Gut Online First, published on March 19, 2014 as 10.1136/gutjnl-2013-306503

ORIGINAL ARTICLE

An updated Asia Pacific Consensus Recommendations on colorectal cancer screening

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Received 30 November 2013
Accepted 18 February 2014

ABSTRACT

Objective Since the publication of the first Asia Pacific Consensus on Colorectal Cancer (CRC) in 2008, there are substantial advancements in the science and experience of implementing CRC screening. The Asia Pacific Working Group aimed to provide an updated set of consensus recommendations.

Design Members from 14 Asian regions gathered to seek consensus using other national and international guidelines, and recent relevant literature published from 2008 to 2013. A modified Delphi process was adopted to develop the statements.

Results Age range for CRC screening is defined as 50–75 years. Advancing age, male, family history of CRC, smoking and obesity are confirmed risk factors for CRC and advanced neoplasia. A risk-stratified scoring system is recommended for selecting high-risk patients for colonoscopy. Quantitative faecal immunochemical test (FIT) instead of guaiac-based faecal occult blood test (gFOBT) is preferred for average-risk subjects. Ancillary methods in colonoscopy, with the exception of chromoendoscopy, have not proven to be superior to high-definition white light endoscopy in identifying adenoma. Quality of colonoscopy should be upheld and quality assurance programme should be in place to audit every aspects of CRC screening. Serrated adenoma is recognised as a risk for interval cancer. There is no consensus on the recruitment of trained endoscopy nurses for CRC screening.

Conclusions Based on recent data on CRC screening, an updated list of recommendations on CRC screening is prepared. These consensus statements will further enhance the implementation of CRC screening in the Asia Pacific region.

Significance of this study

What is already known on this subject?
In previous Asia Pacific consensus recommendations:

- Consensus on Colorectal Cancer (CRC) screening should be started at the age of 50 years.
- Faecal immunochemical test (FIT), guaiac-based faecal occult blood test (gFOBT), flexible sigmoidoscopy and colonoscopy are recommended for CRC screening.
- FOBT is the first choice for CRC screening in resource-limited countries.

What are the new findings?
In this updated Asia Pacific consensus recommendations:

- Age range for CRC screening is defined as 50–75 years.
- A risk-stratified scoring system is recommended to select high-risk patients for early colonoscopy.
- Quantitative FIT, but not gFOBT, is preferred for average-risk subjects.
- Quality control measures should be included in CRC screening programmes.

How might it impact on clinical practice in the foreseeable future?

- The Asia Pacific Colorectal Cancer Working Group believes that these consensus statements will further enhance the implementation of CRC screening in the region. It may also be relevant to CRC screening programme in other geographic locations with resource constraints.

INTRODUCTION

Unlike many regions in Europe and North America, the colorectal cancer incidence and mortality rates in Asia continue to increase at an alarming rate without sign of abating.[1 2] Since the publication of the first Asia Pacific Consensus on Colorectal Cancer (CRC) in 2008,[3] there has been substantial advancement in our knowledge and experience of CRC screening and therapy. There are already some countries in Asia that have implemented CRC screening, either opportunistic or population-based. A better understanding of the use of flexible sigmoidoscopy (FS), colonoscopy and their disadvantages, the advent of new technology such as endoscopic imaging techniques and capsule endoscopy, the unveiled pathological understanding and consequences of serrated flat adenoma, the development of risk stratification in Asia and its potential use in prioritising screening, and the attitude and compliance of Asian subjects to screening procedures all may impact upon the strategy for CRC screening. Recently published updates in the US,[4] UK[5] and European guidelines[6 7] on CRC screening have introduced new concepts

To cite: Sung JJY, Ng SC, Chan FKL, *et al*. *Gut* Published Online First: [*please include* Day Month Year] doi:10.1136/gutjnl-2013-306503

and strategies in those regions. The Asia Pacific Working Group sees a need to update our understanding and recommendations in colorectal cancer screening, with emphasis on the special needs within this region.

A 2-day meeting was held on 9–10 June 2013 in which key opinion leaders from 14 Asian countries or regions gathered to review the data and update the guidelines and recommendations. The aim of this Consensus Conference was to provide an updated set of consensus recommendations for the region, with the view that each individual country or region should be able to further modify them to suit their specific needs.

METHOD

Membership of the Consensus Panel

Memberships of the Consensus Group were selected using the following criteria: (1) demonstrated knowledge/expertise in CRC by publication/research or participation in national or regional guidelines; (2) geographical representation of the Asia Pacific countries/region; (3) participation in the Asia Pacific Working Group for CRC screening research projects and/or the previous Asia Pacific Consensus Recommendations process in 2008. In order to use references and experience from other regions, four international members who have played key roles in drafting other regional/national guidelines for CRC screening were invited (EJK, DL, LR and RJS).

Provisional statements

The consensus is grouped into five main areas of interest. These sections included (i) who to screen for colorectal neoplasia, (ii) how to screen for colorectal neoplasia, (iii) who should be considered for earlier screening, (iv) how to minimise missed lesions or interval cancers and (v) other issues. For each area of interest, relevant statements were drafted by the chairman (JJYS) and steering committee (JJYS, SCN, FKLC). The statements focused on current practice and areas of controversy in CRC screening particularly relevant to Asia. The Steering Committee drafted a list of statements and circulated them electronically in advance to the panel members. Participants were invited to amend or edit any statement as deemed appropriate based on literature.

Literature search

A comprehensive literature review was carried out by the Steering Committee. We identified relevant articles published in the English language using AMED, BIOSIS Previews, EBM Reviews, Global Health, NASW Clinical Register, Embase, Ovid MEDLINE and the Cochrane Trials Register in human subjects up to May 2013. Searches were performed using the following keywords: colorectal cancer (CRC) screening, guidelines, Asia, randomised controlled trials (RCTs), colonoscopy, faecal immunochemical test (FIT)/FOBT, FS, CT colonography (CTC) and colon capsule. National and international guidelines on CRC screening were solicited. Additionally, meeting abstracts from Asia Pacific Digestive Week, American College of Gastroenterology, American Gastroenterological Association (AGA), American Society of Gastrointestinal Endoscopy (ASGE), British Society of Gastroenterology (BSG), United European Gastroenterology Week and review articles from the preceding 5 years were screened. Our initial search identified 813 abstracts. The steering committee reached consensus on which references were the most appropriate based on the following criteria: (i) randomised controlled data and prospective cohort study; (ii) relevant literature published since the first Asia Pacific Consensus Recommendations established in 2008; (iii) data pertaining to the Asian population; and (iv) latest international and national guidelines on CRC screening. Approximately 80 relevant articles were selected and circulated to the panel members before the conference.

Voting process

The working parties then gathered in a 2-day meeting to seek consensus on the statements. As in the previous consensus process, a modified Delphi process was adopted to develop the statements. Individual panel members were assigned to present an overview of the literature for each individual statement prior to the discussion and voting process. On the first day, an up-to-date literature overview was presented for each of the 18 statements. On the second day, a summary literature was provided for each statement and panel members were asked to vote based on review of the literature on a Likert scale anchored by 1–5 (1=accept completely, 2=accept with some reservation, 3=accept with major reservation, 4=reject with reservation, 5=reject completely). All votes were anonymous. Consensus was considered to be achieved when >80% of the voting members indicated 'accept completely' or 'accept with some reservation'. A statement was refuted when >80% of the voting members indicated 'reject completely' or 'reject with reservation'. For statements in which a consensus could not be reached, the entire group would discuss and modify the statements accordingly. Then a second voting was conducted. If there was still no consensus reached, the statement would be modified for the last time, and a third and the last vote was conducted leading to definite acceptance or refutation. Each statement was graded to indicate the level of evidence available and to indicate the strength of recommendation (table 1).

Final consensus statements

The final document on each topic was written by JJYS in conjunction with their working party. Consensus guideline

Table 1 Voting, quality of evidence and classification of recommendations

Category and grade	Description
Voting on recommendations	
A	Accept completely
B	Accept with some reservation
C	Accept with major reservation
D	Reject with some reservation
E	Reject completely
Quality of evidence	
I	Evidence obtained from at least one RCT
II-1	Evidence obtained from well-designed control trials without randomisation
II-2	Evidence obtained from well-designed cohort or case–control study
II-3	Evidence obtained from comparison between time or places with or without intervention
III	Opinion of respected authorities, based on clinical experience and expert committees
Classification of recommendation	
A	There is good evidence to support the statement
B	There is fair evidence to support the statement
C	There is poor evidence to support the statement but recommendation made on other grounds
D	There is fair evidence to refute the statement
E	There is good evidence to refute the statement

RCT, randomised controlled trials.

statements displayed are followed by comments on the evidence and opinion. Statements are intended to be read in context with qualifying comments and not read in isolation. The final text was circulated and approved by the participants. In some areas, the level of evidence is generally low, which reflects the paucity of RCTs. Consequently, expert opinion is included where appropriate.

RESULTS

A 2-day consensus conference was held on 9–10 June 2013 under the auspices of the Asia Pacific Society of Gastroenterology. Representatives from 14 Asia Pacific countries/regions participated in the meeting from Australia, Brunei, China, Hong Kong, India, Israel, Japan, Malaysia, Philippines, Singapore, Korea, Taiwan, Thailand and Vietnam. A total of 18 statements were presented for the first vote. Thirty-six members participated in the voting.

WHO TO SCREEN FOR COLORECTAL NEOPLASIA?

Statement 1: Population screening for colorectal cancer is recommended in those Asia Pacific regions where the incidence of CRC is high. In both genders, subjects aged 50–75 years are the target for CRC screening.

Level of agreement: A=69.4%, B=30.6%, C=0%, D=0%, E=0%.

Quality of evidence: II-2.

Classification of recommendation: B.

The high incidence in Asian countries has been defined as countries with reported CRC incidence rates of greater than 30 per 100 000.[8] Although the overall incidence and mortality of CRC is rising in the Asia Pacific region, there is a wide variation in the country-specific incidence within the region. In China, Japan, Korea, Singapore, Australia, New Zealand and Taiwan, the incidence of CRC is much higher than that in India, Indonesia, Thailand and Vietnam. Therefore, the group recommend CRC screening be implemented in countries or regions where the incidence of CRC is high.

While screening guidelines in the USA and Europe recommend screening to start at 50 years old,[4 7 9] the age to stop screening is unclear. The US Preventive Services Task Force (USPSTF) guideline recommended that subjects aged 76–85 years are subjected to individualised consideration and they do not recommend screening individuals aged 85 years or above.[10] The American Cancer Society (ACS), US Multi-Society Task Force (USMSTF) on CRC and the American College of Radiology (ACR) guidelines, on the other hand, do not specify the age to stop screening.[11] The European guidelines recommend to stop FS and colonoscopy at age 75, but to continue faecal occult blood test until the age of 80 years.[6–7 9]

It is clear that the potential benefit of screening colonoscopy in extending life expectancy decreases with age of the subject screened. Screening subject between 75 and 79 years has a lower benefit in terms of life-years saved than screening those between 50 and 74 years.[12] Furthermore, the increased comorbidities of the elderly subjects and the increased risk of complications associated with invasive procedures such as colonoscopy could counteract the benefit of screening beyond a certain age limit.

In Asia, the life expectancy at birth in countries or region such as Hong Kong, Japan, Korea, Singapore and Taiwan are on par or even longer than that reported in Europe and the USA. Therefore, the discontinuation of CRC screening is an important issue. Healthcare providers and respective health authorities must balance between benefit of screening against comorbidity, cost benefit and complications arising from screening procedures. The Asia Pacific Consensus panel agreed that screening at 50 years is recommended as the Western guidelines, and 75 years for both men and women in this region is a reasonable age limit to stop screening.

Statement 2: There are ethnic differences in CRC risk and screening programme should take this into account.

Level of agreement: A=69.4%, B=27.8%, C=2.8%, D=0%, E=0%.

Quality of evidence: II-3.

Classification of recommendation: B.

It has been previously reported that among the Asian populations, Japanese, Koreans and Chinese have a higher CRC incidence than other ethnic groups such as Indians, Malays and Indonesians.[13] Apart from differences in the overall incidence, the age of onset is also different, although in most ethnic groups in Asia the incidence of CRC is rising.[14 15] The ethnic difference in CRC incidence should be taken into account by individual country or region in Asia in devising their CRC screening policy in order to maximise the benefit of a screening programme with the lowest cost.

Statement 3: In the Asia Pacific region, age, male gender, family history, smoking and obesity are risk factors for CRC and advanced neoplasia.

Level of agreement: A=75%, B=25%, C=0%, D=0%, E=0%.

Quality of evidence: II-2.

Classification of recommendation: A.

In the previous Asia Pacific Consensus, advanced age, male gender, family history, smoking and obesity were identified as the potential risk factors for CRC and advanced neoplasia.[3] There is new evidence to suggest that these risk factors have significant impacts in identifying advanced neoplasia. In a case–control study comparing asymptomatic siblings of CRC patients versus siblings of normal subjects, Ng *et al*[16] have found a threefold increase in advanced neoplasia. Tsoi *et al*[17] pooled data from 27 studies and found that compared with non-smokers, both current smokers and former smokers have modest (around 20%) increased risk for CRC. The risk of obesity has also been assessed in a meta-analysis pooling together studies from Europe,[11] North America[6] and the Asia Pacific region.[6 18] The results showed that while there is a general increased risk of CRC in overweight subjects, the effects are more prominent in men than in women, and more significant for colonic cancer than rectal cancer. Furthermore, the risk of colorectal adenoma was also found significantly increased in obese subjects.[19] While these risk factors do not differ from those applying in countries outside of the Asian region, confirmation of these risk factors raises the possibility of devising a risk stratification system to prioritise screening for the higher-risk individuals (see below). This might be particularly relevant in Asia where the burden to healthcare system is high and the use of a risk-based algorithm directs screening to those who will benefit the most makes sense.

Statement 4: The Asia Pacific Risk Score is useful to identify subjects with a high risk of colorectal advanced neoplasia.

Level of agreement: A=55.6%, B=38.9%, C=5.5%, D=0%, E=0%.

Quality of evidence: II-2.

Classification of recommendation: B.

The Asia Pacific Working Group, based on the risk factors identified in Asian populations, have developed a scoring system that stratifies risk for colorectal advanced neoplasia in asymptomatic subjects.[20] This was a prospective colonoscopy-based study enrolling asymptomatic subjects above 50 years of age

from 17 centres in 11 Asian cities. The demographic data, colonoscopy findings and histology were analysed by multivariate logistic regression and an Asia Pacific scoring system was developed. In a separate validation cohort, the scoring system was validated in an independent set of prospective patients. The scoring system uses age, sex, family history and smoking as the risk factors and a score is attached to each of these parameters (tables 2 and 3). The score ranges from 0 to 7. Using score 0 as the reference group, the relative risk of finding advanced neoplasia in these asymptomatic rose from 1.6-fold to 11.1-fold. These scores are grouped into low risk, intermediate risk and high risk. Using low-risk group as the reference population, the relative risks of finding advanced neoplasia in the intermediate-risk and high-risk asymptomatic individuals were 2.6× and 4.3×, respectively (tables 2 and 3). This scoring system has subsequently been validated in two cohort studies: one in Singapore (Yeoh *et al*, unpublished data) and another independent Asia Pacific study to confirm its validity.[21]

In Asia, and perhaps in other countries/region, where burden for CRC screening is overwhelming and/or when healthcare resources are limited, this scoring system could be useful in prioritising high-risk individuals for earlier screening. The scoring system can also be used in combination with a hybrid model of screening (ie, two-step screening programme) in reducing workload and healthcare spending (see below). Since the Asia Pacific Risk Score include only gender, age, family history and smoking habits without including obesity, diabetes and other possible risk factors, there may be opportunities to further improve on the predictive value of the scoring system in the future.

HOW TO SCREEN FOR COLORECTAL NEOPLASIA?

Statement 5: Stool-based occult blood test.

5a: Stool-based occult blood testing is of proven value for CRC screening.

Level of agreement: A=80.6%, B=19.4%, C=0%, D=0%, E=0%.

Quality of evidence: I.

Classification of recommendation: A.

5b Guaiac-based stool testing should be replaced by FIT.

Level of agreement: A=88.9%, B=11.1%, C=0%, D=0%, E=0%.

Quality of evidence: I.

Classification of recommendation: A.

The value of stool-based occult blood testing in detecting early cancer and reducing CRC-related mortality is well established. Randomised studies have proven that an annual or biennial guaiac-based faecal occult blood test (gFOBT) reduces CRC mortality by 18–30%.[22] However, gFOBT is non-specific for haemoglobin, requiring dietary restrictions and hence inconvenient to use. Furthermore, gFOBT is poor in detecting adenomas.

Table 2 Asia Pacific CRC screening score[20]

Risk factor	Criteria	Points
Age	50–69 years	2
	>70 years	3
Sex	Male	1
	Female	0
Family history	First-degree relative with CRC	2
Smoking	Current or past smoking	1
	Never smoke	0

CRC, colorectal cancer.

Table 3 Risk stratification and relative risk of finding advanced neoplasia in the validation cohort[20]

Risk factor	Criteria	Points
Low risk	0–1	Reference
Intermediate risk	2–3	2.6 (1.1–6.0)
High risk	4–7	4.3 (1.8–10.3)

Previous studies from the west comparing FIT against gFOBT have demonstrated improved accuracy of the former in detecting invasive cancer as well as adenomas.[23–26] Head-to-head comparison studies from Asia have shown that FIT is superior to gFOBT because of its improved sensitivity and specificity. gFOBT screening is associated with high false-positive rates in Asia, which is probably related to failure of dietary restriction. FIT detects approximately twice as many lesions of interest compared with gFOBT at approximately the same colonoscopy rate. This result was repeatedly demonstrated by studies from Hong Kong,[27] Malaysia[28] and Korea.[29]

Because of easy sample collection, without the need for dietary control, FIT may improve participation and adherence of the target populations.[30 31] In a large-population RCT comparing gFOBT against FIT, van Rossum *et al*[25] showed that FIT improved participation in screening programme, detection of advanced adenomas and cancer.[26]

FIT is not an all-or-none test. Quantitative FIT tests quantify of blood in stool sample hence allowing different cut-off points for positive tests to be considered. The cut-off value for FIT may affect its performances. Park *et al* compared test performance at difference cut-off levels. The higher levels of blood predicted increased probability of neoplasia and hence providing flexibility for health providers. The authors found that at a cut-off of 100 ng/mL one can achieve the optimal sensitivity and specificity for CRC.[29] Automation of the test procedure further simplifies and standardises the test result. Based on these advantages, the Asia Pacific panel concluded that quantitative FIT is a preferred choice for CRC screening instead of gFOBT.

Statement 6: Faecal immunochemical test identifies individuals who should be referred for colonoscopy.

Level of agreement: A=83.3%, B=16.7%, C=0%, D=0%, E=0%.

Quality of evidence: II-2.

Classification of recommendation: A.

As the specificity of FIT for CRC is around 92%,[29] those who test positive should be referred immediately for colonoscopy. Using FIT as a first-line test for early detection of CRC, the number of colonoscopies required may actually be reduced relative to gFOBT or colonoscopy screening. Besides detecting CRC, FIT has been shown to have almost a twofold increase in the detection of advanced adenoma.[26 32] The improved ability to detect advanced adenomas is another advantage of using FIT over gFOBT. Unfortunately, there is no RCT comparing the outcome of individuals with positive FIT who were referred for colonoscopy versus FIT-positive individuals who were not referred for colonoscopy as it is not ethical to do so. This statement, which attests to the effectiveness of FIT in selecting subjects for colonoscopy, can only be supported by indirect evidence.

Recent data also suggest that FIT may also be used in between surveillance colonoscopies in detecting missed or rapidly

developing lesions.[33] In this study, subjects with a family history of CRC or past history of neoplasia who received at least two colonoscopies were offered FIT in between the examinations. Among 1071 asymptomatic subjects who received at least one FIT, 86% of the invasive cancers and 63% of the advanced adenomas were identified by positive FIT. However, the positive predictive value of FIT for cancer and advanced adenomas is low.[34 35]

Statement 7: Flexible sigmoidoscopy is effective for CRC screening.

Level of agreement: A=72.2%, B=25.0%, C=2.8%, D=0%, E=0%.

Quality of evidence: I.

Classification of recommendation: A.

FS is an office-based procedure requiring minimal bowel preparation, no sedation and can be done by trained personnel without a medical license with high safety profile. It is therefore an attractive alternative in screening for CRC.

To date, there are four RCTs testing the efficacy of FS as a tool for CRC screening. The UK Flexible Sigmoidoscopy (UKFS) screening trial, which recruited over 170 000 subjects aged 55–64 years from 14 UK centres, provided convincing results in reduction of CRC mortality. Once-only FS with referring of positive cases for colonoscopy can reduce CRC incidence by 23% and CRC mortality by 31%.[36] The US Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (US PLCO), which targeted individuals aged 55–74 years and enrolled close to 75 000 in each group of either FS or usual care, showed 21% reduction in CRC incidence and 26% reduction in CRC mortality.[37] The Italian 'once-only sigmoidoscopy' (SCORE) trial, which recruited almost 35 000 subjects aged 55–64 years from six centres, showed FS, compared with usual care, can reduce CRC incidence by 18% and CRC mortality by 22%.[38] The Norwegian Colorectal Cancer Prevention Trial (NORCCAP), which recruited over 55 000 subjects aged 55–64 years from urban and mixed rural populations, compared once-only FS with no screening. FS showed 27% reduction of CRC mortality.[39] When combining results from FS-based screening RCTs in a meta-analysis, Elmunzer *et al*[40] reported a similar reduction in CRC incidence (18%) and CRC mortality (28%). Based on the existing data, the panel supported the recommendation that FS is an effective choice for CRC screening.

All studies using FS showed no reduction in proximal CRC incidence, which is probably not surprising as the examination is limited to the left colon. However, there is evidence to suggest that even a full colonoscopy is not able to significantly reduce the mortality of right-sided colonic cancer.[41–43] There are multiple reasons for these so-called 'interval cancers', but missed cancer in the proximal colon is the most likely explanation.

Statement 8: Colonoscopy

8a Colonoscopy is effective for CRC screening.

Level of agreement: A=83.3%, B=16.7%, C=0%, D=0%, E=0%.

Quality of evidence: II-2.

Classification of recommendation: B.

8b Colonoscopy is the preferred choice of CRC screening in increased risk individuals.

Level of agreement: A=72.2%, B=19.5%, C=8.3%, D=0%, E=0%.

Quality of evidence: II-2.

Classification of recommendation: B.

Colonoscopy is considered the gold standard in all the imaging modalities in the detection and treatment of colonic lesions leading to CRC. With optimal endoscopy technique, the detection rate of adenoma in asymptomatic individuals above 50 years is at least 30% and CRC around 0.1–1% in Western populations. Complications arising from colonoscopy include bleeding (around 0.3–3.2 per 1000 procedures) and bowel perforation (0.1–2 per 1000 procedures), which usually occurs after colonoscopy polypectomy.[44]

The efficacy of colonoscopy is best demonstrated by the National Polyp Study (NPS) conducted over 20 years ago. Results of the NPS provide a recent evaluation that the long-term benefits of colonoscopic polypectomy reduce CRC mortality by 53%.[45] This result is echoed by a recent study that CRC mortality after screening colonoscopy can be reduced by 68%.[41] Similar results were reported in case–control or cohort studies.[42 46 47] To date, however, there is no RCT with mortality data. A randomised study from Spain is underway to compare the CRC-related mortality rates of colonoscopy versus FIT in CRC screening for asymptomatic subjects aged between 50 and 69 years.[32] These data are pending. Another important ongoing study is the NordICC trials.

Colonoscopy, however, is an invasive and labour-intensive procedure requiring higher level of expertise. The efficacy depends on the quality of the colonoscopy (see below). It is also one of the more expensive methods for CRC screening. In a resource-limited country or region, it might not be feasible to be used as a first-line test. The panel therefore recommends prioritising colonoscopy for those with an increased risk of CRC based upon family history of CRC and other risk factors for colorectal neoplasia.

Statement 9: CTC: CTC is not recommended for colorectal cancer screening. It may be used in cases when total colonoscopy is not possible.

Level of agreement: A=63.9%, B=22.2%, C=2.8%, D=11.1%, E=0%.

Quality of evidence: II-1.

Classification of recommendation: B.

CTC has been well studied as a screening test for CRC and advanced neoplasia.[48] It has been listed as one of the options for CRC screening in the ACS/USMSTF/ACR guidelines[11] but is not so readily accepted in Europe. In a systematic review and meta-analysis of CTC versus colonoscopy recruiting over 11 000 subjects from 49 studies, CTC was shown to have a sensitivity of 96% for CRC detection, a very comparable result with conventional colonoscopy.[49] An overview of five studies in a screening setting reported that CTC had a sensitivity of 83% in detecting polyps of at least 10 mm in size and 68% for polyps measuring 6–9 mm. The specificities for polyp detection were above 95%.[50] CTC is therefore listed as an appropriate screening test of the US guidelines.[4]

CTC requires full bowel preparation and expensive equipment for the test. In a randomised study from the Netherlands comparing non-cathartic (ie, limited bowel preparation) CTC with conventional colonoscopy, CTC required less time and allowed screening subjects to return to their daily activities earlier. However, CTC was associated with a twofold longer duration of screening-related symptoms. Feelings of anxiety, pain and quality of life scores were similar during colonoscopy and CTC screening.[51] Before the procedure was carried out, subjects anticipated that CTC would be a simpler procedure. However, after the tests they found that CTC was more burdensome, caused more pain and embarrassment than conventional colonoscopy.[52] In addition, CTC was less effective than colonoscopy in detecting advanced lesions.[53]

The cost effectiveness of CTC has been studied for population screening. Comparing the cost-effectiveness of CTC to

conventional colonoscopy or FIT in a 10-year simulation model assessing asymptomatic average-risk population 50–74 years of age, CTC is not the most cost-effective method for CRC screening.[54] CTC with non-reporting of diminutive lesions was found to be the most cost-effective and safest screening option evaluated according to a study conducted by radiology experts.[55] However, in Asia, polyps measuring 6–9 mm and <5 mm may still have a substantial risk of advanced neoplasia and invasive cancer.[56] Non-reporting policy for small polyps may not be entirely safe.

Statement 10: Capsule endoscopy: A role for capsule endoscopy in CRC screening is not defined. It may be used in cases when total colonoscopy is not possible.

Level of agreement: A=63.9%, B=33.3%, C=2.8%, D=0%, E=0%.

Quality of evidence: II-2.

Classification of recommendation: B.

Capsule endoscopy has been tested in comparison to conventional colonoscopy for the detection of colorectal polyps and cancer. In a prospective multicentre study from Europe, the first-generation capsule endoscopy was found to be able to detect polyps 6 mm or larger with a sensitivity of 64% and specificity 84%. Cancer detection was achieved in 14 out of 19 cases (74%).[57] This result has room for improvement.

In the second-generation capsule endoscopy for colon (PillCam Colon 2), frame speed has been increased from a fixed speed of 4 pictures per second to a variable 4–35 pictures per second depending on the capsule movement. The angle of view has also been widened from 156 to 172° on both ends. These improvements should be able to improve performance of capsule endoscopy. Two prospective controlled studies have been conducted from Israel and Europe to compare the new-generation capsule endoscopy with conventional colonoscopy. The sensitivity of detecting polyps ≥6 mm in size was reported as 84–89% and with a corresponding specificity of 76–92%.[58 59]

The most recent study enrolled 884 patients from 16 centres in the USA and Israel.[60] The sensitivity and specificity for detecting adenomatous polyps ≥6 mm in size were 88% and 82%, and for detecting adenomatous polyp ≥10 mm in size were 92% and 95%, respectively. All patients with CRC were detected by capsule endoscopy in this study. The report also indicated that capsule endoscopy is safe and well tolerated by patients and hence might improve the acceptance and adherence in a screening programme.[60]

In the recent European Society for Gastrointestinal Endoscopy Guideline for Colon Capsule Endoscopy, international experts have recommended capsule endoscopy as a feasible and safe tool for visualisation of the colonic mucosa in patients with incomplete colonoscopy.[61] They further commented that patients at high risk of CRC should be referred for colonoscopy. However, in patients for whom colonoscopy is inappropriate, failed to be completed or not possible, the use of capsule endoscopy could be discussed with the patient. The Asia Pacific Working Group accepts this recommendation and has included this in the current consensus.

WHO SHOULD BE CONSIDERED FOR EARLIER SCREENING?

Statement 11: First-degree relatives of patients with sporadic CRC diagnosed at age <50 are at an increased risk of colorectal neoplasm and early screening is warranted.

Level of agreement: A=63.9%, B=33.3%, C=2.8%, D=0%, E=0%.

Quality of evidence: II-2.

Classification of recommendation: B.

Family members of inherited diseases such as familial adenomatous polyposis, Peutz–Jeghers syndrome and Lynch syndrome need to receive timely genetic and screening for CRC. In this consensus, we focused on non-inherited subjects or sporadic CRC, which accounts for 70% of familial CRC.[62]

Familial clustering of CRC is a well-known phenomenon, and it has been estimated that the first-degree relatives (FDR) of CRC patients have a threefold increased risk of dying from CRC.[63] The risk of CRC appears to increase with the number of CRC-affected FDR.[64] The risk is inversely associated with the age at which CRC was diagnosed in affected family members. Several meta-analyses based on case–control and cohort studies have indicated that the risk ranges from 2–3-fold to 3–4-fold.[65–67]

All societies (ACS/USMSTF/ACR and BSG) recommended earlier screening of FDR of patients with an adenoma before the age of 60. The guidelines recommend that screening should start at 40 years of age.[11] However, the evidence in support of this statement was based on retrospective studies. Prospective data assessing the risks of CRC in FDR of patients with adenoma are lacking. It has been suggested that screening for FDR of patients with adenoma is too aggressive.[68]

Recent studies have shown that among FDR of index cases with CRC the frequency of adenoma detection is also elevated. A study from Taiwan reported that among FDR of patients with CRC the risk of adenoma detected by colonoscopy was 2.5-fold and the risk of high risk adenoma was 4.5-fold compared with control subjects who had no family history of CRC.[69] A study from Hong Kong compared the risk of advanced neoplasms among asymptomatic FDR of patients with CRC to those with a negative family history of CRC.[16] The risk of detecting adenoma was 2.19–fold, and the risk of detecting advanced neoplasms was 3.07-fold increased in the first group. The increased risk is more remarkable if the index case had been diagnosed with CRC before the age of 50 years. This study indicates that performing CRC screening among FDR of CRC patients allows earlier detection of cancer and may provide an effective way to prevent cancer development through colonoscopic polypectomy. Therefore, early screening for FDR of patients with CRC is warranted.

Statement 12: A stratified screening approach based on the risk for CRC is recommended.

Level of agreement: A=72.2%, B=25%, C=2.8%, D=0%, E=0%.

Quality of evidence: II-3.

Classification of recommendation: B.

While colonoscopy may provide the best single examination of the colon and opportunity of polypectomy, it carries a heavy burden on healthcare systems that may not be feasible in some resource-limited countries. On the other hand, the cost of colonoscopy and its invasive nature is prohibitive for those who are unwilling to pay for the examination and for some elderly subjects.[70 71] One way to reduce the cost and the workload of CRC screening by colonoscopy is to adopt a stratified approach. A study from Taiwan proposed to use age as a triage to direct younger subjects, for example, below the age of 60 years to receive FS.[72] Screening subjects with an adenoma in the distal colon are offered a full colonoscopy. On the other hand, colonoscopy is offered to all above the age of 60 years as they have a higher frequency of having adenoma.

The Asia Pacific Working Group on CRC screening has developed a risk-stratifying system using four risk factors (age, gender, family history and smoking habit). This simple scoring

system can be used to identify moderate-to-high-risk individuals requiring colonoscopy.[20] In contrast, an FIT is sufficient for the average risk individuals followed by colonoscopy in case of a positive result. This scoring system has recently been validated in 15-country multicentre Asian study that recruited asymptomatic subjects.[21]

The consensus panel considered risk stratification based on a few simple demographic parameters as a useful approach for CRC screening with the benefits of reduced burden and increased affordability for the healthcare system. The scoring system can be modified for regional usage and the triage system can be adapted to the local resources and needs. However, some kind of risk stratification would increase adherence to the CRC screening strategy through improved motivation.

HOW TO MINIMISE MISSED LESIONS OR INTERVAL CANCERS?

Statement 13: Surveillance interval for colonoscopy should be tailored to risk for colorectal neoplasia.

Level of agreement: A=86.1%, B=13.9%, C=0%, D=0%, E=0%.

Quality of evidence: II-1.

Classification of recommendation: A.

There are two main questions regarding the appropriate time for surveillance colonoscopy: (i) When should colonoscopy be repeated after a negative examination? (ii) When should colonoscopy be repeated after an adenoma is removed?

The USMSTF guideline on CRC screening recommends that the interval of colonoscopy surveillance should depend on the findings at the baseline colonoscopy. Those with a low-risk adenoma (defined as 1–2 tubular adenoma <10 mm) can have a repeat colonoscopy in 10 years. Those with a high-risk adenoma (defined as adenoma with villous histology, high-grade dysplasia, >10 mm, or three or more adenomas) should have a shorter surveillance interval in 3 years.[73 74] The European guidelines stratified risk into three levels: low risk (1–2 adenoma <10 mm), intermediate risk (3–4 small adenoma or one >10 mm) and high risk (>5 small adenomas or >3 with at least one >10 mm). They recommend that the high-risk group undergo surveillance at 1 year, the intermediate-risk group at 3-yearly intervals until two consecutive examinations are negative and the low-risk group requires no surveillance colonoscopy or 5-yearly colonoscopy until one negative examination after which surveillance can be ceased.[5]

Cohort studies have shown that after a negative colonoscopy the risk of identifying an advanced neoplasm ranges from 1.3 to 2.4%, practically the same as the baseline risk in the general population.[75–78] Three studies have shown that 10 years after CRC screening, a negative colonoscopy was associated with a subsequent reduced risk of developing CRC (adjusted OR 0.26).[79–81] Based on this evidence, the latest AGA recommendation is that 10 years would be the appropriate interval for repeating colonoscopy after a negative examination in subjects with no family history of CRC.[74] For those who have family history of CRC before the age of 60 years, it was recommended that a repeated examination should be conducted in 5 years.

More recently, the USMSTF published their revised guidelines on colonoscopic surveillance after screening and polypectomy with additional criteria.[74] Basically, the surveillance interval depends on (i) findings of polyps (hyperplastic or adenoma), (ii) number and size of adenomas, (iii) the presence of villous architecture and high-grade dysplasia of the adenoma and (iv) the presence of serrated lesions or serrated polyposis syndrome (>20 serrated polyps of any size throughout the colon). The interval of screening or surveillance is recommended from 1 to 10 years depending on the risk stratification (table 4).

A multicentre retrospective cohort study from Japan showed that patients with any adenoma ≥6 mm or intramucosal cancer at the initial colonoscopy have a high risk of advanced neoplasia in subsequent colonoscopy.[82] The risk is more significant in the right colon, a feature probably related to the higher frequency of non-polypoid lesions found in this location. In view of this concern, the Japan Polyp Study (JPS), which is a multicentre RCT conducted in 11 centres since 2003 is currently evaluating the risk of colorectal neoplasia one year after a 'clean' colonoscopy. Final follow-up results of this important study are still pending.[83]

The Asia Pacific Consensus group recommended that surveillance interval should be tailored to the risk level. However, since there is in general a lack of prospective data, precise guidelines on interval of surveillance cannot be given.

Statement 14: Right-sided lesions and sessile serrated polyps can be difficult to detect and contribute to interval cancers.

Level of agreement: A=77.8%, B=19.4%, C=2.8%, D=0%, E=0%.

Quality of evidence: II-2.

Classification of recommendation: A.

Sessile serrated polyps were once thought to have little clinical implications, but ample evidence now shows that they represent an alternate pathway of colorectal carcinogenesis. The serrated pathway associated with these lesions involves an epigenetic aberrant mechanism with abnormal hypermethylation of CpG islands located in the promoter regions of tumour suppressor genes. BRAF mutation is often involved. There are three distinct subtypes of serrated neoplasia: hyperplastic polyp (70%), sessile serrated adenoma (25%) and traditional serrated adenoma (5%). The last two forms are considered to be precursors of CRC. These lesions are usually flat or sessile, large and occasionally covered by a mucous cap. They are commonly

Table 4 Recommendations for surveillance and screening intervals after baseline colonoscopy: adapted from US Multi-Society Task Force on Colorectal Cancer Guidelines for Colonoscopy Surveillance after screening and polypectomy[66]

Baseline colonoscopy: most advanced finding(s)	Recommended surveillance interval (years)
No polyps	10
Small (<10 mm) hyperplastic polyps in rectum and sigmoid	10
1–2 small (<10 mm) tubular adenomas	5–10
3–10 tubular adenomas	3
>10 adenomas	<3
One or more tubular adenomas ≥10 mm	3
One or more villous adenomas	3
Adenoma with high-grade dysplasia	3
Serrated lesions	
Sessile serrated polyp(s) <10 mm with no dysplasia	5
Sessile serrated polyp(s) ≥10 mm OR	3
Sessile serrated polyp with dysplasia OR	
Traditional serrated adenoma	
Serrated polyposis syndrome	1

Serrated polyposis syndrome: Based on the WHO definition of serrated polyposis syndrome, with one of the following criteria: (1) at least five serrated polyps proximal to sigmoid, with two or more >10 mm; (2) any serrated polyps proximal to sigmoid with family history of serrated polyposis syndrome; and (3) >20 serrated polyps of any size throughout the colon.

found in the proximal colon and, because of their flat appearance, could be easily missed.

There is accumulating evidence that a sizeable proportion of interval cancers is related to these sessile serrated polyps. There are more interval cancers found in the proximal colon (6–14%) than in the distal colon (2–7%).[84–87] The molecular characteristics of interval cancers are also significantly different from non-interval cancer with higher prevalence of microsatellite instability (30% vs 10%), less KRAS mutation (13% vs 29%), higher CpG island methylator phonotype (57% vs 33%) and BRAF mutation (28% vs 19%).[88–90] These evidences point to the fact that sessile serrated lesions in the proximal colon are frequently missed and present subsequently as interval cancers. Therefore, the Asia Pacific Consensus group felt that there is a need to emphasise the need for meticulous examination of the proximal colon.

Statement 15: Colonoscopy: Good quality colonoscopy is key to success of a screening programme and quality of colonoscopy should be audited.

Level of agreement: A=86.1%, B=11.1%, C=0%, D=2.8%, E=0%.

Quality of evidence: II-2.

Classification of recommendation: A.

The effectiveness of screening and diagnostic colonoscopy in reducing CRC mortality depends on adequate visualisation of the entire colon, diligence in examining the mucosa, successful removal of premalignant lesions and a proper follow-up. Quality indicators include appropriate indication, bowel preparation quality, colonoscope withdrawal time from the caecum, adenoma detection rate, appropriate surveillance interval and adverse or unplanned events after colonoscopy. The importance of quality colonoscopy cannot be overemphasised for the success of a screening programme. Quality of colonoscopy can be assessed by the rates of successful caecal intubation, avoidance of missed lesions, completeness of lesion removal and prevention of adverse events (table 5).

Table 5 Quality indicators for colonoscopy screening and surveillance

Colonoscopy quality indicator by type	Examples
Documentation	Patient demographics Preprocedure assessment of risk Appropriate indication of procedure Documentation of prior exam and interval Technical description of the procedure Documentation of quality of bowel preparation Description of colonoscopic findings and management Recording of unplanned events and interventions Follow-up plan
Performance	Caecal intubation with documentation Adenoma or polyp detection rate Withdrawal time at least 6 min Immediate unplanned events or interventions
Follow-up/communication	Appropriate documentation of pathology Recommended follow-up/surveillance interval consistent with evidence-based guidelines or rationale for deviation from guideline Communication to primary provider and patient
Key outcomes	Interval colorectal cancer Adverse events

Adapted and modified from Lieberman.[74 124]

The adenoma detection rate of a colonoscopist is identified as one of the most reliable quality indicators.[91–93] A large-scale study from Poland showed that the endoscopist's rate of detection of adenomas is significantly associated with the risk of interval CRC.[91] Besides the skills of the endoscopists, bowel preparation (including the use of split preparation)[94 95] and endoscope withdrawal time (more than 8 min)[96–98] have been reported as important modifiable factors that influence the adenoma detection rate.[99]

There are initiatives from various countries to audit and monitor colonoscopy quality and auditing programmes.[93 100–102] The Asia Pacific Consensus group strongly believes that an audit system should be introduced in each country or region on the quality of colonoscopy.

Statement 16: Colonoscopy: Ancillary methods with the exception of chromoendoscopy have not proven to be superior to high-definition white light endoscopy in identifying adenoma.

Level of agreement: A=63.9%, B=36.1%, C=0%, D=0%, E=0%.

Quality of evidence: I.

Classification of recommendation: A.

High-definition white light colonoscopy with high-definition video processor and high-definition monitor are best for identification of adenomas in the colon. Pooled data from five studies showed the superiority of high-definition white light colonoscopy in detecting all polyp types and adenomas compared with conventional white light colonoscopy.[103] A more recent prospective study also showed that high-definition white light colonoscopy has a higher adenoma detection rate[104] (Table 6).

Chromoendoscopy, using a indigo carmine (0.1–0.4%), crystal violet (0.5%) or methylene blue (0.1%) on the surface of the mucosa to highlight the pits and pools dyes in the mucosal crevices, is a well-established method in colonoscopy. Compared to high-definition white light colonoscopy, high-definition chromoendoscopy in average-risk CRC screening has been shown to marginally increase in the detection of flat lesions and small adenoma detection.[105 106] By pooling results of five prospective randomised studies, the Cochrane Review confirmed that chromoendoscopy detects at least one neoplastic lesion per colonoscopy more than conventional colonoscopy, but the withdrawal time is significantly longer than conventional colonoscopy.[107]

Narrow band imaging (NBI) uses specific filtered wavelengths in the bands of blue (400–430 nm) and green (530–550 nm)

Table 6 Endoscopic imaging modalities and efficacy in CRC screening

Technology	Effective in improving adenoma detection rate	Hassle free	Available
High-definition white light	Probably yes	Yes	Yes
Chromoendoscopy	Yes	No	Yes
NBI	No	Yes	Yes
FICE	No	Yes	Yes
I-scan	Mixed (limited data)	Yes	Yes
AFI	Mixed	Yes	No
Cap-assisted colonoscopy	Mixed	Yes	Yes
Third eye retroscope	Yes (limited data)	No	Yes

AFI, autofluorescence; CRC, Consensus on Colorectal Cancer; FICE, Fujinon Intelligent Colour Enhancement system; NBI, narrow band imaging.

light to illuminate the mucosa leading to deeper penetration of light and enhancement of superficial mucosa and vascular pattern. A recent study showed that NBI can better differentiate neoplastic from non-neoplastic polyps.[108] Yet six clinical studies and their pooled data failed to demonstrate that using NBI endoscope will increase the detection rates for adenoma.[109] This was confirmed by a Cochrane Database review based on 11 studies comparing white light colonoscopy and NBI.[110] Similarly, the Fujinon Intelligent Color Enhancement system (FICE) fails to provide any advantages.[111–113] Autofluorescence (AFI) technology also failed to demonstrate significantly better results in the detection of flat lesions and adenoma.[114 115] So far, none of the new imaging modalities have proven advantage over white light colonoscopy, but this does not preclude future advancement in imaging technology may break the ground.

Cap-assisted colonoscopy helps to flatten haustral folds and keeping the mucosa at an appropriate distance from the lens. This technique does not require any expensive equipment or specific training. It may improve visualisation of the proximal aspects of folds and flexures of the colon. In 16 RCTs including close to 9000 subjects, cap-assisted colonoscopy showed marginal benefit over conventional colonoscopy with an 8% increase in polyp detection, 0.64 min shorter time for caecal intubation and a shortened procedure time.[116]

The third-eye retroscope is an auxiliary device that passes through the working channel of the colonoscope and permits a wider angle of vision with a retroflexed visualisation of the proximally facing mucosal folds commonly missed during conventional colonoscopy. The Third Eye Retroscope Randomised Clinical Evaluation (TERRACE) was a randomised controlled, multicentre trial that suggested that the third-eye retroscope increases adenoma detection compared with the conventional colonoscope.[117 118] There are so far insufficient data to support endorsing their usage in routine screening for colorectal neoplasia.

Statement 17: All components of a CRC screening programme should be audited and quality controlled.

Level of agreement: A=88.9%, B=11.1%, C=8.3%, D=0%, E=0%.

Quality of evidence: III.

Classification of recommendation: C.

CRC screening is not a single diagnostic test but a sophisticated programme that involves logistics, resource availability, clinical skills, education and population acceptance and adherence. The Asia Pacific Consensus group strongly believe that all components of a CRC screening programme need to be audited and the quality of individual components be subjected to quality control on a regular basis.

The UK National Health Service Bowel Cancer Screening Program introduced a set of monitoring parameters including selection of screening subjects, call-and-recall mechanism, logging receipt of test kits and test results, booking of clinic appointments, recording of colonoscopy and histopathology results, and reporting programme activities in their quality assurance programme (http://www.cancerscreening.nhs.uk/bowel). The ACS/USMSTF/ACR guideline emphasises on quality assurance of screening modalities, training requirement, optimal techniques to complete the examination, screening intervals and appropriate recommendations on follow-up.[11] The European guidelines for quality assurance in CRC screening issued the most comprehensive sets of criteria including quality assurance of endoscopy, professional requirement and training, quality assurance of pathology, management of lesions detected, colonoscopic surveillance following adenoma removal and communications with subjects.[9]

As Asia represents a heterogeneous group of countries and regions with different healthcare systems, resource commitment and population health behaviour, the group did not attempt to propose a single quality assurance programme for the whole region. However, an audit system to monitor the performance and effectiveness of CRC screening programmes in this region is strongly recommended and the audit should be conducted on a regular basis.

OTHER ISSUES

Statement 18: Trained nurse endoscopists are able to perform flexible sigmoidoscopy and colonoscopy effectively.

Level of agreement: No consensus reached.

Quality of evidence: II-2.

Classification of recommendation: Not applicable.

Because of a shortage of colonoscopy workforce for CRC screening, there is suggestion of using trained nurse endoscopists to perform colonoscopy or FS. Studies of nurse endoscopists have been reported from the UK, US and some European countries, but comparative data from large-scale prospective randomised trials are lacking. In a landmark study by Maule *et al*,[119] nurse endoscopists were reported to be safe and accurate in performing FS in CRC screening. A recent study also demonstrated that nurse endoscopists performed colonoscopies with high patient satisfaction.[120] The BSG Working Group has endorsed nurse endoscopists in performing FS.[121] On the other hand, the ASGE guideline did not recommend nurses to perform colonoscopy.[122] In a small-scale non-randomised study in USA, the nurse-endoscopist outperformed medical endoscopist by detecting 2.5-fold more adenoma.[123]

In Hong Kong, a prospective, randomised controlled single-blinded study enrolled 731 patients to receive colonoscopy by either nurse-endoscopist or physician-endoscopists (Hui *et al*, submitted). The nurse-endoscopist group had a higher adenoma detection rate than physician-endoscopist group (44% vs 33%) but required a significantly longer withdrawal time. Caecal intubation rate and complication rate were similar in both groups. In the Asia Pacific Consensus group, a vigorous debate was conducted on whether nurses should be trained to perform colonoscopy and polypectomy under strict guidelines and physician supervision. Due to a divergence of opinions from several countries identifying cultural differences and varying patient acceptance, no consensus can be reached to endorse nurse endoscopists in CRC screening.

CONCLUSIONS

Since the publications of the first Asia Pacific CRC in 2008,[3] there are some countries in this region that endorsed the statements and implemented the screening for colorectal cancers. Compared to the first set of consensus statement, this updated version gives more specific directions on (1) the group of asymptomatic subjects who should receive CRC screening, (2) the preferred choice of screening tools (FIT and colonoscopy in high-risk subjects) and the current status of some screening devices for example, CTC and capsule endoscopy, and (3) the introduction of risk-stratification scoring system in offering early CRC screening by colonoscopy. There is also emphasis on the quality control of the CRC screening programme and address of the use of nurse endoscopists. The target audiences of these consensus statements are practising clinicians. We hope that when the statements are accepted by practitioners in this region they will be able to recommend these to their respective policymakers. The Asia Pacific Colorectal Cancer Working Group believes that these statements will further enhance the

implementation of CRC screening in the region. These suggestions may also be relevant to CRC screening programmes in other countries outside the Asia Pacific Region.

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Acknowledgements On behalf of the Asia Pacific Working Group on Colorectal Cancer Screening, we would like to thank the following members for their contributions: Byeon JS, Chen MH, Chong VH, Ho KY, Huang YQ, Kim TI, Lam PY, Leong R, Li J, Makharia G, Payawal D, Quach DT, Rerknimitr R, Sano Y, Wong MCS, Wu DC, Wu KC and Wu MS.

Contributors Study design: JJYS; literature review: JJYS, FKLC and SCN; draft of the manuscript: JJYS and SCN; revision of the manuscript: all authors.

Funding An unrestricted education grant was received from Olympus Medical System Corporation and Given Imaging. In order to avoid conflict of interest, industrial partners were not allowed to provide input for the statements, add references in the literature search, participate in the discussion and vote in the consensus conference. None of the sponsors contributed towards the development of the consensus statements or in their voting.

Competing interests All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf. JJYS, HMC, HSK, TM, SSMG, JYWL, SZ, NR, KGY, KKFT, EJK, LR, GPY, RJS, DL and KLG declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work. SCN received grants from Ferring Hong Kong, and Janssen Hong Kong. FKLC received speaker's honorarium from Pfizer Inc., AstraZeneca and Takeda Pharmaceuticals (Hong Kong) Ltd. SA reports personal fees from Given Imaging outside the submitted work. JYLC received speaker's honorarium from Elsai Japan, and travelling support to DDW from Given Imaging (Asia).

Provenance and peer review Not commissioned; externally peer reviewed.

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Gut published online March 19, 2014
doi: 10.1136/gutjnl-2013-306503