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FOR THE TREATMENT OF CHRONIC HEPATITIS B (CHB) IN ADULTS WITH COMPENSATED LIVER DISEASE 1

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References:

1. Vemlidy® package insert. 2. TDF vs. VEMLIDY: higher rates of ALT normalization at 96 weeks, 76.1% vs. 81.4%, respectively. 3. Package insert. 4. TDF vs. VEMLIDY: higher rates of HBeAg seroconversion at 96 weeks, 75.0% vs. 63.6%, respectively.

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Message from the President

This is the tenth year of the publication of the *JSPHK*. We can see that we are growing stronger with the addition of dedicated doctors to the editorial board, and with the unfailing support of many contributors. We thank you for reading the journal and welcome your suggestions.

May I wish you a very Happy Year of the Dog and every success in the year to come.

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Pictorial Medical History (17)

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Specialist in Psychiatry (Private Practice)  
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The University of Hong Kong

The activities of the Asclepieion were depicted vividly on bas-relief of the temple.

*Treating patients at the asclepieion.*

The full article can be seen at:  
http://www.hkma.org/english/cme/onlinemce/cme201302main.htm
Metabolic Syndrome and Perspectives for Future Research: A Brief Review

Key words:
Metabolic syndrome (代谢症候群), MetSyn, Type 2 diabetes mellitus (2型糖尿病), Cardiovascular disease (心血管疾病), Gut microbiota (腸道微生物群)

Epidemiology
Metabolic syndrome (MetSyn) is characterized by a cluster of disorders, comprising central obesity, hyperglycaemia, dyslipidaemia, and hypertension.¹ It was estimated by the International Diabetes Federation (IDF) that 25% of the world’s adults had MetSyn.² The prevalence of MetSyn is rising globally due to the increasing obesity rates and sedentary lifestyle behaviours, and has greatly contributed to the clinical and public health burden.³,⁴

The reported prevalence of MetSyn varies widely, depending on the study characteristics, population selection, and diagnostic criteria adopted.³,⁴

Definitions
Several organizations have developed the diagnostic criteria for MetSyn since 1998 (Table). The first definition was provided by the World Health Organization (WHO).⁵ In 1999, the European Group for the study of Insulin Resistance (EGIR) modified the WHO diagnostic criteria.⁶ In 2003, the American Association of Clinical Endocrinologists (AACE) also published its definition of MetSyn.⁷ The WHO, EGIR, and AACE criteria all required oral glucose tolerance testing and hyperinsulinemic-euglycemic clamps to determine the occurrence of insulin resistance; however, yet this method is labour intensive and primarily adopted in a research setting.

In contrast, the US National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) dropped the insulin resistance evaluation when it released its standard for diagnosing MetSyn, which is convenient for family physicians for clinical use; therefore, it has been a basis for the subsequent modifications.⁸ Nevertheless, the ATP III criteria were not applicable to various ethnicities, especially when using different cut-off values of waist circumference to define abdominal obesity.

Key points
• This review focuses on the epidemiology, definitions, complications, management strategies and future research perspectives for metabolic syndrome (MetSyn).
• The prevalence of MetSyn is rising globally and has contributed substantially to public health burden in terms of morbidity and mortality. Reported prevalence of MetSyn varies widely, depending on the study characteristics, population selection, and diagnostic criteria adopted.
• The frequent amendments to the criteria of diagnosing MetSyn over time make it difficult to determine the regional variations and temporal trends in its prevalence.
• MetSyn increases the risk of developing type 2 diabetes mellitus, cardiovascular diseases, and other complications.
• Effective lifestyle modification approaches for MetSyn include weight loss, diet, and exercise.
• The manipulation of the gut microbiota could be a promising therapy for MetSyn. Future research should explore extensively into the pathways by which gut microbiota influence the metabolism of the host to develop more effective approaches.
In 2005, the IDF proposed a new definition of MetSyn, incorporating population-specific cutoffs but mandating abdominal obesity as a required component. In the same year, the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) also gave definitions by slightly modifying the ATP III criteria yet did not require abdominal obesity as a mandatory component. Also, there was no agreement on the criteria of abdominal obesity between the IDF and AHA/NHLBI.

To reconcile the different clinical criteria, a single unifying definition was needed. In the hope of accomplishing this, IDF and AHA/NHLBI representatives held discussions and came to an agreement: (Harmonized 2009) that abdominal obesity should not be a prerequisite for diagnosis. However, it is one of the five diagnostic components; the occurrence of three or more components constitutes a diagnosis of MetSyn.

In China, the Chinese Diabetes Society (CDS) also put forward a diagnostic definition for MetSyn in line with the epidemiological characteristics of Chinese ethnicity in 2004. Recently, the national guidelines for the prevention and treatment of diabetes have updated the quantitative indicators of the MetSyn components.

### Complications

Some studies have indicated that MetSyn increases the risk of developing type 2 diabetes mellitus by 3- to 5-fold and that the probability increases with the number of components of MetSyn that occur. MetSyn is also a risk factor for developing cardiovascular disease (CVD). Individuals with MetSyn are at a 2- to 4-fold elevated risk of stroke, a 3- to 4-fold elevated risk of myocardial infarction, and a 2-fold elevated risk of CVD-related death.

MetSyn is also associated with other complications. Patients with MetSyn are at significantly higher risk for microalbuminuria and chronic kidney disease. MetSyn is also linked to increased serum transaminase, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hepatic fibrosis, and cirrhosis. As for the reproductive system, females with polycystic ovary syndrome have an 11-fold increased risk of MetSyn. In addition, a meta-analysis showed that the presence of MetSyn was associated with liver, colorectal, and bladder cancers in males, with endometrial, pancreatic, breast (postmenopausal), rectal, and colorectal cancers in females.

### Management strategies

Management of individuals with MetSyn is crucial to reducing their risk of subsequent complications. Effective preventive approaches of lifestyle modification include weight loss (weight reduction of 5–10% of pre-intervention weight over a period of four to six months), diet (sodium intake of <65–100 mmol/day with a goal of 90–120 mmol of potassium per day; Mediterranean diet; DASH diet), and exercise (daily moderate intensity activity of a minimum 30 minutes for most days of the week; recommended use of pedometer with a goal of >10,000 steps/day). For those whose risk factors are not sufficiently reduced with lifestyle modifications, pharmacological therapy should be considered. The manipulation of the microbiota in gut could also be a promising treatment for preventing and managing MetSyn.

### Gut microbiota

Accumulating studies indicate that microbiota in the gut is associated with different components of MetSyn, including insulin resistance, obesity, hyperglycaemia, dyslipidaemia, and hypertension. Despite previous evidence identifying the causal relationship between gut microbiota and MetSyn, the pathologic pathways remain to be explored. The well-known mechanism for the initiation of MetSyn is by translocation of endotoxin or direct translocation of gram-negative microbes, resulting in low-grade inflammation which is related to the impaired bowel barrier function and leakage of bacteria in MetSyn. Some studies also find that short-chain fatty acids and bile salt hydrolase play an important role in regulating the development of MetSyn via the regulation of adipogenesis, insulin secretion, fat accumulation, energy homeostasis, and plasma cholesterol levels. Therefore, gut microbiota may act as a potential target for the treatment of MetSyn.

Prebiotics and probiotics are widely used to manipulate the gut microbiota. There has been an increasing research interest in the effect of probiotics and prebiotics on different components of MetSyn. Prebiotics or probiotics can reduce insulin resistance, induce weight loss, and decrease low-grade inflammation and improve barrier integrity in bowel to regulate glucose and lipid levels in the blood. The mechanisms of probiotics and prebiotics that alleviate MetSyn include change of composition of gut microbiota, regulation of energy homeostasis, activation of insulin signalling pathways, modifications of inflammatory signalling, interaction with the immune system, and modulation of cholesterol levels.

However, further investigations are required to get a comprehensive understanding of gut microbiota manipulation in MetSyn treatment and prevention. Future research should explore extensively the pathways by which gut microbiota influence the metabolism of the host, through investigating microbiota modifications over time, changes in metabolites, and genetic and epigenetic effects, to develop new, more effective and personalized approaches to manipulating the gut microbiota. In addition, clinical trials addressing the efficacy and safety of potential therapies for manipulating gut microbiota to manage MetSyn are also needed.
Table. Different definitions of MetSyn

<table>
<thead>
<tr>
<th>IR</th>
<th>WC</th>
<th>HDL-C</th>
<th>TG</th>
<th>BP</th>
<th>FBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO (1998)</td>
<td>IGT, IFG, 12DM, or lowered insulin sensitivity + any 2</td>
<td>Waist-to-hip ratio &gt;0.90 (male) &gt;0.85/BMI &gt;30 (female)</td>
<td>≤35 mg/dL (male)</td>
<td>≥150 mg/dL</td>
<td>≥140/90 mm Hg</td>
</tr>
<tr>
<td>EGIR (1999)</td>
<td>Plasma insulin &gt;75th percentile + any 2</td>
<td>BMI ≥25</td>
<td>≤39 mg/dL (male)</td>
<td>≥150 mg/dL</td>
<td>≥140/90 mm Hg</td>
</tr>
<tr>
<td>AACE (2003)</td>
<td>IGT or IFG + any 1 based on the clinical judgment</td>
<td>BMI ≥25</td>
<td>≤40 mg/dL (male)</td>
<td>≥150 mg/dL</td>
<td>≥140/90 mm Hg</td>
</tr>
<tr>
<td>ATP III (2001)</td>
<td>NA, but any 3</td>
<td>Increased WC (ethnic specific) + any 2</td>
<td>≤40 mg/dL (male)</td>
<td>≥150 mg/dL</td>
<td>≥140/90 mm Hg</td>
</tr>
<tr>
<td>NLBHI (2005)</td>
<td>NA, but any 3</td>
<td>≥102 cm (male)</td>
<td>≤40 mg/dL (male)</td>
<td>≥150 mg/dL</td>
<td>≥140/90 mm Hg</td>
</tr>
<tr>
<td>Harmonized (2009)</td>
<td>NA, but any 3</td>
<td>Increased WC</td>
<td>≤40 mg/dL (male)</td>
<td>≥150 mg/dL</td>
<td>≥140/90 mm Hg</td>
</tr>
<tr>
<td>CDS I (2004)</td>
<td>NA, but any 3</td>
<td>BMI ≥25</td>
<td>≤35 mg/dL (male)</td>
<td>≥150 mg/dL</td>
<td>≥140/90 mm Hg</td>
</tr>
<tr>
<td>CDS II (2016)</td>
<td>NA, but any 3</td>
<td>≥90 cm (male)</td>
<td>≤40 mg/dL</td>
<td>≥150 mg/dL</td>
<td>≥140/90 mm Hg</td>
</tr>
</tbody>
</table>

References

Update on Advanced Biliary Interventions

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Key words:
Endoscopic ultrasound (超聲波內視鏡), ERCP (內鏡逆行性膽管造影), Cholangioscopy (膽道鏡造影), Biliary drainage (膽汁引流)

Introduction

Gallbladder (GB) and bile duct diseases are common disorders that clinicians encounter in daily clinical practice. They include benign conditions such as gallstones-related cholecystitis, bile duct stone-related cholangitis, and malignant disease such as cholangiocarcinoma. With the advances in endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) treatments, many conditions that were treated in the past by surgical methods can now be treated by endoscopic means.

Peroral cholangioscopy

ERCP is commonly used to diagnose biliary obstruction such as biliary stricture and stone diseases. However, ERCP images obtained by fluoroscopy do not differentiate benign from malignant stricture diseases; also, small-size stone may be missed due to masking by contrast injection. Direct endoscopic visualization of the internal lumen of the bile duct could improve the diagnostic accuracy.

Peroral cholangioscopy (POC) can be done in three different ways: 1. inserting a slim endoscope through the working channel of a therapeutic duodenoscope (“Mother and Baby” two operators’ method); 2. inserting an ultrasm endoscope or slim gastroscope directly into the bile duct; and 3. inserting a catheter-based cholangioscopic system (SpyGlass, Boston Scientific) through the duodenoscope into the bile duct. The last two methods can be performed by a single operator. Through POC, the endoscopist can perform fragmentation of stones, direct visualization and biopsy of suspicious biliary stricture, and selective cannulation of intrahepatic bile ducts.

In the case of large and multiple stone impaction in the bile duct, it is difficult to engage the stones by basket or mechanical lithotriptor by ERCP. Using POC, one can employ electrohydraulic and laser lithotripsy for direct stones fragmentation. A recent meta-analysis of 49 studies showed that POC achieved a clearance rate of 88% (95% confidence interval [CI], 85%-91%) for difficult biliary duct stone.1 In a recent international, multicenter study, POC achieved a complete ductal clearance of 97.3% (96.7% of patients with electrohydraulic lithotripsy vs 99% of patients with laser lithotripsy) in patients with difficult bile duct stone.2 In a recent study comparing POC with conventional ERCP, one may detect small stones that were missed by occlusion cholangiogram and avoid late complications.3

For indeterminate biliary stricture, a meta-analysis showed the accuracy of POC in visual diagnosis and in tissue sampling to be 89% (95% CI, 84%-93%) and 79% (95% CI, 74%-84%) respectively.1 Actually, visual diagnosis has a higher diagnostic yield than biopsy due to difficult targeted biopsy and sampling error. The cholangioscopic features of malignant bile duct tumour include the presence of intraductal nodules or masses, dilated and irregular blood vessels, papillary or villous mucosal projections, and infiltrative or ulcerative stricture (Figure). Apart from POC, other endoscopic imaging techniques, including EUS with or without fine needle aspiration, intraductal ultrasound, confocal laser endomicroscopy, bile duct tissue sampling for cytology, and fluorescent in situ hybridization (FISH) can significantly improve the diagnostic accuracy for cholangiocarcinoma.4

Local biliary tumour treatment

For advanced cholangiocarcinoma, palliation of biliary obstruction by self-expandable metal stents (SEMS) was shown to be more effective than the plastic stent in achieving longterm biliary drainage. In a recent meta-analysis of 20 randomized, controlled trials comparing SEMS and plastic stent for palliation, SEMS placement resulted in less late complications (odds ratio [OR]=0.43; 95% CI, 0.37-0.77); sepsis or cholangitis (OR=0.53; 95% CI, 0.37-0.77), blocking from sludge (OR=0.11; 95% CI, 0.07-0.17), and mean number of reinterventions (95% CI, -1.64 – -0.02). Although there was a higher symptom-
Figure. Spyglass cholangioscope with biopsy forceps passes through the duodenoscope (upper left) and passes to the liver hilum (upper right). Direct visual inspection of the bile duct showed nodular tumour obstructing the lumen (lower left). Biopsy of the tumour is possible (lower right).

Cholangitis occurred less in the combined group (OR 0.57; 95% CI, 0.35–0.94). Self-limiting photosensitivity occurred in 10.61% of patients in the PDT group. The study authors concluded that PDT is beneficial, minimally invasive and well tolerated with a favourable side effect profile in palliating patients with nonresectable cholangiocarcinoma.3

**Diagnosis of choledochoolithiasis**

In patients who present with right upper quadrant pain, fever and deranged liver function test, choledocholithiasis-related cholangitis should be suspected. The American Society for Gastrointestinal Endoscopy (ASGE) guideline defined the criteria for high likelihood of choledocholithiasis as: (a) cholelithiasis on abdominal ultrasound (US); (b) bilirubin level >4 mg/dL; (c) bilirubin level 1.8 to 4.0 mg/dL plus a dilated common bile duct (CBD) more than 6 mm; or (d) evidence of clinical cholangitis.10 These criteria are well used by clinicians to refer patients to receive ERCP treatment. However, the accuracy of these criteria is not high enough, and many patients received unnecessary ERCP and suffered from its complications.

In a recent retrospective study of prospective case series of 2,724 patients suspected to have choledocholithiasis, 1,076 (40%) patients were confirmed to have choledocholithiasis. Using ASGE high-risk criteria, the specificity was shown to be 74% (95% CI, 72%–77%), and positive predictive value (PPV) was 64% (95% CI, 61%–67%) only. In that case, more than a third of the patients would have received unnecessary ERCP according to the guideline. To increase the specificity, combining two predictors (choledocholithiasis on abdominal US and bilirubin level >4 mg/dL plus CBD dilatation) would achieve the highest specificity of 94% and PPV of 85%.11

EUS and magnetic resonance cholangiopancreatography (MRCP) have been shown to have high diagnostic
References

EUS-guided bile duct intervention
For patients suffering from cholangitis, there is an urgent need to drain the bile duct and relieve the obstruction. However, cannulation of the bile duct is not easy. In a meta-analysis of 52 articles, the cumulative weighted bile duct cannulation success rate was 89.3% (95% CI 0.866–0.919) only. In case of failure, the patient needs to be shifted to either the interventional radiology suite for percutaneous transhepatic biliary drainage (PTBD), or to surgery for surgical drainage. This will delay patient treatment and increase morbidity. Because the bile duct is very close to the gastric and duodenal lumen, it is easily accessible by EUS-guided needle puncture, followed by guidewire insertion and stent placement.

EUS-guided rendezvous (EUS-RV) technique is performed by passing a guidewire through the fine needle aspiration (FNA) needle across the papilla, through transduodenal or transhepatic puncture approach. After the guidewire is successfully passed through the papilla, the EUS scope is exchanged with the duodenoscope, and the bile duct is cannulated by exchanging the pre-placed guidewire by two-hands technique.

If the EUS-RV failed to place the guidewire across the papilla, or the papilla is not accessible by duodenoscope due to altered anatomy, one can directly insert a plastic stent or SEMS through the puncture sites into the bile duct. The methods include: (a) EUS-guided antegrade stenting by directly inserting a metal stent through the left intrahepatic duct into the CBD and across the papilla; (b) EUS-guided hepaticojejunostomy (HG) by placing a stent into the left intrahepatic duct and drainage obtained through the stomach; (c) EUS-guided cholecdochojunostomy (CDJ) by placing a stent into the CBD with drainage obtained through the duodenum; (d) EUS-guided gallbladder drainage by placing a lumen-apposing metal stent (LAMS) from the duodenum into the gallbladder with drainage obtained through the duodenum.

A LAMS is a specially designed SEMS to provide a secure and fast drainage between two luminal surfaces. Due to the particular design, two flanges in both sides of the stent can hold the luminal surface together to prevent migration, and the central lumen allows for effective drainage from one side (gallbladder, bile duct, pseudocyst) to the gastrointestinal lumen. One example is the rapidly emerging indication of transcudenoal gallbladder drainage with LAMS in a patient who has acute cholecystitis but is not suitable for surgery.

Multiple, large-scale, multicentre studies have confirmed the usefulness of EUS-guided biliary intervention in improving effective drainage with a low complication rate. These techniques are promising alternatives for biliary drainage in case of failed ERCP, or even as the first method to use for drainage without prior ERCP.

Conclusion
Advances in the endoscopic techniques and instruments have made previously difficult biliary intervention possible. A new era of endoscopic biliary intervention may bring significant benefit for patients suffering from various bile duct diseases.
130 Years of Medical Education in Hong Kong: The Originator of Anatomy and Surgery

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Key words:
Medical education in Hong Kong (香港的醫學教育), Origins (起源), History (歷史), Kenelm Hutchinson Digby, University of Hong Kong (香港大學)

Introduction

Born on 4 August 1884, Kenelm Hutchinson Digby entered Guy’s Hospital Medical School, London in 1902. After qualification in 1907, he held post-graduate appointments at Guy’s in surgery, anaesthesia, out-patient clinic, and anatomy.

The Hong Kong University connection

When the University opened its doors in March 1912, there were only two faculties – Medicine and Engineering (Figure 1). In 1913 Digby began his lifelong association with the infant University of Hong Kong as Professor of Anatomy (at a salary of £600 per annum with quarters). Whole-time chairs in preclinical subjects of anatomy and physiology had already been secured. The School of Anatomy had just been opened through a donation of $50,000 by local businessman Mr. Ng Li-hing, and Digby had the privilege of heading his department with its own building, where soon was established a high standard of work (Figure 2).

In February 1915, the next great step towards the establishment of a really modern medical teaching centre was made possible through the generous endowment of $50,000 by Sir Robert Ho-tung towards the cost of the teaching staff, with the proviso that not less than $2,000 a year of the interest should go towards the remuneration of the Ho-tung Chair of Clinical Surgery. Thus was founded the first clinical Chair. Clinical instruction was given at the Alice Memorial, Nethersole and Tung Wah Hospitals. In October 1914 the Government Civil Hospital was opened to medical students.

Modern surgery in Hong Kong owed its inception to Digby, who had the daunting task as Ho-tung Professor of Clinical Surgery as well as surgical consultant to the Government Civil Hospital. The Rockefeller Foundation of New York helped to found three full-time clinical chairs. The whole situation was investigated with characteristic thoroughness, and in the end the foundation donated $750,000 to found these chairs and to enable the university to carry out other very necessary changes in the pre-clinical departments. The new Chair of Surgery then became associated with the Ho-tung Chair of Clinical Surgery and Digby afterwards took over the joint post. 1923 saw the complete separation of the Department of Surgery from that of Anatomy when Digby relinquished the Chair of Anatomy for the full-time Professor of Surgery. When the plans of the new Queen Mary Hospital were recently drawn up, they included a hostel, but economy demanded their subsequent withdrawal. In 1933 the university found itself in the unusual state of having some surplus funds, and it was decided to build a School of Surgery, which was finished at a cost of $24,000 in 1934, and was officially opened in 1935. From 1930 to 1948, Digby was consulting surgeon at the Queen Mary Hospital.

As Dean of the Faculty of Medicine (1915–1916, 1920–1925), Digby was
instrumental in establishing chairs in medicine, surgery, and obstetrics through the endowment by the Rockefeller Foundation. Once funding was available, staff organization, teaching, and research were restructured. Clinical research was fostered due to the stimulus given by the Rockefeller Foundation to the foundation of full-time chairs in clinical subjects. As the first full-time Chair of Surgery, Digby took up the challenge of being head of department, supervision of in-patient and out-patient services, and clinical laboratory. Digby demonstrated surgical operations on cadavers to students. In a real situation, each operation lasted hours because all surgical instruments were handed round by forceps and never touched even with the gloved hands. Digby propagated his former chief’s no-touch technique in surgery to Hong Kong. He was a ‘workaholic’ and his interests were wide ranging. In common with other master surgeons of his generation, Digby was also a skilled anatomist. His interests ranged from general surgery, thoracic surgery, orthopaedics, to neurosurgery and otolaryngology. In 1919, due to Digby’s personal influence, local businessman Ho Kwong, son of Ho Fook (who had donated $50,000 for a School of Physiology) founded an annual scholarship and prizes for medical undergraduates.

The high esteem that Digby had in the University was shown by the following remark in the Medical Society Journal Caduceus in 1923:

“The Medical Society welcomes with satisfaction the appointment of Professor Digby to the new Chair of Surgery. In Hong Kong there is a peculiar tendency to overwork an understaffed department. The University is not free from this peculiarity. For the past few years, Digby has been Professor of Clinical Surgery and Professor of Anatomy and recently again took the duties of Dean. He has taken great pains to improve the Surgical Clinic. If the increasing number of out-patients is anything to go by, the Clinic has certainly gained great popularity. It is anticipated that greater improvements will transpire now that he has anatomy off his hands.”

The aims of university education

Despite constraints in manpower and finance, apart from the obligatory lectures, clinical teachings and demonstrations, Digby and his colleagues were actively engaged in other aspects of medical education, in the review of books and current medical literature.

Each issue of the Caduceus contained a section of information on recent medical publications reviewed by the Professors and senior staff with recommendations to students. Digby reviewed extensively on surgical works.

In the early days of the Medical Faculty, Digby as Dean of Medicine had realized the important role of a university in society. In 1924, as President of the Medical Society, he delivered the following inaugural address:

THE OBJECTS OF A MEDICAL SOCIETY

“A university should not be a mere technical school in which students are taught a number of facts. It should be a place in which students learn to think for themselves. A professor should not be a mere purveyor of knowledge, but a stimulator of thought. There is always a danger for the learner to make a bad habit of merely picking up facts from his teachers, loading and overloading his memory with details and allowing the intelligent part of his brain to atrophy. The student then becomes no better than a gramophone with a large number of records, but still a gramophone, that is a machine that can only play back just what was put into it and nothing more. The medical curriculum is so overcrowded that the danger exists that student may get into the habit of always learning what others think till he ceases to think for himself. This is especially serious for a medical man, for each patient is a novel problem, and each case raises some perplexity not answerable by any simple rule.

One aim of a medical society is to promote the power of original thought and serious criticism. This University is still in its early childhood; it will not have fully established its title till it produces original research of value. By encouraging critical thought this Society may stimulate its members to add to the common store of knowledge, to explore some of the unknown which stretches on every land. We must choose between two things: a static mankind riddled with disease, misgoverned, ignorant and superstitious, or a mankind ready to take the risks of wide-

Figure 2. The Ng Li-hing School of Anatomy, University of Hong Kong is on the left, with the School of Physiology on the right. From: William Hornell, University of Hong Kong- A Souvenir, 1928.
spread education, science and research in an adventure to improve the common lot. Our Society has another value besides encouraging original thought viz. that of promoting social intercourse. This Society was founded on the traditions of two similar societies at Guy’s Hospital where I was a student, and I can ensure you that some of my happiest memories of my old medical school are memories of meetings at these societies. Let us hope that this Medical Society of Hong Kong University will provide pleasant memories for many generations of graduates.”

On the importance of educating student in research Digby had this to say:

**TRAINING OF MEDICAL STUDENTS IN RESEARCH**

“The medical course is so overcrowded and the essentials of medical knowledge so numerous that the undergraduate has little time for research work. Yet he can cultivate the habit of thinking for himself and of testing statements, and he can keep his eyes open for ideas upon which he can work consequently. The best training for a student who contemplates research is to hold house appointments for one year. He will be too occupied during the period to indulge in much systematic research on his own, but his fresh young brain may contribute valuable assistance. After house appointments the would-be researcher should become attached on one of the chief departments, Medicine, Surgery, etc, and work partly at his own ideas, partly in collaboration with his Professor. To assist an older man in a research is a useful training, and the assistance and encouragement received in return should be invaluable. It is the romantic spirit of adventure in research that should appeal to all young men. It is only by delving into natural phenomena that we can find uncharted lands. This Medical Society returns to its earlier traditions of papers by undergraduates in preference to lectures by members of the staff or by distinguished visitors, will serve a valuable purpose in fostering the spirit of research.”

**Digby’s legacy in Hong Kong**

Digby was appointed an Officer of the British Empire in 1939 by King George VI, in the Birthday Honours list for medical services in Hong Kong (Figure 3). During the Pacific War in December 1941, Hong Kong fell to the Japanese after 18 days of resistance. Digby was interned with other University staff at the Stanley camp. After the liberation of Hong Kong in August 1945, Digby spent a short convalescence in England, and then returned to the colony. He soon retired from the Chair of Surgery, but continued an active consulting practice until 1949, when failing health forced him to return to England. Digby died of cancer of the rectum on 23 February 1954 in Guy’s Hospital.

In an obituary in the British Medical Journal on 6 March 1954, his former colleague at the University of Hong Kong, Professor Leslie Davies (Professor of Pathology, 1931–1939) reminisced:

“As a man, Digby was remarkable for his integrity, his honesty of purpose, his enthusiastic attitude to life, and his complete absence of small-mindedness. His colleagues in committees sometimes found him somewhat intransigent when there were differences of opinion, but his opinions were often vindicated by time, and he never nourished rancour. If he did disagree with people he never spoke ill of them. He had no enemies, but many friends among people of all positions and races.

“As a teacher he was remarkable for his zeal, which never flagged notwithstanding advancing age and adverse climatic conditions. Many hundreds of medical students who have passed through his hands owe much to him for his sound teaching of the principles and practice of surgery. As a surgeon he was first rate. He neglected no opportunity of extending his knowledge of new developments, and during his leave of absence from Hong Kong he visited most of the leading surgical centres in Europe and the USA. Despite his heavy commitments as a teacher and a practitioner of surgery, he took a lively interest in research. He wrote papers himself and stimulated his associates to do likewise. Throughout his life he maintained his interest in the role of lymphatic tissues in immunity. Only recently he demonstrated an exhibition of this subject before a scientific society in this country. News of his death will be learnt with great sorrow by his former colleagues, patients and students in the Far East and elsewhere.”

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**Figure 3. Professor Kenelm Hutchinson Digby (1884–1954), OBE 1939, MB, BS London 1907, MRCS 1907, LRCP 1907, FRCS England 1910, Professor of Anatomy 1913–1923, Ho-tung Professor of Clinical Surgery 1915–1923, Professor of Surgery 1923–1945, Dean of Medicine 1915–1916, 1920–1925, Honorary Consultant Surgeon to Hong Kong Government 1915–1948, Emeritus Professor of Surgery 1950. Photograph courtesy of the Department of Surgery, University of Hong Kong.**
THE SOCIETY OF PHYSICIANS OF HONG KONG

LECTURE and AGM  March 28, 2018 (Wednesday)  Free admission for doctors

Welcome note:  Dr Lam Tat Chung, Paul 林達聰醫生
FRCP, FRCPsych, FHKAM (Medicine), FHKAM (Psychiatry)
President of the Society of Physicians of Hong Kong

Speaker:  Dr Yip Wai Chun, Andrew 葉維晉醫生, Specialist in Urology

Topic:  Avanafil-The quest for the optimal PDE5-I

Venue:  HKMA Dr Li Shu Pui Professional Education Centre
2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong

Time:
1:00 pm  Lunch
2:00–2:50 pm  Lecture
2:50–3:00 pm  Q & A

The AGM of the Society will be held in the side room at 1:30 pm. (full members only)

Enquiry: Tel: 2526 2626 (no telephone registration)
Sponsor: A. Menarini Hong Kong Limited
First-come-first-served basis. Pre-registration is required. CME under application.
No confirmation will be sent upon registration. Unsuccessful applicants will be informed.

Registration:  Fax to: 2597 5231  Attention: Ms Wendy Woo
Web registration and further details: www.SOPHYSICIANSHK.org
☐ I wish to attend the lecture and lunch on March 28, 2018 (Wednesday) (Free admission)

Name of Doctor (Surname first): ________________________________ Tel: __________________
(Please print clearly)

Members and Associate Members please present membership cards of
THE SOCIETY OF PHYSICIANS OF HONG KONG
Complete Response to Bevacizumab and Chemotherapy in an Elderly Patient with Metastatic Colorectal Cancer

Dr Ada Ma
(馬天慧醫生)
Specialist in Medical Oncology
Private practice

Key words:
Bevacizumab (貝伐單抗), Capecitabine (卡培他濱), Biologic therapy (生物治療), Chemotherapy (化學治療), Metastatic colorectal cancer (轉移性結腸直腸癌), Elderly (老年人)

Case presentation

A 79-year-old Chinese female presented with constipation and weight loss. Positron emission tomography-computed tomography (PET-CT) scan revealed a 7-cm rectal tumour with no intestinal obstruction; however, there was note of multiple enlarged pelvic lymph nodes, bilobar liver metastases and left ilium bone metastases (Figure 1A). Rectal tumour biopsy confirmed adenocarcinoma positive for KRAS mutation. Her carcinoembryonic (CEA) level was 30 μg/mL. The patient was diagnosed with stage IV, inoperable metastatic colorectal cancer (mCRC).

Case management

The patient underwent immediate induction therapy with bevacizumab, oxaliplatin and capecitabine for eight cycles, starting in October 2016. Oxaliplatin and capecitabine were reduced to 80% of the normal dose, as recommended for a patient of this age. Clinical symptoms resolved after two cycles of therapy and CEA levels normalized after the completion of induction therapy. The treatment regimen was well tolerated; adverse events included mild infusion reactions and loose stools once or twice daily. She experienced no nausea and maintained a good appetite throughout treatment. A PET-CT scan after induction therapy revealed a complete response (Figure 1B). The patient is currently in remission and has been receiving bevacizumab and capecitabine maintenance therapy since April 2017. Findings of a repeat PET-CT scan in September 2017 were unremarkable. She is followed up in the clinic every 3 weeks and receives routine blood monitoring and maintenance therapy.

Discussion

Due to the advanced stage of disease, the patient’s treatment options were

Figure 1. PET-CT scan in a patient with mCRC before (A) and after (B) induction therapy

Liver metastases
either chemotherapy or supportive care. Since the patient was otherwise in good health and had a good performance status, she was encouraged to start chemotherapy, despite her initial reluctance. The European Society of Medical Oncology (ESMO) states that biologics are indicated as first-line treatment of patients with mCRC unless contraindicated due to, for example, reduced organ function, poor performance status or cardiovascular insufficiency. Age is not a direct contraindication for systemic combination chemotherapy plus targeted agents.\(^1\)\(^2\)

The efficacy of bevacizumab in this clinical case corroborates the results of clinical trials which demonstrate a progression-free survival (PFS) benefit of adding bevacizumab to induction and maintenance therapy, compared with chemotherapy-only induction or observation maintenance.\(^3\)\(^4\) Likewise, bevacizumab plus chemotherapy was well tolerated by this patient, with only minor infusion reactions and mild diarrhoea. In the Australasian Gastro-Intestinal Cancer Trials Group (AGITG) mitomycin, Avastin, Xeloda (MAX) study, which evaluated capecitabine, and capcitabine plus bevacizumab in patients with previously untreated mCRC, median PFS was 5.7 months with capcitabine alone compared with 8.5 months with capcitabine plus bevacizumab (hazard ratio [HR]=0.63; 95% confidence interval [CI], 0.50–0.79; Figure 2). Toxicity rates were acceptable and both regimens were well tolerated. Furthermore, overall quality of life (QoL) was similar in all groups. Similarly, in the Avastin in the Elderly with Xeloda (AVEX) study, which investigated response to capcitabine versus capcitabine plus bevacizumab in patients aged ≥70 years with previously untreated mCRC who were not deemed to be candidates for oxaliplatin-based or irinotecan-based chemotherapy, there was a significant PFS benefit in patients treated with capcitabine plus bevacizumab compared with capcitabine alone (9.1 vs 5.1 months; HR=0.53; p<0.001).\(^5\) Grade ≥3 treatment-related adverse events occurred in 22% of patients in the capcitabine group and 40% in the combination group; the most common grade ≥3 events were hand-foot syndrome, diarrhoea and venous thromboembolic events.\(^2\)

This patient demonstrated a complete response after induction therapy. Since the therapy was well tolerated, we decided to continue with maintenance therapy as data have shown that it prolongs PFS without compromising QoL. CAIRO3 was an open-label trial comparing maintenance treatment with capcitabine and bevacizumab to observation in patients with previously untreated mCRC with stable disease or better after induction treatment with six cycles of capcitabine, oxaliplatin and bevacizumab. On first progression, patients in both groups received the induction regimen until second progression (PFS2). The PFS2 in patients who received maintenance therapy was 11.7 months compared with 8.5 months in the observation group (HR=0.67; 95% CI, 0.56–0.81; p<0.0001).\(^4\) Maintenance therapy was well tolerated and the only significant difference in adverse events was an increased incidence of hand-foot syndrome in the maintenance group compared with the observation group (23% vs 0%; p<0.0001).\(^4\) Global QoL did not deteriorate during maintenance treatment and was not different between treatment groups.\(^4\)

In summary, this case highlights that combination chemotherapy with bevacizumab prolongs PFS without compromising QoL in elderly patients with mCRC.

References

The Power of Proof

15 positive pivotal trials across 7 cancer types

Abbreviated Prescribing Information – Avastin Roche Injection 100mg/4 ml (bevacizumab)

Indications and Usage: Avastin Roche has been approved or registered in more than 70 countries for the treatment of metastatic colorectal cancer (mCRC) in combination with platinum-based chemotherapy or as a monotherapy, in combination with fluorouracil in advanced ovarian cancer, in combination with paclitaxel and carboplatin for patients with platinum-sensitive recurrent ovarian cancer, in combination with paclitaxel for patients with advanced non-small cell lung cancer (NSCLC), in advanced renal cell carcinoma (mRCC), in glioblastoma multiforme and paclitaxel and topotecan in patients who cannot receive platinum-based chemotherapy, and in advanced NSCLC and in combination with erlotinib, sunitinib and sorafenib.

Dosage & Administration: The recommended dose for all indications is 10 mg/kg every 2 weeks. The drug is supplied as a 100 mg vial of bevacizumab.

Adverse Reactions: Adverse reactions may include proteinuria, hypertension, arterial thromboembolism, venous thromboembolism, hypertension, proteinuria, and pre-existing hypertension, among others.

Drug Interactions: Bevacizumab is known to interact with other medications and should not be used in combination with other medications.

Contraindications: Bevacizumab is contraindicated in patients with severe hypertension, active arterial thromboembolic events, recent vascular surgery, and patients with active non-arterial thromboembolic events.

Warnings & Precautions: Bevacizumab is associated with an increased risk of hemorrhage, thromboembolic events, and other serious adverse events, and should be used with caution in patients with a history of thrombosis or a history of hypertension.

References: Several studies have been conducted to evaluate the effectiveness of Avastin Roche in various cancer types, including NSCLC, colorectal, ovarian, renal cell, glioblastoma, and breast cancer. These studies have shown promising results, with some studies reporting significant improvements in patient outcomes.

For further information: Roche Hong Kong Ltd.

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