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President Message

Welcome to our June 2019 Newsletter!

The year of 2019 will see continuous efforts of our Society in organizing activities to promote the advancement of gastroenterology. The Annual General Meeting cum Scientific Meeting was held on 7 March 2019 during which honorary fellowship was bestowed upon Prof Richard Peek, Director of Division of Gastroenterology, Vanderbilt University Medical Centre, Nashville, USA cum Editor-in-Chief, *Gastroenterology*. The 21st Joint Annual Scientific Meeting will be held on 1 September 2019 at Cordis Hong Kong at Langham Place, Mongkok. Stay tuned to our website for details.

I would like to thank Dr Wai-Fan Luk for organizing the Annual General Meeting cum Scientific Meeting on 7 March 2019, Prof Wai-Keung Leung for editing this Newsletter, Prof Richard Peek, Prof Paul Moayyedi, Prof Jan Tack, Prof Simon S.M. Ng and Dr Kwan-Lung Ko for their scientific updates in this Newsletter. Last but not least, all the sponsors who rendered support and contributions to the Society.

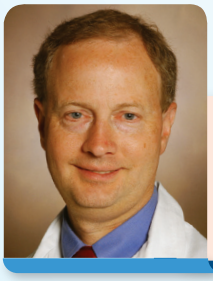
The next newsletter will be published in December 2019.

I look forward to seeing you all at the 21st Joint Annual Scientific Meeting on 1 September 2019.

Dr. Annie O.O. Chan
President, The Hong Kong Society of Gastroenterology

Scientific Updates

Helicobacter pylori and gastric cancer: A case of tragic triangulations



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Gastric adenocarcinoma is the third leading cause of cancer-related death in the world, with a 5-year survival rate of <30%. The Cancer Genome Atlas Network has identified 4 subtypes of gastric cancer based on molecular features: 1) Chromosomal Instability associated with intestinal-type histology, 2) Microsatellite Instability, 3) Genomically Stable associated with diffuse-type histology, and 4) EBV-related.[1] In all anatomic regions of the stomach, Chromosomal Instability tumors with intestinal-type histology are the most common.[1] This subtype progresses through a series of histologic steps from normal mucosa to chronic gastritis, to atrophic gastritis and intestinal metaplasia, and finally to dysplasia and adenocarcinoma.[2] *Helicobacter pylori* infects the stomachs of approximately 4.4 billion persons, representing over half of the global population, and is the most common bacterial infection worldwide.[3] Virtually

all persons infected by this organism develop co-existing gastritis, a signature feature of which is the capacity to persist for decades. Microbial persistence implies a relationship in which signals of the colonizing organism affect signals of the host, allowing host and bacteria to participate in a dynamic equilibrium. Unfortunately, there are biological costs to these long-term relationships.

Chronic infection with *H. pylori* incurs the highest known risk for gastric cancer and *H. pylori* is the only bacterial species designated by the World Health Organization (WHO) as a class I carcinogen.[4] Since virtually all infected persons have gastritis, it is likely that the organism plays a causative role early in this progression. With an estimated 1 million new cases/year, gastric adenocarcinoma claims >780,000 lives annually and approximately 80% of the gastric cancer burden and 5.5% of all malignancies worldwide are attributable to *H. pylori*-induced injury.[4,5] The incidence and mortality rates of gastric cancer are also increasing in the United States among young women and non-Caucasian populations.[6,7] Eradication of *H. pylori* significantly decreases the risk of developing cancer in infected individuals;[8] however, only a subset of colonized persons ever develop neoplasia. Enhanced risk is related to *H. pylori* strain differences, inflammatory responses governed by host genetic diversity, and/or specific interactions between host, environmental and microbial determinants. Universal test and treat strategies for *H. pylori* are not feasible due to the high prevalence of infection as well as the expense and side effects of antibiotic therapy, and eradication rates are often less than 80% in regions of the world where gastric cancer is most prevalent. These observations, in conjunction with evidence that carriage of certain strains is inversely related to esophageal adenocarcinoma, atopic diseases[9,10] and inflammatory bowel disease,[11] underscore the importance of identifying mechanisms that regulate interactions of *H. pylori* with its host which promote carcinogenesis. Such studies will enable physicians to more appropriately focus diagnostic testing and eradication therapy on targeted high-risk populations to prevent the development of cancer.

Microbial Virulence Constituents. The *cag* pathogenicity island is an *H. pylori* strain-specific locus that encodes a type IV secretion system (T4SS) and *cag*+ strains markedly augment the risk for gastric cancer compared to *cag*- strains.[12] The protein product of the *cagA* gene (CagA) is translocated by the T4SS into epithelial cells, undergoes tyrosine phosphorylation, and activates a eukaryotic phosphatase (SHP-2), leading to carcinogenic cellular responses.[13] Non-phosphorylated CagA also exerts pathologic effects via induction of pro-inflammatory signaling, activation of ß-catenin and disruption of apical-junctional complexes.[14,15] Thus, contact between *cag*+ strains and host cells activates signaling pathways that regulate cellular responses with carcinogenic potential, which may heighten the risk for transformation.

Host Factors Linked to Gastric Cancer. Host determinants, acting either alone or in concert with microbial virulence constituents, also affect gastric cancer risk. Membrane-bound ß-catenin is a component of adherens junctions that link cadherin receptors to the actin cytoskeleton, while cytoplasmic ß-catenin is a downstream component of the Wnt pathway. In the absence of Wnt, ß-catenin is bound within a multi-protein complex that includes GSK-3ß, and the adenomatous polyposis coli (APC) protein. Inhibition of GSK-3ß leads to ß-catenin nuclear accumulation, resulting in the transcription of genes implicated in carcinogenesis. Increased ß-catenin expression as well as mutations within *APC* are present in gastric adenocarcinoma specimens,[16] and nuclear accumulation of ß-catenin is increased within gastric adenomas and foci of dysplasia,[17] suggesting that aberrant ß-catenin activation precedes the development of gastric cancer. Our work and work from other laboratories has shown that *H. pylori* increases the expression of ß-catenin target genes that influence proliferation, cell survival, and transformation in a CagA-dependent manner.[18-20]

ß-catenin also regulates stem and progenitor cell homeostasis; correspondingly, aberrant ß-catenin signaling within a susceptible stem cell population may lower the threshold for carcinogenesis.[4] Lrig1 is a transmembrane protein that marks long-lived, quiescent epithelial stem cells and functions as a negative regulator of ERBB signaling.[21] Lineage tracing studies have indicated that Lrig1+ progenitor cells give rise to daughter cells within the stomach and Lrig1-expressing cells have the capacity to regenerate gastric epithelial mucosa following acute injury.[22] Importantly, studies have now shown that targeted activation of ß-catenin within Lrig1-expressing cells leads to the development of hyperplasia, increased proliferation, and high-grade dysplasia in the stomach.[23]

Dietary Factors and Gastric Cancer. Environmental conditions can also modify the risk for carcinogenesis. High salt diets accelerate *H. pylori*-induced gastric cancer in humans and rodents,[24] and high salt conditions alter levels of gene and protein expression within *H. pylori*.[25,26] Iron deficiency is also associated with an increased risk for gastric cancer. Our laboratory demonstrated that iron deficiency accelerates the development of inflammation and injury in mice and cancer in Mongolian gerbils infected with *H. pylori*, and in humans, *H. pylori* strains isolated from patients with low iron states induce more robust inflammatory responses than strains isolated from patients with high iron states.[27] *H. pylori* strains harvested from iron-depleted gerbils exhibit an enhanced capacity to assemble the cag T4SS, translocate CagA, and induce expression of proinflammatory cytokines.[27] We have now used discovery-based techniques including proteomics and metabolomics studies and whole genome sequencing to identify a focused subset of differentially expressed proteins, metabolites, and genetic variants, respectively, among *H. pylori* strains isolated from iron-deficient or high salt- versus normal diet fed gerbils.[27-29] Thus, conditions of high salt or low iron augment the virulence of *H. pylori* and accelerate progression to cancer.

In summary, gastric adenocarcinoma is a highly lethal disease, and colonization by *H. pylori* places persons at increased cancer risk. Infection with this organism, however, is extremely common and most colonized persons never develop cancer; therefore, techniques to identify high-risk sub-populations must utilize other biological markers that stem from hypothesis-driven investigations. Many useful resources now exist including genome sequences (*H. pylori*, rodent, and human), measurable phenotypes (CagA phosphorylation), and practical animal and ex vivo (gastroid) models, to address key unanswered questions regarding mechanisms through which the host response to particular *H. pylori* strains, which may be modified by environmental factors, drives carcinogenesis. Delineation of pathways activated by *H. pylori*-host interactions in conjunction with validation using clinical materials will not only improve our understanding of gastric carcinogenesis, but will also facilitate identification of therapeutic targets for prevention and more effective treatment of this disease. Investigations that focus on *H. pylori*-induced adenocarcinoma will also help to construct a paradigm for other cancers that arise from inflammatory foci such as hepatocellular carcinoma and cholangiocarcinoma. Similarly, chronic esophagitis, pancreatitis, and ulcerative colitis each confer a significantly increased risk for the development of cancer within their respective anatomic sites. Thus, a comprehensive understanding of how *H. pylori* initiates gastric cancer will impact our understanding of how chronic inflammation leads to malignant degeneration in other organ systems.

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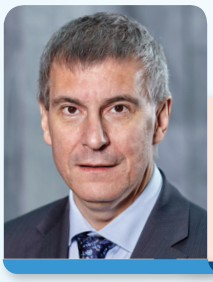
Microbiome and IBS



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A significant proportion of research into irritable bowel syndrome (IBS) has focused on mechanistic causes, such as inflammation, dysmotility, hypersensitivity, food sensitivity and other potential triggers.[1] However, patients generally ask healthcare professionals 'why me and why now?', a question that requires a simple, clear response.

Ultimately, it appears that IBS is related to the state of the gut microbiome.[2] In particular, patients who have recently experienced a gastrointestinal infection have an increased risk of developing IBS.[3] Furthermore, while many of the studies of the gut microbiome in patients with IBS have been small, a systematic review of case–control studies published after 2010 has provided clues as to which bacterial species that inhabit the gut are protective and detrimental with regard to IBS **(Table 1)**. (Pittayanon, unpublished data)

Probiotics in IBS

Probiotics have been investigated in >500 patients with IBS across more than 50 studies and data suggest that the efficacy of probiotics is comparable with conventional pharmacological treatments for IBS (number needed to treat [NNT], 7; 95% confidence interval [CI], 5–12.5).[4] (Quigley EM, et al. unpublished data) While most individual studies are negative for overall symptom improvement, aggregate data suggest that *Bifidobacterium* species, either alone or in combination with other probiotics, are the most efficacious option **(Table 2)**. (Quigley EM, et al. unpublished data) Likewise, *Lactobacillus* does not appear to be efficacious, despite being a common component of probiotic preparations, which is consistent with data derived from gut microbiome studies. (Quigley EM, et al. unpublished data)

Table 1. Conclusions of studies published after 2010 investigating the association between bacterial species in the gut microbiome and IBS identified by a systematic review (Pittayanon, unpublished data)

Bacterial species	Conclusions of studies of the gut microbiome and IBS		
	Beneficial	Neutral	Harmful
Possibly protective			
Bifidobacterium family/genus	•••••	••	—
Faecalibacterium	•••	•	—
Uncultured Clostridiales	•••	—	—
Possibly harmful			
Veillonella	•	—	•••••
Bacteroides	—	••	••••
Enterobacteriaceae	—	••	••••
Lactobacillicus species	—	•	•••

• =conclusion of one study.
IBS, irritable bowel syndrome

Table 2. Continuous outcomes in patients with IBS administered probiotics (Quigley EM, et al. unpublished data)

Probiotic type	Studies	Participants	SMD (95% CI)
Combination	19	1,341	-0.21 (-0.31–-0.10)
Lactobacillus	9	989	-0.09 (-0.25–0.06)
Saccharomyces	4	388	0.12 (-0.27–0.50)
Bifidobacterium	3	501	-0.46 (-0.92–-0.00)

Test for subgroup differences: X^2=8.00, degrees of freedom=3; p=0.05; I^2=62.5%
CI, confidence interval; IBS, irritable bowel syndrome; SMD, standardized mean difference

The number of symptoms of functional gastrointestinal disease is also correlated with an increased probability of a patients with IBS having comorbid anxiety or depression, but *Bifidobacterium* has been associated with protection against behavioural change in preclinical studies.[5,6] A pilot study in humans has now provided proof of concept for *Bifidobacterium* improving the symptoms of depression in patients with anxiety or depression and diarrhoea-predominant or mixed IBS according to the ROME III criteria (p<0.05 versus placebo in the intention-to-treat [ITT] population).[5] Furthermore, patients administered probiotics displayed lesser engagement of areas of the brain involved in mood regulation, such as the amygdala, as well as the frontal and temporal cortices, which are involved in mood regulation.[5] *Bifidobacterium* consumption was also associated with a trend towards improved IBS symptoms (p=0.13 versus placebo in the ITT population).[5]

Antibiotics in IBS

A systematic review and meta-analysis of >2,500 patients with diarrhoea-predominant or mixed IBS in eight randomized controlled studies administered antibiotics indicates comparable efficacy with probiotics and conventional pharmacological therapies (NNT, 7; 95% CI, 5–12.5).[4,7] However, the limited data available indicates that rifaxamin tends to have a modest effect (NNT, 10), whereas small, single studies of neomycin and norfloxacin have indicated a greater efficacy for these antibiotics.[7]

Faecal microbiota transplant (FMT) for IBS

Across the four randomized controlled trials of FMT for IBS included in a systematic review and meta-analysis, no consistent result was observed and it was concluded that FMT did not improve outcomes (relative risk, 1.11; 95% CI, 0.60–2.04).[7] However, more research is required to confirm this result given the low study and patient numbers.

Conclusions

Focusing on the state of the gut microbiome in patients with IBS is worthwhile. Therapies that target the gut microbiome may be efficacious in patients with IBS, but more research and larger studies are required to further investigate therapeutic options. In addition, the effective treatment of IBS by targeting the gut microbiome will require close collaboration between clinical and laboratory scientists.

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Visceral hypersensitivity in functional gastrointestinal disorders

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Functional gastrointestinal disorders (FGID) are characterized by visceral hypersensitivity among other symptoms.[1] Investigations of visceral hypersensitivity in FGID involve evaluating perceived discomfort and pain thresholds in response to balloon distention in different regions of the gastrointestinal tract. In patients with irritable bowel syndrome (IBS) and functional dyspepsia the threshold for inducing pain is lower than in healthy controls.[2-4]

Visceral hypersensitivity and symptom severity

Visceral hypersensitivity is associated with increasing symptom severity for patients with FGID.[3-5] For example, patients with functional dyspepsia who were hypersensitive to gastric distention (34% of all patients) experienced a significantly higher rate of pain, belching and weight loss compared with normosensitive patients ($p<0.005$), which was unrelated to abdominal compliance **(Figure 1)**.[3]

Similarly, reports of moderate-to-severe pain, bloating, diarrhoea, satiety and anxiety were all significantly higher among patients with IBS who had visceral hypersensitivity ($p<0.05$).[4] Overall, the threshold to induce discomfort and symptom severity in patients with functional dyspepsia and IBS is significantly correlated – an association that persists after correcting for anxiety and depression scores, suggesting that psychosocial comorbidities do not drive patients' perception of discomfort or pain.[5]

Where does visceral hypersensitivity originate: the gut or the brain?

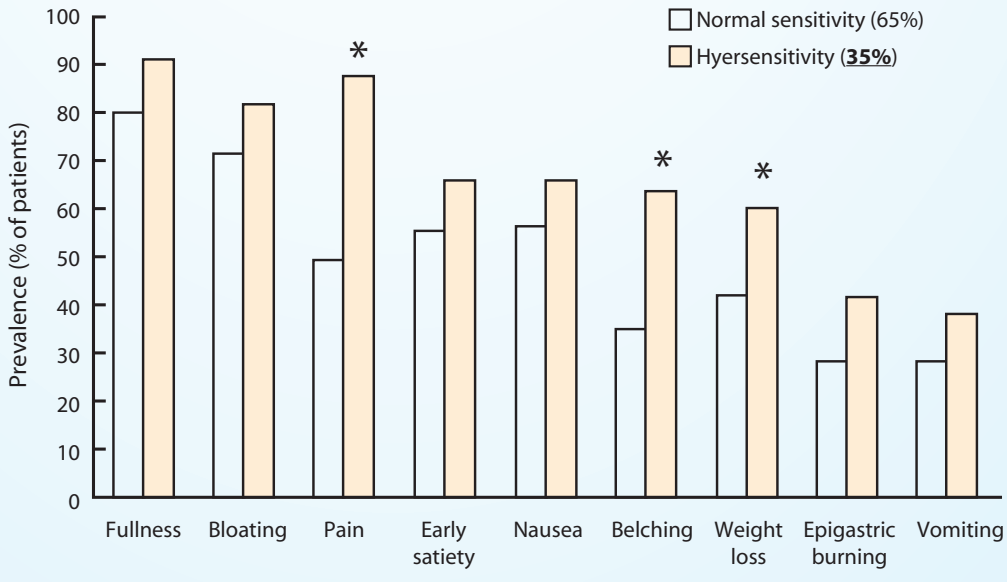
Impaired signal processing in the central nervous system is believed to contribute to visceral hypersensitivity in patients with FGID. According to this theory, physiological signals are continuously delivered from the gastrointestinal tract to the brain, where a filtering mechanism distinguishes between physiologic and noxious stimuli. However, altered signal processing in the brains of patients with FGID means that normal stimuli may be interpreted as noxious and painful.

This theory of visceral hypersensitivity can be tested using a barostat, as both mechanoreceptor sensitivity and initial perception of discomfort or pain can be assessed. An isometric status can be induced in a subject by inflating a fixed volume balloon, before administering neostigmine to induce phasic contractions. The increased contractility can be perceived by the subject,[6] although psychological factors can influence subjects' perception of contractions.

Anxiety can increase perception of both painful and non-painful visceral sensations in patients with IBS with visceral hypersensitivity (**Figure 2**).[7] Similarly, somatization, neuroticism, poor quality of life and a history of child abuse modulate perception of gastric pain in patients with functional dyspepsia and hypersensitivity.[5,8] Thus, psychological factors may also confer hypersensitivity to pain.

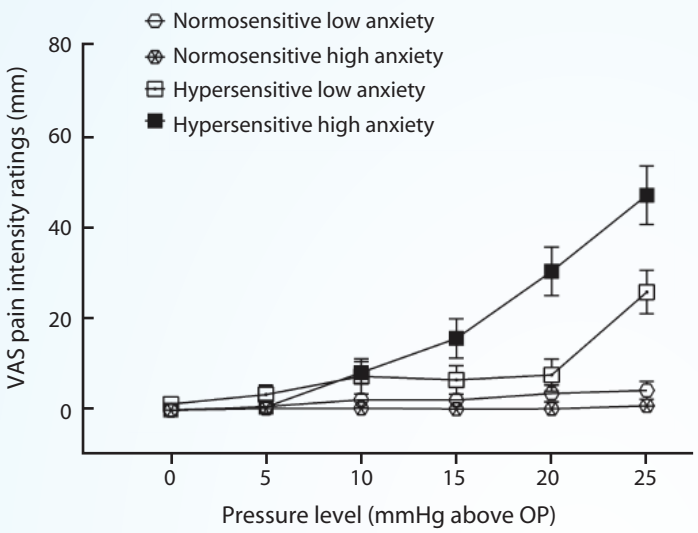
Brain imaging studies indicate that gastric distention activates several brain areas, including the sensorimotor cortices, bilateral orbitofrontal cortices, bilateral cerebellar hemisphere, left superior temporal gyrus and anterior cingulate cortex.[9-11] Interestingly, in hypersensitive patients with functional dyspepsia, many of these same brain areas are activated at lower levels of gastric distention.[10] However, the anterior cingulate cortex is not activated in patients with functional dyspepsia, possibly due to a failure to activate descending antinociceptive pathways in patients with visceral hypersensitivity.[10]

Figure 1. Prevalence of severe symptoms in patients with functional dyspepsia[3]



*p<0.005 versus patients with normal sensitivity to gastric distention.

Figure 2. Pain perception in patients with IBS and anxiety[7]



IBS, irritable bowel syndrome; OP, operating pressure; VAS, visual analogue scale

Therapeutic implications

Because dysfunction in the gut–brain axis contributes to FGID symptoms, including visceral hypersensitivity, pharmacological therapies that modulate neurotransmitter function, such as antidepressants, can provide effective relief for patients with chronic gastrointestinal distress.[1] Indeed, current guidelines for the treatment of functional dyspepsia recommend prescribing tricyclic antidepressants (TCAs) when patients fail to respond to proton pump inhibitors.[12]

Neuromodulators may act via peripheral or central mechanisms. Pharmacological therapies that target gastrointestinal smooth muscle to induce relaxation include antispasmodics, serotonin receptor and chloride channel ligands.[1] For example, a week of treatment with otilonium bromide, which blocks calcium channels, and increases recto-sigmoidal distention pain thresholds in patients with IBS.[13]

Neuromodulators targeting neurotransmitter signalling in the brain modulate pain perception and dorsal horn neuron signalling in the spine.[1] These agents include TCAs, selective serotonin reuptake inhibitors (SSRIs), and serotonin noradrenaline reuptake inhibitors (SNRIs), and operate by blocking the reuptake of dopamine, noradrenaline or serotonin from the synaptic cleft, enhancing neurotransmitter signalling and inducing neurotransmitter receptor downregulation over time.[1] Furthermore, some of these agents have direct effects on the gastrointestinal tract, such as gut motility, tone and secretion.[1]

Tricyclic antidepressants and SSRIs significantly improve symptoms in patients with IBS (56% versus 35% for placebo), and TCAs may also significantly improve patients' perception of pain (52% versus 27% for placebo).[14] Similarly, $\alpha_2\delta$ ligands gabapentin and pregabalin have been shown to significantly increase the threshold pressures for inducing gut distention pain and discomfort in patients with IBS ($p<0.05$).[15,16]

Summary

Patients with FGID who have visceral hypersensitivity experience more severe gastrointestinal discomfort and pain.[3-5] While peripherally acting pharmacological therapies can relax gastrointestinal smooth muscle to alleviate symptoms, altered brain–gut signalling amplifies pain perception in these patients, indicating a role for centrally acting neuromodulators (such as antidepressants) in managing nociception.[1] Furthermore, combining therapies that have different mechanisms of action may provide superior management of gastrointestinal pain. However, clinical studies are needed to establish the benefit of neuromodulators in FGID, particularly in less understood conditions, such as anorectal pain and functional nausea and vomiting, where only case series data are currently available.[1]

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Recent advances in robotic colorectal surgery

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Surgery is a key component in the management of colorectal cancer. Technological advances in recent decades have markedly improved surgical procedures for both surgeons and patients, facilitating a transition away from large wounds to minimally invasive surgery.

Conventional laparoscopic surgery

Laparoscopic surgery offers many benefits and improvements over open surgery including[1]:

- Smaller wounds, resulting in reduced access trauma and less pain for patients
- Faster recovery times and shorter hospital stays
- Reduced morbidity
- Better cosmesis

However, conventional laparoscopic surgery has several shortcomings, which are largely related to technological limitations of the surgical systems available. For example, conventional laparoscopic surgical systems offer a limited two-dimensional (2D) video image that cannot easily convey depth perception or spatial orientation.[1] The surgeon must rely on an assistant to manipulate the camera, leading to an unstable visual display and contributing to problematic surgeries.[1] Furthermore, conventional laparoscopy systems use straight instruments that have a limited range of motion, amplifying the poor ergonomics of the system and potentially magnifying a surgeon's tremor.

Laparoscopic surgery for colorectal cancer

A high rate of conversion (29%) from laparoscopic surgery to open surgery was observed in a large UK trial comparing laparoscopic-assisted and conventional open surgery.[2] While no significant differences were observed in proportion of Dukes' C2 tumours and in-hospital mortality, there was a higher rate of circumferential resection margin positivity among patients undergoing laparoscopic anterior resection (12% versus 6%; p=0.19).[2] There is also a trend toward worse sexual function in men undergoing laparoscopic surgery compared with open surgery, possibly due to a higher rate of total mesorectal excision (TME) in the laparoscopic group.[3]

It is anticipated that technological innovations in surgical systems, such as robotic systems, will overcome the limitations associated with laparoscopic surgery in the future.[1]

The *da Vinci*® Surgical System

The *da Vinci*® Surgical System (Intuitive Surgical, Inc., Sunnyvale, California) is one of the leading robotic surgical systems worldwide, with more than 4,400 systems installed in hospitals globally.[4] There are three core components to the system:

- **The surgeon console**: the surgeon's interface with the robot, providing a three-dimensional (3D) view of the surgical field, a control panel, and manipulators to perform the surgical operation.[1]
- **The patient cart**: positioned next to the patient and housing the robotic arms that manipulate both the camera and the surgical instruments.[1]
- **The vision cart**: provides communication and integration across the different components of the system, including a large video display, so the surgical procedure is visible to the wider operating room.[5]

Evolution of robotic surgery

The Prince of Wales Hospital in Hong Kong has extensive experience with robotic surgery, having used each generation of the *da Vinci*® system since 2005. Indeed, Prince of Wales Hospital was the site of the first robotic rectal resection procedure performed in Hong Kong and China.[6] While the first generation of *da Vinci*® systems was bulky and had only two arms, which necessitated the use of additional laparoscopic instruments, later generations of the system have more, longer and thinner articulating arms and improved imaging, plus new and enhanced instruments that together facilitate a wider range of procedures.

Advantages of robotic surgery

Robotic surgery has several advantages that will help overcome many of the challenges associated with conventional laparoscopic surgery **(Table 1)**. The customizable surgeon console provides a comfortable, ergonomic position. The console also delivers a magnified 3D view to the surgeon for improved depth perception and fluorescent FireFly® imaging allows visualization of otherwise hidden anatomical landmarks, such as the vasculature. As the surgeon controls camera movements, a steady and precise video display is achieved.[1]

Importantly, the console offers more intuitive movement of the robotic arms and tremor filtering ensures surgical movements are smooth and stable compared with conventional laparoscopy.[1] Furthermore, the robotic arm instruments themselves are more advanced than the straight instruments of conventional laparoscopic systems, now offering wrist-like dexterity with seven degrees of freedom and enabling a range of complex movements.[1] Overall, the latest generation of robotic systems provide an intuitive surgical experience that contributes to a shorter learning curve and fewer surgical errors.[1]

Table 1. Solutions provided by robotic surgical systems to challenges associated with conventional laparoscopic surgery[1]

Limitations of laparoscopic surgery	Solutions provided by robotic surgery
Limited 2D view of surgical field: • Compromised depth perception and spatial orientation • Requires counterintuitive mirror-image surgical movements	Magnified 3D view of surgical field. Integrated imaging techniques (eg, infrared fluorescence) provide enhanced visualization of structures
Unstable video display provided by an assistant	Surgeon controls camera movements to provide a steady display
Straight laparoscopic instruments that have a limited range of movement and can amplify a tremor	Instruments have additional joints that allow a wide range of motions and provide tremor control
Surgeon forced to adopt an unnatural, awkward position during surgery	Customizable surgeon console provides comfortable, ergonomic position
Training is difficult and prolonged	Training is simpler and faster

The latest generation of *da Vinci*® surgical systems

The Prince of Wales Hospital in Hong Kong was the site of the first clinical trial of the *da Vinci* SP® model in 2017 (Clinicaltrials.gov identifier: NCT03010813).[7] The study evaluated the safety and feasibility of the SP system for several surgical applications, including colorectal, urological and ear, nose and throat surgery. The SP model, designed for single-port access, uses a single arm to deliver three articulating instruments and one articulating camera through a 25 mm cannula. The combination of a wrist- and elbow-like joint enables each instrument to operate in narrow cavities, making the SP system particularly suited to narrow-access surgeries (eg, transanal, transoral, extraperitoneal), extraction surgeries (eg, transperitoneal) and alternate entry surgeries (eg, transperineal, transvaginal, transgastric), and may even make pure natural orifice transluminal endoscopic surgery (NOTES) possible. Professor Ng and his colleagues' experience using the SP system for 63 patients was that the system is clinically feasible with proven safety, providing easy docking, and both easy camera and instrument manipulation. However, further evaluation is required before this technology can be routinely used in clinical practice.

Summary

Robotic surgical systems are an exciting new technology with the potential to revolutionize surgery and overcome the limitations of conventional laparoscopic procedures. Enhanced imaging and instrument manipulation provide a more natural and sensitive surgical environment for surgeons and may allow a wide range of procedures to be performed with minimal access. While further evaluation of robotic surgical systems is necessary before their mainstream adoption in clinical practice, these systems have the potential to significantly improve outcomes for patients requiring colorectal surgery.

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A large real-world cohort study examining the effects of long-term entecavir on hepatocellular carcinoma and HBsAg seroclearance (Summary of Thesis 2018)

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Introduction

Chronic hepatitis B (CHB) is the leading cause of liver related morbidity and mortality globally and in our locality. In a recent territory-wide prevalence study, the seroprevalence rate of hepatitis B surface antigen (HBsAg) was 7.8% in Hong Kong, translating into 546,000 individuals being infected.[1] Hepatocellular carcinoma (HCC) is the most dreaded complication of CHB, with an estimated global incidence of HCC in 2015 was 854,000 resulting in 810,000 deaths.[2] There is a complex interplay among host, viral and environmental factors in the development of HBV- related HCC. Some of these risk factors may be modifiable by antiviral therapy. These include serum levels of alanine aminotransferase (ALT), HBVDNA, hepatitis B e-antigen (HBeAg) status. Male sex, increasing age, family history of HCC are examples of non-modifiable risk factors. Several risk scores or formulas are established to predict the risk of HCC in treatment-naive individuals with CHB. The Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) model uses age, sex, HBeAg status, serum ALT and HBVDNA level to develop a 17-point nomogram to predict yearly HCC risk up to 10 years.[3] The Guide with Age, Gender, HBVDNA, Core promoter mutations and Cirrhosis (GAG-HCC) score, and the Chinese University (CU-HCC) score, which utilizes age, albumin, bilirubin, HBVDNA and cirrhosis status, are derived and validated in Hong Kong to predict 5- and 10-year risk of HCC in CHB patients with and without cirrhosis.[4,5] In our study, we investigated the effect of entecavir on the development of HCC by comparing the observed incidence of HCC with the expected incidence calculated from risk models applied to the subjects before initiation of treatment. Our secondary aim was to examine the effect of long term entecavir treatment on HBsAg seroclearance.

Methodology

Patient recruitment

Adults over the age of 18 years receiving entecavir for CHB followed up at the liver clinics of Queen Mary Hospital during the period between January 2002 and December 2015, and with blood test before initiation of antiviral for risk score calculation were recruited. All patients were HBsAg positive for at least 6 months. The predicted incidence of HCC for patients was estimated using the three validated risk models: REACH-B, GAG-HCC and CU-HCC risk score. Patients on entecavir for less than 12 months, or with history of HCC, or developing HCC within the first year of entecavir treatment were excluded.

Follow-up and outcome measure

Decision on starting antiviral was based on recommendations from international guidelines available at the time of patient assessment. Patients on entecavir treatment were followed up every 3 to 6 months. Contrast imaging were arranged for patients with abnormal ultrasonography or elevated AFP levels. Diagnosis of HCC was made by contrast imaging with computed-tomography or magnetic resonance imaging or by histology from surgical specimens. Cirrhosis is defined by the following combined parameters: (1)Ultrasonographic evidence of small sized liver with or without development of splenomegaly/ascites/varices; and (2)AST to platelet ratio (APRI) = (AST/upper limit of normal)/platelet count (x10^9/L) x 100)[6] greater than 2. Subjects were censored at diagnoses of HCC, or cessation of entecavir treatment, or the last visit.

HBsAg seroclearance

HBsAg seroclearance was defined as loss of serum HBsAg on repeated testing over a period of 6 months. Patients with HBsAg seroclearance (referred as cases) were matched in a 1:3 ratio to controls from the same cohort without HBsAg seroclearance. The matching criteria included sex, age, duration of entecavir treatment, baseline HBeAg and cirrhosis status. Quantitative HBsAg levels were determined for both cases and controls at baseline, year 3 and year 5 of entecavir treatment. The predictive values of quantitative HBsAg and HBVDNA levels on HBsAg seroclearance were evaluated.

Outcome measures

The primary outcome was the impact of long term entecavir treatment on HCC development by comparing the observed incidence of HCC with the expected incidence estimated from the risk scores. The secondary outcome was to explore the impact of long term entecavir treatment on HBsAg seroclearance.

Statistical analysis

Data analysis was performed using SPSS version 25.0(SPSS Inc., Chicago, Illinois). The predicted yearly HCC incidences were calculated using the REACH-B model. Each patient was assigned a score which was the calculated sum of products between the beta-coefficients of the model equations and the patient's baseline parameter. The score was used to estimate HCC-free survival from year 1 to 10, based on the survival functions obtained from the REACH-B authors.[3] Standardized incidence ratios (SIR) were calculated as a ratio of observed over predicted HCC cases at yearly interval. Predicted 5- and 10- year incidence using the GAG-HCC and CU-HCC scores with comparison to the observed cases were also performed. Kaplan-Meier analysis was used to calculate the cumulative probability of HCC and HBsAg seroclearance over time. ROC curve with AUC value were derived to find an optimal HBsAg level to predict HBsAg seroclearance in entecavir-treated patients.

Results

A total of 1225 patients were recruited during the study period after excluding 5 patients with duration on entecavir treatment less than 1 year. Median follow-up was 6.6 years (IQR 2.8). 61(5.0%) patients were followed up for more than 10 years. 66(5.4%) cases of HCC were observed during the study period, giving a cumulative incidence of 7.8%. 192(15.7%) patients had baseline cirrhosis. 28(14.6%) patients with baseline cirrhosis and 38(3.7%) patients without baseline cirrhosis developed HCC (P<0.001). There were more male (81.8% vs. 63.9%, P=0.003) and more patients with cirrhosis (42.4% vs. 14.2%, P<0.001) in the HCC group. Patients with HCC were started on entecavir at an older age (57.0 vs. 49.4, P<0.001), with higher baseline bilirubin level but lower HBVDNA levels. There was no difference between HCC and non-HCC cases with regards to prior antiviral use, baseline HBeAg status, development of HBeAg seroconversion and baseline ALT levels. After multivariate analysis, only male sex (HR=2.65, 95%CI 1.36-5.16), increasing age (HR=1.06, 95%CI 1.03-1.08) and presence of cirrhosis (HR=2.34, 95%CI 1.30-3.97) were found to be independent risk factors of HCC.

The observed and predicted cases of HCC over the period of follow-up in all patients, patients without cirrhosis and patients with cirrhosis, calculated with the REACH-B model are shown in

Table 1A-C. In all patients, the number of observed cases became significantly lower than the predicted cases from year 6 onwards, with the SIR dropping to 0.68(95%CI 0.535-0.866) by the end of 10 years, signifying a 32 percent reduction of HCC risk with entecavir treatment. In patients without cirrhosis, the observed cases of HCC became consistently lower than the predicted cases from year 5 onwards with the SIR dropping to 0.51(95%CI 0.271-0.704) by the tenth year, indicating almost 50% reduction of HCC risk. In patients with cirrhosis, the SIRs ranged between 0.82 and 1.28, which did not reach statistical significance throughout the observation period. A similar trend of reduction in HCC risk was observed in the overall cohort and in patients without cirrhosis using the GAG-HCC and CU-HCC models, although the SIR at year 10 in patients without cirrhosis using the GAG-HCC was only borderline significant (0.73, 95%CI 0.530-1.00). In patients with cirrhosis, a reduction in HCC risk was demonstrated with both models. The SIR using the GAG-HCC was not significant at year 5 (0.72, 95%CI 0.459-1.13) but reached statistical significance at year 10 (0.38, 95%CI 0.259-0.544), while the SIR was statistically significant at both year 5(0.52, 95%CI 0.331-0.813) and year 10(0.46, 95%CI 0.314-0.659) using estimation with the CU-HCC model.

Table 1A REACH-B estimation of HCC cases in all patients

Time interval (years)	1	2	3	4	5	6	7	8	9	10
Observed cases	0	10	23	36	48	55	60	63	66	66
Predicted cases	10.8	24.7	29.8	43.9	62.1	75.7	84.7	90.8	94.6	97.0
SIR	-	0.40	0.77	0.82	0.77	0.73	0.71	0.69	0.7	0.68
95% CI	-	0.218 - 0.752	0.513 - 1.161	0.592 - 1.137	0.582 - 1.026	0.558 - 0.946	0.550 - 0.912	0.542 - 0.888	0.548 - 0.888	0.535 - 0.866

REACH-B, Risk Estimation of Hepatocellular Carcinoma in Chronic Hepatitis B; SIR, standardized incidence ratio; CI, confidence interval.

Table 1B REACH-B estimation of HCC cases in patients without cirrhosis

Time interval (years)	1	2	3	4	5	6	7	8	9	10
Observed cases	0	7	14	24	29	32	36	36	38	38
Predicted cases	8.2	18.7	22.6	33.5	47.4	58.2	65.1	69.7	72.5	74.2
SIR	-	0.37	0.62	0.72	0.61	0.55	0.55	0.52	0.52	0.51
95% CI	-	0.179 - 0.786	0.367 - 1.047	0.481 - 1.070	0.425 - 0.880	0.389 - 0.778	0.399 - 0.767	0.373 - 0.717	0.381 - 0.721	0.271 - 0.704

REACH-B, Risk Estimation of Hepatocellular Carcinoma in Chronic Hepatitis B; SIR, standardized incidence ratio; CI, confidence interval.

Table 1C REACH-B estimation of HCC cases in patients with cirrhosis

Time interval (years)	1	2	3	4	5	6	7	8	9	10
Observed cases	0	5	9	12	19	23	24	27	28	28
Predicted cases	2.7	6.1	7.6	10.8	15.1	18.0	20.0	21.5	22.5	23.2
SIR	-	0.82	1.18	1.11	1.26	1.28	1.20	1.25	1.24	1.21
95% CI	-	0.342 - 1.976	0.616 - 2.276	0.631 - 1.956	0.804 - 1.977	0.850 - 1.924	0.804 - 1.790	0.860 - 1.828	0.859 - 1.802	0.834 - 1.750

REACH-B, Risk Estimation of Hepatocellular Carcinoma in Chronic Hepatitis B; SIR, standardized incidence ratio; CI, confidence interval.

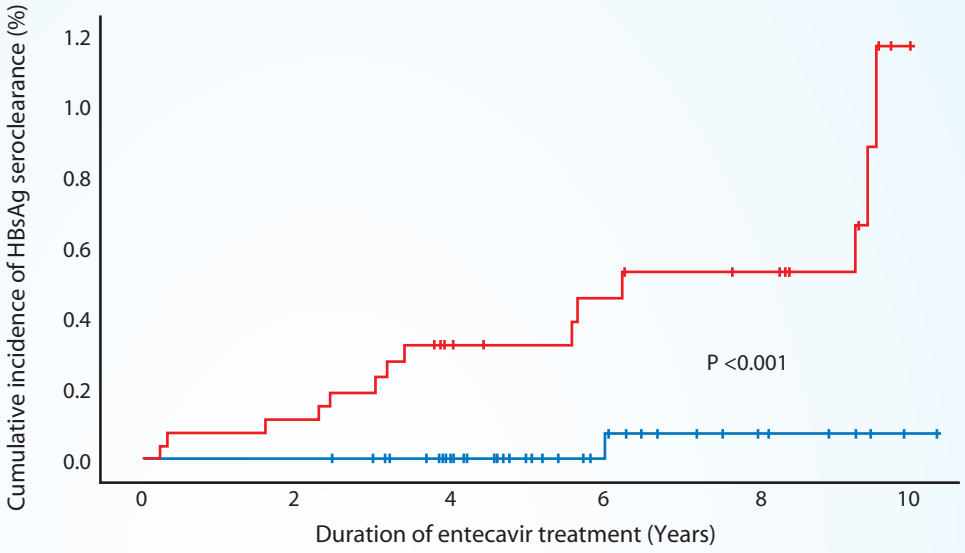
Twenty-one (1.7%) patients underwent HBsAg seroclearance during the study period. The cumulative incidence of treatment-associated HBsAg seroclearance was 5.2%. There was no significant difference in the baseline median level of HBsAg (59.5 vs. 110.7 IU/mL respectively, P=0.743) and HBVDNA (4.8 vs. 6.7 log IU/mL, P=0.085) between the 21 cases and the 63 controls. No baseline parameters were found to be associated with HBsAg seroclearance. The median level of HBsAg became significantly lower in the HBsAg seroclearance group by year 3(0.058 vs. 97.0 IU/mL, P<0.001) and year 5(0.05 vs. 88.0, P<0.001). The median level of HBVDNA for both groups dropped to undetectable level by year 3 and year 5. HBsAg levels at year 3 and baseline-to-3-year percentage reduction of HBsAg level, [(HBsAg level at baseline – level at year 3)/HBsAg level at baseline x 100 %], were found to predict subsequent HBsAg seroclearance. AUC value of HBsAg level at year 3 was 0.833(95%CI 0.691-0.974) and the optimal level was 5.67 IU/mL (sensitivity(SN)=0.727, specificity(SP)=0.930, positive predictive value (PPV)=0.667, negative predictive value (NPV)=0.946). The performance using 200 IU/mL was: SN=1.00, SP=0.351, PPV=0.229, NPV=1.00. None of the patients with HBsAg level over 200 IU/ml after 3 years of entecavir treatment achieved HBsAg seroclearance. The AUC value for baseline-to-3-year percentage reduction of HBsAg level was 0.874 (95%CI 0.787-0.962). The optimal level was 67% (SN=0.933, SP0.712, PPV=0.498, NPV=0.972). The Kaplan Meier analysis is shown in **Figure 1**.

Discussion

The present study demonstrated the efficacy of anti-HBV treatment with entecavir in reducing the risk of HCC in CHB patients. By comparing the observed cases with the predicted cases calculated from the validated risk models, long-term therapy with entecavir for 10 years resulted in more than 30 percent reduction of HCC risk. Also, a reduction in risk was seen even in patients with cirrhosis. The only randomized trial studying the impact of antiviral treatment on HBV HCC is with lamivudine in patients with advanced fibrosis.[7] In the study, lamivudine treatment significantly reduce HCC risk, with a hazard ratio of 0.49. Replicating the trial with entecavir is not possible since withholding antiviral for a prolonged period from patients in the control group would be unethical. Therefore, the published validated risk models are a good alternative to study the effect of newer generation of antiviral agents. The predicted cases calculated with the risk scores served as a "virtual" control group which were then compared with the actual HCC cases observed during treatment. Kim et al applied the REACH-B model to the tenofovir registration study database and reported that treatment was associated with an SIR of 0.4.[8] In their study, only 30% of the population were Asians, and predicted cases with respective SIR were only determined at the time of each incident HCC instead of using yearly estimate, indicating a lack of comprehensive follow-up data. Another American study including patients with cirrhosis showed similar findings with SIR of 0.56 by 8.2 years.[9] The total number of HCC cases was low in this study, with potential under reporting. Also, both studies were unable to show a reduction of HCC risk in patients with cirrhosis.

In the present study, although risk reduction was not apparent using estimation with the REACH-B model in patients with cirrhosis, a clear reduction of HCC risk more than 50 percent was demonstrated with the GAG-HCC and CU-HCC models, echoing the lamivudine trial. The reason for not reaching a statistical difference using the REACH-B model in contrast to using GAG-HCC and CU-HCC is likely related to the fact that the former was established using data from subjects without cirrhosis. The latter two score adopted the factor of cirrhosis in the risk calculation. A longer duration of entecavir treatment and even a larger number of patients with cirrhosis may be needed before a statistical significant difference in reduction of HCC risk can be shown. It is therefore not surprising to observe that the drop in SIR

Figure 1 Kaplan-Meier curve for HBsAg clearance by baseline-to-3-year percentage reduction of HBsAg level



No. at risk	> 67% (Red line)	29	26	18	14	11	0
	< 67% (Blue line)	38	38	29	14	6	1

became significant from year 5, by using CU-HCC score, and year 10 by using both models. The current study represented one of the largest Asian cohorts showing reduction in HCC incidence after 5 years of antiviral treatment and we further provided evidence that such protective effect was sustained with long term treatment till 10 years of follow-up.

The subgroup analysis on HBsAg level showed level of HBsAg after 3 years of entecavir treatment and baseline-to-3-year percentage reduction of HBsAg level were predictive of subsequent HBsAg seroclearance. A study by Seto et al on HBsAg seroclearance after prolong lamivudine treatment showed that lower baseline HBsAg level (<1000 IU/mL) and a greater median rate of HBsAg reduction were predictive factors.[10] In the present study, the median baseline HBsAg level in both the cases and matched controls were similar and both were lower than the published value. However, we found that persistent high level of HBsAg after 3 years of entecavir treatment was negatively associated with HBsAg seroclearance. The optimal level derived from the present cohort was 5.67 IU/ml, with high sensitivity and specificity. However, such low HBsAg level was difficult to achieve in reality, and only 19 patients in our subgroup reached the level. HBsAg level over 200 IU/mL at 3 years had a high negative predictive value, indicating subsequent HBsAg seroclearance being remote. In addition, HBsAg reduction of more than two third by third year of entecavir treatment was associated with subsequent HBsAg seroclearance. With increasing availability of quantitative HBsAg measurement, the level can be used to assess treatment response to nucleoside/nucleotide analogues and the need for adding a second agent if the level of decline is not satisfactory.

The main limitation in our study was lack of histological assessment of degree of fibrosis or cirrhosis at baseline. However, our adoption of non-invasive method with combination of ultrasonography and blood test in assessing cirrhosis reflects daily clinical practice.

In conclusion, entecavir treatment in a large group of Asian CHB patients in the real-world setting was associated with lower incidence of HCC than estimated incidence using validated risk scores. However, HBsAg seroclearance rate remained low. Additional therapy may be considered in patients with adverse predictive factors e.g. HBsAg level greater than 200 IU/mL at year 3 of treatment and/or baseline-to-3-year percentage reduction of HBsAg less than 67% for subsequent HBsAg seroclearance.

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38th Annual General Meeting cum Scientific Meeting of The Hong Kong Society of Gastroenterology

Date: 7 March 2019

Venue: Cordis, Hong Kong at Langham Place, Kowloon

Organizing Chairperson: Dr Wai-Fan Luk

Sponsored by: AstraZeneca, Bristol-Myers Squibb, DCH Auriga, Eisai, Ferring, Gilead, Medtronic, A.Menarini, Novartis, Otsuka, Pentax and Takeda

The annual scientific meeting was very successful and well-attended by 185 healthcare professionals. The honorary fellowship of our Society was bestowed upon distinguished guest, Professor Richard M. Peek, Jr., Director of Division of Gastroenterology, Vanderbilt University Medical Centre, Nashville, USA cum Editor-in-Chief, *Gastroenterology*. He is among the 22 honorary fellows of our Society who are renowned scholars in the specialty.

Professor Peek delivered a lecture on "Helicobacter pylori and gastric cancer: A case of tragic triangulations" which was informative and well received. It was followed by "A case of dilated small bowel" presented by Dr Aston T.C. Tam. The panel discussion led by Dr Kelvin K.C. Ng, Dr Chi-Wai Lau and Dr Wai-Kay Seto was actively participated.

The annual general meeting then followed was attended by 73 fellows and members during which the Society's annual report and financial statements for the year of 2018 were presented. Seven fellows were elected to the Council for the term of 2019-2021.

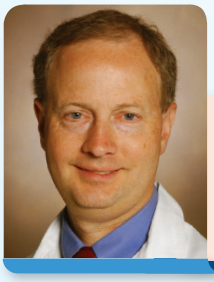
A Certificate of Appreciation was presented to each of the twelve sponsors in appreciation of their support and contributions towards the Meeting.

Most participants stayed for the dinner and continued exchanging their views.

More photographs are available online http://www.hksge.org/photogallery.htm

Welcome! New Fellows

Honorary Fellow



Professor Richard M. Peek, Jr.
Director, Division of Gastroenterology
Vanderbilt University Medical Centre
Nashville, USA

Fellow

Dr A Rashid Nok-Shun LUI
Department of Medicine and Therapeutics
Prince of Wales Hospital
Hong Kong

Coming Soon

21st JOINT ANNUAL SCIENTIFIC MEETING 2019
Sunday, 1 September 2019

Date: Sunday, 1 September 2019

Venue: The Ballroom, Level 7
Cordis, Hong Kong
555 Shanghai Street, Mongkok
Kowloon, Hong Kong

Organizing Chairperson: Prof. Justin Wu

Scientific Chairpersons: Prof. Justin Wu, Prof. Anthony Teoh

Co-organizers:
The Hong Kong Society of Gastroenterology
Hong Kong Society of Digestive Endoscopy
Hong Kong Society for Coloproctology
The Hong Kong Association for the Study of Liver Diseases
The Hong Kong Society of Gastrointestinal Motility
Hong Kong IBD Society

Topics	Speakers
Endoscopic treatment of obesity	Dr. Reem Z. Sharaiha (USA)
Endoscopic treatment of bariatric complications	Dr. Reem Z. Sharaiha (USA)
Update in the management of perianal Crohn's disease	Dr. Joyce W.Y. Mak (PWH)
Esophageal Motility Disorders: What's Next Beyond Chicago Classification 3.0	Prof. C. Prakash Gyawali (USA)
Clinical application of high resolution manometry	Dr. Chun-Yu Say (CMC)
Management of Esophageal Motility Disorders in 2019	Prof. C. Prakash Gyawali (USA)
Advances in HBV infection: new markers and treatments	Dr. Elvis W.P. To (QMH)
Current evidence in the management of rectal prolapse	Dr. Cyrus T.Y. Tse (Private)

Major Meetings

14-16 June 2019
The 7th Annual Meeting of Asian Organization for Crohn's & Colitis
Organizers : Asian Organization for Crohn's & Colitis (AOCC), Taiwan Society of Inflammatory Bowel Disease
Location: Taipei, Taiwan
Website: http://aocc2019.org/

20-22 June 2019
The Liver Week 2019
Organizer: The Korean Association for the Study of Liver
Location: Busan, Korea
Website: www.theliverweek.org/main.php

21-22 June 2019
International Workshop on Diagnostic and Therapeutic Endoscopy (EndoSwiss 2019-Live)
Location: Zurich, Switzerland
Website: www.endoswiss.ch/

11-14 July 2019
GIHep Singapore 2019
Organizer: Gastroenterological Society of Singapore
Location: Singapore
Website: http://gihep.org.sg/

11-15 August 2019
48th World Congress of Surgery (WCS 2019)
Organized by: International Society of Surgery (ISS/SIC)
Location: Krakow, Poland
Website: www.wcs2019.org

16-18 August 2019
2019 American Neurogastroenterology and Motility Society Annual Meeting (ANMS 2019)
Organizer: American Neurogastroenterology and Motility Society (ANMS)
Location: Chicago, USA
Website: www.motilitysociety.org/

22-24 August 2019
5th Singapore International Advanced Therapeutic Endoscopy Course (SIATEC)
Organized by: Tan Tock Seng Hospital
Location: Singapore
Website: http://siatec.com.sg/

4-7 September 2019
7th Biennial Congress of the Asian-Pacific Hepato-Pancreato-Biliary Association
Hosted by: Asia-Pacific Hepato-Pancreato-Biliary Association (A-PHPBA), Korean Association of Hepato-Biliary-Pancreatic Surgery
Location: Seoul, Korea
Website: www.aphpba2019.com/

21-24 September 2019
World Congress of Gastroenterology (WCOG) 2019
Organizer: The World Gastroenterology Organization, in partnership with The Turkish Society of Gastroenterology
Location: Istanbul, Turkey
Website: http://wcog2019.org/

27-29 September 2019
Taiwan Digestive Disease Week (TDDW 2019)
Organizer: The Gastroenterological Society of Taiwan
Location: Kaohsiung, Taiwan
Website: www.tddw.org/

19-23 October 2019
27th UEG Week
Organizer: United European Gastroenterology (UEG)
Location: Barcelona, Spain
Website: www.ueg.eu

25-30 October 2019
ACG 2019 Annual Scientific Meeting and Postgraduate Course
Organizer: American College of Gastroenterology (ACG)
Location: Texas, USA
Website: http://acgmeetings.gi.org/

7-9 November 2019
15th OESO World Conference – Global perspectives in Esophageal diseases
Organizer: The OESO Foundation
Location: Beijing, China
Website: www.oeso.org

8-12 November 2019
The AASLD Liver Meeting
Organizer: The American Association for the Study of Liver Diseases
Location: Boston, USA
Website: www.aasld.org/events-professional-development/liver-meeting

21-24 November 2019
Japanese Digestive Disease Week (JDDW 2019)
Location: Kobe, Japan
Website: www.jddw.jp/jddw2019/en/index.html

12-15 December 2019
Asian Pacific Digestive Week (APDW 2019)
Organizers: Asian Pacific Digestive Week Federation (APDWF), Asia Pacific Association of Gastroenterology (APAGE), Asia Pacific Association for the Study of the Liver (APASL), Asian Pacific Society for Digestive Endoscopy (A-PSDE) and ISDS Asian Pacific
Location: Kolkata, India
Website: www.apdw2019.com/

4-8 March 2020
29th Annual Conference - Asian Pacific Association for the Study of the Liver (APASL 2020)
Organizer: The Asian Pacific Association for the Study of the Liver
Location: Bali, Indonesia
Website: www.apasl2020.org/

(More information is available from www.hksge.org)

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