JGA Keynote Program The 4th International Gastrointestinal Consensus Symposium (IGICS)

Gastrointestinal Cancers; Biomarkers, Screening, and Prevention

February 18–19, 2011, Kyoto, Japan

Abstracts

Guest Editor
Yuji Naito, Kyoto

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JGA Keynote Program The 4th International Gastrointestinal Consensus Symposium (IGICS)

Date February 18 (Fri.) – 19 (Sat.), 2011

Venue Kyoto International Conference Center, Kyoto, Japan

Topic Gastrointestinal cancers; biomarkers, screening, and prevention

IGICS Committee Members

JGA International Exchange Committee Members

Yuji Naito, Japan (Chairperson of the 4th IGICS)

Tetsuo Arakawa, Japan

Shin Fukudo, Japan

Takashi Joh, Japan

Yoshikazu Kinoshita, Japan

Takayuki Matsumoto, Japan

Hidekazu Suzuki, Japan

Shin'ichi Takahashi, Japan

Fumiaki Ueno, Japan

IGICS International Active Members

Ki-Baik Hahm, Korea

Udom Kachintorn, Thailand

Abdul Aziz Rani, Indonesia

Jose D. Sollano, Philippines

Qi Zhu, China

Dear Colleagues,

It is our great pleasure to welcome you to the 4th International Gastrointestinal Consensus Symposium (IGICS) to be held on Saturday of February 18–19, 2011 in Kyoto as a JGA Keynote Program in the 7th Annual Meeting of the Japanese Gastroenterological Association (February 18–19, 2011, President: Prof. Toshikazu Yoshikawa of Kyoto Prefectural University of Medicine). In this time, please note that Poster session will be scheduled on the evening of Feb. 18 and symposium on Feb. 19, 2011. In addition, you can attend some international presentation in JGA, for example, Next generation endoscopy: Molecular Imaging in gastrointestinal cancer by Dr. Seung-Jae Myung and Invited lecture by Amy Foxx-Orenstein, Past President of the America College of Gastroenterology, which are scheduled on the lunch time of Feb. 18, 2011.

The topic for the 4th IGICS is “Gastrointestinal cancers; biomarkers, screening, and prevention”. As the early stages of GI tract cancers are removed endoscopically by the development of equipment and technique, it is getting more and more important to detect GI tract cancer as early as possible. Therefore, we need to establish specific biomarkers, appropriate screening methods to find early GI tract cancers. Furthermore, as the mechanisms of carcinogenesis has been elucidating, prevention of GI tract cancer is now getting possible. In this symposium, we will have 2 special lectures, 18 oral presentations, and 12 poster presentations.

This symposium will provide you the latest information on digestive endoscopy from the Asians’ best clinicians and scientists. We hope that you will find this meeting valuable and stimulating educational experience as we believe it will be greatly enriched by your active participation in the discussion. Young Investigator Awards provided by Japanese Gastroenterological Association (JGA) shall be given to three outstanding speakers.

We sincerely look forward to seeing you in Kyoto in February 2011.

With kind regards,

Yuji Naito, MD, PhD
Chairperson of the 4th IGICS

Friday, February 18, 2011

18:00–19:00

P-

Poster Session

*Poster session of IGICS will be promoted simultaneously with poster sessions of the 7th JGA.

Chairpersons: Dr. Fumiaki Ueno, Ofuna Chuo Hospital, Japan
Dr. Kazuhiko Uchiyama, Kyoto Prefectural University of Medicine, Japan
Dr. Hidekazu Suzuki, Keio University School of Medicine, Japan

- 1 LONG TERM PROGNOSIS OF ESD FOR SUPERFICIAL ESOPHAGEAL CANCER
Dr. Akiko Takahashi, Saku Central Hospital, Japan p. 232
- 2 ENDOSCOPIC AND ONCOLOGIC OUTCOME AFTER ENDOSCOPIC RESECTION FOR EARLY GASTRIC CANCER: COMPARISON OF ABSOLUTE AND EXTENDED INDICATIONS
Dr. Ji Yong Ahn, University of Ulsan College of Medicine, Asan Medical Center, Korea p. 232
- 3 COMPARISON OF ESD AND EMR FOR THE COLORECTAL CARCINOID IN THIS HOSPITAL
Dr. Kei Yamamoto, Tokyo Medical University, Japan p. 233
- 4 CLINICOPATHOLOGICAL FEATURES OF SUPERFICIAL ESOPHAGEAL CANCERS WITH LYMPH NODES METASTASIS: AN IMPLICATION FOR ENDOSCOPIC RESECTION
Dr. Ji Young Choi, University of Ulsan College of Medicine, Asan Medical Center, Korea p. 233
- 5 CO₂ INSUFFLATION DURING ESOPHAGEAL ESD UNDER GENERAL ANESTHESIA PROVIDES SAFE INTRODUCTION FOR NEW ENTRY INSTITUTION
Dr. Kenji Nakamura, Kyorin University School of Medicine, Japan p. 234
- 6 DEVELOPMENT OF GASTRIC CANCER AFTER ENDOSCOPIC RESECTION OF EARLY GASTRIC CANCER
Dr. Takatsugu Yamamoto, Teikyo University School of Medicine, Japan p. 234
- 7 DETECTION RATE OF EARLY GASTRIC CANCER COMPARISON WITH TN-EGD AND TO-EGD IN JAPAN
Dr. Mari Fukuzawa, Tokyo Medical University Hospital, Japan p. 234
- 8 INCIDENCE OF PANCREATIC CANCER IN CHINESE PATIENTS WITH CHRONIC PANCREATITIS
Dr. Liang-Hao Hu, Changhai Hospital, The Second Military Medical University, China p. 235
- 9 STUDY ON EUS GUIDED ONCOLYTIC ADENOVIRUS IMPLANTATION IN PATIENTS WITH UNRESECTABLE PANCREATIC CANCER
Dr. Tingting Gong, RuiJin Hospital, Shanghai JiaoTong University School of Medicine, China p. 235
- 10 COMPARISON OF SEVEN MODELS FOR END-STAGE LIVER DISEASE IN EVALUATING THE PROGNOSIS OF CIRRHOSIS
Dr. Ling Yan Cai, East Hospital, Shanghai Tongji University, China p. 236
- 11 COMPARISON OF OUTCOMES AMONG SECONDARY COVERED METALLIC, UNCOVERED METALLIC, AND PLASTIC BILIARY STENTS IN TREATING OCCLUDED PRIMARY METALLIC STENTS IN MALIGNANT DISTAL BILIARY OBSTRUCTION
Dr. Jae Hee Cho, Kwandong University College of Medicine, Korea p. 236
- 12 GLI1 PROMOTES ANGIOGENESIS BY REGULATING A NEW TARGET GENE—PDGF-B IN PANCREATIC CANCER
Dr. Xuan-Fu Xu, The Tenth People's Hospital of Shanghai, China p. 237

Saturday, February 19, 2011

08:30–08:40

Opening Remarks

Dr. Ki-Baik Hahm, Gachon University of Medicine and Science, Korea

08:40–9:40	O-1-	Oral Session 1 – Screening <i>Chairpersons:</i> Dr. Shin Fukudo, Tohoku University School of Medicine, Japan Dr. Udom Kachintorn, Siriraj Hospital Mahidol University, Thailand	
		1 PHASE II STUDY OF NARROW-BAND IMAGING ENDOSCOPY AND AUTOFLUORESCENCE IMAGING ENDOSCOPY FOR SCREENING OF SQUAMOUS CELL CARCINOMA IN THE ESOPHAGUS Dr. Ryu Ishihara, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan	p. 224
		2 GASTRIC SCREENING EXAMINATION USING PILLCAM ESO 2: A PILOT STUDY Dr. Takafumi Yuki, Shimane University School of Medicine, Japan	p. 224
		3 THE ACCURACY OF FECAL IMMUNOCHEMICAL TEST IN EARLY DETECTION OF COLORECTAL CANCER Dr. Achmad Fauzi, Faculty of Medicine, University of Indonesia, Indonesia	p. 225
		4 HOSPITAL-BASED SURVEY ON KNOWLEDGE AND ATTITUDE TOWARD COLORECTAL CANCER SCREENING AMONG INDONESIAN POPULATION Dr. Murdani Abdullah, Faculty of Medicine, University of Indonesia, Indonesia	p. 225
		5 DIAGNOSTIC VALUE OF FECAL IMMUNOCHEMICAL TEST IN COLORECTAL CANCER SCREENING IN INDONESIA Dr. Abdul Aziz Rani, Faculty of Medicine, University of Indonesia, Indonesia	p. 225
		6 THE PREVALENCE OF ADVANCED COLORECTAL ADENOMA IS INCREASING RAPIDLY RATHER THAN COLORECTAL CANCER IN CHINA: A LARGE MULTICENTER STUDY OF SYMPTOMATIC HOSPITAL-BASED INDIVIDUALS BETWEEN 1990 AND 2010 Dr. Hui-Min Chen, Shanghai Jiao-Tong University School of Medicine Ren-Ji Hospital, China	p. 226
09:40–10:20	O-2-	Oral Session 2 – Biomarker 1 <i>Chairpersons:</i> Dr. Takayuki Matsumoto, Hyogo College of Medicine, Japan Dr. Qi Zhu, Rui Jing Hospital, Shanghai Jiao Tong University School of Medicine, China	
		1 EPIGENETIC SIGNATURE OF GASTROINTESTINAL CANCERS: A ROLE AS DIAGNOSTIC BIOMARKERS FOR CANCERS Dr. Sung Kwan Shin, Yonsei University College of Medicine, Korea	p. 226
		2 15-HYDROXYPROSTAGLANDIN DEHYDROGENASE IN THE GASTRIC ADENOCARCINOMA ARISING FROM ADENOMA Dr. Jeong Hoon Lee, Asan Medical Center, Korea	p. 227
		3 THE EFFECT OF <i>HELICOBACTER PYLORI</i> INFECTION ON THE EXPRESSION OF VEGFR1 AND VEGFR2 IN INTESTINAL METAPLASIA AND GASTRIC CANCER Dr. Noriko Nakajima, Nihon University School of Medicine, Japan	p. 227
		4 CONTRASTING ACTIVITY OF HEDGEHOG AND WNT PATHWAYS ACCORDING TO GASTRIC CANCER CELL DIFFERENTIATION: RELEVANCE OF CROSSTALK MECHANISMS Dr. Jie-Hyun Kim, Yonsei University College of Medicine, Korea	p. 228
10:20–11:00	O-3-	Oral Session 3 – Prevention <i>Chairpersons:</i> Dr. Shin'ichi Takahashi, Kyorin University School of Medicine, Japan Dr. Abdul Aziz Rani, Faculty of Medicine, University of Indonesia, Indonesia	
		1 CHEMOPREVENTIVE MECHANISM BY GUGGULSTERONE FOR THE ESOPHAGEAL ADENOCARCINOMA CELLS Dr. Takanori Yamada, Hamamatsu University School of Medicine, Japan	p. 228
		2 THE SELECTIVE CYCLOOXYGENASE-2 INHIBITOR CELECOXIB ACTIVATES THE TUMOR SUPPRESSOR <i>microRNA-29c</i> IN HUMAN GASTRIC CANCER Dr. Yoshimasa Saito, Kitasato Institute Hospital, Japan	p. 229
		3 PREVENTIVE EFFECTS OF FLAVONOIDS ON HYPERLEPTINEMIA AND COLITIS-RELATED COLON CARCINOGENESIS IN ICR MICE Dr. Akira Murakami, Graduate School of Agriculture, Kyoto University, Japan	p. 229
		4 SODIUM BUTYRATE ENHANCES COMPLEMENT-MEDIATED CELL INJURY VIA DOWN-REGULATION OF DECAY-ACCELERATING FACTOR EXPRESSION IN COLONIC CANCER CELLS Dr. Akira Andoh, Shiga University of Medical Science, Japan	p. 229

11:00–12:00	SL-	Special Lecture 1 <i>Chairperson:</i> Dr. Takashi Joh, Nagoya City University Graduate School of Medical Sciences, Japan	
	1	BIOMARKERS, SCREENING, AND PREVENTION OF COLORECTAL CANCER Dr. Joseph Sung, The Chinese University of Hong Kong, China	<i>p. 223</i>
14:30–15:20	SL-	Special Lecture 2 <i>Chairperson:</i> Dr. Ki-Baik Hahm, Gachon University of Medicine and Science, Korea	
	2	GASTRIC CANCER SCREENING BASED ON THE RISK OF EACH SUBJECT; SERUM MARKERS FLAG UP THE CANCER RISK Dr. Masao Ichinose, Wakayama Medical University, Japan	<i>p. 223</i>
15:20–15:40		Report on the Result of the Questionnaire Dr. Kazuhiko Uchiyama, Kyoto Prefectural University of Medicine, Japan	
15:40–16:20	O-4-	Oral Session 4 – Biomarker 2 <i>Chairpersons:</i> Dr. Shunji Ishihara, Shimane University School of Medicine, Japan Dr. Jose D. Sollano, University of Santo Tomas, Manila, Philippines	
	1	DIFFERENT EXPRESSION PATTERNS OF CANCER STEM CELL MARKERS IN WELL DIFFERENTIATED GASTRIC CANCER AND GASTRIC ADENOMA TISSUES Dr. Akemi Kamatani, Fujita Health University, Japan	<i>p. 230</i>
	2	<i>CDH1</i> ANALYSIS IN FAMILIAL DIFFUSE GASTRIC CANCER IN KOREA Dr. Jun-Won Chung, Gachon University of Medicine and Science, Korea	<i>p. 230</i>
	3	POTENTIAL OF ANTI-IL-6 ANTIBODY AS ANTI-CANCER AGENT TARGETING COLON CANCER STEM CELLS Dr. Masahiko Tsujii, Osaka University, Japan	<i>p. 231</i>
	4	FATTY ACID SYNTHASE (FASN); THE PROTEOMIC BIOMARKERS OF COLITIS-INDUCED COLORECTAL CANCER Dr. Chan Young Ock, Gachon University of Medicine and Science, Korea	<i>p. 231</i>
16:20–16:30		Closing Remarks Dr. Yuji Naito, Kyoto Prefectural University of Medicine, Japan	

SL-1

Biomarkers, Screening, and Prevention of Colorectal Cancer

Joseph Sung

The Chinese University of Hong Kong

International and Asia Pacific Guidelines have strongly supported the use of multitude approach for colorectal cancer screening. An important study from UK (Atkins et al. Lancet 2010) have shown for the first time that a once-only flexible sigmoidoscopy screening can reduce incidence of distal colorectal cancer and reduce the mortality by almost 50%. The benefit of sigmoidoscopy appears to perpetuate even at 10 years after the screening procedure was done. Despite the development of endoscopic modalities, none of these technology have actually confirmed to increase the diagnostic accuracy of white light endoscopy. On the other hand, capsule endoscopy (PillCam COLON) has been shown to provide reasonable but painless screening for colorectal neoplasia. The second generation PillCam COLON is just out in the market and the pilot studies showed promising results. Colorectal cancers are found in 0.2–6.4 case per 1000 patient-year after colonoscopy. It has also been estimated that 2–12% of polyps measuring up to 1 cm are missed during colonoscopy, and most of these missed lesions are in the left colon. A new term called post-colonoscopy CRC is now used to encompass missed cancer, new cancer developed after colonoscopy and the so-called interval cancers. In order to compensate for the possible missed lesions, fecal test for occult blood, for tumor-markers such as DNA and microRNA have been developed with variable success. Markers are now developed in both stool test and blood test and a combination of markers might be useful for future screening of colorectal cancer.

SL-2

Gastric Cancer Screening Based on the Risk of Each Subject; Serum Markers Flag Up the Cancer Risk

Masao Ichinose

Department of Gastroenterology, Wakayama Medical University

Helicobacter pylori (*H. pylori*)-related chronic gastritis is considered a major risk factor for gastric cancer in high-risk areas, including Japan. *H. pylori*-related gastritis causes chronic inflammation in the stomach, leading to gastric atrophy/intestinal metaplasia and eventually to cancer. It is widely accepted that serum pepsinogen (PG) levels, specifically PG I or PG I/II ratio, present a useful and sensitive marker for the extent of gastric atrophy together with intestinal metaplasia. A recent longitudinal cohort study also revealed that a group of subjects with extensive gastric atrophy identified by PG I ≤ 70 ng/ml and PG I/II ratio ≤ 3.0 are at high risk for gastric cancer, showing an annual incidence of over 0.2% (*Cancer Epidemiol Biomarkers Prev* 17: 838–845, 2008). The risk for cancer increased in a step-wise fashion in groups of subjects detected by serum PG, which is used to detect subjects with more extensive gastric atrophy. This strongly indicates that the subjects at high risk for gastric cancer can be identified by serum PG testing and that they should undergo follow-up by endoscopy. In addition, with the combination of two serum tests, *H. pylori* antibody titer and PG, the classification of each subject according to the stage of serial changes in *H. pylori*-related chronic gastritis is possible (*Int J Cancer* 109:138–143, 2004). The risk of gastric cancer increases with the progression of *H. pylori*-related chronic gastritis stage by up to 62-fold, while no gastric cancer developed among subjects with negative *H. pylori* antibody and negative PG test during a study period of 10 years. Evaluation of gastric cancer risk in each subject has become possible based on serum levels of PG and *H. pylori* antibody, which allows the establishment of a strategy for cancer prevention including cancer screening (*Int J Cancer* 123: 917–926, 2008).

Oral Session 1 – Screening

Chairpersons: Shin Fukudo, Udom Kachintorn

O-1-1

Phase II Study of Narrow-Band Imaging Endoscopy and Autofluorescence Imaging Endoscopy for Screening of Squamous Cell Carcinoma in the Esophagus

Ryu Ishihara, Yoji Takeuchi, Noriya Uedo, Koji Higashino, Hiroyasu Iishi

Department of Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

Purpose: This study aimed to investigate the diagnostic yield of narrow-band imaging (NBI) endoscopy and autofluorescence imaging endoscopy (AFI) endoscopy for screening of squamous mucosal high-grade neoplasia in the esophagus. **Methods:** The current clinical investigation was performed during routine endoscopic screening procedures by two experienced endoscopists. The patient inclusion criteria were: (1) patients with present esophageal cancers, (2) patients with past history of esophageal cancers treated with endoscopic resection, (3) patients with history of head and neck cancer. Phase II study of NBI was performed from October 2007 to January 2009. Screening with NBI was followed by chromoendoscopy with iodine solution. The index lesion for the study was a newly diagnosed superficial squamous cell carcinoma. The primary outcome was the sensitivity of NBI for detecting new lesions. The secondary outcome was the positive predictive value (PPV) of NBI. Phase II study of AFI was performed from July 2009 to August 2010 in a same manner. **Results:** A total of 170 and 188 patients underwent endoscopic examination for phase II study of NBI and AFI, respectively. The sensitivity of NBI was 100% (25/25 lesions) and the PPV of NBI was 45.5% (25/55 lesions). The sensitivity (71.4% [15/21 lesions]) and the PPV (25.4% [15/59 lesions]) of AFI were lower than those of NBI and the sensitivity of AFI did not exceed the expected sensitivity to proceed to a phase III trial. **Conclusion:** NBI endoscopy had sufficiently high sensitivity and acceptable PPV, and can be regarded as the standard screening modality for squamous cell carcinoma in the esophagus.

O-1-2

Gastric Screening Examination Using PillCam ESO 2: A Pilot Study

Takafumi Yuki¹, Yuji Amano¹, Ryusaku Kusunoki², Akihiko Oka², Goichi Uno¹, Shunji Ishihara², Yoshikazu Kinoshita²

¹Division of Endoscopy, Shimane University Hospital,

²Second Department of Internal Medicine, Shimane University, Faculty of Medicine

Introduction: PillCam ESO 2 has been developed as a useful device for screening esophageal lesions. Its diagnostic value has not yet been evaluated for neoplastic gastric lesions, although there is much interest in that application in countries with high prevalence of gastric cancer, including Japan. To evaluate whether or not PillCam ESO 2 can be applied to gastric cancer screening, a prospective pilot study was assigned. **Methods:** Five healthy volunteers were enrolled in a preliminary study to determine the best screening procedure for the upper gastrointestinal tract using PillCam ESO 2. Twenty patients with any type of upper abdominal symptom were then consecutively enrolled in a clinical study for evaluation of the image quality of PillCam ESO 2, using the screening procedure standardized in the preliminary study. The stomach was divided into 18 regions, and capsule endoscopic images were evaluated with regard to whether or not correct diagnosis was possible. **Result:** High-quality PillCam ESO 2 images were obtained for 15 out of 18 regions with the established screening procedure. However, accurate diagnosis was impossible at the lesser curvature or posterior wall of the gastric corpus in 3 out of 20 patients, because images were too dark or blank. **Conclusion:** Capsule endoscopy using PillCam ESO 2 allowed observation of almost all of the gastric mucosa and may be applicable to screening for early gastric cancer, although a further evaluation for the performance must be undertaken.

O-1-3

The Accuracy of Fecal Immunochemical Test in Early Detection of Colorectal Cancer

A. Fauzi¹, M. Abdullah¹, M. Simadibrata¹, A.F. Syam¹, T. Wijayadi², A.A. Rani¹

¹Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Indonesia/ Dr. Cipto mangunkusumo Hospital, Jakarta, ²Department of Internal Medicine, Gading Pluit Hospital, Jakarta, Indonesia

Introduction: Guaiac based Fecal Occult Blood Test (FOBT) showed a low sensitivity and specificity in detecting colorectal cancer (CRC). The study was performed to determine the accuracy of Fecal Immunochemical Test (FIT) in detecting CRC in Indonesian population. **Methods:** The patients who underwent colonoscopy due to any indication except rectal bleeding were recruited consecutively from December 2009 – April 2010 in six hospitals (RSCM, RSII, RSP, RSGP, RSAW and RSMKKG) in Jakarta. The FIT (OC Light® and Oncoprobe®) was performed according standard procedure using immunochromatography. The data was analyzed using SPSS version 16. **Result:** Of the 82 patients (57.3% male and 42.7% female), the mean (SD) age was 52.3 (13.8) years with ranging 20–83 years, consisted of 49 (59.8%) Malay and 33 (40.32%) Chinese patients. The OC Light® vs Oncoprobe® for significant CRC showed sensitivities, specificities, Positif Predictive Value (PPV), and Negative Predictive Value (NPV) were 88.9% vs 88.9%, 82.2% vs 78.1%, 61.9% vs 66.7%, and 98.4% vs 98.3%, respectively. The relative risk for detecting significant CRC was superior in patients with OC Light® (RR 36.9; CI 4.2–321.3) than with a Oncoprobe® (RR 28.5; CI 3.3–245.0). **Conclusion:** Though OC Light® seen to be superior to Oncoprobe®, however both test have a good diagnostic value in detecting CRC.

O-1-4

Hospital-Based Survey on Knowledge and Attitude toward Colorectal Cancer Screening among Indonesian Population

M. Abdullah, A. Fauzi, A.F. Syam, D. Makmun, M. Simadibrata, A.A. Rani

Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Indonesia/ Dr. Cipto mangunkusumo Hospital, Jakarta, Indonesia

Introduction: Several western countries have recommended colorectal cancer (CRC) screening, however the yield of CRC screening is still low. The acceptability of CRC screening is influenced by people's knowledge and attitude. This study was conducted to evaluate the knowledge and attitude of Indonesian people toward CRC screening. **Methods:** Adult Indonesian population aged 30–65 years was recruited in this hospital-based survey. Subject were family or patients attending out patient clinic consecutively (GI clinic were excluded). Knowledge and attitude toward CRC screening were assessed by using structured questionnaires consisting of nine

chapters. **Result:** There were 896 respondents recruited in this study. Most respondents (99.7%) have poor knowledge about CRC. The result of bivariate analysis shows that education ($p=0.001$), perception of CRC ($p=0.002$) and CRC screening ($p=0.001$), family income per month ($p=0.000$), risk factor ($p=0.039$), relatives history ($p=0.000$), media exposure ($p=0.000$), and medical professional affection ($p=0.000$) are significant related to attitude for CRC screening. And the result of multivariate analysis shows that medical professional affection ($p=0.000$; OR=26.5), relatives history ($p=0.030$; OR=2.6), and media exposure ($p=0.043$; OR=3.3), are the most dominant variable that related to people go for screening CRC. Perception of CRC screening has a negative impact on screening ($p=0.003$; OR=0.666). **Conclusion:** The general population in Indonesia had deficient knowledge of CRC and screening. Medical professional affection, relatives history, and media exposure significantly influence the people to go for screening.

O-1-5

Diagnostic Value of Fecal Immunochemical Test in Colorectal Cancer Screening in Indonesia

A.A. Rani¹, M. Abdullah¹, A. Fauzi¹, M. Simadibrata¹, A.F. Syam¹, T. Wijayadi²

¹Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Indonesia/ Dr. Cipto mangunkusumo Hospital, Jakarta, ²Department of Internal Medicine, Gading Pluit Hospital, Jakarta, Indonesia

Introduction: Colonoscopy is empirically recommended as the first choice in colorectal cancer (CRC) screening. However, the cheaper test will be preferable. This study assessed the diagnostic value of FIT for detecting Advanced Colonic Lesion (ACL) in Indonesian population. **Methods:** The patients were recruited consecutively from December 2009 – April 2010 from six hospitals in Jakarta. All patients who underwent colonoscopy due to any indication except rectal bleeding. ACL defined as cancer, adenomatous polyp > 1 cm, and villous adenomatous polyp. The FIT (OC Light® and Oncoprobe®) was performed according standard procedure using immunochromatography. The data was analyzed using SPSS version 16. **Result:** Of the 82 patients (57.3% male and 42.7% female), the mean (SD) age was 52.3 (13.8) years with ranging 20–83 years, consisted of 49 (59.8%) Malay and 33 (40.32%) Chinese patients. Four frequent colonoscopic findings were infective colitis (40.2%), polyp (32.9%), CRC (11.0%), ileitis (9.8%). The ACL was found in 37 (45.1%) patients. The FIT for significant ACL showed sensitivities, specificities, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were 40.5 % vs 43.2%, 86.7% vs 82.2%, 28.6% vs 33.3%, and 63.9% vs 63.8%, respectively. **Conclusion:** The diagnostic value of FIT was relatively low. However comparable with the data reported in western country.

O-1-6

The Prevalence of Advanced Colorectal Adenoma is Increasing Rapidly rather than Colorectal Cancer in China: A Large Multicenter Study of Symptomatic Hospital-Based Individuals between 1990 and 2010

Hui-Min Chen^{1*}, Yu-Rong Weng^{1*}, Bo Jiang², Jian-Qiu Sheng³, Ping Zheng⁴, Cheng-Gong Yu⁵, Xiao-Yu Chen¹, Zhi-Zheng Ge¹, Jing-Yuan Fang^{1#}

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*The two authors contributed equally to this work

Background & Aims: Most of patients with colorectal cancer (CRC) were developed from advanced colorectal adenoma (CRA), but it is not clear that the comparison of the prevalence between advanced CRA and CRC, especially in China. The aim of this study is to determine whether the prevalence rates of advanced CRA and CRC increase simultaneously during the recent two decades in China. **Methods:** We retrospectively investigated 157943 patients who underwent total colonoscopy at five medical centers in China from 1990 to 2009. Of the patients who satisfied the diagnostic criteria for advanced CRA or CRC, the clinical data, endoscopy and histopathology reports were analyzed. A total of 6777 patients diagnosed with advanced CRA and 3486 cases with advanced CRC were included in the analysis. **Results:** During the 2000s, the prevalence of advanced CRA was approximately 1.88 times more than during the 1990s. However, with regards to CRC, the prevalence of CRC had only increased by 0.73 times more than the 1990s. The advanced CRA and CRC at a significantly higher rate in men than in women on the 2000s compared with the 1990s. The advanced CRA prevalence in patients younger than 49 yrs increased from 0.86% in the 1990s to 2.74% in the 2000s. The adenoma in 3.40% of advanced CRA patients located in the distal colon without any occurrence of advanced CRA in the proximal colon in 2000s than in 1990s (1.23%). Of the 1990s group with advanced CRA, 111 (0.43%) had more than one adenoma, but 1504 (1.14%) had more than one adenoma found on the 2000s. **Conclusions:** We detected the prevalence of advanced CRA of symptomatic hospital-based individuals increased significantly more rapidly than that of CRC in China over the last two decades. **Keywords:** Colorectal cancer; Advanced colorectal adenoma; Colonoscopy; Prevalence; Clinical pathological characteristics. **Abbreviations used in this paper:** CRC, colorectal cancer; CRA, colorectal adenoma.

Oral Session 2 – Biomarker 1

Chairpersons: Takayuki Matsumoto, Qi Zhu

O-2-1

Epigenetic Signature of Gastrointestinal Cancers: A Role as Diagnostic Biomarkers for Cancers

Sung Kwan Shin

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The improvement of understanding of the molecular biology of gastrointestinal (GI) cancers has revealed that not only genetic alterations including mutations and deletions, but also epigenetic inactivation of tumor suppressors play an important role in carcinogenesis. Epigenetic instability includes *de novo* hypermethylation of CpG dinucleotide clusters present in the promoter regions of ~50% of human genes, causing transcriptional silencing of the gene and a resultant loss of growth inhibitory property of tumor suppressor genes. Of interest, a subset of stomach cancers and colon cancers has shown to exhibit wide-extent of these epigenetic changes.

The identification of specific methylation events occurring early in multistep carcinogenesis and the suggestion that epigenetic silencing of genes may play a causative role in tumor development, have generated significant interest in the use of DNA methylation as a diagnostic marker of GI cancers. The inactivation of variety of tumor suppressor genes by aberrant DNA hypermethylation has been more frequently observed than the loss of function of these genes by mutations in stomach cancer. Moreover, there has been shown that methylation index of certain genes such as *CDH1*, *DAPK*, *p14*, *THBS1*, *TIMP-1* is significantly increased in the process of multistep gastric carcinogenesis from atrophic gastritis to stomach cancers. Several studies have indicated that aberrantly regulated DNA methylation is one of the key mechanisms for tumor suppressor gene silencing during the adenoma-to-carcinoma and serrated adenoma-to-carcinoma sequence in the colon. The aberrant methylation of certain tumor suppressor genes has been reported in colonic adenomas and aberrant crypt foci. In one study, a gradual increase of aberrant methylation of *MGMT* in a normal-to-adenoma-to-carcinoma progression was found. This investigation suggested that methylation at this DNA repair gene may evolve and spread throughout the promoter in a gradual manner as the colonic epithelial cells move through the progressive, multistep cascade. In another study, whether loss of one Netrin-1 receptor, *UNC5C*, was mediated via epigenetic silencing of its promoter region in the colon was asked. Interestingly, a rare evidence of *UNC5C* methylation in the normal colon was observed, but an increased frequency of methylation in adenomas and colon cancer was found. When these data were compared with allelic losses at a second Netrin-1 receptor, *DCC*, hypermethylation of *UNC5C* occurred predominantly in the earlier lesions (adenomas and early colon cancers), whereas *DCC* losses occurred frequently in advanced colon cancers. These data clarified the importance of epigenetic silencing as an earlier event (*UNC5C* methylation), compared to

genetic alterations (*DCC* loss) that happen at later stages in multistep colorectal carcinogenesis.

The recognition which epigenetic alterations were not only the pathogenic events in the premalignant lesions such as atrophic gastritis or colonic adenomas but also neoplasm-specific events has been accumulated, the notion that this epigenetic signature may have the potential to be used as molecular biomarkers of pre-malignant tumors in the stomach and colon has been highlighted. In fact, novel methodologies using feces, body fluid or blood for the early detection of pre cancerous or malignant lesions that are possibly less expensive and might be better accepted by patients are being compared to the most commonly used screening methods which have the invasive nature. Pilot studies have shown promise for an approach using tumor-derived DNA mutations in the feces of cancer patients for the early detection of GI cancers. Of note there is evidence to suggest that epigenetic signatures can be detected in the blood and stools of patients with premalignant lesion or early staged GI cancers.

Although it may seem like that further studies are necessary to validate the assays based on methylated genes for the detection of pre-malignant or cancerous lesions in GI tract, it is likely that the detection of epigenetic signatures can be a useful tools for the clinicians to diagnose GI neoplasm in premalignant or earlier stages in the near future.

O-2-2

15-Hydroxyprostaglandin Dehydrogenase in the Gastric Adenocarcinoma Arising from Adenoma

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Introduction: 15-hydroxyprostaglandin dehydrogenase (15-PGDH) is the rate-limiting enzyme in catalyzing degradation of prostaglandin and its role as a tumor suppressor has been mostly studied in colon cancer. Although some reports dealt with 15-PGDH in gastric cancer, there was no report regarding 15-PGDH from the point of early phase carcinogenesis. Therefore we aimed to analyze 15-PGDH of early gastric adenocarcinoma in the background of adenoma. **Methods:** Thirty specimens consecutively obtained from the endoscopic resection of early gastric cancer in 2007 were analyzed with 15-PGDH immunohistochemistry by using a monoclonal anti-15-PGDH antibody. The diagnosis of selected specimen was adenocarcinoma arising from adenoma and we re-confirmed the diagnosis. We have divided specimens into five groups according to the proportion of staining; 0, 1~10%, 11~33%, 34~66%, and more than 66%. Also surrounding metaplasia type was determined. We determined negative 15-PGDH staining as 10% and less in proportion. **Result:** The average age and percent male of 30 patients were 70.8 year and 76.7% respectively. Most specimens showed low proportion of staining; 13 specimens to 0%, 14 specimens to 10% and less, 3 specimens to 33% and less. The negative 15-PGDH staining accounted for 90% of cases. The adenoma cells as well as adenocarcinoma cells were hardly stained. There were no significant differences in age, sex and metaplasia type between 15-PGDH negative and positive group.

Conclusion: Expression of 15-PGDH is decreased in early phase gastric adenocarcinoma.

O-2-3

The Effect of *Helicobacter pylori* Infection on the Expression of VEGFR1 and VEGFR2 in Intestinal Metaplasia and Gastric Cancer

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Helicobacter pylori (HP) infection causes chronic gastritis (CG), gastroduodenal ulceration and gastric cancer (GC). GC arises through a multistep process from CG to intestinal metaplasia (IM) and then finally to invasive GC. The overexpression of VEGF receptors, including VEGFR1 and VEGFR2, is thought to play a central role in cancer growth. IL-16 is involved in the pathophysiological process of chronic inflammatory diseases. The **aim** of this study is to determine the changes in the expression of VEGFR1 and VEGFR2 in CG, IM and GC as well as the effect of HP infection and IL-16 on epithelial cell proliferation and VEGFR1&2 expressions in gastric cells *in vitro*. **Methods:** Gastric biopsies were classified by histological findings as CG; either with (CG+) or without HP infection (CG-), IM; either with (IM+) or without HP (IM-) and GC with HP (GC+). For *in vitro* studies, AGS cells were incubated with combinations of HP and IL-16. Cell proliferation was studied by BrdU uptake. The expression of VEGFR1 and VEGFR2 was studied by ABC, ELISA and RT-PCR. **Results:** IL-16 expression was detected in all HP infected gastric mucosa. In CG, there was no significant difference in VEGFR1 and VEGFR2 expression between biopsies with and without HP infection (VEGFR1; CG+:2.43±2.90% vs. CG-:1.37±2.22%, VEGFR2; CG+:0.88±0.93% vs. CG-:0.62±0.65%). In HP infected mucosa, VEGFR1 expression was significantly higher in IM+ than CG+ (VEGFR1; IM+:4.23±5.06% vs. CG+:2.43±2.90%, $p<0.01$). VEGFR1&2 expressions were higher in GC+ (VEGFR1; 12.14±7.28%, VEGFR2; 9.53±6.24%, $p>0.01$) than in CG+ and IM+. *In vitro* studies: HP infection alone significantly decreased cell proliferation. Administration of IL-16 increased BrdU uptake and VEGFR1&2 expressions in AGS cells which had been decreased by HP. Administration of IL-16 increased the expression of VEGFR1&2 mRNA and protein in HP infected AGS cells. **Conclusions:** The expression of VEGFR1&2 in long-term HP infected gastric mucosa may indicate an early stage of carcinogenesis because it appears before a definitive diagnosis of GC. The expression of IL-16 by HP infection may be a trigger for the expression of VEGFR1&2 in gastric mucosa, and it may also be a factor for development of gastric carcinogenesis.

O-2-4

Contrasting Activity of Hedgehog and Wnt Pathways according to Gastric Cancer Cell Differentiation: Relevance of Crosstalk Mechanisms

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Introduction: Gastric cancer displays different biological behaviors according to histological differentiation. The different histological behavior may involve the activation of distinct signaling pathways necessary for the growth and survival of cancer cells in gastric cancer. We investigated the differentiation-related signal interaction between Hedgehog (Hh) and Wnt signaling pathways in gastric cancer cells. **Methods:** AGS and MKN-45 gastric cancer cells and HT-29 colon cancer cells were used. Differentiation of gastric cancer cells were induced by sodium butyrate and/or all-*trans* retinoid acid. Sonic hedgehog (Shh), patched (Ptc)-1, and glioma-associated oncogene (Gli)-1 for Shh signaling, and nuclear β -catenin for Wnt signaling were analyzed. Paraffin-embedded tissues from human gastric cancers were used to evaluate the expression of Shh, Gli-1, and β -catenin *in vivo*. Secreted frizzled-related protein (sFRP)-1 was analyzed as a regulator between Hh and Wnt signaling. **Result:** The Shh signal expressions were increased during the cellular differentiation. In contrast, the expression of Wnt signaling decreased during the differentiation. Ectopic expression of Gli-1 increased the level of the sFRP-1 transcript, whereas inhibition of Gli-1 by siRNA reduced the level of the sFRP-1 transcript. Chromatin immunoprecipitation assay showed that Gli-1 induced the transcriptional regulation of sFRP-1 gene expression. Ectopic expression of Gli-1 decreased the nuclear β -catenin staining, but the inhibition of Gli-1 by siRNA induced the reversal of nuclear β -catenin over-staining. Ectopic expression of β -catenin also decreased the expression of Gli-1 in the sodium butyrate treated cancer cells. sHh- and Gli-1 immunoexpression were in greater degree in well differentiated than in poorly differentiated gastric cancer tissues while nuclear β -catenin immunoexpression was lower in well differentiated compared to poorly differentiated cells. **Conclusion:** The Shh and Wnt signaling pathways are involved in gastric cancer cell differentiation. The analysis of differentiation-specific signal changes, combined with signals related to the process of tumor progression or migration, may be helpful in understanding the molecular heterogeneity of gastric cancers.

Oral Session 3 – Prevention

Chairpersons: Shin'ichi Takahashi, Abdul Aziz Rani

O-3-1

Chemopreventive Mechanism by Guggulsterone for the Esophageal Adenocarcinoma Cells

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Objective: Induction of cyclooxygenase-2 (COX-2) and caudal type homeobox 2 (Cdx2) expressions by acid and/or bile acid via NF- κ B in the lower esophagus is the critical molecular events in the development of Barrett's esophagus and esophageal adenocarcinoma. Although PPIs can reduce acid exposure in the lower esophagus, there are few remedies targeting bile exposure. Thus, we hypothesized that guggulsterone, a NF- κ B inhibitor, may inhibit the development of Barrett's esophagus and esophageal adenocarcinoma through suppressing COX-2 and Cdx2. **Methods:** COX-2 and Cdx2 expressions were analyzed by qRT-PCR and immunoblot analysis in esophageal adenocarcinoma cell lines, OE19 and OE33. Prostaglandin E2 (PGE2) was measured by ELISA with conditional cell culture medium. The cell viability and the cell cycle were also examined. **Results:** The qRT-PCR revealed COX-2 and Cdx2 expressions in esophageal adenocarcinoma cell lines were increased by the bile acid (DCA, deoxycholic acid) treatment and guggulsterone reversed this DCA-induced COX-2 and Cdx2 expressions. Guggulsterone also reduced basal COX-2 and Cdx2 mRNA expression. In the immunoblot analysis COX-2 and Cdx2 protein expression level was also seen the similar tendency. Guggulsterone reduced PGE2 production in esophageal adenocarcinoma cell lines. Further, guggulsterone reduced the cell viability along with the induction of a G1/S phase arrest and the accumulation of cells in the subG1 phase. **Conclusion:** Guggulsterone reduced both COX-2 and Cdx2 expressions and it also suppressed cell growth in esophageal adenocarcinoma cell lines. These results suggest that guggulsterone can be a chemopreventive agent as for the esophageal adenocarcinoma as well as Barrett's esophagus.

O-3-2

The Selective Cyclooxygenase-2 Inhibitor Celecoxib Activates the Tumor Suppressor *microRNA-29c* in Human Gastric Cancer

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Introduction: microRNAs (miRNAs) are small non-coding RNAs that function as endogenous silencers of target genes and play critical roles in human malignancies. We have recently shown that epigenetic activation of tumor suppressor miRNAs may be a novel therapeutic approach for human cancers (Saito Y et al. *Cancer Cell* 9: 435, 2006; *Oncogene* 28: 2738, 2009). The selective cyclooxygenase-2 (COX-2) inhibitor celecoxib has been proposed to be a potential drug for the chemoprevention of gastrointestinal tumors. To investigate the role of miRNAs in anticancer effect of celecoxib, miRNA expression profile was examined. **Methods:** Human gastric cancer cell lines were exposed to celecoxib and miRNA expression profile was analyzed by microarray and quantitative RT-PCR. A total of 53 patients with gastric tumors including gastric adenomas (atypical epithelia), early gastric cancers and advanced gastric cancers were examined. Expression of miRNA target gene was analyzed by Western blotting and immunohistochemistry. **Result:** miRNA microarray analysis revealed that *miR-29c* was significantly activated by celecoxib in gastric cancer cells. *miR-29c* was significantly downregulated in gastric cancer tissues compared to non-tumor gastric mucosae. Downregulation of *miR-29c* was associated with the progression of gastric cancer and was more prominent in advanced gastric cancers compared to gastric adenomas and early gastric cancer ($p < 0.05$). In addition, expression of the oncogene *Mcl-1*, a target of *miR-29c*, was significantly increased in gastric cancer tissues compared to non-tumor gastric mucosae. Activation of *miR-29c* by celecoxib induced suppression of *Mcl-1* and apoptosis in gastric cancer cells. **Conclusion:** These results suggest that downregulation of the tumor suppressor *miR-29c* plays a critical role in the progression of gastric cancer and that *miR-29c* is a novel therapeutic target for COX-2 positive gastric cancer. Selective COX-2 inhibitors may have clinical promise for the chemoprevention of gastric cancer via activation of *miR-29c*.

O-3-3

Preventive Effects of Flavonoids on Hyperleptinemia and Colitis-Related Colon Carcinogenesis in ICR Mice

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Introduction: Colorectal cancer is one of the leading causes of cancer-related death in the western countries. A number of recent studies have indicated that some adipocytokines may significantly influence the proliferation of malignant cells *in vitro*, whereas it remains unclear whether they have similar roles *in vivo*. In this study, we determined serum levels of adipocytokines in mice with azoxymethane (AOM)- and dextran sulfate sodium (DSS)-induced colon carcinogenesis. **Methods:** Five-week-old male ICR mice were given a single intraperitoneal injection of AOM (week 0), followed by 1% DSS in drinking water for 7 days. Nobiletin, a citrus flavonoid, was given in the diet (100 ppm) for 17 weeks (from week 3 to 20). Thereafter, the incidence and number of colon tumors, and serum concentration of adipocytokines were determined at the end of week 20. **Result:** The serum leptin level in AOM/DSS-treated mice was 6 times higher than that in untreated mice, whereas there were no significant differences in the levels of triglycerides, adiponectin, TNF- α , and IL-6. Feeding with nobiletin abolished colonic malignancy and notably decreased the serum leptin level by 75% ($P < 0.05$). Further, nobiletin suppressed the leptin-dependent, but not -independent, proliferation of HT-29 colon cancer cells and decreased leptin secretion, but not that of adiponectin in differentiated 3T3-L1 mouse pre-adipocytes in a dose-dependent manner. **Conclusion:** Taken together, our results suggest that higher levels of leptin in serum promote colon carcinogenesis in mice, while nobiletin has chemopreventive effects against colon carcinogenesis, partly through regulation of leptin levels.

O-3-4

Sodium Butyrate Enhances Complement-Mediated Cell Injury via Down-Regulation of Decay-Accelerating Factor Expression in Colonic Cancer Cells

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Decay-accelerating factor (DAF) expressed on the surface of colonic cancer cells presents a barrier to complement-mediated clearance by contributing to the ineffectiveness of the humoral immune response. In this study, to investigate the mechanisms responsible for the anti-tumor effects of butyrate, we evaluated how butyrate modulates DAF expression in colonic cancer cells. Three colonic cancer

cell lines (HT-29, Caco-2, and T84 cells) were studied. DAF protein expression was assessed by western blot, and DAF mRNA expression was evaluated by northern blot. Complement C3 deposition on the surface of colonic cancer cells was determined by enzyme-linked immunosorbent assay (ELISA). The promoter activity of the DAF gene was assessed by a reporter gene-luciferase assay. Butyrate reduced the basal and interleukin-4 (IL-4)- and tumor necrosis factor- α (TNF- α)-induced expression of DAF protein and mRNA in HT-29 cells. It increased the susceptibility to complement attack and enhanced C3 deposition on HT-29 cells. The inhibitory effect of butyrate on DAF mRNA expression was also observed in T84 and Caco-2 cells. Butyrate decreased basal DAF expression at both transcriptional and post-transcriptional levels. The inhibitory effect of butyrate on IL-4-induced DAF expression was closely associated with a blockade of IL-4-induced DAF mRNA stability. TNF- α -induced transcriptional activation and the increased stability of the DAF gene were also blocked by butyrate. Similar but weak effects were induced by trichostatin A, a potent histone deacetylase inhibitor, suggesting that histone acetylation might participate in butyrate activity. These observations indicate that both a down-regulation of DAF expression and the induction of susceptibility to complement attack contribute to the anti-tumor effects of butyrate in colonic cancer.

Oral Session 4 – Biomarker 2

Chairpersons: Yoshikazu Kinoshita, Jose D. Sollano

O-4-1

Different Expression Patterns of Cancer Stem Cell Markers in Well Differentiated Gastric Cancer and Gastric Adenoma Tissues

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Introduction: Cancer stem cells (CSCs) are identified which possess the ability to initiate tumor growth and sustain self-renewal. Recently, CD133/prominin-1 and CD44 were reported as potential gastric CSC markers by flow cytometry analyses and xenograft tumorigenicity experiments. Although these markers suggested being able to isolate potential gastric CSCs, the development and progression of these CSCs in initial stage of gastric cancer are unknown. In this study, we examined expression patterns of these CSCs markers in gastric adenoma and very well differentiated gastric cancer tissues by immunohistochemistry. **Methods:** Total 15 samples which was diagnosed gastric adenoma by biopsy samples through endoscopy were studied. All samples were resected by endoscopic mucosal resection for final diagnosis, and diagnosed pathologically as 8 carcinoma and 7 adenoma. **Result:** The CSC markers' expression area were limited in abnormal glands, however the location of expressions

were different. CD133 was expressed in the bottom of abnormal gastric glands. CD44 was expressed in abnormal cells, especially surface area of abnormal gastric glands. The expression strength between adenoma and carcinoma was not different in both CD133 and CD44.

Conclusion: These results of immunohistochemistry showed the different expression patterns of these CSC markers. Both markers were expressed in early steps of carcinogenesis. Further study will be needed to specify the true CSC in gastric cancer tissue.

O-4-2

CDH1 Analysis in Familial Diffuse Gastric Cancer in Korea

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Introduction: Gastric cancer is the most common malignancy in Korea. Germline mutation of the E-Cadherin gene (*CDH1*) has been identified in familial gastric cancer patient in Western population. However, there were few reports about E-Cadherin gene mutation in Asian population. The aim of our study was to find *CDH1* genomic rearrangements in Korean. **Material and Method:** We screened 28 gastric cancer patients to investigate germline mutations of *CDH1* gene. The inclusion criteria were 1. Isolated individual diagnosed with pathologically confirmed diffuse gastric cancer less than 30 years of age 2. Two or more cases of gastric cancer with at least, one DGC diagnosed before age 35. Screening of the entire coding region of the *CDH1* gene and all intron/exon boundaries was performed by bi-directional sequencing. **Results:** Six patients with criteria 1 and twenty-two patients with criteria 2 were enrolled. Only one proband (28 year-old male without family history) have *CDH1* gene mutation in the splicing mutation in (715G>A, G239R), which was also found in another family member. Other cases have the wild type *CDH1* gene. **Conclusions:** *CDH1* gene mutation is relatively rare in Korean population. Further study is needed focused on other gene mutation.

O-4-3

Potential of Anti-IL-6 Antibody as Anti-Cancer Agent Targeting Colon Cancer Stem Cells

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Background and aims: Recent studies have shown that cancer stem cells can initiate and sustain tumor growth, and exhibit resistance to cytotoxic therapies. Therefore, cancer stem cells are thought to be the main potential target for anticancer therapy. Oct-4, Klf-4, c-Myc (iPS related genes) and Bmi-1 (polycomb gene) play an important role in stem cell biology. On the other hand, high serum levels of IL-6 have been reported in colorectal cancer patients, suggesting IL-6 trans-signaling is involved in carcinogenesis. However, the involvement of IL-6 in cancer has been quite controversial; IL-6 promotes CSCs self-renewal in breast, liver, and lung cancer, and glioma, but inhibits the growth of myeloma. In the present study, we investigated the effect of IL-6 and anti-IL-6 neutralizing antibody on stem cell biology and chemo-resistance of colon cancer stem cells. **Methods:** The colon cancer cell line WiDr were cultured as spheroid-forming cells in serum free non-adherent condition, because three dimensioned, non-adherent spheroids are reported to enrich in stem cells, suggesting that spheroid formation is one of useful techniques to define cancer stem cells through functional assays. The expression of c-myc, Oct-4, KLF4, Bmi1, and IL-6 was investigated, by RT-PCR. The effects of IL-6 and anti-IL-6 antibody treatment on spheroid formation, and the expression of these genes, and chemoresistance were determined. **Results:** Spheroid forming cells were expressing higher levels of oct-4, klf-4, bmi-1, and IL-6, and accelerated chemoresistance, comparing with control cells cultured in adherent condition. IL-6 antibody treatment decreased spheroid formations and oct-4, klf4, and bmi1 expression, and suppressed chemoresistance of 5FU in spheroid forming cells, although IL-6 treatment enhanced these stem cell phenotypes. **Conclusion:** These results indicate that IL-6 antibody has inhibitory effects on colon cancer stem cell biology and it has the potential as effective anti-cancer drug targeting in cancer stem cells.

O-4-4

Fatty Acid Synthase (FASN); The Proteomic Biomarkers of Colitis-Induced Colorectal Cancer

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Introduction: As the incidence and prevalence of inflammatory bowel disease (IBD) is explosively increasing in East Asian includ-

ing Korea and Japan, might be due to the change of diet behavior in to Western style and environmental modification, the screening and prevention of colitis-associated colorectal cancer has been emphasized these days. We previously established repeated dextran sodium sulfate (RDSS) model as colitis-induced colorectal carcinogenesis animal model, in which chronic colitis alone triggers carcinogenesis without any intervention of carcinogen (Proteomics 2005, Cancer Prevention Res 2010). The comparative proteomic study of RDSS model with acute IBD model and normal mice could give us valuable candidates of biomarker which not only predicts disease severity but also helps us to understand the progression of IBD to colitis-associated colorectal cancer. **Methods:** C57BL/6 mice were exposed to 15 cycles of DSS with each cycle consisting of 0.7% DSS for 1 week followed by sterilized water for 10 days. After killing, the proteins extracted from colon tissues are analyzed by quantitative mass spectrometry using iTRAQ tagging methods. The up-regulated and down-regulated proteins are identified by spectrum-mill software and ipi. MOUSE.v3.67 database, confirmed by Western blot analysis. Caco-2 human colon carcinoma cells were cultured to investigate the biologic roles of FASN as validation model. **Result:** Quantitative mass spectrometry results showed that 37 up-regulated and 1 down-regulated proteins were identified in RDSS group compared with normal group. Among those, the levels of expression of FASN and anti-apoptotic proteins were significantly increased and AKT and ERK pathways were activated in RDSS treated mice. Caco-2 cell line treated with AKT inhibitor (LY294002) and ERK inhibitor (PD98059) reduced FASN expression, and FASN inhibitor (cerulenin, orlistat) induced apoptosis through endoplasmic reticulum stress and caspase activation. **Conclusion:** FASN is up-regulated in RDSS mice and AKT and ERK pathways are involved in the transcription of FASN, and the role of FASN is crucial not only in energy metabolism of cancer, but also in triggering anti-apoptotic properties of cancer.

P-1

Long Term Prognosis of ESD for Superficial Esophageal Cancer

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Methods: Our study aims to clarify the long-term prognosis of ESD for esophageal SCC. 208 patients (206 males and 21 females) with 243 lesions of esophageal SCC were treated by ESD from January 2000 to February 2009. The median age and follow up period was 68 (42–91) age and 46 months, respectively. The median diameter of the lesions was 23 (1–85) mm. The invasion depth was 219 EP-LPM and 46 MM-SM1. The en-bloc complete resection was defined as en-bloc, horizontal and vertical margin negative. Cases of vascular invasion positive in MM-SM1 underwent chemoradiotherapy (CRT) or operation. Cases of vascular negative in MM-SM1 were given non-therapy or CRT. **Results:** 1. The en-bloc resection rate was 98.1% (260/265). The en-bloc complete resection rate was 96.6% (256/265). 2-1. CRT was performed on four in 9 cases of MM-SM1 with vascular invasion, and there were no recurrence. Operation was performed for one patient, and the patient died of distant metastasis. 4 remaining patients were followed up without additional treatment. 2 patients had LN metastasis, and were treated by CRT. 1 patient had lung and LN metastasis, and was treated by chemotherapy. 1 patient died of other disease. 2-2. CRT was performed on five in 37 cases of MM-SM1 without any vascular invasion, and there were no recurrence. The remaining 32 cases were not given any therapy later. One case had LN metastasis 31 months after ESD. 3. The local recurrence rate was 0%. The five-year survival rate of overall survival curve was 85.8%, and the five-year survival rate of cause specific survival was 98.6%. **Conclusion:** Long term prognosis of EP-LPM was excellent. However, metastasis was not so rare in MM-SM1 with lymph duct involvement. Therefore, additional therapy should be recommended for the patients.

P-2

Endoscopic and Oncologic Outcome after Endoscopic Resection for Early Gastric Cancer: Comparison of Absolute and Extended Indications

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Introduction: Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are novel techniques that can remove early gastric cancer (EGC) en bloc. However, there is no consensus about the criteria for their use. We aimed to assess the clinical outcomes of endoscopic treatment based on indication criteria and endoscopic method. **Methods:** EMR or ESD was performed on 1340 cases of EGC of 1187 patients from July 1994 to January 2009 in Asan Medical Center. Of the 1340 EGCs, 856 were placed in the absolute indication group for EMR or ESD (differentiated mucosal cancer; elevated lesions ≤ 20 mm in diameter and depressed lesions ≤ 10 mm without ulceration), and 484 were placed in the extended indication group (differentiated cancer; mucosal cancer without ulceration, regardless of tumor size, mucosal cancer with ulceration ≤ 30 mm and located < 500 μ m from the muscularis mucosae; and submucosal invasive cancer ≤ 20 mm in size). Each group was sub-divided according to whether EMR or ESD had been performed. **Result:** Although the en bloc resection rates were similar in the absolute and extended indication groups (86.8% vs 84.9%, $p=0.339$), the complete resection rate was significantly higher in the absolute indication group (96.8% vs 88.2%, $p<0.001$). The risks of complication and operation were higher in the extended indication group, but there was no between-group difference in local recurrence rate. In the extended indication group, ESD resulted in a significantly higher resection rate and a significantly lower operation rate than EMR, but complication rates were similar. **Conclusion:** ESD resulted in a higher resection rate and a lower operation rate than EMR, especially in the extended indication group, with acceptable clinical outcomes. Endoscopic treatment may be useful in patients with extended criteria for EGC. ESD is superior to EMR, except for small lesions, despite the longer procedure time for ESD.

P-3

Comparison of ESD and EMR for the Colorectal Carcinoid in this Hospital

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Introduction: Rectal carcinoid is a low-grade tumor of the malignancy. Recently we introduced the endoscopic submucosal dissection (ESD) for the colonic tumor-related lesion. **Aim & Methods:** The aim of this study was to evaluate the feasibility of ESD for rectal carcinoid. The case intended for 64 rectal carcinoid cases 10mm or less from Jan/1988 to May/2009 and weighed a treatment outcome of ESD against EMR about sex, average age, procedure time, complication, and a vertical margin positive case. We assigned the EMR case to A group, and ESD case to B group. (A/B) **Result:** As for the number of cases, as for 75/4, sex, it is 2.4:1/2.5:1, the average age in 57.7/60.3 years old, and, at an average lesion size 6.3/8.0 mm, as for an average of procedure time 8.0/59.6 minutes (for 3–14/30–85 minutes), vertical margin positive rate, as for 25/0 (33/0%), complication showed one case was perforation in EMR. **Conclusion:** We tended to be long procedure time in ESD, but the ESD cases did not show the vertical margin positive case and complication. Rectal ESD is feasible endoscopic treatment to En-bloc resection about carcinoid.

P-4

Clinicopathological Features of Superficial Esophageal Cancers with Lymph Nodes Metastasis: An Implication for Endoscopic Resection

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Introduction: The application of endoscopic resection in superficial esophageal cancer (SEC) is limited by the presence of lymph node metastasis (LNM). So, It is very important to establish which patients have virtually no risk of LNM. We investigated clinicopathological parameters predicting LNM in patients who underwent esophagectomy for SECs and to identify the best candidate patients for endoscopic resection. **Methods:** A total 194 patients who underwent esophagectomy for SECs between 1991 and 2008 were enrolled. We evaluated clinicopathological factor associated with LNM. **Result:** Among 194 patients, LNM was found in 41 patients (21.1 %). The rates of LNM were 0.0 % (0/18), 8.5 % (4/47), 25.0 % (6/24), 15 % (3/20), 27.6 % (8/29) and 38.5 % (20/52) for m1, m2, m3, sm1, sm2, and sm3 lesions, respectively. On multivariate analysis, lymphovascular invasion ($p=0.001$), superficial tumor size ($p=0.002$), and LMM (lamina muscularis mucosa) invasion width ($p<0.001$) were significantly associated with LNM in patients with SEC invading LMM. Among 64 patients with mucosal or sm1 cancer < 3 cm, only one patient had LNM without lymphovascular invasion showing LMM invasion width > 3.0 mm. The surgical mortality, in-hospital mortality, and postoperative morbidity were 1.5 %, 2.6 %, and 74.7 %, respectively. **Conclusion:** Considering the high mortality and morbidity of esophagectomy, endoscopic resection should be more actively applied to patients with low risk of LNM.

	Group A (n = 57)	Group B (n = 7)	
Average age	58.0 (31~86)	58.4 (36~77)	*NS
Sex	2.1:1	1.3:1	*NS
Average tumor diameter (mm)	6.1 (1~10)	6.7 (3~10)	*NS
Procedure time (min)	9.5 (3~14)	52 (40~90)	*p < 0.05
En-block resection rate	100%	100%	**NS
Vertical margin positive rate	21%	0%	**p < 0.05
Complication rate	1.7%	0%	
	(Perforation 1 case)		
Vascular invasion positive rate	1.7%	14.3%	*NS

* χ^2 - Authorization & Fisher Ratio **t - Authorization

Figure for Poster 3.

P-5

CO₂ Insufflation during Esophageal ESD under General Anesthesia Provides Safe Introduction for New Entry Institution

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Objective: The technique of ESD in the esophagus is generally thought to be more difficult compared to that in the stomach, and adequate sedation of the patient is a key factor for a successful operation of the delicate technique in the esophagus. The accidents that occur in the esophagus, such as perforation, tend to become severer. Our study aimed to reveal the usefulness of combining CO₂ insufflation under general anesthesia when introducing esophageal ESD. **Method:** Patient background, treatment outcomes, and accidents were reviewed regarding 10 lesions in 8 patients (all men, average age 67 years, range 51–78) who underwent esophageal ESD during this 2 years. **Results:** The sites of the tumors were Ut in 1 patient, Mt in 7 patients, Lt in 2 patients. The average diameter of the tumor was 26.9 mm (10–53 mm), and the average diameter of resection was 36.2 (20–67 mm). The average duration of the ESD technique was 162 minutes (102–322 min). En bloc resection was possible for all the patients, and 8 lesions had a curative resection but the remaining 2 lesions were positive in horizontal margin and had non-curative resection. As to accidents involved, low density area in the CT scan of the chest, in which pneumomediastinum could not be ruled out, was found in 1 patient. But the patient recovered conservatively with only transient fever. We considered that it would be benefit by the CO₂ insufflation. **Conclusion:** Esophageal ESD with CO₂ insufflation under general anesthesia was useful in that a stable intraoperative management could be achieved with the support of the anesthesiologist, which allowed the operator to concentrate on the technique, and that accidents were likely to be prevented from becoming severe by the combination of CO₂ insufflation.

P-6

Development of Gastric Cancer after Endoscopic Resection of Early Gastric Cancer

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Endoscopic mucosal resection is widely performed against early gastric cancer because of its noninvasiveness and high curability. However, it is clinical problem regarding this treatment that cancer develops at high rate at the other site in same patients subsequently.

Eradication therapy for *Helicobacter pylori* is reported as effective for suppressing the development of cancer, but the effect seems limited. Here we conducted this clinical review of the patients underwent endoscopic mucosal resection in our hospital, to clarify the rate of development of new gastric cancer after the treatment. The study subjects were 27 patients who underwent endoscopic mucosal resection against early-stage gastric carcinoma at Teikyo University Hospital (Tokyo, Japan), from 2002 till 2005. All of them were received periodical endoscopic examination after the endoscopic procedure more than one year. New gastric cancers developed in two patients; one was *Helicobacter pylori*-positive and the other was negative. Both the lesions could be resected endoscopically. We concluded that periodical endoscopic follow-up is important for improving the prognosis of newly developed gastric cancer as well as eradication therapy of *Helicobacter pylori*.

P-7

Detection Rate of Early Gastric Cancer Comparison with TN-EGD and TO-EGD in Japan

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Introduction: In Japan transnasal ultrathin esophagogastroduodenoscopy (TN-EGD) is very popular. Problems have been identified with TN-EGD, however, including poor endoscopic imaging quality. In this study, we investigated detection rates for early gastric cancers using comparison with TN-EGD and conventional transoral EGD (TO-EGD). **Method:** The subjects were 1915 patients who underwent TN-EGD, 18604 patients who underwent TO-EGD from 2005 to 2008. We investigated the detection rates for early gastric cancer. **Result:** The detection rate was 0.99% (19/1915) in TN-EGD, 0.92% (171/18604) in TO-EGD respectively. The cancer type (0-I:0-IIa:0-IIb:0-IIc:0-IIa+IIc:0-IIc+III:0-III) was 5.3%:21.1%:0%:63.1%:10.5%:0%:0% in TN-EGD, 5.8%:35.1%:0.6%:48.0%:9.3%:0.6%:0.6% in TO-EGD respectively. **Conclusion:** Detection rate of early gastric cancer using TN-EGD was high at 0.99%. There was no significant difference in detection rate using between TN-EGD and TO-EGD. So TN-EGD is useful for screening of gastric cancer.

P-8**Incidence of Pancreatic Cancer in Chinese Patients with Chronic Pancreatitis**

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Background and Aim: It is suggested that patients with chronic pancreatitis (CP) have a markedly increased risk of pancreatic cancer compared with the general population. This study was designed to determine the rate of pancreatic cancer in CP patients in China. **Methods:** This was a semi-prospective, single centre study including 420 consecutive CP patients (285 males and 135 females, median age at onset 39.5 years), with the median follow-up time being 102.3 months (range 24–419 months). We calculated the standardized incidence ratio (SIR) based on the pancreatic cancer incidence in the general population of China. **Results:** Four cases of pancreatic cancer (0.9% of patients) were observed in 3591 patient-years (expected number of cases 0.15; SIR 27.2, 95% confidence interval (CI) 7.4–69.6). Similar results were seen in alcoholics and non-alcoholics, and in smokers and non-smokers. When patients lost to follow up were considered to be followed up until the end point without having developed pancreatic cancer (4280 patient-years), SIR was 22.8 (CI 6.2–58.4). Based on the Cox model, with inserting factors being sex, age at the time of CP clinical onset, the type of pancreatitis, and the presence or absence of diabetes, calcification, alcohol use and smoking status, only age was found to correlate positively with the occurrence of pancreatic cancer (>50 year, Hazard Ratio, 1.8±0.5; $p=0.044$). **Conclusion:** The risk of pancreatic cancer is markedly increased in CP patients in China compared with the general population, indicating that screening for pancreatic cancer should be performed in CP patients, especially in older patients. **Keywords:** Pancreatic cancer, chronic pancreatitis, standardized incidence ratio (SIR).

P-9**Study on EUS Guided Oncolytic Adenovirus Implantation in Patients with Unresectable Pancreatic Cancer**

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Background: Pancreatic cancer is usually unresectable at the time of diagnosis. EUS-FNI has provided a new way for interventional treatments of pancreatic cancer. **Objective:** To observe the safety and clinical therapeutic efficacy of oncolytic adenovirus (H101) intratumoral implantation under EUS guidance combined with intravenous gemcitabine in patients with unresectable pancreatic cancer. **Design:** Prospective single-center study. **Setting:** Tertiary referral hospital. **Patients:** The study involved 9 patients with unresectable advanced pancreatic cancer from November 2006 to October 2009. **Interventions:** H101 was delivered locally into the pancreatic lesion under EUS guidance on day 1 and intravenous chemotherapy of gemcitabine was performed on days 2, 9, 16. 4 weeks was established as a treatment cycle and a total of 2 cycles were given. Tumor volume and tumor perfusion imaging at baseline and weeks 2, 4, 8 after the treatment were assessed by CT scanning. **Main Outcome Measurements and Results:** Tumor volumes were obviously decreased in 7 cases ($p=0.025$) with identified liquefaction and necrosis at week 8 after treatment, but without statistical difference ($p=0.053$) in total 9 patients. In a single case, there was a decrease in the area of liver metastasis. Perfusion imaging showed that blood flow (BF) and blood volume (BV) after treatment were on a downward trend, while mean transit time (MTT) and permeability surface (PS) showed a rise. The overall estimated median survival time was 7.0 months (95 % confidence interval 1.9 - 12.1 months). Major adverse effects associated with H101 implantation were fever and flu-like symptom. There were no obvious complications following therapy. **Conclusions:** EUS guided oncolytic adenovirus implantation on advanced pancreatic cancer is potentially feasible and safe, and combined with gemcitabine, may provide some rationale for further assessing this chemo/biologic combination.

P-10

Comparison of Seven Models for End-Stage Liver Disease in Evaluating the Prognosis of Cirrhosis

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Introduction: The aims of our study were: 1 to test the prognostic values of a specific prognostic model (Lille Model); 2 to compare seven models (CTP, MELD, MELD-Na, MESO, iMELD, Lille Model-PT, Lille Model-INR), for early identification of patients with decompensated liver cirrhosis at high risk of death at 3/6 months.

Methods: A total of 99 patients with decompensated liver cirrhosis were enrolled in the study. Baseline data (TB, Cr, PT, INR, Na, Alb, ascites, encephalopathy) and a change in bilirubin at 7 day were tested. In addition, CTP, MELD, MELD-Na, MESO, iMELD, Lille Model-PT and Lille Model-INR scores were calculated. All of the patients were followed for 6 months. The prediction of the model was expressed by the area under the receiver operating characteristic (AUROC) curves. Analysis of variance (ANOVA) was used to assess the scores of seven models between the living and deceased patients. Kaplan-Meier survival curves were drawn. **Result:** Of the 99 patients, 5 patients died within 3 months, and 14 patients died within 6 months of follow up. CTP, MELD, MELD-Na, MESO, iMELD, Lille Model-PT and Lille Model-INR scores in deceased patients were significantly higher than that in survival patients ($P < 0.05$). The AUROC of Lille Model-PT at 3 month was 0.860, higher than the Lille Model-INR (0.856), MELD (0.847), MESO (0.809), iMELD (0.806), MELD-N (0.789), CTP (0.769) was the smallest ($P < 0.05$). While The AUROC of Lille Model-INR at 6 month was 0.856, higher than the Lille Model-PT (0.871), iMELD (0.799), MELD (0.777), MESO (0.760), MELD-Na (0.726), CTP (0.723) still was the smallest ($P < 0.05$). Kaplan-Meier survival curve analysis showed that with the cutoff 0.86, 0.85, 20, 20, 1.45, 1.5, 10, Lille Model-PT, Lille Model-INR, MELD, MELD-Na, iMELD, MESO and CTP could clearly discriminate patients who would survive or died within 6-month follow-up ($P < 0.01$). **Conclusion:** Typical Lille Model could predict the 6-month prognosis of patients with decompensated liver cirrhosis, and was superior to that of MELD, MELD-Na, iMELD, MESO and CTP.

P-11

Comparison of Outcomes among Secondary Covered Metallic, Uncovered Metallic, and Plastic Biliary Stents in Treating Occluded Primary Metallic Stents in Malignant Distal Biliary Obstruction

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Introduction: The self expandable metallic stent (SEMS) has been widely used for unresectable malignant biliary obstruction but eventually becomes occluded by tumor in/over-growth and sludge. Therefore, we aimed to determine the therapeutic effectiveness of secondary stents and to find differences according to various combinations of the first and second stents for the management of occlude. **Methods:** Between 1999 and November 2008, 77 patients with malignant biliary obstruction underwent secondary biliary stent placement as “stent-in-stent” at three university hospital in Korea (40 covered; 26 uncovered; 11 plastic stents). The membrane of covered SEMS was regarded as the barrier against tumor ingrowth, we categorized them into three groups based on using covered SEMS as either the first or second stent; membrane-SEMS (18 covered-covered; 9 covered-uncovered; 22 uncovered-covered SEMS), bare-SEMS (17 uncovered-uncovered SEMS), and plastic stent (3 covered-plastic; 8 uncovered-plastic) group. **Result:** The median patency of second stents was 138 days, 109 days, and 88 days (covered, uncovered and plastic stents), and second covered SEMSs had a significantly longer patency than plastic stents ($p = 0.047$). In a multivariate analysis including membrane-SEMS, bare-SEMS and plastic stent groups, the bare-SEMS had worse cumulative stent patency (HR 2.04, CI: 1.08–3.86) and survival time (HR 2.37, CI: 1.25–4.49) than the membrane-SEMS. Patients with ampulla of Vater cancer had better stent patency (HR 0.27, CI: 0.08–0.98) and survival (HR 0.17, CI: 0.04–0.77) than those with other pancreatobiliary malignancy. In addition, anti-tumor treatment prolonged survival time (HR 0.50, CI: 0.26–0.99). **Conclusion:** The placement of additional biliary stents using the “stent-in-stent” method is an effective treatment. In addition, double biliary SEMS placement using at least one covered SEMS (in the primary and/or secondary procedure) might provide longer cumulative stent patency and survival than using uncovered SEMSs in both procedures.

P-12

Gli1 Promotes Angiogenesis by Regulating a New Target Gene—PDGF-B in Pancreatic Cancer

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Background & Aims: Early metastasis is a critical reason leading to poor prognosis of pancreatic cancer and angiogenesis is a necessary condition for local and systemic expansion of the tumor mass. Since hedgehog (Hh) signaling pathway has been reported to be related to early development of pancreatic cancer and PDGF-BB to be an important pro-angiogenic factor in pancreatic cancer, we hypothesized that Hh signaling pathway may initiate angiogenesis by regulating PDGF-B gene in pancreatic cancer. **Methods:** Firstly, the expressions of SHh, Gli1, PDGF-BB were studied in pancreatic cancer tissues and the correlations between expression levels of these genes and microvascular density (MVD) were analyzed; then the regulation of transcription factor Gli1 to PDGF-B gene was studied by using

RNAi and XChIP assays in pancreatic cancer cells; finally, the effect of Gli1 knocked-down in pancreatic cancer cells to angiogenesis were investigated by using transwell chamber and xenografts model of nude mice. **Results:** The results of immunohistochemistry and QRT-PCR showed the expression level of PDGF-BB was correlated with that of SHh and Gli1, the MVD of PDGF-BB, SHh or Gli1 positive groups were increased significantly than negative group of them respectively and SHh, PDGF-BB and MVD were correlated with tumor size and lymph node metastases. The XChIP and RNAi assays showed that Gli1 protein bound to promoter region of PDGF-B gene in pancreatic cancer cells and Gli1 knocked-down decreased expression level of PDGF-B gene significantly. Results of transwell chamber and xenografts model assays showed that Gli1 knocked-down in pancreatic cancer cells not only inhibited proliferation and migration of co-cultured HUVECs in vitro but also decreased angiogenesis in xenografts model. **Conclusions:** Our study suggested Hh signaling pathway enhances angiogenesis in pancreatic cancer and it may be one of the mechanisms that Gli1 promotes the transcription of PDGF-B gene through binding enhancers in promoter of this gene, which implied that Gli1 might be an effect targeted therapy site to pancreatic cancer for its ability of promoting angiogenesis. **Keywords:** pancreatic cancer; angiogenesis; Gli1; PDGF-B.

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