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THE SOCIETY OF PHYSICIANS OF HONG KONG

LECTURE and AGM      March 29, 2017 (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:  Professor Ma Ching Wan, Ronald (馬青雲教授) FRCP  
The Chinese University of Hong Kong

Topic:  Overview of new oral hypoglycemic agents: an update for physicians

Chairman:  Professor Wong Chi Sang, Martin (黃至生教授) MD, FHKAM(Family Med)  
The Chinese University of Hong Kong

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

Time:  1:00 pm       Light lunch       2:00–3:00 pm       Lecture

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: Novartis Hong Kong Limited  
On 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 Form:  Fax to: 2577 0274   Attention: Ms. Iris Poon of Novartis

Web registration and further details: www.SOPHYSICIANSHK.org

☐ I wish to attend the lecture and lunch on Wednesday, March 29, 2017 (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
Message from the President

This is the ninth year of the publication of the Journal. We are glad that during the years we have produced consistently highly readable material and excellent updated medical information for your reference. With the New Year, our Editorial Board is joined by Professor Wong Chi Sang, Martin (黃至生教授), MD, FHKAM (Family Medicine) of the Chinese University and Professor Hung Fan Ngai, Ivan (孔繁毅教授), MD, FRCP, Specialist in Infectious Disease and Professor of Microbiology and Medicine of the University of Hong Kong. We welcome and thank them and we look forward to a great year ahead.

Professor Kung Wai Chee, Annie (關慧慈教授) will be leaving the Executive Committee at the end of this term. I would like to thank her for her great contribution to the Society in the last few years.

Pictorial Medical History (15)

Dr Lam Tat Chung, Paul
(林達聰醫生)
FRCP, FRCPsych, FHKAM (Medicine), FHKAM (Psychiatry)
Specialist in Psychiatry (Private Practice)
Honorary Clinical Assistant Professor,
The University of Hong Kong

As patients came for treatment at the Asclepieion at Epidaurus, they took their offerings to the temple of Asclepius. In this bas-relief, Asclepius can be seen seated on the left. The head of the bull is in the middle, and the five figures on the right are the patient and relatives.

The full article can be seen at:
http://www.hkma.org/english/cme/onlinecme/cme201302main.htm
Introduction

Worldwide, colorectal cancer (CRC) is the third most common cancer in males and the second most common cancer in females, with an estimated 1.4 million cases and 693,900 deaths reported in 2012. In Hong Kong, the crude incidence rate of CRC in both sexes (66.3 per 100,000) exceeded that of lung cancer for the first time in 2013, and was the second leading cause of cancer death in that year. Colonoscopy, the gold-standard diagnostic tool for CRC, is also a common screening tool. Owing to its ability to remove polyps, it has been found to be an effective strategy in reducing CRC mortality. International guidelines recommend that prevention of CRC by detection and removal of colorectal polyps be the primary goal of screening. Effective strategies to perform post-polypectomy surveillance by colonoscopy should be based on the best evidence in order to control CRC in the most optimal and efficient manner. Although overly frequent colonoscopy surveillance will increase unnecessary complications, costs and use of colonoscopy resources, underperformance of colonoscopy surveillance could result in missed diagnoses, especially in patients at high risks for CRC. From 2000 to 2002, surveillance colonoscopy for previous cancer or polyps in the United States accounted for 21.9% of all colonoscopies performed in patients aged 50 and older. This review aims to summarize the latest post-polypectomy colonoscopy surveillance (PCS) guidelines formulated by various authorities for conventional adenomas and serrated adenomas, and examine the adherence of these PCS guidelines in clinical practice.

The following basic principles have been highlighted by most guidelines: (1) the primary aims of PCS are to detect early cancers in those at increased risk or to remove high-risk adenomas at a minimum frequency; (2) the risk stratification strategy in PCS can only be applied after complete removal of all the index adenomas (adenomas detected during baseline colonoscopy) by high quality colonoscopies; (3) the indication and interval for surveillance are determined primarily by characteristics of the adenoma at index colonoscopy (size, number, histology findings, etc), and modified by taking patients’ age, co-morbidities and wishes into consideration; (4) a reassessment should be performed after follow-up examination to determine the subsequent surveillance interval; (5) colonoscopy is a costly, invasive and precious resource, especially in countries with a limited capacity for colonoscopy. Most importantly, the PCS guidelines reviewed in this article are for asymptomatic adults; diagnostic colonoscopy for symptomatic patients should be arranged based on the professional judgement of the gastroenterologist and the patient’s medical condition.

In most guidelines, there are three types of index adenomas, classified according to their risks and histological background: High-risk adenomas, low-risk adenomas and serrated adenomas/polyps. There are also some exceptions; for instance, the Japanese PCS guideline has no specific stratification and recommends that PCS be performed within 3 years for all index adenomas ≥6 mm, because patients with an adenoma ≥6 mm or intra-mucosal cancer at baseline colonoscopy have a high risk of advanced neoplasia in subsequent colonoscopies.

Guidelines for PCS in high-risk adenomas

There are two PCS frameworks for high-risk adenomas with varied definitions.
and recommendations for surveillance intervals (Table 1). A 1-year surveillance interval is recommended for patients in the “extremely high-risk group” as per the US guideline, i.e., for those with over 10 index adenomas. The UK and EU guidelines recommend a 1-year surveillance interval for high-risk patients, i.e., patients with ≥5 small adenomas or ≥3 adenomas with at least 1 adenoma ≥2 cm. Martinez et al. performed a pooled analysis of four prospective studies of 1-year follow-up colonoscopy based on the criteria of the US versus the UK guidelines. Surveillance colonoscopy 1 year after the first examination for the high-risk group based on the UK criteria (12.1% of all patients) resulted in a higher detection rate of advanced neoplasia without resulting in a substantial increase in the overall rate of surveillance colonoscopies compared with the US guidelines (only an additional 3% of colonoscopies per patient every 5 years).

Incomplete endoscopic polypectomy is not uncommon in clinical practice due to unsatisfactory bowel preparation and the histopathological features of index adenomas. For large or sessile adenomas that are incompletely excised, or excised in a piecemeal manner, an even shorter surveillance interval of 2–6 months is recommended. However, these recommendations on surveillance colonoscopies are not for subjects in the high-risk group. Hence the guidelines highlighted the importance of endoscopists providing appropriate post-polypectomy surveillance advice.

**PCS guidelines for low-risk adenomas**

Unlike high-risk adenoma, the definitions of low-risk index adenoma are quite similar among most PCS guidelines (Table 2). These refer to 1–2 tubular adenomas <10 mm without villous histology or high-grade dysplasia. One meta-analysis demonstrated that patients in the low-risk group had a higher risk of metachronous advanced neoplasia than patients without adenomas at baseline, corresponding to a relative risk of 1.8 (95% confidence interval [CI] 1.3–2.6), although the absolute risk was low in both groups (3.6% vs 1.6%, respectively). The baseline prevalence level of advanced neoplasia in screening subjects was 5.1% in Hong Kong. Hence, the recommendation for colonoscopy surveillance for the low-risk group is similar to that for the general population. As surveillance colonoscopies in low-risk individuals occupy the main PCS burden, it is important to clarify and align the PCS guideline for low-risk patients. For example, in a recent Hong Kong CRC screening programme, 31% of eligible Chinese participants aged 50–70 years (n=5,220) had low-risk adenomas.

**Guidelines for PCS in serrated polyps**

Through the serrated pathway, about 15% of CRCs arise from serrated polyps, which can be classified into the following subgroups: hyperplastic polyps (HP), sessile serrated adenomas/polyps (SSA/P) and traditional serrated adenomas (TSA). Owing to the paucity of observational studies after endoscopic resection of serrated lesions, only a few consensus guidelines referred to serrated lesions, of which the latest...
review and expert recommendation from 2012 is one of the most important (Table 3).23 Apart from the size and number of the lesions, the location of serrated polyps is also a determinant of surveillance interval because detection of serrated lesions at a proximal site is associated with synchronous advanced neoplasia.24 Rex et al. stressed that PCS recommendations for patients with serrated lesions are subject to modifications based on physician judgment.23 For example, the surveillance for SSA/P was similar to that for high-risk groups.9 The guideline for PCS with serrated lesions will be based on higher quality data once available.25

**Adherence to PCS guidelines**

Although inconsistent recommendations from different guidelines may confuse clinicians, under-surveillance is undoubtedly a significant contributor to metastatic CRC, while overseer surveillance colonoscopy will expose patients to avoidable risks and stress without any potential benefit.26 Adherence to surveillance includes both physician and patient compliance. Data about physician compliance with surveillance recommendations are controversial. Substantial overutilization of surveillance colonoscopy has been observed particularly among low-risk individuals, whilst underutilization among individuals with advanced index findings has also been observed.27,28 Moreover, adherence to PCS guidelines varies substantially among physicians; surveillance intervals have been reported to be either too long or too short.25,29

Data on patient compliance are comparatively limited considering the large volume of PCS. However, an average inappropriate surveillance rate of 37% was reported in an organized CRC screening program in Italy, while the inappropriate surveillance rate was as high as 67% in patients with low-risk adenomas.30 Theoretically, a uniform PCS guideline should be issued by an organized screening program to prevent interphysician variation and improve overall surveillance adherence.31 Given the high impact of PCS, research on adherence with guidelines from the perspectives of both physicians and patients is warranted.

**Conclusion**

All PCS guidelines recognize the importance of high-quality baseline colonoscopy and complete removal of all index adenomas before providing surveillance recommendations. Risk stratification strategy based on clinicopathologic profiles was widely applied to guide surveillance intervals. After more CRC screenings are applied in organized programs, screening programs should have a clear surveillance policy with a different level of priority for different risk groups based on resource availability.19 Thus, in this post-screening era, evidence-based research on PCS and studies on adherence to PCS guidelines will be warranted to promote evidence-based practice.

### Table 3. Consensus opinion on PCS in serrated lesions23

<table>
<thead>
<tr>
<th>Histology</th>
<th>Size (mm)</th>
<th>Number</th>
<th>Location</th>
<th>Surveillance Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSA/P with dysplasia</td>
<td>Any</td>
<td>Any</td>
<td></td>
<td>1–3 years</td>
</tr>
<tr>
<td>SSA/P</td>
<td>≥10</td>
<td>≥3</td>
<td>Any</td>
<td>1–3 years</td>
</tr>
<tr>
<td>SSA/P or TSA</td>
<td>&lt;10</td>
<td>≥2</td>
<td>Any</td>
<td>3 years</td>
</tr>
<tr>
<td>SSA/P or TSA</td>
<td>≥10</td>
<td>1</td>
<td>Any</td>
<td>3 years</td>
</tr>
<tr>
<td>SSA/P or TSA</td>
<td>&lt;10</td>
<td>&lt;3</td>
<td>Any</td>
<td>5 years</td>
</tr>
<tr>
<td>HP</td>
<td>&gt;5</td>
<td>≥1</td>
<td>Proximal to sigmoid</td>
<td>5 years</td>
</tr>
<tr>
<td>HP</td>
<td>≤5</td>
<td>≤3</td>
<td>Proximal to sigmoid</td>
<td>10 years</td>
</tr>
<tr>
<td>HP</td>
<td>&lt;10</td>
<td>Any*</td>
<td>Rectosigmoid</td>
<td>10 years</td>
</tr>
</tbody>
</table>

HP: hyperplastic poly; PCS: post-polypectomy colonoscopy surveillance; SSA/P: sessile serrated adenoma/poly; TSA: traditional serrated adenoma.

*Patients with ≥20 HPs should be recognized as serrated polyposis with shorter intervals.

† If multiple HPs 6–9 mm in size in the rectosigmoid, should be followed in 5 years.

SSA/P, sessile serrated adenoma/poly; TSA, traditional serrated adenoma.

A complete list of references can be downloaded from www.SOPHYSICIANSHK.org

### References

Early Diagnosis of Pancreatic Cancer

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Introduction

Pancreatic cancer (PC) is a deadly disease and the incidence is growing worldwide. In the United States, it was estimated that more than 53,000 people will be diagnosed with PC and about 43,000 people will die from it in 2017. According to the Hong Kong cancer registry, there were 655 new cases in 2014 and the crude incidence rate was 9 per 100,000 persons; PC was the sixth major cause of cancer death (N=576, crude mortality rate of 8 per 100,000 persons).

Patients with PC have a very low 5-year survival rate (up to 6%) due to late diagnosis. Upon diagnosis, only approximately 20% of patients are eligible for initial resection. After potent curative resection, the 5-year survival rate has been reported to range from 6.8% to 32%. Tumour size is the most important independent prognostic factor for survival after surgery.

Pathological studies have shown that PC develops from precursor lesions such as pancreatic intraepithelial neoplasia (PanIN) lesions. It may take up to 11 years for a PanIN lesion to develop into PC. However, once PC is formed, it only takes around 1 year for stage T1 PC to progress to stage T3 or T4. Therefore, early diagnosis is essential for improving overall survival once PC has developed.

Risk factors for pancreatic cancer

Risk factors for PC are described in Table 1. Male gender, increasing age (>55 years old), smoking, consumption of a high calorie and high fat diet, and obesity all increase the risk of PC. Large epidemiology studies have demonstrated that increased waist circumference, waist/hip ratio and increased body mass index (BMI) are also associated with an increased risk of PC.

A positive family history of PC, especially with age of onset earlier than 60 years, significantly increases the risk. For example, a person with two first-degree relatives who had PC would have a 5–10 fold increased risk of developing PC compared with the normal population. Furthermore, the risk increases by more than 10 fold for those with three first-degree or second-degree relatives with PC.

Patients with certain underlying genetic diseases such as Lynch syndrome, Von Hippel-Lindau syndrome, familial adenomatous polyposis, Peutz-Jeghers syndrome, and BRCA1 and BRCA2 mutations have a higher risk of PC. Patients with underlying chronic pancreatitis, pancreatic cystic lesions (estimated life time risk of more than 22 fold that of the general population) and diabetes also have a significantly increased risk of PC. Studies have shown that patients who have recent onset diabetes carry a higher risk of PC than patients with longstanding diabetes.

Symptoms of PC include epigastric pain that may radiate to the back, weight loss, obstructive jaundice, and symptoms related to distant metastases. However, early PC has minimal or no symptoms. Diagnosis is usually due to incidental radiological findings, obstruction of the distal bile duct causing jaundice, or the pancreatic duct resulting in pancreatitis, or during regular screening of high risk individuals.

Table 1. Categories of PC risk factors

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (&lt;5 fold increase)</td>
<td>Male, black, obesity, smoking, diabetes, Helicobacter pylori infection, History of any cancer in a first-degree relative, Hereditary non-polyposis colorectal cancer, Familial adenomatous polyposis, History of PC in one first-degree relative, BRCA1 mutation carrier</td>
</tr>
<tr>
<td>Moderate risk (5-10 fold increase)</td>
<td>History of PC in two first-degree relatives, Cystic fibrosis, Chronic pancreatitis, BRCA2 mutation carrier</td>
</tr>
<tr>
<td>High risk (&gt;10 fold increase)</td>
<td>Familial atypical multiple mole melanoma (FAMMM) kindreds with p16 germline mutation and at least one case of PC in a first- or second-degree relative, Peutz-Jeghers syndrome, Hereditary pancreatitis, ≥3 first-, second- or third-degree relatives with PC, Possibly: BRCA1 mutation carrier with at least one case of PC in a first- or second-degree relative</td>
</tr>
</tbody>
</table>

Key words:
Pancreatic cancer, Diabetes, Screening, Endoscopic ultrasound
Biomarkers

A blood test for cancer antigen (CA) 19-9 is commonly used to detect PC. It is the only biomarker currently recommended by the National Comprehensive Cancer Network (NCCN) for clinical use. It is useful for pre-operative and post-operative assessment of PC. However, CA 19-9 is also markedly elevated in benign biliary stricture, extra-pancreatic malignancies that cause biliary stricture, cholangitis, and pancreatitis. Other malignant diseases of the thyroid, colon, and duodenum can also raise CA 19-9 levels (>37 U/mL).

CA 19-9 was used to screen asymptomatic patients for PC in two studies of more than 80,000 patients. The positive predictive values were only 0.4–0.6%. In a recent meta-analysis, the mean sensitivity of CA 19-9 in detecting PC was 78.2% and the mean specificity was 82.8%. Carcinoembryonic antigen (CEA) is also commonly used for screening of colorectal cancer and PC. A meta-analysis showed that the mean sensitivity of CEA in detecting PC was 44.2% and the specificity was 87.5%. CA 125 levels are also elevated in some PC patients. The combined use of CA 125 and CA 19-9 in screening may be beneficial for patients who are nonsecretors of CA 19-9.

Imaging studies

Imaging studies can be divided into non-invasive and invasive methods. Non-invasive methods include ultrasound (US), computed tomography (CT) scan, magnetic resonance imaging (MRI) and positron emission tomography (PET) scan. Invasive methods include endoscopic retrograde cholangiopancreatography (ERCP) with brush cytology, direct pancreatoscopy plus biopsy, and endoscopic US (EUS) plus fine needle biopsy.

US is a simple and readily available test that can be performed in the office. However, the accuracy of US in detecting PC is only 50-70%. It is not sensitive nor accurate in detecting small lesions, particularly in the tail region, due to air interference in the stomach.

CT scan is more sensitive and accurate for detecting PC. Features of pancreatic ductal interruption, upstream ductal dilatation, and mass with hypoattenuation in a CT scan with contrast is suggestive of malignancy. The overall accuracy of multi-detector CT is around 90%. However, for small lesions that are less than 1 cm, the sensitivity of CT can drop to below 80%. Due to exposure to radiation, CT scan is not suitable for repeat examinations. Also, a CT scan is unable to differentiate PC from mass-forming inflammatory lesions.

MRI has a high sensitivity and accuracy in detecting PC, comparable with CT scan. As there is no radiation exposure, MRI is a suitable test for repeat examinations. However, it is not suitable for patients with metallic implants or for those suffering from claustrophobia. MRI is also unable to differentiate inflammatory from malignant lesions.

PET scan has a high sensitivity and specificity in detecting PC. In a meta-analysis of 16 studies, the pooled sensitivity and specificity were 91% and 88%, compared with 85% and 91% for diffusion-weighted MRI. It is good at differentiating benign (such as mass-forming chronic pancreatitis) from malignant lesions. The pooled sensitivity and specificity of PET in differentiating between PC and chronic pancreatitis was 90% and 84% in a meta-analysis of 35 studies. However, the high radiation dose makes it an unsuitable method for screening. Also, in the event of a positive PET finding, a tissue sample is still required to differentiate an inflammatory lesion from a malignant process in suspicious cases.

Endoscopic diagnosis

ERCP is a traditional method for diagnosing pancreatic cancer. It can reveal pancreatic ductal stricture or biliary obstruction. Brush cytology and direct biopsy of the stricture can also be done via ERCP. The recently developed per-oral video cholangiopancreatography with narrow band imaging can provide direct visual diagnosis of the ductal lesion and can be used to obtain a tissue biopsy. The overall sensitivity and specificity are 85% and 84%, respectively. However, due to its radiation exposure, invasiveness, and associated complications that may lead to severe morbidity and mortality, it should be reserved for therapeutic treatment such as stenting to relieve obstructive jaundice, rather than as a primary diagnostic method.

EUS is an endoscopic investigation that has a high diagnostic value in detecting PC. EUS-guided fine needle aspiration (FNA) can provide tissue diagnosis to differentiate benign from malignant lesions. The accuracy of EUS-FNA in detecting PC ranges from 80-100%, irrespective of the tumour size or tumour location. There is no radiation exposure related to EUS and the complication rate is low, making EUS a suitable method for screening. However, the high cost and requirement of expertise limits its use to specialized centres.

Who and when to screen

There is no role for screening the general population for PC due to its low prevalence. Regular screening of high risk individuals (HRI) who have at least a >5 fold increased risk for PC (Table 1) seems to be the most viable option.

For HRI with a history of familial pancreatic cancer (FPC), the International Cancer of the Pancreas Screening Consortium (CAPS) recommends yearly MRI plus magnetic resonance cholangiopancreatography and EUS imaging screening to detect relevant pancreatic lesions, such as hypoechoic nodules, cystic lesions, ductal abnormalities and PanIN 3 lesions. In previous studies, a high prevalence (33–53%) of cystic lesions was detected in HRI. Once a suspicious lesion is identified, EUS-FNA can be performed to obtain a tissue-based diagnosis before considering surgery. The appropriate age to start screening is not well defined.
Most published programmes start screening at the age of 40–45 years old or 10 years below the youngest age of onset in the family. However, a recent study showed that screening can be started at the age of 50, with MRI-based yearly screening supplemented by EUS at baseline and every 3rd year, or when changes in MRI results occur. This approach was found to be efficient and cost-effective.

Since PC can be diabetogenic, screening of patients with early onset of diabetes may uncover underlying PC. A recent prospective study used CA 19-9 and US for PC screening in patients with newly-onset type 2 diabetes. In 115 patients, 3 PC cases were detected. The value of the standardized incidence ratio was 198.6 (95% CI, 6.25–46.9). How - 

A recent prospective study used CA 19-9 for screening for the development of PC. Further studies of using other screening tests such as MRI or EUS may detect early lesions that can be surgically removed to improve patient survival.

**Conclusion**

PC is difficult to diagnose in the early stages. Screening of HRI with appropriate tests such as MRI or EUS may detect early lesions that can be surgically removed to improve patient survival.

**References**

Constitution is common in our daily clinical practice. Many older persons are taking laxatives chronically. Assessment of constitution requires an appreciation of the interplay among different disease processes, iatrogenesis and environmental factors.

Our colon receives around 1–1.5 L of fluid, salt, fibre and other residues each day. Approximately 90% of water and salt is reabsorbed and 100 g of stool, which consists of 70 mL of water and 30 g of solid material, is produced. The degree of desiccation of bowel content is related to the transit time along the colon. Colonic transit does not appear to change with ageing.

**Definition of constitution**

Different people define constitution differently. 99% of the population has between 3 bowel movements per day and 3 bowel movements per week. Many older persons insist on a daily bowel movement for them to be healthy, stressing on the traditional Chinese concept that toxins inside the body are required to be cleared. Such belief will result in the overuse of laxatives.

According to the American Gastroenterological Association (AGA) Medical Position statement, the symptoms of constitution from patients’ perspectives (in decreasing order of importance) include straining, stool that is excessively hard, unproductive urge, infrequency and feeling of incomplete evacuation.

**The Rome III diagnostic criteria**—which describe a group of functional bowel disorders—define functional constitution as persistently difficult, infrequent or seemingly incomplete defaecation, and help give a better idea of what constitution is, at least for epidemiological purposes (Table 1). Likewise, clinicians can explain to patients that a healthy bowel does not depend solely on the frequency of bowel movements. A change in bowel habits appears to be more important in the clinical setting than the number of daily bowel movements.

**Epidemiology of constitution in older persons**

The prevalence of constitution in the general population worldwide ranges from 0.7%–79%. Studies on whether the prevalence of constitution increases with age have yielded markedly inconsistent results. However, it is generally believed that physician visits for constitution are significantly more common among elderly people and laxatives are used more commonly by elderly women.

In Hong Kong, the prevalence of constitution as defined by the Rome III criteria was reported to be 14.3%, with a female to male ratio of 1.3. The prevalence did not differ between younger and older age groups. However, a 2003/2004 Hong Kong population survey on various heath conditions found an increased prevalence of acute constitution in older age groups (14.1% in those aged 65–74 years and 22.8% in those aged 75 years and older) than in younger age groups (8.8–11.5%).

**Pathophysiology of constitution**

Traditional classification of functional constitution into slow transit, dyssynergic and normal transit types has been suggested to be a gross oversimplification as there is significant overlap in symptomatology and pathophysiological characteristics.

In older persons, a meticulous look for secondary causes of constitution is of high clinical importance and

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**Table 1. Rome III criteria**

<table>
<thead>
<tr>
<th>Must include 2 or more of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Straining during at least 25% of defaecations</td>
</tr>
<tr>
<td>• Lumpy or hard stools in at least 25% of defaecations</td>
</tr>
<tr>
<td>• Sensation of incomplete evacuation for at least 25% of defaecations</td>
</tr>
<tr>
<td>• Sensation of anorectal obstruction/blockage for at least 25% of defaecations</td>
</tr>
<tr>
<td>• Manual manoeuvres to facilitate at least 25% of defaecations (eg, digital evacuation, support of the pelvic floor)</td>
</tr>
<tr>
<td>• Fewer than 3 defaecations per week</td>
</tr>
</tbody>
</table>

**Loose stools are not present without the use of laxatives**

**Insufficient criteria for irritable bowel syndrome (IBS)**

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*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.*
relevance. Many medical conditions and medications are associated with constipation (Table 2). These conditions are often more prevalent in the elderly population. On the other hand, the cause of constipation in an elderly person is usually multi-factorial, with interplay among various disease processes and iatrogenesis.

The possibility of drug induced bowel disorder should always be considered. Drug-related constipation is extremely common. Moreover, a drug that causes constipation in one person can cause diarrhoea in another. Clinicians often need to have a high index of suspicion in order to make a correct and timely diagnosis of iatrogenesis.

Clinical assessment of constipation
The first question to be answered during clinical assessment is whether the patient is truly constipated or not. A stool diary, paying attention to the frequency of bowel movements and stool form, is preferable; if necessary, the Rome criteria can be used to guide the assessment. For functionally constipated individuals, stool consistency, which can be assessed and graded by the Bristol stool form scale (Table 3), correlates with colonic transit. Sensation of incomplete evacuation and anorectal blockage together with the need to use manual manoeuvres to facilitate defaecation may suggest dyssynergic defaecation. Abdominal pain relieved by bowel motion is a key diagnostic criterion of IBS. Dietary and lifestyle factors should be assessed. Since diseases as well as iatrogenesis are more prevalent in the elderly population, the differential diagnosis listed in Table 2 should be consulted alongside the signs and symptoms of the patient’s condition. Clinicians should be able to identify ‘red flag’ signs and symptoms without overlooking sinister underlying causes for the constipation. Recommendations on gastroenterologist referral (Table 4) for patients with alarming clinical features are available for reference. Medication history, in particular laxative usage, should be reviewed. Rectal examination should be focused on detecting perineal and perianal pathology and assessing sphincter tone and the presence of faecal impaction. Proctoscopic examination revealing blood descending from above the anal canal is an important sign for locating pathology proximal to the anal canal, instead of attributing rectal bleeding to haemorrhoids. Laboratory investigations should be directed by clinical findings. Complete blood count, renal function and electrolytes, calcium, glucose, thyroid function, faecal occult blood and colonoscopy may be indicated in specific clinical settings. However, the American College of Gastroenterology has recommended against a routine use of these investigations in every constipated individual. Sophisticated investigations such as balloon expulsion test, colonic transit study, anorectal manometry and defecography is available in tertiary gastroenterological referral centres. Finally, the psychosocial well-being of the constipated individual should also be assessed and counselling may be needed.

Management of constipation
Individuals who do not meet the diagnostic criteria for constipation may only

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**Table 2. Common medical conditions associated with constipation**

<table>
<thead>
<tr>
<th>Mechanical obstruction</th>
<th>Metabolic conditions</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Colorectal cancer</td>
<td>• Diabetes mellitus</td>
<td>• Opiates</td>
</tr>
<tr>
<td>• External compression from malignant lesions</td>
<td>• Hypothyroidism</td>
<td>• Anticholinergic agents</td>
</tr>
<tr>
<td>• Strictures</td>
<td>• Hypercalcaemia</td>
<td>• Calcium channel blockers</td>
</tr>
<tr>
<td>• Large rectocele</td>
<td>• Hypocalcaemia</td>
<td>• Tricyclic antidepressants</td>
</tr>
<tr>
<td>• Megacolon</td>
<td>• Hypomagnesaemia</td>
<td>• Antipsychotics</td>
</tr>
<tr>
<td>• Post-surgical abnormality</td>
<td>• Uraemia</td>
<td>• Calcium supplements</td>
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<tr>
<td></td>
<td>• Heavy-metal poisoning</td>
<td>• Iron supplements</td>
</tr>
<tr>
<td><strong>Painful anal conditions</strong></td>
<td><strong>Neurological conditions</strong></td>
<td><strong>Miscellaneous</strong></td>
</tr>
<tr>
<td>• Anal fissure</td>
<td>• Parkinson’s disease</td>
<td>• Depression</td>
</tr>
<tr>
<td>• Prolapsed piles</td>
<td>• Spinal cord injury or tumour</td>
<td>• Cognitive impairment</td>
</tr>
<tr>
<td>• Perianal abscess</td>
<td>• Cerebrovascular disease</td>
<td>• Immobility</td>
</tr>
</tbody>
</table>

**Table 3. Bristol stool form scale**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Separate hard lumps, like nuts.</td>
</tr>
<tr>
<td>2</td>
<td>Sausage-shaped but lumpy.</td>
</tr>
<tr>
<td>3</td>
<td>Like a sausage or snake but with cracks on its surface.</td>
</tr>
<tr>
<td>4</td>
<td>Like a sausage or snake, smooth and soft.</td>
</tr>
<tr>
<td>5</td>
<td>Soft blobs with clear-cut edges.</td>
</tr>
<tr>
<td>6</td>
<td>Fluffy pieces with ragged edges, a mushy stool.</td>
</tr>
<tr>
<td>7</td>
<td>Watery, no solid pieces.</td>
</tr>
</tbody>
</table>

**Table 4. Indications for gastroenterology referral of constipated individuals**

<table>
<thead>
<tr>
<th>Recent onset of constipation associated with</th>
<th>Chronic constipation in conjunction with</th>
<th>Chronic constipation necessitating the use of high doses of laxatives</th>
<th>Recent onset of faecal incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Weight loss</td>
<td>• Change in stool form or frequency</td>
<td>• Abdominal pain and bowel training programme</td>
<td>• Anemia</td>
</tr>
<tr>
<td>• Anemia</td>
<td>• Unintentional weight loss</td>
<td>• Haem positive stool or family history of colonic cancer</td>
<td>• Weight loss</td>
</tr>
<tr>
<td>• Abdominal pain</td>
<td>• Anaemia</td>
<td>• Failure to alleviate constipation despite compliance with high fibre diet and exercise regime</td>
<td>• Change in stool form or frequency</td>
</tr>
<tr>
<td>• Blood per rectum</td>
<td>• Unintentional weight loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Haem positive stool or family history of colonic cancer</td>
<td>• Anaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Abdominal pain</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
need reassurance and an explanation of normal healthy bowel habits. The need for reduction of excessive laxative use should also be stressed. Healthy bowel habits includes a prompt response to the urge to defaecate. The establishment of a consistent time for defaecation is desirable, with the aid of the gastrocolonic response at the post-prandial period, particularly in the morning. During defaecation, maintaining the body upright with the hip flexed shall make the anorectal angle less acute. This will theoretically help stool passage. For very frail older persons who cannot maintain balance while sitting, an aid to keep the person sitting upright is essential for passing stool comfortably. The availability of appropriate toilet facilities is important for individuals with mobility problems. Bed pans should be avoided, wheelchair accessibility should be evaluated and toilet facilities should be modified as needed (e.g., installation of a hand-rail or raised toilet seat).

Dietary fibre can increase stool weight and accelerate colonic transit. A fibre intake of 20–30g per day is usually recommended. Fibre supplementation in the form of wheat bran, fruit (e.g., prunes, blackberries, grapes) and vegetables (e.g., beans, peas, broccoli) in a palatable form to institutionalized older people is of particular importance. A high fibre diet may result in gastrointestinal upset such as bloating and flatulence, which can be minimized by starting low and going slow. Despite a lack of evidence that extra fluid and exercise help to relieve constipation, maintaining adequate hydration, particularly for those who are taking bulk-forming or osmotic laxatives, and encouraging mobility is still beneficial to individuals in general. Observations from patients with anorexia nervosa suggest that adequate caloric intake is also important for normal colonic transit.

Many patients need to resort to laxatives for their bowel problems despite trying life-style modifications. Bulk-forming laxatives, including natural (psyllium) or semi-synthetic (methylcellulose) fibres are the most commonly used. These agents increase colonic residue and stimulate peristalsis. As with other fibre supplements, the gastrointestinal side effects may be intolerable to some patients.

Osmotic laxatives draw water into the intestine along the osmotic gradient and soften stool. Saline laxatives containing magnesium should be used with caution in patients with renal insufficiency. Lactulose is commonly used but sorbitol appears to be a cheaper yet equally effective alternative. These poorly absorbed sugars cause significant gas production and hence bloating and flatulence as a side effect. There has been an increase in use of polyethylene glycol in small packs in recent years since these polymers are not metabolized by gut bacteria and cause less bloating and cramping than lactulose. Polyethylene glycol (macrogol 4000) sachets are available over the counter in Hong Kong. However, osmotic laxatives can cause fluid and electrolyte disturbances, particularly when taken in excessive amounts and with inadequate fluid intake.

Stimulant laxatives have a bad reputation since they have been linked to serious side effects such as pseudo-melanosis coli, cathartic colon, enteric neuronal degeneration together with malignancy and potential for abuse. However, except for liquid paraffin (which can cause malabsorption of fat soluble vitamins and anal seepage with long-term use and lipid pneumonia when aspirated) and phenolphthalein (which was observed to have carcinogenic properties in animal studies), most stimulant agents (e.g., senna, bisacodyl, docusate and sodium picosulphate) are usually thought to be safe and effective when used no more than 2–3 times per week, even for prolonged periods. The risk of melanosis coli, cathartic colon and potential malignancy has been questioned as inconclusive in human studies.

Newer agents have been introduced to the market in the past decade. 5-HT₄ receptor agonists are prokinetic agents that induce peristalsis. Prucalopride has been proven to be effective in improving symptoms of constipation and is available in Hong Kong. Secretagogues promote intestinal secretion leading to softer stools and accelerate intestinal transit. Lubiprostone (acts on type 2 chloride channels [CIC-2]) and linaclotide (acts on guanylate cyclase-C [GC-C]) were both proven to be effective in clinical trials. Peripherally acting mu-opioid receptor antagonist methylnaltrexone, administered subcutaneously, is effective in inducing laxation in palliative care patients with opioid-induced constipation and where conventional laxatives fail.

Despite intake of multiple laxatives, some patients still rely on the use of suppositories or enemas which cause bowel distension and produce an evacuation reflex. Almost any form of enema can achieve this. Use of per-rectal drug administration should be restricted to less than 2–3 times per week.

Other agents that have been reported to be of use in treating constipation include colchicine and misoprostol; however, side effects limit their use.

The American Gastroenterological Association Medical Position Statement on Constipation 2013 has suggested a practical approach to the medical management of constipation. An initial gradual increase in fibre intake is suggested, with or without addition of inexpensive osmotic agents, such as milk of magnesia or polyethylene glycol. Depending on stool consistency, the next step may be to supplement the osmotic agent with a stimulant laxative (e.g., bisacodyl or glycerol suppositories), which is preferably administered 30 minutes after a meal to synergize the pharmacologic agent with the gastrocolonic response. Newer agents should be considered when symptoms do
not respond to traditional laxatives.

The use of probiotics in treating and preventing constipation in older persons has attracted attention since it has been found that elderly subjects have a low diversity of microbiota, despite a large inter-individual diversity. The elderly have fewer *Bifidobacterium* species and more *Enterobacteriaceae* species in their guts. A recent systematic review concluded that probiotics may improve gut transit time, stool frequency and stool consistency in adults, with subgroup analyses indicating beneficial effects of *Bifidobacterium lactis*, in particular. However, the authors commented that caution is required when interpreting the data due to the high heterogeneity and risk of bias.

There has been an increase in use of complementary and alternative medicine (CAM) in the West in recent years. Manual colonic massage appears to be the simplest treatment. This has been widely practiced in palliative and long-term care settings. Other CAM options include probiotics, acupuncture, homeopathy, shiatsu, herbalism, reflexology and aromatherapy.

**Faecal impaction**

Faecal impaction is an important topic in geriatrics as it is common and leads to significant morbidity but is easily missed. Faecal impaction is the inability to pass a collection of stool, usually hard in consistence. Constipation results in faecal retention; the colon’s normal absorption of salt and water contributes to the hardening of stool, and peristalsis causes packing. Typical symptoms include anorexia, nausea, vomiting and abdominal pain. The hard stool irritates colonic or rectal mucosa resulting in mucus production, which dissolves and liquefies the surface bowel content. As a result, there is a leakage of liquid faeces around hard impacted faeces causing paradoxical diarrhoea (spuriously diarrhoea) and, as a result of rectal sensation impairment and anal sphincter relaxation, faecal incontinence. The urinary bladder is in close proximity with the rectum such that faecal impaction can result in urinary frequency, retention and overflow incontinence. Patients will be prone to urinary tract infections. Other complications include stercoral ulcerations with bleeding or perforation, intestinal obstruction, idiopathic megacolon, volvulus and fecaloma. Mental confusion has also been a reported complication, presenting as delirium in an individual with pre-existing cognitive impairment.

Diagnosis of faecal impaction, especially when a patient presents with non-specific complaints like anorexia and nausea, requires a high index of suspicion. Rectal examination is crucial in all cases but a judicial use of plain abdominal X-ray can help in picking up proximal or ‘high’ impaction. It should be noted that impacted stool can be of any consistency (soft to rock-hard) and can take many forms (a single mass or multiple pellets).

Manual fragmentation and extraction, with the aid of lignocaine jelly, of the faecal mass is often needed as the first treatment of faecal impaction. Repeated enema or suppository, to the extent of daily use for a week, may also be required. Whole gut irrigation using 2 L of polyethylene glycol electrolyte balance colonic lavage solution is a useful alternative in non-emergency cases without complete obstruction. Occasionally, lavage directed by sigmoidoscopy or surgery may be needed in severe cases. Prevention of further impaction is essential. This may be achieved with lifestyle methods but the use of regular bulk-forming or osmotic laxatives with adequate hydration might seem necessary in some cases.

**Conclusion**

Constipation is common in older persons. Diagnosis of constipation does not rely solely on the frequency of bowel movements. Expectations of daily bowel movements in some older persons will result in misuse of laxatives. Assessment should focus on recent changes in bowel habits. In older persons, secondary causes of constipation should be meticulously considered and the possibility of iatrogenesis should not be overlooked. Faecal impaction is common and can cause significant morbidity but is easily missed. Management of constipation in older persons should be individualized and may require involvement of multiple domains including lifestyle modifications, toilet modifications, posture maintenance, environmental modifications, increased intake of fibre, pharmacological therapies and, in some cases, complimentary therapies.

**References**

Exploring a New Era of Second-line NSCLC Treatment

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Specialist in Medical Oncology

Lung cancer can be broadly divided into two categories: Small cell lung cancer and non-small cell lung cancer (NSCLC), with the latter making up 85% of cases. NSCLC consists of two major histologic subtypes: Squamous cell carcinoma and adenocarcinoma (falling under the umbrella of non-squamous cell carcinomas). While NSCLC patients with particular gene mutations can receive selected targeted therapies, the standard first-line treatment for the vast majority of metastatic NSCLC patients is cytotoxic, platinum-based doublet chemotherapy; however, the median survival benefit is only around 8 months. Subsequently, for second-line treatment of advanced NSCLC, standard chemotherapy also continues to yield low response rates and effects on survival are weak with reported median overall survival (OS) rates as low as 6 months.

However, new models of immunology and a better understanding of the interactions between the immune system and tumours have enabled the development of a new generation of immuno-oncotherapies for NSCLC. Recent breakthroughs have shown that tumour programmed cell death-ligand 1 (PD-L1) expression is prevalent in NSCLC, and the interactions between programmed death (PD)-1 and PD-L1 and PD-L2 inhibit T-cell activation and promote tumour immune evasion. Nivolumab, a fully human immunoglobulin (Ig) G4 PD-1 immune checkpoint inhibitor blocks T-cell inhibitory signaling pathways by preventing engagement of PD-1 to its ligands (PD-L1/2) to restore antitumour immunity. Nivolumab has demonstrated activity in various Phase III clinical trials in NSCLC with various histologic features.

In the CheckMate-017 (squamous NSCLC) and CheckMate-057 (non-squamous NSCLC) Phase III trials, patients who had received prior platinum-based chemotherapy irrespective of their tumour PD-L1 expression were given either nivolumab or docetaxel. In CheckMate-017, the median OS was 9.2 months.

![Figure 1. CheckMate 017 – Kaplan-Meier curves for OS in patients with squamous NSCLC](image)

<table>
<thead>
<tr>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>9.2 (7.3, 13.3)</td>
</tr>
<tr>
<td>12-month OS rate, % (95% CI)</td>
<td>42 (34, 50)</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>86/135</td>
</tr>
</tbody>
</table>

HR=0.59 (95% CI: 0.44, 0.79; p<0.001)

CI, confidence interval; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival

Key words:
Lung cancer (肺癌), Non-small cell lung cancer (非小細胞肺癌), Biologic therapy (生物療法)
with nivolumab versus 6.0 months with docetaxel, demonstrating a significant 41% risk reduction (Figure 1). At 1 year, the OS rate was 42% with nivolumab versus 24% with docetaxel. Furthermore, the response rate was significantly higher with nivolumab at 20% versus 9% with docetaxel.4 Meanwhile, in CheckMate-057, the median OS in patients administered nivolumab was 12.2 months versus 9.4 months in patients administered docetaxel, similarly showing a significant risk reduction of 28% (Figure 2). At 1 year, the median OS rates of patients administered nivolumab and docetaxel were 51% and 39%, respectively. With additional follow-up at 18 months, the respective OS rates of the nivolumab and docetaxel groups were 39% and 23%.

Moreover, nivolumab demonstrated a significantly higher response rate of 19% compared with 12% for docetaxel.5 It is important to note that the survival benefit of nivolumab was observed regardless of tumour PD-L1 expression levels, showing that PD-L1 expression was neither prognostic nor predictive of survival in squamous NSCLC patients.4 As for nonsquamous NSCLC, although the analysis showed a predictive association between PD-L1 expression and survival benefit from nivolumab treatment, the improved safety profile and durability of responses still suggest that nivolumab is a reasonable option for patients regardless of PD-L1 expression.5

In conclusion, nivolumab offers a durable survival benefit to responders as suggested by the flattening trend seen in both OS curves. Together with its well-tolerated safety profile which shows minimal chemotherapy-like hematological adverse effects, nivolumab is a promising agent for efficacy, durability and quality of life retention in NSCLC patients undergoing second-line treatment.4,5

**References**

EVIS LUCERA ULTRASOUND GASTROVIDEOSCOPE

TGF-UC260J

Forward-viewing ultrasound gastrovideoscope pioneers new opportunities in EUS-guided treatment
References:


