 1.18% (353) for cancer patients aged < 35 years, 3.12% (932) for those aged < 40 years and 7.47% (2230) < 45 years among the 29,854 patients with gastric cancer. Therefore, because of the high probability of gastric malignancy in patients with dyspepsia over 40 years of age, prompt upper endoscopy should be performed in patients with dyspepsia aged 40 or over to exclude the organic cause including gastric cancer. Delayed gastric emptying and abnormal gastric accommodation have been identified in a large number of patients with FD. However, identifying the abnormal pathophysiologic mechanisms that underlie the development of FD symptoms has not directly altered treatment strategies, and is not accurately related to symptoms. Therefore, routine motility test for patients with FD are not recommend.[4]

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Pharmacological therapy

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Dyspepsia is a common problem. If the dyspeptic symptoms develop within a short period of time, organic diseases should be suspected such as gastroesophageal reflux disease, peptic ulcer diseases, pancreatoduodenal diseases, and gastrointestinal cancers. If the symptoms would be chronic or recurrent after eliminating the underlying disease, functional dyspepsia (FD) should be considered. FD was classified into two subtypes, epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS). In addition, these two subtypes may overlap. Patients with the EPS subtype can be treated with proton pump inhibitors (PPIs), while patients with PDS subtype can be managed primarily with prokinetics. In the case of the patients with EPS and PDS, PPIs and prokinetics can be used together. *Helicobacter pylori* (*H. pylori*) eradication therapy can be treated with a strategy of test and treat for patients who are not effective in PPIs and prokinetics, or who have chronic dyspepsia in younger patients. Although almost every consensus suggested *H. pylori* eradication as a primary treatment for dyspepsia, accepting this agreement in Korea will require careful consideration. Tricyclic antidepressants can be used as a secondary treatment because it is effective for patients with EPS subtype. Because the pathophysiology of FD is diverse, it is necessary to elaborate on dietary education and stress management in addition to medical therapy. The FD treatment algorithm in Korea is presented as follows.

Key Words: Dyspepsia; Guideline; *Helicobacter pylori*; Proton pump inhibitors

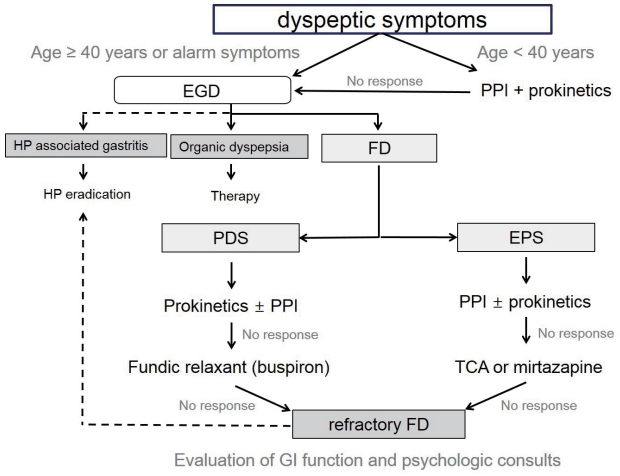
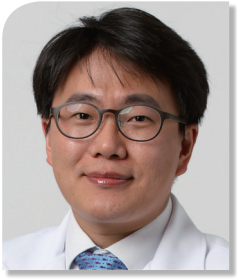


Figure. Treatment algorithm for dyspepsia in Korea.
EGD, esophagogastroduodenoscopy; EPS, epigastric pain syndrome; FD, functional dyspepsia; HP, *Helicobacter pylori*; PDS, postprandial distress syndrome; PPI, proton pump inhibitor.



Non-pharmacological therapy

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INTRODUCTION

Functional dyspepsia (FD) is diagnosed based on the symptoms such as epigastric pain, epigastric burning, postprandial fullness, and early satiation in the absence of organic disorders. Under the assumption that a distinction between meal-related and meal-unrelated symptoms might be pathophysiologically and clinically relevant, FD has been subdivided into postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). However, there are significant overlaps between two subtypes, and the ROME IV criteria was newly revised, which emphasizes that FD should not be considered as a single disorder.[1]

The pathophysiology of functional dyspepsia is a combination of several mechanisms, including gastric motility disorders, visceral hypersensitivity, central nervous system dysregulation, and inflammation. Psychosocial factors and stress also play an important role in the development and continuation of FD.[2]

NON-PHARMACOLOGICAL THERAPY OF FD

Non-pharmacological treatments for FD include dietary modulation, probiotics, prebiotics / fiber, vitamin supplement, herbal products, homeopathy, acupuncture, relaxation, and cognitive-behavioral psychotherapy.[3] In this section, dietary management, psychotherapy, and acupuncture will be discussed in detail.

DIETARY MODULATION

The most important principle of dietary management in the treatment of FD is to avoid foods that cause symptom. Several studies and systemic review reported that wheat-containing foods, fatty or spicy foods, and carbonated drinks was associated symptoms.[4] However, all kinds of foods can be potential candidates to trigger symptoms, and the leading cause of the symptoms varies according to the geographic region and race. Therefore, restriction of certain nutrient or ingredient is not recommended. Rather, it is desirable to avoid specific food that causes symptom.

Medical food which is formulated and usually received safety reviews by toxicologists may be helpful.[5] Several mechanisms has been proposed, including anti-inflammatory and analgesic effect, smooth muscle relaxation, improvement of gut barrier dysfunction, and stimulation or inhibition of gastrointestinal receptors.[5]

Caraway oil and peppermint oil are widely used in Western countries.[6-9] In addition, several studies showed that probiotics and prebiotics were effective in the improvement of FD symptoms.[10,11]

PSYCHOTHERAPY

Currently, cognitive behavioral therapy, psychoanalytic psychotherapy, and hypnotherapy are used for the treatment of FD. Although several studies showed encouraging data, there is limited evidence of psychotherapy in FD. Recent guidelines suggested psychologic therapy as effective treatment for patients with dyspepsia.[12] In a previous study, psychotherapy was more effective than the control group and number needed to treat was only three patients. However, this study has limited value because methods and populations were heterogeneous.[12]

According to a review article about hypnotherapy recently published, patients showed overall improvement in physical and mental health.[13] Another study showed that hypnosis was much more effective than cisapride, and relaxing music reduced gastric emptying time in both dyspeptic patients and healthy volunteers.[14] In addition to the improvement of gastric emptying, hypnosis can reduce visceral hypersensitivity by reducing anterior cingulated cortical activity on brain imaging studies, resulting in the decrease of reported pain sensation in response to pain stimuli.[15] Additional randomized controlled trials are required before taking a firm position on treatment of FD.[13]

ACUPUNCTURE

Acupuncture has been used to treat FD in Eastern countries for thousands of years, but the underlying mechanism is still unclear. The practice of acupuncture consists in inserting fine and hard needles (32 to 36 gauge) into selected body point. The four classic acupuncture points most frequently used in the study of FD are ST34 (Liangqiu), ST36 (Zusanli), ST40 (Fenglong) and ST42 (Chongyang).[16] Acupuncture points can also be stimulated passing electrical currents through an inserted needle to stimulate as mentioned four gastric disease acupuncture point. Unlike manual acupuncture, electrical acupuncture could provide objective and quantified method.[17]

In a previous RCT consists of 712 FD patients, the overall response

rate of the acupuncture group was significantly higher than in the other group with the lowest response in the sham acupuncture group.[18] Another study used fluorine-18 fluorodeoxyglucose positron emission tomography computed tomography scans (PET-CT) to detect cerebral glycometabolism changes during acupuncture. In this study, acupuncture treatment showed extensive deactivation in cerebral activities compared with the sham acupuncture group. In particular, the deactivations of the brainstem, anterior cingulate cortex, insula, thalamus, and hypothalamus were related to the decrease in dyspepsia symptom score.[19]

CONCLUSION

Non-pharmacological treatments are promising alternative treatment option for FD. Although non-pharmacologic treatment may become a part of standard treatment of functional dyspepsia in the future, currently, there is limited evidence regarding non-pharmacologic treatment. Further well-designed studies which can demonstrate treatment effects as well as adverse effects are warranted.

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KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

[09:00-10:30, Diamond Hall]

Big Data Research (KSG) English

Beyond big data to artificial intelligence (AI) in colon cancer

Chairs: **Ming-Shiang Wu** (National Taiwan University, Taiwan)

Hyun-Soo Kim (Wonju Severance Christian Hospital, Korea)

Population-based tailored approach by age and sex dependent cutoffs of FIT

Chang Mo Moon

Department of Internal Medicine-GI/Hepatology, Ewha Womans University Mokdong Hospital, Seoul, Korea

Big Data Driven Economical Appraisal for Colorectal Cancer Screening Program

Ming-Fang Yen, Ph.D.

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In the wake of evidence-based medicine (EBM) that has provided scientific basis for medicine and public health, synthesis science has gained momentum for guiding the prevention of non-communicable disease in order to render clinical and public health practice fit in with scientific principle. It includes meta-analysis, decision analysis, and economic evaluation by integrating various kinds of data and information as a synthetic scientific framework. Synthesis science plays an important role in the era of big data on the provision of systematic and efficient scientific evidence.

The prevention of colorectal cancer is of paramount importance to the rising tide of colorectal cancer incidence. Despite secondary prevention of colorectal cancer through screening has gained attention. It is still worthwhile to provide a systematic viewpoint on the prevention of colorectal cancer (CRC). These include biological properties, infrastructure and clinical capacity, and health decision-makers of health care, personal preference given informed-decision making. The biological properties are manifested with heterogeneous cause of CRC. Infrastructure and the clinical capacity of health care given limited resources determined the type of delivery of preventive care for CRC. The third is pertaining to the recently proposed individually-tailored policy after informed decision-making.

A mathematical model of multi-state and multi-factorial model to incorporate fecal hemoglobin (f-Hb) concentration, life style factors, co-morbidity, chromosomal instability (CSI), and CpG island methylator phenotype (CIMP) with the application of five-state Markov model for the natural history of CRC was developed to translate the medical research to the practice of personalized screening strategy.

The cost-effectiveness analysis of personalized screening, including universal FIT screening by different interscreening intervals, primary colonoscopy screening, and the personalized screening strategies suggested by personal characteristics (including f-Hb concentration, life-style, comorbidity, and genetic and epigenetic factors) will be provided under the framework of synthesis science on the prevention of CRC.

Given heterogeneous causes of CRC and manifold screening modalities, the final decision-making for the choice of preventive strategies is still pivotal in health decision-makers at population-average-risk level and clients at individual-specific-risk level depending on state-run, out-of-pocket or a mixture of both structures. The final elements of personalized screening should also put emphasis on "informed decision making" to aid decision-makers and clients understand the consequences of being screened and participate in decisions about their own screening.

AI image classifier for the prediction of histology and endoscopic resectability

Wai Keung Leung, M.D.

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Artificial intelligence (AI) is increasingly used in clinical medicine, particularly on image analysis. Recent studies have demonstrated the promising role of AI on diagnosis and characterization of endoscopic lesions, particularly for colorectal polyps. Studies have demonstrated the feasibility of using artificial intelligence (AI) to classify colorectal polyps with high accuracy. In the latest ASGE PIVI initiatives, it is recommended that a negative predictive value of >90% is required for optical diagnosis of small hyperplastic polyps, and a >90% agreement in assigning post-polypectomy surveillance intervals. Hence, AI may assist the endoscopists in the adoption of "diagnose and leave" or "resect and discard" policy for diminutive (< 5mm) colorectal polyps by acting as a virtual supervisor, particularly for those who are less experienced on optical diagnosis of colorectal lesions. In our recent meta-analysis, we showed that the AI has a sensitivity of 91.8% and specificity of 87.6% in predicting the presence of neoplasia in colorectal polyps. The area under the curve of AI for histology prediction of diminutive polyps by using narrow band imaging could be as high as 0.97.

Another potential role of AI is on assessing the possible depth of invasion of large colonic lesions to determine whether it is endoscopically resectable. We have recently evaluated the role of AI in predicting deep submucosal invasion of colorectal lesions and the AI image classifier had an overall accuracy of 94.3% in predicting curative endoscopic resection, which were based on non-magnified NBI endoscopic images only. This could also help to guide the endoscopists, particularly the less experienced one, on the real-time decision-making process of choosing the most appropriate management of large colorectal polyps.

We have just entered an exciting era of AI assisted endoscopic diagnosis and further studies will help to establish the role of AI in gastrointestinal endoscopy.

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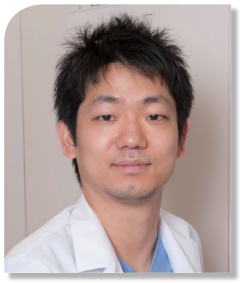

Deep learning based treatment decision for T1 cancer; endoscopy vs. surgery

Katsuro Ichimasa, M.D., Ph.D.

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Background/Aims: Most T1 colorectal cancers (CRCs) undergo surgical colectomy with lymph node dissection despite the low incidence (approximately 10%) of lymph node metastasis (LNM). Therefore, many patients without LNM undergo unnecessary surgeries. The aim of this study was to investigate whether artificial intelligence (AI) can predict LNM presence of T1 CRCs after endoscopic resection, thus minimizing the need for additional surgery.

Methods: Data on 710 consecutive patients with T1 CRCs that were surgically resected in 2001–2017 were retrospectively analyzed. We divided patients into two groups according to date: data from 590 patients were used for machine learning for the artificial intelligence model, and the remaining 120 patients were included for model validation. The AI model analyzed 44 clinicopathological factors and then predicted positivity or negativity for LNM based on support vector machine. The AI model was validated by calculating the sensitivity, specificity, and accuracy for predicting LNM, and comparing these data with those of the American and European guidelines.

Results: Sensitivity was 100% (95% CI, 62%–100%) in all models. Specificity and accuracy of the AI model, American and European guidelines were 63% (54%-72%) vs. 43% (34%-53%) vs. 0% (0%-5%), and 67% (58%–75%) vs. 48% (39%-58%) vs. 9% (5%-16%), respectively. The rate of unnecessary surgeries of the AI model was calculated as 78% in comparison with American 84% ($P<0.01$) and European 91% ($P<0.01$).

Conclusion: AI will help in making decisions as to whether additional surgery is indicated after endoscopic resection of T1 CRCs.

KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

[09:40-10:20, Grand Ballroom B+C]

Special Lecture (KSGC) English

Chair: **Hyun Yong Jeong** (Chungnam National University Hospital, Korea)

Development of Effective Immune Checkpoint Cancer Therapy

Mien-Chie Hung, Ph.D.

Department of the Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan

Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as promising therapeutics for many diseases, including cancer. My group showed that combination of c-Met and PARP1 inhibitors synergized to suppress growth of breast cancer cells in vitro and xenograft tumor models (Nature Medicine 22:194, 2016). We are working with clinicians at MD Anderson and initiate clinical trials using combinational therapy of PARP and c-MET inhibitors.

Anti-PD-1/PD-L1 therapy is a promising approach in cancer therapy. We showed that glycosylation of PD-L1 is required for its protein stability and interaction with PD-1 (Nature Communications 7:12632, 2016). Furthermore, we developed an effective combination therapy by metformin-activated AMPK kinase to downregulate PD-L1 through alteration of glycosylation of PD-L1 and functionally mimics anti-PD-L1 to block PD-L1/PD-1 interaction. It exhibited a highly potent synergistic effect of combination therapy of metformin, a drug that has been treated patients with diabetes and anti-CTLA4 in different syngeneic mouse models. The therapeutic efficacy could reach to the survival rate of 50-70% in different syngeneic mouse models which were treated by this combination therapy (Molecular Cell 71:606, 2018). We demonstrated that epithelial-mesenchymal transition (EMT) enhances PD-L1 in cancer stem-like cells (CSCs) by the EMT/β-catenin/STT3-PD-L1 signaling axis. Etoposide, a commonly used anti-cancer chemotherapy drug is able to suppress this signaling axis, resulting in downregulation of PD-L1 to sensitize cancer cells to anti-Tim 3 therapy (Nature Communications 9:1908, 2018). We identified two mechanisms in HCC to develop effective combination therapy with immunotherapy (Gastroenterology 156:1849, 2019 & Journal of Clinical Investigation in press, 2019). We identified TNFα as a major factor triggering cancer cell immunosuppression against T cell surveillance via stabilization of programmed cell death-ligand 1 (PD-L1) (Cancer Cell 30:925, 2016). To this end, in collaboration with StCube Pharmaceuticals Inc., we have developed monoclonal antibodies against glycosylation-specific PD-L1. Impressive therapeutic effect was observed through antibody-drug-conjugate approach (Cancer Cell 33:187, 2018). PD-L1 is heavily glycosylated which makes it difficult to accurately detect PD-I1 expression and has been a puzzle to use PD-L1 expression to stratify patients for treatment. Lately, we developed a method to resolve this issue by removing the glycan moieties from cell surface antigens via enzymatic digestion. We demonstrated that improved PD-L1 detection after deglycosylation is associated with response to anti-PD-1/PD-L1 therapy as well as Increased PD-L1 signal after deglycosylation is beneficial to therapeutic selection. We also showed that antigen retrieval by protein deglycosylaton improves predictive ability of PD-L1 as a biomarker for immunotherapy. (Cancer Cell 36:168, 2019).

If time allows, this talk will include our recent discoveries on developing therapies for lung or pancreatic cancers (Cancer Cell 34:9549, 2018 & Cancer Cell 33:752, 2018) as well as role of exosome-PD-L1 and PD-L1 palmitoylation in T-cell killing (Cell Res 28:862, 2018; Cell Res 29:83, 2019); these finding could provide new alternative approaches to improve anti-PD-L1/PD-1 therapeutic efficacy.

KDDW 2019 Korea Digestive Disease Week

DAY 1

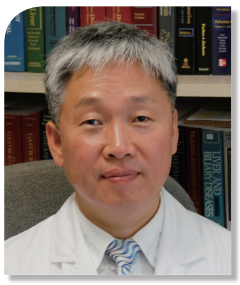
November 28 (Thursday)

[11:00-11:30, Convention Hall A+B]

Presidential Lecture (KASL) Korean

Chung Yong Kim Memorial Lecture

Chair: **Kwan Sik Lee** (Gangnam Severance Hospital, Korea)



Alcoholic Liver Disease -Past, Present, and Future

Dong Joon Kim, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Hallym University College of Medicine, Chuncheon, Korea

Brewing fermented beverages in China dates back as early as the seventh millennium B.C., and fermented drinks were first mentioned in the founding story of the Goguryeo Kingdom during the reign of King Dongmyeong (B.C. 37-B.C. 19) in the "Poetic Records of Emperors and Kings (Jewangun-gi)". Drinking "ear-quickening wine (gwibalgisul)" in the hopes of hearing good news at the first full moon of the lunar New Year is one of the long-lasting Korean traditions.

Notwithstanding, evidence of drinking alcohol does not necessarily mean the presence of alcoholic liver disease. Due to general food shortages before the modern times, it is assumed that alcoholic beverages were used only in secular or religious ceremonies and drinking for leisure was confined to rulers and upper class individuals. In the "History of Korean Medicine and of Diseases in Korea", Sakae Miki described that "cirrhosis hepatis (liver cirrhosis) is relatively common but it is difficult to identify the cause."

The hepatitis B antigen (called "Australia antigen") was first reported by Bloomberg et al. in 1965. Thus, attribution of causality or determination of the etiology of chronic liver disease was only possible after the 1970s in Korea. Even in the early 1970s, there were debates on the causality of alcohol in the development of chronic liver disease. In the 1990s, alcoholic liver disease became an important health problem in Korea. This marked change between the 1970s and 1990s was thought to be due to rapid development of the economy and the availability of cheap hard liquor ('soju') after the Grain Management Act in 1965.

Excessive alcohol consumption not only causes a variety of illnesses, including alcoholic liver disease, but also indirectly causes accidents. Every year, approximately 2.5 million people die from alcohol worldwide, with 320,000 deaths among 15-29 aged people. According to the Organization for Economic Cooperation and Development (OECD) report in 2012, 2.3% of all deaths in Southeast Asia and more than 5% in the western Pacific were due to alcohol consumption.

The Korean culture is lenient toward drinking. Alcohol consumption is considered a social activity, and drinking is thought to be an important component in business and various other social interactions. Alcohol consumption has increased over the past 40 years in Korea concomitantly with the country's rapid socioeconomic development. The per-capita alcohol consumption in Korea is now considered to be among the highest in the world.

As a result, alcohol-related deaths and mortality continue to increase in Korea. Furthermore, the social costs of alcohol (including loss of productivity, health care costs, automobile accidents and crime-related costs) are significant, and these social costs account for approximately 2% of the GDP in Korea. According to recent Korean studies based on data from the 2009 KNHANES, approximately 7% of Korean adults are heavy alcohol consumers (men: >40 g/day, women: >20 g/day), and approximately 25% of these heavy alcohol consumers exhibit abnormal liver-function tests.

In the WHO report, Korea is rated as a country where the alcohol burden is high but a national plan for alcohol has not been implemented. To drastically lower alcohol-related diseases and the socioeconomic burden of alcohol in Korea, the establishment of basic law such as Japan's "Basic Law on Measures Against Health Problems Caused by Alcohol Intake (Act No. 109 of 2013)" should be prioritized. Enactment of a law that obligates the national and local governments to establish measures to reduce alcohol-related problems can appropriately improve the alcohol-related policy in Korea.

Alcohol has been recognized as a direct hepatotoxin for over 5 decades now. Alcohol-related liver injury results from both the direct effects of alcohol on the liver as well as the indirect effects of acetaldehyde-mediated damage on the gastrointestinal mucosa. Over the last 3 decades, the importance of the ''gut-liver axis" in alcohol-induced liver damage has been recognized. There are over 100 trillion bacteria living within our gastrointestinal lumen and its mucosa, where they perform the important functions of maintaining gut integrity and innate immunity. There is evidence that alcohol consumption changes the gut flora, reducing the levels of beneficial microorganisms and increasing the levels of harmful bacteria in the intestines.

Since the 1970s, substantial progress has been made in understanding the pathogenesis of ALD. However, therapy for AH has not evolved in the past four decades. The STOPAH study taught us an important lesson, that we need to take a fresh look at how we address and manage our patients with severe AH. Over the last few years the National Institute on Alcohol Abuse and Alcoholism (NIAAA) have encouraged and supported many consortia in the US to conduct clinical trials to examine novel targets and to develop viable treatments options for the management of severe AH. Based on their mechanism of action, these drugs can be classified as drugs acting on the gut-

liver axis, anti-inflammatory agents, antioxidants, and drugs with regenerative benefits. The enthusiasm of investigators would provide a ray of hope in the development of newer pharmacological therapies for patients with severe AH in the future.

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KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

[11:00-12:30, Convention Hall C]

In-depth Symposium 02 (KSG) English

Current status and perspective for early diagnosis of pancreatic cancer

Chairs: **Laufey Amundadottir** (National Cancer Institute, National Institutes of Health, United States)

Yong Tae Kim (Seoul National University, Korea)

Protein science; liquid-chromatography-tandem mass spectrometry : Mass spectrometry-based proteome profiling of extracellular vesicles and their roles in biology of Pancreatic ductal adenocarcinoma

Kwang Pyo Kim, Ph.D.

Department of Applied Chemistry, Kyung Hee Univerity, Yongin, Korea

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer. It is the fourth cause of cancer-related death worldwide with a 5-year survival below 6% due to lack of early diagnostic markers and the poor efficiency of the treatment.

Cancer cells communicate with surrounding cells in microenvironment. Extracellular vesicles (EVs), such as exosomes and microvesicles have emerged as key mediators of cell and microenvironment communication. EVs have various biological molecules, including proteins, mRNAs and microRNAs that deliver their information to other cells. Therefore, EVs are very important sources for novel biological markers for cancer detection.

The aim of our project is to identify new molecular markers and drivers of PDAC initiation, progression and metastasis from EVs with liquid chromatography-mass spectrometry (LC-MS). In this presentation, comparison of proteomes of EVs isolated from various PDAC cell lines and serum of patients will be presented. Our study might deepen the understanding of the etiology of PDAC that could explain pathophysiological regulation of PDAC development and identify potential marker proteins for PDAC diagnosis.

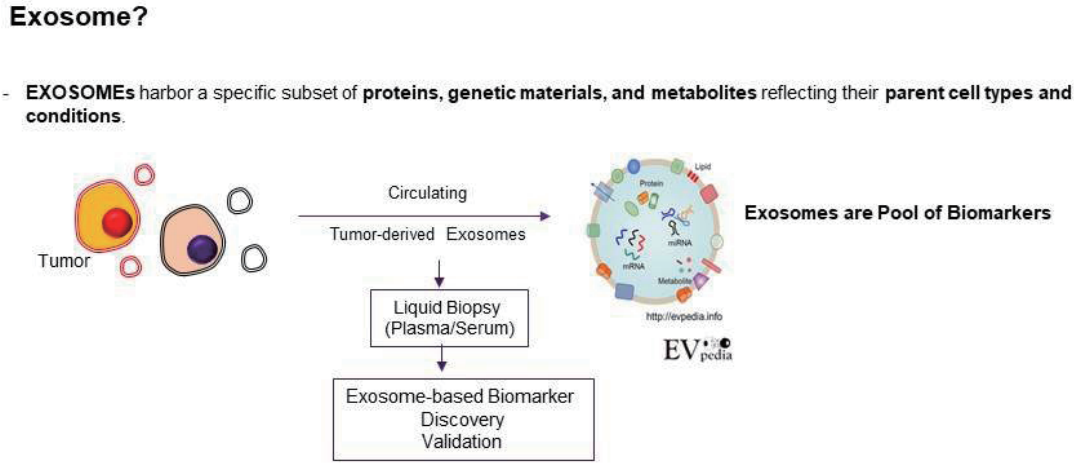

Figure 1. EXOSOMEs harbor a specific subset of proteins, genetic materials, and metabolites reflecting their parent cell types and conditions.

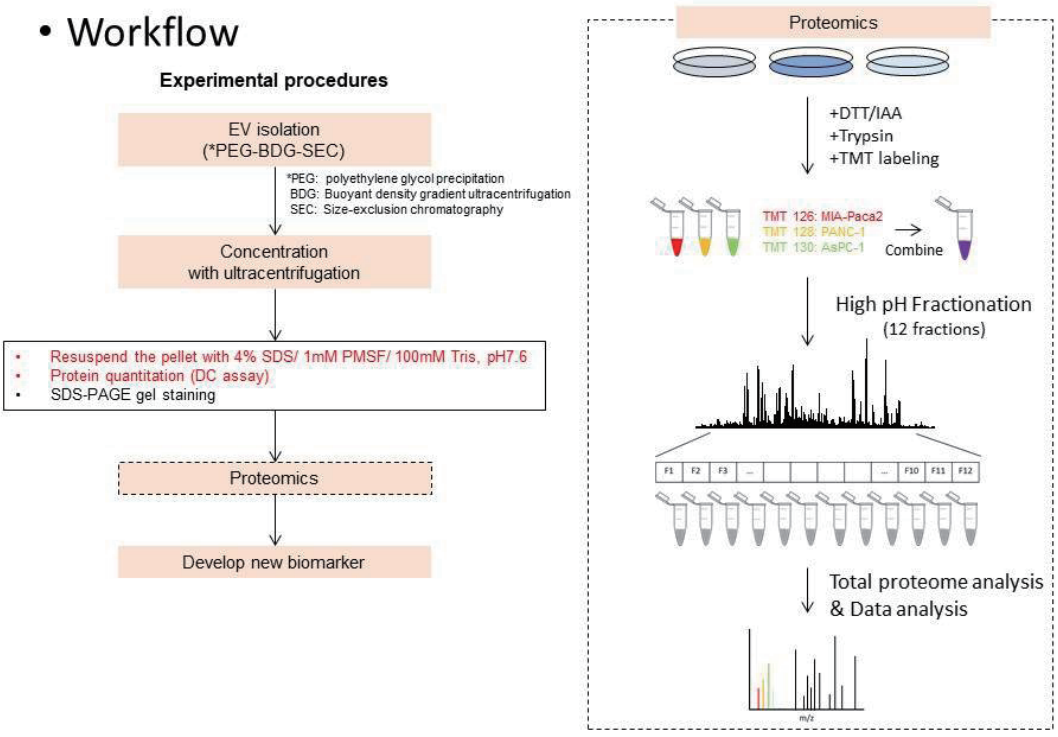

Figure 2. Workflow.

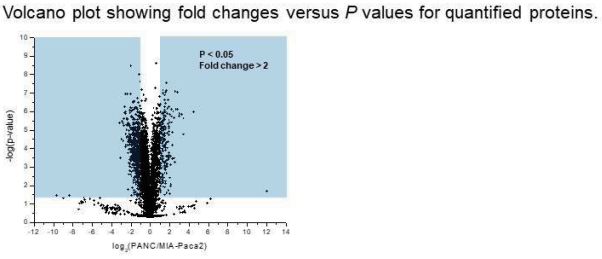

Figure 3. Volcano plot showing fold changes versus P values for quantified proteins.

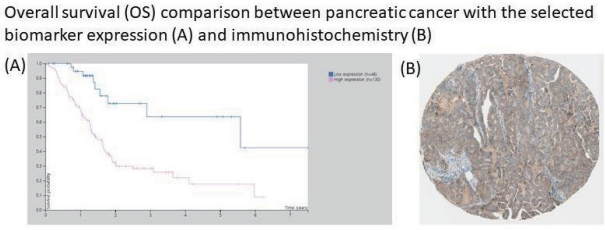

Figure 4. Overall survival (OS) comparison between pancreatic cancer with the selected biomarker expression (A) and immunohistochemistry (B).

Circulating tumor DNA and cells for pancreatic cancer

Dong Uk Kim, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Pusan National University Hospital, Busan, Korea

Pancreatic ductal adenocarcinoma (PDAC) is a 5th leading cause of cancer mortality in Korea and a 4th leading cause in the United States. PDAC showed a dismal prognosis with a 5-year survival rate of below 9% because most patients are detected in the late phase due to its own characteristics such as rapid progression and early metastasis. Therefore, the lack of early detection of PDAC is still challenging. The diagnosis is accepted by getting tissues. However, there is not always possible to get the tissues. Even when the tissues were acquired at initial diagnosis, we could not get the tissue at the time of recurrence or progression of a tumor.

The liquid biopsy is a good alternative method for getting genetic materials that can be used for downstream applications such as whole-exome sequencing. The liquid biopsy is composed of three big components: circulating cell-free tumor DNA (ctDNA), extracellular vesicles, and circulating tumor cells (CTCs).

ctDNA is a major source of tumor-originated DNA in circulation. Theoretically, ctDNA should be detected in circulation if the patients have pancreatic cancer. However, technology is not sensitive to detect ctDNA with low allele frequency (AF). Recently, the digital PCR method was introduced to detect genetic mutation with low AF. The sensitivity and specificity of the new methods are getting higher. Targeted NGS is another accurate method. A high level of ctDNA at baseline is associated with poor prognosis in patients with pancreatic cancer. Furthermore, serial monitoring of ctDNA level is very good parameters for predicting the recurrence after curative surgery or the progression during chemotherapy.

Circulating tumor cells (CTCs) originate from primary and metastatic tumors. The CTCs come into circulation directly or through the epithelial-mesenchymal transition (EMT). In some tumors, there was a close relationship between CTC counts and tumor prognosis. Unfortunately, patients with pancreatic cancer showed no relationship between counts and prognosis because all CTCs maybe not detected in peripheral circulation due to hepatic sequestration. In another aspect, single CTC analysis is promising to prove the tumor heterogeneity and predict the response of treatment.

ctDNA and CTCs are getting close to early diagnosis with technical advancement and accumulation of clinical data in patients with pancreatic cancer. In the future, we may be able to detect pancreatic cancer earlier without getting real tissues.

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Pancreatic cancer specific immunological marker: Paradigm shifting in combating with pancreatic cancer

Dong Ki Lee, M.D., Ph.D.

Department of Internal Medicine, Gangnam Severance Hospital, Seoul, Korea

Aim: Though the general improvement of mean survival rate of other malignancies, to date, the prognosis of pancreatic ductal adenocarcinoma (PDAC) still remains dismal. The immune system plays a key role in both the positive and negative regulation of tumor development and progression, and crosstalk between cancer cells and immune cells has been incorporated into the list of major hallmarks of cancer. However, about PDAC, it is a poorly immunogenic tumor and the exact mechanisms for the immunoresistance has not fully understood. The purposes of this study is to identified PDAC-specific bone marrow derived immune cells (PBMIC) from the patient's blood, determine surface marker analysis, and investigate the functional roles of these cells.

Materials and Methods: The subjects who has diagnosed as PDAC, chronic pancreatitis (CP), bile duct cancer (BDC), lung cancer, and colon cancer were included this prospective case control study. Clinical and image data and peripheral blood were collected from all the subjects. From the whole blood, white blood cells were separated from the plasma and analyzed cell surfaces markers and transcriptomes by flow cytometry (FACS) and single cell RNA-sequencing technique (RNA-Seq). Additionally, with syngeneic and orthotropic xenograft tumor model, the specific functional role of PBMICs and their interactions with PDAC cells were evaluated.

Results: PDAC patients showed higher CD11b+ or CD14+ expressed mononuclear cells compared to naïve or CP or other cancer patients from the blood. From the single cell analysis as well as cell sorting FACS technique, PBMIC were expressed higher levels of type II cytokine receptors, especially IL-22R1 and IL-10R2 ($p<.0001$) compared with naïve, CP, and other cancers. Surprisingly, by combination of both markers, the cancer detection sensitivity and specificity compared with naïve and CP were found as 0.867 and 0.889, respectively. Moreover, as an alarm system for tumor recurrence after complete resection, those markers appeared at least 3 months faster than any other markers including CA19-9. IL-10R2/IL-22R1markers were also found in plasma exosomes as increased mRNA levels (4.8 times higher than naïve control, $p=0.003$ and <00013.9, respectively). Through animal works as well as TCGA data, the higher expressed case of IL-22R1+ and/or IL-10R2+ cases found as poor prognosis and limited survival time.

Conclusions: IL-10R2/IL-22R1 expressed PCMIC were specifically expressed highly PDAC patient, correlated with the mass size, and alarmed the cancer recurrence after surgery. Therefore, these markers may be considered as a novel PDAC markers and can be useful for detection and monitoring of the PDAC.

Exosome in pancreatic cancer surveillance

Takahiro Ochiya, Ph.D.

Department of Molecular and Cellular Medicine, Institute of Medical Science, Tokyo Medical University, Tokyo, Japan

Cancer cells secrete small membranous extracellular vesicles (EVs) into their microenvironment and circulation. Although their potential as cancer biomarkers has been promising, the identification and quantification of EVs in clinical samples remains challenging. Here we describe a sensitive and rapid analytical technique for profiling circulating EVs directly from blood samples of patients with colorectal cancer. EVs are captured by two types of antibodies and are detected by photosensitizer-beads, which enables us to detect cancer-derived EVs without a purification step. We also show that circulating EVs can be used for detection of pancreatic cancer using two types of antigen, which are embedded in cancer-linked EVs. This talk describes a new liquid biopsy technique to sensitively detect pancreatic cancer-specific circulating EVs and provides perspectives in translational medicine from the standpoint of diagnosis and therapy.

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KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

[11:00-12:30, Emerald Hall A]

PG Course 02 (KSGC) Korean

Clinical problems overlooked in patients with GI cancer

Chairs: **Geun Am Song** (Pusan National University Hospital, Korea)

Kwang Ro Joo (Kyung Hee University Hospital at Gangdong, Korea)

Screening and management for high risk patients

Yun Jeong Lim, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Dongguk University Ilsan Hospital, Goyang, Korea

Cancer is a major health problem in Korea, causing one in every three deaths. One of the most important approaches to reducing cancer morbidity and mortality rates is the screening and management of high-risk individuals. Currently, curative treatment for esophageal, stomach, and colon cancer is useful for detecting patients with early-stage, usually asymptomatic, disease. To detect early-stage cancer or its precursor lesions, it is important to identify high-risk patients and consider endoscopic surveillance in these groups. The National Cancer Institute of Korea proposed screening guidelines for gastric and colon cancer. For gastric cancer, endoscopic screening is recommended once every two years for adults ages 40 to 74. Screening endoscopies definitely have been shown to reduce gastric cancer mortality for asymptomatic adults in this age group in Korea. For colon cancer screening, fecal occult blood testing is recommended annually for adult's ages 40 to 80 years. Screening with high-sensitivity stool tests, colonoscopy, and other options is associated with a significant reduction in colorectal cancer incidence and mortality through the detection and removal of adenomatous polyps, as well as the early detection of cancer. Colorectal cancer screening decisions for individuals aged 76 through 85 are based on patient preference, life expectancy, health status, and prior screening history. The options for colorectal cancer screening are annual fecal immunochemical tests; annual high-sensitivity, guaiac-based fecal occult blood tests; multi-targeted stool DNA tests every three years; or a colonoscopy every five years. For persons with a family history of colon cancer, Lynch syndrome, or longstanding ulcerative colitis, a surveillance colonoscopy program is recommended to reduce CRC-associated morbidity and mortality. High-risk groups for esophageal cancer include patients after curative treatment for head and neck cancer, previous endoscopic resection of esophageal cancer, and caustic injury. Mass screening by endoscopy is not cost-effective. For these high-risk people, surveillance chromo-endoscopy using lugol or NBI endoscopy is useful. Careful endoscopic examination for mucosal color change and loss of capillary loops is the most important point for the early detection of superficial esophageal cancer.

Nutitional support guideline

Min Kyu Jung, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Kyungpook National University Hospital, Daegu, Korea

There are many gastrointestinal cancers, which cause the cachexia, in South Korea. Cancer cachexia is a complex syndrome with multifactorial causes, involving tumor- and host-derived signaling factors and alterations in metabolism that ultimately lead to muscle protein degradation. Importantly, the muscle wasting observed in cachectic patients is not reversible with conventional nutritional support. If you ignore it, cachexia is strongly related with the mortality. Although cancer patients often present with combined anorexia and cachexia, the loss of both skeletal muscle and fat, as well as the dysregulation of metabolic markers, separates cachexia from weight loss owing to poor nutritional intake or malabsorption. The combination of cachexia, anorexia, insulin resistance, anemia, and chronic inflammation ultimately lead to a patient that is fatigued, immunosuppressed, unable to tolerate conventional chemotherapy, and at risk for death due to failure of respiratory muscles.

Malnutrition—a condition in which patient caloric intake fails to meet metabolic demands—is common in patients suffering from metastatic gastrointestinal cancer. This may result in a catabolic state due to a combination of inadequate intake of nutrients and a pathologic process of increased nutrient consumption as a result of tumor cytokine release. Many of these patients then experience cachexia, a severe condition involving pathological weight loss due to the wasting of skeletal muscle and adipose tissue. Ultimately, gastrointestinal cancer patients with malnutrition or cachexia experience a lower quality of life, increased morbidity and mortality, longer hospital stays, and a reduced response to treatment.

Weight stabilization in case of metastatic gastrointestinal cancer is thus associated with improved survival and quality of life. Patients maintaining stable weight and body composition have a better prognosis. Various studies have revealed that malnutrition leads to skeletal muscle wasting and fat degradation, longer hospital stay, increased risk of complications as well as reduced response to treatment, shorter survival time, reduced quality of life and increased morbidity and mortality. If oral nutritional intake is not sufficient, additional nutritional therapy is absolutely essential for cancer patients to stabilize body weight and composition.

Proinflammatory cytokines are drivers of cancer-induced cachexia. Proinflammatory cytokines IL-6 and TNF-α activate downstream signaling of NF-kB resulting in overstimulation of NF-kB and degradation of muscle proteins through the production of catabolic cytokines. Cytokines can also activate Jak2/STAT3 signaling pathways that can lead to skeletal muscle protein degradation (Figure 1).

Advances in the understanding of cancer cachexia have identified prognostic and mechanistic information important in identifying potential therapeutic targets; however, current pharmacologic options for cachexia are limited. We are going to discuss about the different nutritional therapies, such as enteral nutrition, parenteral nutrition and special nutritional supplements, on nutritional status, quality of life and survival.

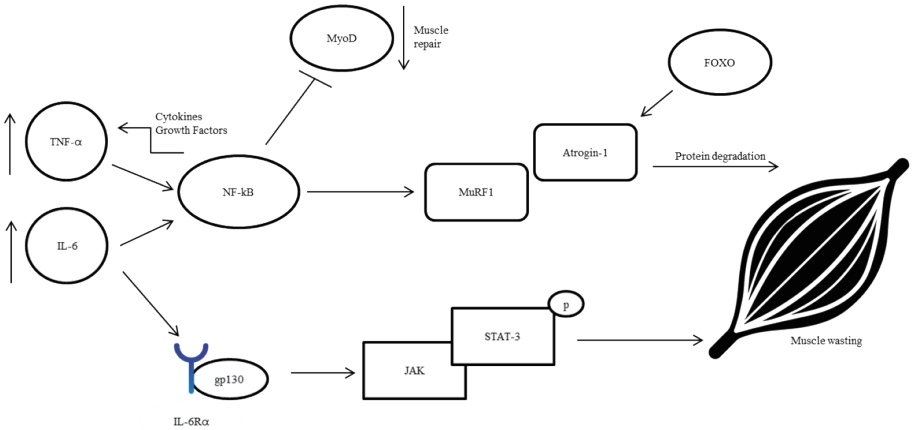

Figure 1. Proinflammatory cytokines and cancer-induced cachexia.

Cancer survivorship supporting program

Ji Soo Park, M.D., Ph.D.

Department of Cancer Prevention Center, Yonsei Cancer Center, Seoul, Korea

Recent cancer statistics presented that the overall cumulative risk of developing cancer from birth to life expectancy was 36.2% in Korea. With the advances in screening and treatment of cancer, the survival outcome improved over the several decades. As a result, among 1,739,951 Korean cancer patients, 916,880 (52.7%) patients lived longer than 5 years since they were diagnosed with cancer. Although a cancer survivor is a person with cancer who is still living, we generally refer to these long-term patients (especially, who are currently cancer-free) as 'cancer survivors'.

For the increasing cancer survivors, survivorship programs were developed and improved to include surveillance, screening, monitoring and management of long-term complication and late effects. Many long-term complications or late effects diminish the quality of life. However, it is hard to recover them completely to the condition before diagnosis and/or treatment of cancer. How can we manage the cancer survivors' problems?

Several clinical guidelines established possible management options for supporting cancer survivors. For general cancer survivors, anxiety, fatigue, cognitive dysfunction, pain, sleep disorder, chemotherapy-induced peripheral neuropathy and sexual dysfunction are frequently reported problems by the patients. For gastrointestinal cancer survivors, there are cancer-specific complications including indigestion, anemia, Vitamin B12 deficiency, and dumping syndrome for gastric cancer survivors and constipation, diarrhea, low anterior resection syndrome for colorectal cancer survivors.

In this presentation, we will review frequently reported cancer survivors' problems, clinical guidelines, and applicable supporting programs in clinical practice. To overcome the socioeconomic burden in labor shortage and rising healthcare cost, public welfare and medical specialists are required to make a collaborative effort in every part of the survivorship care.

Now and future direction of hospice and palliative care

Chung-Woo Lee, M.D

Department of Family Medicine, Korea University Guro Hospital, Seoul, Korea

To understand the prospects of palliative care, we need to know the definitions of terms related to palliative care. According to World Health Organization (WHO) defined palliative care as "an approach that improves the quality of life of patients (adults and children) and their families who are facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and correct assessment and treatment of pain, and other problems, whether physical, psychosocial or spiritual."1 In short, palliative care is a broad term containing all holistic care for all patients with life-threatening illness and their families. Palliative care is divided into specialist palliative care and general palliative care, depending on the provider. Specialist palliative care is a palliative care service provided by a multidisciplinary team of physicians, nurses and social workers to patients and families with complex problems. General palliative care is a medical service provided by all practitioners to relieve suffering in concordance with the daily care of the patient. In Korea, specialist palliative care corresponds to the palliative care by the hospice & palliative care multidisciplinary team, which is usually carried out in hospice medical institutions. On the other hand, the concept of general palliative care may be largely unfamiliar to the public. This presentation mainly deals with the concept, necessity and future direction of general palliative care.

The 2014 World Health Assembly declared that palliative care should be included in the continuum of care for people with chronic, life-threatening conditions.1 In other words, palliative care services should begin at the time the disease is diagnosed and be provided with curative treatment at the same time. In particular, cancer patients have needs for palliative care services once the diagnosis is made by health professionals.2-4 Advanced cancer patients have holistic needs, ranging from physical care, including the control of physical symptoms that can be experienced early the time of diagnosis, to holistic care and the development of care plans. Providing palliative care can help patients throughout this process. In addition to specialist palliative care, general palliative care by all practitioners can also play an important role. The importance of general palliative care by generalists or primary care physicians is well known. At the same time, however, the importance of general palliative care by treating specialists, is likely to be of greater importance.5 Treating specialists refer to the clinicians who have been qualified to treat specific areas of diseases, such as oncologists, gastroenterologists, hepatologists, surgeons etc. First of all, as noted above, the need for palliative care continues to grow which exists from the beginning of life-threatening illnesses such as cancer. Therefore, it is not possible to meet all of these patients needs with the specialist palliative care team, and so it is necessary to simultaneously provide palliative care by the clinicians who have been treating the patient. Secondly, in many developed countries, including Korea, the deaths in medical institutions, especially acute hospitals, continue to grow.6, 7 Under these circumstances, the needs for providing quality care with dying patients by medical staff at hospitals that provide acute medical treatments are also increasing. In this sense, treating specialists also need to be competent for general palliative care.

Competence for general palliative care consists of 1) basic management of pain and symptoms, 2) basic management of depression and anxiety, and 3) basic discussion about prognosis, goals of treatment, suffering, and code status.5 Experts in medical specialties such as oncology, gastroenterology, hepatology, and surgery also need to be aware of the needs for primary palliative care skills. There is also a need for education and training to develop general palliative care skills for treating specialists.

On June 24th, 2019 the Ministry of Health and Welfare announced the first Comprehensive Plan for Hospice and Life-sustaining Treatment. The plan, with the vision of "guaranteeing the dignity and comfort of the end of life," aims to 1) increase access to hospice and palliative care services, 2) ensure the people's self-determination of life-sustaining treatment, and 3) improve the quality of life for end-of-life patients and their families. The expected changes to enhance access to hospice palliative care services include: 1) strengthening access to hospice services through expansion of palliative home care and palliative hospital support, and 2) expanding diseases targeted for palliative care.8 In the midst of these changes, the provision of general palliative care by treating specialists is also expected to take an important role. Therefore, capacity of general palliative care for treating specialists is required.

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KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

[11:00-12:30, Emerald Hall B]

Symposium 02 (KSNM1) English

Updates in GERD

Chairs: **Sung Pyo Hong** (Bundang CHA, Korea)

Suck Chei Choi (Wonkwang University School of Medicine & Hospital, Korea)

Novel new options in the medical management of GERD

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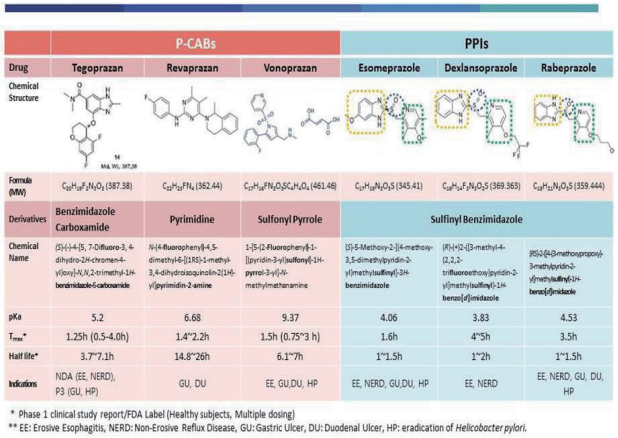
Gastroesophageal reflux disease (GERD) is a prevalent digestive disease that results from reflux of gastric contents into the esophagus. The prevalence of GERD in East Asian countries is increasing, and is reported to be 4.5%-15.7%.[1] The spectrum of GERD includes erosive oesophagitis (EE) and nonerosive reflux disease (NERD). Currently, proton pump inhibitors (PPIs) are the first-line drug for treating EE and controlling symptoms, which have shown high healing rates (88%-96%) in EE after 8-week treatment with a PPI once daily. However, the PPI response rates at 8 weeks were different between EE and NERD (P = 0.02); refractory rates were higher in the NERD group (16.7%) compared with the EE (6.0%)[2] suggesting of unmet demand of PPI. Recently potassium-competitive acid blockers (P-CABs) have been developed (Table).[3] It is a novel, potent, and highly selective P-CAB with a mechanism of action distinct from that of the PPIs.[3,4] Unlike PPIs, that require a chemical transformation into their active form and bind covalently to the gastric H+/K+-ATPase,[5] P-CAB inhibits H+/K+-ATPase in a reversible and K+-competitive manner without a need for any conversion. It is an acid-resistant weak base which can remain in highly acidic canaliculi of gastric parietal cells. Nonclinical studies have shown that this compound suppresses gastric acid secretion faster and more potently than esomeprazole treated group.[1] Therapeutic potential of vonoprazan[4] and tegoprazan[1], the most studied P-CAB is may be derived from its ability to accumulate at high concentrations in the canaliculi of gastric parietal cells. Consequently, it is slowly cleared from the gastric glands and exerts its effects independent of acid levels; leading to a strong and sustained effect.[1] Another strong point of P-CAB is that the efficacy of P-CAB is independent of food intake by pharmacodynamics and pharmacokinetics studies. Many clinical trial data have consistently demonstrated superiority of vonoprazan over conventional PPIs in terms of achieving healing of mucosal breaks and maintaining the healing[4] and non-inferior efficacy of tegoprazan in healing EE and tolerability to that of esomeprazole 40 mg[1] P-CAB may provide an excellent, if not complete, option for fulfilling some of the unmet needs for current GERD therapy.

Table. Drugs in the markets and the trials of potassium-competitive acid blockers[2]

Drug	Phase
Revaprazan (YH1885)	Market (2007 South Korea, India)
Vonoprazan (TAK-438)	Market (2015 Japan)
	Phase III (Asia)
	Phase IIb (EU)
Tegoprazan (RQ-4)	Phase III (South Korea)
	Phase I (Japan)
YH4808	Phase II (South Korea)
DWP14012	Phase II (South Korea)
KFP-H008	Preclinical (China)



* Phase 1 clinical study report/FDA Label (Healthy subjects, Multiple dosing)
** EE: Erosive Esophagitis, NERD: Non-Erosive Reflux Disease, GU: Gastric Ulcer, DU: Duodenal Ulcer, HP: eradication of *Helicobacter pylori*.

Figure. Backbone structure of potassium competitive acid blocker (P-CAB) and proton pump inhibitor (PPI).

Key words: Gastroesophageal reflux disease, proton-pump inhibitor, potassium-competitive acid blocker, H+/K+-ATPase

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Usefulness of esophageal impedance measurement in diagnosis of GERD

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After meals or during PPI treatment, most reflux episodes are weakly acidic or non acidic and these episodes can provoke typical or atypical reflux symptoms. Esophageal impedance monitoring allows detection of reflux events regardless of the pH. This technique also allows distinction of reflux composition (air, liquid or mixed), proximal extent, and clearance times. Impedance-pH monitoring offers the additional possibility of detecting patients with a positive association between symptoms and weakly acidic and/or gas reflux. Furthermore, impedance-pH monitoring is much more sensitive than pHmetry in detecting rumination and belching disorders. Impedance-pH tracings should be analysed in a quantitative fashion, similar to pH-metry, by searching for increased numbers of reflux episodes (acid and non-acid), prolonged acid or volume exposures, or increased numbers of proximal reflux events. In addition to quantitative measurement of esophageal acid or non-acid exposure, pH and impedance monitoring allow measurement of association between reported symptoms and acid or non-acid reflux events. Symptom index (SI) and symptom association probability (SAP) are the two most common indices utilized. Other impedance parameters (apart from number of reflux episodes or volume exposure) such as gas movement, impedance baseline and the post-reflux swallow-induced peristaltic wave (PSPW) are recently proposed to increase the yield of diagnosis of reflux disease. Impedance allows a precise tracking of intra-esophageal air movement and distinction between typical gastric belching from "supragastric belching". Analysis of impedance pH monitoring tracings allows measurements of baseline impedance (stable impedance values in the absence of swallow, belching or reflux induced impedance changes). Impedance baseline values correlate well with esophageal mucosal integrity status. Low baseline impedance is observed in erosive esophagitis, Barrett's esophagus, eosinophilic esophagitis and in case of bolus stasis secondary to severe esophageal motility disorders. Impedance changes can also be used as a measure of peristalsis-associated esophageal clearance. Gastro-esophageal reflux is followed by reflex swallow-induced or secondary peristalsis. The clearance effect of such peristaltic activity can be measured as changes in impedance after reflux. The post-reflux swallow-induced peristaltic wave (PSPW) index has been designed to assess the clearance abilities in patients with different GERD phenotypes. Similarly to impedance baseline, the PSPW index is low in patients with GERD and NERD but normal in patients with Functional Heartburn.

The Lyon Consensus; how is it differ from previous ones?

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Gastroesophageal reflux disease (GERD) is a complex disease with a heterogeneous symptom profile (I,e, ranging from typical manifestation including heartburn and/or regurgitation to atypical manifestations, including chest-pain, dysphagia, cough, asthma, hoarseness, sleep disturbances, etc.) and a multifaceted pathogenic basis that defies a simple diagnostic algorithm or categorical classification. Clinical history, questionnaire data and response to antisecretory therapy such as proton pump inhibitors (PPIs) are insufficient to make a conclusive diagnosis of GERD in isolation, but are of value in determining need for further investigation. In particular, PPIs showed adequate sensitivity (about 70%) but low specificity (about 50%) when compared with more objective testings like endoscopy or pH-metry. Thus, the use of PPI trail cannot be considered an accurate method to define GERD. In this context, the Lyon Consensus defined parameters on endoscopy and esophageal testing that conclusively establish the presence of GERD and characteristics that rule out GERD. Conclusive evidence for reflux on endoscopy include high grade erosive esophagitis (Los Angeles grades C and D), long-segment Barrett's mucosa (intestinal metaplasia with an extension of more than 3 cm) or peptic strictures on endoscopy or distal oesophageal acid exposure time (AET) >6% on ambulatory pH or pH-impedance monitoring. A normal endoscopy does not exclude GERD, but provides supportive evidence refuting GERD in conjunction with distal AET <4% and <40 reflux episodes on pH-impedance monitoring off proton pump inhibitors. Reflux-symptom association as assessed by symptom index or symptom association analysis on ambulatory reflux monitoring provides supportive evidence for reflux triggered symptoms, and may predict a better treatment outcome when present. When endoscopy and pH or pH-impedance monitoring are inconclusive, adjunctive evidence from biopsy findings (histopathology scores for microscopic esophagitis, presence of dilated intercellular spaces or basal cell hyperplasia), motor evaluation at high-resolution manometry (hypotensive lower esophageal sphincter, hiatus hernia and esophageal body hypomotility on high-resolution manometry) and novel impedance metrics such as nocturnal baseline impedance and post-reflux swallow-induced peristaltic wave index can add confidence for a GERD diagnosis; however, diagnosis cannot be based on these findings alone. An assessment of anatomy, motor function, reflux burden and symptomatic phenotype will therefore help direct management. While acknowledging the limitations of currently available esophageal testing in GERD, the Lyon Consensus proposes this model as a guide to direct management. Future GERD management strategies should focus on defining individual patient phenotypes based on the level of refluxate exposure, mechanism of reflux, efficacy of clearance, underlying anatomy of the esophagogastric junction and psychometrics defining symptomatic presentations. As the GERD diagnostic paradigm evolves, using diagnostic testing to define a precision approach tailored to the individual patient becomes possible. The goals of evaluation should therefore transition towards defining GERD phenotypes to facilitate tailored treatment.

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Current status of endoscopic management in GERD

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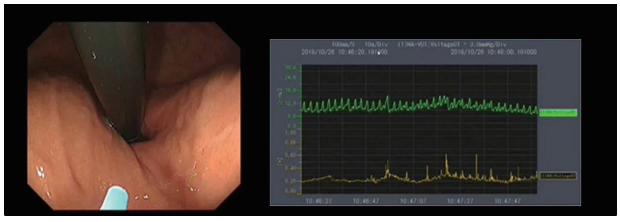
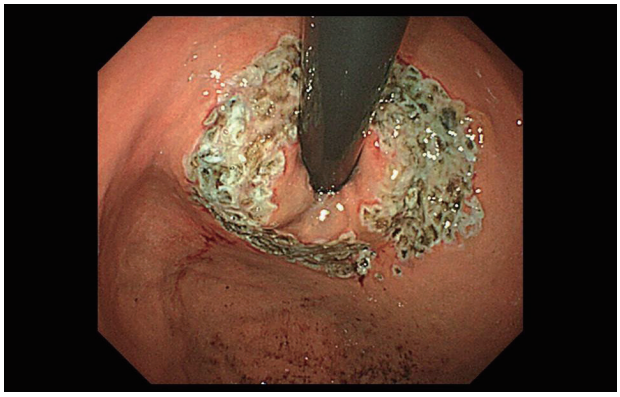
Gastroesophageal reflux disease (GERD) is a common disorder with an increasing prevalence. Apart from symptoms and endoscopic findings, 24-hour pH-monitoring is being utilized as the gold standard for the diagnosis of GERD. However, 24-hour pH monitoring is time consuming and may cause nasal discomfort during the examination. We have developed a novel endoscopic diagnostic tool, the endoscopic pressure study integrated system (EPSIS), which allows the monitoring of intragastric pressure (IGP)1. Using a dedicated pressure measuring device and a through-the-scope catheter, maximum IGP and IGP waveform pattern (uphill/flat) were recorded and the performance of EPSIS for the diagnosis of GERD was evaluated. Based on our findings, a waveform pattern of IGPand a maximum IGP could distinguish GERD and NERDfrom disorders with similar symptoms withfair-good accuracy. A multivariate model showed that a diagnosticmodel comprising EPSIS, age, and the presence ofesophagitis could further aid GERD diagnosis at the time of initial endoscopy. EPSIS can be a reliable adjunct to routine gastroscopy for GERD diagnosis, and helpfulfor the stratification and management of patients with refluxdisorders.

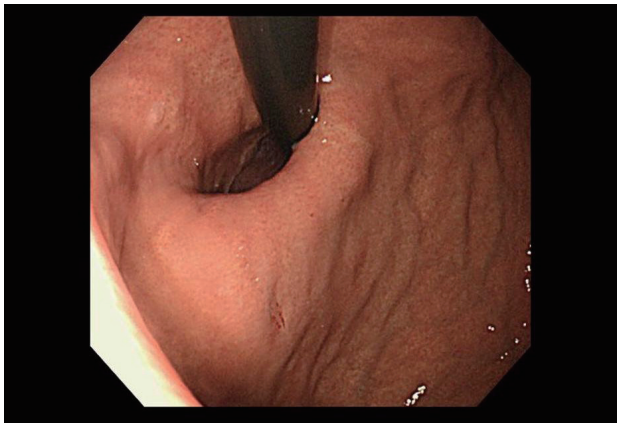
As for GERD treatment, proton pump inhibitors (PPIs) are effective in achieving symptom control and preventing complications, however, the incidence of PPI-refractory GERD has been increasing. While laparoscopic anti-reflux surgery (LARS) remains the gold standard for PPI-refractory GERD, less invasive anti-reflux interventions are highly anticipated. In 2014, we reported the first case series of anti-reflux mucosectomy (ARMS) as an endoscopic anti-reflux procedure2. By causing scarring of the artificial ulcer created by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) at the gastric cardia, it allows tightening of the cardiac opening.



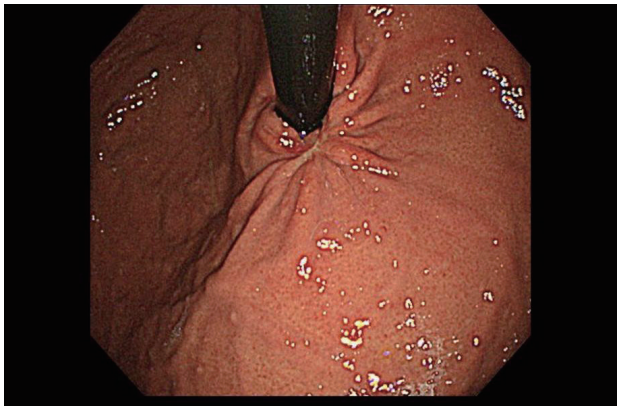
EPSIS



ARMA



Pre-ARMA



2 months post-ARMA

Furthermore, we developed a modified minimally invasive treatment, anti-reflux mucosal ablation (ARMA), similar to ARMS but scarring is formed by ablation. In both methods, median GERD-HRQL (Health Related Quality of Life Questionnaire) score and median Frequency Scale for the Symptoms of GERD (FSSG) assessment significantly improved, and acid exposure time and DeMeester composite score on 24-pH monitoring decreased3. These procedures do not require specific expensive devices and do not leave any artificial material *in situ*.In our experience, a new endoscopic treatment for PPI-refractory GERD, ARMS and ARMA, are simple, safe, and improve GERD-related symptoms and objective acid reflux parameters.

Recently, endoscopic management of GERD in terms of diagnosis and treatment has advanced significantly. EPSIS can be used for diagnostic purposes inGERD, either as a single test or as part of a composite model adjunct to routine EGD useful for patientstratification and management. ARMS and ARMA are promising endoscopic anti-reflux procedures that have potential of becoming the standard treatment for PPI-refractory GERD.

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KDDW 2019 Korea Digestive Disease Week

DAY 1
November 28 (Thursday)

[11:00-12:30, Diamond Hall]

Multidisciplinary Session 01 (KCHUGR) Korean

Understanding of eosinophilic esophagitis

Chairs: **Soo-Heon Park** (Youido St. Mary's Hospital, Korea)
Jung Mogg Kim (Hanyang University College of Medicine, Korea)

Eosinophils in gastrointestinal tract

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Eosinophils are terminally differentiated pro-inflammatory leukocytes involved in the pathogenesis of allergic disorders and implicated in the protection against helminth infections. Effector functions of eosinophils have been attributed to their capacity to release cationic proteins packaged within cytoplasmic granules by degranulation. However, eosinophils are now being recognized for multifunctional leukocytes based on their ability of releasing a number of immune mediators and broad range of tissue distribution. Although eosinophils are recognized as circulating cells, composing 1-5% of peripheral blood leukocytes, they are primarily resident in the lamina propria of the gastrointestinal (GI) tract, where they compose a substantial fraction of the cellular population. A standard protocol for the isolation of murine eosinophils from the intestinal lamina propria using eosinophil-specific surface markers was established, and the development of eosinophil-deficient mouse strains has expanded the understanding of the role of intestinal eosinophils. Eosinophils in the GI tract express higher levels of myeloid marker CD11b, CD22, and signal regulatory protein α than blood eosinophils, and these molecules prevent overactivation of intestinal eosinophils under homeostatic conditions. The GI tract, exposed to potentially harmful commensals and pathogens, protects itself via production of IgA, the most abundant antibody isotype in the human body for neutralization of microbes in a noninflammatory manner. Eosinophils support mucosal production of IgA and maintain intestinal mucus secretion and microbial composition. Whole-genome RNA sequencing of the small intestinal tract of eosinophil-deficient mice further suggested potential role of GI eosinophils for the regulation of a series of physiologic responses including innate immunity, regulation of lipid metabolism and axon development. Taken together, these findings provide a foundation for future studies uncovering the function role of eosinophils in the GI tract.

Pathophysiology of food allergy and eosinophilic esophagitis

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With increasing prevalence, food allergy has been an important health issue in the world. Food allergy is a reproducible immune-mediated reaction to a given food. It is classified by the underlying immune responses: IgE-mediated, non-IgE-mediated, or a mixture of both.

IgE-mediated food allergy represented by urticaria, angioedema, rhinitis, bronchospasm, diarrhea, and anaphylaxis, occurs when food allergen-specific IgE antibodies are developed after an initial exposure to an allergen. Antigen-presenting cells present processed food proteins to T helper cells. Activated Th2 cells subsequently release pro-inflammatory cytokines including IL-5, IL-13, and IL-14). This results in the activation of B cells to produce specific IgE against the specific food allergen. A second exposure to the same allergens leads to IgE binding and activation of basophils, mast cells as well as eosinophils, which release histamine and other inflammatory mediators to cause allergic symptoms.

Food protein-induced enterocolitis syndrome (FPIES), food protein-induced proctocolitis (FPIP), and food protein-induced enteropathy are classified as non-IgE-mediated food allergy. The pathogenesis of non-IgE-mediated food allergy is hypothesized as a T cell-mediated, particularly Th2 process. Peripheral blood mononuclear cells in the patients with non-IgE-mediated food allergy are stimulated by food allergens and show an increased Th2 cytokine profile, such as IL-3, 5, and 13, to recruit eosinophils in the gastrointestinal tract.

Eosinophilic esophagitis (EoE) is a chronic Th2 type inflammatory disease limited to the esophagus and belongs to a mixed IgE- and non-IgE-mediated food allergy. EoE is an antigen-driven Th2 disease as shown that the removal and rechallenge of foods induce EoE resolution and relapse. Complex interactions between innate and adaptive immune cells are involved in the pathogenesis. Both genetic risk variants (TSLP, filaggrin, and clapain14) and early-life environmental risk (dysbiosis associated with cesarean birth, antibiotics, and formula feeding) are important for the development of EoE A positive family history and the association with SNPs in filaggrin, TSLP, and calpain-14 genes in EoE suggest that genetic factors are strongly engaged in the pathogenesis. Esophageal epithelial barrier function is disrupted in EoE allowing allergen crossing of the epithelial barrier. Epithelial cells release cytokines, such as TSLP, IL-25, IL-33 and eotaxin, and thereby recruit and activate antigen presenting cells and other immune cells. In particular TSLP promote dendritic cell differentiation into a Th2-promoting phenotype. The vicious cycle is expanded by differentiation of T helper cells into Th2 cells and the release of further cytokines (IL-4, IL-5, IL-9, and IL-13) amplifying the inflammatory response. Chronic perpetuating Th2 inflammation with increasing TGF-beta causes epithelial and subepithelial remodeling, with loss of barrier function, fibrosis, angiogenesis, and smooth muscle hypertrophy. These molecular events cause complications of esophageal rigidity and dysmotility, with clinical symptoms of vomiting, dysphagia, food impactions, and strictures.

In conclusion, unlike IgE-mediated, immediate and short-lived reactions in classical food allergy, EoE should be considered as a complex disease with a disordered interplay between the epithelial barrier, innate and adaptive immune responses together with the composition of the microbiota.

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Updated diagnostic guideline and pharmacologic treatment

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Eosinophilic esophagitis (EoE) is a chronic, allergen-driven, immune-mediated disease of the esophagus. In 1993, the first article to describe the syndrome that is now recognized as eosinophilic esophagitis (EoE) was published. The incidence of EoE has been increasing. The second leading cause of chronic esophagitis after gastroesophageal reflux disease (GERD). By 2018, a response to PPIs excluded a diagnosis of EoE. However, patients with PPI-responsive esophageal eosinophilia (PPI-REE) had virtually every feature of EoE, the only difference being that, by definition, they responded to a PPI. In 2018, the AGREE (A Working Group on PPI-REE) Conference published consensus guidelines that removed PPIs as a diagnostic test for EoE, and instead considered PPIs a treatment for EoE. The conference also concluded PPI-REE is essentially indistinguishable from EoE.

EMERGING VISUAL DIAGNOSTIC TOOLS

Transnasal endoscopy (TNE) is a recent diagnostic tool that may become widely adapted by clinicians given its safety, cost effectiveness, feasibility, and high patient preference. TNE is performed in an unsedated patient, even though pediatric patients. And, Endoscopic functional lumen imaging probe (FLIP) is a novel and widely accepted endoscopic method to assess esophageal caliber and distensibility in EoE patients. FLIP uses high-resolution impedance planimetry during volumecontrolled distention to determine variations in luminal pressure and geometry in a cross-sectional area of the esophagus along an axial plane. FLIP studies in EoE patients have demonstrated reduced esophageal distensibility, which is associated with increased food impactions and the need for esophageal dilation.

EMERGING NON-INVASIVE DIAGNOSTIC TOOLS

Cytosponge, a string-tethered spherical mesh sponge that is compressed in a dissolvable gelatin capsule, is swallowed by an unsedated patient and retrieved by withdrawing the string through the mouth. The cytosponge is safe, well-tolerated, and the esophageal tissue specimen obtained by this method appears adequate for histopathologic analysis. The sensitivity and specificity of the cytosponge to assess EoE histologic activity are 75% and 86%, respectively. Similarly, the esophageal string test captures adherent luminal secretions containing eosinophil-derived proteins that reflect mucosal inflammation in EoE. Other approaches similar to the cytosponge and esophageal string test methods, such as endoscopic esophageal brushings and blind esophageal brushings via a nasogastric tube, have been recently proposed. Extending the analysis of esophageal brushings to include esophageal levels of eosinophil-derived neurotoxin (EDN), which is highly expressed in the EoE esophagus, appears to improve EoE detection and disease monitoring. Further investigation, optimization, and validation of these emerging non-invasive diagnostic tools in larger patient cohort remain to be established.

Measurement of electrical impedance at the esophageal mucosal surface is another emerging modality to assess disease activity in EoE. The mucosal impedance probe detects changes in the electrical impedance, thought to be related to a defect in the esophageal barrier function. Real-time mucosal impedance measurements correlate inversely with esophageal eosinophil counts and spongiosis severity in EoE, allowing the ability to quickly determine and monitor EoE disease activity.

TREATMENT OF EOE

There are currently no drugs approved by the Food and Drug Administration (FDA) for the treatment of EoE. The current EoE management includes chronic corticosteroid treatment, proton-pump inhibitors (PPI), dietary antigen restriction, and repeated endoscopic diagnostic and therapeutic evaluations. The fluticasone administered as an aerosolized and swallowed formulation and oral viscous preparations of budesonide are the two most frequently used topical corticosteroids for EoE. Recently, there are two randomized, double-blind, clinical trial about the topical steroid treatments on EoE patients. One is the clinical trials directly comparing the oral viscous budesonide (OVB) or fluticasone MDI in USA. The initial treatment of EoE with either OVB or fluticasone MDI produced a significant decrease in esophageal eosinophil counts and improved dysphagia and endoscopic features. However, OVB was not superior to MDI, so either is an acceptable treatment for EoE. The other is that budesonide oral tablets were significantly more effective than placebo in inducing clinical and histologic remission in Europe.

Elemental diet remains the most effective strategy; however, therapy compliance is a significant challenge. More recently, esophageal prick test (EPT) with food antigens was proposed a potential novel safe and feasible method to guide elimination diets. A novel step-up food elimination strategy was recently proposed. In a multicenter prospective clinical trial, a 2-4-6 step-up elimination diet strategy in EoE patients achieved clinicohistologic response and identified food triggers of EoE early, and thus avoided unnecessary dietary restriction Several biologic agents are being investigated for the management of EoE. An anti-IL-13 monoclonal antibody, RPC4046, however, reduced esophageal eosinophilia, but also improved endoscopic features and dysphagia in EoE patients, particularly in steroid-refractory EoE patients. The dupilumab, a monoclonal antibody that targets the α -chain of interleukin (IL)-13 and IL-4 receptor have emerged to suggest that in adult EoE patients, controlling esophageal inflammation may decrease the need for subsequent esophageal dilation

CONCLUSIONS

Recent advances in EoE are improving our diagnostic and therapeutic approaches. EoE's chronic nature, close follow-up with assessment of disease activity should be strived. In addition, optimal doses for the maintenance phase have still to be defined and dose-finding trials are definitely needed.

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Eosinophilic esophagitis in pediatrics and dietary treatment

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BACKGROUND

Eosinophilic esophagitis (EoE) is clinicopathologic disorder characterized by the marked invasion of the esophagus of eosinophils through allergic immune reaction.[1] Gastroesophageal reflux disease (GERD) and EoE are the most important causes of chronic esophageal inflammation in children. Esophageal eosinophilia is shown on both diseases but Basically, EoE has the characteristics such as showing the refractoriness on proton pump inhibitor (PPI) though there are some responders called as proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) group and the recovery of symptoms and histology on restriction of specific diets.[2,3] Many studies have been made since it was first mentioned as a new area of disease in the early 1990s.[1,4,5] In pediatric case, Kelly et al[6] first reported in 1995. They observed that 10 pediatric patients have refractory GERD with esophageal eosinophilia show symptomatic and histologic improvement through exclusion diets with amino-acid formula. After that, when the specific food protein such as milk, soy, wheat, and peanut were open challenged reflux symptom was recreated. This study has become a fundamental study that is thought to be caused by the immune reaction that EOE can be induced by certain food antigens. The increasing trend of incidence and prevalence on EoE has been reported in worldwide.[7-9] However, there have been questions on whether the true increase of new EoE cases or the increase of developing diagnostic endoscopy and awareness on disease. The answer is both, that is to say, the increase of new cases diagnosed and of number of esophageal biopsies can be causes the increase of incidence and prevalence on EoE.[9] The incidence rate of EoE has been rapidly increasing regardless of research methods such as prospective, population based studies, and using institutional electronic medical records and databases.[4,9] The overall current incidence and prevalence of EoE has ranges from 0.7/100,000 to 10.7/100,000 and 10/100,000 to 57/100,000 respectively.[9] Studies in US pediatric populations had also shown that incidence and prevalence increase with years (Fig. 1).[8,10] It has been reported that the prevalence and incidence of Caucasians is higher than Asian and Hispanics.[11-13] However, it has not reported yet that the study on difference in pediatric EoE patients. The Further study for pediatric EoE would be needed. EoE may develop at any age but the majority of cases are lower than 50 years old and the peak age of prevalence is 35-45 age range.[4,14] Also, there is discrepancy of prevalence on gender in all ages, that is to say males is higher prevalence than female in children and adults.[4,8,14]

The natural history of EoE is that if EoE is not treated, persistent symptoms and inflammation are going then lead to esophageal fibrosis and stricture as esophageal remodeling.[4,7] The duration of untreated is the major risk factor of esophageal stricture and remodeling.[4] A retrospective study on long term prognosis in pediatric patients with EoE showed dysphagia rates was 49% and food impaction rates was 40% after mean 15 years follow-up.[15]

CLINICAL SYMPTOMS

Clinical manifestations of EoE vary by patient's age and the ability of elucidating symptoms.[4,16] Symptoms are vaguer in younger children than in teenagers and adults.[17] This is the reason that it is difficult to diagnosis EoE in younger children. In younger children shows nonspecific gastrointestinal symptoms such as feeding difficulties, gaging, and feeding refusal.[2,16] Especially, the most common symptom in younger children under the age of 5 years is reflux symptom and the rarest symptoms is food impaction.[17] On the other hand, teenagers present with dysphagia and impaction of solid foods (Table 1).

THE ASSOCIATION WITH ALLERGIC DISEASES.

EoE has the similarities with other allergic diseases because EoE is triggered by food allergens and environmental allergens.[18] Basically,

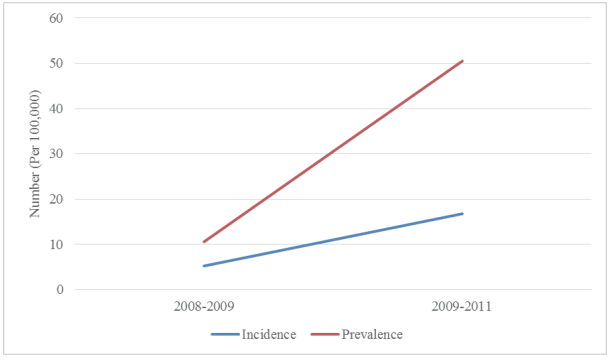

Figure 1. The tendency of incidence and prevalence in USA pediatric EoE patients (references[8,10]).

this like immune reaction of allergens is mediated by Th2-lymphocytes and then these cells produce cytokines such as IL-4 and IL-3.[18] In active EoE, epithelial barrier dysfunction of esophagus is observed through a down-regulation of expression adhesion protein desmoglein-1 like atopic dermatitis.[18]

Most EoE patients have concomitant atopic disorders like asthma, eczema, allergic rhinitis, and food allergies.[4] These prevalence rates of atopic disorders in EoE patients are three times higher than in general population.[18] It was reported through systematic review and meta-analysis that allergic rhinitis was the most common concomitant atopic disorder in overall EoE patients.[19] Vernon et al said that the presence of asthma history in 52% of children with EoE was the only difference regarding 24% of adults.[20] There was no difference rate between adults and children EoE patients on history of atopic dermatitis, allergic rhinitis, food allergy and family history of atopy.[20] Hill et al, evaluated on the prevalence of EoE in pediatric patients with IgE-mediated food allergy through electrical medical record (EMR) cohort of one children's hospital.[21] In this study, they reported that 68% patients of EoE had IgE-mediated food allergy and the prevalence of EoE in patients with IgE-mediated was approximately 1 in 20.[21] Among food allergens, milk, egg, and selfish were associated with a risk factor of a diagnosis of EoE and as the number of food allergies increased, the risk of EoE increased.[21] EoE is also driven by aeroallergens.[18] Mishra et al described the development of esophageal eosinophilia in mice was exposed by fungus.[18] They explained a mechanism that aeroallergen sensitization started at first via intranasal exposure and then aeroallergen delivered to the esophagus leads to EoE.[18] This like claim was supported by studies with increasing the diagnosis of EoE in pollen seasons or.[18] However, EoE could develop with non-IgE mediated reactions, as IgE-depleted mice showed esophageal eosinophilia and food impactions.[18] This point could be said that it was difficult to find out the causes of EoE developed and aggravated.

Table 1. Clinical manifestations of EoE in younger children and teenagers

Younger children	Teenagers
Reflux like symptoms	Dysphagia
Vomiting	Solid food impaction
Nausea	Chest pain
Regurgitation	Retrosternal pain
Chocking	Vomiting
Food refusal	Regurgitation
Failure to thrive	
Dysphagia	

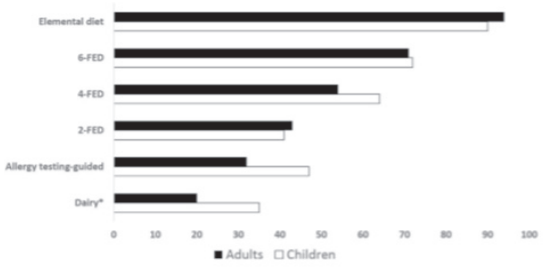

Figure. 2 Histologic remission rates between age group with different modalities of dietary therapy (ref.[22]).

DIETARY TREATMENT

The dietary treatment is the only treatment of targeting the primary cause of the disease.[22] The first try of dietary treatment in pediatric EoE patients was at 1995. This study showed complete recovery of esophageal eosinophilia with an amino acid-based formula for at least 6 weeks.[6] Since then, numerous trials have been accomplished. Dietary treatment options are consisted with the 3 primary options, which are elemental diet, an empiric elimination diet, and a food allergy testing-guided elimination diet. Histologic remission rates broken down by age group shown different modalities of dietary treatment (Fig. 2).

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KDDW 2019 Korea Digestive Disease Week

DAY 1
November 28 (Thursday)

[11:00-12:00, Grand Ballroom B+C]

Gender Specific Medicine in Gastroenterology (KSG) -01 English

Clinical application of gender medicine: from research to bedside

Chairs: **Etsuko Hashimoto** (Tokyo Women's Medical University, Japan)
Seun Ja Park (Kosin University Gospel Hospital, Korea)

Is it important to know gender difference for FGID patients?

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In the treatment of functional GI disorders (FGIDs), gender difference seems to become important in various aspects. The majority of FGID, including IBS, bloating, constipation, chronic functional abdominal pain, and pelvic floor dysfunction, are more prevalent in women than men (1). I would like to discuss gender difference on FGIDs or gastrointestinal function based on recent reports.

There is evidence for gender-related differences in IBS. Limited studies suggest that gender differences in visceral perception, gastrointestinal motility, and brain activation patterns to visceral stimuli exist in IBS. There appears to be a greater clinical response to serotonergic agents developed for IBS in women compared to men(1). A large-scale Internet survey across Japan (2) showed that IBS-D was more common in men, while IBS-C predominates in women. According to the other more recent internet survey in Japan (3), the expression rate of abdominal discomfort, distention, and fullness was significantly higher in female than male IBS-Cs. The above trend might be partially explained by gender difference in colon length (4). According to the data in Latin America (5), there were higher proportions of women with IBS and dyspepsia compared with the control. In IBS, women more frequently reported changes in the number of bowel movements (BMs) associated with the onset of abdominal discomfort/pain, fewer than 3 BMs/week and abdominal fullness/bloating/swelling. Men with IBS more frequently reported swallowing air to belch and abdominal pain that improved after a BM than women. In Mexico, both IBS and dyspepsia were more common in women than men(5). Symptoms related to constipation and bloating in IBS were more common in women (5).

Delayed gastric emptying is one of the reasons why functional dyspepsia (FD) occurs. According to the study by Mori et al. (6), as gastric emptying was delayed in healthy women compared with that in healthy men, they set the cut-off points of Tmax at 60 min in men and at 75 min in women. By using these cut-off points, in patients with FD, the prevalence of delayed gastric emptying was not different between men and women. On the other hand, in terms of ghrelin levels, lower level of plasma acyl ghrelin in FD patients was significant only in male. In contrast, female FD patients had a higher anxiety and depression score than male FD, and anxiety score was correlated with epigastric pain only in female FD patients (7). The impairment of overall QoL was more prominent in female FD patients than male (7).

Finally, although not FGID, I also looked at the sex difference of gastroesophageal reflux (GER) in terms of gastrointestinal function. Central obesity with excessive visceral fat has been suggested as a risk factor for gastroesophageal reflux disease (GERD). Visceral fat area was associated with the presence of reflux esophagitis both in men and women (8). Smoking and serum triglyceride (TG)level were also associated with the presence of reflux esophagitis in men(8). In men, excessive alcohol consumption on a drinking daywas associated with both the severity of reflux esophagitis and the presence of Barrett's esophagus (8).The severity of GER was worse among men than among women, whereas the severity of reflux symptoms was worse among women (9). The severity of GER was associated with age and serum TG levels in men, and with the serum LDL cholesterol levels in women (9). There were more women than men with reflux symptoms but without GER ('presumed' functional heartburn), compared with subjects with neither GER nor reflux symptoms. The prevalence of GER was greater among men; conversely, the prevalence of functional heartburn was greater among women. Recently, Jang et al. (10) investigated work-life patterns via prospective data collection for the time consumed at work and home as well as occupation-related symptoms among 222 gastroenterologists. As a result, they discovered a significant correlation between work-life balance and musculoskeletal pain, functional gastrointestinal symptoms, mental symptoms, and burnout. As female gastroenterologists spent more time with their families, despite having a workload similar to that of male doctors, the prevalence in FGID symptoms could be higher in female than in male gastroenterologists. FGID symptoms, especially related to work-life imbalance in female doctors, should be carefully evaluated and urgently addressed not only for doctors' themselves but also for their patients (11).

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Gender difference in gastric cancer

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Although the age-standardized incidence and mortality of gastric cancer are declining, the number of incident gastric cancer remains high due to the increase in the elderly population. Gastric cancer was the fifth and the third most common causes of new cancer cases and cancer-related deaths, respectively, worldwide in 2018. Risk factors for gastric cancer include male sex, elder age, *Helicobacter pylori* infection, genetic susceptibility, diet and lifestyles, such as smoking, high-salt diet, pickled food, obesity, etc.

The incidence and mortality of gastric cancer were reported to be greater in men than in women. The incidence rates of gastric cancer varied between men and women in different countries. The incidence of gastric cancer was about 2 to 3 times in men higher than in women. The actual reasons for such difference are not clear. The regulation at genetic level and sex hormone may result in gender difference of gastric cancer; and for example, estrogen might protect against the incidence of gastric cancer. Besides, different environmental or occupational exposures between men and women may also play a role. The sex-specific disparities lead to different incidence and mortality of gastric cancer, and even sex imbalance of chemotherapy.

Further study for the impact of gender difference in gastric cancer is warranted.

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Different approach to treat liver disease by gender difference

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The purpose of gender medicine is to ensure that each individual man and woman would receive best treatment based on scientific evidences. Biological sex differences and sociocultural gender differences produce biological variations in liver diseases. The sociocultural characteristics such as dietary patterns and exercise are as important as sex differences such as hormonal status and metabolic factors. However, biological sex differences that influence development and progression of liver diseases will be primarily reviewed.

Gender medicine focuses on understanding the differences of pathophysiology, clinical signs, prevention and treatment of disease equally represented in men and women. The differences may come from biological sex differences that arise principally from sex chromosomes and sex hormones, and may also be influenced by socio-cultural factors, namely gender differences.[1] Although sex and gender differences have tended to be neglected in approaches of precision medicine, it has been extensively studied in recent years. However, studies on sex differences in liver diseases are still very few compared to other areas of the study.

Clinical data suggest that men and women exhibit differences in the epidemiology and the progression of some liver diseases such as autoimmune liver diseases and nonalcoholic fatty liver disease. The liver is known to be the best example of a sexually dimorphic non-reproductive organ with over 1,000 genes differently expressed between sexes.[2] Therefore hepatic damage may produce different consequences in men and women.

1. Autoimmune liver diseases

Studies reported that there are sex differences in the immune system probably due to sex hormones. Women have higher number of $CD4^+$ T lymphocytes with increased $CD4^+/CD8^+$ ratio than men.[3] However, more detailed explanation for sex differences in autoimmune liver diseases is yet to be presented since each autoimmune liver disease, such as primary biliary cholangitis, autoimmune hepatitis and primary sclerosing cholangitis shows various sex differences that cannot be explained by current knowledge on the immune system. Primary biliary cholangitis manifests a female preponderance (F:M=10:1) while primary sclerosing cholangitis demonstrates male predominance (F:M=3:7).[4,5] In addition, although actual prevalence of autoimmune hepatitis is unknown, it is characterized by a strong female preponderance (F:M=3.6:1).[6]

2. Alcoholic liver disease

Some reported that hepatic damage after heavy alcohol drinking (weekly alcohol consumption of 336-492 g) developed faster in women than in men with higher relative risk of alcoholic liver disease in women. This difference may be due to differences in corporal structures, different enzymatic activity and hormonal differences. Various studies demonstrated that blood level of gastric alcohol dehydrogenase, which plays the main role in alcohol metabolism affecting the blood ethanol concentration.[7] Moreover, amount of alcohol distributed in water determines the blood alcohol concentration and women have proportionally more fat and less water than men resulting in less ethanol distribution volume.[8]

3. Nonalcoholic fatty liver disease (NAFLD)

The pathophysiology of NAFLD is not well depicted yet although it has been agreed that it probably encompasses complex and multiphasic process. The sex differences in clinical and pathophysiologic manifestation of NAFLD have been reported. The overall NAFLD prevalence is higher in men than in premenopausal women although the prevalence significantly increases in postmenopausal women.[9,10] Hormone replacement therapy in postmenopausal women may lower the prevalence of NAFLD, suggesting the protective role of estrogen in NAFLD.[11]

CONCLUSION

Sex differences exist in the prevalence, risk factors and clinical outcomes of some liver diseases. The study of disease mechanism based on sex differences would offer more efficient precision medicine.

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KDDW 2019 Korea Digestive Disease Week

DAY 1
November 28 (Thursday)

[12:00-12:30, Grand Ballroom B+C]

Gender Specific Medicine in Gastroenterology (KSG) - 02 English

Development of career promotion program for women and young doctors

Chairs: **Hidekazu Suzuki** (Tokai University School of Medicine, Japan)
Nayoung Kim (Seoul National University Bundang Hospital, Korea)

Japan experience

Etsuko Hashimoto, M.D.

Department of Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan

For many years, the United Nations (UN) faced serious challenges in its efforts to promote gender equality globally, including inadequate funding and absence of a single recognized driver to direct UN activities on gender equality issues. In January 2011, the United Nations Entity for Gender Equality and the Empowerment of Women, also known as UN Women, became operational to address such challenges.

In these global situations, one of the most important Japanese issues is the new era in which women shine. A new law called The Basic Act for Gender Equal Society was enacted in 1999. The fourth plan of The Basic Act for Gender Equal Society indicates the "expectation that women will occupy at least 30% of leadership positions by 2020 in all areas of society and further efforts are to be made". The goals are to be set for each field, and for the medical academic world, it is 20%. The future of female candidates in leadership positions should be expanded; in addition to environmental development such as continued employment and work-life balance, it is also necessary to boldly advance a wide range of support measures including training and development for female leadership. For these purposes, a law called The Act on Promotion of Women's Participation and Advancement in the Workplace was enacted in 2016. Thus, an age will soon come in which female leaders are equally active in society.

The Japanese Society of Gastroenterology (JSGE) established the "Support Committee for Female Gastroenterologists" in 2011, and under the direction of female chairperson Prof. Keiko Shiratori, we have been working to support the work continuation and, career improvement among women and holding seminars for women's sessions at JSGE's general meetings. In these women's sessions, the topics covered talks by good women role models about their career development, lectures on the government action of "The Basic Act for Gender Equal Society" or "The Act on Promotion of Women's Participation and Advancement in the Workplace" etc. Years later, we realized that these themes were not attractive, particularly for young female doctors who are our most important targets. The audience has always consisted of only senior female doctors, particularly members of the Support Committee for Female Gastroenterologists, and a few male professors. It is probable that the younger generations are greatly interested in acquiring new knowledge about gastroenterology and achievement of their research at the general meeting. Moreover, the committee's missions just for women's support were not effective. Subsequently, from 2015, with the main goal of supporting both male and female young physicians and researchers, the name of the committee was changed to "The Career Support Committee", and since 2017, I have acted as its chairperson.

One of the missions of this committee is to create interest in gastroenterology among young physicians and researchers, and we are developing activities to realize this mission. At the general meetings of the JSGE, we hold the "Young Talent Presentation Conference–Learning from Case Studies" by young residents who were selected for awards for outstanding presentation in each JSGE branch and invited to the general meetings. The high-level case reports and active questions and answers by young physicians led to the creation of a fruitful and fulfilling program for them. Several expert gastroenterologists helped them with their presentation and also attended the meeting to support them. They were also invited to the presidential dinner. They have had several opportunities to talk to each other and several experts in the gastroenterology field outside their hospitals. This splendid exchange among young physicians is one of the great successes of this project.

Regarding providing support for young female doctors and researchers, we think that the JSGE branches could provide more detailed supports compared to us. JSGE has 10 branches nationwide, from Hokkaido to Kyusyu. JSGE established groups for female physicians in each branch in 2018. Female leaders of each branch play extremely important roles for women's support and promotion. They hold hands-on seminars, create e-learning systems for studying at home, prepare child daycare centers at the venue of the meeting, hold women's seminars and party for their friendships, and have also proactively introduced promotion measures such as increasing the number of female chairpersons and chapter councilors. General meetings of the JSGE hold "special sessions for women's career-up" organized by the Career Support Committee and leaders of each branch group of female physicians aimed at improving the work and careers of female physicians and researchers. Currently in JSGE, there are 34922 members with 14% females, 21607 board certified gastroenterologists with 13% females, 2300 chapter councilors with 8% females, 1192 active members with only 3% females, and 24 directors with 8% females. These percentages should be equal in the future.

In American Gastroenterological Association (AGA), women's programs are very advanced; AGA holds a women's luncheon every year at the Digestive Disease Week (DDW) and leadership development programs for women in gastroenterology, creates networking and mentoring opportunities etc. A landmark event occurred at DDW in 2017. For the first time in history, all the following four gastroenterology and hepatology societies had women presidents: the AGA, the American Association for the Study of Liver Diseases, the American College of Gastroenterology, and the American Society for Gastrointestinal Endoscopy. We held a small meeting with AGA women's committee members at DDW.

We will continue our activities so that the young generation can be active in the clinical practice and research and contribute to the development of the global field of gastroenterology. Globalization is extremely important. We females would sincerely appreciate global understanding and support in all aspects.

Korean experience

Seon Mee Park, M.D., Ph.D.

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Our activities began by attending a Women's luncheon meeting in DDW2015. Korean women doctors introduced this meeting to propose the Women's Committee in the Korean Society of Gastroenterology (KSG). The KSG Board committee of Directors proposed one session regarding gender-specific medicine in each Spring or Autumn KDDW instead of a Women's Committee. Sessions on gender medicine in gastroenterology have been held since 2016. During activities over the last 3 years, limitations were identified: small number of attendees, little data to apply in clinical activities, and insufficient support to conduct research. In addition, our activities were limited to studying gender medicine.

The number of women doctors in Korea has increased in recent years. The proportion of women doctors in Korea was one-fourths, while young women doctors (20s and 30s) were one-thirds of all doctors. However, a limited number of women doctors had success in academic landing. Women doctors need to learn how to make a successful transition from fellowship to faculty in an academic medical center. Personal and organizational factors can contribute to the success of new faculty. We examined the survey "Work-life conflict and its health effects on Korean gastroenterologists according to age and sex." This survey[1] reported that Korean gastroenterologists suffered from adverse musculoskeletal, gastrointestinal, and mental symptoms and were highly prone to burnout due to long and strenuous work. Work–life imbalance and burnout were most severe in young women doctors due to their domestic demands. To support career promotion for them, we proposed the committee again and chose the name based on diversity instead of woman. Diversity represents minorities in KSG including women, young men, and disabled or foreign doctors. We performed a survey titled "Importance of a Diversity Committee in Advancing the KSG."[2] Most participants of this survey expected that the Diversity Committee would contribute to the advancement of the KSG. On the other hand, in most of the priorities of the target, purpose, specific activities, and expected effects of the Diversity Committee, there was a difference in the perceptions between men and women. Therefore, continuous efforts are needed to reduce the differences within the KSG.

A temporary Diversity Committee in the KSG was established in April 2019. The aims of this committee are to support research or education about gender medicine in gastroenterology, develop career promotion programs for minorities in KSG, and do national and international networking with women committees of other societies. The members of the diversity committee comprise 7 female and 2 male gastroenterologists, who have different subspecialties. This year, the diversity committee held a symposium about gender medicine and a luncheon meeting under title of "academic career promotion." For networking, our committee held a Japan and Korean woman gastroenterologists' meeting during DDW 2019. We also had a Taiwan and Korean woman gastroenterologists' meeting during TDDW 2019. For national networking of the women's committee, we touched the meeting of Korea Foundation of Women's Science & Technology Association (KOFWST), (www.kofwst.org), and Gender Innovation Center (http://genderedinnovations.gister.re.kr).

The Diversity Committee in KSG is a turning point to make a leap forward. We have plans to conduct research[3] and develop education programs[4] about gender medicine in gastroenterology. By promoting careers of women and young doctors, the committee becomes a leading group to advance the KSG. Encouragement and shared achievement by the national and international networking of the diversity committee could support our continuous progression.

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Taiwan experience

Mei-Jyh Chen, M.D., Ph.D.

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The proportion of female physicians in the world is rising, but in many countries, the proportion of female physicians in the Department of Gastroenterology is relatively low compared to the proportion of female physicians in other disciplines. In Taiwan, about one fifth of doctors are female physicians, but the proportion of female gastroenterologists is only 6.7%. The difference in gender is worthy of attention.

Practice of self-advocacy, self-confidence, support of good mentor and joining professional societies would help young and female gastroenterologists to improve their early careers. The government and professional societies need to provide funding supports for younger doctors regarding academic research, scientific presentation and participation in international conference.

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KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

[14:00-15:30, Convention Hall A+B]

Symposium 03 (KASL2) Korean

Modulation of gut-liver axis in liver diseases: How far have we come?

Chairs: **Jin Mo Yang** (The Catholic University of Korea St. Vincent's Hospital, Korea)

Kwang Cheol Koh (Samsung Medical Center, Korea)

Serotonin signals through a gut-liver axis to regulate hepatic steatosis

Hail Kim, M.D., Ph.D.

Department of Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology, Daejeon, Korea

Nonalcoholic fatty liver disease (NAFLD) is increasing in worldwide prevalence, closely tracking the obesity epidemic, but specific pharmaceutical treatments for NAFLD are lacking. Defining the key molecular pathways underlying the pathogenesis of NAFLD is essential for developing new drugs. Here we demonstrate that inhibition of gut-derived serotonin synthesis ameliorates hepatic steatosis through a reduction in liver serotonin receptor 2A (HTR2A) signaling. Local serotonin concentrations in the portal blood, which can directly travel to and affect the liver, are selectively increased by high-fat diet (HFD) feeding in mice. Both gut-specific Tph1knockout mice and liver-specific Htr2aknockout mice are resistant to HFD-induced hepatic steatosis, without affecting systemic energy homeostasis. Moreover, selective HTR2A antagonist treatment prevents HFD-induced hepatic steatosis. Thus, the gut TPH1-liver HTR2A axis shows promise as a drug target to ameliorate NAFLD with minimal systemic metabolic effects.

Dysbiosis in patients with liver cirrhosis

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Gut and liver communicate via tight bidirectional links through the biliary tract, portal vein and systemic circulation. In heathy adult, intestinal microbiome has various functions that affect biochemical, metabolic and physiologic processes both within the intestine and elsewhere in the body[1]. However, there is a change in the existing balance within the intestinal microbiota in cirrhosis showing a reduction in microbial phylogenic and metagenomic diversity, and this change is referred to dysbiosis[2]. In addition, the oral cavity microbiome also undergoes dysbiosis, and it follows intestinal dysbiosis trends and associated with inflammation in cirrhotic patients.[3,4] Dysbiosis begins before development of cirrhosis during progression of chronic liver disease, such as alcoholic liver disease or nonalcoholic fatty liver disease, and directly involved in the hepatic fibrogenesis[5,6]. Because microbial dysbiosis shows tendency that autochthonous taxa decrease and the pathogenic taxa decrease, there have been efforts to use the microbial dysbiosis as biomarker for diagnosis and prognostication[7]. In cirrhosis, alteration in the gut microbiota have been associated with complications; spontaneous bacterial peritonitis[8], hepatic encephalopathy[9], hepatorenal syndrome[10], and variceal bleeding[11]. Microbial dysbiosis is emerging as treatment target in cirrhotic patients. In practice, treatment option to modulate or reverse microbial dysbiosis, such as lactulose, rifaximin, and probiotics, are used in the management of cirrhosis. In the future, a greater understanding of the microbial dysbiosis could provide optimal treatment options to cirrhotic patients.

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Gut microbiome and hepatocarcinogenesis

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Non-resolving inflammation is a recognized hallmark of cancer that substantially contributes to the development and progression of hepatocellular carcinoma (HCC), one of the leading causes of cancer-related death worldwide. Observations from recent studies have accounted for the involvement of the gut–liver axis in the pathophysiological mechanism responsible for HCC. The human intestine nurtures a diversified colony of microorganisms residing in the host ecosystem. The intestinal barrier is critical for conserving the normal physiology of the gut microbiome. Therefore, a rupture of this barrier or dysbiosis can cause the intestinal microbiome to serve as the main source of portal-vein endotoxins in the progression of hepatic diseases. Recent research has revealed the carcinogenic effects of small molecules including lipopolysaccharide (LPS), bile acids (BAs), and lipoteichoic acid (LTA) produced by the gut microbiome that downregulate the immune system in the liver. LPS can activate Toll-like receptor (TLR) 4 to contribute to the pathogenesis of liver cancer. Secondary BAs regulate liver cancer via natural killer T (NKT) cells. A study by Ma et al. showed that gut microbiome composition in mice closely associates with liver cancer by influencing the immune system. This group provided evidence showing that changing commensal gut bacteria in mice affected the accumulation of hepatic C-X-C chemokine receptor type 6 $(CXCR6)^{+}$ NKT cells through mediation of chemokine (C-X-C motif) ligand 16 (CXCL16) expression in liver sinusoidal endothelial cells. CXCL16 is the only ligand for the chemokine receptor CXCR6, which mediates NKT cell survival and accumulation in the liver. The accumulation of CXCR6 in hepatic NKT cells enhances the production of interferon-γ upon antigen stimulation, which contributes to the inhibition of tumor growth. The accumulation of NKT cells is known to be mainly regulated by a type of *Clostridium* species that metabolizes primary BAs to secondary BAs because depletion of *Clostridium* by vancomycin increases hepatic NKT cells and colonization of *C. scindens* induces a rapid decrease in liver NKT cells. This evidence highlighted the significant contribution of the gut microbiome to regulating anti-tumor immunity in liver and hepatic cancers. LTA, a major constituent of the cell wall of gram-positive bacteria, has also been shown to accumulate in the livers of high-fat diet (HFD)-fed mice in the presence of DMBA (7,12-dimethylbenz(a)anthracene, a chemical carcinogen) that can give rise to HCC. Both deoxycholic acid and LTA cooperatively induce the senescence-associated secretory phenotype (SASP) of hepatic stellate cells to produce various inflammatory and pro-tumorigenic factors, including interleukin-6, growth-regulated oncogene-alpha, CXCL9, and prostaglandin E2 (PGE2), leading to a tumorigenic microenvironment that promotes liver cancer development in mice.

Thus, manipulation of the gut microbiota may represent a novel way to treat or prevent HCC. Targeting the gut–liver axis by nonabsorbable antibiotics such as rifaximin might not only prevent the development of HCC, but additionally reduce other complications and improve survival. Probiotics have been suggested as a novel, safe and cost-effective approach to prevent or treat HCC. Mechanisms by which probiotics exerts their anti-cancer effects include their ability to bind carcinogens, modulation of gut microbiota, improvement of intestinal barrier function, and immunomodulation. Prebiotics, food ingredients that selectively stimulate the growth or activity of beneficial microorganisms, have great potential for prevention of HCC through improving metabolism and the intestinal barrier, as well as reducing endotoxemia. Future research might offer mechanistic insights into the specific phyla targeting the leaky gut, as well as microbial dysbiosis, and their metabolites, which represent key pathways that drive HCC-promoting microbiome-mediated liver inflammation and fibrosis, thereby restoring the gut barrier function.

Keywords: hepatocellular carcinoma immunotherapy, gut, microbiome, probiotics

Modulation of gut-liver axis in liver diseases: How far have we come?

Ki Tae Suk, M.D., Ph.D

Department of Internal Medicine, Chuncheon Sacred Heart Hospital, Chuncheon, Korea

Human gut microbiota is an ecological community comprised of commensal, symbiotic, and pathogenic microorganisms totaling 1-2 kg in weight. Gut microbiota are integral for immunological, hormonal, and metabolic homeostasis of the host. However, an overall understanding of gut microbiota, including variations due to geographical region, gender, and age, has yet to be established. The close relationship between the gut and liver appears to be a crucial factor in liver injury. The liver receives most of its blood and nutritional supply from the gut through the portal vein and is the first organ to be exposed to gut-derived toxic factors, including bacteria, damage-associated metabolites, and bacterial products. Furthermore, some gut microbes produce ammonia, ethanol, and acetaldehyde, which are largely metabolized in the liver and associated with activation of Kupffer cells and inflammatory cytokine pathways. Additionally, dysbiosis, which is defined as quantitative and qualitative changes in intestinal bacteria, and small intestine bacterial overgrowth can both lead to an increase in intestinal permeability and translocation of endotoxins to the portal tract, which activates the signal pathways of a wide array of inflammatory cytokines in the liver.

Worldwide, alcohol consumption ranks third among the various risk factors for disease and disability. The large absolute increase in alcohol consumption has led to a rapid increase in alcohol-related diseases and accidents.[3] Alcoholic liver disease (ALD) is responsible for approximately 25% of deaths resulting from alcohol consumption. Activation of Kupffer cells has been identified as an essential element in the pathogenesis of ALD. Alcohol induces bacterial overgrowth and the translocation of the endotoxin lipopolysaccharide (LPS) from the gut to the liver. Alcohol has been known to disrupt the gut barrier function, which consequently promotes the translocation of microbial LPS from the lumen of the intestines to the portal vein, where it travels to the liver. Kupffer cells and macrophages recruited to the liver can be activated by bacterial endotoxin such as LPS through toll-like receptor (TLR) 4. The levels of LPS in the portal vein and in the systemic circulation are increased with excessive alcohol intake. These observations suggest that gut-derived LPS is the central mediator of inflammation in alcoholic steatohepatitis. Moderate alcohol consumption has also been identified as a strong risk factor for small intestinal bacterial overgrowth. This process of alcohol consumption bringing about changes in the intestinal milieu and inducing consequent downstream immune responses in the liver.

KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

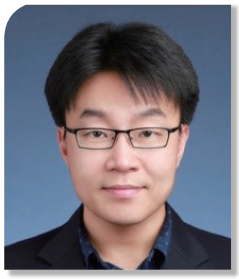
[14:00-15:30, Convention Hall C]

In-depth Symposium 03 (KSG) English

Development of novel targets for pancreatic cancer

Chairs: **Si Young Song** (Severance Hospital, Korea)

Hong Sik Lee (Korea University Anam Hospital, Korea)

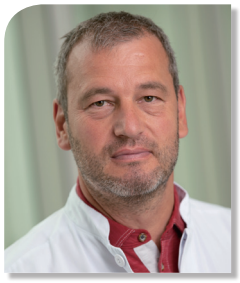


Cancer meet microbiome and immunology

Hansoo Park, M.D., Ph.D.

Department of Department Biomedical Science and Engineering, Gwangju Institute of Science and Technology, Gwangju, Korea

Oxaliplatin induces tumor cell apoptosis by arrest of DNA synthesis, inhibition of RNA synthesis, and triggering of immunologic reactions. These mechanisms made Oxaliplatin to be used as a treatment for cancer. However, some patients respond well to Oxaliplatin treatment but others do not respond. Intestinal microbiome can influence immune pathway, so that it may affect efficacy of Oxaliplatin. Total DNA was extracted using the MO-BIO PowerSoil DNA Isolation Kit and PCR amplification was carried out using primers targeting the hypervariable regions V3–V4 (515f-806r) of the 16S ribosomal RNA gene on the Illumina MiSeq platform. Sequence reads processing was analyzed using the QIIME pipeline. As a result, specific strains were associated with therapeutic outcomes such as several "A" species. Using syngeneic model, we found that "A" species increased the efficacy of Oxaliplatin. Our results suggest that manipulating the microbiome can play a role in modulating cancer therapy.



Tumor microenvironment as a therapeutic target for pancreatic cancer

Volker Ellenrieder

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Drug development with genomic big data and artificial intelligence for pancreatic cancer

Si Young Song, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Severance Hospital, Seoul, Korea

Pancreatic cancertherapy remains a formidable challenge. Partially as a result of improvementsin the treatment of other cancers and an aging population, pancreatic cancerwill become the second leading cause of cancer- associated mortality within thenext decade in the world. Worldwide, the incidence of pancreatic cancer ispredicted to be ~420,000 by the year 2020, with an associated mortality ofaround 410,000 and expected to become the second leading cause of cancermortality by 2030. Surgical resection is the only curative treatment, but evenafter surgery, 5 year survival does not reach to 20%. The reason for lowobjective response rate to conventional standard therapy is because of theinherent genetic instability of pancreatic cancer cells, immunosuppressivemicroenvir onment at the tumor site, and the complex peritumoral stroma. Our ever- growing understanding of the complex genetic,epigenetic and metabolic alterations as well as of the equally complexinterplay of cancer cells with stromal cells, immune cells and endothelialcells has not yet resulted in a dramatic change in the overall outcome forpatients with pancreatic cancer.Challenges include identification of at- riskpopulations for screening and prevention, early detection by advanced imagingand novel cancer biomarkers and most notably better therapeutic options thatovercome the resistance of pancreatic cancer to current treatment modalities,including chemotherapy, immunotherapy, targeted therapies and personalizedtherapies.

An enormous figure looms over scientists searching for new drugs: theestimated US$2.6-billion price tag of developing a treatment. A lot of thateffectively goes down the drain, because it includes money spent on the nineout of ten candidate therapies that fail somewhere between phase I trials andregulatory approval. Few people in the field doubt the need to do thingsdifferently. Artificial intelligence (AI) uses personified knowledge and learnsfrom the solutions it produces to address not only specific but also complexproblems. Remarkable improvements in computational power coupled withadvancements in AI technology could be utilised to revolutionise the drugdevelopment process. At present, the pharmaceutical industry is facingchallenges in sustaining their drug development programmes because of increased R&D costs and reduced efficiency. Currently AI is widely applicated infinding the hit or lead compounds, synthesis of drug-like compounds, predictingthe mode-of-action of compounds, selection of a population for clinical trials,and drug repositioning. Here, I will present a perspective on currentand future drug development of pancreatic cancer therapies based on big dataand AI.

KDDW 2019 Korea Digestive Disease Week

DAY 1
November 28 (Thursday)

[14:00-15:30, Emerald Hall A]

PG Course 03 (KASID) Korean

Update on diagnosis of small bowel disease: lessons from cases

Chairs: **Hyun Soo Kim** (Chonnam National University Hospital, Korea)
Eun Young Kim (Daegu Catholic University Medical Center, Korea)

Capsule endoscopic findings of various small intestinal diseases

Hyun Joo Song, M.D., Ph.D.

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Since small bowel capsule endoscopy (CE) was first introduced in 2000[1] and a large amount of research has been conducted. Small bowel CE is the best methods for examining the full surface of the small bowel and is optimal for small bowel endoscopic imaging.[2] The primary indications for small bowel CE are obscure gastrointestinal bleeding (OGIB), iron deficiency anemia, suspected Crohn's disease (CD), small bowel tumors, non–steroidal anti–inflammatory drugs enteropathy, portal hypertensive enteropathy, Celiac disease, inherited polyposis syndromes, chronic abdominal pain, and more. Herein, we review CE findings of small bowel disease in clinical practice (Fig. 1).

1. ANGIOECTASIA

OGIB refers to gastrointestinal (GI) bleeding of undetermined origin that persists or recurs despite negative upper GI endoscopy or colonoscopy. Approximately 5% of GI bleeding cases are attributed to OGIB.[3] OGIB originates in the small bowel in more than 80% of cases.[4] The etiology of obscure GI bleeding is as follows: Angioectasia (20-25%) is the most common, followed by small bowel tumor (10-20%), Crohn's disease (2-10%), NSAIDs-induced enteropathy (5%), Meckel's diverticulum (2-5%), and miscellaneous.

2. CROHN'S DISEASE

At present, no index for diagnosis of CD exists, and while the presence of clinical symptoms remains an important factor in the diagnostic process, symptoms of abdominal pain or chronic diarrhea alone rarely lead to clinically significant small bowel lesions upon CE.[5] CE is the most accurate diagnostic tool for detecting mucosal lesions in suspected or established CD.[6] In patients highly suspicious for CD,

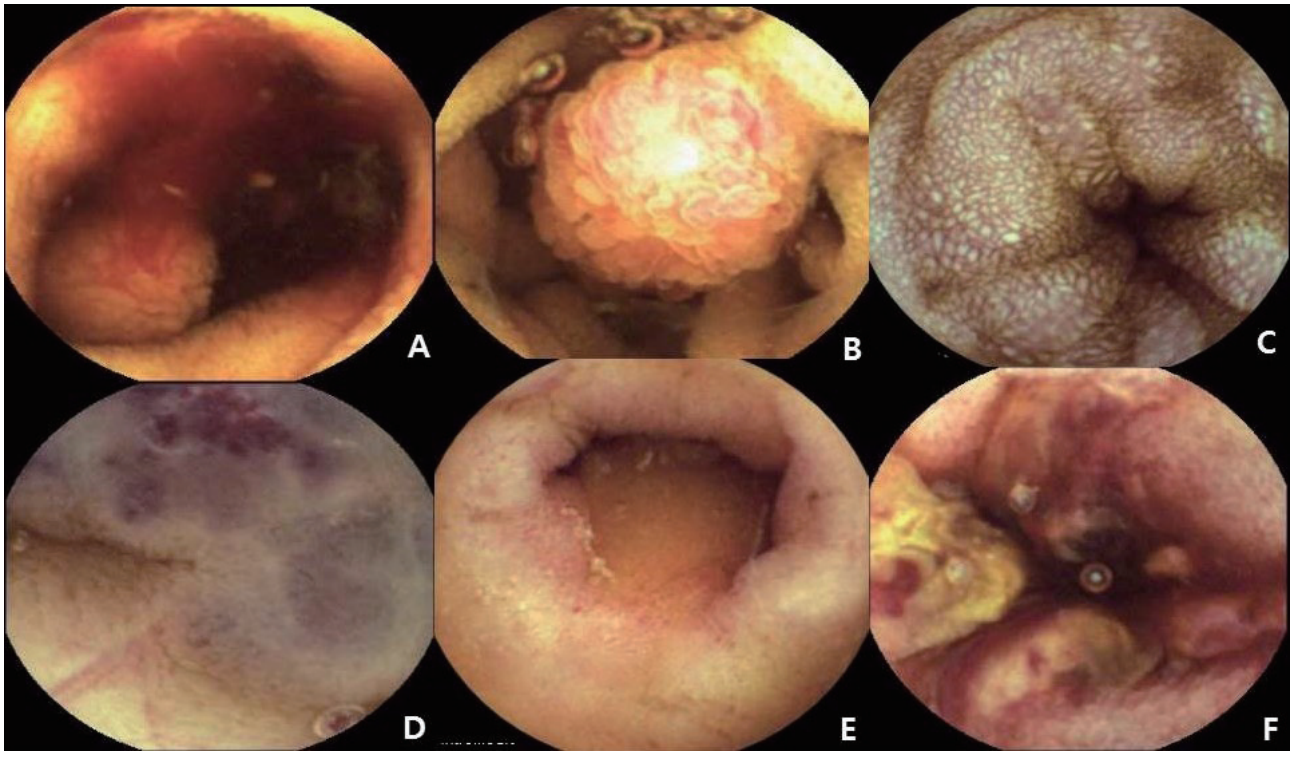

Figure 1. Capsule endoscopic findings of various small bowel diseases. (A) andiodysplasia, (B) Peutz-Jephers syndrome, (C) lymphangiectasia, (D) hemangioma, (E) small bowel tuberculosis, and (F) ischemic enteritis.

CE is a useful diagnostic indicator following negative ileocolonoscopy and small bowel radiologic examination. Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) score evaluates proximal as well as distal segments of the small bowel according to capsule transit time, as validated by multicenter prospective study.[7]

3. SMALL BOWEL TUMOR

Most small bowel tumors are detected during work-up of OGIB or iron deficiency anemia, but represent only about 3.5-5% of such patients.[8] Although the clinical manifestations of small bowel tumors are mostly subclinical, small intestinal bleeding might be the most common symptom. CE proved significantly superior in diagnostic accuracy over radiological procedures for small tumors, especially for those 1 cm in size or less.[9]

4. NSAIDS-INDUCED ENTEROPATHY

NSAIDs–induced enteropathy has recently become a topic of great interest among gastroenterologists, as CE and DBE are available for detecting small bowel lesions. The most common findings were multiple ulcerations (58.6%) and erosions or aphthae (22.9%), according to a Korean multicenter retrospective study (n=140) based on the CE nationwide database registry.[10]

5. MISCELLANEOUS

Portal hypertensive enteropathy, Celiac disease, intestinal lymphangiectasia, ischemic enteritis, intestinal tuberculosis, adenocarcinoma, small bowel lymphoma, H-S purpura, Behcet's disease

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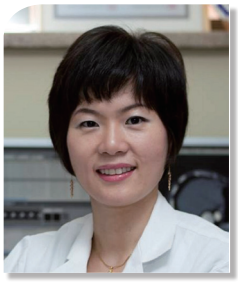

Choice of small intestine imaging study, what and when?

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Small bowel is a challenging organ for both clinicians and radiologists to diagnose its diseases due to the relative inaccessibility of the small bowel to conventional endoscopy and lower diagnostic performance of conventional barium studies. In parallel with the development of new endoscopic techniques, rapid progress has been made in cross-sectional imaging technologies, harnessing the power of multidetector row CT (MDCT), MRI, and ultrasound, facilitating rapid, accurate and minimally invasive investigation of the small bowel and adjacent tissues. Many kinds of disease entities can occur in the small bowel. They include tumors, inflammatory diseases such as Crohn's disease, infectious disease, and ischemic diseases. Although imaging features are usually nonspecific, some features might be pathognomic for some diseases, making a correct diagnosis. In addition to diagnosis, imaging provides valuable information regarding disease activity, treatment response, and the presence of complication related to inflammatory bowel disease.

In this lecture, I will introduce recent advances of each cross-sectional imaging modality for evaluating small bowel disease and present imaging findings of various small bowel diseases in each modality. Finally, I will summarize which imaging modality is appropriate for each small bowel disease.

Diagnostic approach of suspected small bowel bleeding

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Department of Internal Medicine, The Catholic University of Korea, Eunpyeong St. Mary's Hospital, Seoul, Korea

INTRODUCTION

Small bowel bleeding, known previously as obscure gastrointestinal bleeding(OGIB), is relatively rare, accounting for 5-10% of all cases that present gastrointestinal bleeding.[1] But sometimes, it could be life-threatening. According to clinical features, OGIB can be divided into overt, occult, obscure-occult and obscure-overt bleeding. Diagnostic and therapeutic approaches may differ based on these clinical features.

In this article, we will look back on the usefulness of various exams for the diagnosis of suspected small intestinal bleeding and propose an appropriate access algorithm.

DIAGNOSIS AND TREATMENT

In addition to detailed medical history and physical examination, there are various diagnostic modalities for patients with small bowel bleeding including video capsule endoscopy, balloon-assisted enteroscopy and radiographic imaging modalities, like CT and MR enterography, angiography and scintigraphy. Diagnostic approach and management of patients with small bowel bleeding depends on the severity of hemorrhage and patient conditions.

1. Cross-sectional imaging

Cross-sectional imaging techniques for evaluation of small bowel include CT enterography/enteroclysis, CT angiography, and MR enterography/enteroclysis.[2] In clinical practice, abdominal CT scan without enterography/enteroclysis preferentially enforced in patients with OGIB, especially in the emergency room.These imaging techniques not only provide information for tumorous conditions such as cancer, lymphoma and gastrointestinal stromal tumor, mucosal inflammation, and vascular diseases [3] but also allow to know the presence or absence of intestinal obstruction before enforcing capsule endoscopy.

2. Capsule endoscopy

If patients with OGIB are hemodynamically stable, capsule endoscopy (CE) is the first-line diagnostic tool. CE is noninvasive technique and allows observation of the entire small intestine in most patients without discomfort. However, CE has the disadvantage that tissue biopsy and therapeutic treatment is impossible. The diagnostic yield in patients with OGIB ranges from 30% to 70%, and a recent large – scare meta-analysis reported 61%.[4] It is important to improve the diagnostic yield that CE is performed as soon as possible in patients with OGIB.[5]

3. Enteroscopy

There are several types of enteroscopy, such as push enteroscopy, intraoperative enteroscopy and deep enteroscopy(double balloon enteroscopy, single balloon enteroscopy, spiral enteroscopy). Although these procedures are very invasive, they have the advantage of being able to acquire tissues and conduct treatment with hemoclip or argon plasma coagulation. CE and double balloon enteroscopy have similar diagnostic yields of about 60% for evaluation of OGIB. It is recommended to perform CE before DBE for diagnostic and therapeutic effectiveness.[5]

4. Angiography & Nuclear scans

Angiography can be used in patients with active bleeding at a rate of >0.5 mL/min. The advantage of angiography is the ability to perform therapeutic intervention at the same time of diagnosis of the bleeding focus. It is possible for bowel infarction to occur, which is the most serious complication after transarterial embolization.

After CE, the role of bleeding scan has decreased. They require a bleeding rate of 0.1-0.5 mL/min for a positive result. Mechel's scan using 99mTc-pertechnetate is used to find ectopic gastric mucosa in patients with OGIB, especially in children or young adults.

DIAGNOSTIC ALGORITHM

Diagnostic approaches will vary depending on the aspect of bleeding. We propose the approach to diagnosis and management of small bowel bleeding as in Figure 1.

CONCLUSIONS

Although many modalities to evaluate small intestine have been developed over the last decades, small bowel bleeding remains a challenging problem in clinical practice. When choosing the methods to evaluate small bowel bleeding, we have to consider whether the

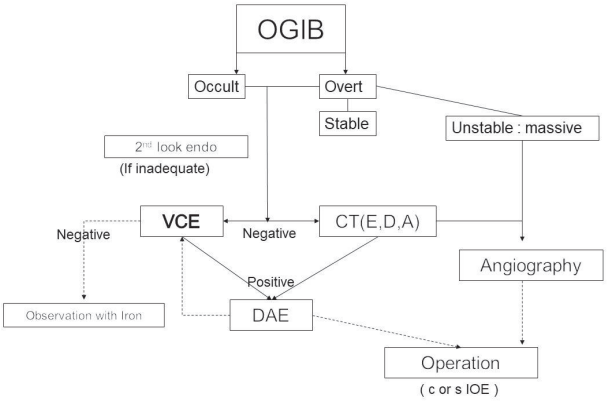

Figure 1. Diagnostic approach of suspected small bowel bleeding.

patients with small bowel bleeding are hemodynamically stable or not, whether the bleeding is overt or occult. CE is a non invasive technique with good diagnostic yield, but considering the time taken for capsule endoscopy, CT scans with or without enterography/enteroclysis can be a good alternative especially in the emergency department. As the clinical features of OGIB are very diverse, different diagnostic and therapeutic strategies are required for each case.

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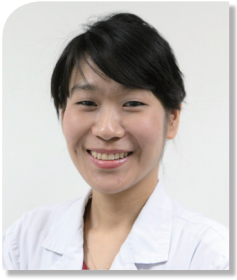

Diagnostic approach of small bowel tumor

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The small bowel is difficult to access endoscopically due to its long, movable, and tortuous anatomy. Capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE) has expanded the range of endoscopic examination of small bowel. CE allows painless endoscopic imaging of the entire small bowel, but it lacks the ability to obtain biopsy specimens and perform therapeutic intervention. On the other hand, BAE is more labor intensive and does not allow examination of the whole small bowel during one examination in most cases.

Although small bowel the mainly occupies the most part of the gastrointestinal tract, small bowel tumors are rare, comprising less than 5% of all primary gastrointestinal tumors.[1] Small bowel tumors are classified as benign and malignant epithelial tumors, mesenchymal tumors, lymphoproliferative disorders, or metastatic tumors.[2,3] Adenocarcinoma, neuroendocrine (carcinoid) tumor, lymphoma, and sarcoma (gastrointestinal stromal tumors) are 4 major histologic types of malignancy.[4] The diagnosis of small bowel tumor is frequently delayed because most are asymptomatic or nonspecific symptom. Therefore, small bowel tumors are detected by CE during work-up of obscure gastrointestinal bleeding (OGIB), iron deficiency anemia, unexplained abdominal pain, and so on.[5]

Europe guideline recommends early use of CE in the search for a small bowel tumor when OGIB are not explained conventional radiological tests.[6] Protruding mass with bleeding, mucosal disruption, irregular surface, discolored area, or white villi are suggested as the CE findings of small bowel tumor.[5]CE proved significantly superior in diagnostic accuracy over radiological tests for small tumors (< 1 cm).[7] Although CE has made it easier to detect small bowel tumors, some studies revealed that CE can miss some significant tumor in the small bowel.[8,9] Capsule retention occurred in 9.7%–25% in patients with small bowel tumors.[3] In a KASID multicenter study, the miss rate of CE for small bowel tumors was 16.5% and missed tumors were most commonly located in the proximal jejunum (55.6%).[10] CE also has the potential for misdiagnosis of transient intraluminal protrusions of the small bowel wall as submucosal tumors.[11] BAE is considered if prior radiological tests have demonstrated suspicion of small boweltumor and these lesions that are not identified by CE are highly suspicious. In indefinite diagnosis of small bowel tumors by CE, DAE should be required for biopsy sampling or to localize the tumor more exactly.

Clinical suspicion of small bowel tumor is important to raise the diagnostic yields in CE and BAE. Systematic approach by CE, BAE and radiologic tests such as CT/MR enterography can serve as proper diagnostic tools for small bowel tumors.

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KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

[14:00-14:40, Emerald Hall B]

Presidential Lecture (KSNM) Korean

Chair: **Young Woo Kang** (Konyang University Hospital, Korea)

Pathogenesis and management of functional dyspepsia

Kwang Jae Lee, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Ajou University Hospital, Suwon, Korea

Functional dyspepsia (FD) is a clinical syndrome comprising chronic symptoms arising from the gastroduodenal region. According to the Rome criteria, the symptoms of FD are bothersome recurrent postprandial fullness, inability to finish a normal sized meal (early satiety), epigastric pain or epigastric burning in the setting of a normal upper endoscopy. However, many patients with FD also complain of other bothersome symptoms including nausea, bloating, belching, and heartburn. FD consists of two clinical syndromes which can frequently overlap. Postprandial distress syndrome (PDS) is characterized by meal-related symptoms such as early satiety or postprandial fullness. Another FD syndrome is epigastric pain syndrome (EPS) where patients present with recurrent and bothersome epigastric pain or epigastric burning.

Visceral hypersensitivity, impaired gastric accommodation to a meal, and delayed gastric emptying are commonly associated with patients with FD. Involvement of several other mechanisms has also been suggested, including duodenal hypersensitivity to the luminal contents, low grade mucosal inflammation of the duodenal mucosa, enhanced permeability of the duodenal mucosa, small bowel dysmotility, psychological disturbances, and central nervous system disorders.

PDS and EPS require different treatment modalities; patients with EPS benefit from acid secretion inhibitors or visceral analgesics, whereas patients with PDS benefit from prokinetic drugs or fundus relaxing agents. Several studies have reported that anti-acid therapy and prokinetic agents are effective for certain subgroups with FD. A recent meta-analysis concluded that prokinetic agents improve the symptoms of early satiety and postprandial fullness. For the treatment of refractory FD, low-dose antidepressants are used as second-line drugs in clinical practice. Dietary recommendations in FD include eating smaller meals and avoiding foods which have been reported to aggravate symptoms. The pathophysiologic mechanisms of FD are heterogeneous, and choice of the appropriate treatment for FD is difficult. Moreover, pharmacological therapeutic options are still limited.

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KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

[14:40-15:20, Emerald Hall B]

Special Lecture (KSNM) English

Chairs: **Young Woo Kang** (Konyang University Hospital, Korea)

Kwang Jae Lee (Ajou University Hospital, Korea)

Ineffective esophageal motility: from the Stanford 2018 symposium

Daniel Sifrim, M.D., Ph.D.

Department of Wingate Institute of Neurogastroenterology, Barts and the London, School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom

Ineffective esophageal motility (IEM) is a minor motility disorder diagnosed when ≥50% ineffective peristaltic sequences (distal contractile integral <450 mmHg.cm.s) coexist with normal lower esophageal sphincter relaxation on esophageal high resolution manometry.

The pathophysiology of IEM involves abnormalities in central control of normal esophageal peristalsis, potential failures in the modulation of esophageal peristalsis by central and peripheral factors, including psychological stress, esophageal sensory stimulation, and gastroesophageal reflux. IEM is not consistently related to disease states or symptoms, and may be seen in asymptomatic healthy individuals. Severe IEM (>70% ineffective sequences) is associated with higher esophageal reflux burden, particularly while supine, but milder variants do not progress over time or consistently impact quality of life. IEM can be further characterized using provocative maneuvers during HRM, especially multiple rapid swallows, where augmentation of smooth muscle contraction defines contraction reserve. The presence of contraction reserve may predict better prognosis, lesser reflux burden and confidence in a standard fundoplication for surgical management of reflux. Other provocative maneuvers (solid swallows, standardized test meal, rapid drink challenge) are useful to characterize bolus transit in IEM. No effective pharmacotherapy exists, and current managements target symptoms and concurrent reflux. Novel testing modalities (baseline and mucosal impedance, functional lumen imaging probe) show promise in elucidating pathophysiology and stratifying IEM phenotypes. Diet, lifestyle modifications and GERD management remain the cornerstone of therapy. Specific prokinetic agents targeting esophageal smooth muscle need to be developed for management.

KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

[14:00-14:40, Diamond Hall]

Presidential Lecture (KCHUGR) Korean

Chair: Jong-Jae Park (Korea University Guro Hospital, Korea)

Extracellular vesicle in gastrointestinal disease and microbiome in gastric carcinogenesis

Jae Gyu Kim, M.D., Ph.D.

Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Korea

The gastrointestinal tract is the internal organ with the most contact with the external environment and as such comes in frequent contact with microbiota contained in ingested food as well as commensal bacteria residing in the gastrointestinal tract

The stomach was previously believed to be a sterile organ, but after the discovery of Helicobacter pylori, the possibility that other microorganisms could also survive the harsh acidic and bile salt conditions of the stomach came to light. The development of next generation sequencing (NGS) technology has made it possible to identify all microorganisms in a sample without having to culture the bacteria. Through this metagenomic NGS approach, many research groups have identified microorganisms in gastrointestinal samples and found that there are more species of microorganisms in the stomach than expected.

Microorganisms and intestinal epithelial cells which exist in the small and large intestine are known to exchange information between cells by actively secreting extracellular vesicles (EVs). EVs are nano-sized spherical materials known to be secreted by both monocytes and karyocytes and are composed of a lipid bilayer that encapsulates cellular proteins, DNA, and RNA. Recently, studies have reported that not only microorganisms and their metabolites, but also the EVs secreted by microorganisms and intestinal epithelial cells play an important role in the formation of immunity and the development of various diseases.

In light of these recent research developments, our team analyzed the microbiome in gastric samples at each stage of gastric carcinogenesis and the correlation of microbiome of oral and gastric juice in order to study the correlation between gastric cancer development mechanism and the microbiome. H. pylori was isolated at each stage of gastric carcinogenesis and EVs derived from H. pylori were studied to further eludicate the pathogenesis of the gastric cancer. Also, EVs secreted by intestinal epithelial cells were isolated and studied to elucidate the immunological meaning.

Here we will present the meaning of alterations in the gastrointestinal microbiome in gastric cancer development and the role of microbial EVs in the development of gastric disease. Additionally, we will show the meaning of EVs secreted by intestinal epithelial cell related the modulation of host immune system.

KDDW 2019 Korea Digestive Disease Week

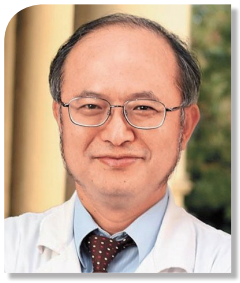
DAY 1

November 28 (Thursday)

[14:40-15:20, Diamond Hall]

Special Lecture (KCHUGR) English

Chair: **Jae Gyu Kim** (Chung-Ang University Hospital, Korea)



Personalized nutrition and gut microbiota

Ming-Shiang Wu, MD., PhD.

Department of Internal Medicine, National Taiwan University, Taiwan, Taiwan

Diet is not only essential to maintain our health but also linked to chronic metabolic conditions such as obesity, type 2 diabetes and cardiovascular disease. Type, quality and origin of our food shape out gut microbes and affect their composition and function. Recent researches have revealed dietary nutrients interact directly with gut microbes and lead to the production of beneficial or detrimental metabolites, impacting host physiology and leading to disease. Studies in humans and animal models have unraveled the host-nutrient-microbe interactions and increasing evidence suggests diet can be used for modulation of gut microbial ecology to promote health. The gut microbiota dependent metabolite, trimethylamine N-oxide (TMAO), was proved to contribute to atherosclerosis and increase the cardiovascular event. We have developed an oral carnitine challenge test (OCCT) for clinical assessment of individual TMAO production. The TMAO-producer phenotypes by OCCT may serve as a personalized dietary guidance for patients with cardiovascular diseases.

KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

[16:00-17:30, Convention Hall A+B]

Symposium 04 (KASL3) Korean

Recent updates in management of liver diseases

Chairs: **Kwang-Hyub Han** (Severance Hospital, Korea)

Han Chu Lee (Asan Medical Center, Korea)

Clinical development of new HBV therapies

Sang Hoon Ahn, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Yonsei University College of Medicine, Seoul, Korea

Chronic hepatitis B virus (HBV) infection is a major global health problem especially in the Asia-Pacific region where more than 40 countries are encompassing a wide geographic area with a large population. It may cause progressive liver fibrosis leading to cirrhosis with end-stage liver disease, and a markedly increased risk of hepatocellular carcinoma (HCC).

Substantial progress has been made in the treatment of chronic hepatitis B in the last two decades. There are currently seven approved drugs for the treatment of chronic hepatitis B: two formulation of interferon (IFN)-conventional and pegylated IFN, and five nucleos(t)ide analogues (NAs)-lamivudine, telbivudine, adefovir, entecavir and tenofovir.

However, HBV is often reactivated after stopping NAs because NAs alone do not directly target covalently closed circular DNA (cccDNA), which is the template for all viral RNAs. Therefore, although suppression of HBV replication is achieved in the majority of patients with currently available antiviral therapies, HBsAg loss is rarely achieved in Asians despite many years of antiviral treatment (only less than 10% of HBsAg loss in 5 years).

Various clinical trials have been conducted on agents that terminate the HBV life cycle in hepatocytes, including inhibitors of HBV-DNA polymerase, virus entry, core assembly, and secretion of hepatitis B surface antigen (HBsAg). A variety of therapeutic agents against HBV are currently in clinical development, including immunomodulatory agents, RNA interference agents, inhibitors of HBsAg release, inhibitors of nucleocapsid assembly, and agents that target cccDNA.

Potential treatment strategies and new agents are emerging to cure HBV. A combination of current and new anti-HBV agents may increase the rate of HBsAg seroclearance; thus, optimized regimens must be validated. Here, we will review the newly investigated therapeutic compounds and the results of preclinical and/or clinical trials.

Management of diabetes and dyslipidemia in patients with nonalcoholic steatohepatitis

Seung-Hyun Ko, M.D., Ph.D.

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Non-alcoholic fatty liver disease (NAFLD) is one of the most important causes of liver disease worldwide. The global prevalence of NAFLD is currently estimated to be about 25%, and the prevalence of NAFLD and non-alcoholic steatohepatitis (NASH) is constantly increasing.

NAFLD and NASH is known to be highly related to several metabolic disorders such as type 2 diabetes (T2DM), obesity, the metabolic syndrome, hypertension and hyperlipidemia. Therefore, it is expected that the incidence of NAFLD should rise steadily in parallel to the increasing incidence of obesity and T2DM. Accordingly, the management of NAFLD and NASH should consist oftreating liver disease as well as the associated metaboliccomorbidities such as obesity, hyperlipidemia, insulin resistance, andT2DM.

To date, lifestyle modifications including energy restriction, weight loss, increased physical activity, and dietary changes remain the treatment of choice for NAFLD/NASH. Recent studies have demonstrated that overall weight loss is the key to improvement in the histopathological features of NASH. In a meta-analysis of eight randomized, controlled trials with posttreatment histology, those adults who were able to lose at least 5% of body weight had improvement in hepatic steatosis, whereas >7% body weight reduction was associated with improved histological disease activity in NASH. Regular moderate-intensity aerobic exercise should be recommended in lifestyle modification for patients with NASH to enhance whole body lipid oxidation and improve steatosis and cardiometabolic risk profile.

For patients with NASH not responding to lifestyle modification, pharmacological treatment should be considered. Currently, there are no approved effective pharmacologic agents for management of NAFLD/NASH for long-term safety and efficacy concern. But, some clinical trials show promising results to target NAFLD/NASH therapeutically. Among them, thiazolidinediones (TZDs), statins, PUFA, and antioxidants have been most extensively evaluated. In addition, vitamin E (antioxidant), pentoxifylline (anti-tumor-necrosis factor-a agent), Obeticholic acid (farnesoid X receptor antagonist), cenicriviroc (CCR2/CCR5 inhibitor), elafibranor (PPARα/δ agonist), and selonsertib (ASK1 inhibitor) have different molecular targets.

Pioglitazone improves steatosis and hepatic inflammation, slow fibrosis progression, and ameliorate glucose and lipid metabolism, and subclinical inflammation with more consistent cardiovascular benefits.

In a meta-analysis, treatment with pioglitazone reversed the more advanced stages of liver disease in NASH regardless of the presence of diabetes. Glucagon-like peptide-1 receptor agonists (liraglutide, lixisenatide, exenatide) are good candidates for the treatment of NAFLD/NASH because they can reduce weight and enhance insulin action. However, it is not currently recommended for the treatment of NAFLD in patients with T2DM because of limited data. Sodium-glucose cotransporter-2 inhibitors (dapagliflozin, empagliflozin, ipragliflozin), can prevent progression of hepatic fibrosis in patients with T2DM and NAFLD who have pre-existing significant liver fibrosis.

Statins significantly improved aminotransferases and cardiovascular outcomes in patients with elevated aminotransferases presumed attributed to NAFLD. Thus, it is reasonable to incorporate lipid-lowering therapy in patients with NAFLD who meet criteria based on current recommendations. However, all lipid-lowering agents, such as ezetimibe, fibrates, niacin, omega-3 polyunsaturated fatty acids, and colesevelam, have not shown consistent results of hepatic steatosis improvement in patients with NAFLD.

The current body of evidence shows bariatric surgery to be beneficial for NAFLD/NASH. In clinical trials and meta-analysis, bariatric surgery lead to complete resolution in histologic features of NAFLD as well as a significant reduction of NAFLD activity score in a substantial proportion of patients.

So, lifestyle modification plus anti-diabetic drugs are likely to have a synergistic effect on reducing the risk factors associated with cardiovascular risk and decreasing hepatic fat accumulation in NASH patients, thereby delaying the progression of inflammation and fibrosis. Therefore, all patients, especially those with T2DM, should be strongly encouraged to adopt both lifestyle changes and anti-diabetic medication.

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Autoimmune hepatitis in real practice

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Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease of unknown etiologies that leads to destruction of the hepatic parenchyma if left untreated. The prevalence of AIH varies widely according to geographic region and ethnicity, ranging from 4.8 per 100,000 persons in South Korea to 24 per 100,000 persons in Europe. AIH is a relatively rare disease with a lower prevalence than other common liver diseases, and this rarity hampers a large-scale clinical studies. Despite the wide clinical spectrum of AIH, the long-term prognosis of AIH patients is believed to be relatively good, if the disease is diagnosed early and treatment is started promptly. However, AIH frequently recurs and consequently lifelong immunosuppressive treatment is required in most cases. According to international guidelines concerning AIH, normalization of alanine aminotransferase (ALT) alone or together with normalization of immunoglobulin G (IgG) is regarded as an indicator of remission and is recommended as a treatment target. Resolution of these laboratory parameters is deemed to ablate liver inflammation because liver biopsy to confirm improvement may be an unattractive option, considering its complications and sampling bias. As surrogate markers in real clinical practice, ALT and IgG are easily assessed to evaluate the treatment efficacy. However, the long-term prognosis of patients who achieve complete biochemical remission (CBR) in comparison with patients who achieve only biochemical remission (BR) is uncertain, particularly in AIH patients in Asian countries. Thus, we aimed to compare the long-term prognosis of AIH patients who achieve CBR and those who achieve only BR. We also monitored liver function parameters and fibrosis related scores during the treatment period.

A total of 291 patients (89.7% female) diagnosed with AIH were retrospectively reviewed in our center. CBR was defined as normal ALT and IgG levels with immunosuppression, while BR was defined as normal ALT levels. CBR was further divided into early CBR (<1 year) and late CBR (≥1 year) by the timing of remission. Liver-related adverse outcomes including liver-related death, liver transplantation, and hepatocellular carcinoma were evaluated. With immunosuppressive treatment, 222 (76.3%) patients achieved CBR (early CBR: 168 and late CBR: 54). BR was achieved in 55 (18.9%) patients and 14 (4.8%) patients remained non-remission. With a median follow-up duration of 6.6 years, the risk of liver-related mortality was the lowest in patients with CBR, followed by patients with late CBR, BR and non-response. The cumulative risk of liver-related adverse outcomes was the highest in patients with non-responder (8.51/100 person-years [PYs]), followed by BR (1.95/100 PYs), late CBR (1.89/100 PYs) and early CBR (0.75/100 PYs). By multivariable analysis, age, cirrhosis, and treatment responses were independently associated with liver-related adverse outcomes.

Upon initiation of immunosuppressive treatment, liver function started to improve immediately and the fibrosis score subsequently improved. Patients who achieved early CBR had a lower risk of liver-related adverse outcomes compared to patients who achieved late CBR or BR. The long-term clinical outcomes did not differ between patients with late CBR and patients with BR. Our results suggest that CBR, particularly early CBR is a more reliable surrogate marker than BR to reflect long-term clinical outcomes in patients with AIH.

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Local ablation therapy of hepatocellular carcinoma

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INTRODUCTION

Liver transplantation, surgical resection, and local ablation therapy such as radiofrequency ablation (RFA) are known as curative treatments for patients with hepatocellular carcinoma (HCC). Especially, local ablation therapy is preferred in patients at early stage who are not candidates for surgical resection because of poor residual liver function or tumor location. However, there are limitations to perform the RFA in tumor larger than 2.5-3.0 cm, multifocal, near major vascular or biliary structures, and inconspicuous tumor. Recently some methods or techniques been proposed to overcome this. In this session, I review the main local ablation therapies for HCC, and describe some of the recent methods or techniques to overcome the limitations of the local ablation therapies.

LOCAL ABLATION THERAPY FOR HCC

1. Percutaneous ethanol injection (PEI)

PEI was the first ablative technique used for HCC. PEI induces coagulative necrosis of the lesion as a result of cellular dehydration, protein denaturation, and chemical occlusion of small tumor vessels. Although PEI is known to induce about 90% of necrosis in HCCs less than 2 cm, it is reported that recurrence rate up to 49% in patients with HCCs larger than 2 cm who underwent PEI.[1]

2. Radiofrequency ablation (RFA)

RFA is a localized thermal treatment technique designed to induce tumor destruction by heating the tumor tissue to temperatures that exceed 60°C.[2] The thermal injuries in RFA are based on the frictional heat generated using high-frequency alternating current. RFA is widely accepted as the most important ablative modality in patients with three or fewer HCCs less than 3 cm in diameter who are not suitable for surgery. RFA has several limitations including limited ablation volume, difficulty performing depending on the location of tumor (close to the gallbladder, diaphragm, major vessels, or bowel), and heat-sink effect.[3]

3. Microwave ablation (MWA)

MWA uses electromagnetic fields to heat tissue resulting in the destruction of tumor cells surrounding the microwave antenna.[4] Commercial MWA systems work in the range of 915 MHz–2.45 GHz, delivering power up to 100 W. It can reach high temperature (100-150°C) around the probe more rapidly than RFA, which enables larger ablation volume in a shorter time period. Another advantage is that it is less susceptible to heat sink effects from adjacent large vessels. Although MWA has many advantages over RFA, more clinical research is warranted on safety and effects.

4. Others

Several methods using various energy sources such as cryoablation, laser ablation, high-intensity-focused ultrasound ablation, and irreversible electroporation have been developed and adopted for the treatment of malignant liver tumors.

5. Techniques to overcome the limitations of the local ablation therapies

Local ablation therapies with artificial pleural effusion and/or ascites are useful for tumors located on the liver surface and in the hepatic dome. Fusion imaging between the real-time ultrasound and reference CT/MR images or contrast-enhanced ultrasound can be used for inconspicuous lesions on conventional ultrasound.[5]

CONCLUSIONS

Various methods and techniques in local ablation therapy for HCC have been developed to increase effectiveness and reduce side effects. Local ablation therapy should be considered to improve survival in patients with early stage HCC who are not suitable for surgery.

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KDDW 2019 Korea Digestive Disease Week

DAY 1
November 28 (Thursday)

[16:00-17:30, Convention Hall C]

In-depth Symposium 04 (KSG) English

New hope for treating pancreatic cancer

Chairs: **Volker Ellenrieder** (University Medical Center, Germany)
Ho Soon Choi (Hanyang University Medical Center, Korea)

Direct targeting oncogenic Ras mutants by IgG-format cytosol-penetrating antibody

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Oncogenic Ras mutants, and most frequently KRas mutants (86% of Ras-driven cancers), are found in approximately 25% of human cancers and are high-priority anticancer drug targets. Despite 30 years of effort to develop drugs that directly target oncogenic Ras mutants, no effective pharmacological inhibitors for these mutants are clinically available, mainly because of the lack of suitable surface binding pockets for small molecules.

More than 50 therapeutic antibodies have been clinically approved against many extracellular proteins. However, such antibodies do not have the capacity to localize in intracellular cytosolic regions after receptor-mediated endocytosis, restricting their therapeutic application for targeting cytosolic proteins.

Our group recently developed a platform technology of cytosol-penetrating antibody, which in the IgG format can reach the cytosolic space of living cells owing to its endosomal escaping ability after receptor-mediated endocytosis. Exploiting the cytosol-penetrating antibody technology, we have engineered a human IgG1 format antibody, named iMab (internalizing & protein-protein interaction (PPI) interfering monoclonal antibody), which internalizes into the cytosol of living cells and selectively binds to the activated GTP-bound form of oncogenic Ras mutants. iMab specifically binds to the PPI interfaces of activated Ras with effector proteins to block the associations, thereby inhibiting the Ras downstream oncogenic signaling and exerting anti-proliferation effects on oncogenic Ras mutant tumor cells. For in vivo anti-tumor efficacy assessment, we further engineer iMab to have tumor tissue homing ability by fusion of tumor-associated integrin $\alpha v\beta 3/\alpha v\beta 5$ binding cyclic peptide to the N-terminus of light chain. When systemically administered, the iMab variant significantly inhibited the in vivo growth of oncogenic Ras-mutated tumor xenografts in mice, but not wild-type Ras-harboring tumors.

Our results demonstrate the feasibility of developing antibody therapeutics that directly target cytosolic proteins involved in disease-associated PPIs, such as oncogenic Ras mutants, by systemic administration, similar to conventional therapeutic antibody regimens. Because the oncogenic Ras targeting antibody holds many desirable features of the conventional IgG antibody, it shows great potential for development as a first-in-class anticancer antibody.

Extracelluar vesicles (EVs): exosomes and microvesicles

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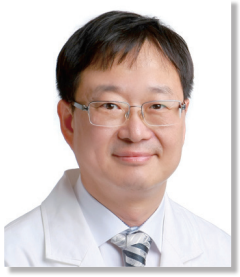
Department of Life Sciences, POSTECH, Pohang, Korea

The secretion of nano-sized lipid bilayered exosomes is a universal cellular process occurring from simple organisms to complex multicellular organisms. Recent progress in this area has revealed that exosomes, also known as extracellular vesicles and microvesicles, play multiple roles in intercellular and interspecies communication, suggesting that exosomes are NanoCosmos, i.e., extracellular organelles that play diverse roles in intercellular and interkingdom communication (http://evpedia.info). This presentation will briefly introduce the state-of-art exosome research and focuses on our recent progress in novel mammalian and bacterial exosome-mimetic technology for targeted drug delivery, theranostics, and epigenetic reprogramming as well as for adjuvant-free, non-toxic vaccine delivery system against bacterial infection.Moreover, bacterial exosome-based cancer immunotherapy will be introduced. Future research directions on our exosome isolation technology 'ExoLutE' for basic researches and clinical applications will be briefly introduced.



Targeting altered metabolism in pancreatic cancer

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Department of Division of Cancer Biology, National Cancer Center, Goyang, Korea

Cancer specific metabolism has been discovered about 90 years ago, which is known as the Warburg effect. Since then, many researchers looking for a cure to cancer have been thwarted, because most biochemical metabolic pathways were not discovered at the time. Recently, cancer therapy has made a significant change in heading toward regulating the immune system, despite the fact that most cancers are not induced by mutation of the immune system. This implies a very important shift in focus, from what causes cancer to how we can cure cancer. The real matter resides in the question of how we can distinguish cancer cells from normal cells. Cancer metabolism is quickly becoming a major drug target for the treatment of a variety of cancers. Cancer specific metabolic inhibitor enasidenib has been approved for acute myeloid leukemia therapy (2017) by the US FDA and will likely continue to expand. A series of studies on cancer specific metabolic dependency may find use of the list of metabolic inhibitors as therapeutic agents. That will be the ultimate answer for how we can kill only cancer when systemically mixed with normal cells. This talk focuses on the connection between cancer specific metabolism and their possibility as therapeutic targets, with an emphasis on novel inhibitors and new therapeutic possibilities targeting metabolic pathways. Finding cancer specific metabolic target is the hard core of Biochemistry, which is understood by the mechanism of Molecular Biology as well as by the cancer specific mutations.

Establishment of PDAC organoids model using EUS-guided tissue biopsy: a new window into understanding PDAC and drug discovery

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KDDW 2019 Korea Digestive Disease Week

DAY 1

November 28 (Thursday)

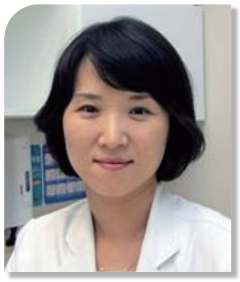
[16:00-17:30, Emerald Hall A]

PG Course 04 (KCHUGR) Korean

Recent updates in UGI diseases

Chairs: **Sang Young Seol** (Inje University Busan Paik Hospital, Korea)

Sang Woo Lee (Korea University College of Medicine, Korea)



Recent update in *Helicobacter pylori* infection

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Although *Helicobacter pylori* (*H. pylori*) infection is on the decline, it isvery prevalent as one of the most common infectious diseases in the world. It leadsto several gastrointestinal pathology including peptic ulcer disease, mucosaassociated tissue lymphoma and gastric cancer. The most important antibioticsin the treatment of *H. pylori* areclarithromycin, metronidazole, and amoxicillin. Antibiotics resistance plays animportant role in the failure of eradication treatment. Clarithromycinresistance rates have now passed where clarithromycin-based triple therapycannot be considered valid. Interest in the sequential, concomitant, and hybridtherapies does not appear as strong as it was some years ago, however, it canbe recommended as an alternative to standard triple therapy. Bismuth quadrupletherapy may be recommended as a first line or rescue regimen. Tailored (susceptibilityguided) therapy may be one of the option for *H. pylori* eradication with cost effectiveness in high antibioticsresistance era. High dose PPIs or potassium pump inhibitors, may help partiallyovercome clarithromycin resistance, but need to be robustly examined. Also weneed a well-designed education program to improve the adherence.

Table. Current management of *Helicobacter pylori* eradication

Regimen	Duration, days	Drugs used	Notes
Triple therapy	7–14	PPI (standard dose) bid, amoxicillin 1 g bid and clarithromycin 0.5 g bid	First line therapy in areas with low clarithromycin resistance
Sequential therapy	10	1st 5 days: PPI (standard dose) bid and amoxicillin 1 g bid 2nd 5 days: metronidazole 0.5 g bid and clarithromycin 0.5 g bid	First line therapy
Concomitant therapy	7–10	PPI (standard dose bid), amoxicillin 1 g bid, metronidazole 0.5 g bid and clarithromycin 0.5 g bid	First line therapy
Hybrid therapy	10-14	1st week: PPI (standard dose) and amoxicillin 1 g bid 2nd week: PPI (standard dose), amoxicillin 1 g, metronidazole 0.5g/ clarithromycin 0.5g bid	First line therapy
Bismuth-containing quadruple therapy	10–14	PPI (standard dose) bid, tetracycline 0.5 g qid, metronidazole 0.25 g qid and bismuth standard dose qid	First line or second line therapy
Levofloxacin-based triple therapy	10	PPI (standard dose) bid, levofloxacin 0.5 g qid and amoxicillin 1 g bid	Second line therapy if there is no fluoroquinolone resistance
Levofloxacin-based quadruple therapy	10	PPI (standard dose) bid, bismuth standard dose qid, levofloxacin 0.5 g qid and amoxicillin 1 g bid	Third line therapy if there is no fluoroquinolone resistance
Culture-guided therapy	10	PPI (standard dose) bid, bismuth standard dose qid and two antibiotics selected by sensitivity tests	Third line therapy
High-dose dual PPI therapy	14	PPI (high dose) qid and amoxicillin 0.5 g qid	Third line therapy
Rifabutin triple therapy	14	PPI (standard dose) bid, rifabutin 0.15 g bid and amoxicillin 1 g bid	

Recent updates in treatment of drug-induced PUD

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1. NSAIDS-ASSOCIATED UPPER GI DISEASE

As number of patients and related medical cost of arthritis is significantly increasing in Korea, total prescription amount of nonsteroidal anti-inflammatory drugs (NSAIDs) would inevitably increase, which in turn, may lead to serious adverse events including injury of upper gastrointestinal (UGI) tract. Several previous pivotal studies demonstrated that annualized incidence of UGI clinical events from non-selective NSAID which include uncomplicated symptomatic ulcers and their complications were 2.7~4.5%, and that of UGI complications were 1.0~1.5%.[1-4] A previous Korean cohort study showed that prevalence of *H. pylori* infection in Korea significantly decreased from 1995 to 2000, however, that of peptic ulcer (PU) and gastric ulcer (GU) significantly increased, which might be caused by increased use of NSAIDs, while that duodenal ulcer (DU) did not change.[5] Concerning predominant age, a recent Korean study showed that peak incidence of UGI bleeding in patients with osteoarthritis ranged from 70 to early 80, and was significantly higher than overall population among subgroup who had no *H. pylori* infection.[6] One of main risk factors for asymptomatic PU is also known as long-term NSAID use, especially for GU, and serious complications such as perforation may occur in NSAID-associated PU, which is especially predominant among elders and patients with comorbidities.[7] Taken together, NSAID-associated UGI injury is often asymptomatic and occurs more frequently among old age with comorbidities. These clinical manifestations are expected to contribute to the development of serious complications such as bleeding and perforation. Underlying mechanisms of NSAID-related UGI injury are roughly classified as 1) direct topical injury; and 2) systemic effect by inhibition of COX-1, and the latter is considered as the main mechanism. Interaction between NSAID and *H. pylori* NSAIDs are not well understood, however, both may act each other as additive/synergistic, or antagonistic. However, clinical data showed that prevalence of PU among NSAID users is significantly higher in patients with *H. pylori* infection than patients without *H. pylori*,[8] and *H. pylori* infection may contribute to the increase of the risk of NSAID-related GI complications.[9] By previous data and guideline statements, it is recommended that high-risk patients receiving long-term NSAID therapy take low dose of PPI for prevention of peptic ulcer and its complication, and if risk of cardiovascular disease is low, use selective COX-2 inhibitor is recommended as the long-term NSAID therapy for prevention of peptic ulcer and its complication.

2. NSAID-INDUCED PU AND *H. PYLORI*

Several studies showed the role of *H. pylori* infection in NSAID-induced PU, and a recent meta-analysis showed that prevalence of PU among NSAID users is 3 times more frequent in *H. pylori* positive group than negative group (odds ratio (OR) 3.08, 95% confidence interval (CI) 1.26-7.55).[8] That is, *H. pylori* infection is one of the major cause of NSAID-induced GI complications including PU, and *H. pylori* infection and NSAID use are independent and synergistic risk factors for complicated or uncomplicated PU.[10] Several studies reported the effect of *H. pylori* eradication for primary prevention of NSAID-induced PU, and Vergara et al published a meta-analysis that *H. pylori* eradication significantly reduced the prevalence of PU among NSAID users without history of PU (OR 0.43, 95% CI 0.20-0.93), and such effect is more prominent among NSAID-naïve patients (OR 0.26, 95% CI 0.14-0.49) rather than chronic users (OR 0.95, 95% CI 0.53-1.72).[11] However, there are some debate about secondary prevention. Chan et al[12] compared *H. pylori* eradication alone with omeprazole for one week among NSAID-naïve patients with history of PU, and the prevalence of overall and complicated PU is significantly lower in *H. pylori* eradication alone group. Meanwhile, Pilotto et al[13] showed that gastric mucosal injuries such as ulcers or erosions among NSAID-naïve old patients with history of PU were significantly more frequent in eradication alone group than pantoprazole-treated group (29.9 vs. 9%, p=0.03). Furthermore, Chan et al reported another pivotal study, which included naproxen users with history of PU bleeding, and rebleeding rate after 6 months was significantly higher in *H. pylori* eradication group than omeprazole maintenance group (18.8 vs. 4.4%, p=0.005).[14] Based on previous studies, American (American Colleague of Gastroenterology),[15] Japanese (Japanese Society of Gastroenterology)[16] and Korean (Korean College of Helicobacter and Upper Gastrointestinal Research)[17] guidelines for *H. pylori* treatment recommended that *H. pylori* eradication may be effective for prevention of PU among NSAID-naïve patients, but not among chronic NSAID-users.

3. LDA-INDUCED PU BLEEDING AND *H. PYLORI*

Several studies showed the role of *H. pylori* in the formation of PU among LDA users. Lanas et al[18] published a case-control study which showed that *H. pylori* infection is an independent and significant risk factor for UGI bleeding among LDA users (adjusted OR 4.69, 95% CI 2.02-10.91). Recent Maastricht V/Florence Consensus Report stated that *H. pylori* infection is a significant risk factor for PU among aspirin users as well as NSAID users, and concomitant use of antiplatelet or anticoagulant agent may increase the risk of ulcer bleeding.[19]

Few studies showed the effect of *H. pylori* eradication for primary prevention of PU among LDA users, and a current on-going study of randomized, placebo-controlled study have followed up LDA users with *H. pylori* infection for 2.5 years (Helicobacter Eradication Aspirin Trial(HEAT)), and it is expected to demonstrate the effect of eradication for primary prevention of PU among LDA users.[20] Meanwhile, several studies showed the effect of eradication for secondary prevention of PU among long-term LDA users, and aforementioned study by Chan et al[14] showed the similar rebleeding rate between eradication alone group and omeprazole maintenance group among LDA users with history of ulcer bleeding (1.9% vs. 0.9%, 95% CI 1.9-3.9, p>0.05). However, Lai et al[21] compared observation group and lansoprazole maintenance group after *H. pylori* eradication among LDA users with history of PU bleeding, and showed that rebleeding rate was significantly lower than lansoprazole maintenance group (14.8 vs. 1.6%, p=0.008). Meanwhile, a recent cohort study by Chan et al[22] subdivided long-term LDA users with history of PU bleeding as 3 cohort (*H. pylori*-eradicated group, *H. pylori* negative group, average-risk group) and followed up for more than 10 years. This study showed that the incidence of ulcer bleeding (per 100 patient-years) in the *H pylori*-eradicated cohort (0.97; 95% CI, 0.53-1.80) did not differ significantly from that of the average-risk cohort (0.66; 95% CI, 0.38-0.99), however, concomitant use of drugs which may cause UGI bleeding (i.e. antiplatelet agent, anticoagulant) significantly increase the incidence rate in *H. pylori*-eradicated cohort than average-risk cohort (incidence rate ratio 7.01, 95% CI 2.25-21.89). Therefore, we can assume that *H pylori* eradication may be effective for prevention of rebleeding among patients who take LDA only, however, co-therapy with anti-ulcer agent such as PPI may be necessary if patients concomitantly use antiplatelet agent or anticoagulant. Aforementioned Japanese guideline stress on the maintenance of PPI after *H pylori* eradication among LDA users with history of PU bleeding,[16] however, Korean guideline stated the necessity of *H pylori* eradication among long-term LDA users with history of PU bleeding.[17]

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Recent updates in diagnosis and treatment of gastric SET

Yonghwan Kwon, M.D., Ph.D.

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With the wide use of esophagogastroduodenoscopy, gastrointestinal subepithelial tumors (SETs) are generally found and their incidence has gradually increased. Most SETs are asymptomatic and therefore clinically insignificant, however, carcinoid tumors, lymphomas, glomus tumor and gastrointestinal stromal tumors (GISTs) are malignant or have the potential to become malignant. Therefore it is important to distinguish malignant from benign lesions. For the accurate diagnosis of SETs, endoscopy alone is not reliable. Accurate diagnosis can be achieved with endoscopic ultrasonography (EUS), which provides useful information on the exact size, layer-of-origin, and characteristic morphologic features to support a definitive diagnosis. Histology is the "gold standard" to differentiate between the different types of SETs, however this evaluation can only be obtained through invasive techniques such as endoscopic mucosal resection, fine-needle aspiration (EUS-FNA), or surgical resection. In follow-up studies of asymptomatic upper gastrointestinal tract subepithelial lesions, the lesions increased in size in fewer than 10% of patients. Previous Korean study which evaluated 989 gastric SETs <30 mm in size using endoscopy or EUS. The changes of lesions were significant in size, echogenicity, or surface integrity in 84 (8.5%) of the patients, and 21 showed alterations in echo patterns and size. The prognosis of patients with GISTs in the stomach is relatively good compared with GISTs in other organs. Along with the location of the tumor, its size and mitotic count are major factors that determine the malignant potential of GIST. Small (<2 cm) asymptomatic GISTs usually have benign clinical course. Asymptomatic subepithelial lesions smaller than 2 cm usually have a benign course, and it is recommended that they be managed by periodic surveillance using endoscopy or EUS. GIST proven by biopsy should be removed completely regardless of tumor size For the treatment of gastrointestinal SETs, surgical resection was exclusively chosen as initial treatment, previously. Although the indications for the endoscopic treatment of patients with SETs remain to be established, the feasibility and safety of endoscopic dissection, including the advantages of this method compared with surgical treatment, have been validated in many studies. The development of endoscopic techniques, such as endoscopic submucosal dissection, endoscopic enucleation, endoscopic excavation, endoscopic submucosal tunnel dissection, submucosal tunnel endoscopic resection, and endoscopic full-thickness resection has enabled the removal of SETs while reducing the occurrence of complications.

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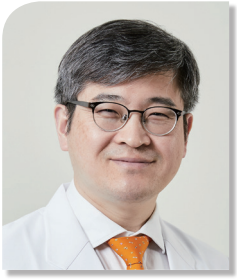

Recent updates in treatment of non-variceal upper gastrointestinal bleeding: Introduction of new Korean guideline

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Department of Internal Medicine-GI/Hepatology, Incheon St. Mary's hospital, The Catholic University of Korea, Incheon, Korea

Non-variceal upper gastrointestinal bleeding (NVUGIB) is one of the most commonly encountered medical emergency. Some guidelines have been introduced from Asia-Pacific area, Europe, and Japan, but Korean guideline has not been established yet. Recently, Committee of Guideline, Korean Society of Gastroenterology developed a new guideline for NVUGIB in association with Korean Society of Gastrointestinal Endoscopy, Korean College of Helicobacter and Upper Gastrointestinal Research, Korean Gastric Cancer Association, and Korean Society of Interventional Radiology. This guideline was made from adaptation of other guidelines. In this session, the new Korean guideline will be discussed.

KDDW 2019 Korea Digestive Disease Week

DAY 1
November 28 (Thursday)

[16:00-17:30, Emerald Hall B]

Multidisciplinary Session 02 (KSNM-KASID-KSCP) Korean

Colonic pseudo-obstruction: still unknown motor disorder but clinicians should know

Chairs: **Kyu Joo Park** (Seoul National University Hospital, Korea)
Seung-Jae Myung (Asan Medical Center, Korea)

What is colonic pseudo-obstruction?

Kee Wook Jung, M.D., Ph.D.

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The term of *pseudo-obstruction* refers to the failure of the propulsive forces of intestinal peristalsis to overcome the natural resistances to flow. Primary idiopathic chronic intestinal pseudo-obstruction (CIPO) is a rare disease in adult patients, with an estimated prevalence of less than 1 per 2000 people.[1] Diagnosis of CIPO requires the exclusion of mechanical obstruction in the gut, identification of underlying diseases responsible for the secondary manifestation of CIPO, and exploration of idiopathic CIPO and its possible complications, by performing radiological, endoscopic, laboratory, and other examinations.1 Theoretically, CIPO involves small bowel dysmotility confirmed with motility tests, including small bowel manometry, in combination with episodic or chronic signs mimicking a mechanical obstruction of the small bowel.[2] A radiological finding of dilated bowel should be present. Patients usually show a severe clinical course with frequent surgeries and need nutritional support. Sometimes, they need intestinal transplantation. Contrary to CIPO, enteric dysmotility is defined as a documented abnormal contractile activity, with no history of episodes or current signs mimicking mechanical obstruction.2

On the other hand, colonic pseudo-obstruction is a pseudo-obstruction confined to the colon, without involvement of small bowel dysmotility. A similar term is *megacolon*. A recent systematic review of acquired megacolon has proposed the diagnostic criteria for chronic idiopathic megacolon in adult patients. Diagnosis of megacolon requires the exclusion of organic disease, a sigmoid colonic diameter of more than 10 cm in radiological studies, and presence of constipation, distension, and abdominal pain. In Korea, patients with colonic dilation usually show a stricture area in the colon. These findings form a unique pattern that is not usual in Western patients. Most patients show relatively good prognosis after surgical procedures including subtotal colectomy.

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Radiologic diagnosis of colonic pseudo-obstruction

Hye Jin Kim, M.D.

Department of Radiology, Ajou University Hospital, Suwon, Korea

The role of radiological imaging in CIPO evaluation is to exclude all other possible mechanical obstructive diseases, access CIPO itself, and detect CIPO-related complications.

Simple radiography is useful for evaluating the degree of intestinal obstruction in CIPO patients and for serial follow-up these patients to confirm the improvement or recurrence of intestinal obstruction after medical of surgical treatment, but there is a limitation in ruling out the other possible obstructive lesions such as cancer. By contrast, CT and MRI can precisely access both inside and outside the intestinal wall as well as the intestinal wall itself as a cause of mechanical obstruction.

CT and MR imaging can help distinguish between the primary and secondary forms of CIPO although they have a limited role. The presence of an obvious transitional zone that represent an intermediate region located between the markedly dilated proximal and abruptly narrowed distal bowel suggests the possibility of CIPO of neurogenic origin, such as adult onset Hirschsprung's disease of segmental hypoganglionosis.

Moreover, CT and MR imaging can provide the location, extent, and degree of the distended bowel loops by tracing the bowel lumen. This is important because the above described findings can help predict the likelihood of CIPO related complications. Concurrent other abnormal lesions accompanied by secondary CIPO and indirect complications can be found incidentally on CT or MR imaging.

Follow through study is considered an accurate imaging study to evaluate the distended and narrowed bowel loops, but has rarely been used due to procedure related complications or patient noncompliance.

Recently, functional imaging studies have been added as a new imaging modality for GI motility evaluation, but further detailed studies are needed in the near future.

Medical approach of colonic pseudo-obstruction

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Acute colonic pseudoobstruction (ACPO, Ogilvie syndrome), is a rare clinical entity characterized by severe colonic distension in the absence of mechanical obstruction. The epidemiology of ACPO is unknown, but one study reported ACPO occurred in approximately 100 cases per 100,000 inpatient admissions. ACPO. The pathophysiology of ACPO is poorly understood, with the several hypotheses including inflammatory response, electrolyte disturbances, increased sympathetic drive, and reduced parasympathetic activity. ACPO excessively affects elderly and comorbid patients with acute illness on a background of cardiac, respiratory, kidney or neurologic diseases. The common description of ACPO has recently undergone abdominal or non-abdominal surgery. ACPO symptoms include abdominal pain, distension, nausea, and vomiting. In the diagnosis of ACPO, ruling out of the presence of any mechanical obstruction is essential. The initial management strategy for ACPO is a medical approach with good success rate. Conservative measures include correction of electrolytes and fluid imbalance, stop all opiates/constipation related medications, nasogastric tube decompression and encouraging ambulation, This measures may continue up to 72 hours if cecal diameter < 12 cm and no peritoneal signs. If conservative treatment fails, neostigmine can be administered in a cardiac monitored setting. For those patients who failed pharmacologic therapy, endoscopic decompression should be attempted. It should be noted that colonoscopic decompression requires specific expertise and more time. The technique has not listed for Korean insurance coverage. This lecture focuses on medical therapy and therapeutic endoscopy for the treatment of ACPO. Medical management of colonic megacolon and chronic intestinal pseudoobstruction is also reviewed.

Surgical approach of colonic pseudo-obstruction

Seung-Bum Ryoo, M.D., Ph.D.

Department of Surgery, Seoul National University Hospital, Seoul, Korea

Constipation is a common clinical problem with multiple etiologies, affecting approximately 16.5% of the population in South Korea and 5%-20% of the Western world. Most patients with constipation have various symptoms, representing different pathologic processes and including infrequent or difficult evacuation, abdominal pain, and bloating, which are often resistant to medical therapy or dietary manipulation. Constipation is believed to be frequently observed in women, elderly people, and those of low socioeconomic status. When chronic idiopathic constipation is diagnosed, a conservative treatment is generally conducted as a firstline treatment. If such a conservative treatment fails, surgical treatment is then considered. The British surgeon Lane first performed surgery for constipation in 1908. Since then, total colectomy (TC) with ileorectal anastomosis has been suggested as a standard option for the management of refractory chronic constipation. In our previous report, we demonstrated favorable surgical outcomes for patients with features of chronic pseudoobstruction (CPO) with distinct transitional zone (TZ).

We analyzed the long-term surgical outcomes of patients with chronic idiopathic constipation and features of CPO, and compare these results with treatment of patients with slow-transit constipation (STC). Consecutive 42 patients who underwent surgery for chronic constipation within the last 13 years were prospectively collected. We identified a subgroup with colonic pseudo-obstruction (CPO) features, with dilatation of the colon proximal to the narrowed transitional zone, in contrast to typical slowtransit constipation (STC), without any dilated colonic segments. The outcomes of surgical treatments for chronic constipation with features of CPO were analyzed and compared with outcomes for STC. Of the 42 patients who underwent surgery for constipation, 33 patients had CPO with dilatation of the colon proximal to the narrowed transitional zone. There were 16 males and 17 females with a mean age of 51.2 ± 16.1 years. All had symptoms of chronic intestinal obstruction, including abdominal distension, pain, nausea, or vomiting, and the mean duration of symptoms was 67 mo (range: 6-252 mo). Preoperative defecation frequency was 1.5 ± 0.6 times/wk (range: 1-2 times/wk). Thirty-two patients underwent total colectomy, and one patient underwent diverting transverse colostomy. There was no surgery-related mortality. Postoperative histologic examination showed hypoganglionosis or agangliosis in 23 patients and hypoganglionosis combined with visceral neuropathy or myopathy in 10 patients. In contrast, histology of STC group revealed intestinal neuronal dysplasia type B (n= 6) and visceral myopathy (n = 3). Early postoperative complications developed in six patients with CPO; wound infection (n = 3), paralytic ileus (n = 2), and intraabdominal abscess (n = 1). Defecation frequencies 3 mo after surgery improved to 4.2 ± 3.2 times/d (range: 1-15 times/d). Long-term follow-up (median: 39.7 mo) was available in 32 patients; all patients had improvements in constipation symptoms, but two patients needed intermittent medication for management of diarrhea. All 32 patients had distinct improvements in constipation symptoms (with a mean bowel frequency of 3.3 ± 1.3 times/d), social activities, and body mass index (20.5 kg/m^2 to 22.1 kg/m^2) and were satisfied with the results of their surgical treatment. In comparison with nine patients who underwent colectomy for STC without colon dilatation, those in the CPO group had a lower incidence of small bowel obstructions (0% vs 55.6%, $P < 0.01$) and less difficulty with long-distance travel (6.7% vs 66.7%, $P = 0.007$) on long-term follow-up. Chronic constipation patients with features of CPO caused by narrowed transitional zone in the left colon had favorable outcomes after total colectomy.

KDDW 2019 Korea Digestive Disease Week

DAY 2

November 29 (Friday)

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DAY 2

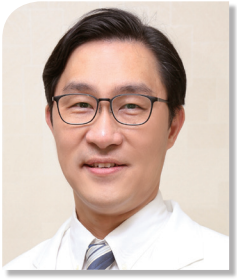
November 29 (Friday)

[07:30-08:30, Skylark]

MTP 01 (KASID) Korean

Meet the Professor

Chair: **Yoon Tae Jeen** (Korea University Anam Hospital, Korea)



Biologic therapies in IBD: past, present and future

Chang Hwan Choi

Department of Internal Medicine-GI/Hepatology, Chung-Ang University Hospital, Seoul, Korea

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease, is a chronic immune-mediated inflammatory disorder with multifactorial pathogenesis. Definite cause of IBD is unknown, but the disease is considered to be caused by a combination of genetic and environmental factors and gut microbiota leading to abnormal immune responses. The disease phenotypes of IBD vary widely in individual patients, and the main inflammatory mechanisms may be different in each patient, even if the disease phenotypes are similar.

Conventionally, 5-aminosalicylic acids, corticosteroids and immunomodulators, such thiopurine and methotrexate, have been used for the treatment of IBD, and recently, various biologic agents have been used for the better control of the disease, since the approval of infliximab in 1998. Presently, the mainstay of biologic treatments for IBD is anti-tumor necrosis factor (infliximab, adalimumab, certolizumab, and golimumab), anti-$\alpha 4\beta 7$ integrin (vedolizumab) and anti-interleukin (IL)-12/IL-23 (ustekinumab) therapies. Recently, a small molecule agent targeting Janus kinase (tofacitinib) has been approved to use in UC. The quality of life of IBD patients has improved greatly with the use of these agents. However, although the treatment options have recently expanded, it is not yet clear what the optimal treatment approach is. We are not yet sure at what point is the best to start biologics in individual patients, or whether combination therapy with immunomodulator is necessary. Also, which therapy to initiate, or which drug to try next remained largely uninformed. To solve these problems, head to head treatment trials and algorithmic strategy studies are needed. In addition, considering the different treatment response in individual patients, developing prediction model for each treatment is necessary to identify the next optimal therapy for the patients.

With the discovery of new pathways involved in the pathogenesis of IBD, new drugs are being developed that may be more effective and safe. The new drugs are targeting Janus kinase, adhesion and chemotaxis molecules, IL-6, spingosine-1-phosphate, phosphodiesterase 4, and others. Developing the better new drugs and identifying the optimal treatment strategies with currently available drugs are expected to improve the quality of life of patients with IBD in the future.

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DAY 2

November 29 (Friday)

[07:30-08:30, White Heron]

MTP 02 (KSGC) English

Meet the Professor

Chair: **Moo-In Park** (Kosin University Gospel Hospitalm, Korea)

Pancreatic cancer, GWAS, population stratification, genomics methods for post-GWAS analyses

Laufey Amundadottir, Ph.D.

Department of Laboratory of Translational Genomics, National Cancer Institute, National Institutes of Health, GAITHERSBURG, United States

Discussions will cover pancreatic cancer, cancer genetics (somatic and germline), identifying and fine-mapping inherited germline risk loci, cancer genomics (mapping noncoding regulatory elements, assessing histone modification marks, linking potential functional variants to gene expression or gene function).

KDDW 2019 Korea Digestive Disease Week

DAY 2

November 29 (Friday)

[09:00-10:30, Convention Hall A]

Symposium 05 (KCHUGR1) English

Limits and prospects of acid inhibitors

Chairs: **Yong Chan Lee** (Severance Hospital, Korea)

Shin Maeda (Yokohama City University, Japan)

Current long-term use of PPI in Asia

Kee Don Choi, M.D., Ph.D.

Department of Gastroenteroloy, Asan Medical Center, Seoul, Korea

Proton pump inhibitors (PPIs) are one of the most widely used drugs and are mainly prescribed for gastric acid-related diseases, and prevention of nonsteroidal anti-inflammatory drug (NSAID)-induced gastropathy.

Although PPIs have an excellent overall safety profile, adverse effects including bone fracture, dementia, myocardial infarction, enteric infections, micronutrient deficiencies, and kidney diseases, have been proposed. Many studies on the risk of long-term use of PPIs also been published in Asian countries. A recent study suggested that long-term use of PPI was associated with an increased risk of gastric cancer in Asian subject even after *Helicobacter pylori* eradication. The use of PPIs is associated with profound acid suppression, which could worsen atrophic gastritis. PPIs stimulate the production of gastrin, which is a potent growth factor, and hypergastrinemia has been shown to induce hyperplasia of enterochromaffin-like cells.

Despite the long list of potential adverse effects associated with PPI therapy, the quality of evidence underlying these associations is consistently low. Studies assessing PPI risks are retrospective observational studies. The intervention (PPI) is not assigned at random but is associated with patient characteristics. This results in differences between PPI users and non-users in factors that may impact study outcomes and confound results.

The recent randomized controlled trial by Moayyedi et al. showed that no statistically significant difference between the pantoprazole and placebo groups in safety events except for enteric infections (1.4% vs 1.0% in the placebo group; odds ratio, 1.33; 95% confidence interval, 1.01–1.75). For all other safety outcomes, proportions were similar between groups except for C. difficile infection, which was approximately twice as common in the pantoprazole vs the placebo group, although there were only 13 events, so this difference was not statistically significant. The authors concluded that the benefits are likely to outweigh the risks of these medications provided they are used for clinically appropriate indications.

In conclusion, it is important to prescribe PPIs only for patients who can get substantial clinical benefits. It is also important to continue to investigate adverse effects with high-quality prospective research.

PPI and GI tumor: Really associated?

Wai Keung Leung, M.D.

Department of Medicine, University of Hong Kong, Hong Kong

Proton pump inhibitor (PPI) is one of the top selling drugs in the world. With the potent acid suppression, it is probably the best treatment for gastroesophageal reflux and peptic ulcer diseases. It is also increasingly used in the prevention of gastrointestinal bleeding in patients taking anti-platelets or anti-coagulants. However, with the long-term potent acid suppression, it is invariably associated with disruption of normal gastric physiology resulting in hypergastrinemia, gastric atrophy and changes in gastrointestinal microbiota. These factors could potentially lead to increase in risk of gastric and even colonic cancer.

The role of PPIs on gastric cancer development remained controversial in the literature due to difference in patient's selection, indication and immortal time biases as well as the presence of *H. pylori* infection. Although one would presume that eradication of *H. pylori* could improve the chronic gastritis and possibly gastric atrophy, our recent data showed that the use of PPI even after *H. pylori* eradication would still increase the risk of gastric cancer development. In a population-based cohort of 63,397 *H. pylori* eradicated subjects, we found that the use of PPI would increase the risk of gastric cancer development by 2.4-fold [1]. There is also a significant trend of higher cancer risk with longer duration of PPIs. The use of H2-receptor antagonist, with less potent acid suppression, was however not associated with a higher risk of gastric cancer. Since the publication of our study, there are a few studies trying to investigate the association between PPI use and gastric cancer risk which all reached similarly positive findings. The Swedish study showed that the standardized incidence ratio (SIR) of gastric cancer with PPI use was 3.38 [2]. Three Asian studies also showed a significantly increase in gastric cancer risk among PPI users, ranging from 1.6 to 3.6-fold increase [3-5]. Nonetheless, in a recent randomized trial of 17,598 Canadian patients with median follow up 3 years, the use of PPI was not associated with a higher risk of all gastrointestinal cancer [6]. As yet, the negative association may be explained by the relatively short follow up in a low gastric cancer risk population.

On the other hand, whether the potential change in gut microbiota by PPIs would alter the risk of colorectal cancer remains to be confirmed in future studies.

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Is P-CAB really superior to PPI in *H. pylori* eradication?

Shin Maeda, M.D., Ph.D.

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BACKGROUND

Vonoprazan, a potassium-competitive acid blocker, is a new class of acid-suppressing agent. The acid-inhibitory effect of vonoprazan has been well documented. The *H. pylori* eradication rate of vonoprazan-based triple therapy (combined with amoxicillin and clarithromycin/metronidazole) (V-AC or V-AM) was reported to be higher than PPI-based triple therapy in a phase III study in Japan. To evaluate the efficacy of vonoprazan in real world, we performed several prospective studies for vonoprazan-based *H. pylori* eradication.

METHODS

1) To validate the first-line eradication rate of V-AC or PPI-AC using CAM-susceptible strains, multicenter, prospective, randomized trial was performed. 2) To assess the efficacy of vonoprazan-based first-line the eradication with penicillin allergy, V-CM regimen prospectively applied. 3) To establish the third-line therapy for the patients after failure of V-AC and V-AM, prospective, randomized trial of the efficacy of vonoprazan-based and PPI-based 7-day triple regimens with amoxicillin and sitafloxacin (V-AS) was performed.

RESULTS

1) No significant difference was observed between the V-AC (88.9%) and PPI-AC (86.7%) regimes in CAM-susceptible patients in per-protocol (PP) analysis. PP eradication rates of V-AC in the CAM-resistant patients were 82.9%. 2) In PP analyses, the eradication rate of the V-AS group (100%) was significantly higher than that of the PPI-AS group (82.7%) in patients with penicillin allergy. 3) In PP analyses, the third-line eradication rate of the V-AS group (83.3%) was significantly higher than that of the PPI-AS group (57.1%).

DISCUSSION AND CONCLUSION

1) The eradication rate of V-AC treatment in the CAM-susceptible H. pylori-infected patients was <90%, as was that by PPI-AC, thus V-AC is not ideal regimen in CAM-susceptible H. pylori. However, the 82.9% eradication rate of V-AC in the CAM-resistant infections may indicate the potential of V-AC with modified dose, dosing interval, and treatment duration. 2) Triple therapy with VPZ, CAM, and MNZ is well tolerated and effective for eradicating *Helicobacter pylori* in patients allergic to penicillin. 3) 7-day triple therapy with vonoprazan, amoxicillin, and sitafloxacin is more effective than proton-pump inhibitor, amoxicillin, and sitafloxacin as a third-line regimen for eradicating *H. pylori*. Overall, the vonoprazan-based triple therapy showed superior efficacy in terms of *H. pylori* eradication as compared to the PPI-based triple therapy.

GERD treatment: which is your choice between PPIs and P-CABs?

Beom Jin Kim, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Chung-Ang University Hospital, Seoul, Korea

Gastroesophageal reflux disease (GERD) is a troublesome condition that causes symptoms such as heartburn and acid regurgitation by reflux of stomach contents. GERD is prevalent in Western countries, and recently it has been dramatically increasing in many Asian countries. GERD includes erosive esophagitis (EE) and non-erosive reflux disease (NERD) diagnosed by esophagogastroduodenoscopy, but the severity of symptoms is not necessarily proportional to the degree of mucosal injury.

Generally, proton pump inhibitors (PPIs) have been the mainstay for the management of GERD. Indeed, PPIs have been beneficial in patients with both EE and NERD, and patients with EE showed 20% greater improvement of GERD symptoms than patients with NERD. Although PPIs are widely used in clinical practice, the standard dose of PPI does not always induce sufficient gastric acid suppression in all patients because of their pharmacological limitations. In fact, 10–20% of patients with severe EE (Los Angeles classification C and D) do not heal despite 8 weeks of continuous double-dose PPI therapy. Moreover, it has been well documented that achieving complete symptomatic relief with PPI is more difficult than simply healing mucosal breaks, resulting in dissatisfaction of current therapy in about one third of patients with GERD.

Recently, a novel potassium-competitive acid blocking agent (P-CAB) has been developed that is stronger, faster, and exhibits longer-lasting acid suppression than conventional PPIs. The acid-inhibitory effect of P-CAB has been reported to be more potent than that of PPIs, with greater impact against acid-related diseases such as GERD, *Helicobacter pylori* infection, gastric and duodenal ulcers, and prevention of recurrence in nonsteroidal anti-inflammatory-drug or low-dose-aspirin ulcer.

P-CAB may have an efficacy comparable to or better than that of PPIs in the treatment of GERD. There is a growing number of reports comparing the effectiveness of P-CAB with that of PPIs in treating GERD. However, the findings have been variable, and reported outcomes are conflicting. Therefore, it is necessary to assess and compare the effects of P-CAB and PPIs in the treatment of GERD. It is also important to provide useful clinical information on the choice of acid inhibitors in the management of GERD.

KDDW 2019 Korea Digestive Disease Week

DAY 2

November 29 (Friday)

[09:00-10:30, Convention Hall B]

Symposium 06 (KASID1) Korean

Optimal strategies of colonoscopy in LGI disease

Chairs: **Suk-Kyun Yang** (Asan Medical Center, Korea)

Sung-Ae Jung (Ewha Womans University Mokdong Hospital, Korea)

Endoscopic findings mimicking inflammatory bowel disease

Jaeyoung Chun, M.D.

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INTRODUCTION

Inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) is defined as an idiopathic chronic inflammatory disorder in the gastrointestinal tract showing a relapsing and remitting disease course. Based on the current guideline, a gold standard for diagnosis of CD and UC does not exist, and the diagnosis is established by clinical, laboratory, and radiologic imaging as well as endoscopic findings with histopathologic examinations.[1-4] Due to the ambiguous diagnostic criteria, the exact diagnosis of IBD is challenging in real practice. Other causes mimicking IBD such as infectious enterocolitis should be excluded before the diagnosis of IBD. Endoscopy is one of the most crucial diagnostic methods for IBD, and repeat endoscopy with histopathologic review by experts may be necessary in some cases with remaining diagnostic doubts. In this lecture, the endoscopic findings of IBD and other diseases mimicking IBD are discussed.

IBD

1. Ulcerative Colitis

In patients with UC, the inflammation involves the rectum and spreads proximally. The typical endoscopic findings of UC include edematous mucosa with erythema, loss of vascularity, and friability. More severe colitis has erosions, ulcers or spontaneous bleeding on the colonoscopic exams. Luminal narrowing, loss of haustration and inflammatory pseudopolyps can occur due to chronic relapsing colitis. Periappendiceal inflammation is noted in up to 75% of patients with UC.[5] Backwash ileitis can be observed in some patients with UC. Atypical distribution of inflammation such as skip inflammation and rectal sparing is also observed in approximately 20% of patients with newly diagnosed UC.[6]

2. Crohn's Disease

Typical endoscopic findings of CD include longitudinal direction of ulcers with cobblestone appearance mainly involved in the ileocecal area. Perianal inflammation such as ulcer, fistula and abscess can be observed in up to 50% of patients with CD. On the histopathologic evaluation, the presence of non-caseating granuloma suggests CD but the diagnostic usefulness may be low due to the sensitivity which ranges from 13 to 36%.[7]

OTHER DISEASES MIMICKING IBD

1. Intestinal Tuberculosis

Patients with intestinal tuberculosis have characteristic endoscopic findings similar to those of CD. Intestinal tuberculosis predominantly involves the ileocecal area and ascending colons, and shows ulcers with inflammatory pseudopolyps and fibrotic scars around the ileocecal valve. Compared to CD, however, the transverse direction of ulcers is a characteristic endoscopic finding of intestinal tuberculosis. On the histopathologic evaluation, the presence of ceseating granuloma with positive acid-fast staining and/or isolation of *M. tuberculosis* from the culture of biopsy specimen is a gold standard for diagnosing intestinal tuberculosis, but the sensitivity is relatively low.

2. Intestinal Behcet's Disease

Intestinal Behcet's disease has typical endoscopic findings including a single or a few, large-sized, round-shaped, deep and discrete ulcers with elevated margins in the ileocecal area. The presence of systemic manifestations such as recurrent oral ulcers, genital ulcers, and uveitis is required to diagnose intestinal Behcet's disease. Compared to CD, the absence of a cobblestone appearance and round-shaped ulcers are the most sensitive and specific findings indicative of intestinal Behcet's disease, respectively.[7] More focal distribution of inflammation also suggests intestinal BD rather than CD.

3. Infectious Colitis

Infectious colitis can present with endoscopic feature similar to those of UC, and should be excluded to make the correct diagnosis of UC.

4. Others

The other differential diagnosis of UC includes ischemic, drug-induced and radiation colitis, and solitary rectal ulcer syndrome. A history taking of clinical manifestations, medication use, radiation therapy or straining during defecation can be helpful to accurately diagnosing UC. Lymphoproliferative disorders and solid cancers are also considered as a possible differential diagnosis of IBD.

CONCLUSION

Atypical endoscopic findings of IBD make it hard to accurately diagnose IBD in real practice. Clinical manifestations, laboratory findings and radiographic imaging as well as endoscopic features with histopathologic evaluations should be considered comprehensively before the final diagnosis in patients with atypical endoscopic findings of IBD.

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How to conduct surveillance of dysplasia in IBD

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INTRODUCTION

Patients with longstanding ulcerative colitis and colonic Crohn's disease have an increased risk of colorectal cancer (CRC) compared with the general population. In contrast to these earlier studies, data published over the past 20 years have shown that most dysplasia is visible, in many populations in the incidence of colorectal cancer has decreased, and that precancerous lesions can be managed endoscopically in many cases and do not necessarily require removal of the colon. These data, in addition to improved techniques via the recognition of flat polyps, use of enhanced dysplasia detection techniques such as chromoendoscopy, technical advances in imaging such as high definition scopes, better control of underlying inflammation due to more effective therapies, and finally improved resection of polyps and comfort with advanced techniques such as endoscopic mucosal resection have resulted in greater comfort in seeing and resecting precancerous lesions. As a result, there has been a move away from surgery and toward greater surveillance for patients for precancerous lesions.

SUMMARY OF THE DATA AND TECHNICAL ADVANCES THAT GUIDE OUR CURRENT PRACTICE

In the systematic review with network meta-analysis: endoscopic techniques for dysplasia surveillance in inflammatory bowel disease1,Chromoendoscopy, high definition white-light endoscopy (WLE), narrow band imaging (NBI), autofluorescence, FICE and full spectrum high definition WLE may be comparable for dysplasia surveillance. Standard definition WLE and i-SCAN probably provide lower yields for neoplasia identification. Full spectrum high definition WLE may represent the first-line approach.

In the strategies for detecting colon cancer in patients with inflammatory bowel disease2, data suggest that colonoscopic surveillance in IBD may reduce the development of both CRC and the rate of CRC-associated death through early detection, although the quality of the evidence is very low. The detection of earlier stage CRC in the surveillance group may explain some of the survival benefit observed. RCTs assessing the efficacy of endoscopic surveillance in people with IBD are unlikely to be undertaken due to ethical considerations.

In the Augmented Endoscopy for Surveillance of Colonic Inflammatory Bowel Disease: Systematic Review With Network Meta-analysis3, dye-spray chromoendoscopy was associated with higher likelihood of discovering dysplastic lesions than WLE. Chromoendoscopy is the best supported endoscopic technique for IBD surveillance.

In the Comparison of Endoscopic Dysplasia Detection Techniques in Patients With Ulcerative Colitis: A Systematic Review and Network Meta-analysis4 although they did not find any single technique to be superior, chromoendoscopy is probably more effective than standard definition– WLE for detecting any dysplasia, and there is low confidence in estimates supporting its use over high-definition WLE or narrow band imaging NBI. There is very low-quality evidence to inform the comparative efficacy of these interventions in detecting advanced neoplasia or preventing future colorectal cancer..

CONCLUSION

Augmented endoscopy such as chromoendoscopy or high definition WLE migh be the best supported endoscopic technique for IBD surveillance. Pragmatic, parallel-group RCTs with longitudinal follow-up are warranted to inform optimal dysplasia surveillance techniques

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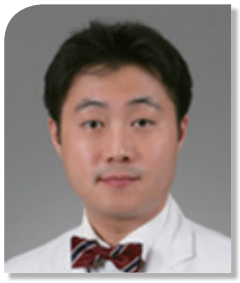

Measures for the high quality colonoscopy

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Colonoscopy is widely used for the diagnosis and treatment of colon disorders. Polyps can be removed during colonoscopy, thereby reducing the risk of colon cancer. Optimal effectiveness of colonoscopy depends on patient acceptance of the procedure, which depends mostly on acceptance of the bowel preparation. Preparation quality affects the completeness of examination, procedure duration, and the need to cancel or repeat procedures at earlier dates than would otherwise be needed. Ineffective preparation is a major contributor to costs. Meticulous inspection and longer withdrawal times are associated with higher adenoma detection rates (ADR). A high ADR is essential to rendering recommended intervals between screening and surveillance examinations safe. Technical expertise and experience will help prevent adverse events that might offset the benefits of removing neoplastic lesions.

There are many evidences that gastroenterologists are more effective than surgeons or primary care physicians at preventing CRC by colonoscopy. This most likely reflects higher rates of complete examinations (ie, cecal intubation) and higher rates of adenoma detection among gastroenterologists. All endoscopists performing colonoscopy should measure the quality of their colonoscopy. Institutions where endoscopists from multiple specialties are practicing should reasonably expect all endoscopists to participate in the program and achieve recommended quality benchmarks.

For colonoscopy, the recommended priority indicators are (1) ADR, (2) use of recommended intervals between colonoscopies performed for average-risk CRC screening and colon polyp surveillance, (3) cecal intubation rate with photographic documentation, and (4) adequate bowel preparation, and (5) longer withdrawal times. For each of these indicators, reaching the recommended performance target is considered strongly associated with important clinical outcomes. These indicators can be measured readily in a manageable number of examinations and, for each, there is evidence of substantial variation in performance. Reduction in variation in quality has emerged as an important priority for colonoscopy practice. The continuous quality improvement process should be instituted and embraced in all colonoscopy practices.

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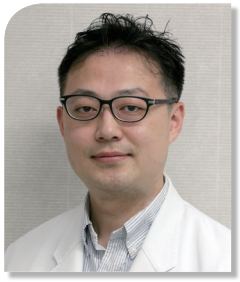

Polypectomy strategies base on polyp size and characteristics

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INTRODUCTION

Colorectal cancer is the third most common incidence cancer and incidence of colorectal cancer has increased in Korea.[1] Recently a study was demonstrated the colonoscopic removal of adenomatous polyps prevents death from colorectal cancer based on the results of the long term follow up.[2] Therefore, all colonoscopists should be able to perform polypectomy effectively. The resection technique is carefully selected based on several factors, such as histology, location, and size of the lesion, to ensure en bloc resection and reduce the possibility of local recurrence and complications. In this chapter, I'd like to review the polypectomy strategies base on polyp size and characteristics

POLYP-SPECIFIC POLYPECTOMY TECHNIQUES

1. General principles of polypectomy

The primary aims of polypectomy are to remove a polyp completely and safely, whilst retrieving the specimen for histological analysis. Size is one the main characteristics of polyps in terms of potential for malignancy and it is the most important characteristic of the polyps when choosing the technique for resection. in combination with size, morphology is the main feature used for decision-making in polypectomy. During performing polypectomy, the scope shaft should be straightened and rotated to align the polyp with the instrument channel (usually in the 5 or 6 o'clock position).[3]

2. Diminutive polyps (< 5 mm)

Although cold biopsy forceps (CBF) is acceptable for 1-3mm polyps, the CBF technique should be carefully consider using for polyps of more than 3 mm, owing to increased rates of incomplete excision above this size, particularly where more than one biopsy is required to remove the polyp.[4] An RCT of 146 patients with 231 diminutive polyps showed noninferiority of histologic eradication for 1-3 mm polyps with CBF compared with cold snare polypectomy (CSP); however, for polyps >3 mm, the histologic eradication rate failed to show noninferiority versus CSP.[5] ESGE recommends CSP as the preferred technique for removal of diminutive polyps (size ≤ 5 mm) because this technique has high rates of complete resection, adequate tissue sampling for histology, and low complication rates.[6]

3. Small (6-9 mm) polyps

The two appropriate polypectomy modalities for 6-9 mm polyps are hot snare polypectomy (HSP) or CSP. A multicenter Japanese RCT of 796 sessile 4-9 mm polyps (538 patients) revealed a complete resection rate for CSP of 98.2% compared with 97.4% for HSP (non-inferiority p<0.0001).[7] A meta-analysis concluded that for removing small polyps, CSP is time-saving with similar resection rates and safety to HSP.[8] The evidence of the benefit of adding in a submucosal lift (endoscopic mucosal resection, EMR) for small polyps is mixed, and should probably be targeted at polyps where its use may increase the endoscopist's confidence of complete en bloc excision. An RCT of 358 patients with 525 6-9mm polyps showed the incomplete resection rate (IRR) for adenomatous polyps was significantly higher with CSP than HSP-EMR (18/212, 8.5% vs 3/203, 1.5%; P = .001).[9]

4. 10-19 mm non-pedunculated polyps

HSP is the main technique for removing 10-19 mm non-pedunculated polyps. Until recently there have been no feasible alternative techniques, hence very few trials. Most studies have focused on modifications of the HSP technique, such as sub-mucosal injections, type of injection solution, use of an underwater technique, and on the use of adjuncts to reduce complications.[3] In a recent RCT of underwater versus conventional EMR for 10-20 mm polyps, underwater EMR significantly increased the rate of en bloc resection (89% vs. 75%; P=0.007) and R0 histology (69% vs. 50%; P=0.011) without increasing adverse events or procedure time.[10]

5. Pedunculated polyps

The snare should be placed around the stalk of the polyp, ensuring a clear margin from the polyp head so that even after diathermy there will be histologically evidence completeness of excision, especially if malignancy is suspected (9); however, the snare should be placed high enough on the stalk to avoid the risk of diathermy-related deep tissue injury and to leave sufficient stalk to allow it to be re-grasped if bleeding occurs. The main complication is post-polypectomy bleeding (PPB), caused by under-cauterized blood vessels within the stalk, particularly where the stalk is >5 mm in diameter.[11] Two further RCTs indicate that mechanical prophylaxis with endoloops or endoclips,

either alone or in combination with adrenaline injection, may be superior, particularly for larger (>20 mm) or thicker-stalked polyps.[12,13]

CONCLUSIONS

Appropriate choice of polypectomy technique will help reduce incomplete excision rates. If polypectomy is performed according to proper polypectomy strategies base on polyp size and characteristics, it is expected to remove polyps more safely and completely.

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KDDW 2019 Korea Digestive Disease Week

DAY 2

November 29 (Friday)

[09:00-10:30, Convention Hall C]

Joint Symposium (ANMA-KSNM) English

Therapeutic advances in constipation

Chairs: **Joon Seong Lee** (Soon Chun Hyang University Seoul Hospital, Korea)

Noriaki Manabe (Kawasaki Medical University, Japan)

Constipation in older adults

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Chronic constipation is a common gastrointestinal disorder with a prevalence around 10-20 in the general population. The incidence is even disproportionately high among the elderly, which might be from the immobility, poly-medications, and aging process in the population. Though chronic constipation is not life-threatening, it does bring a significantly negative impact on quality of life, individual healthcare costs, and a large economic burden. In Western countries, it is estimated that there are approximately 7 million physician visits per year with 2.5 million of these made by persons over the age of 65. To explore detailed clinical history and physical examination (including rectal examination) is important to unmask the primary and secondary forms of constipation as well as to guide the subsequent diagnostic and therapeutic considerations. With the application of anorectal manometry, defecography, and transit study, we can then distinguish from pelvic floor dysfunction, slow and normal transit constipation. Non-pharmacologic treatment for constipation would include bowel training and biofeedback as well as fiber addition. Laxatives are still the mainstay of therapy. Newer agents targeting at chloride channel, serotonin receptor, guanylate cyclase-C receptor, bile acid, Ghrelin receptor, and opioid receptors have shown to be effective in adults with chronic constipation. However, the safety data of these new agents in the elderly are still lacking. Surgery can be considered after a complete evaluation and deep discussion with in medically refractory patients. Neuromodulation or Botulinum toxin is not ready for routine use in constipation at this time. It is imperative to identify the etiology of chronic constipation in the elderly and the appropriate treatment should be based on the patient's overall clinical status and capabilities.

Opioid-induced constipation

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In the western country, the prevalence of opioid-induced constipation (OIC) varies from 41% to 94% among the patients receiving opioids for chronic cancer and non-cancer pain. However, the prevalence of OIC in Korea is thought to be much lower than in western country because of less prescription from the physicians and strict regulation from the authority. For that reason, doctors are not aware of OIC and may not ask patients about constipation. The problem is that OIC is still under-recognized, and undertreated.

The key aspect of managing OIC is early recognition. The constipation is rarely due to opioids consumption alone, so other different factors including diet, immobility, other drugs, pain during evacuation, comorbidity, gastrointestinal obstacles, especially in advanced cancer patients should be considered. Therefore, management of OIC needs to be tailored to the individual patient based on their overall clinical picture.

Initial management includes lifestyle modification such as increasing fluid intake, exercise, and standard laxatives as well as addressing exacerbating factors. Counseling and education of patients as to the side-effects of opioids is also important.

There may also be benefit in 'opioid switching' or changing to an equianalgestic dose of an alternative less-constipating opioid, for example, changing oral or parenteral morphine preparations to fentanyl or combination of opioid agonist/antagonist agents (eg, oxycodone + naloxone). Rationale for combination of oxycodone with extended-release naloxone (fixed ratio 2:1, approved at maximum dose of 40 mg and 20 mg, respectively) is based on the slow release of naloxone allowing it to exert a local antagonistic effect on opioid receptors in the GI tract, with a minimal impact on analgesia due to extensive first –pass metabolism in the liver. Tapentadol is a μ-opioid agonist and norepinephrine reuptake inhibitor. Combined effects of tapentadol on pain sensation can be achieved with a relatively lower level of oxycodone, with reduced gastrointestinal adverse effects such as constipation.

Fist line drug for OIC is laxatives. This class includes stool softeners (docusate), osmotic laxatives (magnesium sulfate or citrate, macrogol), lubricants (mineral oil), and stimulant laxatives (bisacodyl, picosulfate and senna). Laxative class agents are generally very safe, widely available over the counter, and inexpensive. Fiber is a bulking agent and soluble fiber is more effective for constipation compared to insoluble fiber. Co-prescription of a standard laxative is advocated when an opioid is commenced, escalated or switched.

Second line drug is peripherally acting μ-opioid receptor antagonists (PAMORA). PAMORAs do not enter the central nervous system but block the μ-opioid receptors in the gut thereby effectively restoring the function of the enteric nervous system. However, the use should be avoided in patients with conditions that compromise the blood brain barrier until safety can be demonstrated due to potential for serious withdrawal and reversal of analgesia. Several PAMORAs can be available. Naloxegol is a pegylated derivatives of naloxone. It was approved by the US FDA as the first PAMORA for the management of OIC in adult patient with chronic non-cancer pain. Methylnaltrexone is a quaternary ammonium cation that has opioid antagonist effects throughout the body. It is available in oral as well as subcutaneous injection forms. Naldemedine is structurally related to naltrexone, and was the latest PAMORA that was approved by the US FDA. Unfortunately, PAMORAs are not available in Korea as yet. Alvimopan, an orally administered PAMORA, has been demonstrated to be numerically superior to placebo in treating OIC. However, its long term use has been associated with increased cardiovascular risk.

Other agents such as intestinal secrtagogues (lubiprostone, linaclotide), selective 5 HT4 agonist (prucalopride) can be considered if available, but there is insufficient data about the effect in OIC treatment.

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New therapeutic strategies for chronic constipation considering colonic transit time

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Constipation is a syndrome defined by abnormal bowel symptoms that may be primary or secondary to an underlying disorder [1]. After excluding organic mucosal disease, strictures, and evacuation disorders, the treatment of constipation is typically based on single or combined treatment with fiber [2,3] or osmotic [4] and stimulant laxatives [5]—to which many patients respond. Practitioners have several choices for treating chronic constipation. Patient responsiveness, however, is based on trial and error with medications. Also, side effects such as abdominal pain sometimes occur because the pathophysiology of chronic constipation varies [6].

Assessing the colonic transit time (CTT) is important in patients with symptoms of colonic dysmotility because it can provide useful mechanistic insights and gauge treatment response [7]. For example, transit studies using radiopaque markers distinguish constipation subgroups (e.g., normal- or slow-transit constipation) and assess segmental transit times in patients with delayed CTT. This method has some disadvantages, however, such as patient compliance, complicated methodology, high cost, and/or radiation exposure. Altered colonic motor function leads to diverse stool and/or gas distributions in the colon and rectum [8-10].

Recently, we have newly developed an ultrasonographic method to evaluate stool and/or gas distribution, which is an indirect indicator of the CTT (Figure 1) [11]. The patients' stool and/or gas distribution was evaluated using the Constipation Index [(ascending (A) + transverse (T), descending (D) + sigmoid (S)+rectum (R))/5] and the left/right distribution ratio [(D+S)/(A+T)] [11]. Based on patients' clinical courses, they were divided into four groups: non-responders (group A) or responders (group B) to fiber- or osmosis-based laxatives; non-responders to any medical therapy (group C); responders to stimulant-based laxatives (group D). The Constipation Index was significantly higher in group A than group B ($p<0.05$), with the receiver operating characteristic curve analysis showing a Constipation Index cutoff of 21.2 for predicting favorable outcomes of either fiber- or osmosis-based laxatives ($p<0.05$). Left/right distribution ratio was significantly lower in group C than group D ($p<0.05$), and the receiver operating characteristic curve analysis showed a left/right cutoff of 0.5 for predicting responders of stimulant-based laxatives ($p<0.05$) [12].

Based on our study results, we established optimal treatment strategies for patients with chronic constipation whose symptoms of chronic constipation were alleviated without side effects (e.g., severe abdominal pain, severe diarrhea, ischemic colitis) (Figure 2). These findings could assist physicians predict favorable outcomes with laxatives without side effects for this patient population. In this lecture, I will focus on the clinical significance of CTT for the pathophysiology of chronic constipation and introduce new therapeutic strategies for chronic constipation using this method.

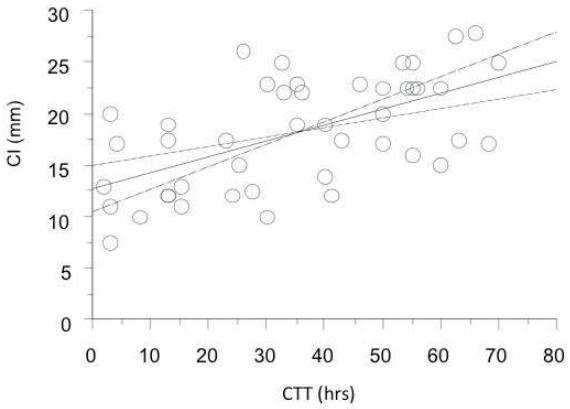

Figure 1. Relation between constipation index and colonic transit time.

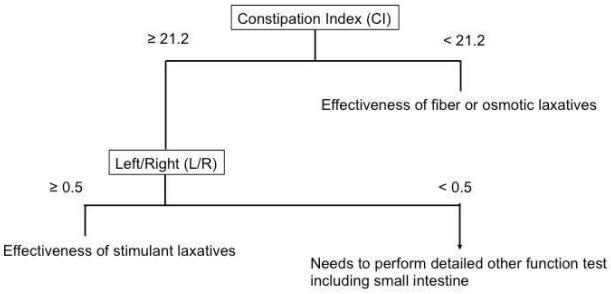

Figure 2. Optimal treatment strategies for patients with chronic constipation.

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KDDW 2019 Korea Digestive Disease Week

DAY 2
November 29 (Friday)

[09:00-10:30, Emerald Hall A]

Combined Symposium 01 (KPBA-KAHBPS1) Korean

Debate in the management of GB cancer

Chairs: **Jae Seon Kim** (Korea University Guro Hospital, Korea)
Hee Chul Yu (Chonbuk National University Hospita, Korea)

Appropriate extent of surgery for gallbladder cancer

Seung Eun Lee, M.D., Ph.D.

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GB cancer (GBC) can be cured with radical surgery, and many efforts have been made in the attempt to improve resectability and the survival rate. However, because GBC has a low incidence, no randomized controlled trials have been conducted to establish the optimal treatment modalities. Although a few retrospective studies have been conducted in large series of patients with GBC, these have been limited in scope.

According to recently published studies, simple cholecystectomy is the standard treatment for T1a,[1-3] and extended cholecystectomy is the standard treatment for GBC above T2[3-6]; however, there are controversies regarding treatment for T1b GBC, which varies across different countries. In the NCCN Guidelines, extended cholecystectomy is recommended in patients with GBC above T1b.[4] However, according to the guidelines published in Korea there is no evidence that extended cholecystectomy increases survival[3]; hence, the additional use of extended cholecystectomy is subject to the surgeon's preference. In the Japanese guidelines, for T1b GBC, simple cholecystectomy is feasible, but only open cholecystectomy is recommended, because laparoscopic cholecystectomy has some risk of port site recurrence or peritoneal dissemination.[6]

For T2 GBC, extended cholecystectomy has been the standard treatment. However, newly published the American Joint Committee on Cancer (AJCC) eighth edition has subdivided T2 GBC into two categories according to the location of primary tumor, peritoneal side tumor (pT2a) and hepatic side tumor (pT2b)[7] and some authors recommend hepatic resection only for hepatic side tumors and not for peritoneal side tumor,[8,9] while others recommend hepatic resection for both hepatic side tumor and peritoneal side tumor.[10] Although several studies described there was no significant difference in survival between simple cholecystectomy and extended cholecystectomy, extended cholecystectomy should be considered till further well-designed prospective study will give an answer.

An extended cholecystectomy is generally recommended for patients with GBC at stage T2 or above.[3,4,6] In patients who are indicated for radical cholecystectomy, a combined approach can also be considered for RO resection. However, extrahepatic bile duct resection should not be seen as mandatory in the radical resection of GBC but rather as an option to be selectively performed in specific types of cases, such as GBC with extrahepatic bile duct invasion[3].

Cytoreductive surgery is not useful in patients with unresectable GBC.[11,12] However, palliative surgery will most likely be able to prolong the short-term survival period and improve the quality of life of patients with unresectable GBC.[3]

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Feasibility of minimally invasive surgery as radical cholecystectomy: is it time to move on?

Chi Young Jeong

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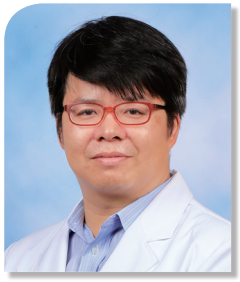

All about the adjuvant treatment after surgical resection

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Bile duct cancer is the 8th most common cancer in Korea with incidence of 6.8/100,000 population. It is also the 6th most common cause of cancer related mortality. About 4,800 patients die every year due to bile duct cancer.[1] Gallbladder cancer is included in bile duct cancer, and it has worse prognosis compared to other bile duct cancers. Because the gallbladder does not have the submucosal layer, metastasis occurs in the early stage.[2]

Surgery is the only potentially curative treatment for bile duct cancer, but even with complete surgical resection, recurrence rate can go up to 60%. Clinical trials to improve survival with adjuvant treatment have been conducted, but the results were not impressive. Two prospective studies reported by Japanese study and ESPAC-3 trial were underpowered and failed to prove the superiority of adjuvant treatment compared to the control group.[3,4] More recent trials also failed to prove that gemicitabine monotherapy and gemcitabine plus oxaliplatin improved overall survival of bile duct cancer after surgery.[5,6] So far, the benefit of adjuvant treatment has been reported only in the pooled analysis.[7]

A recent phase III randomized clinical trial (BILCAP trial) of 447 patients with biliary tract cancers showed that capecitabine adjuvant treatment might improve survival after surgery. The difference of overall survival between the observation group and capeciatbine group was noted in per-protocol analysis (53 vs 36 months), but not in intention-to-treat analysis (51.1 vs 36.4 months, p=0.097).[8]

BICAP trial showed potential of capecitabine as an adjuvant treatment for bile duct cancer.

Further studies are needed to find out who can be benefited most from adjuvant therapy, and capecitbaine can be effective against gallbladder cancer as an adjuvant treatment also.

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How effective is chemotherapy and can it lead to conversion surgery?

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Since gallbladder cancer (GBC) has no symptoms at an early stages, most cases are in advanced stages (40–75%) at the time of initial diagnosis [1]. Prior to 2010, there were no standard chemotherapeutic regimen to treat advanced-stage GBC. After the randomized controlled phase III trial of 410 patients, Advanced Biliary Cancer-02 trial (ABC-02), Randomized phase III trial in 410 patients, combination of cisplatin plus gemcitabine has been widely used. The clinical trial reported median OS of 11.7 months [2]. However, there is still lack of consistent results regarding the efficacy of neoadjuvant or palliative therapy including systemic chemotherapy or chemoradiation therapy. We are going to discuss about several recent studies that demonstrated efficacy of neoadjuvant or palliative therapy in advanced GBC.

In a previous study in 2018 [3], 81 (50.6%) patients received GEMOX, 76 (47.5%) patients received GEMCIS, and 3 (1.9%) patients received Gemcitabine plus carboplatin or capecitabine. Patients were mostly at stage IIIB and about 39.4% of the patients achieved R0 resection after neoadjuvant chemotherapy. In other study [4], various chemotherapy regimens were used; gemcitabine / gemcitabine + platinum-based chemotherapy. Patients were mostly at stage IVB and about 13.5% of the patients achieved R0 resection after neoadjuvant systemic chemotherapy. In a previous study which included patients who underwent neoadjuvant chemoradiation therapy, 28 patients were included [5]. Most of them were at stage IIIB, and 50% achieved R0 resection after the neoadjuvat therapy.

A previous study regarding the downstaging with neoadjuvant therapy in unresectable gall bladder cancer patients investigated the efficaty of concurrent chemoradiation therapy (cisplatin+ 5-FU) and systemic combination chemotherapy (cisplatin+gemcitabine). Most of the patients were at stage IVB, and 66.6%~83.0% of the patients showed down-staging after the neoadjuvant treatment. Six patients (6/40, 15%) achieved R0 resection [6]. Additionally, there was a study which investigated the reduced dose intensity of cisplatin+gemcitabine combination chemotherapy [7]. Most of the patients were at stage IVA, and 52 of 59 patients (88.1%) achieved R0 resection. Another retrospective single-center stage showed that systemic chemotherapy with gemcitabine single therapy leaded 4 of 7 patients who were diagnosed with initially unresectable locally advanced GBC to R0 resection; most of the patients were at stage IVA at the time of diagnosis. In last study [8], 23 patients were treated with CCRT with 5-FU; 14 of the 23 patients (60.9%) underwent curative resection and there were no data available regarding resection margin. Table 1 summarizes the results of the previous studies.

In conclusion, active neoadjuvant or palliative therapy can lead to conversion to curative surgery at the rate of 13.5%~50% in advanced GBC. Since there is no consensus for neoadjuvant treatment regimens and timing for conversion surgery in advanced GBC, future studies regarding standardized regimens for advanced GBC and algorithms for conversion surgery are needed.

Table 1. Summary

Reference	Most common stage (initial)	No of patients	Regimens	R0 resection	Curative resection rate
Chaudhari et al	IIIB	160	GEMCIS / GEMOX /Gemcitabine-based	63	39.4%
Creasy et al	IVB	74	gemcitabine / gemcitabine + platinum-based	10	13.5%
Engineer et al	IIIB	28	CCRT with gemcitabine	14	50%
Agrawal et al	IVB	40	CCRT with cisplatin+ 5-FU / Cisplatin + gemcitabine	6	15%
Gangopadhyay et al	IVA	121	Cisplatin + gemcitabine	52	43%
Kato et al	IVA	7	Gemcitabine	1	14.3%
Aretxabala et al	NA	23	CCRT with 5-FU	NA	NA

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Case discussion

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Gallbladder cancer is one of the refractory diseases. Multidisciplinary approach including immunotherapy for such cancers has received much attention in recent years. A 59-year-old man underwent cholecystectomy for therapy of gallstone and incidentally found GB cancer in final pathology. Chemotherapy was performed and after detection of recurrence in colon and right lower rib area, metasectomy was performed. adjuvant chmotherapy was performed using UFT and he has survived until now. We report here a rare case of a patient who has currently survived almost 10 years with recurrent GB cancer.

KDDW 2019 Korea Digestive Disease Week

DAY 2

November 29 (Friday)

[09:00-10:30, Diamond Hall]

Symposium 07 (KSGC1) Korean

Prevention and treatment of cancer-related infection: tip for clinical practice

Chairs: **Hyun Yong Jeong** (Chungnam National University Hospital, Korea)

Ji Kon Ryu (Seoul National University Hospital, Korea)

Vaccination for cancer patients; when and what?

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Department of Internal Medicine-Infection, Seoul National University Hospital, Seoul, Korea

Cancer patients may die directly from the progression of the cancer itself, but more often from a combined infection. Vaccination is a very safe and effective method to prevent infectious diseases, and are highly recommended in adults as well as children. Especially in the case of cancer patients, proper vaccination can prevent serious complications.

The immunizations of gastrointestinal cancer patients can be broadly classified into: 1) Vaccinations generally recommended for adults, especially those for cancer patients. 2) Vaccinations especially needed if the spleen is to be removed during cancer progression or cancer treatment 3) Vaccinations to be avoided by patients with advanced cancer or undergoing chemotherapy

Common adult immunizations recommended in the Adult Immunization Guide published by the Korean Centers for Disease Control and Prevention 2018 include influenza, pneumococci, tetanus-diphtheria-pertussis, shingles, hepatitis A. Among the vaccinations that are important in gastrointestinal cancer patients are influenza and pneumococcal vaccinations. Influenza is recommended every year for all patients over 50 years of age and at least two weeks apart from chemotherapy. In general, tetravalent influenza vaccine is recommended, but some publications recommend high dose trivalent vaccine in elderly patients over 65 years old, but it is not yet introduced in Korea. Influenza live vaccines are also contraindicated in immunocompromised patients but are not also currently used in Korea.

For pneumococcal vaccination, a single dose of 23 valent polysaccharide vaccine is recommended for normal immune patients aged 65 years or older. In immunocompromised patients, including advanced cancer patients, it is recommended to first be vaccinated with a 13 valent protein conjugate vaccine, followed by a 23 valent polysaccharide vaccine at intervals of 8 weeks or more. For patients who have already received 23 valent polysaccharide vaccine prior to cancer diagnosis, it is recommended to consider 13 valent protein conjugate vaccine at intervals of one year or more.

In gastrointestinal cancers, especially in advanced pancreatobiliary cancers, splenectomy is often performed during surgery to treat disease. After splenectomy, it is known to be susceptible to infections with strains containing capsules. Vaccination against pneumococci, meningococcus and Haemophilus influenzae is recommended.

Live vaccines are contraindicated in patients undergoing chemotherapy or who have been compromised due to cancer progression. In Korea, MMR and varicella/zoster vaccination are available live vaccines. Vaccination of live vaccines is recommended 4 weeks before or 3 months after the start of chemotherapy. Passive immunization with immunoglobulin is recommended rather than vaccination when exposed to risk groups without immunization.

In summary, for patients with newly diagnosed gastrointestinal cancer, it is recommended to first evaluate the likelihood of splenectomy and consider vaccination if necessary. In patients with a low likelihood of splenectomy, it is recommended to check the patient's pneumococcal vaccination history and ensure that appropriate vaccinations are given prior to the start of treatment. And patients undergoing chemotherapy are encouraged to receive the flu vaccine every year for the whole family, and live vaccines are contraindicated.

Role of myeloid growth factor during chemotherapy

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Neutropenia is a major dose limiting toxicity of many chemo therapeutic regimens. The complication s from chemotherapy-induced neutropenia (CIN) can cause significant morbidity and mortality and often requires prolonged hospitalization and broad-spectrum antibiotic use. Myeloid growth factors (MGFs), including granulocyte coloniy-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), are primarily used to reduce the incidence of neutropenia in patients with solid tumors receiving myelosuppressive chemotherapy.

According to the common terminology criteria for adverse event version 4.0 neutropenia is defined as absolute neutrophil count (ANC) ≤ 1500/μl. Clinical significant neutropenia is defined as ANC of < 500/μl or an anticipated decline to ≤ 500/μl in next 48 hours. Febrile neutropenia (FN) is defined as an oral temperature of ≥ 38.3°C or 38.0°C sustained for more than 1 hour with significant neutropenia.

G-CSF is commercially available as filgrastim (Grasin, Leukostim) and lenograstim (Neutrogin), long-acting agent (Pegteograstim, Pegfilgrastim, Teipegfilgrastim, Lipegfilgrastim) to decrease the incidence of FN in patient with non-myeloid malignancies receiving myelosuppressive chemotherapy. G-CSF prophylaxis decrease the risk of neutropenia and the subsequent rates of infection and hospitalization.

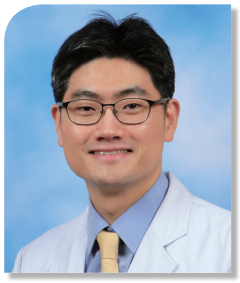
Toxicities associated with G-CSF prophylaxis is mild to moderate bone pain in 10% to 30% of patients. This is usually effectively controlled by non-narcotic analgesics. Rare cases of splenic rupture have been reported with G-CSF use. Physicians should monitor patients closed for signs of splenic rupture including abdominal pain, nausea, vomiting. Some patients may develop allergic reaction to G-CSF involving the skin, respiratory system, or cardiovascular system.

Primary prophylaxis is not recommend if the incidence of NF is expected to be less than 20 percent following chemotherapy. When the expected incidence of NF is over 20 percent, the primary prophylactic G-CSF during all cycles of chemotherapy to reduce the need for hospitalization for antibiotic therapy. When the estimated risk of NF is between 10 and 20 percent, the decision to use G-CSF support should be individualized. The most important patient risk factor for developing severe neutropenia is older age (>65 years). Other risk factors include prior exposure to chemotherapy or radiation therapy, persistent neutropenia, bone marrow involvement by the tumor, poor performance status.

In the examples of disease setting and chemotherapy regimens according to the risk for FN, FOLFIRINOX for pancreatic cancer and FOLFOX for colorectal cancer are listed as regimens with the intermediate risk for FN. FOLFOX for stomach cancer may also have a same risk for FN as FOLFOX for colorectal cancer. If patients who receive these chemotherapy regimens have risk factor, the physician-patient discussion of the risk-benefit ratio of G-CSF use with respect to the likelihood of developing FN, the potential consequences of a neutropenic event, and the implicatioins of reduced chemotherapy dose delivery.

After the first cycle of chemotherapy, FN risk categorization should be performed. If the patient experienced an episode of FN or a dose-limiting neutropenic event (ANC impacting the planned dose of chemotherapy), secondary prophylaxis with G-CSF should be considered for patients who had not received prior G-CSF. The dose reduction rather than G-CSF for secondary prophylaxis also may be the alternative to reduce cost. However, a reduced dose can compromise disease-free survival, or treatment outcomes. In patients who receive prior G-CFS, a dose reduction is recommend.

Filgrastim are administered the next day or up to 3 to 4 days after completion of chemotherapy until post-nadir ANC recovery is normal or near normal levels. Long-acting G-CSF should be administered the day after chemotherapy. Administration up to 3 to 4 days after chemotherapy is also reasonable. In general, there should be at least 12 days between the dose of long-acting G-CSF and next cycle of chemotherapy.

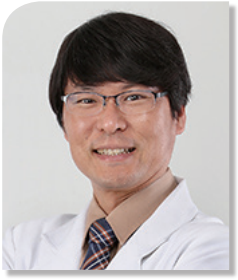


Evaluation and management of cancer-related fever

Hee Seung Lee, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Severance Hospital, Seoul, Korea

Fever is frequently seen in patients with cancer and can be associated with a variety of infectious and noninfectious causes. There is an increased risk of infection in patients with cancer that results in higher morbidity and mortality. In certain instances, the malignancy itself can predispose patients to severe or recurrent infections. Neutropenia has been recognized as a major risk factor for the development of infections in patients with cancer undergoing chemotherapy. Effective strategies to anticipate, prevent, and manage these infectious complications have led to improved outcomes. The initial evaluation should focus on determining the potential sites and causative organisms of infection and on assessing the patient's risk of developing an infection-related complication. A site-specific history and physical examination should be performed promptly, cultures should be obtained, and empiric antibiotics should be started soon after the time of presentation. The common sites of infection for patients with fever and neutropenia are as follows: alimentary tract, skin, lungs, sinus, ears, perivaginal/perirectal, urologic, neurologic, and intravascular access device sites. Neoplastic fever is a well-recognized phenomenon occurring in certain patients with cancer. Since fever is a very common problem in patients receiving cytotoxic chemotherapy and can be caused not only by infection but also by cancer itself, it is crucial for the clinician to be able to establish a definite diagnosis of neoplastic fever during management of cancer. In general, neoplastic fever exhibits no clinical features to be differentiated from other types of fever because of infectious, rheumatic-inflammatory, or miscellaneous disorders. Thus, neoplastic fever is a diagnosis of exclusion, that is, it can be established only after exhaustive evaluation and exclusion identifiable etiologies in the patient with cancer. So, herein, fever-producing conditions in patients with cancer will be introduced, and evaluation and management of cancer related fever will be addressed.



Prevention of reactivation of tuberculosis

Chulho Oak, M.D., Ph.D.

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The preventive treatment of latent tuberculosis infection (LTBI) has gradually gained a vital role in tuberculosis(TB) control worldwide. According to the World Health Organization (WHO), approximately 2–3 billion people in the world are latently infected with Mycobacterium tuberculosis (Mtb), and 5%–15% of these people will suffer from reactivation of TB during their life time(1). Therefore, the treatment of LTBI directly influences the future global prevention of TB infection. At present, the study of LTBI relies heavily on screening for high-risk populations and on treatment strategies for the disease. WHO recommended that Individuals should be asked about symptoms of TB before being tested for LTBI(2). Chest radiography can be done if efforts are intended also for active TB case finding. Individuals with TB symptoms or any radiological abnormality should be investigated further for active TB and other conditions. Either TST or IGRA can be used to test for LTBI in high-income and upper middle-income countries with estimated TB incidence less than 100 per 100 000(1). In South Korea, treatment of LTBI has been recommended only for children aged <6 years who have been exposed to TB, for HIV-infected individuals, for patients receiving tumour necrosis factor-α inhibitors after diagnosis of LTBI using the TST(3). Cancer and pulmonary tuberculosis (TB) are major global health concerns and are associated with substantial morbidity and mortality. Cancer affects populations worldwide, and the global burden of cancer is increasing: 14.1 million new cancer cases and 8.2 million cancer-related deaths were reported in 2012 and 20 million new cases are expected in 2020(4). The association between active TB and subsequent cancer development has been investigated for several decades, and systematic reviews(5,6) have shown a relation between TB and cancer development. Recent population-based studies found that TB might increase the risks of lung cancer(7,8,9) and other cancers(10) (eg, esophageal, head, and neck cancers). Several studies have reported a strong association between tuberculosis and lung cancer. TB-related chronic inflammation and infection is a possible mechanism of cancer pathogenesis Meta-analysis showed that patients with cancer have an increased risk of developing TB, compared to the general population(11,12). Children with solid cancers or haematological malignancies have a high relative risk of developing TB and should be considered for systematic screening and treatment of LTBI, especially when they originate from settings with a high TB incidence(13,14). Adults with cancer, especially those with haematological malignancies, who have additional risk factors (such as being a migrant from a country with a high TB burden), should be considered for LTBI screening and treatment(15,16). At present, the WHO recommends five prophylactic regimens—6INH, 9INH, 3-4RIF, 3-4RIF + INH and 3RPT + INH—none of which has shown superiority over the conventional 6INH or 9INH therapies. The 3-4RIF and 3RPT + INH regimens have been reported to have fewer hepatotoxicity events, but the quality of evidence is low. Further research regarding the treatment efficacy and safety of the 3RPT + INH and 3–4 RIF regimens is required. For high-risk groups, isoniazid monotherapy could reduce the TB risk in HIV-infected patients and transplant recipients, but for others, little evidence is available to draw a conclusion at this time. In the future, high-risk population screening and new preventive treatment therapies for specific target groups and the drug resistance that follows will be the keys to improve the prophylaxis of latent TB(17).

Screening and prevention of hepatitis B, C during chemotherapy

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HEPATITIS B VIRUS

The rates of reactivation during chemotherapy is generally known to be about 20–50%. In many cases, patients are asymptomatic but occasionally present with jaundice, or are found in various stages such as decompensated liver diseases or even death.[1,2] The immune response is suppressed by immunosuppressive therapy or anticancer chemotherapy, then the risk of reactivation increases. The exacerbation of chronic Hepatitis B virus (HBV) infection is defined as an increase of serum HBV DNA by more than 100 times the baseline level in patients with positive HBsAg. The relapse of past HBV infection is defined as seroconversion of HBsAg negative to positive, or detection of serum HBV DNA from none to positive in patients with negative HBsAg and positive anti-HBc. Hepatitis flare is defined as serum ALT level more than 3 times the baseline level or increase by more than 100 IU/L.

The intensity of chemotherapy regimen related to the risk of hepatitis B reactivation can be classified into three categories: high risk group (reactivation risk of 10% or more), moderate risk group (reactivation risk between 1-10%) and low risk group (reactivation risk below 10%).[3] During the chemotherapy for lymphoma, hepatitis B reactivation is reported to be frequent with the rate up to 24–67%. Rituximab therapy increased the risk of hepatitis B reactivation in patients with non-Hodgkin's lymphoma who had seropositive HBsAg or seronegative HBsAg/seropositive anti-HBc combination (relative risk [RR], 2.14; 95% CI, 1.42–3.22; P=0.0003).[4] Reactivation of hepatitis B in patients with solid tumors is known to be about 14–21%, but for those with breast cancer, it is higher at about 41–70%, which is thought to be related to the high dosages of breast cancer treatment agents as well as the use of anthracycline-based chemotherapy and steroids.[5] It is reported that the use of prophylactic antiviral agents in most solid tumors, such as breast and lung cancers, has significantly reduced the rate of hepatitis B reactivation and discontinuation of chemotherapy treatment.[6]

Prior to starting an immunosuppressive therapy or chemotherapy, screening for HBsAg and anti-HBc is necessary. In HBsAg positive cases, regardless of serum HBV DNA level, antiviral prophylaxis is recommended. Antiviral prophylaxis must be administrated at the start of or 7 days prior to the chemotherapy.[7] The reactivation still is reported more than 6 months after the completion of chemotherapy. Therefore, antiviral prophylaxis should be maintained for at least 6 months after the last day of chemotherapy. Especially, for patients receiving chemotherapy involving rituximab, it is recommended to extend the antiviral prophylaxis to at least 12 months after the completion of chemotherapy.[8] In a meta-analysis, entecavir prophylaxis was shown to prevent reactivation of hepatitis B more effectively compared to lamivudine prophylaxis.[9]

HEPATITIS C VIRUS

Hepatitis C virus reactivation usually follows a mild clinical course, and cases of severe hepatitis or hepatic decompensation are rare in contrast to HBV infection.[10] In a retrospective cohort study from Korea, hepatitis was present in 46 patients (38%) and none of the patients were diagnosed with severe hepatitis in 120 patients with chronic hepatitis C. Only 6 patients showed hepatitis associated with enhanced hepatitis C virus replication and no one discontinued systemic chemotherapy due to hepatitis.[11]

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KDDW 2019 Korea Digestive Disease Week

DAY 2

November 29 (Friday)

[11:00-11:30, Convention Hall A+B]

Presidential Lecture (KSG) Korean

Chair: **Jin Hong Kim** (Ajou University Hospital, Korea)

Challenging for unmet needs in pancreatobiliary diseases

Dong Ki Lee

Department of Internal Medicine, Gangnam Severance Hospital, Seoul, Korea

KDDW 2019 Korea Digestive Disease Week

DAY 2

November 29 (Friday)

[11:30-12:00, Convention Hall A+B]

Special Lecture (KSG) Korean

Chair: **Dong Ki Lee** (Gangnam Severance Hospital, Korea)

BIOCON as a translational platform for the collaboration between researchers and clinicians

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Although linking researchers to clinicians is considered crucial to find new cure for decades, it still remains as a big huddle for efficient relaying important discoveries in life science to clinical development. Medicinal Bioconvergence Research Center (BIOCON) was initiated from 2010, especially to solve this problem and facilitate the flow of upstream discovery to downstream development. BIOCON consists of 30-40 principal researchers with specialties in different fields and make tight collaborations with clinicians dedicated to various human diseases. The project is set up from the beginning through the comprehensive analysis of clinical and industrial unmet needs and once the target and primary indication are decided, the project is rapidly transfered to the drug screening and development processes. The package of the target and lead with the appropriate therapeutic or diagnostic applications, it is disclosed to the industry for further downstream development. The BIOCON's unique integrated R&BD platform has been proven extremely efficient for translational research for the novel therapeutics and diagnosis.

RELATED REVIEW

Neenan et al, Biocon's target factory, Nat Biotech, 36: 791-797, 2018.

KDDW 2019 Korea Digestive Disease Week

DAY 2

November 29 (Friday)

[11:00-12:30, Convention Hall C]

Symposium 08 (KSNM2) Korean

Recent updates of esophageal motility disorder

Chairs: **Kwang Jae Lee** (Ajou University Hospital, Korea)

Moo-In Park (Kosin University Gospel Hospital, Japan)

Classification

Kee Wook Jung, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Asan Medical Center, Seoul, Korea

Impedance planimetry enables measurements of bag cross-sectional area at various locations. More recently, the functional lumen imaging probe (FLIP) became available for assessing luminal distensibility. This probe can also measure pressure, serial cross-sectional areas, and tension-strain relationships.[1] Esophagogastric junction (EGJ) distensibility is decreased in patients with achalasia. Several studies have shown a significant correlation between symptom severity score and EGJ distensibility.[1] EndoFLIP is recommended to be applied during peroral endoscopic myotomy (POEM) or myotomy of a dynamic structure by using distensibility measurement in the EGJ. Moreover, endoFLIP can be used to assess esophageal contractility, which is not available with the conventional manometry.[1] EndoFLIP also obtains information regarding the contractile activity and distensibility of the esophageal body in patients with achalasia, including repetitive antegrade or retrograde contractions.[2]

The chronic use of opioids has been an issue in the United States, with an increasing rate of use of up to 4% in adults and even in non-cancer patients.[3] The side effects of opioid-induced bowel dysfunction most frequently occur in gastrointestinal luminal organs and include delayed gastric emptying, and prolonged small and large bowel transit.[3] Symptomatically, these manifest as nausea, vomiting, distension, and constipation.

The effects of chronic opioid use on the esophageal function have been reported recently. Opioid receptors are three different subtypes (δ, μ, and κ), and the mu-type opioid receptor is associated with dysphagia or gastroesophageal reflux disease.[3] In earlier experimental reports, injected morphine induced the loss of peristalsis in the distal esophageal body and increased lower esophageal sphincter (LES) tone in humans. Moreover, morphine decreased transient LES relaxation in patients with gastroesophageal reflux disease (GERD).[4] Moreover, other mu-type opioid agonists, including loperamide, were attempted in patients with GERD.[5] However, recent papers have reported the effects of long-term opioid use on esophageal motility in a case series of patients with esophageal dysmotility who were receiving chronic opioid therapy.[6-9] Various manometric abnormalities have been reported in patients with dysphagia, including impaired LES relaxation, simultaneous distal esophageal contractions, esophagogastric junction outflow obstruction (EGJOO), and elevated integrated relaxation pressure. These findings can mimic spastic esophageal dysmotility such as achalasia types II and III or EGJOO. Therefore, detailed previous medication history taking should be performed before treatment initiation because stopping opioid medication can restore spastic esophageal dysmotility to nearly normal peristalsis. After the widespread use of invasive treatment including POEM, POEM became the optimal treatment of choice even for EGJOO or other spastic esophageal motility disorders.[10] In patients with spastic esophageal dysmotility disorders, detailed medication history taking, including opioid medications, before treatment initiation is important because the cessation of those medications could reverse their esophageal dysmotility.[10]

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Diagnostic approaches

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High-resolution manometry and the Chicago calssification have led to a major restructuring in the classification of esophageal motility disorders. Along with this has come the recognition that a defiining feature of the major esophageal motility disorders is obstructive physiology, whether the EGJ, the distal esophagus, or both . Although the Chicago calssification has helped crystallize esophageal motility diagnoses, especially the varied phenotypes of achalasia, it has also led to the realization that there are circumstances beyond types I, II, and III achalasia in which therapies once reserved for achalasia are benefiicial. It has become apparent that the cardinal feature of achalasia, impaired lower esophageal sphincter relaxation, can occur in several disease phenotypes: without peristalsis, with premature (spastic) distal esophageal contractions, with panesophageal pressurization, or even with preserved peristalsis. no single manometric pattern is perfectly sensitive or specific for idiopathic achalasia. Furthermore, because no HRM pattern or metric is absolutely sensitive or specific for idiopathic achalasia, complementary assessments with provocative maneuvers during HRM or the endo FLIP can be useful in clarifying equivocal HRM findings. Esophageal motility disorders is classified as the two main pathophysiology as characterized by obstructive physiology at the esophagogastric junction, smooth muscle esophagus, or both. Recognizing obstructive physiology as a primary target of therapy has become particularly relevant with the development of a minimally invasive technique for performing a calibrated myotomy of the esophageal circular muscle, the POEM procedure. With the widespread adoption of POEM, there has come a shift in management strategy toward rendering treatment in a phenotypespecific manner, eg, POEM calibrated to patient-specific physiology as defined by details important treatment considerations for therapeutic interventions for the major esophageal HRM for the spastic disorders and PD for the disorders limited to the LES.

Phamacologic therapeutic apporach

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Swallowing is a complex mechanism based on the coordinated collaboration of tongue, pharynx and esophagus. Disturbances of this interplay or disorders of one or several of these components lead to dysphagia, non-cardiac chest pain or regurgitation. Most primary esophageal motility disorders including achalasia, esophagogastric junction outlet obstruction, and jackhammer esophagus are of unknown etiology. Medical treatment of primary esophageal motility disorders requires agents that reduce esophageal contractile force. Despite the beneficial effect of the various drugs on esophageal motility parameters, the clinical benefit of medical treatment of esophageal motility disorders is rather disappointing. Calcium channel blockers, nitrates, anticholinergics, phosphodiesterase inhibitors, and ß-adrenergic agonists can be used as a medical trial, especially in mild achalasia. However, medical therapy is clearly inferior to endoscopic treatment or surgery. Botulinum toxin injection into the lower esophageal sphincter (LES) has been shown to improve the symptoms (dysphasia, regurgitation, and chest pain), decrease the LES pressure, improve the esophageal emptying, and increase the LES aperture when compared with injection of placebo. However, although multiple trials have demonstrated short term benefits from botulinum toxin injection, single injection of botulinum toxin have clinical effects that are short in duration and result in frequent relapses within several months. Jackhammer esophagus a rare motility disorder presenting with dysphagia and/or chest pain. It is characterized by hypercontraction of the esophageal smooth muscle. Smooth muscle relaxants, including calcium channel blockers, atropine, botulinum toxin, and sildenafil have often been chosen as treatment options. In these numerous trials, however, the results were not consistent enough to establish a consensus. With the exception of botulinum toxin for achalasia, medical therapy of primary esophageal motility disorders is rather limited and the clinical results are poor. Further understanding of esophageal pathophysiology as well as development of new receptor-selective drugs might increase our chances of a successful treatment of primary esophageal motility disorders.

Interventional therapeutic approach

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The ideal therapy for an esophageal motility disorder consists of normalization of swallow function without symptoms and pathologic reflux. However, no current therapy has achieved this objective for any esophageal motility disorders. Recently, peroral endoscopic myotomy (POEM) has widely spread for esophageal motility disorders. Not only does POEM provide an option for myotomy of lower esophageal sphincter, it decreases operative morbidity and supplies a calibrated myotomy. POEM can be applied to each patient with a specific esophageal motility disorder which was diagnosed by recent developed technologies such as high resolution manometry (HRM) studies and/or functional luminal imaging probe (FLIP) measurements.

In a recent meta-analysis for achalasia, the short-term efficacy of POEM was superior to that of Heller myotomy (HM). Erosive esophagitis tended to be more common in the POEM group; however there was no difference in reflux symptoms and pathologic reflux on pH monitoring between POEM group and HM group.[1] Another study showed that POEM was more effective than balloon dilation in providing mid-long-term remission in patients with all subtypes of achalasia.[2] A meta-analysis according to the three achalasia subtypes reported that pneumatic balloon dilatation had a lower but still acceptable success rate compared with POEM or HM in patients with type II achalasia. However, POEM was an excellent treatment modality for type I and type III achalasia, although it did not show any superiority over HM for type II achalasia.[3]

A systematic review and meta-analysis showed POEM was a safe and effective treatment for spastic esophageal disorders. However, long myotomy more than 10 cm and prior endoscopic or medical treatments did not have a significant effect on clinical success.[4] In a retrospective study, POEM was a durable treatment in patients with non-achalasia hypercontractility disorder (15 hypercontractile esophagus, 11 distal esophageal spasm (DES), 14 esophagogastric junction outflow obstruction (EGJOO)).[5]

The interventional therapy for esophageal motility disorders is recommended to apply each patient who was fully evaluated the patient-specific physiology. However, we still need to have long-term follow-up studies and randomized comparative clinical trials for POEM and other treatment modalities for esophageal motility disorders.

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KDDW 2019 Korea Digestive Disease Week

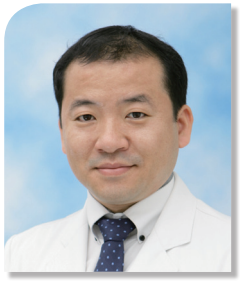
DAY 2
November 29 (Friday)

[11:00-12:30, Emerald Hall A]

Combined Symposium 02 (KPBA-KAHBPS2) Korean

Best treatment opinion for advanced hilar malignancy

Chairs: **Dong Wook Choi** (Samsung Medical Center, Korea)
Sang-Soo Lee (Asan Medical Center, Korea)



Preoperative drainage: Surgeon's opinion

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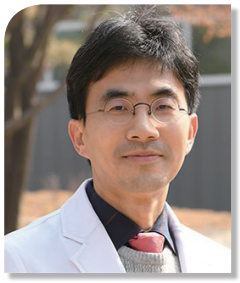
Hilar cholangiocarcinoma is an adenocarcinoma of the extrahepatic bile duct involving the left main hepatic duct, the right main hepatic duct, or their confluence, surgical resection is the only curative treatment for hilar cholangiocarcinoma. Now, major liver resection and caudate lobectomy with bile duct resection is the standard approach for hilar cholangiocarcinoma.

Most patients with hilar cholangiocarcinoma have obstructive jaundice at presentation, which is considered the most important risk factor for postoperative liver insufficiency and mortality from liver failure after major hepatectomy. In clinical practice, preoperative biliary drainage has been widely performed to reverse cholestasis-associated liver dysfunction and impaired hepatic regeneration, but the evidences supporting this practice are still controversial. Several studies demonstrated that preoperative biliary drainage is strongly related with preoperative cholangitis that is the important risk factors for postoperative mortality. The current indications of preoperative biliary drainage may be presence of acute cholangitis and candidate to portal vein embolization for small FLR volume. In patients with enough FLR volume (>50%), preoperative biliary drainage is not recommended because the risk of cholangitis and related mortality developing after drainage seems to outweigh the questionable benefit of biliary drainage.

What is optimal preoperative drainage method among PTBD, ERBD and ENBD is a more controversial issue. Yet, no randomized controlled trial has compared PTBD, ERBD and ENBD to identify the optimal method for PBD in hilar cholangiocarcinoma. In general, endoscopic drainage may be considered as the first approach for initial preoperative biliary drainage in hilar cholangiocarcinoma. PTBD could be considered in some cases involving advanced hilar cholangiocarcinoma, segmental cholangitis, or delayed resolution of jaundice. In this lecture, the pros and cons of each drainage method will be reviewed and discussed.



Preoperative drainage: Physician's opinion

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In hilar malignancy, preoperative biliary drainage should be performed only in helpful patients because it can increase postoperative morbidity and wound infection.[1] However, there is still a debate about the benefits and methods of preoperative drainage in hilar malignancy. In this lecture, I would like to talk about physician's opinions on some issues related to preoperative drainage in hilar malignancy.

There are four primary concerns for preoperative biliary drainage in hilar malignancy. 1) Who should be drained? 2) Which lobe to drain? 3) Which is better, endoscopic drainage, or percutaneous drainage? 4) Once drained, when to resect?

First, preoperative biliary drainage has both advantages and disadvantages in hilar malignancy. The most significant advantage is that it can preserve the liver function of future liver remnant after surgery. The main disadvantages are cholangitis, drainage morbidity, and seeding metastasis.[2] In general, the indications what preoperative biliary drainage is helpful in hilar malignancy are: 1) Cholangitis 2) Patients undergoing preoperative anti-neoplastic therapy 3) Patients with hyperbilirubinemia-induced malnutrition 4) Hepatic or renal insufficiency 5) Patients undergoing Portal vein embolization.

Second, if hilar malignancy requires drainage before surgery, it may be necessary to determine which lobe drainage will help. The most important consideration for this decision is the future liver remnant. This is because of the fewer future liver remnants after surgery, the worse the prognosis. The previous study has shown that aggressive drainage of future liver remnants in patients with future liver remnants <50% may help the patient's prognosis.[2]

Third, if preoperative biliary drainage is required for hilar malignancy, we have to choose between an endoscopic approach and a percutaneous approach. But this is sometimes not an easy choice. Some studies have shown that percutaneous drainage is more useful for type II, type III, and type IV hilar obstruction, but there are also disadvantages of seeding metastasis and liver injury.[3-5]

Finally, once drained, we should decide when to operate. In general, previous studies reported that the appropriate time point for surgery was bilirubin below twice the normal value.[6]

In conclusion, there are still some debates on preoperative drainage in hilar malignancy. However, there is no disagreement that future liver remnant is important for drainage determination, and that postoperative bilirubin reduction may benefit patients. However, a larger number of randomized control trials are needed to determine which drainage method between endoscopic approach and percutaneous approach is better.

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Best treatment opinion for advanced hilar malignancy: palliative option?

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The main goal of management in patients with advanced hilar malignancy is to provide benefits in terms of symptomatic improvement and quality of life through drainage procedure for obstructive jaundice.[1,2] Relief of biliary obstruction is one of main options, and aims to relieve jaundice, improve pain and pruritus, and prevent cholangitis and its-related sepsis. Effective palliative drainage is obtained by endoscopic stent placement or percutaneous transhepatic biliary drainage. However, it is often more challenging and complex in hilar obstruction than in distal biliary obstructions. Bilateral hepatic duct obstruction and more often obstruction of secondary branch add the difficulty of effective long-term biliary drainage. Inoperable hilar malignancy could be managed with non-surgical treatments including endoscopic or percutaneous biliary drainage, chemo- and/or radiotherapy, which may improve the quality of life and length of survival.

BILIARY DRAINAGE: PLASTIC VS. METALLIC

The choice of drainage stent between plastic stent (PS) and self-expendable metallic stent (SEMS) in patients with advanced hilar malignancy is still doubtful. PS has low unit cost and technically easy to insert and revise. However, it has poor patency due to lesser caliber comparing with SEMS and stent migration due to elastic restoring force often occurs.[3,4] Recently, data from a prospective multicenter cohort study showed that fewer stent-related adverse outcomes including re-interventions was observed in SEMS group compared to PS group in advanced hilar malignancy. Other retrospective study demonstrated better patency of SEMS than that of PS with similar complication rates. However, recently published article showed that no differences between two stents. The patency of PS in advanced hilar malignancy seems little shorter than that of distal biliary obstruction, comparing to SEMS; it may be due to the characteristics of PS itself including rigidity, limited conformability, inability to drain side branches. Although the initial selection between two stents in advanced hilar malignancy is still unclear, SEMS have some theoretical merits comparing to PS in terms of larger diameter, excellent conformability, ability to drain side branches, and then potential for prolonged survival.

BILIARY DRAINAGE: UNILATERAL VS. BILATERAL

Unilateral or bilateral stenting is still a controversial issue. In terms of technical difficulty, unilateral stenting is superior to that of bilateral stenting. In the past, bilateral drainage had been strongly recommended because unilateral drainage may not relieve sufficiently cholestasis and cause acute cholangitis when contrast media is introduced into an undrained site. There has only few randomized controlled trials were reported on this issue. One study comparing the unilateral and bilateral deployment of PS, the technical and clinical successes were significantly lower in the unilateral deployment group. However, other retrospective studies revealed the similar technical success rate between two groups with no obvious differences on the difficulty. Bilateral drainage may be more effective than unilateral drainage because it preserves functional volume of the liver and prolongs stent patency. Although there is some debates, multiple or bilateral drainage using metal stent is recommended for optimal drainage of a liver volume more than 50%.[5] Furthermore, active attempt for biliary drainage are considered to be important because the recovery of normal bilirubin level revealed as a prognostic factors of long-term survival.[6]

BILIARY DRAINAGE: STENT-IN-STENT VS. STENT-BY-STENT

There are no recommended guidelines or any clear consensus regarding the choice between stent-in-stent (SIS) and stent-by-stent (SBS) deployment. Bilateral SIS deployment has a more physiologic configuration and is usually placed above the level of the papilla, which reduces duodenal reflux, causing biofilm or sludge formation.[7] However, the SIS method is technically still considered a difficult procedure, particularly for revising a stent after malfunction. In addition, contralateral negotiation of the guidewire through the first inserted metal stent can be difficult if there is a tight stricture. In contrast, SBS deployment may be technically easy. If a guidewire can be inserted into both intrahepatic ducts, sequential stents can usually be inserted. Simultaneous bilateral SBS deployment has also been introduced as a technically high successful method. When stent are placed across the sphincter of Oddi, the stents in the duodenal lumen can be revised in case of malfunction. However, long stents may

not be suitable because of reflux and biofilm formation. A relatively smaller diameter of metal stents may decrease the patency of the stent in an undilated bile duct. Stents that are too large in dimeter bilaterally may compress adjacent vascular structures and overexpand the distal bile duct segment.[8]

ENDOSCOPIC ULTRASOUND-GUIDED BILIARY DRAINAGE

Due to the improvement of metal stents with various designs, feasibility and efficacy of bilateral stent placement are increasingly reported by experts. However, the procedure per se as well as its re-intervention can be technically difficult or even impossible. Technically difficulty lies in passing a guidewire or a device through a tight and complex biliary stricture or a stent mesh. In addition, due to the complexity of hilar stenting, clinical courses are often complicated by liver abscess or smoldering cholangitis and are not necessarily satisfactory. Although percutaneous transhepatic biliary drainage has been reported as a rescue after failed endoscopic drainage procedure, endoscopic ultrasound-guided biliary drainage (EUS-BD) is increasingly utilized in many centers.

In advanced hilar malignancy, intrahepatic biliary EUS-BD, mainly EUS-guided hepaticogastrostomy (EUS-HGS) to the left lobe, is utilized and data on EUS-guided right intrahepatic biliary drainage, hepaticoduodenostomy, are still limited. The advantage of EUS-BD was primarily focused on its technical advantage of biliary access. EUS-BD was reported as a rescue after failed re-intervention of transpapillary stenting. EUS-HGS was mainly performed in the left bile duct approach with technical success of over 95%.[9,10] In addition to overcoming technical hurdles in ERCP, advantage of bypassing the biliary stricture can potentially provide better clinical outcomes after EUS-BD. EUS-guided intrahepatic biliary drainage can be a treatment option when transpapillary biliary drainage fails.

LOCAL ENDOSCOPIC ABLATION TREATMENT

As cholangiocarcionoma often spreads along the biliary tree, local treatment for patency of the bile duct is of crucial interest. Photodynamic therapy (PDT) acts by creating free radicals-associated tumor cell destruction due to porfimer enrichment in tumor cells. Usually, profimers are injected intravenously followed by intraluminal photoactivation. Clinical outcomes are promising, showing overall survival rates following PDT plus stenting from up to 512 days when compared to stenting alone.[11-13] In the latter studies, PDT was associated with higher quality of life, improved biliary drainage, but also hilar biliary/hepatic infection rare. Although these results seem promising, some guidelines do not recommend PDT since other studies did not report any survival benefit. Further studies with randomization and comparison to other treatment options are needed.

Several studies on radiofrequency ablation (RFA) for hilar malignancy has been published. Most studies focused on the technical feasibility and safety on RFA for hilar cholangiocarcinoma.[14,15] Recently, RFA may prolong the stent patency and propose the adjunctive management of stent. In a recent retrospective study, RFA may be comparable to PDT in terms of safety and efficacy. Furthermore, endoscopic RFA may be more convenient that PDT in terms of simple feasibility with directed thermal ablation without the preparation of photosensitizer and the avoidance of sun exposure. Some anecdotal reports showed the risk of hepatic abscess or hemobilia after RFA in hilar cholangiocarcinoma. Therefore, optimal energy setting may be required to prevent procedural adverse events. Furthermore, comparative study between PDT and RFA should be conducted under the clinical trial.

CHEMOTHERAPY

The low rate of resection and high recurrence after surgery render most patients with hilar cholangiocarcinoma as potential candidates for systemic chemotherapy. The role of systemic chemotherapy in the palliation of cholangiocarcinoma is not defined yet. Despite the poor response to chemotherapy, systemic chemotherapy remains as the only viable anticancer treatment option in large proportion of the patients during the course of the disease. So far, no single agent or combination regimen has achieved significant survival advantages.

The most promising anticancer drug for cholangiocarcinoma is gemcitabine which has showed obvious response in patients with pancreatic cancer. In a series of single agent chemotherapy with gemcitabine in patients with biliary tract cancer, overall response rate has been reported to be around 30% with a median survival of 10 months.[16] Compared to gemcitabine alone, gemcitabine-based combination chemotherapy achieved slightly better or similar response. Cisplatin was one of the most commonly combined drugs with gemcitabine and produced overall response rate of 27.5-50% and median survival rates in the range of 5-11.3 months. When capecitabine was combined with gemcitabine, it was well-tolerated in patients with derange liver function and showed 30% of overall response rate.[17] Oxaliplatin, when combined with gemcitabine, also achieved similar response rate of 35.5%.[18] However, available data are still lacking to determine the role of systemic chemotherapy in patients with advanced biliary tract cancer.

CONCLUSION

For patients with advanced hilar malignancy, palliative biliary drainage is mandatory to improve quality of life, to prevent cholangitis, and to prolong survival. Although endoscopic or percutaneous biliary drainage is a mainstay for biliary obstruction, complex nature of hilar area hinders long-term biliary patency. Therefore, additional management to maintain biliary patency is required including systemic chemotherapy, radiotherapy, or photodynamic therapy. Since these palliative managements are still evolving, organized and systemic

clinical trials are needed to optimize biliary drainage in patients with advanced hilar malignancy.

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Advanced hilar malignancy, advanced surgical trial?

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Case discussion

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KDDW 2019 Korea Digestive Disease Week

DAY 2
November 29 (Friday)

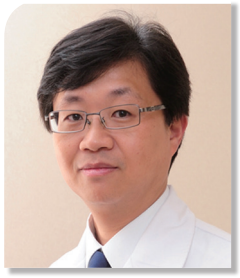
[11:00-12:30, Diamond Hall]

Symposium 09 (KASID2) English

Recent advances in colorectal cancer screening

Chairs: **Dong Kyung Chang** (Samsung Medical Center, Korea)

Joseph J. Y. Sung (The Chinese University of Hong Kong, Hong Kong)



Long-term outcome of FIT-based colorectal cancer screening program

Han-Mo Chiu, M.D., Ph.D.

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Non-invasive colorectal cancer (CRC) screening test enables selection of subjects at risk of significant neoplasm (cancer or advanced adenoma) from a large target population. It may therefore reduce the demand for colonoscopy, increase the likelihood of detecting significant neoplasm at colonoscopy and improve the efficiency of screening.

Many population screening programs use stool-based test, such as guaiac fecal occult blood test or fecal immunochemical test, as the primary screening test. Nevertheless, screening uptake especially in the Asia-Pacific region, is still unsatisfactory and substantial proportion of population are reluctant to undergo stool test. Blood-based test is expected to fill such gap and improve the screening participation. Methylated DNA markers, nucleosome markers, circulating DNA or micro RNA tests are some blood-based test that developed for CRC screening. Whist appraising blood-based test for population CRC screening, some important issues should be carefully considered: 1) test performance (sensitivity and specificity); 2) acceptance of the test by the public; 3) cost of the test. In this talk, several blood-based test will be introduced and the abovementioned issues will also be discussed.

Recent advances in colorectal cancer screening

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According to Globocan report 2018, the incidence and mortality of colorectal cancer (CRC) is increasing in Asian countries. In Korea Central Cancer Registry 2015, the CRC incidence was 2nd rank for male and 3rd rank for female among top 10 major cancers in Korea. In addition, the CRC mortality was 4th rank for male and 2nd rank for female among top 10 major cancers. In this article, update in colonoscopy for colorectal cancer screening will be touched, especially focused on lower age limit, population-based colonoscopy screening and colonoscopy quality. Optimal lower age limit for CRC screening should be reconsidered in each country. Population-based colonoscopy screening may raise safety and quality issues. The most ideal quality indicator for colonoscopy is the PCCRC rate in a National CRC Screening Program.

Increasing trend in young-onset colorectal cancer in Asia

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There is increasing evidence to suggest incidence of young-onset CRC is rising in the United States. At least 5 population-based studies using the SEER (Surveillance, Epidemiology and End Results) registries with consistent findings of increasing trend of young-onset CRC in the country. From the most recent study using data from 1975-2010, it was predicted that CRC incidence will continue to decline in the older adults, but expected to increase in the younger adults with double the rate of rectal cancer by 2030. There is an urgent need to investigate whether this may be a global phenomenon, and if so, how this epidemiological problem should be addressed. In Taiwan (1995-2014), incidence of young-onset CRC significantly increased in both male (colon cancer: 4.9 to 9.7 per 100,000; rectal cancer: 4.0 to 8.3 per 100,000) and female (colon cancer: 5.1 to 9.7 per 100,000; rectal cancer: 3.8 to 6.4 per 100,000). In Korea (1999-2014), incidence of young-onset CRC significantly increased in both male (colon cancer: 5.0 to 10.4 per 100,000; rectal cancer: 4.9 to 14.0 per 100,000) and female (colon cancer: 4.1 to 9.6 per 100,000; rectal cancer: 4.1 to 9.1 per 100,000). The most pronounced change was seen with male rectal cancer increasing by 3.9% per year in Taiwan (AAPC +3.9, 95% CI +3.3 to +4.5, $P<0.05$), 6.0% per year in Korea (AAPC +6.0, 95% CI +4.5 to +7.6, $P< 0.05$). Only significant increase in rectal cancer was noted in Japan (male rectal cancer: 7.2 to 10.1 per 100,000, female rectal cancer 4.7 to 6.7 per 100,000) and Hong Kong (male rectal cancer: 4.4 to 7.0 per 100,000).

Surveillance recommendations for hereditary colorectal cancer syndrome

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Hereditary colorectal cancer syndromes include Lynch syndrome (LS), adenomatous polyposis (familial adenomatous polyposis [FAP] and MUTYH-associated polyposis [MAP]), hamartomatous polyposis (Peutz-Jeghers syndrome, juvenile polyposis syndrome, and Cowden syndrome), and serrated/hyperplastic polyposis syndrome.

According to ACG Clinical Guideline1 and the US Muti-Society Task Force on Colorectal Cancer Guidelines,2 in individuals at risk for or affected LS, screening colonoscopy should be performed at least every 2 years beginning ages 20 and 25 years. Annual colonoscopy should be considered in individuals with confirmed mutation. Colectomy with ileorectal anastomosis is the preferred management of patients affected with LS with colon cancer or colonic neoplasia which cannot be controlled by endoscopy. Segmental colectomy is an option in patients with unsuitable for total colectomy if regular postoperative surveillance is conducted. Hysterectomy and bilateral salpingo-oophorectomy should be offered to women who are known LS mutation carriers and who have finished childbearing, optimally at age 40-45 years. Screening for endometrial cancer and ovarian cancer should be offered to women at risk for or affected LS by endometrial biopsy and transvaginal ultrasound annually, starting at age 30 to 35 years before undergoing surgery or if surgery is deferred. Screening for gastric and duodenal cancer can be considered in individuals at risk for or affected with LS by baseline esophagogastroduodenoscopy with gastric biopsy at age 30–35 years, and treatment of H. pylori infection when found. Ongoing surveillance every 3-5 years may be considered if there is a family history of gastric or duodenal cancer.

In individuals at risk for or affected with the classic adenomatous polyposis syndromes, screening for colorectal cancer by annual colonoscopy or flexible sigmoidoscopy should be performed, beginning at puberty. In families with attenuated FAP or MUTYH-associated polyposis, surveillance should be performed by colonoscopy. In case of FAP, attenuated FAP, and MUTYH-associated polyposis with documented or suspected cancer or significant symptoms, immediate colectomy is indicated. Relative indications for surgery include the presence of multiple adenomas >6 mm, a significant increase in adenoma number, and inability to adequately survey the colon because of multiple diminutive polyps. Screening for gastric and proximal small bowel tumors should be done using upper endoscopy including duodenoscopy starting at age 25–30 years. Surveillance should be repeated every 0.5–4 years depending on Spigelman classification of duodenal polyposis. Annual thyroid screening by ultrasound should be recommended to individuals affected with FAP, attenuated FAP and MAP. Biannual screening should be offered to affected infants until age 7 years with α-fetoprotein and ultrasounds. Postsurgical surveillance should include yearly endoscopy of rectum or ileal pouch, and examination of an ileostomy every 2 years.

Surveillance in affected or at-risk Peutz-Jeghers syndrome patients should include monitoring for colon, stomach, small bowel, pancreas, breast, ovary, uterus, cervix, and testes cancers. Risk for lung cancer is increased, but no specific screening has been recommended. It would seem wise to consider annual chest radiograph or chest computed tomography in smokers

Patients with serrated polyposis should receive colonoscopies every 1–3 years with removal of all polyps >5 mm. Surgery can be considered when the growth of serrated polyps cannot be controlled, or cancer develops. Colectomy and ileorectal anastomosis is a reasonable option considering the risks of metachronous neoplasia.

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KDDW 2019 Korea Digestive Disease Week

DAY 2

November 29 (Friday)

[11:00-11:40, Grand Ballroom B+C]

Presidential Lecture (KSGC) Korean

Chair: **Si Young Song** (Severance Hospital, Korea)

Adjuvant therapy after resection of pancreatic cancer

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Pancreatic cancer is one of the most lethal solid tumors. Due to the rising incidence, late diagnosis, and limited treatment options, it is expected to be the second leading cause of cancer deaths after 2030. Despite recent advances in the management of pancreatic cancer, poor survival rates continue, with 8–11% of patients at 5 years after diagnosis. Due to the lack of early symptoms and early metastatic potential of pancreatic cancer, 80% of patients receive a diagnosis at an advanced unresectable stage. Surgery is the only potentially curative treatment for pancreatic cancer, although only 10–20% of patients have resectable disease at the time of diagnosis. However, even after curative surgery, the oncological results of surgery alone are disappointing, with a median survival of 15–20 months and a 5-year survival of 8–15%, owing to the high frequency of local and distant relapses. Patients undergoing curative resection for pancreatic cancer mostly develop recurrent tumor disease; 69–75% of patients relapse within 2 years and 80–90% relapse within 5 years. Therefore, adjuvant therapy is very important after surgery. With surgery and adjuvant chemotherapy, notable progress has been observed over the past 5 years, with a large increase in median overall survival in the recent adjuvant trials.

Locoregional tumor recurrence is considered a main cause of relapse, with up to 80% of curatively resected patients undergoing an R1 resection. The potential of adjuvant radiotherapy to reduce locoregional recurrence was first tested in a gastrointestinal tumor study group randomized study using fluorouracil as a radiosensitizer in patients with negative resection margins in 1985. The study ended prematurely after the inclusion of 43 patients because the interim analysis showed a statistically significant survival difference ($p = 0.035$) in favor of the chemoradiation and adjuvant chemotherapy arm. The European Study Group for Pancreatic Cancer 1 (ESPAC-1) trial compared, with a two by-two factorial design, three adjuvant strategies with observation: chemoradiotherapy, chemotherapy alone, and chemoradiotherapy followed by adjuvant chemotherapy in 2004. Unfortunately, after a median follow-up of 47 months, adjuvant chemoradiotherapy had a significant deleterious effect on survival. The main critiques of this trial were the absence of radiation quality control and the heterogeneous treatments fields. The RTOG 9704 trial was designed to determine whether the addition of gemcitabine to postoperative radiation with fluorouracil improved survival compared with adjuvant fluorouracil in 2008. There was no difference in overall disease-free survival (DFS) between treatment groups. A retrospective analysis of the US National Cancer Database in 2015 suggested that addition of radiotherapy to adjuvant chemotherapy is associated with improved overall survival (OS). Radiotherapy was associated with an overall survival benefit when radiotherapy began 1–3 months after the beginning of chemotherapy. The above demonstrate the conflicting results that have been reported over the past three decades regarding the combination of chemotherapy and radiation therapy as adjuvant therapy; hence, the impact and the optimal schedule and timing of postoperative chemoradiation remain uncertain.

Upfront resection followed by adjuvant chemotherapy is the gold standard for patients with resectable pancreatic cancer. Considerable advances have been made during the past decade. The ESPAC-1 trial first demonstrated an overall survival benefit of adjuvant chemotherapy using fluorouracil and folinic acid. Patients who received fluorouracil and folinic acid had significantly improved median OS compared with surgery alone (20.1 vs. 15.5 months, respectively; $p = 0.009$). The German CONKO-001 trial in 2013 compared adjuvant gemcitabine administered for six cycles with observation alone. Patients receiving gemcitabine had significantly increased median DFS (13.4 versus 6.9 months; $p < 0.001$). OS was significantly improved, with a 5-year OS rate of 20.7% vs. 10.4%, and 10-year OS rate of 12.2% versus 7.7%. The ESPAC-3 study randomly assigned 1,888 patients to a 6-month course of fluorouracil and folinic acid, or gemcitabine. Results showed no differences in DFS and OS between the two chemotherapy regimens. In 2010, these results established gemcitabine as a standard adjuvant therapy. The Japan Adjuvant Study Group of Pancreatic Cancer performed the randomized non-inferiority phase III trial JASPAC-1 comparing adjuvant S-1 (oral tegafur-based fluoropyrimidine) with gemcitabine in patients with resected pancreatic cancer in 2016. With a median follow-up of 82.3 months, the OS rate at 5 years was 24.4% in the gemcitabine group vs. 44.1% in the S-1 group. The HR for OS of S-1 compared with gemcitabine was 0.57 (95% CI, 0.44–0.72; $p < 0.0001$ for non-inferiority, $p < 0.0001$ for superiority). However, the applicability of these results to a non-Japanese population is unknown. The ESPAC-4 compared gemcitabine and capecitabine with gemcitabine alone in 2017. The authors reported a slight increase in toxicities and a significant OS

benefit with adjuvant gemcitabine plus capecitabine compared with gemcitabine alone (HR, 0.82; 95% CI, 0.68–0.98; p = 0.032). However, OS curves began to separate after 2 years, and no significant benefit in recurrence-free survival was seen. Recently, combination chemotherapy with fluorouracil, folinic acid, irinotecan, and oxaliplatin (mFOLFIRINOX, with no bolus fluorouracil and 150– 180mg/m2 dose of irinotecan) was compared with gemcitabine in the PRODIGE24-CCTG PA6 trial. After a median follow up of 33.6 months, median DFS was 21.6 months in the mFOLFIRINOX group and 12.8 months in the gemcitabine group (stratified HR, 0.58; 95% CI, 0.46–0.73; p < 0.0001). Median OS was 54.4 months in the mFOLFIRINOX group and 35.0 months in the gemcitabine group (HR, 0.64; 95% CI, 0.48–0.86; p = 0.003). These results are the best DFS and OS data reported so far for an adjuvant treatment of resectable pancreatic cancer. However, grade 3–4 adverse events occurred in 75.9% of patients in the mFOLFIRINOX group and 52.9% of patients in the gemcitabine group. The APACT trial (NCT01964430) has explored nanoparticle albumin-bound nab-paclitaxel and gemcitabine in the adjuvant setting compared with gemcitabine alone. Unfortunately, median DFS was not different between arms, 19.4 months (nab-paclitaxel/gemcitabine) and 18.8 months (gemcitabine); HR, 0.88; 95% CI, 0.729–1.063; p = 0.1824). A modest but significant increase in OS was seen at interim analysis in favor of the combination arm (HR, 0.82; 95% CI, 0.68–0.996; p = 0.045). A further analysis of the ESPAC-3 study was performed to investigate the optimal timing between surgery and the start of chemotherapy, and the optimal duration of chemotherapy. No difference in survival was seen between patients commencing chemotherapy within 8 weeks of surgery and those commencing chemotherapy later than 8 weeks after surgery. Patients who completed all six planned cycles of treatment had better survival than those who received between one and five cycles only (HR, 0.516; 95% CI, 0.443–0.601; p < 0.001). Completion of therapy was also an independent factor associated with survival. In another retrospective series, including 488 patients from five institutions, delayed initiation of adjuvant chemotherapy >12 weeks after surgery is associated with the same survival benefit than the timely initiation group as compared with no adjuvant chemotherapy.

There are many several kinds of adjuvant chemotherapy regimen but the mFOLFIRINOX regimen has recently shown superiority over gemcitabine alone and may be a new standard adjuvant chemotherapy in fit patients with good performance state. The impact of chemoradiation remains uncertain as an adjuvant treatment and may be considered in some clinical setting such as R1 resection.

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KDDW 2019 Korea Digestive Disease Week

DAY 2
November 29 (Friday)

[14:00-15:30, Convention Hall A]

Combined Symposium 03 (KSPGHAN-KSG) Korean

Intestinal failure: nutritional therapy in medical practice

Chairs: **Jong-Jae Park** (Korea University Guro Hospital, Korea)
Yong Joo Kim (Hanyang University Medical Center, Korea)

Nutritional approach to pediatric intestinal failure

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In children with intestinal failure (IF), the mechanisms of their malabsorptions consists of acid hypersecretion, rapid intestinal transit, impaired residual bowel, loss of surface area, bacterial overgrowth, and bile acid wasting. Regarding the feeding method, continuous feedings are often beneficial [1], because the shorter the remnant bowel is, the less likely to tolerate bolus. In addition, tube feeding is often needed due to gastroesophageal reflux and motility disorders (hypermotility and hypomotility), which are commonly observed in children with IF. An increase of 600-700 kcal per day was noted in an adult group of IF with tube feedings compared to that of only oral feedings [1]. However, small amounts of bolus must be introduced frequently to prevent oral aversion.

The ideal formula for feeding children with IF has not yet been determined and formulae must be appropriate according to adaptation phases: initial, later, and maintenance. Amino acid-based formula and breast milk lessened the duration of parenteral nutrition (PN) dependence [2]. Breast milk feeding is recommended because of its good components; glucagon-like peptide-2, epithelial growth factor, secretory immunoglubins, lysozyme, and interferon, which may enhance the immune system against NEC. Neocate is widely used during early rehabilitation processes of IF, in spite of its unpalatable taste, hyperosmolarity (340 mOsm/kg), and lack of optimal calcium-phosphorous ratio compared to premature formulae. Neocate is thought to decrease bowel inflammation. The transition period from PN to enteral feedings is liable to lead nutritional instability, which was noted in a recent study [3]. In the study, more than one vitamin and mineral deficiencies were noted in 33% and 80% of the children with IF, respectively. Dextrose is the primary source (45-55% of total calories) of entry in most PN regimens and the stable input of the dextrose can be difficult to achieve in an era of lipid minimization and PN cycling.

PN-related liver disease (PNALD) is a relatively common and also serious complication in infants with IF. Six-month direct hyperbilirubinemia was associated to the liver failure in children with SBS [4]. About 40-80% of children with IF endure PNALD [5]. Prematurity, low birth weight, remnant bowel length, duration of parenteral nutrition, blood stream infection, lack of enteral nutrition, and components of PN are associated with PNALD [5]. Among the ways to avoid soybean-based lipid, the introduction of Omegaven® leads us to the new era of lipid management. Omegaven consists of fish oil, which showed immunomodulatory effects on the liver and impaired the biliary secretion less [6, 7]. In a open labeled study, Puder and colleagues showed infants with omegaven had improved survival compared infants with conventional soybean-based lipid emulsions [6]. In addition, they did not have hypertriglyceridemia, coagulopathy, and essential fatty acid deficiency. Lipid minimization seems to be an alternative to Omegaven [8]. Although mild essential fatty acid deficiency developed, children with IF had similar decline in bilirubin as in the Omegaven studies. On the contrary, a recent study stated that lipid reduction did not prevent the cholestasis in children with IF [9]. Therefore, there is a need to find out an optimal amount of lipid between minimal requirement to prevent EFAD and that which avoids PNALD and enhances growth and normal neurodevelopment.

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Intestinal adaptation and management of short bowel syndrome

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Tips for successful home parenteral nutrition

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Intestinal failure (IF) is an increasing disease entity in the field of pediatric nutritional support. Aggressive surgical interventions and supportive cares targeted for patients with volvulus, necrotizing enterocolitis and Hirschsprung disease make this possible. Recently improved postoperative supportive care including parenteral nutrition (PN), use of hydrolysate formula, and various enteral feeding protocols make also better outcomes than yesterdays. However, about one thirds of the patients with extensive bowel loss still could not avoid IF status eventually, so there are many unmet needs for this group of patients.

In this lecture, I will briefly summarize the recent advance of pediatric parenteral and enteral nutrition for the children with IF and short bowel syndrome. Enteral autonomy is the key factor of the treatment to overcome the handicaps of short bowel or non-functioning bowel. To achieve the enteral autonomy, we usually try to use the tolerable enteral nutrition and prevent the intestinal failure associated liver disease (IFALD). Use of omega-3 based emulsion and ursodeoxycolic acids seems to be better for the prevention or treatment of pediatric IFALD according to a few reports. For the patients with PN dependency, home PN could be applied. Process of home PN is a kind of meticulous technique. This needs lots of knowledge, understand, cooperation both from parents and patients. Tips for successful home PN include how to make experienced multidisciplinary nutritional support team, devotion from parents and family, supportive hospital policy, and social support system.

We are still in shortage of resources for the care of IF in children worldwide. Doctors, hospitals managers, governmental officers, pharmaceutical companies and families with patients should cooperate together to overcome this big huddle in health of children.

KDDW 2019 Korea Digestive Disease Week

DAY 2

November 29 (Friday)

[14:00-15:30, Convention Hall B]

Combined Symposium 04 (KASL-KAHBPS) Korean

Approach to cystic hepatic lesions: from simple cyst, complicated cyst, polycystic liver disease, biliary cystadenoma, and cystadenocarcinoma

Chairs: **Won Young Tak** (Kyungpook National University Hospital, Korea)

Hee Jung Wang (Ajou University Hospital, Korea)

Differential diagnosis of cystic lesions

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Hepatic cystic lesions are frequently encountered in routine practices. A cystic lesion is a well-defined lesion with predominant near-water attenuation (0–30 HU) or signal intensity that exhibits negligible enhancement at dynamic imaging. The internal septa refer to the partitions or membranes that divide the lesion into multiple compartments. Septa may vary in thickness, uniformity, extent of enhancement, and mural nodularity. Cystic lesions of the liver can be classified as developmental, neoplastic, inflammatory, or trauma-related lesions. Many overlapping characteristics were shown to exist among the various cystic lesions. Therefore, familiarity with the radiological features, in combination with clinical information will provide enough information for adequate lesion characterization.

A. CYSTIC LESIONS ASSOCIATED WITH THE DUCTAL PLATE MALFORMATION

1. Biliary Hamartomas (Von Meyenburg complex)

Biliary hamartoma is a small lesion composed of dilated bile ducts and interspersed fibrous or hyalinized stroma. It is known as ductal plate malformation of the smaller, more peripheral interlobular bile ducts. Biliary hamartomas typically show marked hyperintensity on T2WI. However, solid, absent, and rim enhancement have been reported. Differential diagnosis of biliary hamartoma includes metastases, microabscesses, and Caroli's disease. Features that suggest hamartoma over metastases are small size (most hamartomas are less than 1 cm), thin rim enhancement with no centripetal progression, and high fluid content.

2. Hepatic cyst

Hepatic cyst is thought to arise from cystic dilatation of Meyenberg complexes. The simple cysts are lined by cuboidal epithelium, surrounded by a thin fibrous stroma, and contain serous fluid. On MR uncomplicated cysts are homogeneously T1 hypointense and T2 hyperintense. Cysts complicated by hemorrhage or infection may have variable T1 and T2 signal intensity and thickened walls.

3. Polycystic liver disease

Polycystic liver disease is attributed to cystic dilatation of the Meyenberg complexes. It vary from less than 1 cm to greater than 10 cm and usually are round but may be polygonal or irregular. There is no communication with each other or biliary tree. Typically, polycystic liver disease shows low T1 and high T2 signal intensity and no contrast enhancement. However, intracystic hemorrhage may result in cysts of varying signal intensity including T1 hyperintensity, fluid-fluid levels, or thickened walls.

4. Caroli's disease

Caroli's disease is characterized by multifocal segmental dilatation of the large intrahepatic bile duct retaining their communication with the biliary tract. It typically manifests as saccular or fusiform cystic dilatation of the intrahepatic bile ducts often containing calculi or sludge. Contrast-enhanced CT or MRI often shows fibrovascular bundles with strong contrast enhancement within dilated cystic intrahepatic ducts (central dot sign). Complications are due to bile stagnation leading to cholangitis, stone formation and liver abscess. Cholangiocarcinomas have been reported with a prevalence of 7%.

B. NEOPLASTIC LESION

1. Biliary cystadenoma and cystadenocarcinoma

It has been reported that 90% of biliary cystadenoma appear in the intrahepatic bile duct; the others occur within the extrahepatic biliary tract or gallbladder. Biliary cystadenoma occurs predominantly in middle-aged women and may potentially transform into cystadenocarcinomas. Biliary cystadenocarcinoma is more evenly distributed between males and females and present a decade later. Typically, they are large, solitary, multilocular cystic lesions with well-circumscribed smooth margins and internal septa. Calcification may be seen within the wall and the septa in a minority of cases. The large polypoid, papillary excrescences in the wall usually indicate malignant transformation.

2. Metastases

Sometimes cystic metastasis predominantly composed of large intratumoral areas of liquid attenuation with negligible contrast enhancement may appear as neoplastic cyst. They are formed through (a) necrosis of hypervascular metastases secondary to rapid growth beyond the vascular supply (eg. neuroendocrine tumor, melanoma,

GIST); (b) abundant mucin production by acinar structure and glandular tissue from mucinous adenocarcinoma. The enhancing septa in a metastatic cystic lesion tend to have an irregular thickness. The inner surfaces are typically ragged, serrated, and ill-defined with multiple mural nodules. The well-documented representative example is the cystic change in metastatic GIST after treatment with imatinib mesylate.

C. DIFFERENTIAL DIAGNOSIS

1. Pyogenic abscess

Pyogenic abscess is the most common cause-biliary tract infection and E.coli is the most frequently identified organism. Diabetes is present in up to half of patients. They may be unilocular or multiseptate. On MRI, most of them are hyperintense on T2WI. The cluster sign, which is grouping of multiple abscesses that may then coalesce into a single larger abscess, is suggestive of pyogenic abscess.

2. Undifferentiated embryonal sarcoma

Undifferentiated embryonal sarcoma (UES) is a highly malignant hepatic neoplasm. It is usually seen in the pediatric age group but it can rarely be seen in the late childhood or early adulthood. UES presents as a large solitary lesion commonly in the right lobe. On unenhanced CT, UES appears cystic lesion, reflecting the high water content of myxoid stroma, and contains septations and peripheral nodules. Contrast-enhanced CT can show different degree of enhancement. It appears cystic on MRI because of myxoid stroma but shows heterogeneous enhancement after contrast administration.

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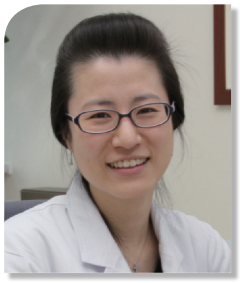

Follow-up strategy

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Hepatic cystic lesions are increasingly found as a mere coincidence on abdominal imaging techniques. The differential diagnoses range from benign lesions of no clinical significance to malignant and potentially lethal conditions. The management of benign hepatic tumors ranges from conservative to aggressive, depending on the nature of the lesions. New imaging modalities, increased experience of radiologists, improved definition of radiologic characteristics, and a better understanding of the clinical features of these lesions have increased the accuracy of diagnoses and reduced the need for invasive diagnostic tests. Despite the lack of data on long-term outcome, we review follow-up strategy for hepatic cystic lesions.

SIMPLE CYST/COMPLICATED CYST

Simple cysts arise congenitally from aberrant bile duct cells and contain a clear, bile-like fluid.[1] Most simple cysts are diagnosed incidentally on abdominal imaging study. The prevalence of simple cysts ranges from 2.5% to 18% and increases with age.[2,3] More than half of individuals older than 60 years are likely to have one or more simple cysts. Most patients are asymptomatic, but in a small fraction of patients could have symptoms such as abdominal pain, early satiety, nausea and vomiting.[4]

Treatment of simple hepatic cyst should be conservative because of their generally benign nature, and no further treatment is required in these cases. However, rare patients have symptoms when complications such as hemorrhage, rupture, infection and biliary obstruction are present.[5] Treatment would be performed when the patients had symptoms or complications.[6-9]

Hepatic simple cysts are usually easily diagnosed, but hemorrhagic hepatic cysts often show complicated imaging findings although intracystic hemorrhage is a rare complication. It is sometimes difficult to differentiate hemorrhagic hepatic cysts from cystic neoplasms, particularly when the former are accompanied by mural nodules that enhance after intravenous contrast medium injection on CT or MRI.[10-14] Generally, spontaneous tumor regression is a rare phenomenon in cystic neoplasm and a decrease in cyst size may be a specific finding of hemorrhagic hepatic cysts with enhancing mural nodules.

POLYCYSTIC LIVER DISEASE

PCLD is characterized by the presence of extensive hepatic cysts that are microscopically similar to simple hepatic cysts but more numerous (usually >20) and larger.[15] A major distinction between simple hepatic cyst and PCLD is that the latter has a strong genetic component resulting in the formation of multiple cysts within the liver. Most patients with PCLD have concomitant polycystic kidneys, and the underlying genetic mutation is in either PKD1 or PKD2.[16] These mutations are inherited in an autosomal dominant manner, so patients with this condition actually have autosomal dominant polycystic kidney disease (ADPKD) with associated polycystic liver. Isolated PCLD (IPCLD), by contrast, can be brought about by at least 2 mutations in PRKCSH and SEC63.[17,18] Most patients have ADPKD, with the remainder having IPCLD.[19,20]

IPLD have relatively preserved renal functions, but ADPKD is a disorder characterized by bilateral renal cysts, urinary tract infection, hematuria, nephrolithiasis, hypertension and progressive renal failure due to progressive enlargement of cysts and fibrosis.[21] It is leading cause of end stage renal disease and the most common inherited kidney disease. Follow up strategy for ADPKD should be based on patient's renal function, hypertension and accompanied complications by nephrologist. Annual follow up is recommended in patients with normal blood pressure and relatively preserved renal function.[22,23]

Most patients are asymptomatic and do not require treatment. Liver failure or complications of advanced liver disease, such as infection or intracystic hemorrhage, are rare. Only less than 5% of patients have acute medical complications. Treatment should be considered in cases of persistent symptoms or associated complications.

BILIARY CYSTADENOMA/BILIARY CYSTADENOCARCINOMA

It is estimated that cystic neoplasms constitute approximately 5% of liver cysts, among which the malignancy is about 5%.[24,25] More than 85% of HC are reported in women, and typically in middle-aged persons in the fifth decade of life. The incidence of HCa is approximately 1 per 10 million patients. The risk of a biliary cystadenoma transforming into a biliary cystadenocaracinoma has been reported to be up to 20%.[26]

The USG characteristics of cystic neoplasms for both cystadenoma and cystadenocarcinoma are the following: a round or oval shape, irregular border, hypoechogenic echo pattern with hyperechogenic septation or solid structures, wall enhancement and dorsal shadowing due to calcified area. Like USG, CT and MRI show markedly similar characteristics for cystadneoma and cystadenocarcinoma: internal septations, thickened and irregular wall, papillary projections, calcifications and wall enhancements.[27,28] Differentiation between cystadenoma and biliary cystadenocarcinoma is very difficult. Cystadenomas predominantly have thinner septa and more regular walls, whereas solid structures, intracystic hemorrhage and vascularised septation on contrast-enhanced CT are more suspicious for cystadenocarcinoma. The diamiter of the mural nodule in cystadenoma is much smaller (< 1 cm) than mural or septal nodules in biliary cystadenocarcinomas (> 1 cm).

The primary treatment of cystadenoma and cystadenocarcinoma is hepatic resection, usually by a major liver resection with 1cm margin, especially for biliary cystadenocarcinomas.[29]

Based on published series for biliary cystadenomas, recurrence rates seem to be very low (5-10%) following appropriate surgical treatment. In a large series of patients with benign biliary cystadenoma and a follow up period of 18 years, overall survival was >90%.[30] Most of the recurrences associated with biliary cystadenocarcinoma are in the liver itself and are probably a reflection of inadequate initial local management. The 5-year survival associated with biliary cystadenomcarcinoma is much better when compared to other hepatic malignancies such as HCC and cholangiocarcinoma (57% vs. 40% vs. 22%).[31]

CONCLUSION

Hepatic cystic lesions encompass a wide spectrum of disorders from simple hepatic cyst to biliary cystadenocarcinoma. The first important step, if hepatic cystic lesion is observed, is to make a definitive diagnosis of the nature of the cystic lesion. The second is determining whether the patient's symptoms are related to the cystic lesion. Lastly, it is need to determine whether treatment is necessary and which treatment is most appropriate for the patients.

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Medical and interventional management

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Surgical management

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To differentiate the different cystic hepatic lesions, with an emphasis on the imaging features is important step to make a treatment plan. A practical algorithm for approaching the diagnosis of these lesions is crucial. In this respect, the number and morphology of the lesions and determination of whether there is a solid component are key imaging features that are helpful for approaching the diagnosis of cystic hepatic lesions (Table 1). Familiarity with these features and knowledge of the clinical associations will help the radiologist to establish a definitive diagnosis or provide a reasonable differential diagnosis.

For treatment plan, developmental cysts have no malignant potential. Thus, they need no further management, if there is no complication. In cases of complications with infection, rupture, or hemorrhage, nonsurgical approach is usually successful. If it fails, consider surgical treatment. Massive polycystic liver disease needs volume reductive surgical treatment including liver transplantation. Inflammatory cysts

Table 1.

Lesion	Key Imaging Findings	Key Clinical Data
Developmental		
Simple cyst	Solitary cyst or multiple cysts	
Biliary hamartoma	Multiple irregular lesions	
	May have enhancing component	
Caroli disease	Multiple lesions	
	Enhancing "central dot" sign	
	Communicating with biliary tree	
Polycystic liver disease	Multiple large cysts	History of polycystic renal disease
	Usually associated with renal cysts	
Ciliated foregut duplication cyst	Classic subcapsular location in medial segment	
Inflammatory		
Pyogenic abscess	Complex cyst with enhancing rim	Clinical and laboratory findings of infection
Amebic abscess	Complex cyst with "double-target" appearance	Patient is from endemic areas
Hydatid cyst	Complex cyst with peripheral daughter cysts	Patient is from endemic areas
Fungal microabscess	Innumerable small cysts	Patient is immunocompromised
	Splenic and renal lesions may be present	
Intrahepatic pseudocyst	Findings of pancreatitis	Clinical and laboratory findings of pancreatitis
	Pseudocysts may be present in lesser sac	
Neoplastic		
Biliary cystadenoma and cystadenocarcinoma	Large complex cystic lesions with enhancing septations	Absence of infection or known metastatic disease
Cystic HCC	Complex lesion	Liver cirrhosis and increased α-fetoprotein level
	Hypervascular component with washout on portal venous phase	
Cystic metastasis	Multiple complex cystic lesions with enhancing component	History of malignancy
Undifferentiated embryonal carcinoma	Large complex cystic lesion on CT and MRI	Usually seen in adolescents
	Solid appearance on ultrasound	
Trauma-related		
Biloma	Large simple cyst with or without an enhancing pseudocapsule	History of trauma, surgery, or intervention
Seroma and hematoma	Cyst with variable density and intensity	History of trauma, surgery, or intervention
	No enhancement	

should be treated with proper medical treatment. In cases of refractory to medical treatment, additional effective drainage is helpful. Mostly, cysts infected with parasites show a much higher rate of failure to medical treatment. Surgical treatment is also more difficult than others because rupture of a cyst during surgical manipulation makes peritoneal seeding of parasites. Neoplastic cysts should be resected with safe margin.

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KDDW 2019 Korea Digestive Disease Week

DAY 2

November 29 (Friday)

[14:00-15:30, Convention Hall C]

Symposium 10 (KSNM3) Korean

Gut microbiota and diet in IBS

Chairs: **Myung-Gyu Choi** (The Catholic University of Korea Seoul St. Mary's Hospital, Korea)

Kyu Chan Huh (Konyang University Hospital, Korea)

Gut microbiota in the pathophysiology of IBS

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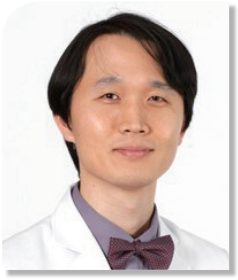
The gastrointestinal (GI) tract harbors a huge number and variety of commensal microbes referred to as the gut microbiota: approximately 100 trillion microorganisms and more than 1000 bacterial species. Interactions between the host and microbiota are very important to maintain homeostasis in host health. The gut microbiota are responsible for developing the host immune function, maintaining normal GI physiology, and metabolizing undigested foods. The complex signaling between the gut microbiota and their hosts can alter physiologic functions of gut by neural, hormonal and immunological pathways, and it can be implicated in diseases including functional bowel disorders, such as irritable bowel syndrome (IBS).

IBS is one of the most common functional GI disorders characterized by chronic or recurring abdominal pain or discomfort associated with altered bowel habits, which affects 5-10% of the general population. IBS is considered a multifactorial disorder associated with genetic, physiological, immunological, psychosocial and environmental factors. Although the causes of IBS are not clearly known, visceral hypersensitivity, altered gut motility, and dysfunction of the brain–gut axis and immune system are suggested as the causes. Recently, alterations in the gut microbiota have been suggested as an important etiological factor. The gut microbiota can influence GI sensory and motor functions, causing IBS symptoms, directly through the neuromodulatory molecules or, indirectly, through the products of microbial metabolism, such as short-chain fatty acids and gases. Methane production, for example, has been linked to slow transit constipation. The gases produced by gut microbiota can also cause abdominal pain directly. In terms of sensory function, hypersensitivity to colonic distension of IBS patients was transferred to rats by the fecal microbiota in the animal model. The perturbation of gut microbiota by antibiotic administration has been shown to increase visceral hypersensitivity, and this effect was reversed by probiotic treatment in a mouse model. Lactobacillus strains induced the expression of opioid and cannabinoid receptors, and modulated visceral pain. Furthermore, although the results are not consistent and the causality is unclear, many studies have reported differing microbial diversity and composition between IBS and controls, and its correlation with clinical phenotypes: decrease in bacterial diversity (richness), increase in Firmicutes to Bacteroidetes ratio, decrease in Lactobacilli and Bifidobacteria population, and increase in Streptococci and Ruminococcus species. The efficacy of probiotics and non-absorbable antibiotics (rifaximin) in patients with IBS provide further supports the role of gut microbiota in pathogenesis of IBS.

The disturbances of gut microbiota can alter GI physiology and lead to functional bowel disorders including IBS, however, on the other hand, alteration of gut motility may also change the diversity and composition of the gut microbiota. The association between the gut microbiota and IBS is still poorly understood, but future longitudinal human studies and mechanistic animal studies may elucidate the exact relationship between gut microbiota and altered GI physiology underlying IBS, and help find more effective and individualized therapies manipulating the gut microbiota in IBS, including diet therapy and fecal microbiota transplantation.



Interactions between diet and gut microbiota

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Gut-brain interaction plays a central role in determining IBS symptom pattern and severity. In human guts, microbiota have a direct effect on the intestinal barrier and immune activity under the indirect effects of diet. The interaction of these factors results in presentation of visceral hypersensitivity and GI motor dysfunction. Mechanisms by which food may result in IBS symptoms include primary effects, including osmotic, chemical, mechanical, neuroendocrine, probiotic, prebiotic effect. Secondary effects may include fermentation byproducts, intraluminal pH, and microbiome modulation. In other words, microbiomes already present in foods (especially fermented foods) are probiotics, and nutrients that can be metabolized by the gut microbiota are likely to directly modulate gut microbiota as prebiotics.

Can we change the composition of gut microbiota by changing our eating habits? If intestinal microbial composition can be altered by diet, these substrates can be administered to induce intestinal microbial metabolism in a healthy way. As an epidemiological study suggesting that possibility, investigators compared fecal microbiota in African and European children based on millet and sorghum.1 Some classes of phylum Bacteroidetes, which are not identified in European children, account for more than half of the total bacterial flora in African children. Animal testing also confirms that short-term dietary changes lead to huge changes in fecal flora.2

There is a study confirming that the composition of microbial clusters observed in feces changes rapidly with the consumption of starch that is not digested and absorbed in the small intestine.3 Supplementation with inulin or galactose has also shown a relative increase in Bifidobacterium.4 These results suggest that carbohydrate intake, which is not absorbed, can lead to changes in the composition of the gut microbiota, which in turn can lead to metabolic changes in the host intestine. On the other hand, bacteria that can flexibly use fermentation substrates may not be affected by these dietary changes.5

Interestingly, both the prebiotics and low FODMAP diet caused the improvement of symptoms of IBS, but the composition of gut microbiota changed in the opposite direction (in aspect of Bifidobacteria and Bilophila wadsworthia).6,7 There are recent reports that food additives may make intestinal barrier compromised in the presence of emulsifiers.8 FODMAPs are also used as food additives (fructose, inulin), so low FODMAP diets and elimination diets not only have a direct effect on gut microbiota, but also have a beneficial effect through avoiding diets that directly alter the intestinal barrier.

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Diet therapies for IBS

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The recent researches have shown that diet could trigger symptoms in majority of IBS patients. Because it is well known to the public, up to 70 percent of patients have been reported to have tried to modify their diet.

The proposed mechanisms included the direct effects of diet on gut such as osmotic, chemical, mechanical, neuroendocrine, and pro/prebiotic effects. The indirect effects on gut environment were also suggested that diet could cause fermentation by-products, altered intraluminal pH and microbiome.

Low fermentable oligo-, di-, mono- saccharides and polyols (FODMAPs) diet as the influencing diet has been focused the most in a recent decade, however, traditional dietary advice and the gluten-free diet (GFD) also are still emphasized. In this lecture, we will review the effects of dietary therapies for individuals with IBS from the current available literatures and suggests some useful dietary advices for control the symptoms.

1. GENERAL DIETARY ADVICE

As a first line dietary therapy for IBS, it includes healthy eating and lifestyle management which based on clinical experiences as well as known physiological effects; regular meals, fiber intake, adequate fluid intake intake, restriction of alcohol and caffeine intake, decreasing fat intake and avoiding ingredients that exacerbate symptoms. Binge drinking has been shown to have a significant association with IBS symptoms, especially, those with diarrhea-predominant IBS. Capsaicin has been demonstrated to cause abdominal pain, however, desensitization is possible with continued use. Soluble fibers are beneficial, but no effect was seen with insoluble fibers like bran.

2. LOW FODMAP DIET

FODMAPs are short-chain carbohydrates which are osmotically active and poorly absorbed, increasing small bowel water content and intestinal transit.

Several studies have shown that the adequate symptom relief was observed in 68% to 76% of patients with IBS who maintained the low FODMAP diet over 4 to 8 weeks. Concerns about the paradoxical changes in gut microbiome, especially reduction in Bifidobacteria species and possible malnutrition in long-term therapy have been raised. However, a recent study showed that long-term FODMAP restriction was a nutritionally adequate and acceptable strategy in >50% of the patients receiving dietary intervention.

There are now a growing number of RCTs demonstrating the efficacy of the low FODMAP diet in the short-term, with some emerging data on the long-term 'adapted' low FODMAP diet. The low FODMAP diet can be delivered with a three-phase process: initially ‘elimination phase’ of a strict restriction of all high FODMAP-containing foods over a 4-to 8-week period, then followed by a ‘reintroduction phase’ of gradual intake the food to tolerance, finally, the ‘personalization phase’ of long-term follow-up. Most IBS patients are seemed to follow an ‘adapted’ low FODMAP diet rather than the strict reintroduction phase at long-term.

3. GLUTEN FREE DIET

There are also several RCTs showing the benefits of a GFD in IBS; up to 10% of the population has suggested self-reporting non-coeliac gluten sensitivity and described gluten-based products to provoke intestinal symptoms compatible with IBS. However, the mechanism is uncertain until now, except for gluten having been reported to alter intestinal barrier function in IBS. One additional possibility is that GFD has the benefits from reducing fructan rather than restricting gluten itself.

All these dietary therapies are viable options for individuals with IBS, and whichever dietary option is chosen, it is also important to prevent malnutrition and abnormal diet behavior.

Future well designed studies are needed to clarify the comparative efficacy and practical usefulness of these diet therapy. Additionally, the clinical implications of altered gut microbiota caused by dietary treatment should also be further elucidated.

Microbiota-based therapies for IBS

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Irritable bowel syndrome (IBS) is a complex, heterogenous disorder and its pathogenesis is multifactorial and may relate to gut dysbiosis, changes in visceral sensation and motility, and genetic and environmental factors. Targeting the gut microbiota for therapeutic intervention in IBS remains an area of significant interest for patients and clinicians. Different therapeutic strategies targeting dysbiosis, including dietary manipulations, probiotics, the use of poorly absorbable antibiotics or fecal microbiota transplantation (FMT), have been suggested.

The majority of patients with IBS associate their symptoms with the ingestion of specific foods. General advice on healthy eating and lifestyle is recommended as the first-line approach in the dietary management of IBS. If first-line approach do not lead to adequate symptoms control, a reduction in intake of foods rich in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs). Observational studies and randomized controlled trials (RCTs) have indicated that the low FDMAP dietary approach leads to symptom improvement in up to two-thirds of patients in IBS. Many IBS patients will respond within 1-2 week of initiating the diet, whereas some can take 3-4 week to respond. Probiotics have been studies extensively in adult and pediatric populations with functional gastrointestinal disorder (FGID). Systematic review of probiotics in IBS suggested evidence for efficacy on global IBS symptoms, abdominal pain, bloating, and flatulence; however there remain many unanswered questions regarding strain-specific effects, mechanisms of action, mode of administration and dosing, and patient selection. Rifaximin is an oral, nonsystemic, broad-spectrum antibiotic that targets the gut and is associated with a low risk of bacterial resistance. After initial small-scale clinical trials in patients with symptoms compatible with FGIDs, a large-scale clinical trial in patients with IBS who did not have constipation has been published, with favorable results showing that 8–10% more patients achieved adequate relief of global IBS symptoms during the 10-week follow-up period after a 2-week treatment with rifaximin than after placebo. Although rifaximin is FDA-approved for the treatment of IBS with diarrhea, relapse among patients who have a response is usual, and the mode of action is unclear, given evidence that the microbiome is not altered. More recently, results of several trials investigating the efficacy of FMT for IBS have been reported. Recent meta-analysis including five RCTs showed no significant improvement in IBS symptoms with FMT vs placebo. However, subgroup analyses demonstrated a potential benefit on IBS symptoms when FMT was administered via lower gastrointestinal tract, but no benefit was observed when the upper gastrointestinal tract. More research regarding the effect of FMT in IBS subgroup is required before FMT can be considered a mainstream treatment for IBS. In addition, many questions including mechanism of action, adequate donor selection, route and number of administration, and short and long term safety require further study.

An increasing number of interventions targeting microbiome are available or are being evaluated in clinical trials. Further research on the potential benefits of these treatments, including an understanding of their effects on the pathophysiologic mechanisms of IBS, is warranted.

KDDW 2019 Korea Digestive Disease Week

DAY 2

November 29 (Friday)

[14:00-15:30, Emerald Hall A]

PG Course 05 (KPBA) Korean

Improve your ERCP skill for CBD stone removal

Chairs: **Seok-ho Dong** (Kyunghee University Medical Center, Korea)

Sang-Woo Cha (Soon Chun Hyang University Seoul Hospital, Korea)

Optimal cannulation

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Performing successful selective biliary cannulation (SBC) is the first challenge of endoscopic retrograde cholangiopancreatography (ERCP) intervention, for common bile duct stone removal. It has been realized that SBC is the most efficient and safe technique to access of the biliary duct minimize complications, especially post-ERCP pancreatitis (PEP). Numerous factors affect SBC success rates, including the morphology of the papilla, altered anatomy, operator experience, the technique, and accessories used. The following section focuses on enhancing the standard cannulation techniques and describes alternate solutions for when standard methods of SBC fail. Proper positioning of the papilla is a key to successful cannulation.[1] The position of the papilla should be en face with the duodenoscope in the short position. When the papilla is en face, the relative location of biliary and pancreatic orifices is toward 11-1 o'clock and 3-5 o'clock, respectively. Because the bile duct usually runs parallel, whereas the pancreatic duct (PD) is perpendicular to the duodenal wall, the next step is to observe the papilla and anticipate the direction of the desired duct before finally attempting cannulation.

There are two methods typically used to achieve deep biliary cannulation; guidewire assisted technique and contrast guided technique. Wire-guided cannulation can be performed in two ways - sphincterotome first or guidewire first. In the latter technique, the guidewire protrudes 2-3 mm outside the sphincterotome, enters the papillary orifice first, and is manipulated into the duct of choice. This technique is especially useful for cannulating small or stenotic papilla. Contrast-guided cannulation has been performed as a conventional cannulation technique; but, it has been suggested that the pancreatic contrast injection might be associated with PEP. Despite this, contrast-guided cannulation and wire-guided cannulation have comparable safety and efficacy in expert hands.[2] It is not uncommon for the guidewire to enter the PD while attempting SBC. In such a case, a reasonable next step is to use the double wire technique, where the guidewire remains in the PD and a second guidewire is passed beside it to cannulate the common bile duct. The first guidewire blocks further entry into PD, and straightens the common channel.

If SBC was not successful using the guide-wire or contrast-guided techniques, alternative techniques like precut biliary sphincterotomy in the form of conventional precut technique and fistulotomy can be considered. The conventional precut technique is usually defined by the use of a needle knife to perform a stepwise incision of the mucosa, starting at the superior lip of the papillary orifice and moving in the direction of the bile duct until the underlying biliary sphincter is visualized. It is beneficial to rehearse this technique adjacent to the papilla before making the actual cut. Early and timely use of the precut technique is considered safe and reduces the risk of PEP.[3] However, it should be noted that the conventional precut technique is not a replacement for the standard cannulation techniques. Needle knife fistulotomy involves performing an incision in the mucosa starting directly over the roof of the papilla, followed by an upward or downward cut until the underlying biliary sphincter is visualized. In this technique, the upper and lower thirds of the papillary roof are spared from cutting and the papillary orifice stays untouched, explaining the reduced risk of PEP compared to the conventional precut technique.[4] Therefore, ESGE recommends needle knife fistulotomy as the preferred technique for precutting.[5] Early needle knife fistulotomy has also been shown to be a safe and effective strategy for performing SBC.[6] If SBC was not achieved by standard or alternative techniques, retrial at a later date might be the best option. Papillary edema caused by repeated attempts at cannulation usually subsides over the next 48-72 hours, so a trial on another day can provide better chance of successful SBC.

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Choice of appropriate accessories

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Since its introduction in 1974, ERCP became the standard method of choice for removing bile duct stones which involves endoscopic sphincterotomy (EST) or endoscopic papillary (large) balloon dilation (EP(L)BD) with balloon or basket-assisted stone extraction. Lithotripsy may be required if the stone is too large to extract even after EPLBD, or there is a bile duct stricture below the stone, or a traditional basket is impacted in the bile duct with a stone. Lithotripsy may be performed by intracorporeal approaches using mechanical, electrohydraulic, or laser devices at the time of endoscopic (via ERCP) or percutaneous access, or by extracorporeal shock wave lithotripsy. In very old patients and those with serious co-morbidities where other endoscopic procedures may confer unacceptably high risks, endoscopic biliary stenting is a useful alternative. Recently, endoscopic ultrasound (EUS)-guided access techniques to the bile duct has been gaining popularity as an alternative to percutaneous transhepatic biliary approach in center with expertise.

The two basic types of stone extraction devices are extraction balloon catheters and basket catheters. Both are designed to extract stones through an ampullary orifice previously treated by endoscopic sphincterotomy or with balloon dilation.

Modern extraction balloons are typically triple-lumen devices: 1 lumen for air to inflate the balloon, 1 lumen for a guidewire, and 1 lumen for contrast material injection. Double-lumen extraction balloons are of an older design but are still commercially available and feature 1 lumen for either a guidewire or the injection of contrast material and a second lumen for air to inflate/deflate the balloon. Some devices come with a built-in Tuohy-Borst adapter to allow contrast material injection and guidewire passage through the same port. The triple-lumen balloon shafts may be stiffer than regular double-lumen balloons and slightly more difficult to pass into the bile duct. Once the catheter is within the bile duct, the balloons is inflated above the stone and pulled back gently until the stone is at the level of the papilla. While maintaining gentle traction on the balloon catheter, the tip of endoscope is deflected downward and rotated to the right to exert more traction force to expel the stone.

Wire baskets are frequently used for stone extraction. A variety of baskets are available in different size and configurations. A common basket configuration (often referred to as a Dormia basket) involves 4 wires arranged radially at 90° intervals. When the basket is in the open position, it assumes a 3-dimensional shape, the borders defined by the wires, which form 2 perpendicular hexagons. Other available baskets include those with a helical wire configuration, which use more than 4 wires (known as spiral baskets), and baskets with more wires in the distal portion of the basket than the proximal portion of the basket (known as flower baskets). Both spiral baskets and flower baskets are generally used to retrieve smaller stone fragments that might otherwise not be retrieved with Dormia baskets. Some stone extraction baskets are advanced into the biliary ducts over a guidewire. Not all stone extraction baskets can function as lithotripters. Some baskets can function as lithotripters without any additional hardware, whereas other baskets require additional equipment should lithotripsy become necessary. The most common and feared complications of mechanical lithotripsy are entrapment of the basket, a broken basket, a traction wire fracture, or a broken handle. To remedy this situation, rescue lithotripsy (Soehendra per-oral lithotripsy) using specialized accessories designed for this occurrence may be required to allow removal of the basket. Some modern stone extraction baskets contain built-in safety features to minimize the risk of basket entrapment/impaction. The Trapezoid Basket (Boston Scientific) is specifically designed to break if forcefully closed against severe resistance, allowing the basket to be removed from the patient (albeit without the stone) in the event of a basket impaction.

In conclusion, along with the advancement of ERCP techniques, the instruments and accessories of ERCP have grown vastly in their variety and complexity. A detailed knowledge of instruments and accessories available to the endoscopist allows for correct selection and usage and is essential to ensure optimal patient care and safety.

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Endoscopic sphincterotomy and endoscopic papillary balloon dilation

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During therapeutic endoscopic retrograde cholangiopancreatography (ERCP), a wide opening of the ampulla of Vater is crucial for a successful endoscopic treatment. Endoscopic sphincterotomy (EST) and endoscopic papillary balloon dilation (EPBD) are common techniques used to open the sphincter.

EST is traditional biliary tract dilatation method that is incise bile duct in the duodenal wall, in addition to the soft tissues of duodenum, and it has been widely accepted as a standard technique for dilatation of bile duct orifice.[1] After Zimmon firstly introducing the EST for stone removal in 1975, EST has become a key treatment method in the field of treatment of pancreaticobiliary diseases.[2] The bile duct run parallel to the duodenal mucosa at 11-12 o`clock. Therefore, the incision direction of EST is maintained to the same direction.[3] EST can be divided into small incision, medium incision and large incision according to the extent of incisions. The small incisions does not exceed the transverse fold, large incision is when the incision reaches the superior margin of the papillary bulge, and moderate incision is in between the small and large incision. To obtain the biopsy or insert stent, median incision is enough. However, large incision is recommended generally for common bile duct stone removal.[4] The superior sphincter extends to the bile duct on the lateral wall of the duodenum, and cutting beyond this area increases the risk of perforation. In relation to the papilla, it is thought that the superior margin of the papillary bulge coincides with the middle sphincter, and it is valid to consider this as the upper cutting limit.[5] Regarding to efficacy of stone removal, EST has 80.9% of success rate for stone removal in first endoscopic session and overall 95.3%.[6] In addition, the adverse event rate is relatively acceptable (3%-10.3%). However, EST cut the sphincter of Oddi permanently, so the sphincter function could not be preserved. Also, procedure related adverse event such as bleeding, and perforation would be occurred more frequently according to the patient`s comorbidity including coagulopathy, taking oral antithrombic drug, and acute pancreatitis.[7] In addition, endoscopic removal of the large stone over 1 cm with EST frequently required mechanical lithotripsy (ML) and patients should take the risk of complication of ML.[8] Therefore, the other methods for wide opening of bile duct is required.

Endoscopic papillary balloon dilation (EPBD) is one of most commonly used widening opening of bile duct method. EPBD is straightforward which is generally performed with 8-10mm balloon dilation for 1 to 2 minutes.[9] Especially in beginner of ERCP, EPBD is easy than EST in terms of technical challenges, and EPBD can reduce the risk of bleeding in the patient with coagulopathy including liver cirrhosis for common bile duct stone removal.[10] The success rate of EPBD for stone removal is not lower than those of EST, in which 73.5% in first endoscopic session and the overall success rate is over 90%.[6] Generally, the diameter of balloon for dilation is lesser than 10 mm. Therefore, huge bile duct stone larger than 1 cm is difficult to removal with conventional EPBD. In such case, large balloon (12-15 mm) is applicable and the success rate and adverse event of large balloon are not different with those of EST.[11,12] Despite the advantages of EPBD, many investigators were concerned about the high risk of post-ERCP pancreatitis after EPBD, which might cause mortality.[9] Therefore, EST with balloon dilatation (ESBD), which includes both EST and EPBD, was introduced. It demonstrated efficient stone clearance and acceptable adverse events.[13]

Recently, many results of meta-analysis about comparison of EST, EPBD, and ESBD in terms of efficacy for stone removal and adverse events were reported. Most of them showed the efficacy and adverse event were not different between EST and EPBD, and ESBD is more potent for stone removal than EST alone.[6]

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Prevention of complication

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Endoscopic retrograde cholangiopancreatography (ERCP) is a relatively complex endoscopic procedure since it requires specialized equipment and has a long learning curve to develop proficiency. Its benefits in the minimally invasive management of biliary and pancreatic disorders are challenged by a higher potential for serious complications than any other standard endoscopic technique. Post-ERCP complications may be divided into focal (specific), occurring at the point of endoscopic contact (e.g, perforation, bleeding, pancreatitis), or nonspecific, occurring in organs not traversed or touched (e.g, cardiopulmonary problems). Post-ERCP pancreatitis is the most common complication of ERCP. Several independent risk factors have been associated with PEP. Prophylactic PD stenting has been shown to be highly effective in preventing PEP. Recent studies have suggested that NSAIDs, especially rectal indomethacin, could by itself be effective in preventing PEP. Other complications include ERCP induced bleeding, perforation, and cholangitis. Bleeding is related to morphological, procedural, and patient-related factors. Early identification and correction of the risk factors are of paramount importance in preventing bleeding. Recently, stenting with standard biliary fully covered self-expandable metal stents has been reported as a successful treatment for intractable bleeding after biliary sphincterotomy. Post-ERCP perforation is the most feared complications of ERCP and occasionally leads to death. The risk of perforation can be minimized when ERCP is performed by well-trained endoscopists and assistants abiding by the technique-related preventive principles (e.g, proper orientation of the sphincteromy, step-by-step incision, avoiding a zipper cut). Risk of infection is particularly high during ERCP. It is important to ensure complete drainage of obstructed biliary system in order to reduce the risk of post-ERCP cholangitis. In conclusion, post-ERCP complications should be recognized and managed early, and there should be proper preventive measures.

KDDW 2019 Korea Digestive Disease Week

DAY 2
November 29 (Friday)

[14:00-15:30, Emerald Hall B]

Symposium 11 (KSGC2) English

Colorectal cancer: new topic and issue

Chairs: **Seun Ja Park** (Kosin University Gospel Hospital, Korea)
Yoon Tae Jeen (Korea University Anam Hospital, Korea)

The current understanding and optimal approach of early-onset colorectal cancer

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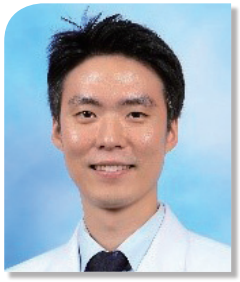
Colorectal cancer(CRC) is the third most common cancer worldwide and is the second leading cause of cancer-related deaths.[1] In South Korea, CRC ranks second in cancer incidence and fourth in cancer mortality.[2] Although the overall incidence and mortality rates of CRC have been steadily decreasing in the United states and Europe in recent decades, the incidence of early-onset CRC(EOCRC), which is generally defined as CRC that occurs under age 50, is increasing in several countries, and has emerged as an important health problem.[3] However, to date, the actual scale and the underlying causes of such an increase of EOCRC is still unclear. EOCRC is a very heterogeneous disease. Hereditary genetic syndromes are only a minority of cases, and more than half of EOCRCs occur sporadically without genetic factors. Therefore, it is difficult to explain the recent increase of EOCRC only by genetic factors.[4] Possible reasons of recent increase could involve the lack of routine screening in young patients, and generational differences in diet, environmental exposure, and lifestyle factors.[3, 5] EOCRC shows different clinical and pathological features from CRC diagnosed in the older adults. EOCRC tends to be symptomatic at diagnosis and takes longer to diagnose after symptoms appear. It also occurs more commonly in the left-sided colon and rectum than in the right-sided colon. In addition, EOCRC is commonly diagnosed at an advanced stage, with a higher percentage of histologic types with poor prognosis such as mucinous, signet cells, poorly differentiated and undifferentiated carcinomas.[3,6] There is a growing evidence that patients with EOCRC have a distinctive molecular profile that is different from late-onset CRC, but there are currently no specific treatment guidelines for EOCRC, and the same treatment guidelines apply to young and old patients.[7] In practice, clinicians tend to treat EOCRC more aggressively, but the survival data is still conflicting.[8] Therefore, further studies are needed to better understand the molecular mechanisms underlying EOCRC, and it is necessary to develop precise treatment methods that is applicable according to the molecular biological characteristics of EOCRC. In addition, in order to prevent EOCRC, high-risk patient groups should be identified and appropriate screening tests performed properly. Since more than half of the EOCRCs occur sporadically without genetic disease or family history, further research and analysis of various risk factors should be conducted to develop screening and clinical management strategies that can be applied according to individual risk factors.



Carbon-ion therapy for recurrent rectal cancer

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Recently, particle therapy facilities have emerged across the world, with over 30 proton centers in operation or under construction in the United States alone, and 10 centers treating patients with carbon ions (C-ions) worldwide. The factors unique to charged particles that can contribute to an overall superior delivery of radiation dose when compared to PhXRT include: (1) spread-out Bragg peak, leading to enhanced dose distribution and lateral focusing; (2) potential for dose verification via available imaging; (3) superior linear energy transfer and; (4) magnetic steering of the ion beams (scanning beams). These properties theoretically should lead to optimal delivery of maximally safe and potentially curative doses of radiation to the tumor while simultaneously sparing at risk adjacent structures.Thus, C-ions have potential to be an ideal heavy particle candidate for cancer treatment, and have significant potential to overcome resistance afforded by DNA repair mechanisms. The clinical data available thus far suggest reasonable outcomes in even hard to treat tumors, such as those that are deep seated, critically located, traditionally thought to be radio-resistant, or are recurrent and highly aggressive. Treatment outcomes for rectal cancer have considerably improved in recent years owing to advances in multidisciplinary treatments including surgery, radiotherapy (RT), and chemotherapy. Particularly, neoadjuvant concurrent chemoradiotherapy (CCRT) and total mesorectal excision have contributed to a decreased rate of local recurrences. However, despite advances in treatment modalities, local recurrences still occur in 5–15% of patients, and the majority of locoregional recurrences occur within the initial RT field. Recurrences within the pelvis are associated with increased morbidity and mortality, and surgery is the first treatment option in these cases. However, many patients are ineligible for surgery due to poor general condition or tumor extent and location. In these cases, RT can help in achieving R0 resection, improving local control, or palliating the symptoms, and re-irradation (reRT) will be necessary in the majority of these patients since most recurrences will be within the initial RT field. However, retrospective and prospective studies on reRT are limited, and the treatment schemes, median survival, and toxicity rates vary in these studies. Carbon-ion therapy can be a safe and effective treatmentoption for locally recurrent rectal cancer and may serve as an alternative to surgery In this presentation, I will summarize these physcial and biological rationales, as well as, give an overview of the available preclinical and clinical data that demonstrate the increased efficacy of carbon-ion therapy over conventional radiation therapy.

Emerging treatment in recurrent and metastatic colorectal cancer

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The survival of patients with mCRC has improved dramatically in recent years, with overall survival exceeding 3 years in large randomized clinical trials. There are now several Tx options for patients with mCRC. In addition to CTx backbones utilizing 5FU, oxaliplatin, and irinotecan combinations, biologic agents that target specific oncogenic pathways have contributed to the improved survival observed in this patient population. This class of medications includes epidermal growth factor receptor (EGFR)-targeted drugs (cetuximab and panitumumab) and vascular endothelial growth factor (VEGF)-targeted therapies (bevacizumab, ramucirumab, ziv-aflibercept, and regorafenib). EGFR-directed treatment should be restricted to patients with extended RAS and BRAF wild-type tumors. Tumor sidedness may be a more powerful prognostic and predictive biomarker than tumor mutational profile. Patients with left-sided primary tumors derive greater benefit from EGFR-targeted therapies whereas patients with right-sided primary tumors benefit more from bevacizumab. MSI-H tumors harbor excessive mutations and can generate "neoantigens" which can serve as a target for immunotherapy agents. Pembrolizumab is evaluated by Le et al. in a phase II study in which 53 mCRC patients with dMMR and proficient MMR (pMMR) were treated with pembrolizumab. Activating BRAF mutations mostly occur in codon 600 and is known as the V600E mutation; this is found in < 10% of sporadic CRC cases. There is strong evidence for its use as a prognostic factor compared to its predictive value, although data are emerging with respect to predicting response to anti-EGFR therapy. As interest in the use of predictive clinical and genetic biomarkers continues to increase, human epidermal growth factor 2 (HER2) presents as an attractive target for further development. Tailoring existing therapies based on tumor sidedness, KRAS, MSI, or BRAF status as well as individualizing treatments for elderly or DM patients represent our current efforts to provide more personalized care in oncology. However, these likely reflect only initial steps and more work is clearly warranted on furthering our understanding on additional clinical and pathological characteristics that can be used to personalize treatment in CRC.

The EGFR Pathway and Anti-EGFR Therapy

Cetuximab

Panitumumab

The VEGF Pathway and Anti-VEGF Therapy

Bevacizumab

Ziv-aflibercept

Ramucirumab

Combination Biologic Therapy

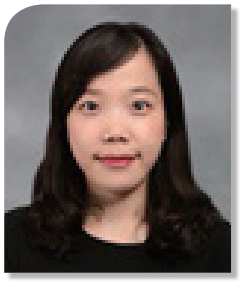
Selection of Biologic Therapies in the 1st Line

Tumor Sidedness as a Prognostic and Predictive Marker

Microsatellite Instability: Its Role with Immunotherapy Agents

BRAF: Prognostic and Possible Predictive Factor

All patients with metastatic colorectal cancer should undergo testing for KRAS, NRAS, and BRAF status and microsatellite instability/mismatch repair status. The addition of EGFR inhibitors to chemotherapy in the 1st line setting in patients with RAS and BRAF wild-type metastatic colorectal cancer improves survival. Patients with right-sided primary colon tumors have worse overall survival and derive less benefit from cetuximab (even if their tumors are KRAS wild-type) than patients with left-sided tumors. Combination biologic therapy should be avoided outside the context of a clinical trial. While great strides have been made, many patients still do not experience an OS benefit; additional novel therapies and combination approaches are needed.



Future clinical and translational research in colorectal cancer

Bun Kim, M.D., Ph.D.

Department of Devision of Translational research, National Cancer Center, Goyang, Korea

Translational research is a link between clinical research and basic research. Nevertheless, its scope is not clear. Basic research is the systematic study directed toward greater knowledge or understanding of the fundamental aspects of phenomena and is performed without thought of practical ends. In contrast clinical research is Determination the safety and effectiveness (efficacy) of medications, devices, diagnostic products and treatment regimens intended for human use. Therefore, translational research makes basic research a reality. Compared to basic research, the translational research methodology uses a fairly similar methodology. In general, clinicians may think of doing translational research by borrowing basic research methodologies because they conduct research based on or with real clinical use.

In clinical research, there were multiple designs to be used including systematic review. As a gastroenterologist, Clinical research field in colorectal cancer could include medication (Chemotherapy, chemoprevention), colorectal cancer screening or surveillance (colonoscopy, sigmoidoscopy, stool test etc), endoscopic technology for detection and prevention of early colorectal cancer, colorectal cancer preventive or risk factors (Nutrition, diet etc), hereditary colorectal cancer and colorectal cancer survivorship.

For translational research, Patient-Derived Xenograft (PDX) Models, Patient derived organoid (PDOs), Microbiome and Liquid biopsies (CTC, ctDNA etc) are actively used in colorectal cancer field.

Colorectal cancer constitutes a unique case to illustrate clinical perspectives revealed by PDX studies, as they overcome limitations intrinsic to conventional ex vivo models. Furthermore, the success of molecularly annotated "Avatar" models for co-clinical trials in other diseases suggests that this approach may provide an additional opportunity to improve clinical decisions, including opportunities for precision targeted therapeutics, for patients with CRC in real time.

PDOs have the capacity to capture intratumoural and temporal heterogeneity when multiple biopsies are performed, and are stable over multiple growth passages. These data suggest that co-clinical trials using organoids could be a cost-efficient and accurate method to determine individual patient sensitivity to chemo or targeted therapy. In drug screening assays using PDOs we confirmed expected sensitivities in molecularly selected PDO models In future, development of PDOs in a timely manner may be helpful in determining specific chemotherapy and targeted therapy regimens for gastrointestinal cancer patients. PDOs into clinical trials and in future, routine clinical care as predictors of response to treatment which could reduce needless toxicity and provide and allow for more effective use of resources.

The interaction of gut microbiota and CRC has been a major focus of research recently. The effect of environmental factors on CRC is mainly dependent on microbial dysbiosis. Indeed, microbial studies have revealed that the microbial composition has been perturbed in CRC and in precancerous lesions. A pathological imbalance in gut microbiota has been detected in subjects with CRC compared with healthy controls gut microbiota contributes to the initiation and development of CRC in early days specific bacteria. The underlying mechanisms during the interaction between microbial dysbiosis and colorectal carcinogenesis include the promotion of inflammation, pathological bacteria adhesion and induction of tumorigenesis. It would be full of potential to lower the risk of CRC through modulating gut microbiome by dietary control or antibiotic treatment to eliminate tumor associated bacterial pathogens.

Liquid biopsy, involving the use of circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and exosomes, may offer a promising noninvasive alternative for diagnosis and for real-time monitoring of tumor evolution and therapeutic response compared to traditional tissue biopsy. Monitoring of the disease processes can enable clinicians to readily adopt a strategy based on optimal therapeutic decision-making.

In conclusion, future clinical and translational research in colorectal cancer is vary and wide field. As an opportunity to expand the medical horizon that can be realized as a clinician, it is expected that many present and future gastroenterologists will devote themselves to research for colon cancer.

KDDW 2019 Korea Digestive Disease Week

DAY 2
November 29 (Friday)

[14:00-15:30, Diamond Hall]

Basic/Translational Symposium 01 (KPBA) English

Battle against cholangiocarcinoma: bench to clinical application

Chairs: **Hong Sik Lee** (Korea University Anam Hospital, Korea)

Chang Nyol Paik (The Catholic University of Korea Seoul St. Vincent's Hospital, Korea)

Genetic and transcriptomic analyses of the biliary tract cancer

Tatsuhiro Shibata, M.D., Ph.D.

Department of Laboratory of Molecular Medicine, University of Tokyo, Tokyo, Japan

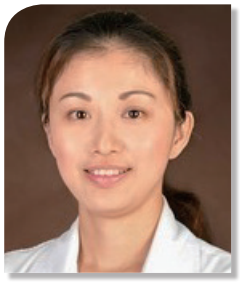
The incidence of biliary tract cancer, including intra-hepatic (ICC) and extra-hepatic (ECC) cholangiocarcinomas and gallbladder cancer (GB), has rapidly increased globally; however, no effective targeted molecular therapies have been approved and the cure rate is very low. Here we characterized 260 BTCs by a combination of exome and transcriptome sequencing and uncovered spectrums of molecular alterations that included novel therapeutic targets. Gradient spectrum of mutational signatures with higher burden of the APOBEC-associated signature in GB and ECC was observed. Thirty-two driver genes were identified as significantly altered genes and nearly 40% of cases harbored molecularly targetable genetic alterations. Organ-specific dysfunctions were also identified in epigenetic regulators, often in unique combinations with growth-promoting alterations (e.g., IDH1 mutations without RAS mutations). The group with the poorest prognosis had a characteristic elevation of both immune response signatures and counteracting immune checkpoint molecules, implying that immune-modulating therapies could also be potentially promising options for those patients.

Development of patient-derived preclinical models for cholangiocarcinoma

Yun-Hee Kim, Ph.D.

Department of Division of Convergence Technology, National Cancer Center, Goyang, Korea

Cholangiocarcinoma (CCA) is an aggressive malignancy with poor prognosis that is caused by the high heterogeneity of tumor, severe resistance to treatment and progression by unknown mechanism. Although recently druggable target for CCA were reported through multilateral omics studies, however, there is a limitation of available model system for drug development. The preclinical model systems that reflect the genetic heterogeneity of tumors are urgently needed to guide optimal treatment and drug discovery. Patient-derived xenograft (PDX) models enable the examination of tumor in native environment with the heterogeneity and stromal architecture, considering that patient-derived cell line has the limitation of disease homogeneity and their success rate of establishment is less than 10% due to the characteristics of highly desmoplastic tumors such as CCA and pancreatic cancer. In addition, PDX can be used as an amplification tool of small-sized tumor tissue such as percutaneous liver gun biopsy (PLB). However, PDX models has some hurdle to be a usual preclinical assay system for high-throughput screening in the view of time- and cost efficiency despite of many advantages. To overcome this problem, we introduced organoids being intermediate between cancer cell lines *in vitro* and xenografts *in vivo*. Here we described the development of patient-derived preclinical platform for CCA, based on patient-derived xenograft (PDX)-mediated tissue amplification and subsequent organoid generation. Our PDX system using surgical tumor tissues and PLBs covers extrahepatic cholangiocarcinoma (EHCC), intrahepatic cholangiocarcinoma (iHCC) and especially intraductal papillary neoplasms of the bile duct (IPNB) as well as gall bladder cancer (GBC). These retained the histopathological architecture and genetic alterations of corresponding patient tumors from immunohistochemistry and genomic analyses. Tumor organoids were subsequently generated from F1 tumor tissue of PDX. This method, which enriched the tumor cellularity, enhanced the success rate of organoid formation. We performed the PDX-derived organoid-based screening of drugs used clinically and predicted the drug responsiveness of original patients. Further cross-validation of effect to drugs as well as biomarkers in both organoids and corresponding PDX models may provide reliable evidence of drug responsiveness and target value in patients with CCA. Collectively, this PDX-organoid system may constitute an important preclinical model platform with enhanced clinical relevance, suggesting that these models may be useful for translational research and drug discovery in CCA.



Circulating biomarkers in cholangiocarcinoma

Nai-Jung Chiang, M.D.

Department of National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan

Surgery is the first choice of early stage cholangiocarcinoma (CCA). For unresectable and metastatic CCA, chemotherapy and genetic alternation-guided targeted therapy remain the therapeutic cornerstone. However, there is no well-elucidated biomarkers for clinical utility to predict early disease, post-operative tumor recurrence, or to select patients most likely to have benefit from certain therapeutics. In recent years, liquid biopsy (including circulating tumor cells and circulating tumor DNA) has emerged as a technique for the characterization of circulating biomarkers, providing a strong basis for the individualized treatment of patients. As a noninvasive detection method, liquid biopsy is expected to play an important role in the early diagnosis, dynamic monitoring of cancer patients and drug screening. Emerging integration of molecular profiling datasets led to the disclosure of frequently altered genes and proteins that could lead to perturbation of intracellular signaling pathways and their microenvironment. In this talk, we will summarize the clinical applications, recent studies and future prospects of circulating biomarkers in CCA.

Developmental therapeutics

Seungmin Bang, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Severance Hospital, Seoul, Korea

Cholangiocarcinoma is a group of malignant diseases arising epithelial lining of bile duct. It can be classified into intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinma (including perihilar and distal cholangiocarcinoma) and gallbladder cancer based on their anatomic location. In terms of treatment, surgical resection is the only way to achieve cure from the disease. However, most of cases are usually diagnosed in advanced stages, not suitable for curative resection. And currently available palliative treatments including chemotherapy and radiotherapy do not seem to be very effective for elongating the overall survival of the patients. As the first line treatment for advanced cholangiocarcinoma, gemcitabine and cisplatin is recommended. So, the overall survival of advanced cholangiocarcinoma is still less than 1 year.

Advances in understanding the molecular or genetic changes during carcinogenesis of various cancer shows the potential target for new drug development. For example, understanding of immune check point inhibition lead to develop anti-PD-1 and anti-PD-L1 inhibitors, which are successful in handling lung cancer and melanoma. For cholangiocarcinoma, there are several novel drugs under preclinical or clinical validation. In this talk, we will briefly introduce the novel drugs for cholangiocarcinoma

KDDW 2019 Korea Digestive Disease Week

DAY 2
November 29 (Friday)

[16:00-17:30, Convention Hall A]

Combined Symposium 05 (KCHUGR-KGCA) Korean

Recent debates on EGC with undifferentiated type histology

Chairs: **Jae Moon Bae** (Samsung Medical Center, Korea)
Jae J Kim (Samsung Medical Center, Korea)

Biologic and clinical features of EGC with undifferentiated type histology

Hye Seung Lee, M.D., Ph.D.

Department of Pathology, Seoul National University Bundang Hospital, Seongnam, Korea

Gastric cancer is divided in two groups by the Nakamura classification: differentiated and undifferentiated type. Differentiated type includes well and moderately differentiated tubular and papillary adenocarcinomas, whereas undifferentiated type includes poorly differentiated adenocarcinoma and poorly cohesive carcinoma. Mucinous adenocarcinoma can be classified into either differentiated or undifferentiated histologic type based on predominant tumor cell morphology. Originally, Nakamura et al. proposed that differentiated carcinoma originates in the epithelium of intestinal type and undifferentiated carcinoma originates in the ordinary gastric mucosa. When compared to Lauren, Japanese, and WHO histologic classifications, minor histologic subtypes such as carcinoma with lymphoid stroma, hepatoid adenocarcinoma, and adenocarcinoma of fundic gland type are not defined by the Nakamura classification.

Undifferentiated type histology has been generally reported to be associated with worse prognosis. In many previous studies, undifferentiated type histology was one of poor prognostic factor, but not independent of TNM stage. To predict lymph node metastasis, undifferentiated type of gastric cancer has a high risk of lymph node metastasis. However, undifferentiated type includes various histologic subtypes and each subtype has its distinct clinical characteristics. For example, signet ring cell carcinoma has been reported to have a lower risk of lymph node metastasis, but more frequent endoscopic resection margin involvement. Undifferentiated type mucinous adenocarcinoma is associated with dismal prognosis. Moreover, minor histologic subtypes such as carcinoma with lymphoid stroma and adenosquamous carcinoma can be diagnosed as poorly differentiated adenocarcinoma by endoscopic biopsy specimen. Gastric carcinoma with lymphoid stroma has poorly differentiated histologic feature, but is associated with lower lymph node metastasis and better prognosis.

Mixed histology with dominantly undifferentiated type has similar clinicopathologic characteristics as undifferentiated type, thus many researchers has been interested in mixed histology with dominantly differentiated type of gastric cancer to predict lymph node metastasis. Previous studies reported that mixed histology with dominantly differentiated type of gastric cancer had a high risk of lymph node metastasis, but if lesions meet the current ESD criteria, the risk of lymph node metastasis was not high. Further study is necessary for confirming the clinical implication of mixed histology.

Finally, early gastric cancer with undifferentiated type histology includes various histologic and clinical features. Additional and detailed histologic information may be helpful for optimal treatment of early gastric cancer patients with undifferentiated type histology.

Optimal management for EGC with undifferentiated type histology: Gastroenterologist's view

Jun Chul Park, M.D.

Department of Internal Medicine-GI/Hepatology, Severance Hospital, Seoul, Korea

Endoscopic submucosal dissection (ESD) is a standard treatment for patients with intramucosal early gastric cancer (EGC) at negligible risk of lymph node (LN) metastasis. ESD is a minimally invasive procedure that preserves the majority of the stomach, thereby improving a patient's quality of life. Moreover, its efficacy is similar to that for surgical treatment. However, generally, the indications for ESD are limited to differentiated-type adenocarcinoma, and treatment of EGC of undifferentiated histology (UD-EGCs) using ESD is considered controversial due to a greater risk of LN metastasis, compared to that for differentiated-type adenocarcinoma. The technical feasibility of ESD for UD-EGCs is supported by a recent meta-analysis [1]. Furthermore, other reports have found the clinical outcomes for UD-EGCs treated with ESD to be favorable and the technique to be efficacious [2-4].

Recently, we designed comparative study to evaluate the long-term outcomes of ESD for UD-EGCs in our institution [5]. We performed propensity-scored matching analysis to minimize

differences in baseline demographic features that could potentially be associated with prognosis. In this study, we provided strong evidence that if strict expanded indications are applied to UD-EGCs, ESD might be a feasible and safe procedure, especially in SRC-type histology, although the risk of recurrence was higher in patients who underwent ESD. Likewise, upon propensity-scored matching, survival analysis showed similar results with those in overall comparisons.

In conclusion, although the risk of recurrence was higher in the ESD group, overall survival did not differ significantly between ESD and surgery, especially for tumors of SRC histology. Therefore, we recommend ESD as a complementary option for the treatment of UD-EGCs, along with appropriate follow-up endoscopic examination for detecting recurrence, in patients who satisfy the expanded indications for ESD.

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Optimal management for EGC with undifferentiated type histology: Surgeon's view

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Department of Surgery, The Catholic University of Korea Seoul St. Mary's Hospital, Seoul, Korea

Endoscopic mucosal dissection (ESD) is a standard treatment for early gastric cancer (EGC) with absolute indication.[1] In case of expanded criteria, the choice between gastrectomy and ESD is still controversial. Although many benefits, the main drawback of ESD is the inability to perform lymph node (LN) dissection, which is difficult to implement if the risk of LN metastasis is high.

According to the WHO classification, mucinous adenocarcinoma is defined as the tumor contains extracellular mucin pools more than 50% of the tumor area, and signet ring cell carcinoma is defined as the tumor consists of isolated or small groups of malignant cell with intracytoplasmic mucin. In addition, poorly differentiated adenocarcinoma is defined as tubular adenocarcinoma composed of highly irregular glands that are recognized with difficulty, or single cells that remain isolated or are arranged in small or large clusters.[2] These poorly differentiated adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma mainly showed poor gland formation, and classified as undifferentiated (UD) type histology according to Japanese Gastric Cancer Association classification.[3] The rich mucin pools of UD type EGC are known to simulates dipersion and invasion, and inhibits the inflammatory and immunologic reaction of tumor cells.[4] Moreover, mucin pool with neuropilin-1 expression regulate tumorigenesis through epithelial-to-mesenchymal transition (EMT) pathway.[5] EMT is a cellular changes such as a reduction of cell to cell adhesion and/or loss of apical to basolateral polarity. Activation of EMT process increases the ability of tumor migration and invasion with related to E-cadherin and N-cadherin.[6] These mechanisms suggest that LN metastasis is more likely to be present in UD type EGC.

Clinically, numerous studies reported that UD type histology such as poorly differentiated tubular adenocarcinoma, poorly cohesive carcinoma, and signet ring cell carcinoma is independent risk factor for LN metastasis as larger tumor size, submucosal invasion, or lymphovascular invasion.[7-9] Moreover, not only UD type histology, but also mixed histology is reported as independent risk factor for LN metastasis.[10]

In terms of complication after gastrectomy, a well-designed randomized controlled trial reported that total complication rate of laparoscopic gastrectomy was 13.0%, while mortality rate was extremely rare (0.6%). Moreover, 5-year cancer specific survival after laparoscopic gastrectomy for gastric cancer was 97.1%.[11] These results suggested that gastrectomy is recommended safely for the patients with high risk of LN metastasis.

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Recent debates on EGC with undifferentiated-type histology: Case-based discussion

Jong-Han Kim, M.D., Ph.D.

Department of Surgery, Korea University Guro Hospital, Seoul, Korea

According to the expanded indication of endoscopic submucosal dissection (ESD), tumors of ≤ 20 mm in diameter with the absence of ulcerative findings and mucosal undifferentiated-type early gastric cancer (EGC) can be treated by treated by endoscopic resection with surgery. However, because all undifferentiated-type EGC carry a high risk of lymph node metastasis, traditional surgical treatment remains the current standard treatment. Also, undifferentiated predominant mixed-type, submucosa invasion and tumor diameter of > 20 mm are considered high risk factors for lymph node metastasis.

Herein, we report EGC cases who underwent surgical resection due to non-curative ESD with undifferentiated-type histology. Among them, we could find the case with lymph node metastasis in mixed-type submucosal EGC and some cases showed residual tumor in gastrectomy specimen. Also one patient showed local recurrence in two years after the curative gastrectomy due to non-curative ESD with undifferentiated-type histology.

In conclusion, the decision to perform ESD for undifferentiated-type EGC should be made carefully and in accordance with strict criteria based on the unique biological features of it.

Case-based discussion

Hyo-Joon Yang, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Kangbuk Samsung Medical Center, Seoul, Korea

Age and Gender: 54 years old, male

Chief Complaints: synchronous gastric cancer detected during surveillance esophagogastroduodenoscopy (EGD) after endoscopy resection of gastric adenoma

Present Illness: He had undergone endoscopic resection of gastric adenoma and *Helicobacter pylori* eradication. At 1-year follow-up EGD, a tiny slightly depressed focal atrophic lesion was revealed. He had no gastrointestinal symptoms and no prior history of abdominal surgery.

Past history: None

Family history: His father was diagnosed gastric cancer at age 65.

Medication history: None

Physical Examination and Laboratory findings: Unremarkable

Endoscopic and Radiologic Findings:
EGD: a tiny slightly depressed focal atrophic lesion at the posterior wall side of upper body near cardia.
Abdominal computed tomography: unremarkable

Hospital Progress: The patient received endoscopic submucosal dissection.

KDDW 2019 Korea Digestive Disease Week

[16:00-17:30, Convention Hall B]

Combined Symposium 06 (KASID-KSPGHAN) Korean

Successful transition from pediatric to adult care: what we have to know

Chairs: **Young Sook Park** (Eulji Hospital, Eulji University, Korea)

Byung-Ho Choe (Kyungpook National University Chilgok Hospital, Korea)

Childhood-onset IBD vs. adult-onset IBD

Jung Ok Shim, M.D., Ph.D.

Department of Pediatrics-G-I/Hepatology, Korea University Guro Hospital, Seoul, Korea

Pediatric IBD (pIBD) has been increasing rapidly since early 2000s particularly in teenagers. pIBD is still rare in children younger than 6 years of age, but it is diagnosed more often than in the past. pIBD research has been focusing on better phenotyping at diagnosis, and molecular genetics. Genetic factors are hypothesized to play a stronger role in pIBD pathogenesis as children lack many of the typical environmental exposures that are associated with adult IBD.

Children with 'neonatal IBD' or 'infantile onset IBD' have higher rates of affected first degree relatives, more severe disease course and a high rate of resistance to immunosuppressive treatment. Subgroups of 'pediatric-onset IBD' (< 17 years), 'early onset IBD' (< 10 years), 'VEO-IBD' (< 6 years), 'infantile onset IBD' (< 2 years), and 'neonatal IBD' (< 28 days) have been suggested according to the phenotype including disease location and severity, and the presence of monogenic defect.

Sixty monogenic defects have been discovered in children with IBD-like phenotype, including defects in IL10 signaling pathway, XIAP deficiency, IPEX syndrome, chronic granulomatous disease and other neutrophil defects. Most monogenic defects present before 6 years of age, particularly before 1 year of age. Next generation sequencing could become an important diagnostic tool in children with suspected genetic defects particularly in children with VEO-IBD with severe disease phenotypes.

Risk classification based on genotype might lead to unconventional treatments such as biologic therapy targeting pathway defects, and stemcell transplantation.

Growth restoration is one of the important treatment targets in children with pIBD. Early antitumor necrosis factor therapy can promote linear growth. On the other hand, loss of response to biologics, and malignancy in male adolescents and young adults should be considered. Psychosocial problem and poor compliance are common particularly in adolescents and lead to worse outcome.

Dietary therapy including exclusive enteral nutrition (EEN) can be treatment option for IBD. EEN will be the first-line treatment option for induction in pIBD in the newly developing guideline. EEN showed similar rates of clinical remission and relapse compared to corticosteroids.

Childhood IBD, particularly VEO-IBD is different disease entity from adult IBD. It might require different treatment strategies. Moreover, pIBD can give new inspiration to adult IBD.

Nutritional therapies in IBD – from children to adults

Sang Yong Kim, M.D.

Department of Pediatrics-G-I/Hepatology, Incheon St. Mary's hospital, The Catholic University of Korea, Incheon, Korea

Inflammatory bowel diseases, including Crohn disease, ulcerative colitis, and IBD-unclassified, are chronic and relapsing disorder, causing abdominal pain, diarrhea, rectal bleeding, and weight loss. Treatment goals of pediatric inflammatory bowel disease have focused on relieving symptoms, optimizing growth, and improving quality of life while minimizing drug toxicity. Nutritional deficiencies and growth retardation can develop during active disease state, especially in pediatric Crohn's disease, or steroid-dependent disease course.

Nutritional therapies on inflammatory bowel disease encompass several topics including nutritional rehabilitation for malnourished patients, exclusive enteral nutrition as primary therapy for Crohn's disease, and the role of specific nutrients having beneficial or deleterious effect on the disease course. Exclusive enteral nutrition for the induction of remission of pediatric Crohn's disease has been established as a primary therapy on the basis of the increasing evidence regarding the efficacy of exclusive enteral nutrition. Fortunately, Korean health insurance has conceded a polymeric diet to be prescribed in pediatric Crohn's disease on out-patient basis since June 2019. Elemental diets can be supplied complimentarily for the same purpose in the aspect of public welfare.

Although several trials have been made to define new therapeutic routes to the diet treatment of pediatric inflammatory bowel disease, to date, physicians involved in the care of the patients should be aware of no recommendations for the use of specific diet with sufficient evidence in the therapy of inflammatory bowel disease, and the steps in instituting dietary or nutritional management in light of the current evidence.

Understanding adolescent IBD patients

Yeoun Joo Lee, M.D., Ph.D

Department of Pediatrics-G-I/Hepatology, Pusan National University Yangsan Hospital, Yangsan, Korea

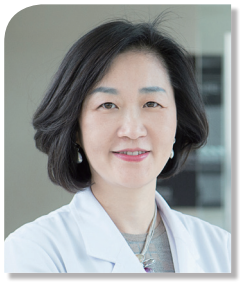
Adolescence is an intermediate stage of the physical and psychosocial development process from child to adult. The growth and development of puberty is not a linear process, but a process of achieving adolescent milestones one by one. Adolescents with IBD need to overcome one more milestone called IBD than other healthy peers. Adolescents with IBD are those who have had IBD since childhood or have been diagnosed with IBD during the most dynamic periods.

Pediatric onset IBD has a more extensive disease and shows more aggressive and rapid progress. On the other hand, there are further restrictions on the diversity and amount of drugs that can be used for drug approval, as well as the effects of growth, puberty, and education.

There is also a high difference in pharmacokinetic differences among children, adolescents and adults. There are differences in drug bioavailability, distribution volume, protein binding, liver metabolism isoenzymes and kidney removal by age groups. Sometimes physician need to use a relatively higher dose of medicine compared to an adult. Endoscopy, which is essential for diagnosis and follow-up, is more difficult to perform than an adult. Bowel preparation, sedation and school absenteeism make work more complicated than adults.

It is not easy to choose the most effective drug without affecting growth and development. Also in adolescence, the compliance of the drug is much lower. And physicians must to consider many other things, such as college entrance exams, military issues and vaccinations.

Successful transition requires an understanding and approach to the characteristics of diverse and complex pediatric IBD. Pediatricians and adult physicians will need to determine the transition method based on a good understanding of adolescent IBD so that adolescent IBD patients can overcome another hurdle.



The meaning of graduation from pediatric IBD care

Sung-Ae Jung, M.D., Ph.D.

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Pediatric-onset IBD shows extensive disease and rapid progression requiring early immunomodulatory therapy. And more careful consideration is needed in deciding medical treatment because it can affect many aspects including growth, education, employment, psychosocial and sexual development in pediatric patients. A smooth and successful transition from pediatric to adult care is important because failure to successful transition could lead to compromised emotional and physical health outcomes.

The goal of the transition care is to provide consistent, harmonious and comprehensive healthcare which is appropriate the medical, psychosocial and educational needs of adolescents and young IBD patients. Transition of care usually begin early in adolescence (age 10–12 years), with final transfer of care occurring most often between 18 and 23 years. Transition care might be a challenging process for both the physicians and patients because of significant differences between pediatric- and adult-IBD care as well as different disease characteristics. Pediatric care is family-centered, and multidisciplinary practice compared with adult care which is patient-centered, and provided by a single physician. In addition, pediatric care focuses on growth and development whereas adult care focuses on cancer surveillance, sexual function, fertility and pregnancy. Thus, for the adult gastroenterologist, it is difficult to get a handle on complex history and management and to build a rapport with the patient and maintain the continuity of care. And during the transition care, the patients should learn knowledge about the disease and its treatment, independence and assertiveness (independent health behaviors responsible for medications, doctor's visits) and self-advocacy (school, work, insurance issues).

Successful transition requires a flexible and tailored plan which is based on individual developmental ability and situation. The healthcare provider should have a comprehensive understanding of the transition steps, and provide a personalized transition program.

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KDDW 2019 Korea Digestive Disease Week

DAY 2
November 29 (Friday)

[16:00-17:30, Convention Hall C]

Multidisciplinary Session 03 (KPBA-KAHBPS) English

Effective multidisciplinary approaches to IHD stone

Chairs: **Jin Hong Kim** (Ajou University Hospital, Korea)
Kyo-Sang Yoo (Hanyang University Guri Hospital, Korea)

Multidisplinary approach IHBD stone -Endoscopy intervention-

Mitsuhiro Kida, M.D., Ph.D.

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Recently Therapeutic endoscopy such as ERCP and EUS-BD etc. have become popular in the treatment of intrahepatic bile duct (IHBD) stone. Concerning about treatment of IHBD stone, there are several ways such as ERCP, percutaneous transhepatic cholangioscopy (PTCS), EUS-BD, and surgery. The indications of IHBD stone are in cases with clinical symptoms such as elevation of liver enzyme, cholangitis, and jaundice, etc.

ERCP is the golden standard of bile duct (BD) stones, however, IHBD stone is not always good indication for ERCP. Only stones of IHBD near liver hilum seem to be good candidates for ERCP. Concerning IHBD stones in cases of surgically altered patients, because short balloon enteroscopy (BE) allow us to treat IHBD stones with most of ERCP devices, especially with guide-wire system. Compering EUS-BD and short BE treatment, these clinical success rate is about 90% and 60%, however these adverse events are 20% and 4%, respectively. Concerning about bile duct stone removal, the success rate of antegrade removal with EUS-BD are 72%(21/29) in cases with 10mm BD stones in average size. On the other hand, we can employ electrohydrotic lithtripsy(EHL) under direct short BE even in cases with large stones and treat them in the same day. With EUS-BD, we have to create fistula with long term stenting, then stones will be treated by EHL under baby cholangioscopy. At the moment, we have believed that short BE is the first choice of treatment in patients with surgically altered anatomy, then EUS-BD is the second choice.

Nowadays, treatment for IHBD stones with PTCS is very limited such as peripheral stone and patients with high risk for surgical operation etc.

I would like to share our knowledge and experience at KDDW.

Radiologic intervention

Myungsu Lee

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Surgical approach

Seog Ki Min, M.D., Ph.D.

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Intra hepatic duct (IHD) stones occur for a variety of causes, and clinical results range from simple to very severe. In some cases of severe IHD stones, complete treatment itself is difficult, so, despite the benign nature of the disease, it is often called clinical malignancy. The treatment for IHD stones requires various approaches. In addition, the patient's condition and the condition of the disease should be considered for adequate decision.

IHD stones are often found in older patients as they progress slowly through chronic progression at the time of discovery, and are either accidentally discovered or have undergone acute symptom or sign. For this reason, surgical treatment of IHD stones cannot be easily determined from the outset, and should be selected considering the patient's condition and disease state.

IHD stones can cause cholangitis, the bile duct obstruction accompanied by jaundice, liver abscess and sometimes cholangiocarcinoma. Therefore, we must do our best for complete elimination if possible. In view of this premise, surgical procedures are the most effective treatment methods to increase the chance of complete removal compared to other treatments. Of course, in some cases, even surgical removal of the complete removal may not be possible, but it is obvious that the treatment can be the closest to the therapeutic purpose. However, surgery has the major disadvantages of possibility of complications associated general anesthesia and surgery itself. Therefore, careful decision is required for the best results.

1. INDICATIONS FOR SURGICAL TREATMENT

Surgical treatment of IHD stones may be performed in the following cases: first, when removal by conservative treatment or relatively mildly invasive procedure fails, or when complete removal is impossible; Second, The patient's condition cannot withstand other procedures. Third, the complications associated with IHD stones should be accompanied by liver resection. Fourth, cholangiocarcinoma is suspected. Fifth, the patient should be performed other biliary system or abdominal surgery.

2. METHOD OF SURGICAL TREATMENT

Surgical treatment of IHD stones can be divided into minimally invasive surgery (MIS) which is typical of laparoscopic surgery and conventional open surgery. Recently, MIS such as laparoscopic surgery and robotic surgery, which are faster to recover after surgery, are widely used in patients than open surgery. Methods of its operation include IHD exploration with choledochoscopy and stone removal, Roux en Y choledochoenterostomy bypass after stone remove, ductoplasty for stricture of bile duct after stone remove, and liver resection. Theoretically, if bilateral multiple IHD stones and severe cholangitis are repeated, liver transplantation may be selected as a treatment, but in reality, liver transplantation for benign diseases is controversial.

IHD exploration method is most as basic surgical procedure. After IHD or extrahepatic bile duct open and then we removed IHD stones by variety of ways, using such as saline flushing, stone basket, Fogarty catheter, EHL. Try to remove it completely. This method is applied to stones that are mainly confined to the central part rather than to the periphery of the hepatic bile duct. In the presence of strictures of distal IHD, access to the bile ducts is restricted and can be difficult to remove. Further, if the bile duct curve is severe bending, stones complete remove may also not possible. It is as important to prevent recurrence as it is to remove stones. For maintaining a smooth flow of bile, Roux en Y choledochoenterostomy or ductoplasty for narrowing stircuture duct are effective surgical methods. This is the case. However, the additional prevention of relapse is not complete, but it can be seen as an advantage over other treatments.

Liver resection is the best option for IHD stone. This is also possible for both minimally invasive surgery such as laparoscopic surgery and open surgery. Mainly indications are severe IHD stone with liver atrophy, liver abscess with distal stricture and cholangiocarcinoma is suspected. The possibility and extent of liver resection is the same as for general liver resection method. Although there is a risk of surgery of liver resection, it can become the most reliable treatment method in many cases. Especially in the case of bilateral IHD stones, the rate of complete removal can be very low, so various treatments should be attempted together. Surgically, in this case, one side of the severe mesenchyme is resected and the other side is conducted IHD exploration through the open bile duct with choledochoscopy. It can minimize the risk of recurrence. If complete remove is impossible, we can choice the next best method for postoperative management of remnant stones. The external drainage such as T tube or transhepatic

percutaneous drain indwelling during operation. After surgery, we can continuously attempt remove of remnant stone through this tract, repeatedly.

In conclusion, IHD stones are very demanding benign diseases and it is difficult to achieve complete treatment with only one treatment. Surgical treatment is the most reliable and maximized success rate, but you should always keep in mind the potential for complications associated with surgery and general anesthesia. Surgical treatment is obvious that is a higher probability of success than other treatments. Nevertheless, after sufficient discussion with other specialists, a combination of the various treatment methods can be used to make best result for patient. Surgical treatment is one attractive option to choose from among many treatments.

Case discussion

Seung Bae Yoon, M.D., Ph.D.

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Age and Gender: 57-year-old woman

Chief Complains: fever with chilling

Present illness:
The patient had epigastric pain and fever for 3 days. She visited the emergency room of our hospital.

Past History:
Seven years ago (in 2008), she underwent cyst excision with Roux-en-Y Hepaticojejunostomy due to choledocal cyst.
The final pathology is consistent with choledocal cyst with epithelial hyperplasia.
Two years later (in 2010), because of multiple IHD stones, she received intra-operative stone removal with choledocosocpe and re-anastomosis of Hepaticojejunostomy.

Physical Examination:
Physical examination revealed mild tenderness on upper abdomen.

Laboratory Findings:
Initial laboratory data were follows; WBC 13,820/mm3 (Seg. Neutrophils: 90.3%), hemoglobin 13.2 g/dL, platelet 89,000/ mm3, AST 63 U/L, ALT 81 U/L, Alkaline phosphatase 178 U/L, r-GTP 361 U/L, total bilirubin 2.79 mg/dL, direct bilirubin 1.27 mg/dL, CRP 16.06 mg/dL

Hospital Progress: Will be presented.

KDDW 2019 Korea Digestive Disease Week

DAY 2

November 29 (Friday)

[16:00-17:30, Emerald Hall A]

PG Course 06 (KASL) Korean

Updated KASL guidelines: HBV, Cirrhosis

Chairs: **Soonkoo Baik** (Wonju Severance Christian Hospital, Korea)

Jin-Woo Lee (Inha University Hospital, Korea)

HBV: Patients with elevated serum HBV DNA levels, but normal ALT levels

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Most of the medical decisions are drawn based on the comparison between risk and benefit or between cost and benefit.[1] Current international guidelines on the management of chronic hepatitis B recommend no antiviral treatment for immune-tolerant chronic hepatitis B (CHB) patients – when hepatitis B virus (HBV) is very replicative (reflected by high serum HBV DNA level and positivity for HBeAg), but alanine aminotransferase (ALT) level is normal – except for those with advanced fibrosis.[2-4] Those recommendations can be explained by the insufficient data on both efficacy and safety of a life-long anti-HBV treatment. It has been still uncertain whether antiviral treatment started from immune-tolerant phase can reduce the risk of cirrhosis and hepatocellular carcinoma development more profoundly compared to antiviral treatment initiated in active hepatitis phase. Thus, at this time, it is clear that there is few evidence supporting the early antiviral treatment for immune-tolerant phase CHB patients.

However, this issue might have to be re-evaluated in near future. During the recent two decades, highly potent antivirals (i.e., entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide fumarate) were developed and consequently the long-term risk of antiviral resistant mutation was dramatically reduced. In addition, several evidences showed that the immune-tolerant phase of CHB is not a completely safe status. HBV can directly induce HCC without developing advanced fibrosis and this direct carcinogenic effect with viral DNA integration to host genome followed by clonal hepatocyte expansion already started from immune-tolerant phase.[5,6] In a recent Korean study, untreated patients in immune-tolearnt phase showed significantly higher risk of HCC compared to patients who received antivirals for immune-active hepatitis,[7] although another Korean study reported comparable risk of HCC and liver-related events between untreated CHB patients in immune-tolerant phase and those achieving virological response by antivirals.[8] A Korean retrospective multicenter study reported that patients who underwent an early antiviral treatment from immune-tolerant phase was significantly associated with lower risk of HCC occurrence compared to patients who started antiviral treatment according to current guidelines.[9]On the other hand, chronic HBV infection was reportedly related to non-liver cancers such as a lymphoma, pancreatic cancer, and stomach cancer, and a study using big data reported that antiviral treatment was associated with attenuation of the HBV-related increased risk of extrahepatic malignancies.[9] Of course, these potential benefit of antiviral treatment from immune-tolerant phase should be studied further and validated with well-designed prospective studies.

In conclusion, current evidence-based guidelines do not recommend antiviral treatment in immune-tolerant phase of CHB. However, there are several recent data that favor antiviral treatment for immune-tolerant CHB. Further studies may give us chance to reevaluate the risk-benefit of antiviral treatment for immune-tolerant patients in near future.

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HBV: Pregnant women and women preparing for pregnancy

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INTRODUCTION

Clinical practice guidelines for the management of chronic hepatitis B (CHB) were originally published in 2004 by the Korean Association for the Study of the Liver (KASL) in order to provide specific medical information regarding CHB that would facilitate treatment of infected patients. Other than an update on treatment of antiviral resistance in 2014, which is a partial revision, the guidelines for the treatment of CHB have been revised entirely three times in 2007, 2011, 2015 and 2018.[1, 2] This presentation summarize updates for management of CHB in specific situations; female patients of childbearing age.

CONCLUSIONS

Guidelines for pregnant or patient preparing for pregnancy had been very conservative recommendation in 2015 KASL guidelines as well as previous US and European guidelines. Recently, safety of tenofovir-DF about these special populations has reported. As data have accumulated, several current guidelines recommended use of tenofovir-DF in pregnant women and even in breast-feeding women.[1,3,4]

If pregnancy is confirmed while using tenofovir-DF, we recommend continuing treatment. Even if you are using a drug other than tenofovir-DF, we recommend replacing it. Also, for pregnant women with HBV DNA> 200,000 IU/m, administration of tenofovir DF is recommended for the prevention of vertical transmission, starting at 24–32 weeks of gestation and stopping 2–12 weeks after delivery.

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Updated KASL Guidelines for the management of female patients of childbearing age

[3]2018 KASL Guidelines[1]	2015 KASL Guidelines[2]
Title and terms	
Pregnant women and women preparing for pregnancy	Female patients of childbearing age
Treatment agents (recommended before and during pregnancy)	
▪The administration of NAs in pregnant women or in patients preparing for pregnancy should follow the general principles of CHB treatment. Therapy should be carefully chosen considering the short- and long-term effects on both the mother and fetus, and tenofovir DF is currently recommended.(B1) ▪If a CHB patient becomes pregnant while taking an NA other than tenofovir DF, it is recommended to switch the medication to tenofovir DF, which is relatively safe for the fetus as well as for pregnant women and is not contraindicated during breastfeeding.(B1)	▪Peginterferon-α has an advantage in female patients who are planning pregnancy due to its finite treatment duration.(C1) ▪When antiviral treatment is needed during pregnancy, pregnancy category B NAs are recommended. (B1) ▪The antiviral treatment strategy during pregnancy is based on the general principles of CHB treatment; however, decisions should be based on analysis of the risks and benefits for both the mother and fetus. (C1)
Treatment agents (contraindicated during pregnancy)	
▪Child-bearing is contraindicated during peginterferon alfa treatment, and it should not be used in pregnant women. (A1)	▪However, the side effects pertaining to fetal malformations make peginterferon-α treatment contraindicated during pregnancy, and it should be recommended in combination with contraception. (A1)
Prevention of mother to child transmission of HBV with NAs	
▪For pregnant women with serum HBV DNA levels >200,000 IU/mL, administration of tenofovir DF is recommended for the prevention of MTCT (A2), starting at 24–32 weeks of gestation and stopping 2–12 weeks after delivery. (B1)	
Regarding to breast feeding	
▪There are no limitations regarding breastfeeding in CHB patients without antiviral treatment. (B1)	▪Breastfeeding is not recommended in females receiving treatment with NAs. (C1)

Management of varices

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Gastroesophageal varices (GEVs) are a frequent complication of liver cirrhosis and a leading cause of mortality in patients with liver cirrhosis. The incidence of esophageal varices (EVs) in cirrhotic patients without varices at baseline is 5–9% at 1 year and 14–17% at 2 years,[1,2] and small EVs progress to large varices in 12% at 1 year and 25% at 2 years.[2] The 1-year incidence of variceal bleeding in patients with cirrhosis and varices without a previous history of bleeding is approximately 12%, and the main risk factors of bleeding are larger varices, the presence of redness over the varices, and decompensated disease.[3] Portal hypertension, which is the most common complication of liver cirrhosis, is the main determinant in the development of GEVs. Increased intrahepatic vascular resistance to portal flow leads to the development of portal hypertension, which is aggravated by splanchnic vasodilatation and an increase in portal blood flow caused by hyperdynamic circulation.[4-6] When the portal pressure increases above a threshold, collaterals develop at the site of communication between the portal and systemic circulation, of which GEVs are the most important. With the aggravation of portal hypertension, the collaterals grow and eventually rupture. Bleeding from GEVs is a major complication of portal hypertension and a leading cause of mortality in patients with liver cirrhosis. Although the mortality rate has decreased significantly during the past several decades thanks to improvements in diagnostic and therapeutic modalities,[7,8] it remains as high as 12–22%.[9-12] In addition, rebleeding is frequent, up to 60% within 1 year, without appropriate treatment to prevent it.[13] Therefore, preventing variceal development and progression, preventing bleeding from GEVs, appropriately managing acute bleeding from GEVs, and preventing variceal rebleeding are critical in patients with liver cirrhosis.

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The management of hepatic encephalopathy

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Hepatic encephalopathy (HE) is a critical complication of liver cirrhosis that seriously reduces patients' quality of life.[1] The optimal management of HE is recently updated in KASL clinical practice guidelines for liver cirrhosis: Varices, hepatic encephalopathy, and related complications. This is a summary regarding management of HE from revised practice guidelines.

1. MANAGEMENT OF OVERT HEPATIC ENCEPHALOPATHY

The goals of treatment for overt hepatic encephalopathy (OHE) are as follows: 1) prevention of secondary damage caused by decreased consciousness and normalization of the patient's state of consciousness, 2) elimination of social and economic restrictions by preventing recurrence, and 3) improvement of patient prognosis and quality of life. Therefore, appropriate supportive care should be provided to prevent secondary damage. Furthermore, the precipitating factors should be identified and managed appropriately as soon as possible, and treatments should be initiated using medications that can decrease or eliminate the production of ammonia, the major pathogenic material.

The primary treatment for HE is nonabsorbable disaccharides such as lactulose (β-galactosido-fructose) or lactitol (β-galactoside sorbitol), which lead to recovery in 70–90% of HE patients.217 If patients have severe HE, an enema of 300 ml lactulose and 700 ml water can be performed 3–4 times per day until clinical improvement is achieved. Rifaximin, a rifamycin derivative, has a positive effect in managing HE.[2] A meta-analysis of those RCTs found that rifaximin had a therapeutic effect similar to that of lactulose or lactitol.[3] Furthermore, in a recent clinical trial, patients treated with a combination of rifaximin and lactulose showed a better recovery from HE within 10 days (76% vs. 44%, P = 0.004) and shorter hospital stays (5.8 vs. 8.2 days, P = 0.001) than those treated with lactulose alone.[4] Ornithine and aspartate are important substrates used to metabolize ammonia to urea and glutamine. The administration of L-ornithine-L-aspartate (LOLA) can lower plasma ammonia concentrations and lead to improvements in HE.[5] Branched-chain amino acids (BCAAs), such as valine, leucine, and isoleucine, supplementation inhibits proteolysis and plays an important role in muscle metabolism, leading to glutamine production that is useful for detoxifying ammonia.[6]

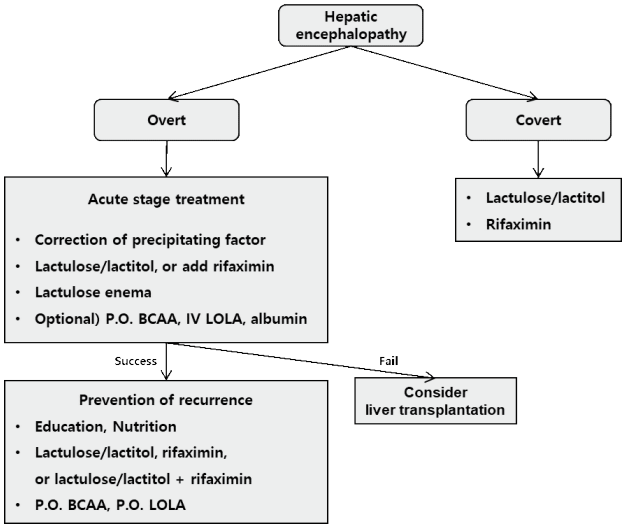

Figure 1.

2. MANAGEMENT OF COVERT HEPATIC ENCEPHALOPATHY

Most studies for covert hepatic encephalopathy (CHE) were performed in a small number of patients with a short duration of treatment and focused on improving cognitive function and quality of life; studies are still needed on extending survival or the development of OHE. As with OHE, it is known that nitrogenous substances, especially ammonia, play a major role in CHE. Therefore, treatments can be given to reduce ammonia. The most studied treatment is lactulose, which showed a marked improvement in cognitive function and quality of life and decreased the occurrence of OHE.[7] Rifaximin and nonabsorbable antibiotics also improved cognitive function and quality of life.[8] However, lactulose treatment is more cost-effective than rifaximin therapy.[9]

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KDDW 2019 Korea Digestive Disease Week

DAY 2
November 29 (Friday)

[16:00-17:30, Diamond Hall]

Basic/Translational Symposium 02 (KSGC) English

Toward the precision medicine

Chairs: **Laufey Amundadottir** (National Cancer Institute, National Institutes of Health, United States)

Tae Il Kim (Severance Hospital, Korea)

Sun Young Rha (Yonsei Cancer Center, Yonsei University College of Medicine, Korea)

Expression quantitative trait locus (eQTL) and chromatin interaction approaches to understand biology of pancreatic cancer risk loci from GWAS

Laufey Amundadottir, Ph.D.

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Pancreatic cancer genome-wide association studies (GWAS) in European subjects have identified 20 risk loci, mostly in non-coding regions of the genome. Identifying functional candidate variants is often challenging due to linkage disequilibrium (LD) and the often-large number of variants that need to be followed up functionally at each risk locus. To simultaneously characterize multiple pancreatic cancer risk loci and identify potential functional variants and the genes they act on, we have used a series of high throughput sequence based genomic approaches such as expression and splicing Quantitative Trait Locus analysis (eQTL, sQTL), Massively Parallel Reporter Assays (MPRA), chromatin conformation approaches in pancreatic tissue samples and cell lines. These approaches will be described, and examples presented where such large genomic datasets aid in the discovery of the underlying biology at pancreatic cancer risk loci.

Exploration of aminoacyl-tRNA synthetases for future medicine

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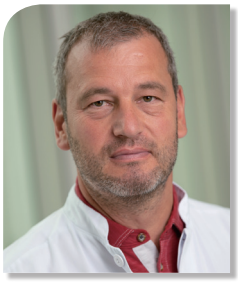
Future medicine is often symbolized by 4P (Personal, Predictive, Preventive and Participatory) medicine. To bring 4P medicine to reality, many new therapeutic targets and biomarkers. Aminoacyl-tRNA synthetases (AARSs) are essential enzymes required for protein synthesis from genetic code. However, human AARSs are also known as multi-functional signal mediators and their aberrant expression and activities are associated with various human diseases. This lecture will introduce these multi-faceted enzymes as rich resource for the development of new therapeutics and diagnosis with some case studies under development.

RECENT REVIEWS

1. Kwon et al, Aminoacyl-tRNA synthetases as therapeutic targets, Nat Rev Drug Discov 18: 629-650, 2019.
2. Forsyth, K. Aminoacyl-tRNA synthetases and tRNAs in human disease, J Biol Chem 294: 5292-5293, 2019.



TGFß signalling and NFAT transcription factors in cancer development and progression

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Intrinsic cancer vaccination

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The need to develop novel strategies for cancer therapy is tremendous. In the late 1800s, Dr. William Coley investigated anti-tumor effects mediated by microbe-derived toxins, establishing initial concept of exploiting the immune system to combat cancer. Since then, the field of cancer immunotherapy has evolved intensively, accompanying our understanding of the complexity of the immune system. In contrast with therapies that act on the tumor itself, immunotherapeutic agents target the patients' immune system to control tumor progression, and such immune responses can be sustained even after the treatment has finished. Research in the field of cancer immunotherapy has flourished in recent years, yielding both crucial breakthroughs and information on important immunosuppressive pathways that can limit the success of cancer immunotherapy.

Tumor cells often overexpress immune checkpoint molecules, which limit the immune system's search function and tamp down the immune response. To overcome this problem, researchers have developed a number of different antibody proteins that block these checkpoint molecules and enable the immune system to destroy tumors. Such cancer immunotherapy can add extra years to patients' lives. However, checkpoint blockade therapies work only when anti-tumor T cells are present but anergic of exhausted; these cells are reactivated *in situ* through the molecular inhibitors. Moreover, not all tumors appear to respond to the current immunomodulatory maneuvers. For instance, only a fraction of patients with melanoma respond to single-agent immune checkpoint blockade using anti-PD-1/PD-L1 therapeutic antibodies. In some cases there is no response even when the checkpoint molecules are blocked, because there are too few active T cells in the vicinity of the tumor or the tumor doesn't display enough of the T cell targets (neoantigens) on its surface. In another immunotherapeutic strategy, T cells are amplified *ex vivo*, activated, genetically engineered to be highly combative (Chimeric antigen receptor T cells, also known as CAR-T), and then reinfused into the patient to target to the tumor. While CAR-T cell therapy has shown great success for the treatment of hematologic tumors, response rates of patients with solid tumors are less favorable; it is also antigen-specific and requires foreknowledge of the relevant cancer antigens to which the patient would be sensitive. Since emerging cancer immunotherapies using immune checkpoint blockades work predominantly at steps 6 and 7 of the cancer-immunity cycle (Figure 1), effective cancer immunotherapies require successful passage through the early stages of the cycle to improve T cell priming and activation (steps 1–3). Thus, rational strategies need to be designed to overcome the activation energy threshold of the immunosuppressive tumor microenvironment (TME) that turn cold tumors hot and allow our primed immune systems to recognize the tumors as foreign or aberrant.

For an anti-cancer immune response to lead to effective killing of cancer cells, the immunogenic cell death (ICD) pathway must initiate a series of stepwise events in which the ICD pathway in the tumor releases neoantigens created by oncolysis, which are engulfed by dendritic cells (DCs) for antigen processing (step-1, Figure 1). In order for this step to yield an anti-cancer T cell response, it should be assisted by immunogenic signals released by dying tumor cells. Notably, ICD is accompanied by the spatiotemporally defined release of damage-associated molecular patterns (DAMPs) and/or danger

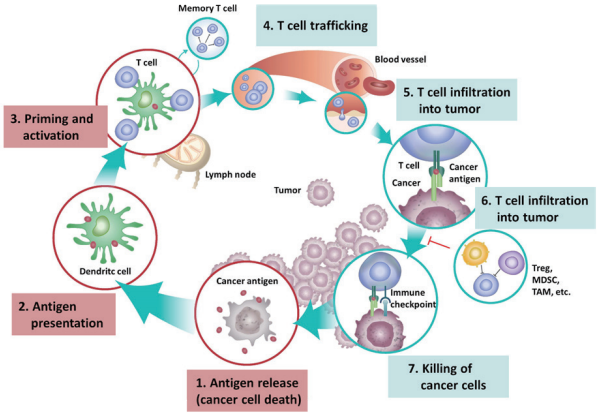


Figure 1. Cancer-immunity cycle. This cycle is a self-sustaining multistep process that involves: (1) the release of cancer cell antigens; (2) cancer antigen presentation; (3) priming and activation; (4) the trafficking of T cells to the tumor; (5) the infiltration of T cells into tumors; (6) the recognition of cancer cells by T cells; and (7) the killing of cancer target cells. Each step is described in the manuscript along with various cancer immunotherapy strategies. Figure modified from Chen and Mellman with permission from Elsevier.

signals that raise the potential immunogenicity of dying cells. Next, DCs engulf and process the tumor-derived antigens, then travel to the lymph node to undergo maturation. DCs use MHC class I and MHC class II molecules to present the captured antigens to T cells (step-2), leading to the priming, activation, and clonal expansion of cytotoxic T cell responses against cancer antigens (step-3) that have triggered incomplete central tolerance. The nature of the immune response is determined at this stage, with the final outcome resting on the critical ratio of T effector cells versus regulatory T (Treg) cells. Finally, the activated effector T cells migrate to and infiltrate into (step-4, 5) the tumor core, specifically bind to cancers via an interaction between T cell receptor (TCR) and the MHC class I-bound cognate antigen (step-6), and conclusively kill tumor cells via the release of cytolytic effectors (e.g., perforin and granzyme A/B) (step-7).

Therapeutic cancer vaccines, which represent a viable option for active immunotherapy, seek to facilitate efficient T cell priming. However, therapeutic vaccination has thus far failed to induce a robust immune response against tumors in clinical trials. Tumor-induced immunosuppressive mechanisms in the TME have been reported to be a major cause of the limited success of the current therapeutic cancer vaccines.

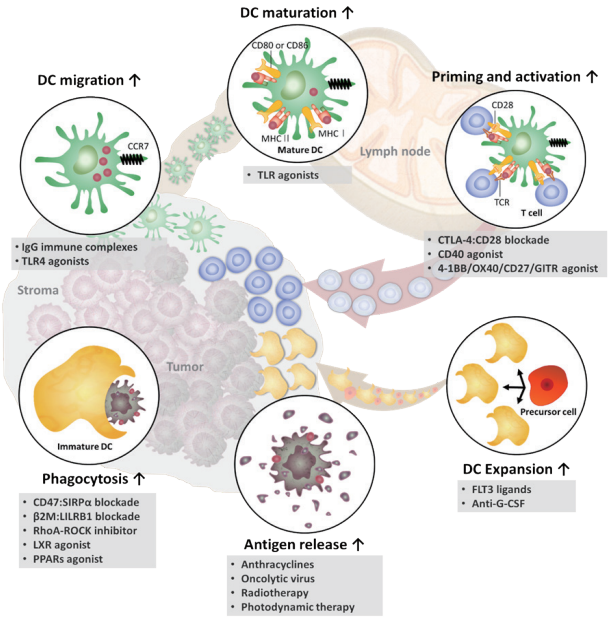


Figure 2. The strategy of intrinsic cancer vaccination. In order to obtain a strong immunity against cancer, APCs should selectively recognize cancer cells as non-self and effectively digest them to activate anti-tumor T cell immunity. This strategy includes: 1) DC expansion; 2) enhancement of non-self signals; 3) enhancement of phagocytosis; 4) DC migration; 5) DC maturation; and 6) enhancement of priming and T cell activation. The enhanced phagocytosis of cancer cells undergoing ICD could improve APC functions, leading to tumor-specific T cell immunity.

Here, we discuss the novel strategy of "intrinsic cancer vaccination", which seeks to control the entire cancer-immunity cycle of cancer neoantigen release, cross-priming and T cell proliferation, cancer cell elimination and converting immunosuppressive TME to an immunogenic microenvironment. In addition, we cover the use of nanoparticle-based platform to improve delivery of immunotherapeutic drugs to specific target tissues and/or to maximize their efficacy. This strategy focuses on allowing our immune system to recognize and eliminate cancer cells, and hence should greatly increase the patient population that will benefit from the cutting-edge science of cancer immunotherapy.

In cancer patients, the cancer-immunity cycle does not work properly for following reasons: 1) Tumor antigens may not be detected. 2) DCs and T cells may consider tumor antigens as self rather than non-self (foreign), thereby stimulating the response of Treg cell rather than effector responses. 3) T cells may not accordingly infiltrate and home to tumors. 4) The tumor may escape immune surveillance and cell death by expressing activating and inhibitory ligands that interact with receptors found on the surface of immune cells. 5) Factors in the TME might suppress the produced effector T cells. Although the clinical efficacy and durable responses seen with immune checkpoint blockades have spurred dramatic changes in our approach to treating cancer, the results from large clinical trials clearly show that only a fraction of patients respond and many will relapse. Therefore, we urgently need to develop a novel immunotherapeutic strategy that meets the following five requirements: 1) targetability to selectively recognize the neoantigens of cancer cells; 2) adaptability to the antigen variability that arises from mutation of cancer cells; 3) self-propagation within the immune system itself, to enhance anti-cancer-immunity; 4) penetration of immune cells to tumor tissues; and 5) durability of the immune effect.

In this review, we discuss new concept of "intrinsic cancer vaccination", which we believe will amplify a sufficient and robust immune response in the early stage of the cancer-immunity cycle (Fig 2). To awaken intrinsic immunity against tumors, this strategy involves killing tumor cells in a manner that exposes new antigens to immune cells via ICD, while also enhancing phagocytosis in order to prime T cells capable of specifically recognizing cancer cells. We also describe the utilizing of nano-formulation for targeted and/or co- delivery of immunotherapeutic drugs. Although the nanoplatform provide great opportunity for improving efficacy of intrinsic cancer vaccination strategy, their own immunogenicity that affect immune responses need to be considered for design and engineering of nanoparticles. In addition, tuning of the general properties of nanoparticles such as size, shape, surface modification, and spatiotemporal drug release is necessary to reduce unwanted immune reactions. As the safety evaluation of nanoplatform is required for the successful clinical applications, the network between nanoparticles and immune system

should be considered in the nano-immunotherapy field.

Note that while intrinsic cancer vaccination is an important strategy of $CD8^+$ T cell-associated anti-cancer immune responses, this is not the only means to facilitate an immune response against cancer. Knowledge of the concepts and mechanisms that underlie intrinsic cancer vaccination-induced T cell activation could provide shed light on new strategies for combining this strategy with novel immunotherapeutic approaches. For example, within the TME, PD-L1 is constitutively expressed in response to oncogenic signaling or induced in response to inflammatory cytokines (e.g., IFN-γ). As discussed in the review, the intrinsic cancer vaccination-mediated induction of T cell immunity overcomes resistance to immune checkpoint inhibitor therapies. Similarly, PD-L1 expression is increased upon intrinsic cancer vaccination treatment, providing a rationale for combined cancer treatment using this strategy and αPD-L1. The combination of intrinsic cancer vaccination with immune checkpoint blockade may yield significantly improved anti-tumor responses by releasing the state of immunosuppressive microenvironment and augmenting tumor-reactive T cell responses.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[07:30-08:30, Flamingo]

MTP 03 (KCHUGR) English

Meet the Professor

Chair: **Sung Kwan Shin** (Yonsei University College of Medicine, Korea)

Endoscopic management for obesity

Roman Turro Arau, M.D.

Department of Bariatric Endoscopy, Centro Medico Teknon, Barcelona, Spain

INTRODUCTION

Obesity is major disease in our society. Minimal invasive procedures, like endoscopic ones, are a potential treatment option for a large group of population.

OBJECTIVES

Review of different endoscopic techniques available for the treatment of obesity grade I-II.

METHODS

Starting from the intragastric ballon to the small bowel procedures, devices with more than 20 years in the market to others that are still in study. Analyze what is the future of the endoscopy for the treatment of obesity.

RESULTS

Review of the results from different techniques.

CONCLUSIONS

The endoscopic procedures are safe and has an enormous potential.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[07:30-08:30, Skylark]

MTP 04 (KPBA) English

Meet the Professor

Chairs: **Jin Lee** (Dongtan Sacred Heart Hospital, Korea)

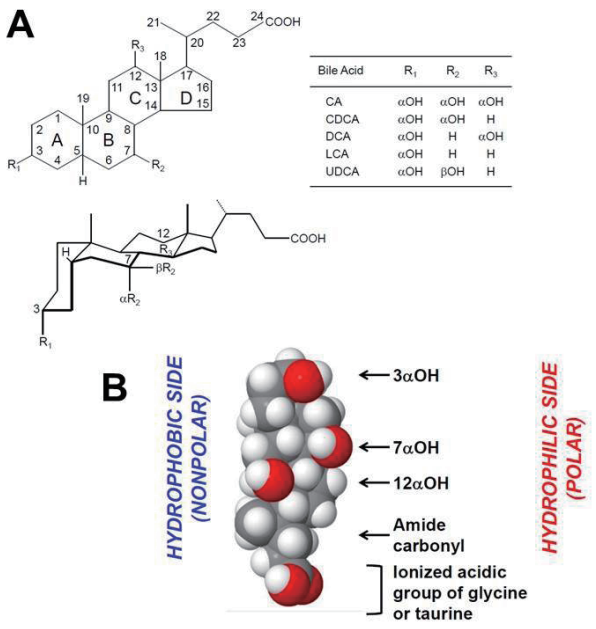
Jin-Hyeok Hwang (Seoul National University Bundang Hospital, Korea)

Bile acids and cancer

David Wang, M.D., Ph.D.

Department of Medicine and Genetics, Albert Einstein College of Medicine, Bronx, United States

The conversion of cholesterol to bile acids is the only significant catabolic pathway for elimination of excessive cholesterol from the body. There are two major pathways for bile acid biosynthesis from cholesterol in mammalian liver: (i) the classical (or neutral) pathway and (ii) the alternative (or acidic) pathway. It is well known that bile acids are physiological detergents important for emulsification of dietary fats, drugs, and lipid-soluble vitamins in the intestine and subsequent absorption and transport to the liver for metabolism and distribution to other organs and tissues. More recent studies have found that bile acids are also important signaling molecules that can activate the nuclear receptor farnesoid X receptor (FXR) and G protein-coupled bile acid receptor-1 (GPBAR-1 or TGR5) to regulate cholesterol, bile acid, triglyceride, glucose, and energy metabolism in the body. In addition, bile acids activate intestinal FXR and TGR5 to stimulate fibroblast growth factor 15 (FGF15) and glucagon-like peptide-1 (GLP-1) secretion. Bile acids have both pro- and anti-inflammatory actions through FXR and TGR5 in the liver and intestine. Animal and translational research have revealed that agonist activation of FXR and TGR5 improves insulin and glucose sensitivity and stimulates energy metabolism to prevent diabetes, obesity, and non-alcoholic fatty liver disease (NAFLD). Clinical trials have found that FXR and TGR5 agonists may have therapeutic potential for treating liver-related metabolic diseases, such as NAFLD and diabetes. Obviously, bile acids not only regulate the absorption of intestinal cholesterol, fat-soluble vitamins, and fatty acids, but also play a critical role as signaling molecules in the modulation of epithelial cell proliferation, and gene expression, as well as lipid, glucose, and energy metabolism. These homeostatic pathways, when disrupted, could promote local inflammation, systemic metabolic disorders, and ultimately, cancer. The effect of hydrophobic bile acids, in particular, can be associated with cancer in several digestive organs such as liver, biliary tract, pancreas, colon, stomach, and esophagus, as well as extra-digestive organs such as breast and prostate through a complex series of mechanisms including direct oxidative stress with DNA damage, apoptosis, epigenetic factors regulating gene expression, increased or reduced expression of nuclear receptors such as FXR, and altered composition of gut microbiota, as well as acting as a common interface between environmental factors, including diet, lifestyle, and exposure to toxics, and the molecular and cellular events promoting cancerogenesis. Primary prevention strategies, including changes in dietary habits and lifestyle, as well as reduction in exposure to environmental toxics, are highly likely to modify gut microbiota and the epigenome. The use of hydrophilic bile acids to counterbalance the negative effects of more hydrophobic bile acids might be a potential strategy for the prevention and the management of these gastrointestinal tract cancer in the near future. After completion of this session, you will learn many novel concepts regarding (i) the physical-chemistry and biochemistry of bile acids; (ii) the molecular regulation of bile acid synthesis and metabolism, including the enterohepatic circulation of bile acids; (iii) the roles



A. Molecular structure of common bile acids, showing common steroid ring and side-chain structure. The numbering of the carbon atoms in bile acids is shown in the structural formula (top panel). Hydroxyl group(s) location and orientation are given for each bile acid (bottom panel). Abbreviations: CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; UDCA, ursodeoxycholic acid. **B.** Space filling model of the taurine conjugate of cholic acid (viewed from the side) showing its planar amphipathic structure with a hydrophilic and a hydrophobic side.

Figure 1. Molecular structure of common bile acids.

of bile acid-activated nuclear receptors FXR and TGR5 in metabolic regulation, including lipid, glucose, and energy metabolism; (iv) bile acids as therapeutic drugs to treat liver diseases such as cholesterol gallstones, NAFLD, and cholestasis, as well as diabetes, and obesity; and (v) the critical roles of disrupted bile acid metabolism in the pathogenesis of gastrointestinal tract cancer.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[09:00-10:30, Convention Hall A]

Combined Symposium 07 (KASID-KSCP) Korean

Topic 1. Inter-disciplinary approach in IBD

Topci 2. Management of a visible high-grade dysplasia in a patient with ulcerative pancolitis

Chairs: **Won Ho Kim** (Severance Hospital, Korea)

Suk-Hwan Lee (Kyung Hee University at Gangdong, Korea)

Perianal Crohn's disease: Stem cell therapy or anti-TNFs?

Yong Sik Yun, M.D., Ph.D.

Department of Surgery, Asan Medical Center, Seoul, Korea

Perianal fistulizing Crohn's disease (CD) remains a significant clinical challenge greatly affecting patients' quality of life due to pain, discharge, and abscess formation. At least 23%~26% of Western CD patients develop perianal fistulas within 20 years after diagnosis. The incidence of Crohn's perianal fistula is especially high, up to 45% in Korean CD patients. Achieving complete fistula healing is often a long process accompanied by multiple relapses. Patients frequently fail to respond to current medical options, including antibiotics, immunosuppressive agents, and anti-tumor necrosis factor (TNF) biologicals. To prevent abscess formation, surgical placement of noncutting setons is often required. In more severe cases, fecal diversion is needed to attenuate perianal disease. The ultimate treatment goal is complete fistula healing without sphincter damage. Unfortunately, despite the best available therapies, durable remission rates of complex perianal fistulas remain low at 37.0%.

Anti-TNF agents including infliximab are regarded as an effective therapeutic to Crohn's perianal fistula. In the development of a top-down therapy, infliximab is considerable as an initial treatment for moderate-to-severe Crohn's disease prior to other therapeutics. Especially, combined surgical and infliximab therapy showed improved healing rates and reduced recurrent rates in the complex fistulas. However, because perianal fistulas are categorized by various subtypes depending on their locations and fistula openings, the assessment for treatment response of infliximab is required in accordance with fistula subtypes. Although the response of the anti-TNF agents in Asia

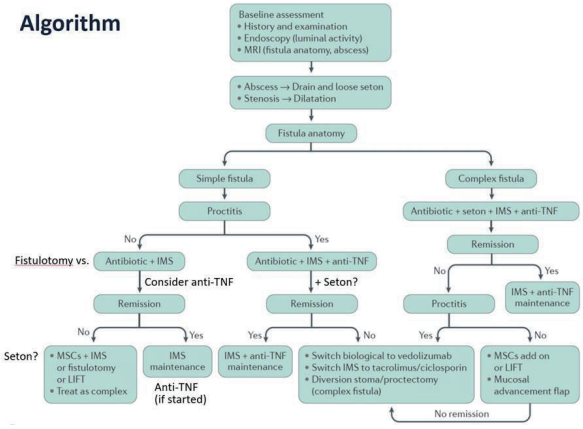


Figure 1. Treatment Algorithm for Crohn's Perianal Fistula (Modified from Panés J, Rimola J. Perianal fistulizing Crohn's disease: pathogenesis, diagnosis and therapy. Nat Rev Gastroenterol Hepatol. 2017 Nov;14(11):652-664).

Table 1. Published clinical trials using stem cell for the treatment of Crohn's Perianal Fistula

Authors, Year	Study Design	Source of Cells	Results
Garcia-Olmo, 2005	Phase I clinical study (n=4)	ASC (autologous)	Complete closure: 50% of patients 75% fistulas
Garcia-Olmo, 2009	Open-label, multicenter, phase II study (n=14)	ASC + fibrin glue (autologous)	Fistula healing: 71% vs 14%
Ciccocioppo, 2011	Prospective study (n=10)	MSC (autologous)	Reduction in CDAI, PDAI, and pain / discharge
Mannon, 2011	Open-label phase II study (n=10)	MSC (allogeneic) IV	Reduction in CDAI and fistula drainage
Guadalajara, 2012	Retrospective follow-up of Garcia-Olmo phase I study (n=10)	ASC + fibrin glue (autologous)	58% sustained fistula closure at end of follow-up by mean 3 years
Cho, 2013	Open-label, multicenter, dose escalation phase I study (n=10)	ASC (autologous)	Healing in 50% receiving >2 x 107 cells/mL
Lee, 2013	Open-label, multicenter, phase II study (n=42)	ASC (autologous)	Fistula closure in 82% PP, 67% ITT analysis
de la Portilla, 2013	Open-label pilot study (n=24)	ASC (allogeneic)	Complete closure: 56.3%
Ciccocioppo, 2015	5-year follow-up of 2011 study	MSC (autologous)	37% fistula relapse free 4 years later
Cho, 2015	1-year follow-up of 2013 Lee's study	ASC (autologous)	Complete closure maintained in 75% at 2 years ITT analysis
Garcia-Olmo, 2015	Retrospective, open label (n=3)	ASC (allogeneic and autologous)	Healing in 2/3 CD fistula patients
Molendijk, 2015	Double-blind, placebo-controlled, phase II study	MSC (allogeneic)	Healing up to 85%
Panes, 2016	Phase III, RCT	ASC (allogeneic)	52% closure vs. 36% (placebo) at 24wks.
Panes, 2018	Phase III, RCT	ASC (allogeneic)	56% closure vs. 39% (placebo) at 52wks.

ASCs, adipose-derived stem cells; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; ITT, intention to treat; IV,intravenous; MSCs, mesenchymal stem cells/ mesenchymal stromal cells; PDAI, Pouchitis Disease Activity Index; PP, per protocol; SC, stem cells.

is expected to be higher than the Western countries, there is a lack of published reports on the efficacy of infliximab for perianal Crohn's disease. Therapeutic algorithm is depicted according to complexity of fistula, presence of proctitis, and response of medications (Figure 1).

An emerging therapeutic approach is the use of mesenchymal stromal cells (MSCs). These are non-hematopoietic multipotent cells able to down-regulate immune responses and promote tissue healing. It has been reported that human MSCs are able to inhibit generation of dendritic cells from monocytes, are capable of down-regulating expression of presentation and costimulatory molecules on mature dendritic cells preventing T-cell activation, and promote the generation of regulatory T cells. In addition, MSCs participate in tissue-repair processes, providing a strong rationale for the use of these cells as a treatment for Crohn's perianal fistula. Recently, phase I and II clinical trials have shown promising results on the healing rates of perianal fistulas. Locally injected MSCs demonstrated 69%~82% fistula healing. Table 1 summarizes trials of stem cell therapy for perianal Crohn's fistula.

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What surgeons need to know: updates of biologics and small molecules

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, idiopathic inflammatory disease of GI tract with waxing and waning clinical course, which may lead to irreversible bowel damage and a loss of bowel function. Cumulative intestinal damage results in complications such as stricture or fistulae, and eventually a large number of IBD patients undergo surgery. The advent of anti-tumor necrosis factor (anti-TNF) has revolutionized the therapy of IBD. In the past two decades since the advent of infliximab, the first anti-TNF, the surgical rates for IBD has been decreasing in proportion to the increased use of anti-TNFs. However, we now face several unmet clinical needs – failure to or loss of response to anti-TNFs, intolerance to drugs, and adverse event such as infection and malignancies – that require safer, better-tolerated treatment options with different mod of action.

NOVEL THERAPIES FOR IBD

As our understanding of the pathogenesis of IBD has increased, novel drugs targeting specific steps in highly complex pathogenesis are being developed. Table 1 lists the biologics and small molecule currently available in Korea for the treatment of IBD.

1. Anti-cell adhesion molecules

The α4β7 integrins on the surface of leukocytes and the mucosal addressin cell adhesion molecule (MAdCAM) on the vascular endothelium play a pivotal role in the migration of gut-homing leukocytes. Anti-cell adhesion molecules inhibit gut inflammation by blocking this pathway at many sites. The drugs in this class include vedolizumab (specific IgG1 antibody blocking α4β7), natalizumab (targeting the α4 subunit of the α4β7 and α4β1 integrins), etrolizumab (blocks the β7 integrin subunit), and MAdCAM inhibitors. Natalizumab, the first anti-integrin, showed efficacy in inducting and maintaining clinical benefit in moderate to severe Crohn's disease (CD). However, occurrence of a serious adverse event (progressive multifocal leukoencephalopathy, PML) limits its use in clinical practice. Compared to natalizumab, vedolizumab selectively prevents leukocyte trafficking to the gut without targeting α4β1 integrin, which modulates brain trafficking. In pivotal studies, VDZ was more effective than placebo as induction and maintenance therapy in moderate-to-severe ulcerative colitis (UC) and CD. No PML case was reported under vedolizumab treatment. In addition, due to the gut-selective blockade of α4β7, vedolizumab has an excellent safety profile without any risk of serious or opportunistic infections.

Table 1. Currently available biologics and small molecule for the treatment of IBD in Korea

Class	Drug	Ulcerative colitis	Crohn's disease
Anti-TNF	Infliximab	O	O
	Adalimumab	O	O
	Golimumab	O	X
Anti-integrin	Vedolizumab	O	O
Anti-IL12/IL23	Ustekinumab	X*	O
JAK inhibitor	Tofacitinib	O	X

TNF: tumor necrosis factor, IL: interleukin, JAK: Janus kinase.
*Ustekinumab has been approved for the treatment of UC by EMA, but not yet by KFDA.

2. Anti-cytokines

Recent data have implicated the innate immune system and the IL-23/Th17 axis as being pivotal to the pathogenesis of IBD. Ustekinumab is a fully human IgG1 monoclonal antibody that blocks the p40 subunit of IL-12/IL-23. Clinical trials showed short-term and long-term efficacy and safety of ustekinumab for the treatment of CD. Recently, similar efficacy and safety of ustekinumab were confirmed in UC clinical trial. Novel drugs that selectively targets the p19 subunit of IL-23 are under investigation, such as risankizumab, guselkumab, and mirikizumab.

3. Janus kinase (JAK) inhibitors

Since nearly all cytokines use the Janus kinase (JAK) signal transducer and activator of transcription pathway as a common signaling pathway, JAK inhibitors block the activity of multiple cytokines simultaneously. JAK inhibitors are small molecules which have some merits compared to antibodies – short half-life (allowing interference with the immunosuppressive effect in case of infection, surgery, or pregnancy), orally administered (improving patients' acceptance), and lower risk of immunogenicity and allergic reaction. Tofacitinib is a pan-JAK inhibitor and clinical trials confirmed its efficacy in induction and maintenance therapy compared to placebo in patients with moderately

to severely active UC. In contrast, tofacitinib treatment failed to show efficacy in CD. Observed adverse events were herpes zoster infection and increased lipid levels. Recently, US Food and Drug Administration published a black box warning regarding an increased risk of pulmonary embolism and death among patients with rheumatoid arthritis treated with 10 mg tofacitinib twice daily. Other orally administered selective JAK-1 inhibitors, filgotinib and upadacitinib, are under investigation for UC and CD treatment.

4. Sphingosine-1-Phosphate Receptor Modulator

Sphingosine-1-phosphate (S1P) is a signaling molecule that regulates the traffic of lymphocytes out of the lymphoid organs into the bloodstream and to inflamed tissue. S1P receptor modulators are small molecules down-regulating S1P receptors on lymphocytes and prevent lymphocyte trafficking out of the lymph nodes to the site of inflammation. Ozanimod and etrasimod are selective S1P receptor modulators showing promising results in phase II clinical trials for UC.

IMPACT OF BIOLOGIC EXPOSURE ON POSTOPERATIVE COMPLICATIONS

Although introduction of anti-TNFs has contributed to declining surgical rates for IBD, a significant number of patients on biologic therapy still need surgery. There is controversy on the impact of biological exposure on postoperative morbidity. It has been reported that there is no difference in the rate of postoperative complications between anti-TNFs and vedolizumab exposed patients with IBD. It is clear that interrupting biologic therapy is an appropriate strategy if elective surgery is planned and there is no additional benefit of continuing the biologic. For Crohn's disease, however, there may be a benefit to continuing therapy in patients with remained inflammatory burden. If continued therapy is required after surgery, it could be beneficial to schedule surgery in the middle of an 8-week dosing interval.

CONCLUSIONS

Multidisciplinary approach is mandatory for the appropriate management of IBD, as it is a chronic progressive disease showing complex and heterogeneous clinical outcomes. Since new drugs with various mechanisms of action are being introduced into clinical practice, IBD surgeons also need to be aware of their effects and impact on surgery.

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Total proctocolectomy should be first

Hee Cheol Kim

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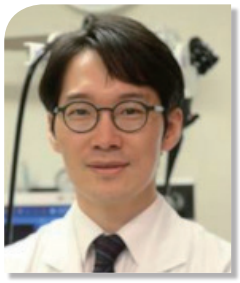

Endoscopic resection should be first

Dong-Hoon Yang, M.D., Ph.D.

Department of Gastroenterology, Asan Medical Center, Seoul, Korea

The risk of colorectal cancer (CRC) increases in the patients having long-standing ulcerative colitis (UC).[1-3] In addition to the long disease duration, the following conditions are known to be associated with the risk of dysplasia or CRC in UC: extent of disease (pancolitis or extensive colitis), combined primary sclerosing cholangitis, familial history of CRC in the first degree relatives, severe histologic inflammation, colonic strictures, and multiple inflammatory pseudopolyps. Dysplasia is considered as a precancerous lesion of CRC in the long-standing UC,[4] and can be categorized into indefinite for dysplasia, low-grade dysplasia (LGD), and high-grade dysplasia (HGD). Traditionally, total proctocolectomy (TPC) had been regarded as a standard treatment not only for CRC but also for dysplasia in UC patients.[4] However, since early studies about the feasibility of polypectomy for dysplasia,[5,6] subsequent studies have supported the therapeutic role of colonoscopic polypectomy for polypoid dysplasia in colitic patients. The pooled incidence of CRC after endoscopic resection of polypoid dysplasia is 5.3 cases per 1000 patient-years in the colitic patients,[7] and the incidence of post-colonoscopy CRC was 2.5 cases per 1000 patient-years according to a recent large surveillance study for the colitic patients.[8] Therefore, recent guidelines suggest that endoscopic resection as a key modality for the treatment of visible and endoscopically resectable dysplasia in the colitic patients.[9-11] However, there are still concerns about the endoscopic treatment for HGD in UC, as patients having HGD carry higher risk of CRC occurrence during follow-up than those with LGD.[12] Based on the currently available evidences regarding the advantage and limitation of endoscopic resection for HGD, the therapeutic strategy for HGD in UC patients will be suggested in this lecture.

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KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[09:00-10:30, Convention Hall B]

Video Session 01 (KSG-UGI) English

Chairs: **Pinghong Zhou** (Zhongshan Hospital, Fudan University, China)

Vu Van Khien (108 Central Hospital, Vietnam)

Gwang Ha Kim (Pusan National University Hospital, Korea)

Magnifying endoscopy with NBI in the stomach, especially for EGC

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Narrow-band imaging (NBI) system utilizes two narrow-band illuminations of 415 nm and 540 nm by the NBI filter, corresponding to peak absorption of hemoglobin.[1] Therefore, thin blood vessels in the mucosal layer can be seen more distinctly than in conventional endoscopy. On NBI, most early esophageal squamous cell carcinomas (SCCs) are seen as brownish areas.[2] Especially, magnifying endoscopy with NBI (ME-NBI) is a powerful tool to characterize the lesion.[3] With magnification, regularity of the intraepithelial papillary capillary loops (IPCLs) can be evaluated. IPCLs which can be observed during ME-NBI work as an indicator of tissue atypia in the squamous epithelium.[4] ME-NBI also enables evaluation of detailed visualization of microstructures and microvessels within the superficial layer of the gastric mucosa.[5] For example, my recent study reported that the appearance of a light blue crest and a white turbid band in the mucosa is a distinctive endoscopic finding that suggests an increased probability of intestinal metaplasia.[6] Yao et al. first reported unique ME-NBI findings based mainly on the subepithelial microvascular (MV) and microsurface (MS) architecture characteristics of differentiated-type early gastric cancers (EGCs).[7] ME-NBI is also be capable of predicting the histological characteristics of EGCs; a fine network or intralobular pattern suggests differentiated-type carcinomas and a corkscrew pattern suggests undifferentiated-type carcinomas (Figure).[8,9] Clinically ME-NBI is useful for the differential diagnosis of focal gastritis and small depressed cancer and for determining the horizontal extent of early gastric cancer for successful endoscopic resection.[5] Advantages of ME-NBI over conventional endoscopic imaging techniques with white light include accurate diagnosis and cost effectiveness.

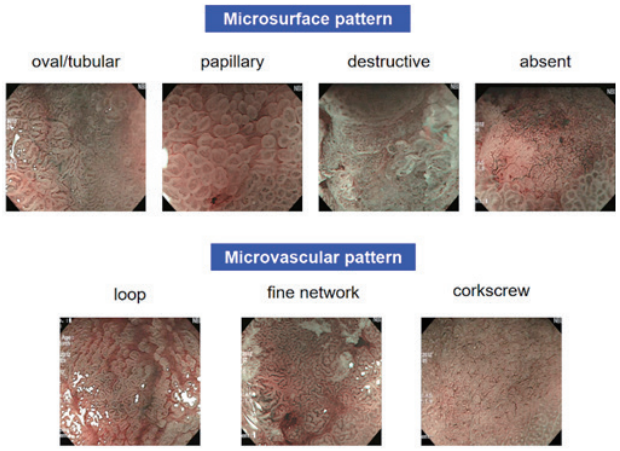

Figure. ME-NBI findings of early gastric cancer.

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Active GI bleeding: how to treat

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Non-variceal upper gastrointestinal bleeding continues to be an important cause of morbidity and mortality. The most common causes include peptic ulcer disease, Mallory–Weiss syndrome, erosive gastritis, duodenitis, esophagitis, malignancy, angiodysplasias and Dieulafoy's lesion. Initial assessment and early aggressive resuscitation significantly improves outcomes. Upper gastrointestinal endoscopy continues to be the gold standard for diagnosis and treatment. Endoscopy is considered the gold standard for diagnosis and treatment of nonvariceal upper gastrointestinal bleeding. Endoscopy is recommended within 24 hours of presentation, after appropriate stabilization and resuscitation has been completed. Endoscopy within 24 hours has been shown to decrease hospital stay length, reduce risk of rebleeding, or need for further surgical intervention. There are currently several different treatment modalities available to the endoscopist including injection therapy, hemoclips, thermal coagulation, fibrin sealant, and hemostatic powder. The most commonly used forms of endoscopic intervention are thermal coagulation and hemostatic clips. The usefulness of each method has been reported. The above modalities can achieve an initial hemostasis in 90% or more of cases. Arterial bleeding is known to recur, however, in up to 25% of cases. As rebleeding is often associated with a high mortality, the goal of endoscopic treatment should be achieve a definitive hemostasis. Currently, the efficacy and safety of endoscopic hemostasis rely on the identification of lesions that are suitable for endoscopic therapy, the selection of the appropriate hemostatic devices, attention to technique, and prompt recognition and management of procedure related adverse events. The suitable technique should be chosen based on the appearance of the bleeding focus and the related risk for persistent or recurrent bleeding. Of all the listed modalities, application of hemoclips would appear to be one of the best treatment modality. In contrast to the other modalities, hemoclips provide a direct, mechanical hemostasis without injuring the surrounding tissues. Therefore, the risk of rebleeding is minimized. Some bleeding lesions could not response to endoscopic treatment. Therefore, radiologic intervention and/or surgery are also another alternative.

ESD with traction method

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Endoscopic submucosal dissection (ESD) has become the standard treatment for gastrointestinal tumors. However, ESD in certain situations (upper third, lesion with fibosis, and esophageal lesion) is technically difficult and procedure time is longer and complications such as intraoperative perforation and bleeding occur more frequently than in easier locations. Traction and counter-traction is one of the fundamental principles in surgery and makes better and optimal exposure of surgical field and visualization of dissection plane. In ESD, traction methods are also used to facilitate visualization of the submucosal layer, thus enabling accurate identification of the cutting line and submucosal vessels. Traction is thus a promising approach to help reduce the procedure time and complications and may lead to more widespread adoption of ESD. Recently, various traction methods have been introduced to facilitate ESD procedures, such as clip with dental floss, external forceps, suture device, clip and snare, internal traction, double scope, and magnetic anchor. Each method must be used appropriately according to the anatomical characteristics. The clip-dental floss method is the easiest and simplest way of traction, so is widely used. A dental floss (approximately 1m in length) is tied to the arm part of the clip. After circumferential cutting, a clip applicator device is inserted into the accessory channel of the endoscope, and the clip with dental floss is mounted on the tip of the applicator. The scope is inserted again, and the clip with dental floss is attached to the edge of the lesion. The lesion is then pulled toward the oral side using the dental floss. Although this technique is simple, traction is directed only to the oral side and control of the traction direction is impossible. In this video, we introduce recently proposed traction methods for ESD based on the characteristics of various anatomical sites and mostly discuss the clip-dental floss method.

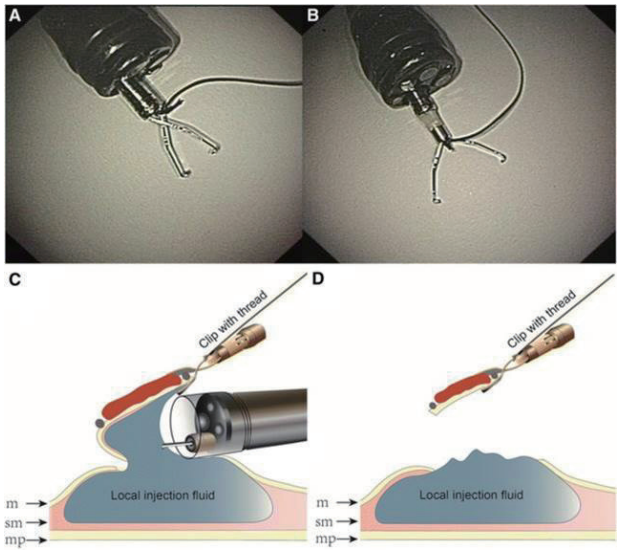

Figure 1. Traction with clip-dental floss.
From Surg Endosc. 2017 Jan;31(1):462-468. doi: 10.1007/s00464-016-4939-1

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POEM, the submucosal endoscopy: tips and know-how to be an expert

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Per-oral endoscopic myotomy (POEM) is an innovative natural orifice flexible endoscopic procedure that involves myotomy of distal esophagus via a sub-mucosal tunneling approach. Since the procedure was first performed by Inoue et al., POEM is becoming a standard treatment for achalasia.

We are facing with various difficult situations while doing POEM procedure. The difficult situations we can face can be divided into three main categories: the difficulty of training, advanced achalasia with sigmoidization, and redo-POEM.

POEM is technically challenging procedure and requires a certain degree of skill and competency. However, The low incidence of achalasia, in combination with the potential serious complications related to the technically demanding POEM procedure, has made training difficult. Learning curves vary among operators, being influenced by innate ability, previous experience, motivation, available technology, operative findings, and institutional factors. It is important that proficiency is not always decided from an absolute number of the procedures, but rather on concrete quality metrics that can be individually assessed with each procedure.

The sigmoid-shaped esophagus considered to be a difficult situation to manage, in which the esophageal lumen is significantly dilated and distorted. In such a tortuous megaesophagus, it may easy to be lost the right direction in the tunnel during the procedure. Thus, during submucosal tunneling, the dissection plane should be always maintained to be perpendicular to the circular muscular layer in order to avoid losing the direction; repeatedly pulling the scope out of the tunnel to confirm the direction is also recommended. The dissection plane should also be located nearly on the surface of the muscularis and the repeated injection of saline should be performed at any moment that the dissection plane becomes unclear to avoid mucosal injury.

Previous surgery of the cardia, prior botulinum toxin injections, and even earlier dilations may also lead to substantial fibrosis of the submucosal planes and altered anatomy, making myotomy more difficult. From a technical point of view, redo myotomy is more difficult than primary myotomy. Because of the previous POEM operation, the submucosal space may be obliterated in the original operation site, and it may be very difficult to confidently and easily create the submucosal tunnel, as can be accomplished in those who have not had prior therapy. Therefore, after identifying the earlier myotomy site, we often placed the re-myotomy in the unscarred area on the opposite side.

In conclusion, operators who intend to perform POEM must keep in mind the following basics requirement. Firstly, understanding pathophysiology of achalasia is important to perform procedure in properly selected patients. POEM is a procedure that requires capabilities of good endoscope manipulation, recognition of luminal structures, and knowledge of extraluminal structures, particularly mediastinal anatomy. In addition, the operator should know how to perform the procedure, should be capable of handling possible adverse events.

Endoscopic management of esophageal fistula and anastomotic leak

Hyuk Soon Choi, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Korea University Anam Hospital, Seoul, Korea

Esophageal fistula and leak can be caused by transmural defect in which the esophageal wall structure is damaged in full-thickness level. Esophageal leakage occurs mainly in the anastomosis site after surgery, and the communication in and out of the gastrointestinal tract occurs due to damage of the gastrointestinal wall. Esophageal fistulas can be defined as a connection between the gastrointestinal tract with an adjacent organ (trachea, bronchus, etc.) or with an abscess. If an esophageal leak persists, they may form a fistula. In this article, we aimed to investigate various clinical features of esophageal leakage and fistula, and their treatment methods, especially through endoscopy.

Acute and chronic anastomotic leaks can occur in inflammatory or malignant diseases, but postoperative anastomotic leaks are most common. These leaks not only extend the hospital stay of the patients, but also could delay the treatment and cause higher mortality, so early diagnosis and active treatment for these leaks are essential. If the contents of the esophagus leak to the thoracic cavity or adjacent lungs, they can result in severe infection and require aggressive treatment.

Researches on the most effective treatment for esophageal leaks are ongoing. Many conventional and conservative treatments include antibiotic treatment, nasogastric intubation, total parenteral nutrition and drainage through proper intubation. Many endoscopic treatments using clips, stents, various sealants, vacuum therapy, and endoscopic suturing devices have been attempted as well. There is also a various surgical methods such as aggressive reoperation.

Treatment of esophageal leaks, fistulas and perforations should be done in close cooperation between the gastroenterology, surgery and radiology departments. Usage of endoscopy in treating these esophageal lesions are rapidly increasing because of the advantages of preventing reoperation and shortening the duration of conservative treatment like simple drainage. In addition, new endoscopic devices and treatment methods have improved the treatment outcome of esophageal damage, and it is expected that endoscopic treatment will become one of major treatment methods in near future. However, endoscopic treatment may not be suitable in all cases. Physicians should evaluate the case thoroughly, keep in mind the limitation of each treatment methods, and try to choose a proper therapeutic method.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[08:30-10:30, Convention Hall C]

Joint Symposium (IASL1) English

Global unsolved issues in viral hepatitis

Chairs: **Kwang-Hyub Han** (Severance Hospital, Korea)

Myungken Lee (Severance Hospital, Korea)

Markus Peck (Klinikum Klagenfurt Am Wörthersee, Austria)

Current situation and strategic plan of Hepatitis B in Africa

Benjamin Djoudalbaye

Department of Policy and Health Diplomacy, African Union Commission, Africa Centres for Disease Control and Prevention, Addis Ababa, Ethiopia

Development of international program for Hepatitis B management

Hoon Sang Lee

Department of Graduate School of Public Health, Yonsei University, Seoul, Korea

Economic burden and cost effective control of viral hepatitis

Yock Young Dan

Department of Gastroenterology and Hepatology, National University Hospital, Singapore

Viral hepatitis constitutes one of the major causes of morbidity and mortality worldwide. Some 250 million and 70 million people are believed to have chronic hepatitis B (HBV) and chronic Hepatitis C (HCV) infection respectively with more than half of them in Asia and concentrated in lower income countries. The high cost of both antiviral therapy and treatment for liver complications including decompensated liver cirrhosis, liver cancer and liver transplantation are substantial. Adding to this is that these disease strike patients who are frequently still in their productive age groups, resulting in a significant economic burden.

Most Asian countries do not have universal insurance and the government frequently provide subsidies to keep healthcare affordable to patients. Yet for developing countries or those where generic drugs are not available, this create challenges for health care affordability and impacts drug access and subvention policies. Cost effectiveness can be a powerful tool to lobby and shape healthcare policies as well as guide pharma companies in lowering drug prices to better fit the economic spending power of specific country.

In the example of Chronic Hepatitis B, there was long delay in Asian healthcare authorities extending subsidies to new generation low resistance antivirals such as entecavir and tenofovir in view of cost. Cost effectiveness modelling taking into account unique conditions of each countries showed that in the long term, these drugs can be more cost effective than sequential therapy.

The development of the oral antivirals for Hepatitis C heralded the new era of super high cost drugs. When sofosbuvir/ledipasvir was first launched in the west, the list price was USD90000 for a full course and ignited a flurry of controversy over drug cost and patient

Example of Hepatitis B Cost-effectiveness Modelling in Singapore

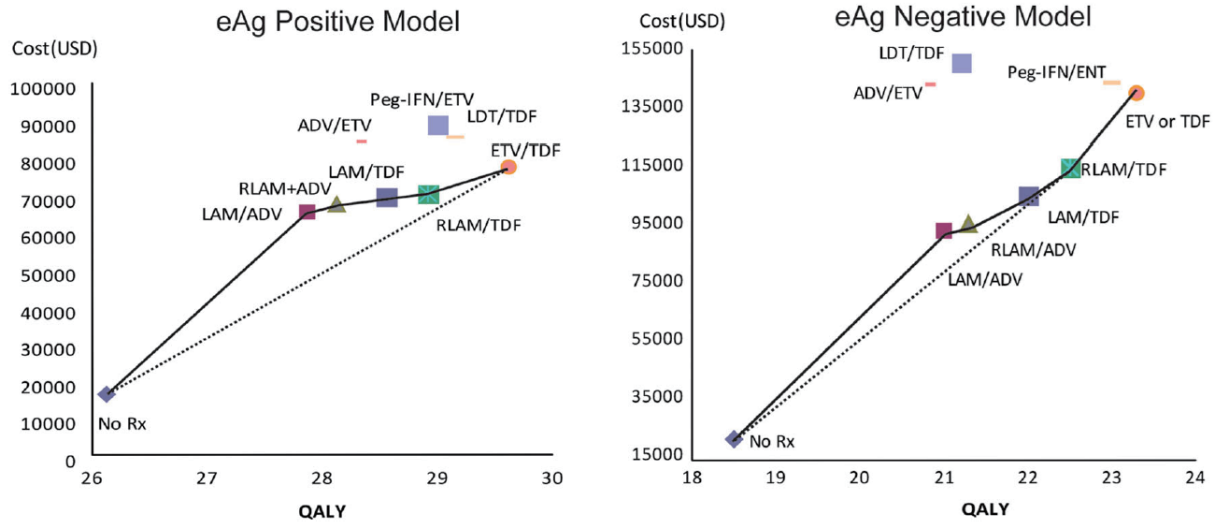

Figure. Cost-effectiveness of hepatitis B treatment in Singapore Cost-effectiveness graph shows that the cost for treating HBeAg positive patients are fairly similar as savings from cheaper NUCs with low resistance barrier is offset by need for combination therapy subsequently. In fact, NUCs with high resistance barrier end up more cost-effective (dotted line with lowest gradient compared to no antiviral treatment). All strategies falling above the dotted lines are dominated (cost more and are less effective) or are weakly dominated (extended dominance because less efficient use of resources). For HBeAg negative patients, R-LAM/TDF-S or ETV/TDF are equally cost-effective but ETV/TDF saves more lives from liver mortality, albeit at a higher cost. The incremental cost-effectiveness ratio (ICER) gauges whether the drug provides sufficient value (or benefit) to justify its cost in reference to willingness to pay threshold of the country. From Hepatology International (2014) 8:382–394.

rights. While extremely efficacious, the impact on health budget was significant and Hepatitis C therapy became the single highest cost item in heath budget of many countries. While most authorities suggested a prioritised strategy based on the degree of liver fibrosis, cost-effectiveness analysis showing that it was more cost effective to treat patients with low fibrosis score were used to campaign and advocate universal treatment for all patients. This however, was not practical as it would bust most of the healthcare budget in Asia had it not been for the availability of generic drugs in some countries. Again, with specific cost effectiveness, it was possible to look at ideal strategy for specific countries and successfully used to lobby pharmaceutical companies to lower their price through competitive negotiations.

The World Health Organisation has bravely set a lofty target to eradicate Hepatitis B and C in the world by year 2030. While this is technically possible, eradication requires a more comprehensive systematic health strategy for public education, screening penetrance, registry monitoring for adherence as well as infrastructure for universal healthcare to achieve therapeutic accessibility. Cost-effectiveness need to include the setup of such a comprehensive system and take into account training, sustainability, audit and impact review so as to achieve maximal success.

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Global strategy to prevent viral hepatitis; focusing on introducing Hepatitis B birth dose in low- and middle-income countries

Daniel Rhee, M.D.

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At the 69th World Health Assembly in 2016, World Health Organization (WHO) Member States endorsed three jointly developed global strategies, HIV, viral hepatitis, and sexually transmitted infections for disease elimination by 2030. The continuum of hepatitis prevention and treatment services within the concept of universal health coverage frame were emphasized to mitigate mortality and morbidity associated with hepatitis infection. The elimination plan calls for 90% reduction in incidence, and 65% reduction in mortality by 2030 (30% reduction in incidence, and 10% reduction in mortality by 2020) [1]. Of many service coverage targets, hepatitis B virus (HBV) childhood and birth-dose vaccination coverage were targeted for 90% by 2030. With global efforts on expanded programme on immunization, relative success has been documented for HBV childhood vaccination (reported as 82% among infants by the WHO in 2015), however similar success has not been replicated for HBV birth-dose implementation (38% coverage in 2015). Despite HBV birth dose being a key intervention tool for preventing HBV infection among infants [2], administering birth dose within 24 hours of delivery in communities where a large portion of birth occurs outside the healthcare facility has been challenging.

Most of infants who do not receive a HBV birth dose reside in low-income countries, where further work remains to be done to ensure HBV birth dose is added to routine immunization programs. HBV birth dose vaccination integrated into a broader maternal and child care practices is essential. Existing thermo-stability data of HBV vaccine supports controlled temperature chain (CTC) strategy is financially and scientifically a valid strategy to reach home births [3]. Several innovative approaches to ensure the timely administration of the HBV birth dose in South-East and South Asia should be considered for implementation in African countries [4]. Unique opportunities lie to increase HBV birth dose in a near future as GAVI recently has approved to support for HBV birth dose beginning in 2021 by providing funding to establish platforms as catalytic support for the introduction of HBV vaccine administered at birth [5]. Increasing coverage of safe and effective HBV vaccine coverage, through universal childhood vaccination and by timely delivery of birth-dose, will drastically reduce incidence of HBV infection by preventing mother-to-child transmission, ultimately reducing rates of chronic illness and mortality.

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Role of IASL to strengthen global partnership

Kwang-Hyub Han

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The International Association for the Study of the Liver (IASL) is one of the oldest international nonprofit organization fighting against liver and biliary tract diseases. It was established in 1958, aiming to train experts in hepatology; encourage basic and clinical research; facilitate internationally the prevention, recognition and treatment of diseases of the liver and biliary tract. This was to be done by holding the biennial meeting of IASL with one of the continental societies on a rotating basis. Successful Associations are present in Africa, South American, Asia-Pacific, Europe and North America.

We are excited about our continuing association with the continental societies but also excited about new initiatives and their impact on hepatology in emerging counties. As a lack of educational opportunities for many physicians in the world, the role of IASL will continue to strengthen global partnership. This is a critical time for IASL and we must move in new directions to remain an important part of international education.

In this summer, we had a workshop in Africa and we discussed how to strengthen the partnership with the African Network for Viral Hepatitis and how to set up an education program for African young doctor. We already have experiences to give opportunities to learn and study through educational programs(EP). To facilitate the partnership with African Network for viral hepatitis, we may need to develop international program for Hepatitis B management. There are many programs to support this issue. To strengthen the partnership with the African Network for Viral Hepatitis, we may need more systematic approaches by multilateral program with IASL.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[09:00-10:30, Emerald Hall A]

Editor Session Korean

Tips to become a good journal

Chairs: **Young S. Kim** (University of California, United States)

Sang Woo Lee (Korea University College of Medicine, Korea)

Publication Ethics

Dong Soo Han, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Hanyang University Guri Hospital, Guri, Korea

The concept of publication ethics is rapidly changing recently. Fabrication, falsification, and plagiarism are evoked most frequently as forms of misconduct. Big stream for transparency and accountability in research integrity changes research environments widely. Also, the introduction of general data protection regulation (GDPR) by EU and a culture of open research impact on our environment. Authorship is a valuable commodity, for which authors receive enormous credit. The various type of authorship disputes make complicated matters in combination with conflict of interest. The open science concept makes post-publication peer review popular. Also, reproducibility issues are important for research integrity. Researchers should have complex responsibilities for their own works. Therefore, "transparency in describing all aspects of the research process, from planning, proposing, performing, and reporting, goes a long way towards allowing better selection, scrutiny, and use of research" The proper training and education in research integrity should be allocated efficiently, especially directed towards junior scientists.

Past and new decade of Gut and Liver

Jong Pil Im

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Gut and Liver is an international journal of gastroenterology, focusing on the gastrointestinal tract, liver, biliary tree, pancreas, motility, and neurogastroenterology. Gut and Liver is the first Korea's international journal of gastroenterology and has achieved remarkable growth in the short term, since it was launched in 2007. On 27th February 2006, Chung Yong Kim, emeritus chairmen, and Jin Ho Kim, chairmen of the Korean Society of Gastroenterology proposed to launch the international journal to raise the level of the domestic journal and disseminate and promote academic developments by the Korean researchers. The task force (publishing committee after the journal launch) was made up with the six participating society (the Korean Society of Gastroenterology, the Korean Society of Gastrointestinal Endoscopy, the Korean Association for the Study of the Liver, the Korean Society of Neurogastroenterology and Motility, the Korean College of Helicobacter and Upper Gastrointestinal Research, the Korean Association for the Study of Intestinal Diseases) and prepared for publishing the journal including submission, review, publishing system, and so on. The editorial committee consisted of the director of publication committee from 6 participating society and professor Young S. Kim, University of California San Francisco, waselected as an Editor-in-Chief.

On 30th of June 2007, the first issue of the Gut and Liver was successfully published. After 1 year, publication interval was shortened from biannually to quarterly as submitted and published articles steadily increased. Since the first issue of the 2013 (Vol 7. No1), it has been published bimonthly. In June 2007, the Korean Pancreatobiliary Association, and January 2012, the Korean Society of Gastrointestinal Cancer joined the publishing committee, and currently operated by 8 affiliated societies.

In February 2009, Gut and Liver was approved to be indexed in Science Citation Index Expanded (SCIE) and impact factor increased rapidly from 0.219 in 2010 to 2.968 in 2018 (Figure 1). Gut and Liver was indexed Scopus & Embase databases and approved as a member journal of the Korean Association of Medical Journal Editors. In addition, the journal was indexed in Google Scholar and KoreaMed in 2009. Gut and Liver was approved to be indexed in PubMed Central (PMC) on 30th April 2010, and in MEDLINE on 6 November 2013.

Several kinds of efforts are required to improve the journal quality and impact in the category by increasing more cites. The editorial board should try to invite and publish good articles worldwide which can attract international readers. The publisher should support the editorial activity financially and systematically. The participating society members should encourage to cite more articles in the journal, and it is also necessary to establish well organized and updated publishing strategy. As of October 2019, journal impact factor 2019 of Gut and Liver is 2.348 and expected to achieve the impact factor over 3 through these efforts.

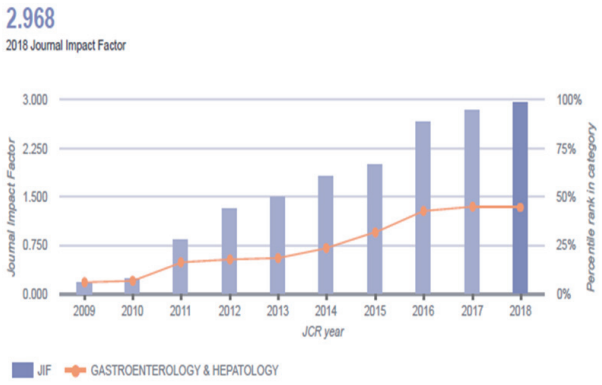

Figure 1. 2018 Journal Impact Factor & percentile rank in category for Gut and Liver

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Strategy to be an SCI journal: Clinical and Molecular Hepatology

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Is the Clinical and Molecular Hepatology eligible to be indexed in the Social Science Citation Index (SSCI) or the Science Citation Index Expanded (SCIE)? How did we prepare for application? What are the remaining challenges? In this lecture, the effort of the Clinical and Molecular Hepatology to be a sci jounal will be discussed.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[09:00-10:30, Emerald Hall B]

Metabolism & Obesity 01 (KSG-KSMBS-KSPGHAN) English

Obsetiy and metabolic syndrome: where are we now and where are we going?: pathophysiology, epidemiology, diagnosis, classification etc.

Chairs: **David Wang** (Albert Einstein College of Medicine, United States)

Hyun Wook Baik (Bundang Jesaeng Hospital, Korea)

Joo-Ho Lee (Nowon Eulji Medical Center, Eulji University, Korea)

Pathophsiology of metabolic syndrome: the cutting edge

David Wang, M.D., Ph.D.

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The metabolic syndrome, by definition, is not a disease, but is a clustering of individual metabolic risk factors that are associated with increased prevalence of type 2 diabetes and cardiovascular disease (CVD), which is a clustering of clinical findings made up of abdominal obesity, hyperglycemia, atherogenic dyslipidemia, and low high-density lipoprotein cholesterol levels, and hypertension. The reported prevalence of the metabolic syndrome varies, greatly depending on the definition used, gender, age, socioeconomic status, and the ethnic background of study cohorts. According to the World Health Organization (WHO), the prevalence of obesity has doubly increased worldwide in the past 30 years, the prevalence of the metabolic syndrome will also increase in parallel. Of special note is that the high

Comparison of definitions of the metabolic syndrome

Comparison of definitions of the metabolic syndrome

	WHO	EGIR	NCEP/ATPIII	AACE	AHA/NHLBI/ADA Updated NCEP/ ATPIII	IDF	Harmonized Definition[a]
Year	1999	1999	2001	2003	2004	2005	2009
Number of risk factors	IFG/IGT/T2DM or insulin resistance[b] and 2 of…	Insulin resistance[c] and 3 or more of…	Three or more of….	IGT/IFG with any of the following…	Three or more of…	Obesity and 2 of…	Three or more of…
Obesity	Waist/hip ratio >0.9 M, >0.85 F or BMI >30 kg/m^2	Waist circumference ≥94 cm M ≥80 cm F	Waist circumference ≥102 cm M ≥88 cm F	BMI ≥25 kg/m^2	Waist circumference ≥102 cm M ≥88 cm F	Waist circumference ≥94 cm M ≥90 (Asian M) ≥80 cm F	Waist circumference[d] Geographic and ethnic specific
Dyslipidemia	HDL-C <0.91 mmol/L M (35 mg/dL) <1.0 mmol/L F (<39 mg/dL) TG ≥1.7 mmol/L (150 mg/dL)	HDL-C <1.0 mmol/L (39 mg/dL) TG ≥2.0 mmol/L (177 mg/dL) or treated	HDL-C <1.0 mmol/L M (40 mg/dL) <1.3 mmol/L F (50 mg/dL) TG ≥1.69 mmol/L (150 mg/dL)	HDL-C <1.0 mmol/L M (40 mg/dL) <1.3 mmol/L F (50 mg/dL) TG ≥1.69 mmol/L (150 mg/dL)	HDL-C <1.0 mmol/L M (40 mg/dL) <1.3 mmol/L F (50 mg/dL) TG ≥1.69 mmol/L (150 mg/dL) or treated	HDL-C <1.0 mmol/L M (40 mg/dL) <1.3 mmol/L F (50 mg/dL) TG ≥1.7 mmol/L (150 mg/dL) or treated	HDL-C <1.0 mmol/L M (40 mg/dL) <1.3 mmol/L F (50 mg/dL) TG ≥1.7 mmol/L (150 mg/dL) or treated
Hyperglycemia	T2DM FPG >6.1 mmol/L (110 mg/dL) 2 h OGT >7.7 mmol/L (140 mg/dL)	Not T2DM FPG >6.1 mmol/L (110 mg/dL)	T2DM FPG ≥110 mg/dL (6.1 mmol/L)	Not T2DM FPG ≥110 mg/dL (6.1 mmol/L) 2 h OGT >7.7 mmol/L (140 mg/dL)	T2DM FPG ≥5.6 mmol/L (100 mg/dL)	T2DM FPG ≥5.6 mmol/L (100 mg/dL)	FPG ≥5.6 mmol/L (100 mg/dL) or treated
Hypertension	SBP ≥140 DBP ≥90	SBP ≥140 DBP ≥90 or treated	SBP ≥130 DBP ≥85	SBP ≥130 DBP ≥85	SBP ≥130 DBP ≥85 or treated	SBP ≥130 DBP ≥85 or treated	SBP ≥130 DBP ≥85 or treated
Additional components	Microalbuminuria ≥20 μg/min Albumin/creatinine ≥30 mg/g	—	—	Insulin resistance (family history T2DM, age, ethnicity, sedentary, lifestyle, PCOS)	—	—	—

Abbreviations: AHA, American Heart Association; BMI, body mass index; DBP, diastolic blood pressure in mm Hg; F, female; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; M, male; NHLBI, National Heart, Lung and Blood Institute; OGT, oral glucose tolerance test; PCOS, polycystic ovarian syndrome; SBP, systolic blood pressure in mm Hg; TG, triglyceride.

[a] Joint statement from the IDF, AHA/NHLBI, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity.

[b] If fasting glucose <110 mg/dL (6.1 mmol/L), insulin resistance measured by hyperinsulinemic-euglycemic clamp with lowest quartile for glucose uptake.

[c] Modification to WHO definition to use upper quartile of fasting insulin levels.

prevalence of the metabolic syndrome is not unique to the USA and Europe, it is being increased in most Asian countries as well.

The descriptions of the metabolic syndrome could differ by components or criteria, but all point toward a similar dysmetabolic phenotype. Although there were several definitions of the metabolic syndrome, a harmonized international definition has been proposed recently (see Table), which incorporates the criteria for the National Cholesterol Education Program (NCEP) definition and suggests that population-specific waist circumference thresholds should be used for obesity. Notably, the absence of diagnosis of the metabolic syndrome does not imply safety from CVD because ~20% of the patients without a diagnosis also suffer from CVD. Moreover, of all the criteria of the metabolic syndrome, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are most strongly associated with diabetes. Nonalcoholic fatty liver disease (NAFLD) and cholesterol gallstone disease are two fellow travelers with the metabolic syndrome.

Obviously, insulin resistance has explained and will continues to elucidate most, if not all, of the metabolic syndrome. It is very clear that insulin resistance contributes to hyperglycemia. In addition, obesity (or energy imbalance) is recognized as the leading cause since it strongly associates with all metabolic risk factors. Clinical and epidemiological studies have found that the metabolic syndrome all begins with excess central obesity. When β-cell function is responsive, it leads to an increase in plasma insulin levels, but fasting and postprandial insulin concentrations often remain normal for years. However, in the subjects with genetic predisposition, there are defects in insulin secretion and IFG and/or IGT. Furthermore, a major contributor to the development of insulin resistance is an overabundance of circulating fatty acids. Plasma fatty acids are derived mainly from adipose tissue triglyceride stores released through the action of the cyclic AMP-dependent enzyme hormone sensitive lipase. Furthermore, insulin resistance is closely associated with abnormalities in nitric oxide bioavailability and reduced PI3K/Akt signaling in the vascular wall, both of which have a crucial role in mobilization of endothelial progenitor cells from bone marrow. In addition, insulin resistance itself also leads to structural or functional damage to the endothelium and apoptosis in the arteries.

After completion of this session, you will learn the latest concepts regarding the history, definitions, pathophysiology, pathogenesis, and diagnosis of the metabolic syndrome, as well as its preventive measures and therapeutic strategies.

Gut microbiome and metabolic syndrome

Myung-Shik Lee, M.D., Ph.D.

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Gut and gut microbiota are criticalnot only in the energy extraction but also in the control of systemic and local intestinal immunity. The disturbance of gut microbiota has been observed in numerous diseases such as colitis, inflammatory bowel diseases, metabolic disorders, cancer, neurological disorders, etc, and appears to contribute to the disease processes of such diseases. Recent papers showed that changes of microbiota can also affect aging process. Alteration of internal milieu and microbiota of gut could be particularly important in the development of metabolic disorders and diabetes since gut is one of the first organs contacting excessive dietary fat or sucrose that is implicated as a major culprit of those diseases. Gut microbiota are significantly affected by dietary components. For instance, enterotypes are determined by long-term dietary pattern: animal fat or protein intake increases the proportion of Bacteroides, while carbohydrate ingestion favors Prevotella. Changes of gut microbiota associated with high-fat diet ingestion, low-fiber diet intake, obesity or insulin resistance include altered proportions of Akkermania municiphila, Bacteriodes thetaiotaomicron, Prevotella copri or Bacteriodes vulgatus or Methanobrevibacter smithii. Gut immunity also shows significant changes in association with obesity or high-fat diet ingestion such as alteration of innate lymphoid cells, macrophages, Th17 cells, CD8+ intraepithelial lymphocytes or IgA level etc. These findings provide a novel perspective and clueto understand the complex pathophysiological context related to the development of metabolic syndrome or diabetes, and can provide a unique opportunity to develop new therapeutic agents of innovative concept.

Recent Issues in diagnosis and classification of obesity

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The prevalence of obesity is increasing in Korea, especially in men according to the 2019 obesity factsheet published by the Korean Society for the Study of Obesity (KSSO). Moreover, obesity increases the risk of type 2 diabetes, hypertension, dyslipidemia, cardiovascular diseases, and mortality (Figure 1).

The Committee of Clinical Practice Guidelines of KSSO revised the clinical practice guidelines for obesity in 2018 using National Health Insurance Service Health checkup data from 2006 to 2015 to improve the management of obesity through research and education after reviewing systemic evidence using expert panels. In these guidelines, KSSO added a category, class III obesity, which includes individuals with body mass index (BMI) ≥35 kg/m^2 (Table 1).

This stage III obesity category is agreeing with the International Federation for the Surgery of Obesity and Metabolic Disorders, Asian Pacific Chapter consensus. Also the KSSO determined that bariatric surgery is indicated for Korean patients with BMI≥35 kg/m^2 and for Korean patients with BMI ≥30 kg/m^2 who have comorbidities.

Although there are still some controversy on the definition of obesity and the cutoff value of obesity, BMI ≥25 kg/m^2 and the cutoff value of abdominal obesity, waist circumference WC ≥ 90cm in men and ≥ 85cm in women are reasonable and some on-going studies will contribute to the revised guideline of the KSSO in the future.

Table 1. Risk of comorbidity according to obesity and abdominal obesity

Classification	Body mass index (kg/m^2)	Risk of comorbidity according to abdominal obesity	
		<90 cm (men), <85 cm (women)	≥90 cm (men), ≥85 cm (women)
Underweight	<18.5	Low	Average
Normal	18.5–22.9	Average	Increased
Pre-obese	23–24.9	Increased	Moderate
Obese class I	25–29.9	High	Severe
Obese class II	30–34.9	Moderate	Very severe
Obese class III	≥35	Severe	Very severe

Pre-obese may be defined as overweight or at-risk weight, and obese class III may be defined as extreme obesity.

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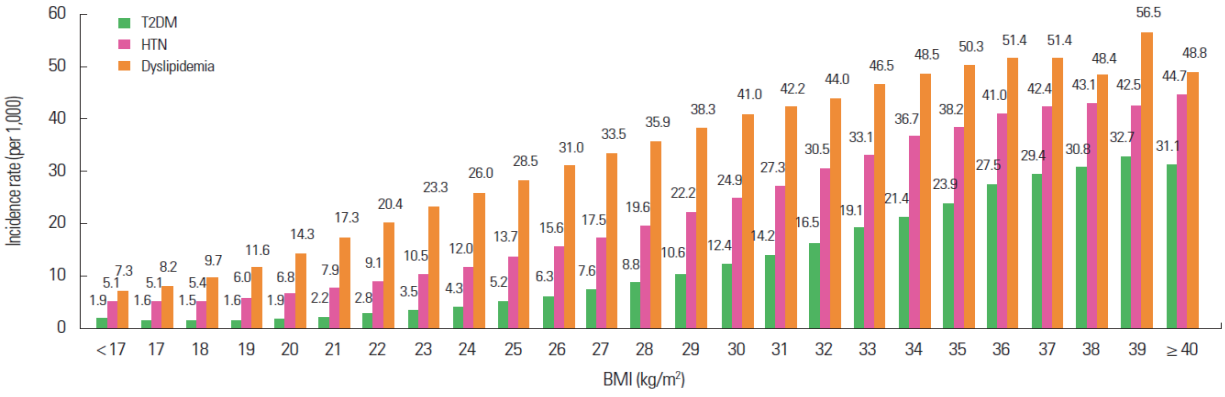

Figure 1. Body mass index (BMI) and the incidence rates of type 2 diabetes mellitus (T2DM), hypertension (HTN), and dyslipidemia. Adapted from Seo MH, et al. J Obes Metab Syndr 2018;27:46-52.

Metabolic syndrome in children and adolescents

Ki Soo Kang, M.D., Ph.D.

Department of Pediatrics, Jeju National University Hospital, Jeju, Korea

According to the global health observatory data from the World Health Organization, 18% of children and adolescents aged 5-19 were overweight or obese in 2016. In Korea, the obesity prevalence of school-age children (7 to 18 years) markedly increased from 8.4% in 2018 to 14.4% in 2018. The actual number of obesity is estimated to 804,131 of the total student number 5,584,249 who were school-age children in 2018. In a systematic review of the literature, the median prevalence of metabolic syndrome in whole population was 3.3%, in overweight children was 11.9%, and in obese populations was 29.2%. In a child obesity clinic, which operated by this author, the prevalence of metabolic syndrome was 34.3%.

Childhood obesity is defined as the body mass index (BMI) more than 95th percentile for age and sex in children and adolescents > 2 years of age. Metabolic syndrome (MetS) in adults is a clinical constellation consisting of 5 cardiometabolic risk factors (hyperglycemia, increased central adiposity, elevated triglycerides, decreased high-density lipoprotein cholesterol, and elevated blood pressure). MetS identify adults with at least 3 of 5 cardiometabolic risk factors who were at increased risk of diabetes and cardiovascular disease. However, in children, the construct of MetS is difficult to define and has unclear implications for clinical care. In the clinical settings for obese children, it is more important to focus screening for and treating the individual risk factor components of MetS rather than defining a pediatric MetS. Hypertension, hypertriglyceridemia and hyperinsulinemia are prevailing in school age children with obesity. However, most children do not physically suffer from their MetS components caused by obesity.

Insulin resistance is also a major pathophysiologic factor of MetS in obese children. Glucose intolerance, which is defined as fasting glucose ≥ 110 mg/dL (≥ 6.1 mmol/L), is rare in childhood obesity. However, insulin resistance, which can be calculated as HOMA-IR (fasting serum insulin, μU/mL x fasting glucose, mmol/L divided by 22.5), is frequent in the children with obesity. The most frequent complication of MetS is nonalcoholic fatty liver with or without nonalcoholic steatohepatitis in childhood obesity. Type 2 diabetes mellitus rarely develops in that child.

There are few of drugs beneficial to control of MetS in child obesity. Of course, the lifestyle modification by behavioral intervention is the most effective treatment for child obesity with MetS.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[09:00-10:30, Diamond Hall]

Multidisciplinary Session 04 (KSGC-KGCA) Korean

Which treatment in locally advanced cancers

Chairs: **Jin Tae Jung** (Daegu Catholic University Medical Center, Korea)

Young-Woo Kim (National Cancer Center, Korea)

Locally advanced Esophageal cancer; Pro CCRT versus Pro Surgery

Young Sin Cho, M.D., Ph.D.

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INTRODUCTION

Esophageal cancer is the ninth most common cancer and the sixth most common cause of cancer death globally.[1] This cancer requires extensive treatment and therefore significantly lowers the quality of life of the patients and also has a poor prognosis. Locally advanced esophageal cancer can be defined as those restricted to the esophagus or resectable periesophageal tissue (T2-4) and/or lymph node involvement (N1-3) in the absence of distant metastasis.[2] Historically, surgery has been the standard treatment for the resectable esophageal cancer. However, surgery alone fails to contend against the natural history of disease owing to the presence of occult micrometastasis and fatal distant and loco-regional disease relapse is common. To improve poor outcomes of locally advanced esophageal cancer, many treatment modalities have been attempted such as addition of adjuvant radiotherapy and/or chemotherapy, neoadjuvant radiotherapy and/or chemotherapy, and definitive chemoradiotherapy. Although esophageal cancer is no definitively established yet, most widely accepted multimodality treatment is neoadjuvant chemoradiotherapy followed by surgery.

PRO CCRT IN LOCALLY ADVANCED ESOPHAGEAL CANCER

Based on previous studies, a pathological complete response of neoadjuvant chemoradiotherapy was obtained in 15-43% of patients, although the clinical stage and histological type differed among studies.[3] A pathological complete response was critical for improving the prognosis of patients. In Western study showed that the pathological response is an independent factor predicting the survival, and they proposed a revision of the esophageal cancer staging system to accommodate pathological responses following neoadjuvant chemoradiotherapy.[4] In a recent study, the patient age, smoking habit andtumor length were reported to be predictors of a pathologicalcomplete response.[5] The investigators proposedthat these factors might be used to predict the outcomesfor patients with esophageal cancer receiving neoadjuvant chemoradiotherapy to develop risk adaptedtreatment strategies.

The clinical significance of neoadjuvant chemoradiotherapy for locally advanced esophageal cancer is controversial in terms of the survival benefit. However, recent CROSS trial of preoperative chemoradiotherapyin esophageal cancer versus surgery alone establisheda new global standard of care, with particularly strikingbenefits for preoperative chemoradiotherapy seen inpatients with squamous cell esophageal cancer.[6] Meta-analysis of 24 randomized trials suggeststhat both neoadjuvant chemotherapy and chemoradiotherapyimprove overall survival for patients withoperable esophageal cancer (hazard ratio [HR]for chemotherapy0·87, 95% CI 0·79-0·96; HR forchemoradiotherapy 0·78, 0·70–0·88).[7]

CONCLUSION

For several decades, there have been many efforts to improve poor outcomes of locally advanced esophageal cancer. Although not established yet, multimodality treatment with neoadjuvant chemoradiotherapy followed by surgery has been performed as a standard treatment in the locally advanced, potentially resectable esophageal cancer based on recent randomized trials and meta-analysis. When patients are carefully selected for multimodality therapy, preoperative chemoradiotherapy followed by surgery offers the greatest chance for long-term overall survival and should be the standard of care.

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Locally advanced Esophageal cancer; Pro CCRT versus Pro Surgery

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Esophageal cancer is highly aggressive upper gastrointestinal malignancy, which can be systemic in relatively early stage of the disease. Numerous debates have been made regarding optimal treatment strategy. However, nobody insists that surgery alone or nonsurgical treatment, for example, chemoradiotherapy alone would be enough, especially in the treatment of locally advanced cancer. An esophagectomy whether it is minimally invasive or conventional open surgery is a highly invasive procedure with the risks of high postoperative morbidity or mortality. Therefore, general condition of the patient can be a hurdle for undergoing the treatment. For such patients whose general condition does not fit for surgery or who are unwilling to undergo surgery definitive chemoradiotherapy can be an alternative option.

According to the ESMO guideline, surgery alone is not a standard treatment in locally advanced (cT3-T4 or cN1-3 M0) disease, since a complete (R0) tumor resection cannot be achieved in 30% (T3) ~ 50% (T4) of cases. Furthermore, even after complete tumor resection, long term survival rarely exceeds 20%. Of note, preoperative treatment (chemotherapy or chemoradiotherapy) has been shown to increase R0 resection and survival rates. Therefore, preoperative treatment is clearly indicated in operable patients with locally advanced esophageal cancer.

Squamous cell carcinoma: Recent studies demonstrate that patients with locally advanced disease benefit from preoperative chemotherapy or, most likely to a greater extent, from preoperative chemoradiotherapy, with higher rates of complete tumor resection and better local tumor control and survival. On the basis of CROSS study, weekly administration of carboplatin and paclitaxel for 5 weeks and concurrent radiotherapy, followed by surgery, can be recommended as a contemporary standard of care.

Adenocarcinoma: On the basis of the recent meta-analyses and the largest prospective randomized controlled studies, perioperative chemotherapy with regimens containing a platinum and a fluoropyrimidine for a duration of 8-9 weeks in the preoperative phase as well as 8-9 weeks in the postoperative phase or preoperative chemoradiotherapy should be considered standard in locally advanced adenocarcinoma of the esophagus, including gastroesophageal junction cancer. Even after complete tumor response to preoperative chemo(radio)therapy, operable patients with adenocarcinoma should proceed to surgery.

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Locally advanced Gastric cancer; neadjuvant versus adjuvant therapy

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Globally, gastric cancer is still highly prevalent and accountsfor a considerable amount of mortality around the world,with poor survival rates. And also gastric cancer is a complexdisease that is affected by multiple genetic and environmentalfactors.The incidence of gastriccancer is higher in eastern Asia, eastern Europe, and SouthAmerica, while North America and Western Europe havethe lowest rates[1] In Korea, gastric cancer is the second mostcommonly diagnosed cancer in men and the fourth mostcommonly diagnosed cancer in women. Gastric cancer representsthe fourth leading cause of cancer-related deaths inmen and women.[2]

The 5-year survival rate is much higher (approximately 75%) for patients with localized disease without regional lymph node (LN) involvement. However, in Stage II of the disease (or higher), the overall 5-year survival rate of patients decreases to approximately 20–30%. Surgery is the mainstay treatment of locally advanced gastric cancer (AGC). R0 resection is the only way to achieve long-term survival. Despite this radical surgery, some patients relapse with local and systemic recurrence, after which survival rates are poor.According to the NCCN guidelines, if a tumor is Stage T2 or higher and in any N stage, preoperative chemotherapy is a Category 1 recommendation. In the European guidelines, preoperative chemotherapy is also considered a treatment option for locally AGC, but preoperative chemoradiation is not (Table 1) in Korea and Japan, neoadjuvant treatment is not routinely recommended. Instead of, adjuvant treatment have been mostly carried out. the lesion is because that Diagnosis and treatment of stomach cancer different between the East and the West.In surgical treatment, extended LN dissection (D2 dissection) is a standard procedure in Korea and Japan, but not in Western countries, where perigastric LN dissection (D1 dissection) is widely used (Table 2). To achieve better outcomes for locally advanced states, curative surgeries have been used. D2 dissection, postoperative chemoradiotherapy (CRT), perioperative chemotherapy (ChT), and postoperative ChT are considered the current standards of care for locally advanced, resectable gastric cancer. These strategies

Table 1. Results of phase Ⅲ preoperative chemotherapy trials in gastric and GE junction cancer

Study	Treatment	No.of patients	R0 resection rate (%)	Pathologic CR rate	Survival		Local failure*
					Median	Overall	
Cunningham et al.[3]	PeriopECF+surgery	250	69	0%	24 months	5-year 36%	14%
	Surgery	253	66	N/A	20 months	5-year 23%	21%
Ychou et al.[4]	Periop 5FU/Cis+surgery	109	87	NS	NS	5-year 38%	24%
	Surgery	110	74	N/A	NS	5-year 24%	26%
Schumacher et al.[5]	Preop 5FU/LV/Cis+surgery	72	82	7.1%	64.6 months	2-year 73%	NS
	Surgery	72	67	N/A	52.5 months	2-year 70%	

Ciscisplatin, CR complete response, ECF epirubicin, cisplatin, 5-fluoruoracil, LVleucovorin,
N/A not applicable, NS not stated

Table 2. Results of phase Ⅲ postoperative chemotherapy trials in gastric cancer

Study	Treatment	No.of patients	Survival		Local failure
			Median	Overall	
Sasako et al.[6]	Surgery	530	NR	5-year 61%	2.8%
	Surgery+S-1	529	NR	5-year 72%	1.3%
Noh et al. [7]	Surgery	515	NR	5-year 78%	44%
	Surgery+Capeox	520	NR	5-year 69%	21%
Tsuburaya et al.[8]	Adjuvant UFT or S-1	723	NS	3-year* 54%	NS
	Adjuvant paclitaxel→ UFT or S-1	710	NS	3-year* 57%	NS

Capeoxcapecitabine/oxaliplatin, CR complete response, N/A not applicable, NR not reached,
UFT tegafur/uracil

are based on the outcomes of Phase III randomized trials and have been shown to improve disease-related outcomes compared to surgery alone. But neoadjuvant chemoradiation treatment is not yet. Neoadjuvantchemoradiation therapy to treat locally advanced gastric cancer is under study and currently in progress.

In a locally advanced state, after complete resection, both local and distant recurrences are still problematic. despite aggressive combined modality therapy. So To achieve better outcomes for locally advanced states, curative surgeries, D2 dissection, have been used. Postoperative Chemoradiotherapy, perioperative chemotherapy & postoperative Chemotherapy are considered the current standards of care for locally advanced gastric cancer.

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Locally advanced Gastric cancer; neadjuvant versus adjuvant therapy

Beom Su Kim

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KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[09:00-11:00, Flamingo]

Nursing Session 01 (KASID) Korean

Chairs: **Jin-Oh Kim** (Soon Chun Hyang University Seoul Hospital, Korea)

Young-Seok Cho (The Catholic University of Korea Seoul St. Mary's Hospital, Korea)

Perioperative pharmacological considerations in IBD

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INTRODUCTION

Theperioperative management of patients with inflammatory bowel disease ischallenging and requires a multidisciplinary approach between thegastroenterologist, surgeon and patient. In patients with UC, most commonlytotal proctocolectomy (TPC) with ileal pouch-anal anasomtosis (IPAA) would berecommended in case of patients who failed medical therapy or seriouscomplications such as uncontrolled hemorrhage, perforation, and colorectalcarcinoma or dysplastic lesions not amenable to endoscopic approach arise. Infact, complete removal of all the potential disease-bearing site istheoretically curative in UC, and will no longer require immunosuppressanttherapy. However, in contrast to UC, surgery for CD is not curative, anddisease recurrence is common. One-third of patients with Crohn's disease (CD)will require a major abdominal resection within 5 years of their diagnosis, andtwo-thirds might receive the surgery at least once during their life-time. Withinthe first year of surgery, 70 to 90% of patients will develop endoscopicrecurrence, and this incidence increase to 80 to 100% within 3 years. Thus, thedecision of continuation and discontinuation of immunosuppressive medicationsin perioperative periods has great impact on the clinical outcomes for patientswith CD.

5-Aminosalicylic acid(5-ASA) agents remain the mainstay of therapy for the induction and maintenanceof remission in mild to moderately active UC and CD. These compounds have shorthalf-life of 6-10 hours, are extensively metabolized, and excreted by thekidney. In general, the effect of 5-ASA is considered to be small inrecurrence, but it is relatively safe in the treatment of CD after surgery.Aminosalicylates can be continued up to the day before surgery and then resumedon discharge after surgery unless there is a susceptibility for decreasedglomerular filtration.

The therapeutic roleof corticosteroid in the treatment of IBD is primarily to decrease theintensity of inflammation and many patients with IBD will requirecorticosteroids during the course of their disease. Despite the effect ininducing clinical remission, long-term use of corticosteroids is associatedwith dependence as well as clinical relapse. Moreover, long-termcorticosteroids use may have a negative impact on wound healing, postoperativesurgical complications, severe infections, and glycemic control. To minimizeadverse effects associated with corticosteroids in postoperative IBD patients, itis necessary to reduce unnecessary use of corticosteroids, and a clearunderstanding of the indications, dosing and duration for perioperative use isrequired. The lowest effective dose that induces remission should be used, along with early institution of steroid-sparing medications. Apart from thepotential risk of complications, long-term steroid use also leads tosuppression of the hypothalamic-pituitary-adrenal axis and adrenalinsufficiency. The administration of "stress-dose" corticosteroids to IBDpatients in the perioperative period has become a common practice. However,more recently, a randomized prospective studies have demonstrated that low-doseperioperative steroids are equivalent to high-dose steroids, with decreasedinfectious complications in the low-dose group. Thus, it begun to move awayfrom the stress dose corticosteroids and instead are using low-dose regimens. Given these findings, some have proposed standardized algorithms for the managementof perioperative stress dose steroids in an effort to balance patient safetyand risk.

6-mercaptopurine/azathioprinehas been widely used as glucocorticoid-sparing agents for the maintenance ofremission in IBD. This agent has been demonstrated to be effective comparedwith placebo and superior to mesalamine in the prevention of postoperativerecurrence on CD. Fortunately, use of immunosuppressive agents such as6-mercaptopurine, azathioprine, or methotrexate do not seem to lead toincreased perioperative infectious complications despite their suppressiveeffect on bone marrow and resultant leukopenia. Therefore, it is recommended tostart these immunomodulators within 2 weeks after surgery or to resume whenoral medications are resumed, if there has risk of recurrence.

The impact of anti-TNFαtherapy on surgical outcomes remain controversial, with a lack of evidence thatthe use of anti-TNFα in the preoperative period significantlyincreases postoperative complications. The controversial results may reflect thatthe patient's severity of disease and their concomitant immunosuppressant use,rather than the medication itself, can lead to postoperative complications.Currently, several studies do not recommend the discontinuation of anti-TNFα agents in the perioperative setting. However, the clinician shouldbe aware of all possible complications, including serious infections, insurgical patients receiving these agents. The most well studied anti-TNFα agents in the postoperative prophylaxis of CD recurrence isinfliximab. Initial reports of randomized controlled trials comparinginfliximab to placebo administered 4 weeks

postoperative showed significantdecrease in histologic recurrence at 1 year (27.3% vs 84.6%, p=0.01). Infliximab therapy also seemssuperior to thiopurines for the prevention of postoperative recurrence. Increasing evidence shows otherwise favorable data for adlimumab. Recentstudies have demonstrated that the adalimumab is very effective in reducingpostoperative recurrence for CD. Adalimumab was also comparable to infliximabfor the prevention of postoperative endoscopic, clinical and histologicrecurrence. No differences were found between the 2 groups.

Vedolizumab, a gut-selective monoclonalantibody to $\alpha 4\beta 7$ integrin,appears to be safe and effective for treatment of moderate to severe UC and CD. Despite the safety profile, there was a concern about the increasedpostoperative complications because vedolizumab targets leukocyte migration, anecessary component of wound healing. Theoretically, wound healing could be impaired,and it could increase the risk of postoperative infecions and othercomplications. However, in a recent systematic review of 5 studies, thepreoperative vedolizumab treatment in IBD patients does not appear to beassociated with an increased risk of postoperative infectious or overallpostoperative complications compare to either preoperative anti-TNF therapy orno biologic therapy.

CONCLUSIONS

Patientswith IBD commonly require surgical intervention despite the explosion of newpowerful immunomodulative medications. Understanding of the optimal approach toperioperative medication management is necessary to improve the surgicaloutcomes for patients with IBD in terms of postoperative complications as wellas recurrence.

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Complementary and alternative medicine for IBD

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1. INTRODUCTION

Complementary and alternative medicine (CAM) is a group of diverse medical and health care systems, practices, and products that are not considered part of conventional medicines[1]. CAM includes whole medical systems, Mind-body medicine, biologically based therapies, Manipulative and body-based practices, and Energy medicine.

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is characterized by chronic relapsing inflammation in the gastrointestinal tract. The increase in the use of CAM is particularly true in patients with chronic diseases, such as inflammatory bowel disease (IBD)[2,3]. Reasons for CAM use include a desire for holistic approaches to supplement conventional therapy; the perception that herbal remedies are more natural, less toxic, or harmless; a lack of response to or undesirable side effects of conventional therapy; and the desire for more control of the disease and symptoms to improve quality of life (QOL).

2. USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE IN KOREA

Approximately 30% of IBD patients in Korea reported the use of CAM[4]. Most commonly used CAMs are oral products such as vitamins, red ginseng, and probiotics. Independent predictors for CAM use are a high level of education, higher income levels, and longer disease duration. However, only 28.7% of patients discussed CAM use with their physician. In addition, 13.9% of CAM users discontinued conventional IBD therapy while using CAM[5].

3. CLINICAL DATA OF COMPLEMENTARY AND ALTERNATIVE MEDICINE IN IBD

Compound	Conclusion
Cannabis/ Marijuana	Improve symptoms, not inflammation
Turmeric and Curcumin	Superior for UC induction for those failing 2 weeks 5-ASA Improvement at 6 months for UC maintenance; reasonable data
Fish Oil	Not effective in maintaining remission in CD or UC
Indigo Naturalis	Improve clinical response in active UC
Aloe Vera	Improve clinical response in mild-moderately active UC but not remission or endoscopic change
Andrographis panniculata extract (HMPL-004)	2 RCT mild-moderately active UC- similar to 5-ASA and better than placebo
Probiotics	VSL#3 for maintenance of remission of recurrent pouchitis after induction of remission with antibiotics; VSL#3 for preventing pouchitis after IPAA; VSL#3 possibly for mild-moderate UC though not recommended; No good data for CD
Trichuris suis	Negative CD study(2 RCTs); Response in active UC(small RCT)
Acupuncture and Moxibustion	Small studies; Small superiority in UC activity index Superior in CD activity index; doubt it with hurt
Mind-Body Therapies	Improve psychological status and QoL in patients with IBD, but may not affect inflammatory activity directly
Exercise	Provide multiple benefits to patients with IBD

4. CONCLUSIONS

CAM use is common in IBD, However, the studies of CAM were usually small-sized, and had difficulties with design of rigorous, randomized, placebo-controlled trials. These RCTs encountered lack of quality control for herbal preparations and problems with adequate blinding for psychological interventions, acupuncture, and exercise. However, physicians should understand the nature and evidence behind the various CAMs to offer rational advice to IBD patients.

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Opportunistic infections in IBD: Case-based discussion

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1. HEPATITIS B VIRUS REACTIVATION

- 46 years old, male patients with Crohn's disease
- Developed RLQ pain
- Pain on Right inguinal area, Right leg
- Fever and diarrhea for months
- HBsAg(+) – inactive carrier
- Prednisone for months

2. CYTOMEGALOVIRUS REACTIVATION

- 58 years old, female patients with ulcerative colitis for 7 years
- Never received steroids, but 6MP 1.5T qd
- On sigmoid biopsy, CMV IHC/PCR(+, A few/-), on sigmoidoscopy, deep ulcer(-)
- 36 years old, female patients with ulcerative colitis for 4 years
- Received methylprednisolone 0.8mg/kg (iv) without thiopurine
- On sigmoid biopsy, CMV IHC/PCR(+, A few/+), on sigmoidoscopy, deep ulcer(+)

3. *PNEUMOCYSTIS JIROVECII* PNEUMONIA

- 60 years old, female patients with abdominal pain & diarrhea (2MA)
- diagnosed as new-onset ulcerative colitis
- received 5-ASA, steroids, and azathioprine
- developed pneumoperitoneum
- developed pneumonia

Adult vaccination recommendations focused on IBD

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Patients with inflammatory bowel diseases (IBD) have a reduced immune function and an increased risk of developing infectious diseases not only by the disease itself but also by therapeutic agents. Vaccination is one of the most effective way to prevent infectious for IBD patients. However, depending on the patients' condition, the type of the therapeutics used, the type of vaccine, and the timing of vaccination, the vaccine may be less effective or may be contraindicated. Therefore, when vaccinating IBD patients, various circumstances should be considered comprehensively.

In general, it is preferable to perform the necessary vaccination before the administration of immunosuppressants or immunomodulators in the early stage of diagnosis of IBD in terms of safety and effectiveness. To this end, vaccination history and serum antibody testing should be performed early in the diagnosis of IBD. Inactivated vaccines can be used safely even if immunosuppressants are used, but they may be less effective due to the medications. There is a possibility that almost no antibodies will be produced by vaccination if the biologics are used that can cause depletion of B cells. Live attenuated vaccine (LAV) is contraindicated during the use of immunosuppressants or immunomodulators. The organisms included in the vaccine are attenuated, but there is still a risk of causing infection. LAV should be administered 4 weeks before the immunosuppressive drug because LAV requires at least 2-3 weeks for the organism to multiply and induce immunity. However, if a low dose of immunosuppressant (prednisolone <20 mg/day, MTX ≤0.4 mg/kg/week, azathioprine ≤3.0 mg/kg/day, 6-mercaptopurine <1.5 mg/kg/ day) are used, LAVs such as varicella vaccine or zoster vaccines can be used. If a high-dose immunosuppressant is already in use, LAV should not be used until the agent is discontinued. The timing of LAV vaccination after discontinuation of immunosuppressants or immunomodulators depends on the type of agents. In general, LAV can be administered 1-3 months after discontinuation of high dose steroid, 3-6 months after discontinuation of disease-modifying antirheumatic drugs (DMARDs), and 3-12 months after discontinuation of biologics. After vaccination, it is recommended to check for serum antibody formation after 4-6 weeks if possible.

The most recommended vaccines for IBD patients are the influenza vaccine and the pneumococcal vaccine. Influenza vaccines should be given once every October to November with an inactivated vaccine. There are two types of pneumococcal vaccines that can be used for adults: 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23). Both pneumococcal vaccines are recommended for IBD patients. Patients without a history of pneumococcal vaccination should receive PCV13 first and PPSV23 at least 8 weeks later. PPSV23 needs to be re-vaccinated 1-2 times every 5 years, depending on the patient's age and the use of immunosuppressants. The maximum number of vaccinations of PPSV23 is three times. The other inactivated vaccines such as hepatitis A vaccine, hepatitis B vaccine or tetanus-diphtheria-pertussis vaccine (Tdap) can be used according to general recommendations. IBD patients have at high risk for herpes zoster. But there is only LAV in Korea for the zoster, and the vaccine cannot be administered to the patients who are using immunosuppressants or immunomodulators. If the inactivated zoster vaccine is available in Korea in the future, it is expected to be used more effectively and safely for IBD patients using immunosuppressants.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[11:00-12:30, Convention Hall A]

Korean GI Frontiers (KSG) Korean

Chairs: **Won Ho Kim** (Severance Hospital, Korea)

Jong Sun Rew (Chonnam National University Hospital, Korea)

Transarterial chemoembolization plus external beam radiotherapy vs. sorafenib in HCC

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The key step for a successful research is choosing a good research question. A good clinical research question is based on critical, urgent, and important clinical unmet needs. The results of the study should be interesting to the researcher, patients, and medical community and provide an important answer regardless of the nature of the result advancing knowledge by filling a critical knowledge gap. The research question is the objective of the study, and a "guiding light" for the project.

The research question is the uncertainty about something in the population that the investigator wants to resolve by making measurements on his study subjects. The clinical research question should be clearly described in one-sentence, composed of population or patients (P), intervention of interest (I), comparison (C), and outcome (O).

Randomized controlled trials (RCTs) are seen as the gold standard for assessing the relationship between an intervention, exposure or risk factor and an outcome. One of the most important features of this study design is randomization, which ensures that the groups formed are similar, except for chance difference, in all aspects.

Randomization reduces biases by making treatment and control groups "equal with respect to all features," except the treatment assignment. When randomization is performed correctly, differences in efficacy found by statistical comparisons can be attributed to the difference between the treatment and control.

The main difference between an RCT (experimental design) and an observational study (non-experimental design) is the absence of random allocation of the intervention by the investigator.

Observational, nonrandomized studies have a role when RCTs are not available, and, even when RCTs are available, to quantify effectiveness and other real world experiences. There is an expanding body of literature using observational designs, partly because observational studies are less resource intensive than RCTs as they often use electronic healthcare data that have already been collected, which have become more available in the last decade. About nine of ten research papers published in clinical specialty journals describe observational research.

However, even with the best of designs, observational studies, unlike the RCTs, do not automatically control for biases and confounders. Lack of randomization in observational studies may result in large differences on the observed (and unobserved) participant characteristics between the treatment and control groups. These differences can lead to biased estimates of treatment effects. Bias and confounding are well-recognized potential pitfalls in case-control studies, and in cohort studies to a less degree.

Bias and confounding can create apparent differences between groups when differences do not actually exist in nature or obscure differences when they really do exist. Before concluding the real causality between the intervention and the outcome in observational studies, four rival explanations must be considered.

Patients with hepatocellular carcinoma (HCC) showing macroscopic vascular invasion (MVI) bear an extremely poor prognosis. Sorafenib is the sole treatment option for these patients, with unsatisfactory response and survival benefit. Combined treatment with transarterial chemoembolization (TACE) plus external beam radiotherapy (RT) has shown promising results in these patients by observational studies. Therefore, we have conducted a randomized, open-label trial to evaluate the efficacy and safety of TACE plus RT compared to sorafenib in patients with HCC and MVI.

Between 2013 and 2016, 90 treatment-naive patients with liver-confined HCC showing MVI were randomly assigned to receive sorafenib (400 mg twice-daily; n=45; sorafenib group) or TACE (every 6 weeks) plus RT (within 3 weeks after the first TACE, maximum 45 Gy with the fraction size of 2.5-Gy to 3-Gy; n=45; TACE+RT group).

The primary endpoint was 12-week progression-free survival (PFS) rate by intention-to-treat analysis. Radiologic response was assessed by independent review according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). Treatment crossover was permitted after confirming disease progression.

Patients were 33 to 82 years of age, and 85.6% were male. All patients had portal vein invasion of HCC and Child-Pugh class A liver function. The median maximal tumor diameter was 9.7 cm. Most (78.9%) patients had multiple lesions. At week 12, the PFS rate was significantly higher in the TACE+RT group than the sorafenib group (86.7% vs. 34.3%; P<0.001). The TACE+RT group showed significantly higher radiologic response rate at 24 weeks (33.3% vs. 2.2%; P<0.001), significantly longer median time to progression (31 weeks vs. 11.7 weeks; P<0.001), and significantly longer overall survival (55 weeks vs. 43 weeks; P=0.04), compared with the sorafenib group. Curative surgical resection was conducted in 5 patients (11.1%) in the TACE+RT group owing to downstaging. No patients in the TACE+RT

group discontinued treatment due to hepatic decompensation.
In conclusion, in patients with advanced HCC showing MVI, first-line treatment with TACE+RT was well-tolerated and provided improved PFS, objective response rate, time to progression, and overall survival, compared with sorafenib treatment.

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Helicobacter pylori eradication for the prevention of metachronous gastric cancer

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In Korea, 30,504 gastric cancer (GC) cases are diagnosed in 2016, and it was the most common type of cancer. The Korean government launched the National Cancer Screening Program (NCSP) which included GC screening in 1999 and gradually expanded to include all population aged 40 or more. The secondary prevention strategy is a quite expensive approach and if possible primary prevention strategy can be an effective strategy. Although *H. pylori* infection is the most important risk factor for gastric cancer development, primary prevention strategy by eradicating *H. pylori* have not been incorporated into NCSP due to a lack of definite evidence. Because gastric cancer incidence is quite low even in the high-risk region including Korea, the primary prevention trial should be performed in large-scale long-term follow-up studies. Thus, we performed a high-risk group study to prove whether *H. pylori* treatment reduces gastric cancer risk. For study feasibility, we designed our study in a very high-risk group who underwent endoscopic resection for early gastric cancer.

In National Cancer Center Korea, a prospective, double-blind, placebo-controlled, randomized trial was performed in patients with early gastric cancer (EGC). We evaluate whether *Helicobacter pylori* eradication could reduce the risk of metachronous gastric cancer. During 13 years (median 5.9 years), a total of 396 patients were included in the study. Metachronous gastric cancer developed in 14 among (7.2%) 194 patients in the treatment group, and in 27 (13.4%) among 202 patients in the placebo group (HR=0.05 in the treatment group. P = 0.03). We also found that the severity of gastric corpus atrophy in the treated patients improved more than in the placebo group (48.4% vs. 15.0%, respectively). Based on the data, we could conclude that *H. pylori* treatment prevents metachronous gastric cancer and improve gastric corpus atrophy even in EGC patients.In this presentation, our experience in publishing an original article in the New England Journal of Medicine will be shared.

Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in Crohn's disease

Youngho Kim, M.D., Ph.D.

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Treatment of inflammatory bowel diseases has been revolutionized due to the introduction of biological agents including anti-TNF agents. Demand for biologics is growing due to successful clinical use, the patent expiry for the major biological brands is coming and health costs should be reduced due to the financial crisis because the use of biological agents is associated with greater costs compared with the mainly anti-inflammatory and immunosuppressant drugs used in the pre-biological era. Biosimilar is defined as a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product. Biological agents are complex proteins involved in the immune response and their exact replicas are extremely difficult.

The critical questions about biosimilar is indication extrapolation.

Extrapolation is the regulatory and scientific process of granting a clinical indication to a medicine without any own or new clinical efficacy and safety data to support this indication. It is said that biosimilar is the science of extrapolation. Without extrapolation of indication there is no financial motivation for the development of biosimilar. Approval of CT-P13 in inflammatory bowel disease and other non-rheumatological indications was based on extrapolation. Such extrapolation is awarded by regulatory authorities if biosimilarity has been proven and is scientifically justified. However, concerns about extrapolation have been expressed. This study was designed to establish non-inferior efficacy of CT-P13 compared with infliximab in patients with active Crohn's disease who were naive to biological therapy. The results of this study provide the first high-level evidence of the non-inferior efficacy of CT-P13 to infliximab in anti-TNF agent-naive patients with active Crohn's disease. Additionally, the study confirmed the validity of extrapolation for this biosimilar monoclonal antibody.

Observation time in esophagogastroduodenoscopy

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Esophagogastroduodenoscopy (EGD) is commonly used to detect upper gastrointestinal (GI) neoplasms. However, there is little evidence that longer examination time increases rate of detection of upper GI neoplasia. We investigated the association between length of time spent performing a normal screening EGD and rate of neoplasm detection.

We performed a retrospective analysis of data from 111,962 subjects who underwent EGD as part of a comprehensive health-screening program from January 2009 to December 2015 in Korea. Endoscopy findings were extracted from reports prepared by 14 board-certified endoscopists. Endoscopists were classified as fast or slow based on their mean examination time for a normal EGD without biopsy during their first year of the study. All endoscopists used the same endoscopy unit. We obtained findings from histologic analyses of GI biopsies from patient records; positive findings were defined as the detection of neoplasms (esophageal, gastric, or duodenal lesions). We examined the association between examination time and proportions of neoplasms detected. The primary outcome measure was the rate of neoplasm detection for each endoscopist (total number of neoplastic lesions detected divided by the number of subjects screened) and as the proportion of subjects with at least 1 neoplastic lesion.

-The mean examination time was 2 minutes 53 seconds. Using 3 minutes as a cutoff, we classified 8 endoscopists as fast (mean duration, 2:38 ± 0:21 minutes) and 6 endoscopists as slow (mean duration, 3:25 ± 0:19 minutes). Each endoscopist's mean examination time correlated with their rate of neoplasm detection (R^2 = 0.54; P = .046). Fast endoscopists identified neoplasms in the upper GI tract in 0.20% of patients, whereas slow endoscopists identified these in 0.28% of patients (P ¼ .0054). The frequency of endoscopic biopsy varied among endoscopists (range, 6.9%–27.8%) and correlated with rate of neoplasm detection (R^2 = 0.76; P = .0015). On multivariable analysis, slow endoscopists were more likely to detect gastric adenomas or carcinomas than fast endoscopists (odds ratio, 1.52; 95% CI, 1.17-1.97).

In an analysis of data from more than 100,000 subjects who underwent EGD in a screening program, we found slow endoscopists detected a higher proportion of neoplasms than fast endoscopists. Examination time is therefore a useful indicator of quality for EGD.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[11:00-12:30, Convention Hall B]

Video Session 02 (KSG-LGI) English

Chairs: **Han-Mo Chiu** (National Taiwan University Hospital, Taiwan)

Bo-In Lee (The Catholic University of Korea Seoul St. Mary's Hospital, Korea)

Diagnosis and differential diagnosis of colorectal polyps: up-to-date imaging technique

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Detection and diagnosis is the main task during colonoscopy and correct diagnosis of colorectal polyps can facilitate clinical decision-making. After detection of a lesion, there are three crucial steps: 1) differentiating neoplastic vs. non-neoplastic lesions; 2) differentiating cancerous vs. non-cancerous lesions; and 3) invasion depth estimation for suspicious cancerous lesions. This workflow is crucial, because benign neoplastic lesions and superficial T1 cancers are good candidate for endoluminal treatment (polypectomy, EMR or ESD), whereas surgical resection is justified for deep invasive cancers and we can thereby maximize the effectiveness of colonoscopy.

Application of image enhanced endoscopy (IEE) technology, either optical- or dye-based, is the key to make the correct diagnosis. Both NBI and BLI enable visualization of micro-vasculatures of mucosal layer and characterization of the lesion by combining the surface and vascular features. Using the JNET classification system applying magnifying observation, differentiating neoplastic from non-neoplastic lesion becomes much easier, and enables diagnosis of cancerous change and invasion depth. Dye-based IEE using crystal violet staining can achieve a higher accuracy of invasion depth estimation of cancerous neoplasms with better inter-observer agreement. Endocytoscopy can also facilitate real-time histological diagnosis of colorectal lesions. Recent studies also demonstrated that combination use of the above IEE modalities together with artificial intelligence (AI) is able to help on the abovementioned three steps and achieve even higher accuracy of diagnosis. It is expected that applying state-of-the-art AI technology can minimize the discrepancy of endoscopist performance and improve the efficiency of colonoscopy examination. Finally, whether the abovementioned approach can really impact CRC incidence or mortality is of utmost important and need further exploration.

Surveillance for dysplasia in IBD: Chromoendoscopy and image-enhanced endoscopy

Sung Noh Hong, M.D.

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The optimal strategies to detect the dysplasia surveillance in patents with inflammatory bowel disease (IBD) are still lacking. Although white-light endoscopy with targeted and/or random biopsies are routinely performing in e practice, chromoendoscopy showed a higher detection rate of dysplasia than white-light in patients with IBD under surveillance. In addition, targeted biopsy policy is obtained significantly fewer samples. Therefore, chromoendoscopy with targeted biopsy is considered as both more accurate and more cost-effective compared with white-light endoscopy. Therefore, professional societies have now updated their guidelines to advise the use of chromoendoscopy for dysplasia surveillance. However, chromoendoscopy can be quite cumbersome and time consuming. Image-enhancing endoscopy including narrow band imaging, i-scan, FICE, and SPICE compensate the limitation of chromoendoscopy, however in accordance with a previous study using narrow-band imaging showing no difference in dysplasia yield between chromoendoscopy and high-definition white-light endoscopy.

Cold method for colon polpectomy; why, when, and how?

Bong Min Ko, M.D.

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Colorectal polyps are classified into nonneoplastic and neoplastic polyps according to the malignant potential. Colonoscopy and sigmoidoscopy were associated with a reduced incidence of cancer of the distal colorectum; colonoscopy was also associated with a modest reduction in the incidence of proximal colon cancer.[1] More than 70% of the polyps found in colonoscopy are less than 1 cm in size, and most of them are reported to be less than 5 mm.[2,3] Recently, As interest in small polyps is increasing, various studies on treatment method for small polyps has been attempted. Cold forceps biopsy polypectomy is a method of passing the forceps through the endoscopic channel and removing the surrounding mucosa, as a biopsy. Regardless of the skill of the procedure, it is very easy and quick to perform, high polyp retrieval rate, and because it dose not use electrocoagulation, complication such as perforation are extremely low. However, since the complete resection rate is relatively low, it can be tried in diminutive polyps of less than 3 mm, and for complete resection, it is essential to check the presence of residual tissue.[4] In order to increase the rate of complete excision, there are methods of repeated biopsy and the use of jumbo forceps with a large-capacity to obtain a large amount of tissue at once.[5,6]

The cold snare polypectomy is a method of inserting mini-oval snare 10-15 mm in diameter through an endoscopic channel, gently absorbing the air in the intestine, and capturing the polyps and a 1-2 mm of surrounding normal tissue, and slowly tightening them and cutting them with mechanical force. The advantages include short procedure time, high complete resection rate, and very low complications such as perforation or bleeding.

In selecting the optimal method for the removal of diminutive and small polyps, consideration should be given to high complete resection rates and low complications. In addition, the procedure is not difficult, and the procedure time should be short. Although there is a lack of well-planned randomized comparative studies, it is believed that the removal of diminutive polyps (≤ 5 mm) may be recommended first, except in very small size poly, and in some cases, try a cold biopsy method using a jumbo biopsy forceps. Small polyps (6-9 mm) can be removed by cold snare, hot snare or endoscopic mucosal resection. However, it is thought that cold snare polypectomy method can reduce procedure time compared to other methods and can be considered first since it has a lower incidence of complications.

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Tips for complete and safe colorectal ESD for difficult cases

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Colorectal endoscopic submucosal dissection (ESD) is a still challenging procedure. Major obstacles of colorectal ESD are higher risk of perforation from thin colonic wall, technical difficulties, and longer procedure time. Various techniques and devices have been developed to overcome those difficulties.

LARGE COLORECTAL LESIONS

The size of lesion is definitely associated with procedure time.[1] Dissection speed can be increased by using the pocket creation method.[2] Combined use of the blade-type knife can be also helpful to decrease the procedure time.

Significant stenosis can occur even after colorectal ESD in case of more than 90% dissection of the luminal circumference.[3]

LESIONS WITH SEVERE FIBROSIS

When submucosal fibrosis is predicted before dissection, precut should be performed at least 1.5-2 cm apart from the lesion so that the mucosal flap with less fibrosis at the anal side can be used as a good flap to be flipped.

Dissection of the most fibrotic portion can be deferred until less-fibrotic portions was dissected sufficiently. Manipulating the fibrotic portion can be easier after dissecting the less-fibrotic portion.[4]

CECAL LESIONS

ESD of cecal tumors may be challenging because dissection should be performed with perpendicular approach to muscularis propria, which is associated with higher risk of perforation. Lesions located at the ileocecal valve or the appendiceal orifice can interfere with effective and safe dissection.

LESIONS ABUTTING THE DENTATE LINE

ESD of distal rectal lesions abutting the dentate line can be difficult because of immediate and delayed bleeding from hemorrhoidal plexus, pain from inferior rectal nerve, and folded mucosa in the anal canal. Lidocaine can be mixed with the solution for submucosal injection to decrease procedure-associated pain. Dissection between musculus submucosa ani and muscularis propria can be helpful to avoid from bleeding of hemorrhoidal plexus.[4]

LESIONS AT A DIFFICULT LOCATION

Paradoxical movement of the endoscope is associated with technical difficulty in colorectal ESD.[5] Avoidance of loop formation and minimal inflation is very important for maintaining good endoscopic maneuverability during the procedure. The short single-balloon overtube with larger diameter with the pediatric colonoscope with water-jet function may be useful to deceased paradoxical movement[6] although it is not available yet in Korea.

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KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[11:00-11:30, Convention Hall C]

Joint Symposium (IASL2) English

Opening ceremony / Special lectures

Chair: **Kwang-Hyub Han** (Severance Hospital, Korea)

Long journey of IASL

Samuel Lee, M.D.

Department of Medicine, University of Calgary, Calgary, Canada

The international Association for study of liver (IASL) was first conceived in the mid-1950s by a legendary trio of clinician-scientists who were prominent at that time: Sheila Sherlock, Adolph Martini and Hans Popper (1). After discussions over drinks, the idea was conceived of starting an international liver society dedicated to fostering research, education and clinical care of patients with liver disease. The first president was Sheila Sherlock (1956-60), and this trio organized the first biennial congress, in 1958. All presidents during the first 24 years of the organization served 4 years. Sherlock was succeeded by, in order: Hans Popper, Adolph Martini, Carroll Leevy, Niels Tygstrup, and Kunio Okuda. Succeeding presidents have served two or three-year terms. The most recent presidents have been Jidong Jia, Samuel Lee and the current, KH Han.

Although IASL was the first of the international liver societies, predating AASLD, EASL and APASL, during the 1980s and 90s as these continental organizations grew, IASL fell into relative inactivity. In the past decade the IASL executive committee and Governing Council have attempted to revitalize the organization concentrating in regions of the world where the continental societies are less active. Thus in 2019-2020, we plan conjoint meetings with national or regional societies in East Asia, SE Asia, the Middle East and Africa. A major goal is a stand-alone meeting sometime in 2021.

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KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[11:30-12:30, Convention Hall C]

Joint Symposium (IASL2) English

Professional platform: how to start and build-up academic career - I

Chairs: **Samuel Lee** (University of Calgary, Canada)

Jacob George (Storr Liver Center, University of Sydney, Australia)

How to conduct a good research

Henry LY Chan, M.D.

Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong

A good clinical research starts with a good idea of clinical question. The idea can be obtained through academic communication, something obvious, guidelines and new technology. Based on the idea, a research question and hypothesis should be generated. The lecture will discuss in detail with examples to inspire the audience the journey staring a good clinical research.

How to write a good paper

Samuel Lee, M.D.

Department of Medicine, University of Calgary, Calgary, Canada

This presentation will briefly discuss the mechanics and methods to write a scientific paper for English-language international journals.[1] I will explain how to write a catchy but informative title, construct a cogent and coherent abstract, and write the methods and results understandably. The primary message will be to 'tell a story' by asking oneself: what is the main message? This concept of a main message is central to the entire aim and methodology of writing a paper and will be illustrated by examples. The KISS style of writing ('keep it simple stupid') will also be explained and illustrated. An excellent example of the KISS method of simple but clear writing is Ernest Hemingway's novel 'The Old Man and the Sea' I will emphasize that modern science writing should use the active, rather than the passive style, eg, "We discovered that…" rather than "It was discovered by us that…"

Finally, the most difficult section, how to write a discussion, will be elucidated. Sometimes, even experienced writers and researchers have difficulty with writing a discussion. A common error here is simply restating the main results with little commentary. The good discussion section should serve to reinforce the main messages of the paper and emphasize the strengths and novelties of the study or piece, while placing the study into context as defined by the literature, ie, how do the results expand knowledge in the field? Examples of good writing and common faults will be used to illustrate concepts.

Some editor's tips on the 'gamesmanship' of submitting and publishing papers will also be explained. This includes how to write a brief but arresting cover letter to the editor, what and how to revise the manuscript, and how to deal with rejection. Don't worry, rejections happen to everybody, even the top scientists in every field!

I will try to cover all these details in 20 short minutes.

REFERENCE

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How to handle big data

Young-Suk Lim, M.D.

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The key step for a successful research is choosing a good research question. A good clinical research question is based on critical, urgent, and important clinical unmet needs. The results of the study should be interesting to the researcher, patients, and medical community and provide an important answer regardless of the nature of the result advancing knowledge by filling a critical knowledge gap. The research question is the objective of the study, and a "guiding light" for the project.

The research question is the uncertainty about something in the population that the investigator wants to resolve by making measurements on his study subjects. The clinical research question should be clearly described in one-sentence, composed of population or patients (P), intervention of interest (I), comparison (C), and outcome (O).

Randomized controlled trials (RCTs) are seen as the gold standard for assessing the relationship between an intervention, exposure or risk factor and an outcome. One of the most important features of this study design is randomization, which ensures that the groups formed are similar, except for chance difference, in all aspects.

Randomization reduces biases by making treatment and control groups "equal with respect to all features," except the treatment assignment. When randomization is performed correctly, differences in efficacy found by statistical comparisons can be attributed to the difference between the treatment and control.

However, RCTs are resource intensive and focus on short-term effects of an intervention among a small population. In addition, there is limited generalizability because of their strict inclusion and exclusion criteria that usually under-represent vulnerable patient groups and only provide results of average patients.

The main difference between an RCT (experimental design) and an observational study (non-experimental design) is the absence of random allocation of the intervention by the investigator.

Observational, nonrandomized studies have a role when RCTs are not available, and, even when RCTs are available, to quantify effectiveness and other real world experiences. There is an expanding body of literature using observational designs, partly because observational studies are less resource intensive than RCTs as they often use electronic healthcare data that have already been collected, which have become more available in the last decade. About nine of ten research papers published in clinical specialty journals describe observational research.

However, even with the best of designs, observational studies, unlike the RCTs, do not automatically control for biases and confounders.

Table. The five explanations when an association between the intervention and the outcome is observed in a sample.

Explanation	Type of Association	Causal Model	Prevention at Design Phase	Prevention at Analysis Phase
Chance (Random Error)	Spurious	-	• Increase sample size	• P values • Confidence intervals
Bias (Systematic Error)	Spurious	-	• Carefully consider study subjects, predictor variables, and outcome variables	• Stratification • Adjustment • Propensity scores • Sensitivity analysis
Effect-Cause	Real	Exposure ← Outcome	• Do a longitudinal study with historical sequence	• Consider biologic plausibility
Confounding	Real	Confounder ↗ ↘ Exposure Outcome	• Restriction (strict inclusion & exclusion criteria) • Matching	• Stratification • Adjustment • Propensity scores • Sensitivity analysis
Cause-Effect	Real	Exposure → Outcome		

Lack of randomization in observational studies may result in large differences on the observed (and unobserved) participant characteristics between the treatment and control groups. These differences can lead to biased estimates of treatment effects. Bias and confounding are well-recognized potential pitfalls in case-control studies, and in cohort studies to a less degree.

Bias and confounding can create apparent differences between groups when differences do not actually exist in nature or obscure differences when they really do exist. Before concluding the real causality between the intervention and the outcome in observational studies, four rival explanations must be considered. The first two of these, chance (random error) and bias (systematic error), represent spurious associations: the intervention and the outcome are associated only in the study findings, not in the population. Even if the association is real, however, it may not represent a cause–effect relationship. Two rival explanations must be considered. One is the possibility of effect–cause (That having an outcome is more likely to make people have the intervention; this is just cause and effect in reverse.) The other is the possibility of confounding, in which a third factor is both associated with the intervention of interest and the outcome.

The basic question in interpreting the results of an observational study is "Are the differences between groups in risk or prognosis related to the particular factor under study or to some other factor(s)?". There are several possible ways of controlling for differences between groups (Table). These methods can be applied during the design or analysis of research. One or more of these strategies should be applied in any observational study that attempts to describe the effect of one variable independent of other variables that might affect the outcome. Potential for bias can be recognized more easily when the investigator knows where it is most likely to occur in the course of a study.

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KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[11:00-12:30, Emerald Hall A]

Basic/Translational Symposium 03 (KASID) English

Go to the deep inside of GI disease

Chairs: **Tae Il Kim** (Severance Hospital, Korea)

Thomas Roberts (Dana Farber Cancer Institute, United States)

Recent update of physiology research of GI sensation and motility

Jae Hak Kim, M.D., Ph.D.

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Irritable bowel syndrome (IBS) is one of functional gastrointestinal (GI) disorders. Resent suggested mechanism of IBS is low grade activation of the GI mucosal immune system. Immune activation plays a role on the intestinal mucosa on epithelial permeability, enteric nervous system function, and sensory nerve activation. A meta-analysis revealed that mast cells are increased in some segments such as the rectosigmoid and descending colon of IBS patients. Colonic mast cells, CD3+ and CD4+ T cells are increased. A study showed that visceral hypersensitivity is reduced to normal levels of sensitivity by the administration of fungicides or compounds interfering with fungal recognition by immune cells in IBS-like hypersensitive rats with fungal dysbiosis. Moreover, in IBS and functional dyspepsia, visceral hypersensitivity is an important contributor to symptom generation. Functional magnetic resonance imaging studies have elucidated central mechanisms involved in normal and altered processing of visceral stimuli. Visceral sensitivity in women with IBS is related to changes in functional connectivity within resting-state networks associated with interoception, salience and sensory processing on functional magnetic resonance imaging study. Disruptions in the brain-gut-microbiome axis involving mainly cortical brain as well as subcortical regions may contribute to visceral hypersensitivity and altered perception of pain.

In terms of motility, glucagon-like peptide 1 receptor (GLP-1R) is expressed in myenteric neural cells throughout the GI tract. Expression of GLP-1R is suppressed in germ-free (GF) mice after transplantation of gut microbiota. GI transit time becomes shorter in GF mice after transplantation of gut microbiota, and correlates with the expression of GLP-1R in myenteric neural cells. Aging causes a shift in macrophage polarization from anti-inflammatory 'M2' to pro-inflammatory 'M1', which results in inflammation mediated degeneration of enteric nervous system. Muscularis macrophages (MMs) reside in close apposition to enteric ganglia in the gut wall. Through direct crosstalk with enteric neurons, MMs are important for GI neuromuscular function and their depletion becomes longer in colonic transit times.

As for anorectal functional aspects in IBD, post-inflammatory changes results in anorectal dysmotility, altered anorectal sensitivity, reduced anorectal compliance, impaired anorectal neuromuscular coordination and anal sphincter weakness.

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The future of PI3K directed therapies in cancer treatment

Thomas Roberts, Ph.D.

Department of Cancer Biology, Dana Farber Cancer Institute, Boston, United States

The discovery of the PI3K pathway by Lewis C. Cantley and Thomas M. Roberts was a true breakthrough in our understanding of one of the fundamental signaling mechanisms underlying many aspects of normal cellular and organismal physiology, as well as various pathological states including cancer and congenital overgrowth diseases. The mechanisms by which growth factors and oncogenes activate PI3K, as well as the pathways downstream of PI3K, were characterized by a continued collaboration between Cantley and Roberts. More recently, these investigators played a significant role in stimulating pharmaceutical companies to develop PI3K inhibitors, particularly isoform-specific compounds. Two of these (idelalisib and copanlisib) have received approval from the FDA. The phase 3 trial of a third inhibitor, alpelisib, in combination with the estrogen receptor antagonist Fulvestrant met its endpoint for PIK3CA mutant ER positive, HER2 negative breast cancer, resulting in FDA approval in May of this year. Roberts and Cantley helped facilitate the development of alpelisib and its clinical success underscores the impact of their 30 years of collaboration. However, this success has led to a series of key questions to be approached going forward. Dr. Roberts' talk will address the challenges presented in optimizing the use of PI3K inhibitors as well as the potential future impact of PI3K inhibition

Recent update of brain-gut-microbiome axis

Geom Seog Seo, M.D., Ph.D.

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The concept of brain-gut-microbiota axis has been established and developed academically through various studies, but it is not yet fully understood. Gut-brain axis refers to bidirectional communication between the gastrointestinal tract and central nervous system through spinal afferents and vagus nerve. The gut-brain-microbiota axis consists of CNS, hypothalamic-pituitary-adrenal axis, enteric nervous system, autonomic nervous system, neurotransmitters, neuropeptides, immune cells and microbial-derived products. Recently, it has been found that gut microbiota is the main factor that can modify the gut-brain axis, thus a new concept of microbiota-gut-brain axis is established.

To study microbiota-gut-brain axis, germ-free models, antibiotics, fecal microbiota transplant, prebiotics, probiotics, psychobiotics and techniques to measure the microbiome are being used. Microbiota is important because it affects our immune system during whole lifespan, there are many factors influencing the microbiota-gut-brain axis such as genetics, epigenetics, mode of delivery, environment, drug, exercise, as well as the various psychiatric disorders.

Although, it is known that dysregulation of bidirectional communication of microbiota-gut-brain axis was shown to be involved in the pathogenesis of neurological diseases, metabolic diseases and liver diseases, the lecture will mainly cover the recent update of microbiota-gut-brain axis in "organic" GI disorder such as inflammatory bowel disease rather than functional GI disorders or other diseases.

Recent update of pathophysiology and therapeutic target of IBD

Seongjoon Koh, M.D., Ph.D.

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Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing disorders characterized by abdominal pain, diarrhea, and hematochezia. The pathogenesis of IBD remains obscure. However, it is well-known that an interplay between host genetic factors, intestinal microbiota, and environmental factors is crucial for the development of IBD. Recently, substantial progress in the understanding of the pathogenesis of IBD has been achieved leading to the development of new therapeutic targets for IBD.

The current treatment options for IBD are focused on the inhibition or regulation of mucosal inflammation based on the mucosal immune pathway. Suppression of tumor necrosis factor (TNF)-α, a dominant pro-inflammatory cytokine in IBD, has shown that this pathway is associated with effective disease control. Although the success of anti-TNF-α agents marked a milestone in the management of IBD, it is still challenging to treat the primary non-responders. In addition, the loss of response may develop over time in up to 20% of the cases annually. Therefore, there is still a need to develop new agents targeting other immune pathways associated with the pathogenesis of IBD.

The differentiation of naïve T cells depends on the stimulation of cytokines, such as IL-4, IL-12, and IL-23. Th_1 cells produce IFN-γ, TNF-α, and IL-2. Th_2 cells are characterized by the secretion of IL-4, IL-5, and IL-13. Classically, CD has been associated with Th_1 and UC with Th_2. The Th_{17} cells, characterized by the secretion of IL-17A, IL-17F, IL-21, and IL-22, have been also observed in the mucosa of patients with CD and UC. Therefore, the Th_1/Th_2 theory has been revised. Ustekinumab is a fully-humanized monoclonal antibody blocking the p40 subunit of IL-12 and IL-23, resulting in the inhibition of both Th_1 and Th_{17} pathways. Ustekinumab has been approved for clinical use and is effective and safe for the remission induction and maintenance in patients with moderate to severe CD (UNITI-1 and 2). Besides, the results of a recent phase 3 trial for the induction and maintenance of remission in patients with moderate and severe UC have been released. The study demonstrated that ustekinumab was more effective than placebo regardless of the prior treatment with conventional or biological drugs. Risankisumab and MEDI2070, p19 blockers, have also shown efficacy in CD in phase 2 clinical trials. Mirikizumab was also effective for inducing a clinical response in patients with UC in a phase 2 study. However, treatment with secukinumab, an IL-17A monoclonal antibody, has failed to show efficacy in CD.

Recent advances in our understanding of the pathogenesis of IBD have demonstrated that leukocyte migration to the gut is critical for intestinal inflammation. Antigens are captured and processed by the antigen-presenting cells, such as macrophages or dendritic cells. These cells migrate to the mesenteric lymph node where they induce differentiation of the naïve T cells into effector T cells and imprint T cells with trafficking receptors that direct them towards the intestines. T cell trafficking of the small intestine is mediated by integrin $\alpha_4\beta_7$-MADCAM-1 and CCR9. Integrin $\alpha_4\beta_7$ and GPR15 mediates T cell homing to the colon. Natalizumab, which targets the α_4 subunit of the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins on T cells, have shown efficacy in IBD. However, it has been associated with an increased risk of developing progressive multifocal leukoencephalopathy (PML), and as a result, was subsequently withdrawn from the market. Vedolizumab, a monoclonal antibody against integrin $\alpha_4\beta_7$, has shown efficacy and safety in the induction and was found to maintain remission in large clinical trials (GEMINI I and GEMINI II) in both CD and UC. Importantly, no case of PML has been reported so far, and it led to the approval of vedolizumab for clinical use in 2014. Etrolizumab is a humanized monoclonal antibody against $\alpha_E\beta_7$, and hence, it can block both $\alpha_E\beta_7$ and integrin $\alpha_4\beta_7$ through interactions with MAdCAM-1 and E-cadherin. Phase 1 and 2 trials have suggested that this drug is a candidate for the management of IBD. Recently, a phase 3 trial is still ongoing. PF-00547659 is a monoclonal antibody that inhibits the binding of integrin $\alpha_4\beta_7$ to MAdCAM-1. TRANDOT was a phase 2 trial to evaluate the efficacy and safety of PF-00547659 for the induction of remission in patients with moderate-to-severe UC. This study has exhibited the efficacy of PF-00547659 in patients with UC regardless of prior anti-TNF-α antibody treatment. In addition, GPR15, CCR9, and sphingosine-1-phosphate receptors are involved in leukocyte migration to the colon and regarded as promising therapeutic targets in IBD.

Small molecule drugs have advantages over biological agents in terms of the route of administration and antigenicity. Tofacitinib is an oral small molecule against the JAK kinase family focusing on JAK1 and JAK3, resulting in the suppression of pro-inflammatory cytokines, such as IL-2, IL-4, IL-6, IL-7, and IFN-γ. A phase 3 trial (OCTAVE) was conducted to evaluate the efficacy and safety of tofacitinib in

patients with moderate-to-severe UC. Tofacitinib was more effective in inducing clinical remission and response than placebo. In a phase 2 study, filgotinib, a selective JAK1 inhibitor, has shown efficacy in induction of remission in patients with moderate-to-severe CD.

Substantial progress in the mucosal immune response highlights the pathophysiology of IBD leading to the development of therapeutic agents. However, there exist unmet needs for the management of IBD. The full understanding of the pathogenesis of IBD could bring a new revolution in its management.

KDDW 2019 Korea Digestive Disease Week

DAY 3
November 30 (Saturday)

[11:00-12:30, Emerald Hall B]

Metabolism & Obesity 02 (KSG-KSMBS-KASL) Korean

Obestiy and metabolic syndrome: What are the links with GI diseases?

Chairs: **Seung-Jae Myung** (Asan Medical Center, Korea)
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NAFLD

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Traditionally, obesity and metabolic syndrome have been considered a problem in Western countries. However, in the past two decades, urbanisation in many Asian countries has led to a sedentary lifestyle and over-nutrition, setting the stage for the epidemic of obesity and metabolic syndrome. This lecture reviews the epidemiological trend of obesity and metabolic syndrome in Asia, with special emphasis on the emerging condition of non-alcoholic fatty liver disease (NAFLD). Currently, the population prevalence of NAFLD in Asia is around 25%, like many Western countries. While hepatocellular carcinoma and end-stage liver disease secondary to NAFLD remain uncommon, a rising trend has emerged. Around 8–19% of Asians with body mass indexes less than 25 kg/m^2 are also found to have NAFLD, a condition often described as ''lean'' or ''non-obese'' NAFLD. Although this condition is generally less severe than that in more obese patients, steatohepatitis and fibrotic disease are well recognized. Central adiposity, insulin resistance and weight gain are major risk factors, and genetic predisposition, such as the PNPLA3 polymorphism appears to be more important in the development of NAFLD in the non-obese population. Lifestyle modification remains the cornerstone of management for obesity and NAFLD, but few patients can achieve adequate weight reduction and even fewer can maintain the weight in the long run. While pharmacological agents have entered phase III development for steatohepatitis, Asian patients are under-represented in most drug trials. Future studies should define the optimal management of obesity and NAFLD in Asia.

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Obesity and functional gastrointestinal disorders

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Functional gastrointestinal disorders (FGID) such as gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), and functional dyspepsia (FD), have a high prevalence and have recently increased. As both obesity and FGIDs are increasing, the relationship between obesity and FGIDs has been suggested and various studies have been conducted. However, many studies have focused on patients with gastrointestinal (GI) symptoms rather than obesity, and reports vary slightly from study to study.

1. OBESITY AND IRRITABLE BOWEL SYNDROME

Recent studies concluded that although there may be differences among subject populations, obesity is associated with IBS. The reasons for IBS in obese people are more frequent are as follows; First, changes in the movements of the small and large intestine can occur in obese people. Second, low fiber and high carbohydrate diets may be associated with symptoms of IBS in obese people. More than 67% of patients with IBS report food intolerance, suggesting that food is associated with symptoms of IBS as well as obesity. In addition, patients with IBS are known to consume a lot of canned food, processed meats, beans, grains, confectionary, and fruits. Taken together, the evidence suggests that food plays an important role in the relationship between IBS and obesity. Third, intestinal microorganisms can be mentioned. Several studies have found intestinal microbial changes in both IBS and obesity. The mechanisms by which gut bacteria change in obese people is not clear, but diet (particularly high-fat Western diets) may affect the intestinal microflora, which may affect the development of symptoms of IBS in obese people. However, to date, there is insufficient evidence to establish a causal relationship between changes in the intestinal microflora and the symptoms of IBS in obese patients.

2. OBESITY AND GASTROESOPHAGEAL REFLUX DISEASE

The prevalence of obesity and GERD is increasing in Korea as well as in the West, and there are significant correlations in various studies. In general, it is known that obese people have a high prevalence of GERD, and symptoms of GERD increase in proportion to body mass index (BMI). A population-based study of 7,124 people in Germany found that obese people had an odds ratio (OR) of 2.6 for GERD compared to non-obese people. Recently, there has been a growing interest in abdominal obesity. Abdominal obesity can cause gastroesophageal reflux symptoms by increasing abdominal pressure and decreasing pressure in the lower esophageal sphincter (LES), and visceral fat is known to produces various cytokines, which affect the function of the esophagus and stomach. The mechanism by which GERD increases in obese people is not clear, but the present studies can be summarized as follows. First, the LES tone is significantly reduced in obese people. Second, the overweight and obese people had significantly increased frequency of transient lower esophageal sphincter relaxation (tLESR) and esophageal acid exposure time compared to the normal weight group. Third, as the BMI increases, the pressure distribution of the gastroesophageal junction changes, suggesting that esophageal hiatal hernia is likely to occur, and the prevalence of esophageal hiatus hernia is high in obese people. Fourth, the rate of clearance of the esophagus in obese people is further reduced. Although the results were not consistent with regards to the improvement of symptoms of GERD when body weight loss, recent well-designed intervention studies have shown that weight loss and improvement of GERD symptoms are observed. It can be seen that the body weight reduction is closely related to the symptoms of GERD.

3. OBESITY AND FUNCTIONAL DYSPEPSIA

A large study of about 35,000 people in France suggested a variety of associations between BMI and FGIDs, notably the U-shaped correlation between BMI and female FD. An Italian study conducted a comparative analysis of the prevalence of FGID between patients with severe obesity that required obesity surgery and normal controls. The prevalence of FD was not significantly different between the two groups, but there was a significant correlation between binge eating obesity and postprandial distress syndrome. In addition, the frequency and intensity of epigastric fullness were significantly higher in obese patients with binge eating than in obese patients without binge eating. Dyspepsia is more frequent in obese people because of the changes in gastric movement and various hormones that control it. Many GI hormones are involved in GI motility, are secreted in connection with food intake, and play an important role in the regulation of satiety and food intake. Cholecystokinin, somatostatin,

neurotensin, gastric inhibitory polypeptide, peptide YY and ghrelin have been studied. Ghrelin, a representative hormone, is an intestinal-derived peptide found in the stomach and plays an important role in the regulation of gastric movement and appetite. Ghrelin mainly plays a role in promoting gastric emptying and reducing gastric adaptation. Obese people have lower levels of blood ghrelin than those of normal weight, and when they lose weight, they increase blood levels of ghrelin.

CONCLUSION

Obesity is associated with GERD, IBS, FD, and many other FGIDs. Various pathophysiological factors, such as changes in the movement of GI tracts related to obesity, various cytokines and GI hormones related to obesity, food effects, and changes in the intestinal microflora, have been proposed. However, more well-designed studies will be needed in the future to identify clearer relevance and underlying pathophysiology, and long-term observational studies on whether obesity treatment can improve symptoms of FGIDs.

Obestiy and metabolic syndrome: What are the links with GI diseases?

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Obesity has become one of the most important public health problems in the worldwide. As the prevalence of obesity increases, so does the prevalence of associated comorbidities, resulting in an enormous burden of obesity-related disease worldwide. The metabolic syndrome also has become a well-known issue associated with obesity which is associated with résistance to the effects of insulin on peripheral glucose and fatty acid utilization and often risk factors of type II diabetes mellitus and cardiovascular diseases. Metabolic syndrome was defined with abdominal obesity, hyperglycemia, dyslipidemia and hypertension (Table 1).

Obesity and MS increases free fatty acids and alters adipocytokines. The pathophysiology between obesity or MS and GI diseases are related with insulin and insulin-like growth factors pathway, adipokines (Leptin, adiponectin, etc), and pro-inflammatory cytokines, such as IL-6, TNF-α, and C-reactive protein.

Obesity is a well-known risk factor for GERDs in both Asian and Western. Large epidemiological studies have demonstrated that obesity is an important risk factor of GERD. The high BMI and High visceral obesity were related with increasing risk of reflux esophagitis. The weight reduction might be relieving the symptoms of GERD. Obesity increased intraabdominal pressure and promoted formation of hiatal hernia, which is a strong risk factor of GERD. GERD and obesity are also related with esophageal adenocarcinoma and Barrett's esophagus. GERD can lead to erosive esophagitis, progressing to a metaplastic, changed intestinal epithelium (Barrett's esophagus, BE). BE progresses to EAC in a small portion, approximately 0.12% to 0.60% per year. Patients with longstanding symptoms, nocturnal symptoms, or more frequent symptoms are at higher risk.

Irritable bowel syndrome was related to MS and elevated TG level in cross-sectional study. There may be a link between visceral adiposity and irritable bowel syndrome, but data about such a connection is still limited.

Obesity is an important risk factor for colorectal adenoma and cancer. Many studies suggested that abdominal obesity and metabolic

Table 1. Definitions of the metabolic syndrome (Most commonly agreed upon criteria for metabolic syndrome (any three of five risk factors)

Parameters	NCEP ATP III (2005)	IDF 2006	WHO (1999)	AACE (2003)
Required		Waist ≥ 94 (men) or ≥ 80 cm (women) (Asian: waist ≥90 cm (men) or ≥80 cm (women))	IR in top 25%;glucose ≥ 110 mg/dL (6.1 mmol/L); 2-hour glucose ≥140 mg/dL (7.8 mmol/L)	High risk of insulin resistance or BMI ≥25 kg/m^2 or waist ≥102 cm (men) or 88 cm (women) (Asian: waist ≥90 cm (men) or ≥80 cm (women))
# of abnormalities	≥3 of:	And ≥2 of:	And ≥2 of:	And ≥2 of:
Glucose	≥100mg/dL (5.6mmol/L) or DM	≥100mg/dL (5.6mmol/L) or DM		≥ 110 mg/dL (6.1 mmol/L); ≥2-hour glucose 140 mg/dL (7.8 mmol/L)
HDL cholesterol	<40 mg/dL (1.0 mmol/L) (men); <50 mg/dL (1.3 mmol/L) (women); or drug Tx for low HDL cholesterol	<40 mg/dL (1.0 mmol/L) (men); <50 mg/dL (1.3 mmol/L) (women); or drug Tx for low HDL cholesterol	<35 mg/dL (0.9 mmol/L) (men); <40 mg/dL (1.0mmol/L) (women)	<40 mg/dL (1.0 mmol/L) (men); <50 mg/dL (1.3 mmol/L) (women)
Triglycerides (TG)	≥150 mg/dL (1.7 mmol/L) or drug Tx for elevated TG	≥150 mg/dL (1.7mmol/L) or drug Tx for elevated TG	Or ≥150mg/dL (1.7mmol/L)	≥150 mg/dL (1.7 mmol/L)
Obesity	waist ≥102 cm (men) or 88 cm (women) (Asian: waist ≥90 cm (men) or ≥80 cm (women))		Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 kg/m^2	
Hypertension	≥130/85 drug mmHg or drug Tx for HIBP	≥130/85 drug mmHg or drug Tx for HIBP	≥140/90 mmHg	≥130/85 mmHg

NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; WHO: World Health Organization; AACE: American Association of Clinical Endocrinologists.

syndrome were stronger predictors of colorectal adenoma than BMI, a marker of general obesity. The visceral obesity was found to have a increasing the risk for subsequent adenoma or advanced neoplasm during surveillance colonoscopies. The risk of colorectal cancer (CRC) is associated with high BMI, with an estimated 3% increase in risk with each unit of BMI. MS is associated with an increased risk of CRC incidence and mortality in meta-analysis. Korea national data also showed that obesity increased the risk of CRC.

The association between obesity and gastric cancer has not been well studied and controversy. However, *Helicobacter pylori* infection was associated with MS in meta-analysis. *H. pylori* may influence the cytokine networks, including tumor necrosis factor-a, interleukin-6, angiotensinogen, free fatty acid, leptin, and adiponectin, which subsequently accelerates abnormalities in metabolic parameters and finally leads to the development of MS.

MS and obesity, particularly abdominal visceral obesity, increased the risk of benign and malignant GI diseases such as GERD, BE, colorectal adenoma, colorectal cancer, and esophageal cancer.

Therefore, we should be concerned about the obesity or MS related with GI diseases and focused the weight reduction or improving the insulin resistance of patients to reduce the GI diseases associated with MS or obesity.

Pancreatobiliary diseases

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Obesity has become a major medical and public health problem worldwide. Obesity is a chronic disease and at the same time associated with various diseases. Although it is associated with metabolic syndrome, type 2 diabetes, and cardiovascular disease, studies have shown that it is also associated with gallstone disease, acute pancreatitis, fatty liver, and digestive cancer.[1] In this article, the current state of our knowledge of obesity related digestive diseases, especially pancreatobiliary disease.

Obesity has been considered as a risk factor for pancreatic diseases, including pancreatitis and pancreatic cancer. Severe acute pancreatitis is significantly more frequent in obese patients. Furthermore, obese patients develop systemic and local complications of acute pancreatitis more frequently. The underlying mechanisms of how obesity may increase acute pancreatitis severity are a focus on cytokines, adipokines, and increased necrosis of intra- and peri-pancreatic fat.[2] In addition, obesity is a poor prognostic factor in acute pancreatitis, and overweight before disease onset appears to be a risk factor for chronic pancreatitis.[3] Several epidemiologic studies have suggested relationship of pancreatic cancer with high body mass and lack of physical activity.[4] The pathogenic mechanism may be hypersinulinemia and increased circulating level of insulin-like growth factor-1. Obesity is associated with negative prognostic factor and increased mortality in pancreatic cancer.[3]

Obesity is a risk factor for the formation of cholesterol gallstones. Clinical and epidemiological studies have suggested that obesity is positively related with the risk of gallbladder cancer. Obesity may modulate lipid and endogenous hormones metabolism, affect gallbladder motility, increase the risk of gallstones, and also increased the risk of gallbladder cancer.[5]

The prevalence of gastrointestinal conditions associated with obesity are increasing worldwide. Thus, it is important to recognize the role of higher BMI and, particularly, increased abdominal adiposity, in the development of gastrointestinal disease and to measure BMI and waist circumference in patients presenting with gastrointestinal complaints.

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KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[11:00-11:40, Diamond Hall]

Presidential Lecture (KPBA) Korean

Chair: **Seok-ho Dong** (Kyunghee University Medical Center, Korea)

Biology of cholangiocytes: from bench to bedside

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Cholangiocytes, the lining epithelial cells in bile ducts, are an important subset of liver cells. They are activated by endogenous and exogenous stimuli and are involved in the modification of bile volume and composition. They are also involved in damaging and repairing the liver.

Cholangiocytes have many functions including bile production. They are also involved in transport processes that regulate the volume and composition of bile. Cholangiocytes undergo proliferation and cell death under a variety of conditions. Cholangiocytes have functional and morphological heterogenecity. The immunobiology of cholangiocytes is important, particularly for understanding biliary disease.

Secretion of different pro-inflammatory mediators, cytokines, and chemokines suggests the major role that cholangiocytes play in inflammatory reactions. Furthermore, paracrine secretion of growth factors and peptides mediates extensive cross-talk with other liver cells, including hepatocytes, stellate cells, stem cells, subepithelial myofibroblasts, endothelial cells, and inflammatory cells.

Cholangiopathy refers to a category of chronic liver diseases whose primary disease target is the cholangiocyte. Cholangiopathy usually results in end-stage liver disease requiring liver transplant.

We summarize the biology of cholangiocytes and redefine the concept of cholangiopathy. We also discuss the recent progress that has been made in understanding the pathogenesis of cholangiopathy and how such progress has influenced therapy.

Key words: Cholangiocyte; Biology; Cholangiopathy; Transport; Receptors

INTRODUCTION

The biliary system is comprised of intrahepatic bile ducts, extrahepatic bile ducts and the gallbladder. Bile is transported by the extensive biliary tract, which measures approximately 2 km in human. A layer of epithelial cells called cholangiocytes lines the intrahepatic bile ducts of this extensive network. The extrahepatic ductal epithelial cells and gallbladder epithelial cells share many features with cholangiocytes. Cholangiocytes comprise only about 3-5% of the total cell mass of the liver, but they are crucial for normal physiologic processes, and they contribute to multiple disease states of the biliary tract.[1-5]

Cholangiocytes serve several functions performed by several important molecules. Most importantly, cholangiocytes participate in the formation and transportation of bile via transmembrane molecules that are expressed on the apical or basolateral membrane. These transporters include channels (i.e., water channels [aquaporins]), transporters (i.e., SGLT1: Na^+-glucose transporter), and exchangers (i.e., SLC4A2: $Cl^-/HCO3^-$ exchanger). Impairing these molecules could lead to cholestasis (Fig.1).[6-8] Cholangiocytes also interact with resident and nonresident cells of the bile ducts via inflammatory and fibrotic mediators, such as tumor necrosis factor α and interleukin-6. On the other hand, diseased cholangiocytes can cause biliary inflammation and fibrosis. Finally, cholangiocytes are involved in cell-cycle phenomena that maintain tissue homeostasis in the biliary system via modulators of apoptosis (i.e., AkT1: protein kinase B α), senescence (i.e., N-RAS transforming protein), and proliferation (ie, platelet-derived growth factor). Damage to the cholangiocytes may result in ductopenia, dysplasia, or malignant transformation of the bile ducts (Fig.2).

Unlike other epithelial cells, cholangiocytes are morphologically and functionally heterogeneous.[9,10] Small cholangiocytes possess proliferative capabilities and display functional plasticity in disease, while large cholangiocytes are involved in hormone-regulated bile secretion. Stem cells in the peribiliary glands that can differentiate into cholangiocytes may be involved in biliary remodeling and pathogenesis of cholangiopathies.[11,12] Understanding the biology of cholangiocytes allows us to understand the mechanisms of cholangiopathy (Fig.2) and to develop adequate treatmenst for these diseases.

Findings from electron microscopy of cholangiocytes show the apical microvilli facing the lumen of the bile duct and various micro-organelles, such as the RER, mitochondria, vesicles, and nucleus in cytoplasm. From such findings, we can speculate that cholangiocytes are incredibly versatile and complex in their functions. The cholangiocyte indeed has many functions, which can be categorized into four broad areas. Firstly, cholangiocytes are involved in transport processes that regulate the volume and composition of bile. Secondly, cholnagiocytes undergo proliferation and cell death under a variety of conditions, some of which are important in our understanding of disease states. Thirdly, the concept of cholangiocyte heterogeneity has attracted attention, as not all cholangiocytes are functionally or morphologically identical. Finally, the immunobiology of the cholangiocyte is important for understanding diseases characterized by vanishing bile ducts, such as PBC, PSC, allograft rejection, and GVHD.

KDDW 2019 Korea Digestive Disease Week

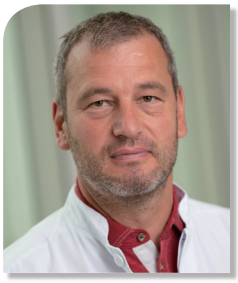
DAY 3

November 30 (Saturday)

[11:40-12:20, Diamond Hall]

Special Lecture (KPBA) English

Chair: **Ho Soon Choi** (Hanyang University Medical Center, Korea)



Targeting genome dynamics in pancreatic cancer

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KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[11:00-12:30, Skylark]

Nursing Session 02 (KPBA) Korean

For the Best Care of Pancreaticobiliary Cancers

Chairs: **Jun Kyu Lee** (Dongguk University Ilsan Hospital, Korea)

Hee Hyuk Im (Soon Chun Hyang University Seoul Hospital, Korea)

Understanding pancretobiliary cancer

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Pancreatobiliary cancers are relatively uncommon malignancies which generally have a poor prognosis. Bile duct cancer and pancreatic cancer was the 8th and 9th most common cancer in Korea in 2016, and the incidence is on the rise. The prognosis of patients with pancreatic cancer and intrahepatic cholangiocarcinoma is poor, with an estimated 5-year overall survival of 2–5%. Patients with extrahepatic bile duct cancer and gallbladder cancer have a slightly better survival, but the overall 5-year survival is still only 12–15%. The mortality rates for bile duct cancer seem to have decreased slightly over recent decades, a trend that may in part be due to improved diagnostic modalities and more widespread application of cholecystectomy for gallstones. Surgical operation has been the dominant procedure for treating pancreatobiliary cancer. But, it is difficult to detect at its initial condition, and most pancreatic cancers are already unresectable at the time of diagnosis. Despite the observed improvements in prognosis, the majority of patients with pancreatobiliary cancer still present at an advanced stage where surgical treatment is impossible. The lack of effective diagnostic tools for early detection of pancreatobiliary cancer is the major factor for the poor prognosis of pancreatic cancer. Of the patients with newly diagnosed pancreatic cancer, almost half have metastatic disease at diagnosis, with an additional 22% having either node-positive disease or a large tumor invading adjacent organs. Bile duct cancers tend to be less advanced at presentation than pancreatic cancer, which probably explains the better prognosis to some extent. Other factors, such as differences in the genetic basis of these cancers, may provide further insight into the differences in clinical outcomes. Adjuvant treatment has been shown to improve the outcome of patients with pancreatic cancer. Although adjuvant chemotherapy or chemoradiotherapy in pacncreatic cancer patients who underwent surgical resection has been shown to be beneficial, most patients who undergo resection eventually experience progression of the disease. The role of adjuvant therapy in bile duct cancer patients who underwent surgical resection is uncertain. Several studies support the role of radiotherapy or chemoradiotherapy, however, the benefits of adjuvant treatment seem modest. The majority of patients will be diagnosed with advanced disease, either at the time of first diagnosis or at a later stage once the cancer recurs. There is thus a great need for improvements in advanced therapy for these malignancies. Advancement in the understanding of the biology of pancreatobiliary cancer has helped identify several molecular targets for the development of novel therapies. Gene therapy and immunotherapy are currently in the spotlight as promising new methods for cancer cure. A better understanding of pancreatobiliary cancer biology will lead the way to more effective treatments, however, clinicians should keep in mind that the single most important factor to improve the survival of pancreatobiliary cancer patient is the early diagnosis in a radically resectable stage.

Endoscopic treatment of malignant biliary obstruction

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Malignant biliary obstruction (MBO) is a common complication of malignancies that involve the pancreaticobiliary system. MBO poses a therapeutic challenge due to the subclinical nature of pancreaticobiliary malignancies, which tend to be asymptomatic until presentation in advanced stages of disease.(1) Once diagnosed, treatment of pancreaticobiliary malignancies is guided by candidacy for surgical resection with or without neoadjuvant chemotherapy or palliation. As patients with unresectable MBO tend to have high operative risk with complicated illness at time of presentation, palliation of obstruction is focused on minimally invasive, cost-effective, and durable approaches to provide biliary drainage to alleviate symptoms.(2)

Endoscopic treatment of MBO allows for a more minimally invasive and better tolerated approach for biliary drainage compared to surgical drainage. Recently, improvement in endoscopic technique and further development of plastic and self-expanding metal stents (SEMSs) has led to endoscopic biliary drainage as the preferred modality of palliation of MBO.(3) Percutaneous drainage has been found to have similar effectiveness without significant differences in survival time or cost compared to endoscopic biliary drainage.(4) However, percutaneous drainage requires an external outlet for biliary drainage, which creates additional potential complications including pain and discomfort at the abdominal wall, leakage and dislocation of percutaneous tubing, bleeding, and risk of cellulitis.(5) Due to these disadvantages associated with percutaneous drainage, ERCP is recommended as the initial strategy for biliary drainage in MBO with percutaneous intervention reserved as a secondary option if endoscopic drainage is unsuccessful.(1)

Distal MBO refers to biliary obstruction at the level of the common bile duct, typically caused by cancer of the pancreatic head or infiltration into the extra-hepatic common bile duct. A plastic or metal biliary stent is subsequently introduced through the accessory channel of the endoscope under fluoroscopic visualization. After the stent is appropriately positioned across the obstruction, the stent is deployed to establish patency of the obstructed bile duct with the distal aspect of the stent projecting out of the duodenal papilla, facilitating access for any potential future endoscopic interventions.(1)

Malignant hilar obstruction refers to biliary obstruction at the level of the common, right, or left hepatic ducts. Similar to distal MBO, palliation of hilar obstruction can be achieved with endoscopic drainage, percutaneous drainage, and surgical bypass. The optimal strategy of biliary drainage is guided by the level of obstruction and degree of involvement of biliary ducts in the hilum, which has conventionally been described using the Bismuth-Corlette classification. The optimal percentage of liver volume drained has been examined, with a retrospective study suggesting that drainage of ≥50% of the liver volume was associated with optimal drainage and an increased survival benefit.(6) Due to the complex nature of hilar obstructions, there is no universal consensus on the optimal approach to palliation of hilar MBTO. Current areas of controversy in approaching hilar MBTO include optimal stent type, unilateral or bilateral drainage, and the method of bilateral stent drainage (stent-in-stent [SIS] or side-by side [SBS]).

Malignant biliary obstruction typically presents in advanced stages that often prohibit curative or surgical treatment with significant impact on the quality of life of patients. The focus of palliation in MBO should revolve around minimally invasive, cost-effective approaches that provide improved quality of life and morbidity in this population. Endoscopic drainage is the optimal palliative approach in this population due to the considerable advances in recent decades such as the development of SEMS and advanced endoscopic techniques. Due to the complexity of distal and hilar MBTO, patients should be referred to tertiary centers for palliative treatment where a multidisciplinary approach including oncologists, surgical oncologists, advanced endoscopists, and interventional radiologists are available to guide treatment.

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Nurse's role of pancreatobiliary cancers

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The primary role of all nurses can be accomplished by a care giver and through interrelated roles as a communicator, educator, counselor, leader, researcher, and advocate.

In particular, patients with cancer became vulnerable mentally and physically which means that they find it difficult to accept and recognize their disease since they imagine themselves in the worst situation about the whole treatment process unnecessarily but also financially, they have to face some problems such as losing their jobs, sick leave. Therefore, the role of nurses who spent most of time with patient is considered most important and needed to be more professional and diverse in the process of care for cancer patients.

The Oncology Nursing Society ([ONS], 2017) defines an oncology nurse navigator (ONN) as "a professional RN with oncology-specific clinical knowledge who offers individualized assistance to patients, families, and caregivers to help overcome healthcare system barriers.

According to 'Annual report of cancer statistics' in 2016, the number of cancer patients was 229180, the number of cancer survivors has been increasing after the treatment.

Late diagnosis usually causes a high symptom burden. Signs and symptoms may include abdominal and back pain, unexplained weight loss, indigestion, loss of appetite, changes in bowel habits, jaundice, nausea and vomiting, difficulty swallowing, recently diagnosed diabetes and psychological distress. Unfortunately, people with pancreatic cancer often continue to experience severe signs and symptoms to the end of life and, as a result, report poor quality of life. Moreover, tumors may progress despite anticancer treatment. Appropriate treatment plans that improve survival while maintaining subjective quality of life (QoL) are essential.

Recent National Institute for Health and Care Excellence (NICE) guidelines (2018) for the diagnosis and management of pancreatic cancer in adults outline the importance of psychological support. People should have access to psychological support throughout their care pathway and support should assess the psychological effects of fatigue, pain, gastrointestinal symptoms, including changes to appetite, nutrition, anxiety and depression that may affect their daily lives. Support should be available on an ongoing basis, relevant to the stage of the person's condition and tailored to their needs (NICE 2018).

In addition, Pancreatic cancer has one of the highest mortality rates of any malignancy, placing a substantial burden on patients and families with high unmet informational and supportive care needs. Nevertheless, access to psychosocial and palliative care services for the individuals affected is limited.

Although patients in general had several problems, physical, emotional, and loss of autonomy (LOA) problems were most common. For these physical and emotional problems, patients also expected professional care, although to a lesser extent for LOA problems. Inadequate care was received for fatigue, fear, frustration, and uncertainty. We conclude that an individualized approach based on problems related to physical, emotional, and LOA issues and anticipated problems with healthcare providers has priority in the follow-up policy of patients with incurable upper gastrointestinal cancer. Caregivers should be alert to discuss needs for fatigue, feelings of fear, frustration, and uncertainty.

Caregivers of individuals with cancer often face high caregiver strain and burden. Nurses are in a key role to assess and intervene with caregivers, but some may have little contact with caregivers or lack confidence in dealing with caregivers' high emotional distress. More attention needs to be directed toward facilitating nurses' contact with caregivers, increasing nurses' understanding of effective caregiver interventions, and helping nurses gain additional skills as needed to address the emotionally demanding situations that caregivers face. Findings point to the importance of interprofessional care and availability of social workers and others for referrals as needed.

I hope this lecture gives you an opportunity to think about How we take care of pancreatobiliary patients not only physically but also emotionally.

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Nutrition managements for pancreaticobiliary cancers

Minkyong Yoo, M.D.

Department of clinical nutrition, National Cancer Center, Goyang, Korea

Pancreaticobiliary Cancer is a cancer with one of the highest mortality rates. Despite the advances in treatment technology, the survival rate is still low because early detection is difficult. Changes in pancreatic function can cause problems such as indigestion, malabsorption, poor appetite or weight loss, which can lead to poor nutrition status. Therefore many pancreaticobiliary cancer patients present with malnutrition at diagnosis and overtime develop severe cachexia. Thus, constant monitoring and early nutritional intervention are crucial for the prevention of malnutrition in pancreaticobiliary cancer patients receiving treatments.

The nutritional statuses of cancer patients can be evaluated by the patient-generated subjective global assessment (PG-SGA), which provides information of disease history and dietary history (weight change, food intake, nutrition impact symptoms, and physical function), as well as the physical exams (body fat loss, muscle mass loss, existence of edema and ascites). Based on nutrition assessment, malnourished patients need perioperative nutritional interventions to reduce postoperative complications, morbidity and mortality, and to improve quality of life (QoL). Especially in severely malnourished patients, preoperative nutrition support is recommended for 10 to 14 days before major surgery, and early feeding is important in postoperative state. If the patient have poor oral intake from regular meals, due to the symptoms of cancer, the oral nutritional supplements (ONS) might promote their health by increasing oral intake and body fat mass, improving PG-SGA scores and decreasing fatigue symptoms.

Pancreatic surgery significantly affects pancreatic function and patients' nutritional status because pancreas plays an important role in digesting food. Pancreatic enzymes are made from exocrine cells in the pancreas, therefore after pancreatic surgery can reduce the number of enzymes that pancreas makes. The patients who had Whipple procedure (pancreaticoduodenectomy, PD) may be complicated by delayed gastric emptying, indigestion, malabsorption, weight loss, diabetes, and nutritional deficiencies. Dumping syndrome can occur because of some part of the stomach are also removed, thus pylorus-preserving pancreaticoduodenectomy (PPPD) is being implemented for less complication. The patients who had total pancreatectomy, which removes the entire pancreas, are left without the cells that make insulin and other hormones that help maintain safe blood sugar levels. These patients develop diabetes, which can be hard to manage because they are totally dependent on insulin shots. Distal pancreatectomy, which removes only the tail of the pancreas, has less postoperative symptoms. Postoperative nutritional intervention start from frequency meals of low volume and avoidance of food difficult to digest (i.e. legumes) are generally recommended. Patients with uncontrolled blood sugar level, calorie-controlled diabetic diet may be needed. Alter fat source if malabsorption or steatorrhea occurs. Patients with pancreatic exocrine insufficiency may require supplement of fat soluble vitamins (vitamin B12) and mineral (zinc). In case oral intakes are not possible, enteral nutrition (EN) should be preferred as a nutritional intervention over total parenteral nutrition (TPN). Immune-enhancing EN, which contains fatty acids and vitamins may reduce morbidity and mortality.

Chemotherapy or radiation therapies are implemented in patients with inoperable pancreatic cancer or post-operation patients to reduce recurrence. These treatments may negatively affect in nutritional status and QoL. These include anorexia, nausea, vomiting, and stomatitis, diarrhea, constipation, fatigue, which can disturb sufficient oral food intake and digestive nutrient absorption, which accompany weight loss, decreased anticancer drug reaction rate, increased anticancer drug toxicity, reduced survival rate, and reduced QoL. There are no foods which should totally avoid during treatment. Symptom management is important and suitable diet adjustments need according to symptoms during chemotherapy or radiation therapies. These patients will need more energy and protein in diet to help maintain weight and recover from treatments.

Pancreatic cancer patients have higher risk of malnutrition throughout the course of treatment. Therefore it is importance that multidisciplinary nutrition screening and intervention in managing pancreatic cancer.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[14:00-14:40, Convention Hall A+B]

Presidential Lecture (KASID) Korean

Chair: Dong Soo Han (Hanyang University Guri Hospital, Korea)

Management strategies to improve outcomes of patients with IBD

Joo Sung Kim, M.D., Ph.D.

Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

Inflammatory bowel diseases (IBDs) such as Crohn's disease (CD) and ulcerative colitis (UC) are chronic relapsing inflammatory diseases of the gastrointestinal tract. IBD is a progressive disease and the prevalence of IBD is increasing worldwide, which leads to heavy a burden on the health care system.

Recent management strategy has been changed from the control of symptoms and improved quality of life toward the blockade of disease progression to prevent bowel damage and disability. This strategy has shown the improved outcomes of patient with IBD. Key steps of the improvement of IBD outcomes are as follows. Frist, development of effective agents including biologic agents (anti-TNFs, anti-interleukins and anti-adhesion molecules) and small molecules (JAK inhibitors) has improved clinical symptoms and induced mucosal healing. Second, conventional treatment algorithm (step-up therapy) shifted to top-down or accelerated step-up therapy, which reduced the rate of IBD progress. Third, introduction of treat-to-target approach, which is the process of target setting, target acquisition and outcome evaluation, induced clinical remission and reduced the mucosal inflammation of IBD.

In this lecture, I suggest four comprehensive practical management strategies to improve outcomes of patients with IBD as follows.

1. Keep diagnostic and therapeutic protocols in IBD
2. Follow current management strategy in IBD
3. Focus on IBD patients' reports and support their participation
4. Update evidence-based medicine in IBD

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[14:40-15:20, Convention Hall A+B]

Special Lecture (KASID) English

Chair: **Joo Sung Kim** (Seoul National University Hospital, Korea)

Recent updates of biomarkers in colorectal cancer screening

Joseph J. Y. Sung, M.D., Ph.D.

Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong

Multitarget stool DNA (mt-sDNA) testing has been on the market in recent years. A large multicentre trial showed that the sensitivity of mt-sDNA for both CRC (>90%) and advanced precancerous lesion (>40%) exceeded that of the FIT by an absolute difference of nearly 20%.The American guidelines recommend mt-sDNA as an option for CRC screening. At present, based on genome-specific data in the Chinese population, several stool DNA tests for CRC screening have been established in China, but the effectiveness of these tests remains to be verified in a large population. Another commercially available molecular approach for CRC screening is the plasma assay of methylated Septin9 (mSEPT9). Prospective study of mSEPT9 in a large screening population showed a sensitivity and specificity for CRC of 48% and 91%, respectively.An updated version of this test yielded an improved sensitivity of 68% for CRC; however, the specificity dropped to 80%. Despite its unattractive performance, mSEPT9 is the only blood-based biomarker for CRC screening approved by the US FDA due to its potential high compliance. In recent years, microbiome biomarkers have been developed and early evidence suggest that it is promising. Candidates identified by metagenome sequencing, including Fusobacterium nucleatum (Fn), Bacteroides clarus (Bc), Roseburia intestinalis (Ri), Clostridium hathewayi (Ch), and one undefined species (labeled as m7), were examined in fecal samples of CRC patients and healthy controls. Strong positive correlations were demonstrated between the quantification of each candidate by our qPCR assays and metagenomics approach ($r=0.801\sim0.934$, all $P<0.0001$). Fn was significantly more abundant in CRC than controls ($P<0.0001$), with area under receiver operating curve (AUROC) of 0.868 ($P<0.0001$). So far, direct comparative analyses of these tests in the same study are still sparse. More studies in this area will be needed.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

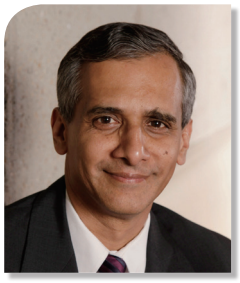
[13:30-14:30, Convention Hall C]

Joint Symposium (IASL3) English

Controversial issues in liver diseases

Chairs: **Kwan Soo Byun** (Korea University Guro Hospital, Korea)

Han Chu Lee (Asan Medical Center, Korea)



NASH Trials: how far have we come?

Jacob George, M.D., Ph.D.

Department of Gastroenterology and Hepatology, Storr Liver Center, University of Sydney, Sydney, Australia

With the development of highly effective curative therapies for hepatitis C and drugs that control hepatitis B replication, the principle liver disease burden of the future will be that related to non-alcoholic fatty liver disease (NAFLD). Epidemilogical studies and meta-analyses indicate that NAFLD affects 1 in 4 people and will soon become the commonest cause of liver transplantation. Like nonA nonB hepatitis 4 decades ago, there are currently no effective pharmacotherapies for NAFLD, or for its inflammatory and potentially progressive form, non-alcoholic steatohepatitis (NASH).

As a disease that is the outcome of the worldwide increase in overweight/obesity and diabetes prevalence, the ideal primary treatment for NASH is reversing overweight/obesity and diabetes. Indeend lifetsyle intervention which has proven effective for diabetes, has also been highly effective for the management and treatment of NASH. In the most robust study to date, weight loss of greater than or equal to 10% was associated with resolution of NASH in 90% of cases and fibrosis improvement in 81% at one year. Proportionally smaller reductions in NASH resultion and fibrosis improvemnet were noted with lesser degrees of weight loss. Even in those that lost 5-7% of body weight, NASH resolution occured in 26%, while fibrosis improved in 38.

Pharmacotherapy for NAFLD is now a major focus for clinical trial activities with over 200 trials recruiting for NAFLD and 197 for NASH. Current therapies seek to target one or multiple components of the inflammatory cascade of NASH including lipid metabolism, oxidative stress, inflammation, glucose metabolism and fibrosis. To date results of phase 2 and 3 trials have shown some benefit, but it would be fair to say that overall, improvements have been less than awe insipring. Major phase 3 trials have read out in 2019 and others will read out in 2020. However, while effective for some key aspects of NAFLD, the difference from the placebo response has been modest. In part, this reflects the known heterogeneity of NAFLD which broadly speaking is an umbrella term for a likely range of pathogenic drivers of differential impact in individual patient groups. In all cases, this gives rise to a narow liver histological spectrum (steatosis, inflammation, ballooning and fibrosis). It is likely that over the next decade, this heterogeneity of NAFLD will be resolved into multiple sub-phenotypes. Once that is achieved, treatment can be driven more precisely by knowledge of the underlying drivers. Thus, while the first generation of treatments are likely to have modest impact, it is hoped that multi-targeted therapy will lead to an era of precision medicine in future, suported by impactful lifestyle intervention strategies.

Non-invasive assessment in cirrhosis or advanced fibrosis

Young Seok Kim, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Soon Chun Hyang University Bucheon Hospital, Bucheon, Korea

Regardless of the causes, the final result of untreated chronic liver disease is consequence of inflammation, loss of liver cell mass, and recuperation by fibrosis and regeneration. The progression of liver fibrosis results in cirrhosis which causes serious complications such as portal hypertension, liver decompensation, and development of malignant tumor. Chronic liver disease including cirrhosis is a significant and growing global medical and social problem.

The diagnosis of cirrhosis indicates an increased risk of morbidity and mortality. Liver fibrosis determination is important in determining prognosis and making treatment, care decisions, and response to treatment in patients with various chronic liver diseases. Liver biopsy is considered the gold standard in last few decades for staging of fibrosis and diagnosis of cirrhosis. However, despite being used universally, liver biopsy is an invasive and a flawed gold standard with numerous limitations.

In order to overcome the drawbacks of liver biopsy, various non-invasive assessment to determine liver fibrosis have been developed. Non-invasive assessment of liver fibrosis or cirrhosis can be divided into two methods using radiologic techniques or serum-based laboratory studies. Radiologic techniques based on ultrasound, magnetic resonance and elastography have been developed to assess liver fibrosis, but are not as widely available as serum based markers of liver fibrosis determinations. Laboratory determinations of liver fibrosis include various general clinical scoring systems and commercially available combination biomarkers. Serum-based determinations of advanced fibrosis and cirrhosis are broadly classified into indirect and direct markers. Indirect biomarkers reflect liver function, which may change when advanced fibrosis or liver cirrhosis developed. Direct biomarkers, reflect extracellular matrix turnover, and are directly involved in liver fibrogenesis.

Radiologic and laboratory determinations of liver fibrosis correlate well with liver biopsy scores, and also useful for assessing whether a patient is at low, intermediate, or high risk of advanced fibrosis/cirrhosis. This feature is definitely clinically useful, and avoids liver biopsy in a substantial proportion of patients.

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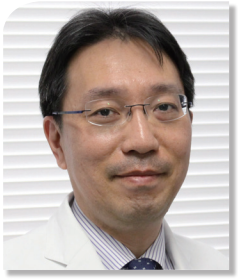

Management of advanced liver disease in elderly patient

Ryosuke Tateishi, M.D., Ph.D.

Department of Gastroenterology, The University of Tokyo Hospital, Tokyo, Japan

Mainly due to the aging population in patients with chronic hepatitis, especially chronic hepatitis C, the mean age of hepatocellular carcinoma (HCC) patients at the initial diagnosis has consistently increased in the last two decades. Today approximately 20% of HCC patients who are admitted to our department for treatment are over 80 years old. Baseline data at the initial diagnosis shows that the proportion of female patients and those with preserved liver function increased in elderly patients. Because the proportion of patients who have medical comorbidity increases according to age, less invasive therapy tends to be selected in elderly patients. Although many studies reported that there was no difference between elderly and young patients in terms of morbidity and mortality of hepatic resection, these studies are mostly prone to selection bias. In fact, we found a significant relationship between patient age and the increased in-hospital mortality of hepatic resection by analyzing a nationwide database. Ablative therapy including radiofrequency ablation (RFA) has a wide indication for elderly patients not suitable for hepatic resection due to other organ impairment or impaired liver function. When we compared the survival rates between groups of HCC patients divided by the threshold of 75 years old with competing risk analysis, HCC-related death rates were comparable between the groups. In contrast, there was a significant difference between the groups in liver unrelated death. The proportion of liver-unrelated death was 34.7% in elderly (≥75) patients and 18.7% in younger (<75) patients. Detailed investigation of the cause of death revealed that infection is the most common, followed by other organ cancer and ischemic heart disease. It is still controversial as to whether molecular-targeted therapy is equally effective to elderly and young patients, dose modification is generally more needed in elderly patients who undergo systemic therapy. In conclusion, even though there is no apparent age threshold in considering treatment choice for HCC, elderly patients are more susceptible to adverse events related to treatments and less invasive therapies are preferable for those patients.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[14:30-15:30, Convention Hall C]

Joint Symposium (IASL3) English

Management of advanced liver diseases

Chairs: **Jin Mo Yang** (The Catholic University of Korea St. Vincent's Hospital, Korea)

Naomi Khaing Than Hlaing (Mandalay General Hospital, Myanmar)

Stem cell therapy for cirrhosis

Soonkoo Baik, M.D., Ph.D.

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Currently, the most effective treatment for end-stage liver fibrosis is liver transplantation; however, transplantation is limited by a shortage of donor organs, surgical complications, immunological rejection and high medical costs. Hence, stem cell transplantation has been suggested as an effective alternate therapy for hepatic disease.

Hematopoietic stem cell, mesenchymal stem cell (MSC), umbilical cord blood cells, fetal liver progenitor cells, adult liver progenitor cells, and mature hepatocytes have been reported to be capable of self-renewal, giving rise to daughter hepatocytes both in vivo and in vitro.

Bone marrow comprises two main populations of stem cells, hematopoietic stem cells and MSC, of which the latter have been considered as alternative cell sources for liver or hepatocyte transplantation because of their high capability for self-renewal and differentiation without ethical or tumorigenic problems.

Indeed, stem cell therapies have shown promising benefits for hepatic fibrosis in experimental and clinical studies. In liver damage, MSC are able to differentiate into hepatocytes, stimulate the regeneration of endogenous parenchymal cells, migrate to damaged sites, and enhance fibrous matrix degradation indicating antifibrotic effect. Furthermore, several clinical studies have demonstrated favorable effects such as MSC improving the liver function and histological grading of fibrosis in patients with cirrhosis.

Recently, multicenter randomized clinical trial conducted in Korea shows clinical efficacy and safety of MSC application, indicating that it has a potential to be a new strategy for chronic liver disease such as cirrhosis. Therefore, further clinical trials are required to validate and support the results for objective confirmation of clinical advantages of MSC therapy.

Keywords: Mesenchymal stem cell, Hepatic regeneration, Cirrhosis

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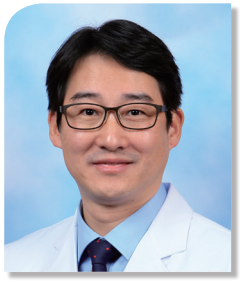

Recent trend of liver transplantation

Dong Jin Joo, M.D., Ph.D.

Department of Surgery-Transplantation, Severance Hospital, Seoul, Korea

Liver transplantation is the best treatment option for end stage liver disease. Traditionally, liver transplantation has been considered as a treatment for patients who have decompensated liver cirrhosis including serious complications. However, the indication of liver transplantation has been widely expanded to many diseases we could not imagine a couple of decades ago. This change can be achieved not only by the development of surgical techniques but also by enormously successful peri-operative management. We are dealing with the current trends of liver transplantation by reviewing the technical and multidisciplinary aspects in this talk.

One of the biggest hurdles of liver transplantation is donor shortage. Regarding the expansion of the donor pool, many efforts have been trying to use marginal liver grafts from deceased donors. Ex vivo machine perfusion system enhances the utilization of marginal liver grafts. Direct antiviral agents can expand the donor pool to make it possible to use HCV positive grafts. Another effort has been doing to utilize liver grafts from circulatory death donors.

Since the number of deceased donor is small in many Asian countries, living donor liver transplantation has been an alternative option to treat liver diseases such as liver cancer and liver failure. Recently, furthermore, to overcome an immunologic barrier of living donor liver transplantation, many centers in Korea have achieved their own desensitization protocol for using ABO blood type incompatible donors, which are going with more simplified than before.

On the recipient side, surgeons who are working in the liver transplant field want to expand the indication of liver transplantation to overcome the advanced liver disease. Down-staging living donor liver transplantation for locally advanced HCC can be one of the trials. Portal vein tumor thrombosis has been conventionally considered as a contraindication of liver transplantation. However, some centers showed good results of living donor liver transplantation for those patients after down-staging with multimodal treatment before transplantation. Other trials are liver transplantation for unresectable colorectal liver metastasis and Klatskin tumor.

In the future, we could encounter a very different situation as many pieces of research are undergoing to develop bioengineered liver or xenograft.

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Emerging therapy of hepatocellular carcinoma

Markus Peck, M.D.

Department of Innere Medizin & Gastroenterologie, Klinikum Klagenfurt Am Wörthersee, Klagenfurt, Austria

Liver cancer (HCC) ist he second most common cause of cancer-related death globally and has seen a dramatic increase over the last 20 years due to an increase in chronic viral hepatitis as well as non-alcoholic fatty liver (NAFLD)-associated HCC.

Fortunately, we also have seen a dramatic improvement in the outcome of management of HCC. This is partly due to the improved efforts in screening of high-risk groups, leading to earlier detection. But is also due to better knowledge on how to best use current treatment options as well as on new treatment modalities, so we can now offer a greater variety of better treatment options for all but the most advanced (BCLC D) patients with HCC.

In the past 3 years we have seen a number of positive phase-III trials for drug treatment of HCC in the second- as well as first-line setting, which have led to increased efforts to study a number of drugs in this indication. Also, great hope has been pinned to the use of immune-oncologic drugs in HCC following encouraging early stage results. Despite the subsequent poor performance of these drugs in single-agent trials, recent data give high hopes that through combination therapy finally we will be able to take a leap forward in better management of this dreadful disease.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[14:00-15:30, Emerald Hall A]

Video Session 03 (KPBA) English

Pancreaticobiliary therapeutic intervention (I)

Chairs: **Myung-Hwan Kim** (Asan Medical Center, Korea)

Jong Ho Moon (Soon Chun Hyang University Bucheon Hospital, Korea)

Hsui-Po Wang (National Taiwan University, College of Medicine, Taiwan)

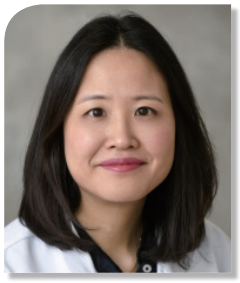
Biliary intervention in patients with surgically altered anatomy - EUS-BD or enteroscopy -

Mitsuhiro Kida, M.D., Ph.D.

Department of Gastroenterology, Kitasato University, Sagamihara, Japan

Recently Therapeutic EUS such as EUS-BD etc. have become popular in the clinical fields and enteroscopic therapy have also been employed in patients with surgically altered anatomy. The indications of EUS-BD are in cases of inaccessible papilla due to duodenal stenosis or surgically altered anatomy etc. and after failed ERCP. If you have a well-trained endosonographer, the technical and clinicall success of EUS-BD is 91% and 87%, similar to that of ERCP or PTBD. Although the adverse events are relatively high, 20-29%. Concerning about EUS-Choldeocho-Duodenostomy (EUS-CDS) and Hepatico-Gastrostomy (EUS-HGS), these patency, clinical success, and adverse events are similar, although stent migration is frequent in EUS-HGS and cholangitis in EUS-CDS, respectively.

On the other hand, short-type balloon enteroscopy (SBE) is employed in cases of surgically altered patients, because SBE allow us to use most of ERCP devices, especially with guide-wire system. However, the success rate of SBE in the group of R-Y choledocho-jejunostomy without gastrectomy is 68% (39/58), relatively low because of not enough length of endoscope. In those patients, most of cases are treated with long-type BE. Compering EUS-BD and SBE treatment, these clinical success rate is about 90% and 60%, however these adverse events are 20% and 4%, respectively. Concerning about bile duct stone removal, the success rate of antegrade removal with EUS-BD are 72% (21/29) in cases with 10 mm BD stones in average size. On the other hand, we can employ electrohydrotic lithtripsy (EHL) under direct SBE even in cases with large stones and treat them in the same day. With EUS-BD, we have to create fistula with long term stenting, then stones will be treated by EHL under baby cholangioscopy. At the moment, we have believed that SBE is the first choice of treatment in patients with surgically altered anatomy, then EUS-BD is the second choice. I would like to share our knowledge and experiences at KDDW.



EUS guided pancreatic cyst drainage and alcohol ablation

Ji Young Bang

Department of Center for Interventional Endoscopy, AdventHealth Orlando, Orland, United States

EUS-guided gallbladder drainage: technical review and future prospects

Takeshi Ogura, M.D., Ph.D.

Department of Internal Medicine, Osaka Medical College, Takatsukishi, Japan

Early surgical treatment using the laparoscopic approach is generally accepted as the treatment of choice for acute cholecystitis (AC) according to Tokyo Guidelines 2018 (TG2018). If the patient is a poor candidate for surgery, such as due to the presence of advanced malignancy or severe organ failure, this treatment may be too invasive. In such cases, gallbladder drainage is considered an alternative treatment method to surgery. Several drainage methods have been established, such as percutaneous transhepatic gallbladder drainage (PTGBD) or endoscopic transpapillary gallbladder drainage (ETGBD) under endoscopic retrograde cholangiopancreatography (ERCP), including naso-gallbladder drainage (ENGBD) and gallbladder stenting (EGBS). PTGBD is a well-established procedure that is relatively easily performed by general clinicians. And ETGBD has been developed as an alternative drainage method. The procedure also calls for guidewire passage across the cystic duct. Therefore, in acute cholecystitis cases who are contraindicated for surgery, PTGBD should be considered before ETGBD, and ETGBD may be considered only in high-volume institutes where expert hands are available, as described in the TG2018. However, there are several limitations to these procedures. Recently, EUS-guided gallbladder drainage (EUS-GBD) is increasingly being performed as an alternative method to PTGBD and ETGBD.

In this lecture, the current status and problems of EUS-GBD are briefly reviewed, including technical review and clinical data of previous papers, current indication, long-term outcome, and comparison data with PTGBD or ETGBD, and their future prospects are discussed.

EUS-guided radiofrequency and fiducial placement for pancreatic cancer

Rungsun Rerknimitr, M.D.

Department of Medicine, Chulalongkorn University, Bangkok, Thailand

Pancreatic adenocarcinoma (PDAC) has been ranked as one of the top ten cancers causing death worldwide.[1] Unfortunately, only 20% of those PDAC patients deemed for resectability and the standard chemotherapy could provide only a 12-month in median survival.[2] Thus, there is a need for additional palliative treatment in those. Radiofrequency ablation (RFA) has been widely used in many solid organ tumors for many years and become the standard palliative treatment in certain malignancies including liver cancer.[3] The initial limitation of RFA as the treatment for PDAC was the accessibility to the PDAC tissue that locates deep inside the abdominal cavity but it recently has been overcome by the advent in a special RFA probe that small enough to insert to the echoenoscope fine needle (14G-19G). The electrical current of RFA system either from the monopolar or bipolar system generates heat at 60-100 Celsius to locally ablate the tumor tissue. The overall reports still came for a small series[4-9] of 1-50 patients that demonstrated acceptable rate of adverse events including acute pancreatitis and abdominal pain. The main objective of RFA in PDAC are to halt tumor progression and pain control. In certain cases, the reduction in tumor volume could be observed.[4-9] Hypothetically the ultimate gold should be an improvement in survival. Currently, the placement of RFA in PDAC is at the stage as an adjunctive therapy while patient still receiving the standard chemotherapy.

Another potential area of therapeutic EUS is the placement of fiducial in PDAC. Since stereotactic body radiation therapy (SBRT) requires the precise target during radiation to reduce the collateral damage to nearby organs. In addition, the respiratory motion could make the precise SBRT becomes more difficult. Thereby, fiducial can help for the better target the radiation beam to the tumor region. Generally fiducial are made of gold in different shapes. At least three fiducials to be placed for PDAC to precisely guide for SBRT target. For PDAC the fiducial could be loaded into 22G-19G needle either as a backload or preload. The preload system is more convenient as it can save a lot of time for placing fiducial.[10] The overall success rate for EUS guided fiducial placement form the recent meta-analysis demonstrated was 98% with the pool adverse event at 4%.[11]

Table 1. EUS-RFA in pancreatic adenocarcinoma (PDAC)

Author	year	Type	N	Feasibility	Adverse event
Arcidiacono et al.	2012	Case series	22	72.80%	Abd pain: 13.6%
Pai et al.	2013	Case series	7	100%	Mild pancreatitis : 15%
Song et al.	2015	Case series	6	100%	Abd pain : 33.3%
Ligresti et al.	2018	Case report	1	100%	none
Crino et al.	2018	Case series	8	100%	Abd pain : 37.5%
Thosani et al.	2018	Case series	10	100%	Abd pain : 2.9%

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KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[14:00-15:30, Emerald Hall B]

Metabolism & Obesity 03 (KSG-KSMBS) Korean

Holistic approach for management of obesity and metabolic syndrome: exercies, diet, life style modification, phamacologic tx

Chairs: **Kyu Rae Lee** (Gachon Univesrity Gil Medical Center, Korea)

Yong Jin Kim (H Plus Yangji Hospital,)Korea

Non-pharmacological approach: life style modification, exercise and diet

Byoungduck Han, M.D.

Department of Family Medicine, Sahmyook Medical Center, Seoul, Korea

Obesity is most common metabolic disorder in the societies, which results from excess fat accumulates in the body. According to epidemiological data, obesity is major cause of medical problems such as heart disease, diabetes, high blood pressure and certain cancers. World Health Organization announced the seriousness of obesity in the near future on their obesity fact sheet in 2017. Major causes of the increasing prevalence of obesity include behavioural and environmental factors, such as sedentary lifestyle, urbanized living habbits, western style high fat diet. finally, obesity is due to imbalance between the excessive energy food intake and less/lack of physical activity.

Although various factors influence obesity treatment through complex mechanisms, the most basic principle of obesity treatment is the control of intake / calorie calories.

Obesity treatment include behavioral therapy, meal therapy, exercise therapy, drug therapy, and surgical therapy. Obesity is a progressive chronic disease that can be defined as a lifestyle disorder. Traditionally, the key treatment for obesity treatment is "lifestyle change". Lifestyle change therapy is important not only for the effects of short-term weight loss but also for long-term weight maintenance. However, the most effective and easy way to treat obesity in the clinic is medication. It is true that various drugs have recently been approved and have a positive effect on the treatment of obesity patients.

Obesity treatment is based on lifestyle correction treatment such as behavioral therapy, meal therapy, and exercise therapy, and medication and surgical treatment are performed according to the degree of obesity.

This lecture discusses exercise therapy, diet therapy, and cognitive behavioral therapy for obesity treatment.

Psychologic issues and intervention

Mirihae Kim, Ph.D.

Department of Psychology, Duksung Woman's University, Seoul, Korea

Obesity results from a highly complex interplay of several factors such as genetic, biological, psychological, social (including familial), and cultural ones. Due to itsmultifactorial trait, evidence-based strategies to treat obesity routinely integrate nutritional, physical, psychological, and if necessary, pharmacological and surgical interventions.
In this presentation, after brief discussion of psychological factors and their influence in the balance of energy intake and expenditure, the psychological interventions will be introduced.

PSYCHOLOGICAL FACTORS FOR OBESITY

How do psychological factors influence eating (and overeating) and physical activities (and exercise)? People eat (and overeat) to improve their feelings when they experience negative psychological states, such as boredom, sadness, anxiety, or stress. In other words, people eat to regulate their mood. People also use exercise to cope with their negative mood such as anger, whereas people with depressed mood may withdraw themselves from any physical activities. Also, according to Restraint theory, if a restrained eater has "forbidden foods" and violates the restraint rules, the 'guilty' feeling and sense of helplessness' may trigger an overeating or binge episode.

The psychological scars of obesity often include negative body image, lowered self-esteem, social withdrawal etc., taking a turn for the worse. Lastly, the effects of weight loss often have been psychologically favorable with improved self-esteem, social functioning and sense of wellness.

PSYCHOLOGICAL INTERVENTION

Psychodynamic therapies and humanistic therapies have been tried to treat obesity with mixed results. Cognitive behavioral therapies (CBT) has been recognized as the best established psychological intervention for obesity, especially in a long-term perspective. Their strategies have been utilized to enhance the effects of diet and exercise. The CBT aims to provide the individual with coping skills to handle various cues to overeat and to prevent relapses in diet and exercise when the mere slips occur. In this presentation, CBT techniques including goal setting, self-monitoring and stimulus control will be introduced.

Pharmacological treatment: an up-to-date

Kyoung-Kon Kim, M.D., Ph.D.

Department of Family Medicine, Gachon University Gil Medical Center, Incheon, Korea

The prevalence of obesity is rapidly increasing in the world. Pharmacotherapy is an option for the management of obesity. In 2019 in Korea, five anti-obesity drugs, orlistat, lorcaserin, naltrexone/bupropion, liraglutide and phentermine/topiramate, are available for long-term treatment of obesity. In this talk, the action mechanisms and the clinical implications of the recently approved anti-obesity drugs will be mainly discussed. Lorcaserin is highly selective serotonin 5HT-2C receptor agonist and stimulates proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons and inhibits neuropeptide Y(NPY)/agouti-related peptide (AgRP) neurons. Lorcaserin is a very safe drug with only mild adverse events, while its effect on appetite suppression is not strong. In obese people, dopamine signalling in striatum, which is a major player in hedonic reward system, is suppressed or distorted. Dopamine reuptake inhibition of bupropion can improve the weakened dopamine signaling in obese people. Mu-opioid receptor(MOP-R) has an important role in hedonic reward system, and MOP-R antagonistic naltrexone can reduce excessive food motivation and food liking. Combination of naltrexone/bupropion can reduce bodyweight in obese people through the handling of hedonic reward system of feeding. The weak point of this drug is its AEs, especially nausea. The hypophagic effect of liraglutide is mediated through the direct activation of POMC/CART neurons and the indirect suppression of NPY/AgRP neurons through γ-aminobutyric acid-dependent signaling. The effect of liraglutide is moderate and the safety is relatively good. The exact action mechanism of phentermine/topiramate is the combination of phentermine's appetite suppression through noradrenaline and dopamine pathway and topiramate's inhibitory effect on NPY/AgRP neuron. Although it is very strong anti-obesity drug, its AEs must be watched carefully. In the aspect of cardiovascular outcome, lorcaserin is safe, liraglutide is beneficial, whereas naltrexone/bupropion is inconclusive and phentermine/topiramate is unknown until now.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[14:00-15:30, Diamond Hall]

Multidisciplinary Session 05 (KSGC-KSCP) Korean

Controversial issues for management of advanced rectal cancer

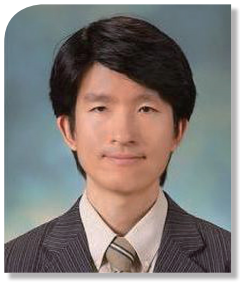
Chairs: **Jonghoon Lee** (Dong-A University Hospital, Korea)

Jun Won Um (Korea University Ansan Hospital, Korea)

Preoperative stenting for left-sided obstructive disease: Should it be reserved for high risk group alone?

Jae Jun Park

Department of Internal Medicine-GI/Hepatology, Severance Hospital, Seoul, Korea



Optimal use of rectal radiation therapy for potentially resectable metastatic disease

Jiho Nam, M.D.

Department of Therapeutic Radiology and Oncology, Pusan National University Hospital, Busan, Korea

Most rectal cancer patients presented with distant metastatic disease cannot be cured with the standard treatment regimen. However, one-third of those stage IV patients have potentially resectable disease.

When the metastatic disease is resectable, the role of radiation therapy has been controversial. Currently, several options are available for the multidisciplinary approach. Radiation therapy schedules are similar to the protocols used in adjuvant treatment. To minimize the possible delay of chemotherapy use, short-course radiation may be a better choice than the standard longer-course radiation therapy. Short-course radiation therapy can be combined with surgery for the resection of both the primary and metastatic disease. Or induction chemotherapy may be used first then followed by short-course radiation therapy, and other curative treatment options may be sequentially integrated. However, longer-course radiation therapy can be used instead. There is no general consensus available for the optimal radiation therapy schedule for the metastatic disease. Current precision radiotherapy techniques can effectively minimize the radiation-related toxicities, additional radiation treatment after surgical resection is also feasible when it might be necessary.

The optimal use of radiation therapy in rectal cancer patients with metastatic disease is still unknown. In the meantime, currently available short- or long-course radiation therapy may be suitable for combining with the various chemotherapy regimen.

Timing of curative surgery for metastatic disease: When should we consult to surgeon?

Jin Yong Shin, M.D., Ph.D.

Department of Surgery, Inje University Haeundae Paik Hospital, Busan, Korea

Approximately 50-60% of patients with colorectal cancer are diagnosed with synchronous or metachronous metastatic colorectal cancer (mCRC), and liver and lung are most common metastatic sites of mCRC. Although the incidence of resectable hepatic or pulmonary metastatic lesions in patients with mCRC was reported in less than 30%. The metastasectomy rate has been increasing based on studies reporting good oncological results after metastasectomy. For patients with potentially resectable liver or lung metastases, clinical variables to be considered before metastasectomy include the definition of resectable metastatic lesions, the use of perioperative chemotherapy before and after metastasectomy, whether the simultaneous resection of metastatic and primary lesion in cases of synchronous metastases, the presence of disappearance of metastatic lesion on radiologic study during chemotherapy, and the degree of hepatotoxicity following chemotherapy and its effect on surgery. This lecture aimed to help to select the optimal treatment strategy through literature review in above-mentioned clinical situation in potentially resectable liver or lung metastases.

Recent advance of preoperative/postoperative systemic therapy

Suk Young Lee, M.D., Ph.D.

Department of Internal Medicine, Wonkwang University Sanbon Hospital, Gunpo, Korea

Traditionally, decision for optimal treatment of patients with locally advanced rectal cancer has been a complicated process. Different from colon cancer, consideration for functional result of treatment such as anal continence and preservation of genitourinary functions, should be included in addition to curability of disease in order to maintain quality of life.

Usually, locally advanced (stage II/III) rectal cancer includes locoregional and systemic therapy as perioperative treatment. Despite the established role of the combined-modality therapy consisting of radiotherapy, fluoropyrimidine-based chemotherapy (or concurrent chemoradiotherapy) and surgery, several issues have been suggested for toxicity of radiotherapy and systemic chemotherapy. Although several sequences of treatment modialities by re-positioning have been suggested to maximize the treatment effect of perioperative therapy and reduce toxicities at the same time, definitive order of those combined modalities has been remained controversial.

In addition, recent advance of biologic agents including bevacizumab, cetuximab, and panitumumab, has also brought introduction of those agents into perioperative therapy. Another intensifying therapy which adds oxaliplatin in fluoropyrimidine based chemoradiotherapy has also been studied in several trials to address the role of oxaliplatin in improving outcomes achieved with the existing concurrent chemoradiotherapy. Recent advance in perioperative therapy and controversial areas in treatment of locally advanced rectal cancer will be reviewed in this section.

1. THE ROLE OF CONCURRENT CHEMORADIOTHERAPY AS THE PERIOPERATIVE THERAPY

The role of perioperative fluoropyrimidine based chemoradiotherapy in locally advanced rectal cancer has been established in reducing local recurrence [1-4].

2. INTENSIFYING THERAPY-ADDITION OF OXALIPLATIN AND INTRODUCTION OF BIOLOGIC AGENTS

Addition of oxaliplatin has been addressed in several randomized phase III studies (STAR-01, ACCORD, German CAO/ARO/AIO-04, R-04, FOWARC). Addition of oxaliplatin to neoadjuvant fluoropyrimidine based chemoradiotherapy showed comparable results in terms of pathologic response while increased adverse events were observed. Based on results of those studies, the addition of oxaliplatin to neoadjuvant chemoratiotherapy has not been recommended [5-11].

The addition of cetuximab in fluoropyrimidine based perioperative chemotherapy with radiation failed to meet primary endpoint, complete response rate [12]. In phase II SAKK 41/07 trial, the addition of panitumumab to preoperative chemoRT showed near-complete plus complete response in 53% of patients in the panitumumab arm versus 32% in the control arm [13]. Another phase II study (RaP Study/STAR-03) evaluating the role of panitumumab in neoadjuvant chemoRT failed to meet the pre-specified level of complete response [14]. Bevacizumab was also evaluated on its effectiveness in perioperative therapy, but primary endpoint of pathologic complete response was not met [15]. Base on these studies, the addition of biologic agents is not recommended in the perioperative therapy.

3. RE-POSITIONING OF PERIOPERATIVE SYSTEMIC CHEMOTHERAPY

Total neoadjuvant therapy (TNT; starting with chemotherapy, then either chemoRT or short-course radiotherapy, and transabdominal resection), neoadjuvant chemotherapy without radiotherapy, watch and wait strategy, and the role of adjuvant chemotherapy will be reviewed.

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KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

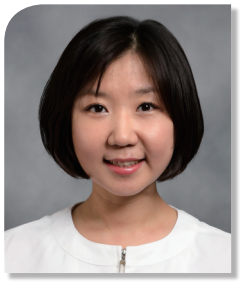
[14:00-15:30, Skylark]

Nursing Session 03 (KSGC) Korean

Advanced nursing in GI cancer

Chairs: **Chan-Guk Park** (Chosun University Hospital, Korea)

Jun Kyu Lee (Dongguk University Ilsan Hospital, Korea)



Oncology emergencies in GI cancer

Chung Eun Lee

Department of Nurse, Severance Hospital, Seoul, Korea

Oncologic emergencies represent either presenting as the initial manifestation before cancer diagnosis or the progression of malignancy disease.(Khan, Shanholtz, & McCurdy, 2017). Most oncologic emergencies can be sorted as metabolic, hematologic structural, and anticancer treatment related(Higdon, Atkinson, & Lawrence, 2018). Structural oncologic emergencies are caused by direct compression of metastatic disease; such as increased intracranial pressure, spinal cord compression, superior vena cava syndrome, and cardiac tamoponade and so on. Metabolic oncologic emergencies, such as disseminated intravascular coagulation, syndrome of inappropriate antiduretic hormone, tumor lysis syndrome, hypersensitivity and anaphylaxis are common problems in advanced cancer patients(Itano, Brant, Conde, & Saria, 2015). These emergencies have a wide range from mild to life threatening, and oncologic emergent situation is required for immediate assessment to prevent permanent injury(Held-Warmkessel, 2005). The knowledge and early identification of the oncologic emergencies enable for oncology nurses to have optimal response and therapeutic management.

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Pain and nursing of GI cancer patients on chemotherapy

Boyoung Byun

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I. INTRODUCTION

One of the most common and agonizing symptoms that cancer patients suffer is a pain. 30% to 50% of early-stage cancer patients or those on anticancer treatment have pain. The pain prevalence ranges from 60% to 70% in patients with progressive cancer, and 80% to 90% of terminal cancer patients experience severe pain. 60% to 70% of cancer patients have inadequate pain management. Pain is even more excruciating than the terror of death to cancer patients, causing activities, sleep, or attention problems, aggravating depression and anxiety, and thereby undermining cancer patients' quality of life.

II. PAIN MANAGEMENT APPROACHES

1. Principles in Pharmacological Treatment

In 1986, the World Health Organization developed a three-step ladder for cancer pain relief. Pharmacologic treatment manages pain in 90% of cancer patients and 75% of terminal cancer patients. Drugs should be given for oral administration, if possible, by the clock, based on the sequential three-step ladder. Drug selection should be made for each individual, and administration should be done with attention to details. Opioids must be administered by non-invasive routes (including patch), and the oral route is usually preferred. It is not desirable to administer modified-release opioids only on first-time users. MR should be used after dose titration using IR. Giving analgesics at appropriate regular intervals maintains steady-state plasma concentrations and thereby prevents recurrence of cancer pain. Prescription of IR analgesics in advance is recommended to respond to sudden pain occurring to patients with pain well under control previously.

2. Non-opioid Analgesics

Non-opioids are used in step 1 of cancer pain. They can be used as adjuvants throughout all steps. The analgesic effects are no different among a wide range of non-opioid analgesics. They are different only in terms of side effects. Therefore, the selection of medication should be based on the conditions of each patient.

3. Opioid Analgesics

Opioid compounds can be divided into mild opioids and strong opioids based on their potency and into agonists, partial agonists, and agonist/antagonists based on their interactions with various receptor subtypes.

Codein and tramadol are classified as mild opioids and morphine, oxycodone, hydromorphone, hydrocodone, and fentanyl are available options for strong opioids. Oral morphine is prescribed as first-line treatments. The oral route should be considered as the preferred route of administration of opioids as well as non-opioids. Prescription of all opioids should take account of ER and IR formulations. IR formulations are used for dose titration and sudden pain control, and ER formulations are for a maintenance dose.

The use of opioid analgesics can cause a wide array of side effects to patients. The failure to respond to these side effects reduces the effects of treatment. Constipation and sedation are the two most common adverse effects, followed by nausea, vomiting, respiratory depression, dry mouth, incomplete evacuation, pruritus, myoclonus, cognitive impairment, dysesthesia, euphoria, sleep disruption, sexual functioning, physical dependence, tolerance, and inappropriate ADH syndrome.

4. Adjuvant Analgesics for Cancer Pain

Adjuvants are used to boost the analgesic effect of opioids, control specific types of pain, alleviate symptoms associated with pain, or treat side effects of opioids. They can be used in any step of the WHO analgesic ladder, and include steroids, anticonvulsants(gabapentin), antidepressants (amitriptyline), sleep-aid medication (benzodiazepine), and antihistamines.

IV. INTERVENTION THERAPIES FOR CANCER PAIN

Intervention therapies to treat cancer pain include neurolytic nerve block therapy, spinal injection, and PVP(percutaneous vertebral plasty).

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Patient safety and nursing of GI cancer patient on chemotherapy

Geunsook Lee

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Social and emotional health and nursing of GI cancer patients on chemotherapy

Eunju Park

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Cancer patients need enough time from treatment to adjustment on daily life.

So Cancer patients need close attention, care and help.

In August 2017, the Joongang Daily reported that 2.9% of the population is diagnosed with cancer.

Also it reported that the prevalence of mental illness in cancer patients was higher than in general patients.

According to the Korean Society of Psycho-Oncology, the patient's therapeutic situation and the difficulty of mental health have negative consequences for the therapeutic process and prognosis and, in some cases, risk developing mental health disorders and lowering the quality of life

According to the results of a survey conducted by the Seoul National University Cancer Center, on the question of "What part need to be most helpful in during cancer treatment?"

The result following the physical problem was need for help on the mental well-being.

In summary, it is necessary to understand not only on physical aspects but also on psychological aspects in nursing of cancer patients.

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KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[16:00-17:30, Convention Hall A]

Symposium 12 (KPBA1) English

Treating acute pancreatitis; what's next?

Chairs: **Yong-Tae Kim** (Seoul National University Hospital, Korea)

Young Deok Cho (Soon Chun Hyang University Seoul Hospital, Korea)

Etiology and diagnosis, severity classification

Jun Kyu Lee, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Dongguk University Ilsan Hospital, Goyang, Korea

Acute pancreatitis is an increasingly common clinical condition with substantial morbidity and mortality.Gallstones and alcohol are the main etiologies of acute pancreatitis. Among less prevalent causes, there are drugs, hypertriglyceridemia and iatrogenic causes including endosopic retrograde cholangiopancreatography (ERCP) and periampullary surgery. Autoimmune cause, trauma, infection, genetic alterations, and obstruction in cases of celiac disease, Crohn's disease, pancreas divisum and sphincter of Oddi dysfunction are rare etiologies. The 2012 revised Atlanta classification system updated the terms and definitions of diagnosis, type, complications and severity. Especially, the local complications were re-categorized into acute peripancreatic fluid collection (APFC), pancreatic pseudocyst, acute necrotic collection (ANC) and walled-off necrosis (WON). This new categorization turned out to be helpful in providing more effective communications between the members of a multidisciplinary team and standardized treatment planning. However, there still is room for improvement, e.g. inter-observer variation in the computed tomographic diagnosis of extrapancreatic necrosis and recognition of non-homogeneous collections or low sensitivity for diagnosis of severe acute pancreatitis.

Optimal medical management

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Acute pancreatitis (AP) is one of critical medical admissions that could lead to sequel and protracted course as 20% of the cases progress to severe AP. The cascade of AP starts with the production of pro-inflammatory mediators and subsequently follows by vasodilation, vascular leakage, and volume depletion. The process can repeat itself as a vicious cycle without specific treatment to halt it. This process is the main mechanism for the early phase of AP that could last for a week. The main manifestations are shock, adult respiratory distress syndrome, systemic inflammatory response (SIRS), compartment syndrome and acute kidney injury. There many proposed parameters to predict the severity and course of AP, however one of the easiest tests is the degree of hemoconcentration by checking the hematocrit level. The level of hematocrit that higher than 44% was reported to an important predictor of pancreatic necrosis and organs failure[1] and one study reported on the benefit of hematocrit level for predicting AP related mortality[2]. Apart from general medical care, the only proven benefit in treating AP patient is fluid resuscitation with the idea to maintain adequate volume and prevention of further tissue necrosis especially pancreatic necrosis.

The early aggressive fluid administration during the first 24 hours is strongly recommended by giving what considered as one third of calculated volume for replacement. It has been shown that the incidences of SIRS, organ failure, and ICU admission were significantly lower in those AP patients who received early aggressive fluid replacement than those who had the replacement later[3]. Practically the bolus of fluid 1-2 liters can be given and continue with the rate of 200-300 ml/hour per hour during the first 6 hours of admission. The urine out put at least 0.5 ml/hour, dropping in hemoconcentration and BUN are the good predictive signs of adequate fluid replacement. Regard to the choice of fluid, crystalloid agent is more preferred according to the recommendation by the American Gastroenterological Association[4]. A more pH-balanced solution such as Ringer Lactate Solution (LRS) might cool down the systemic inï¬ammation compared with the resuscitation with normal saline. Wu B, et al, has demonstrated the lower rate of SIRS in those who received LRS than those who received normal saline (5% vs. 30%)[5]. One of the culprit in fluid resuscitation is overreplacement that could lead to acute pulmonary edema and perhaps prolonged hospital stay[6]. Regard to prophylactic antibiotics, although, all guidelines do not advocate on this use as this may increases the rate of fungal infection and the practical use is more for those with extra-pancreatic infections, the recent survey still demonstrated that the use of antibiotics for pancreatic indication is among the top three in patients with AP[7].

Lastly, abdominal compartment syndrome (ACS) is a subject to concern when there is a sign of organ failure where the intra-abdominal pressure raises to more than 20 mmHg. Thereby it is important to balance between the volume of fluid resuscitation and the incremental of abdominal girth[8]. In those who are at risk to develop ACS, gastric and rectal decompression are the necessity.

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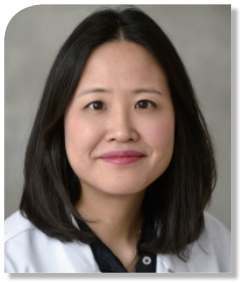

Optimal endoscopic management

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Pancreatic fluid collections can arise as a sequela of acute pancreatitis and can be classified into pancreatic pseudocysts and necrotic collections. Recognition of the different types of pancreatic fluid collections is important for correct management. For instance, EUS-guided drainage is the treatment of choice for pancreatic pseudocysts with resultant high treatment success. However, endoscopic management of walled-off necrosis (WON) is more complex, and the management strategy is dependent on the size and location of the necrotic collection.

Endoscopic therapy is the current treatment of choice in the management of WON. Open surgical necrosectomy has been associated with mortality rate of 15-20% and morbidity rates of 40-55%. In three randomized trials comparing endoscopy and surgery for the management of WON, endoscopy was associated with superior outcomes that included shorter hospital stay, lower costs and lower rates of major complications, especially the formation of pancreaticocutaneous fistulae. In the management of WON, an algorithmic treatment strategy is advised to optimize treatment success, comprising the use of multi-gate technique, endoscopic necrosectomy and dual modality techniques depending on the WON size and location. Another important strategy in the management of pancreatic fluid collections is the diagnosis of disconnected pancreatic duct syndrome (DPDS), as it is associated with persistent WON, pancreatic fistula and pancreaticocutaneous fistula formation. DPDS is also associated with WON recurrence, and therefore if present, placement of plastic stents into the cystogastrostomy tract is recommended to minimize recurrence.

Surveillance

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Acute pancreatitis is closely related to pancreatic cancer, but the mechanism of this association is not fully understood. Generally, acute pancreatitis could be better known as initial clinical manifestation of pancreatic cancer,[1] but on account of some aspects of the clinical treatment, a synchronous malignancy might be underestimated. In another aspect, acute pancreatitis may be a risk factor for pancreatic cancer; however, findings from several studies on this association are also conflicting. Thus, there have always been discussions regarding the magnitude of the risk and the role of surveillance in its early detection.

Acute pancreatitis is a sudden-onset inflammatorydisease of the pancreas. Although experimental research suggests that acute pancreatitis can induce pancreatic cancer,[2] findings from epidemiological studies are conflicting.[3,4] A case-control study of approximately 2500 patients with pancreatic cancer within the US Veterans Affairs population,[5] and a British matched cohort study of approximately 6000 patients with acute pancreatitis, both observed a positive association between acute pancreatitisexcluded pancreatic cancer cases occurring in the first year following acute pancreatitis, which may not allow sufficient time to eliminate reverse causation or surveillance bias. Another US-based case-control study including approximately 300 patients with pancreatic cancer also found a positive association between acute pancreatitis and pancreatic cancer,[6] but did not include any lag period from acute pancreatitis to pancreatic cancer. Furthermore, all 3 studies failed to report estimates of the association at different follow-up times. In contrast, a Swedish cohort study of approximately 25,000 patients with acute pancreatitis reported no association with pancreatic cancer after more than 10 years of follow-up.[3] In the recent epidemiologic study,[7] patients hospitalized with incident acute pancreatitis had an increased risk of pancreatic cancer compared with the general population. Although the risk was highest in the first 2 years following acute pancreatitis diagnosis, it remained elevated throughout the follow-up period. After both 5 and 10 years of follow-up, pancreatic cancer risk in patients with acute pancreatitis was still double that of their matched comparison subjects.

In conclusion, the relatively high incidence of pancreatic cancer diagnoses within 2 years after acute pancreatitis would suggest a need to consider the use of further diagnostic imaging to look for underlying pancreatic cancer after acute pancreatitis in patients more than 40 years of age. Therefore, patients with acute pancreatitis after 40 years of age have an increased risk of pancreatic cancer diagnosis within the following 24 months. This would argue for a potential use of further diagnostic imaging with EUS to diagnose underlying pancreatic cancer.

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KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[16:00-17:30, Convention Hall C]

Joint Symposium (IASL4) English

Global trend of SOC based on Guideline

Chairs: **Henry LY Chan** (The Chinese University of Hong Kong, Hong Kong)

Kwan Sik Lee (Gangnam Severance Hospital, Korea)

Seung Kew Yoon (The Catholic University of Korea, Seoul St. Mary Hospital, Korea)

Hepatitis B

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The Asian-Pacific Association for the Study of the Liver (APASL), the European Association for the Study of the Liver (EASL), and the American Association for the Study of Liver Diseases (AASLD) presented and continued to revise their clinical practice guidelines, and the latest updates were in 2015, 2017, and 2018. However, since the medical environment in each country is somewhat different depending on race, region, institution, and economic conditions, it is necessary to establish and update clinical practice guidelines to reflect own medical environment and research results. In Korea, clinical practice guidelines for the management of chronic hepatitis B (CHB) were published 15 years ago and updated 4 times, by the Korean Association for the Study of the Liver (KASL).

In the latest KASL clinical practice guidelines which were revised in 2018, recent information on newly available antiviral agents has been added, and the goals and the aims of treatment as well as starting and cessation of treatment have been clearly defined. The present guidelines also summarize updates for management of drug resistance, partial virological response, and side effects. In addition, additional data on the topics of epidemiology, prevention, natural history, diagnosis, monitoring, and management of CHB in specific situations are reflected in this update. Expert opinions were solicited in cases of insufficient data to make definitive conclusions. However, as the guidelines do not represent a standard treatment protocol, clinicians should keep in mind that the best management may vary depending on the individual patient.

Hepatitis C

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Hepatitis C virus (HCV) infection is one of the leading causes of chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC). Due to the asymptomatic nature of the infection, many acute cases of HCV infection are left undiagnosed, so screening individuals at risk is an important public health priority. However, HCV eradication, at least in compensated patients, can help improve the outcome of those with chronic liver disease. In the past few years, anti-HCV therapy has evolved rapidly from pegylated interferon plus ribavirin to interferon (IFN)-based strategies combining direct acting antivirals (DAAs) and finally IFN-free combinations of DAAs. New medications offer sustained virologic response rates of over 95%, fewer adverse reactions, and shorter durations of therapy. This lecture reviews the new treatment guidelines for the management of patients with HCV infection.

NAFLD and NASH

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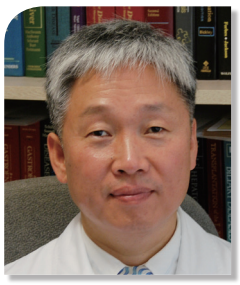
Guidelines on NAFLD has been issued by AASLD, EASL-EASD-EASO and Asia-Pacific Working Party on the Management of NAFLD. NAFLD is closely associated with metabolic syndrome especially diabetes mellitus. Screening of NAFLD in high risk group is still controversial, but probably should be considered in high risk patients. Both prediction scores and elastography can be used to assess the severity of NAFLD. Lifestyle medication remains the mainstay of treatment for NAFLD. Vitamin E and pioglitazone can be considered in selected patients. There is some preliminary data suggesting GLP-1 agonist can improve NASH.



Alcoholic liver disease

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Alcoholic liver disease (ALD) represents a spectrum of liver injury resulting from alcohol use, ranging from hepatic steatosis to more advanced forms including alcoholic hepatitis (AH), alcoholic cirrhosis, and acute alcoholic hepatitis presenting as acute-on-chronic liver failure (ACLF). Since ALD carries a significant stigma in society, it is increasingly recognized by providers that patients and their families seek to reduce the stigma of ALD, and a change from the term "alcoholic" to "alcohol-related" will help; thus, alcohol-related liver disease, alcohol-related steatohepatitis, and alcohol-related cirrhosis are suggested. AH *per se* is a clinical syndrome with a distinct histopathological correlate, called alcohol-related steatohepatitis (ASH). Due to longstanding usage, the term alcoholic hepatitis (AH) and ALD will likely persist.

Worldwide, alcoholic cirrhosis deaths account for ~10% of all alcohol-attributable deaths and nearly half of deaths due to liver disease, resulting in the loss of 22.2 million disability-adjusted life years (DALYs) annually. The relative contribution of ALD to all cirrhosis mortality is predicted to increase as the proportion of deaths due to HBV and HCV cirrhosis declines.

Since publication of the Diagnostic and Statistical Manual (5th Edition), the former categories of alcohol abuse and dependence have been replaced by the term alcohol use disorder (AUD), characterized as mild, moderate, or severe based on the accumulation of negative consequences and symptoms (Table 1).

The public health approach to the problem of alcohol use is termed screening, brief intervention, and referral to treatment (SBIRT). Discussion of alcohol use can be off-putting for patients, who may feel stigmatized or judged. As such, a non-judgmental, open, and accepting interview style can help maintain therapeutic alliance, and limit under-reporting and denial of AUD.

Biomarkers of alcohol use refer to moieties in urine, blood, or hair which identify metabolites or surrogates of alcohol use, and provide an estimated timeframe of recent drinking. A small (~0.1%) amount of alcohol is metabolized by UDP-glucuronosyltransferase and -sulfotransferase, producing ethyl glucuronide (EtG) and ethyl sulfate (EtS). Both are excreted in the urine, but are also found in blood and hair. Phosphatidylethanol (PEth) is a phospholipid formed by the reaction of phosphatidylcholine with ethanol catalyzed by phospholipase D in the erythrocyte cell membrane. PEth has a half-life of approximately 10-14 days and does not appear to be influenced by age, body mass index (BMI), sex, kidney or liver disease.

Since abstinence is the single most important factor in improving survival from ALD, multidisciplinary management with addiction specialists and referral to treatment for AUD, particularly in patients with moderate to severe AUDs or clinically evident ALD, is mandatory. There are three FDA-approved medications: disulfiram, naltrexone, and acamprosate. Disulfiram and naltrexone undergo hepatic metabolism and can cause liver damage, while acamprosate has no hepatic

Table 1. Definitions of moderate drinking, heavy drinking, binge drinking, at-risk drinking, hazardous drinking, and harmful drinking

Definition of moderate drinking, heavy drinking, binge drinking, at-risk drinking (National Institute on Alcohol Abuse and Alcoholism [NIAAA]) 1 standard drinking = 14 g	
Moderate drinking	Male, <65 years: ≤14 standard drinks/week Male, ≥65 years or female: ≤7 standard drinks/week
Heavy drinking	Male, <65 years: >14 standard drinks/week Male, ≥65 years or female: >7 standard drinks/week
Binge drinking	Male, <65 years: ≥5 standard drinks within 2 hours Male, ≥65 years or female: ≥4 standard drinks within 2 hours
At-risk drinking	Heavy drinking or binge drinking
Definition of hazardous drinking, harmful drinking (World Health Organization [WHO])	
Hazardous drinking	A level of consumption or pattern of drinking that is likely to result in harm should present drinking habits persist (a working definition of WHO describe it as a regular average consumption of 20-40 g/day for women, 40-60 g/day for men)
Harmful drinking	A pattern of drinking that causes damage to health, either physical or mental. (A working definition of WHO describe it as a regular average consumption of >40 g/day for women, >60 g/day for men)

Cited from Clin Mol Hepatol 2013;19:216-254.

metabolism. Of note, none of these medications have been studied in patients with AH and alcoholic cirrhosis.

The pathophysiology of ALD is complex. Heavy use results in accumulation of fat through effects on redox state of the liver and on a number of transcription factors which regulate pathways involved in fatty acid synthesis (increased) and oxidation (decreased). Changes in gut permeability lead to increased portal vein endotoxin, activation of the innate immune response, and liver cell inflammation, injury, apoptosis and necrosis, and fibrosis via cytokine and oxidative stress cascades. These cascades involve interactions between the resident macrophages (Kupffer cells), myofibroblasts, endothelial cells, and hepatocytes.

There is no unique presentation of ALD which can be distinguished with confidence from other forms of liver disease. Alcohol use is often not disclosed by the affected patient, while liver injury, whether due to alcohol or other causes, often proceeds silently. Although not all patients with ALD meet criteria for AUD, failure to recognize AUD remains a significant clinical problem. Providers need to have a high index of suspicion for AUD.

Several validated, lab-based scoring systems can be used to assess the severity and short-term prognosis of AH (Table 2). The Maddrey Discriminant Function (MDF) was derived from the results of an early clinical trial comparing corticosteroids to placebo and later modified to identify AH patients with high risk of short-term mortality (30-50% at 28-days) when MDF ≥32. While the MDF is predictive at 1 month, it is less accurate in the intermediate and long-term.

The Lille score differs as a dynamic score by incorporating the change in bilirubin at 7 days after starting corticosteroids to assess early treatment response and the utility of its continuation for 28-days. Nonresponse defined by the Lille score >0.45 predicts poor prognosis, supports cessation of corticosteroids and consideration of clinical trial enrollment or early LT.

Combining static and dynamic models to enhance prediction in AH, Louvet et al. demonstrated that the joint-effect model of MELD plus Lille outperformed other combinations such that for a patient with MELD 21 and Lille 0.45 had a 1.9-fold higher risk of death at 2 months than one with MELD 21 and Lille 0.16 (23.7% vs 12.5%). This strategy of combining models improves prediction by incorporating the early change of disease after an intervention and may aid patient care and the design of future clinical trials.

All patients with ALD should be advised to abstain completely from alcohol use, although harm reduction models, which favor alcohol reduction over total abstinence based on a patient's stated goals, may be appropriate in some contexts. Nutritional therapy has been studied for decades, as patients with AH are typically very malnourished.

Corticosteroids are the most extensively studied intervention in AH. The largest randomized controlled trial in severe AH is the Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial, a multicenter, double-blind, 2-by-2 factorial, randomized trial, that enrolled 1103 patients with clinically-diagnosed severe AH in the UK over 3 years. The study did not demonstrate a statistically significant survival benefit at 28-days in patients receiving corticosteroids compared to placebo (odds ratio [OR] 0.72; 95% CI 0.52–1.01, p=0.06), whereas, on a *post hoc* multivariable analysis, corticosteroids were associated

Table 2. Prognostic models in patients with alcoholic hepatitis

Scoring system	Formula				Test characteristics
Pre-treatment model					
mDF	$4.6\times(PT_{patient}-PT_{control})$(secs)+serum total bilirubin (mg/dL)				Modified DF ≥32 with hepatic encephalopathy predicts >50% mortality within 28 days.
MELD*	$9.57\times\log_e$ [Cr (mg/dL)]+$3.78\times\log_e$ [bilirubin (mg/dL)]+$11.20\times\log_e$ (INR)+6.43				MELD >21 predicts 20% mortality in 90 days.
GAHS	Score	1	2	3	GAHS ≥9 predicts >50% mortality in 28 to 84 days (for score calculated on hospital day 1or day 7).
	Age	<50	≥50		
	WCC (10^9/L)	<15	≥15	–	
	Urea (mmol/L)	<5	≥5	–	
	PT ratio	<1.5	1.5–2.0	>2.0	
	Bilirubin (mol/L)	<125	125–250	>250	
ABIC	(age, years×0.1)+(serum bilirubin, mg/dL×0.08) +(serum Cr, mg/dL×0.3)+(INR×0.8)				ABIC score allows the stratification of risk of death in patients with AH at 90 days and 1 yr.
On-treatment model					
Lille model†	R=3.19–0.101×age (years)+0.147×albumin on day 0 (g/L)+0.0165×evolution in bilirubin level (mol/L) –0.206×renal insufficiency–0.0065×bilirubin on day 0 (mol /L)–0.0096×PT (seconds) Lille score = Exp (-R)/[1+Exp(-R)] Note) Renal insufficiency was rated 0 if absent and 1 if present (below or above 1.3 mg/dL). Evolution in bilirubin level was bilirubin level on day 0 minus that on day 7.				Lille score ≥0.45 predicts 75% mortality within 6 months in patients with corticosteroid therapy

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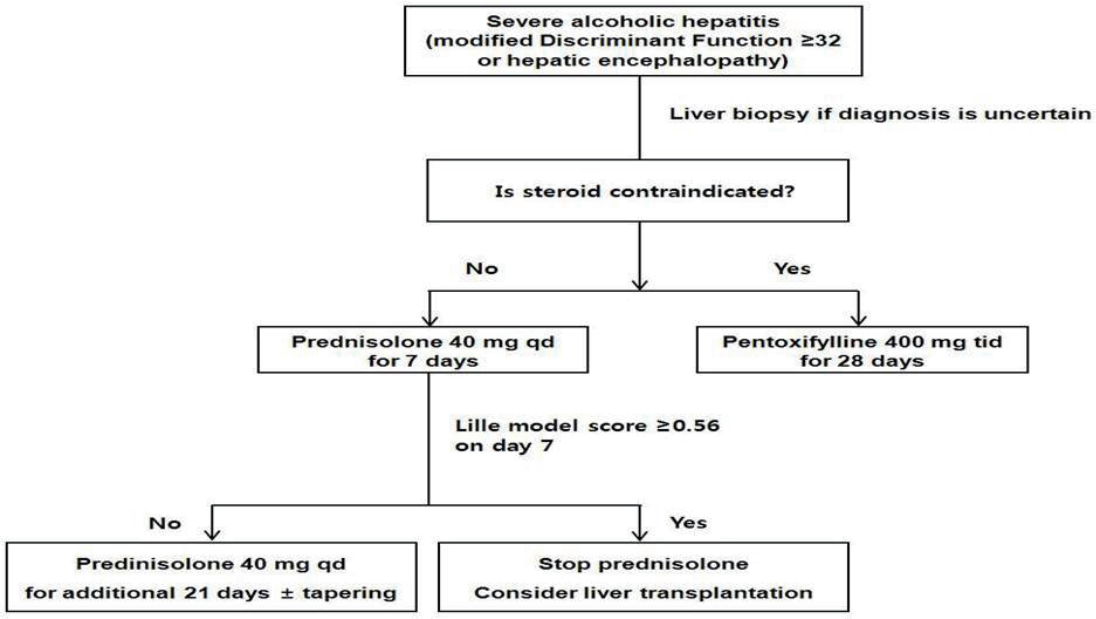

Figure 1. Treatment algorithm for severe alcoholic hepatitis.

with improved 28-day survival (OR 0.609; p=0.015), but not at 90-days (OR 1.02) or one-year (OR 1.01).

ALD is now a leading indication for patients undergoing LT in the US, surpassing HCV infection. Up until recently, LT centers required ALD patients to be abstinent from alcohol for a minimum of 6 months prior to listing for LT, often called the 6-month "rule". In a 1997 consensus conference of the AASLD and American Society of Transplantation, the 6-month "rule" was justified on the grounds that it allowed time to assess liver recovery that in turn might obviate the need for LT. Patients with severe AH not responding to medical therapy have a grim prognosis, with mortality rates as high as 70% at 6 months. A seminal prospective, multicenter study in France and Belgium demonstrated that LT performed "early", prior to six months of abstinence, was life-saving in patients with life-threatening liver failure due to AH (Figure 1). These findings of "early" LT for severe AH have confirmed from the US.

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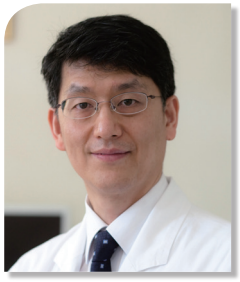

Autoimmune liver disease

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Autoimmune liver disease is comprised of several rare disease entities: autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and immunoglobulin (Ig) G4 associated cholangitis. The epidemiology of global data indicates that the annual incidence of autoimmune liver disease is around 1-2 per 100,000 population.1 Compared to other more common liver diseases, the guidelines for autoimmune diseases show several characteristics. (1) Due to the rarity and chronicity of the disease entity, correct diagnosis is the key component of most guidelines.2 Autoimmune liver diseases are great mimickers, and typically diagnosed after exclusion of other more common disease, usually by histologic confirmation. (2) Being no complete cure except for transplantation, the main therapeutic goal is optimal control of disease activity and prevention of disease progression. (3) Randomized controlled trials are uncommon which establish therapeutic gold standards, and frequently meta-analyses have been performed.3-5 Naturally, current guidelines are usually based on suboptimal ground. (4) Expert opinions play significant role in the generation of therapeutic guidelines. (5) The contribution and interaction of genetic makeup, therapeutic efficacy may show variability in different areas of the world. (6) Disease entity itself may be evolving with the advance of new pathogenesis and biological behavior.6 In this regard, the current guidelines define our limitation of knowledge and therapeutic options, which also defines the starting point of the noble diagnostic and therapeutic development in the forthcoming future.

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Hepatocellular carcinoma

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The global incidence of hepatocellular carcinoma (HCC) has been reported as more than 840,000 in 2018. Moreover, the number of death worldwide has been reported as more than 780,000 in 2018. The incidence and death number rank 7th among all cancer in global. (GBLOBCAN 2018) Therefore, HCC is one of most common cancer and most common cause of cancer-related death worldwide and Korea.

Therapeutic strategy for HCC generally depends on residual liver function and the state of cancer progression. In relatively early stage, curative therapy such as resection, ablation and liver transplantation could be applied according to residual liver function. Transarterial chemoembolization (TACE) is recommended for patients with intermediately progressed tumor and relatively preserved liver function. Advanced HCC and patients who progress after these treatments and cannot receive these treatments anymore could receive systemic therapy.

Although above mentioned treatment strategy generally has been in consensus, each worldwide practice guidelines have recommended somewhat different strategy in specific stage and residual liver function. Moreover, in practice, there were considerable discrepancy of treatment strategy between Western and Eastern and also each countries. Surgical treatment is being recommended only for patients without vascular invasion in Western guidelines, but Eastern guidelines is being recommended for patients with more broader conditions including limited vascular invasion. Transarterial chemoembolization, which is applied to HCC patients most commonly,is being recommended only for patients with Child-Pugh A and some B6, in Western guidelines, but Eastern guidelines is being recommended for patients with more broader conditions of Child-Pugh class.

Recently, much progress have been accomplished in treatment method for HCC patients. In transarterial therapy, TACE with drug eluting bead and transarterial radioembolization have been developed and were increasingly being used for HCC patients. In local ablation, micro-wave ablation and cryoablation so on have been developing.

The biggest development above all was in systemic chemotherapy. Until 2017, there was only available proven therapeutic agents in advanced HCC, sorafenib. However, recently, lenvatinib achieved a non-inferiority for 1st line agent compared to sorafenib in randomized phase III trial and has been approved in many countries including Korea. In second line agents, regorafenib, cabozantinib and ramucirumab achieved superiority compared to placeboin randomized phase III trial and has been approved and approving in many countries. However, these agent is not enough to satisfy the clinician because low response rate, limited survival gain and unsurpassed adverse events. Unfortunately, anticipated immune-oncologic drugs have not proven effective in phase III studies, although combination therapy of targeted agents and immune-oncologic drugs or immune-oncologic drugs each other.

In this lecture, I will summarize and compare the strategy of HCC treatment recommended in diverse worldwide guidelines and would like to anticipate future perspective.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[16:00-17:30, Emerald Hall A]

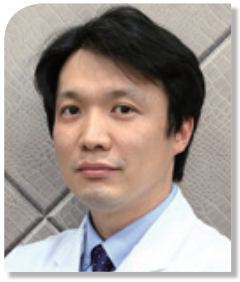
Video Session 04 (KPBA) English

Pancreaticobiliary therapeutic intervention (II)

Chairs: **Sung Koo Lee** (Asan Medical Center, Korea)

Don Haeng Lee (Inha University Hospital, Korea)

Sundeep Lakhtakia (Asian Institute of Gastroenterology, India)



RFA for CBD cancer

Jae Hee Cho, M.D., Ph.D.

Department of Internal Medicine-GI/Hepatology, Gachon University College of Medicine, Incheon, Korea

Case 1

Age and Gender: 82-yo-female

Chief Complains: abdominal pain (10 days) and jaundice

Present illness: She was referred to ER in order to manage abdominal pain and jaundice

Past history: Pulmonary TBc, Cerebral infarction

Laboratory Findings

CBC 7590/12.7/38.4/159K, AST/ALT 216/215 IU/L, ALP/r-GT 475/1098 IU/L

Total bilirubin 7.58 mg/dl, CA19-9 145.21 IU/L

Hospital Progress:

HD#2 EUS-FNAB, ERCP c Bx/ERBD

HD#7 ERCP c RFA

Case 2

Age and Gender: 82-yo-female

Chief Complains: Jaundice (3 days)

Present illness: She was referred to OPD in order to manage jaundice

Past history: Hypertension

Laboratory Findings

CBC 7070/12.9/36.6/262K, AST/ALT 36/73 IU/L, ALP/r-GT 314/834 IU/L

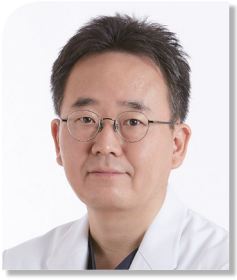
Total bilirubin 11.62 mg/dl, CA19-9 184.46 IU/L

Hospital Progress:

HD#3 PTBD, Rt

HD#5 EUS FNAB, ERCP c Bx/ERBD

HD#11 ERCP c RFA



Stent in stent for perihilar cholangiocarcinoma

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Recently primary endoscopic palliation using plastic or metal stents has had higher technical and clinical success with fewer adverse events rate than has the percutaneous approach for advanced hilar malignant biliary obstruction (HMBO). However, several issues, such as the optimal stent type, number, and deployment method, remain to be resolved. The optimal drainage method is not well known, because of the dearth of controlled studies of sufficient size. Also, endoscopic biliary stenting for HMBO is considered technically complex and challenging, particularly in cases that require multiple metal stents. Compared with stenting of extrahepatic distal obstructions, technical and clinical success rates are lower, and the risk of procedure-related complications is higher, in patients with advanced HMBO.

However, recently endoscopic interventions are being done more and more frequently because of advances in metal stents, accessories, and techniques. Bilateral stenting methods with self-expandable metal stent (SEMS) such as stent-in-stent (SIS) and stent-by-stent (SBS) deployment have resulted in higher technical feasibility and clinical success.

BILATERAL METAL STENTING METHOD OF SIS AND SBS DEPLOYMENT

SBS technique: SBS refers to sequential or simultaneous parallel placement of two SEMS into both intrahepatic duct (IHD) or multiple branches. First, two guidewires are passed into branches of the bile duct. In cases in which cannulation of the guidewire to the intended branches is difficult, coordination can be achieved by using a rotatable papillotome. Second, following successful deployment of the first stent through the guidewire into the IHD of one segment (or side), a second stent is inserted through a second parallel guidewire using the 'side-by-side' method. The distal ends of both stents should be placed at the same level within the CBD or across the ampulla of Vater. Simultaneous SBS placement is possible using a 6 Fr stent-delivery system. Technically, after deployment of the first SEMS, insertion of the second delivery system may be hampered by resistance or contact with the previously deployed SEMS. However, pneumatic balloon dilatation prior to deployment of the first stent enables sequential SBS deployment in patients with severe obstruction. Other technical issues with SBS deployment include entanglement of the two guidewires and the difficulty of precise deployment of both ends of the stents to facilitate endoscopic revision upon stent occlusion.

SIS technique: SIS involves placing the second stent through the first SEMS. The second stent crosses the central portion of the wire mesh of the first SEMS. After reaching the target ducts, as per SBS deployment, the first SEMS is inserted over one of the double guidewires. The branch that is more difficult for the guidewire insertion should be selected as the first stent placement target, to ensure easy insertion of the second stent. Next, the guidewire used to deploy the first stent is pulled out up to its central portion and reinserted into the contralateral bile duct through the central wire mesh of the first stent. At this time, the second guidewire can be used as a landmark. However, contralateral guidance can be difficult in patients with advanced hilar stricture. In such cases, pneumatic balloon dilation through the initially deployed stent, or bilateral balloon dilation before insertion of the first stent, facilitates second stenting and insertion of the guidewire into the contralateral duct. After insertion of the primary guidewire into the contralateral duct, the landmark guidewire is removed. Finally, sequential insertion and deployment of the second SEMS over a guidewire into the contralateral duct results in a bilateral Y-shaped configuration. The distal ends of the stents are typically placed above the level of the papilla. To preserve the function of the sphincter of Oddi as much as possible, and to prevent duodenal reflux, large endoscopic sphincterotomy should not be performed routinely.

ADVANTAGES OF SIS DEPLOYMENT

The overall technical success rate of the SIS and SBS techniques ranges from 73.3 to 100%. Each method has advantages and disadvantages, and deciding on the optimal technique is still difficult. SIS deployment has the following advantages. First, the Y-shaped configuration resulting from use of SIS is more physiological; SIS requires less axial force and exerts less pressure on the proximal and distal bile-duct wall and surrounding vascular structures. Second, because the distal end of the stents is usually placed above the level of the papilla, it may prevent duodenal reflux and depositing of organic material or bacteria, which can lead to sludge or stone formation within the stent. Third, multi-sectoral drainage for primary stent insertion or revision is possible with SIS deployment.

However, SIS is associated with difficulty in manipulating the guidewire through multiple ducts, achieving second stent insertion, or revision after a malfunction. If a stent malfunctions because of tumor ingrowth, the bilaterally crossed wire mesh may prohibit reinsertion of a guidewire or plastic/metal stent.

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Endoscopic techniques for post-endoscopic biliary sphincterotomy bleeding

Sundeep Lakhtakia

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Post-ERCP bleeding is most frequently seen after biliary sphincterotomy. Majority of the ERCP related bleeding are mild and self-limiting. Significant bleeding after ERCP is defined as hematemesis and/or melena or haemoglobin drop >2 g/dL. Bleeding may be immediate, mostly self-limited, or delayed and become evident hours to 7-10 days following ERCP. The overall significant post ERCP bleeding rate is about 1%, of which about 70% are moderate grade, and about 4% are severe. The mortality related to post ERCP bleed is 0.04%.

Patients at high risk of post-sphincterotomy bleeding (PSB) have at least one of the following factors: anticoagulant intake, platelet count <50000/mm^3, cirrhosis, end-stage renal disease especially on dialysis, intra-procedural bleeding, low endoscopist experience, or unsuccessful cannulation with pre-cut.

For difficult CBD stones, small ES with endoscopic papillary balloon dilation (EPBD) should be considered instead of large endoscopic sphincterotomy (ES). The latter carries a higher risk of bleeding. With respect to the technique of ES, the papilla should be incised in the 10–11 o'clock region because it contains least (only 10%) density of all papillary arteries. Blended current or Endocut, is recommended as opposed to pure-cutting current, as it reduces the incidence of bleeding without increasing the risk of PEP.

In patients already on anti-platelet agents or anticoagulants, the underlying principles of management depend on a balance between the risk of bleed due to the procedure if drugs are continued vs. the risk of thrombosis if antithrombotic therapy is modified or interrupted. With respect to antiplatelet agents (aspirin &/or clopidogrel) or anti-coagulants, consider stopping 5 days prior to high-risk procedures (sphincterotomy, sphincteroplasty, ampullectomy), and restart 48-72 hours post procedure. For patients on anticoagulants, warfarin should be discontinued for 5 days to allow the International Normalised Ratio (INR) to reduce to <1.5 in order to perform ES.

Management of Post Sphincterotomy Bleeding (PSB)

The following options may be considered to control PSB.

1. Diluted epinephrine (1:10000) injection in the papilla is generally the first line treatment. Alternately balloon tamponade may be considered. Spray irrigation with diluted epinephrine, alone or mixed with dextrose, may also be effective in minor bleedings.
2. Haemostatic clips may be used after failed epinephrine therapy. They may be delivered through a cap fitted forward viewing endoscope or a duodenoscope (the elevator may make clip delivery challenging).
3. Monopolar coagulation with the tip of a snare, where epinephrine injection failed, may occasionally help. Mechanical or thermal therapies should not be applied in close vicinity to the pancreatic orifice. Adherent clot should be removed to treat the underlying area. Cholangitis is more frequent in patients who present PSB, some experts suggest to insert a naso-biliary drain following haemostasis of PSB to prevent bile duct obstruction from intra-biliary clots.
4. Temporary placement of a biliary fully covered self-expandable metal stent (FCSEMS) in case of post-sphincterotomy bleeding refractory to standard haemostatic modalities.
5. PSB refractory to conventional endoscopic haemostasis can require arterial embolization or even surgery. Fully covered SEMS are an effective second line modality before resorting to embolization or surgery.
6. Haemostatic powder and fibrin glue are other possible rescue therapies with limited published reports.

Rebleeding occurs in 5-20% of patients following successful endoscopic haemostasis for PSB. Initial moderate/severe bleeding (defined as the need for transfusion or angiographic/surgical intervention) and serum bilirubin levels >10 mg/dL are independent risk factors for rebleed.

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

[16:00-17:30, Emerald Hall B]

Metabolism & Obesity 04 (KCHUGR-KSMBS) English

Endoscopic and surgical intervention for obesity

Chairs: **Seung Ho Choi** (Gangnam Severance Hospital, Korea)

Roman Turro Arau (Endoscopia Digestiva, Centro Medico Teknon, Spain)

History, indication and reimbursement issue

Sung IL Choi, M.D.

Department of Surgery, Kyung Hee University Hospital at Gangdong, Seoul, Korea

HISTORY

The surgical treatment of obesity began with the simple concept that by restricting intake, producing malabsorption, or both, one could reduce body weight and maintain that reduction. The first operation was intestinal bypass, which made use of the "short gut syndrome" a result of extensive bowel resection for cancer or loss of intestinal blood supply. Because the intestine was bypassed instead of removed, the operation was reversible, which established an important guideline for all subsequent operations used to control body weight.

In 1954, when the use of intestinal bypass was first mentioned at a meeting of the American Surgical Association, obesity was not recognized as a disease. The concept that obesity was a disease that could be successfully treated by an operation was accepted first by the severely obese; they welcomed relief from their morbidity, their repeated failures in dieting, and the disrespect shown them by society. In 1994, the first laparoscopic gastric bypass was performed by Alan Wittgrove and the exponential growth of bariatric and metabolic surgery had definitely started. It is estimated that in 2011, more than 340,000 procedures have been performed worldwide and a bout179,000 operations being performed in 2013. Sleeve gastrectomy allowed for a significant weight loss with low perioperative morbidity, maintained digestive continuity and was easy converting to other bariatric surgeries. This surgery has proven to be safe (even if sleeve fistulas are harder to treat, due to the high-pressure system in the gastric reservoir) and although more long-term studies are required, it has so far resisted the test of time and the concerns about pouch dilatation.

INDICATION

Indication of Western country

The indications to undergo bariatric surgery, are based on body mass index (BMI) as well as the presence of comorbidity. Patients with a BMI of 40 kg/m^2 or greater without coexisting medical problems, and for whom bariatric surgery would not carry an excessive risk, should be candidates for one of the surgeries mentioned above.

Patients with a BMI greater than or equal to 35 kg/m^2 and 1 or more severe obesity-related comorbidities, including type 2 diabetes, hypertension, hyperlipidemia, obstructive sleep apnea (OSA), non-alcoholic fatty liver disease (NAFLD), GERD, asthma, venous stasis disease, severe urinary incontinence, debilitating arthritis, or considerably impaired quality of life, would also qualify as surgical candidates. Patients with BMI OF 30 to 34.9 kg/m^2 with diabetes or metabolic syndrome also may undergo weight loss surgery, although there is a lack of sufficient data to demonstrate long-term benefits in such patients.

Indication of Korea

Indication of Bariatric surgery in Korea are decided by reference of IFSO-APC Consensus statements 2011.

Bariatric surgery should be considered for the treatment of obesity for acceptable Asian candidates with BMI ≥ 35 with or without co-morbidities.

Bariatric/GI metabolic surgery should be considered for the treatment of T2DM or metabolic syndrome for patients who are inadequately controlled by lifestyle alternations and medical treatment for acceptable Asian candidates with BMI ≥ 30.

The surgical approach may be considered as a non-primary alternative to treat inadequately controlled T2DM, or metabolic syndrome, for suitable Asian candidates with BMI ≥ 27.5.

A paradigm shift is occurring and both obesity and diabetes will be increasingly treated with surgical and endoscopic procedures. Indication of surgery will be changed according to many future studies including low BMI diabetes patients, and adolescent obesity.

Preliminary results with the gastric endoscopic sleeve plication (GESP)

Roman Turro Arau

Department of Bariatric Endoscopy, Centro Medico Teknon, Barcelona, Spain

INTRODUCTION

Obesity is major disease in our society. Minimal invasive procedures, like endoscopic ones, are a potential treatment option for a large group of population.

OBJECTIVES

Study the safety and effectiveness of the Gastric Endoscopic Sleeve Plication (GESP) for the treatment of obesity grade I-II.

METHODS

This is a multi-center, prospective pilot study. Study was Ethics approved at institutions. Written consent obtained. Indications have been obesity grade II. Use of the Incisionless Operating Platform (IOP) TM with a defined new pattern of disposition of the transmural plications with the g-cathTM EZ suture anchors in the greater curvature shortening and tubulizing the stomach to potentially reduce gastric volume / accommodation for an enhanced physiological effect.

Follow up data will be obtained prospectively every 2 weeks initially for the first 2 months and then monthly for the next 10 months on as part of our multidisciplinary long term follow-up program.

RESULTS

39 operations in 39 patients were successfully performed (M: 17 F: 22). Mean BMI 36.9 (range 31.2–40.3). Mean number of anchors placed was 18.3. All patients were discharged ≤ 24 hours. No serious adverse events (SAE). % Mean Total body weight loss at 5 months for the 34 patients was 13.93 ± 4.14 Kg.

CONCLUSIONS

The GESP procedure seems to be a safe intervention without significant adverse effects to date. Initial results in weight loss are encouraging. However, long term follow-up and further study remains necessary to assess its value in treating the etiology of obesity.

Surgical management of obesity - Bariatric surgery to metabolic surgery -

Yong Jin Kim, M.D., Ph.D.

Department of Surgery, H Plus Yangji Hospital, Seoul, Korea

In June 2016, American diabetic association's official journal, the diabetes care, included the bariatric surgery under the name of metabolic surgery as the standard care of diabetes management. It's been 60 years that bariatric surgery began, and also 25 years that the national institute of health proposed the guideline. It was challenging journey. Ironically, the relation between the gastrointestinal surgery and diabetes, goes back to 1920 when the insulin developed. "Diabetes and operation; A note on the effect of gastrojejunostomy upon a case of mild diabetes mellitus with a low renal threshold", the title of "THE LANCET" in 1925. In other words, trial of connecting stomach and small intestine have made the urine glucose disappear as side effect. After that many similar case reports came in intermittently. Although there were no specific reasons proved, people were able to perceive that with clinical experiences, gastrointestinal surgery shows more positive outcomes in diabetes. It was 1964 that the real incretin was specified.

Historically, the reason of the major influence of this change is the thesis "Annals of surgery" published by Dr. Walter J. Police in 1995. The title of maintenance and no recurrence of gastric bypass is "who would have thought of it? An operation proves to be the most effective therapy for adult onset diabetes mellitus". After 2000, with the laparoscopic view, the bariatric surgery (gastric bypass) rapidly expanded both quantitatively and qualitatively. At the same time, the rigorous scientific research was made up and the cause was lightened. The most major research was Dr. Francesco Rubino's. The research was through various gastrointestinal surgery, he revealed the change in incretin system. After that, many supportive clinical research' results was accumulated. Especially in 11 randomized clinical trial which compare operation and existing treatment discovered that different factors (like a period of diabetes, usage status of insulin and c-peptide so on) had more effect on improvement in diabetes than preoperative base weight. Because of that research, Diabetic Surgery Summit has admitted the bariatric surgery as the standard of diabetes's treatment. As you can see, the transition of paradigm from bariatric surgery to metabolic surgery didn't happen all of a sudden, It has been accomplished through a long period of effort. Also, there are enough supportive scientific and clinical evidences. And now the rest of the day, we have to share the information with both society and medical researchers, and also have to be equipped with training system and the guideline to guarantee the safety of the patient. On a given subject, I would like to empathize the motivations with the subtitle "Bariatric surgery to metabolic surgery, paradigm shift".

KDDW 2019 Korea Digestive Disease Week

DAY 3

November 30 (Saturday)

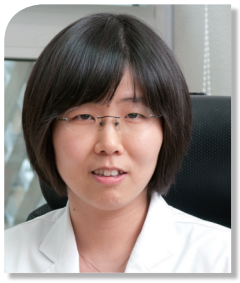
[16:00-17:30, Diamond Hall]

Primary Care Session (KSNM) Korean

Solving 10 most frequently asked questions from FGID patients in the clinic

Chairs: **Soo Teik Lee** (Chonbuk National University Hospital, Korea)

Poong-Lyul Rhee (Samsung Medical Center, Korea)



Gastroesophageal reflux disease (GERD)

Jie-Hyun Kim, M.D., Ph.D.

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GERD is now one of the most common chronic diseases. Throughout time our insight in the pathophysiology of GERD has been characterized by remarkable back and forth swings, often prompted by new investigational techniques. Even today, the pathophysiology of GERD is not fully understood but it is now recognized to be a multifactorial disease. Among the factors that have been shown to be involved in the provocation or increase of reflux, are sliding hiatus hernia, low lower esophageal sphincter pressure, transient lower esophageal sphincter relaxation, the acid pocket, obesity, increased distensibility of the esophagogastric junction, prolonged esophageal clearance, and delayed gastric emptying. Moreover, multiple mechanisms influence the perception of GERD symptoms, such as the acidity of the refluxate, its proximal extent, the presence of gas in the refluxate, duodenogastroesophageal reflux, longitudinal muscle contraction, mucosal integrity, and peripheral and central sensitization. Understanding the pathophysiology of GERD is important for future targets for therapy as proton pump inhibitor (PPI)-refractory GERD symptoms remain a common problem. A therapeutic trial of acid-suppressive PPI therapy is often the initial management, with endoscopy performed in the setting of alarm symptoms and to exclude other conditions. If symptoms persist and endoscopy does not reveal evidence of GERD, esophageal function tests are performed, including esophageal manometry (high resolution manometry, HRM) and ambulatory reflux monitoring. In this setting, HRM identifies motor pathophysiology conducive to gastro-esophageal reflux and ambulatory reflux monitoring describes pathological esophageal reflux burden and symptom–reflux association. Other novel parameters on pH testing or pH-impedance testing, including mean nocturnal baseline impedance (MNBI) and the post-reflux swallow-induced peristaltic wave (PSPW) index, might complement conventional reflux parameters in improving confidence for a reflux diagnosis. In the future, understanding GERD pathophysiology in more detail, particularly the inter-relationship between GERD and esophageal motor dysfunction, and evaluating esophageal reflux burden with novel metrics could help identify GERD phenotypes better and improve management outcomes. A need now exists for prospective and collaborative outcome studies to determine the clinical value of esophageal function testing in predicting symptomatic outcome. Aggressive PPI maintenance therapy is recommended for severe erosive GERD, and on-demand therapy or continuous maintenance therapy is recommended for mild erosive GERD or PPI-responsive non-erosive GERD. Moreover, PPI-resistant GERD (insufficient symptomatic improvement and/or esophageal mucosal break persisting despite the administration of PPI at a standard dose for 8 weeks) is defined, and a standard-dose PPI twice a day, change in PPI, change in the PPI timing of dosing, or addition of a prokinetic drug are recommended for its treatment. If no improvement is observed even after these treatments, pathophysiological evaluation with esophageal impedance pH monitoring or esophageal manometry at an expert facility for diseases of the esophagus is recommended. We will discuss most frequently asked questions from GERD patients in the clinic in this lecture.

Functional dyspepsia

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Functional dyspepsia (FD) is a chronic upper gastrointestinal (GI) symptom complex that routine diagnostic work-up, such as upper GI endoscopy, blood tests, or radiological examination, shows no organic causes. It is one of the most prevalent functional gastrointestinal (GI) disorders encountered in clinical practice. The prevalence of FD varied according to geographical region and diagnostic criteria. It is defined by Rome IV criteria as the presence of one or more of following symptoms which include bothersome postprandial fullness, early satiation, epigastric pain and burning with no evidence of structural disease as seen in upper GI endoscopy. Two subtypes of FD are recognized based on the predominant symptoms although these often overlap clinically. Epigastric pain syndrome (EPS) is characterized by the presence of epigastric pain or burning, while postprandial distress syndrome (PDS) is characterized by the presence of postprandial fullness and/or early satiation.

The pathogenesis of FD is likely complex and remains unclear. Classically, motordisorders, visceral hypersensitivity, and brain-gut interactions have been implicated in the pathophysiology of FD, but recently animportant role for duodenal low-grade inflammation, eosinophilia, infection and microbiome dysbiosis in FD has been reported. A clinical diagnosis of FD consists of a history, blood tests, and endoscopic evaluation to exclude other causes of dyspepsia. Prompt upper GI endoscopy is recommended in dyspepsia patients aged 40 or older to exclude organic causes, including gastric cancer. Testing for and treating *Helicobacter pylori* infection is recommended in dyspepsia patients who are not responding toacid suppressants or prokinetics.

FD remains a challenging condition to manage and therapeutic options are limited. Initial management by reassurance and explanation are recommended and may help maximize the placebo response, but they have not been studied systematically. Dietary modification may be effective for symptom relief in patients with FD. Generally, it is desirable to avoid foods that induce dyspeptic symptoms. However, there are no clear evidences of a role for dietary intervention in dyspeptic symptom relief and well-designed studies are needed to gain a better understanding of this topic. Avoidance of high fat intake, NSAID, alcohol and smoking is commonly recommended.

The primary pharmacologic therapy is mostly based on the subtype of FD and has been aimed at the control of gastric acid secretion and gastric motility. Acid suppression with proton pump inhibitors (PPIs) should be recommended as a first line treatment for FD in patients with EPS and overlapping GERD. Histamine type 2 receptor antagonists (H2RAs) are another option for treatment of EPS. Prokinetics can be useful as a first line treatment for FD in patients with PDS. Although previous meta-analyses have reported improved symptoms of FD in patients treated with prokinetics, these results are driven by small positive studies as larger studies were negative. Acotiamide acts as a muscarinic receptor antagonist and cholinesterase antagonist, improves gastric emptying, and enhances fundic relaxation. Some dopamine D2 receptor antagonists need to be used carefully due to adverse reactions. Fundic relaxant drugs may be effective in improving generalized dyspeptic symptoms, postprandial fullness, and early satiety.In a randomized, double-blind study, buspirone significantly reduced the PDS-related symptoms. Psychotropic drugs, especially antidepressants, are often used as second-line drugs in FD. Tricyclic antidepressants (TCAs) may be effective in refractory FD patients especially for patients with the EPS.One clinical trial of mirtazapine suggested a trend towards symptom improvement compared with placebo in FD. Psychological therapies can be considered in severely affected FD patients not responding to drug therapies. A systematic review showed insufficient evidence on the efficacy of psychological therapies in patients with FD. Other emerging treatment options include probiotics, non-absorbable antibiotic rifaximin, potassium-competitive acid blocker (P-CAB), and novel compounds that attempt to treat the underlying gastric and duodenal inflammation. Further studies will be needed as to whether these new drugs can efficiently manage FD symptoms.

Irritable bowel syndrome

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Irritable bowel syndrome (IBS) is a multifactorial disorder with the pathogenesis of abnormal gastrointestinal motility, low-grade inflammation, visceral hypersensitivity, communication in the gut-brain axis, and so on. Traditionally, IBS has been treated with dietary and lifestyle modification, fiber supplementation, pharmacological and psychological therapy. Carbohydrates have a range of foods regularly consumed including grains such as rye and wheat, vegetables, fruits, and legumes. Short-chain carbohydrates poorly absorbed exert osmotic effects in the intestinal lumen increasing its water volume, and are rapidly fermented by bacteria with consequent gas production. These effects may be the basis of the beginning of gastrointestinal symptoms. This made the use of lactose-free diets in those with lactose intolerance and of fructose-reduced diets for fructose malabsorption. All dietary poorly absorbed short-chain carbohydrates have similar and additive effects in the intestine, so a concept has been developed to regard them collectively as FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) and to evaluate a dietary approach that restricts them all. Based on observational and comparative studies and on randomized-controlled trials, FODMAPs trigger gastrointestinal symptoms in patients with IBS. Food choice via the low FODMAP and potentially other dietary strategies is now a realistic and efficacious therapeutic approach for symptoms of IBS. In Korea, the strategy of Korean diet for Korean patients with IBS needs apposite to the Korean cases. Antispasmodics plus stool consistency modifiers to treat the major symptoms and defecation are the first-line drug treatment. In IBS-C patients, bulking agents can provide overall symptom relief and osmotic laxatives could increase the number of bowel frequency. In IBS-D patients, loperamide is recommended to improve stool consistency and decreases bowel frequency.Antispasmodics is effective in treating abdominal discomfort and abdominal pain in IBS-C and IBS-D patients. The 5-hydroxytryptamine (5-HT) receptors in the gastrointestinal tract particularly 5-HT_3 and 5-HT_4 receptors [DU1] are involved not only in modulating gut motility but in visceral sensory pathways. Both classes of drug appear to reduce visceral sensitivity and have inhibitory effects on motor activity in the distal intestine. The 5-HT_4 [DU2] agonists may improve IBS-C by normalizing bowel habit and thereby reducing abdominal pain. 5-HT_3 receptor antagonists, is effective in improving stool consistency, abdominal pain/bloating, and health-related quality of life in IBS-D patients. Rifaximin may be effective at reducing global symptoms of diarrhea predominant irritable bowel syndrome. Probiotics may be considered to relieve global symptoms, bloating, and flatulence in irritable bowel syndrome.Tricyclic antidepressants may be considered in partial responder to the conventional therapy for abdominal pain relief and global symptoms improvement. Selective serotonin reuptake inhibitors may be considered in patients with irritable bowel syndrome for improvement of the well-being sense.

Chronic constipation

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Constipation has a prevalence rate of 16.5% in Korea, and is a common gastrointestinal functional disease that affects the quality of life in many patients.[1] Patients have various questions about constipation. Patients also believe and follow indiscriminate and unfounded information through the Internet and other media to answer questions about constipation. This can lead to worse constipation and unexpected complications. There is not enough accurate information about constipation that can answer patients' questions. It is not easy for a doctor to answer patients' questions during outpatient care. I would like to find out the appropriate answers to the patients' questions about constipation.

The most frequently asked questions are as follows

1. Why does constipation occur? Why is constipation worsening?
2. I can't defecate every day. Is it constipation?
3. Does it help to drink a lot of water and fiber?
4. Are there any exercises that can help? What kinds of exercises can help constipation?
5. What foods can improve constipation?
6. Does using a bidet help constipation?
7. Can regular stool removal help constipation?
8. Does taking probiotics help constipation?
9. Does any complication or resistance develop after long-term use of laxatives?
10. Does constipation increase risk of colon cancer?

Constipation can be primary or secondary to other medical conditions, including neurological, metabolic, and endocrine diseases. One of the most common causes of constipation is medication, including anticholinergics, opioid analgesics, calcium channel blockers, antidepressants, antihistamines, antispasmodics, anticonvulsants, aluminum antacids, and iron supplements.[2,3] The prevalence of constipation in elderly populations increases because of multifactorial causes with co-morbid diseases, impaired mobility, reduced dietary fiber intake, and drugs contributing to constipation.[3] Dietary fiber appears to be effective in relieving mild to moderate, but not severe constipation.[3] When fiber are used, inadequate fluid intake can result in abdominal gas or bloating, which may then paradoxically predispose the patient to bowel obstruction.[3,4] Increased physical activity might offer symptomatic improvement, especially in elderly constipated patients with low levels of physical activity.[3] Probiotics can be considered for use in conjunction with other drugs in the treatment of chronic constipation.[3] A systematic review of randomized controlled trials to evaluate the efficacy and safety of probiotic supplementation for the treatment of constipation suggested a favorable effect of treatment with Bifidobacterium lactis DN-173010, Lactobacillus casei Shirota, and Escherichia coli Nissle 1917 on defecation frequency and stool consistency.[5] Long-term administration of nonabsorbable carbohydrate or polyethylene glycol had rarely serious adverse reactions[3]. In subjects with no alarm symptoms, the rate of adenoma or colon cancer by colonoscopy has been found to be similar between groups reporting simple constipation and asymptomatic populations undergoing screening.[6] Colonoscopy should be performed to exclude conditions of secondary constipation in patients with chronic constipation if the patients have alarm symptoms, such as blood in the stool, anemia, unexplained weight loss, new-onset constipation, or a family history of colon cancer.[3]

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