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Treatment strategy of diminutive colorectal polyp <5 mm in size – Should it be removed and discarded without pathologic assessment?

Cold polypectomy techniques for diminutive polyps in the colorectum

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Adequate colonoscopic polypectomy is a very important intervention for the prevention of colorectal cancer progression during screening and surveillance colonoscopy. Whereas various techniques are used for the removal of diminutive polyps, including cold biopsy forceps, hot biopsy forceps, hot snare, and cold snare, hot polypectomy techniques with electrocautery have been associated with an increased risk of electrocautery-related complications, including immediate and/or delayed bleeding or perforation. In contrast, recent studies have found a polypectomy technique without electrocautery, so-called cold polypectomy, to be a safer and more efficacious technique. The present article discusses the use of cold polypectomy techniques and describes how cold biopsy forceps polypectomy using jumbo biopsy forceps designed with a greater capacity for removing larger tissue samples, and cold snare polypectomy, are adequate for removing diminutive polyps completely and safely and shorten withdrawal time of the colonoscopy procedure.

Key words: cold biopsy forceps polypectomy, cold polypectomy, colonoscopy, diminutive polyp

INTRODUCTION

ADEQUATE COLONOSCOPIC POLYPECTOMY remains as one of the most important interventions during screening and surveillance colonoscopy in the prevention of colorectal cancer progression based on the adenoma-carcinoma sequence and hence reduces colorectal cancer mortality rates.[1,2] Since its introduction to practice, appropriate endoscopic resection techniques have generally been chosen based on polyp size and morphology; however, various approaches have been adopted by individual endoscopists. Historically, polyps ≥6 mm have been removed by snare polypectomy as the technique of choice;[3,4] however, this was done almost exclusively with electrocautery, particularly for polyps >10 mm.

According to a survey of 285 US gastroenterologists in 2004, various techniques for removal of polyps (≤6 mm) have been used. For polyps measuring 4–6 mm, 19% reported using cold biopsy forceps, 21% hot biopsy forceps, 59% hot snare, and 15% cold snare.[3] More recently, however, studies have found that a cold polypectomy technique for diminutive polyps (≤5 mm) and small polyps (<10 mm) is also safe and efficacious.[5–7] The present review focuses on the utility, safety and efficacy of the cold polypectomy technique for removing diminutive polyps in the colorectum.

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COMPLICATIONS OF THE HOT POLYPECTOMY TECHNIQUE

THE APPLICATION OF hot polypectomy techniques including hot snare polypectomy (HSP), endoscopic mucosal resection (EMR) and hot biopsy forceps polypectomy (HBP) have been associated with an increased risk of electrocautery-related complications such as immediate and/or delayed bleeding and perforation. Specifically, immediate bleeding has been associated with the use of cutting current in HSP, whereas the possibility of delayed bleeding accompanies the use of coagulation current. In a questionnaire survey of 517 American Society for Gastrointestinal Endoscopy (ASGE) members,[8] 47 delayed bleeding (0.38%) and six delayed perforations (0.05%) were reported with 12 367 hot biopsies. In a subanalysis, limiting the use of hot biopsies to the ascending colon, higher rates of delayed bleeding (0.52%) and delayed perforations (0.26%) were

reported. Another questionnaire survey of 107 Japanese institutions[9] showed that rates of delayed bleeding after HBP were 0.26% (38/14 382) and perforation was 0.01% (2/14 382).

Although immediate bleeding can be managed with endoclips or argon plasma coagulation, patients with serious delayed post-polypectomy bleeding require urgent repeat colonoscopy that may necessitate the use of several methods to control bleeding.[10,11] Additionally, delayed perforation has also been known to be a more serious complication. When this occurs, intestinal fluid with digestive enzymes and fecal fluid with large amounts of bacteria leak into the peritoneum via the perforated site, requiring surgical intervention as the first choice of treatment. A porcine study revealed that the use of monopolar hot biopsy forceps electrocauterization resulted in significantly deeper colon injury than HSP, confirming the hazardous potential of the practice, especially in the right colon.[12] The ASGE has not recommended this technique as the preferred method for small polyp removal.[13] In addition, the 2011 United Kingdom Bowel Cancer Screening Program Quality Assurance Guidelines for Colonoscopy also reported that 'anecdotal experience suggests the risk of perforation with HBP is high'.[14] It follows, then, that techniques without the use of electrocautery may be preferable for these diminutive polypectomies and this warrants further study.

COLD POLYPECTOMY TECHNIQUES

ALTHOUGH COMPLICATIONS CAN occur even with proper technique, polypectomy techniques for diminutive or small polyps must be effective and minimize complications. Cold polypectomy techniques such as cold biopsy forceps polypectomy (CBP) and cold snare polypectomy (CSP) are preferred for most diminutive polyps.

Cold biopsy forceps polypectomy

Cold biopsy forceps polypectomy (CBP) is commonly used for the removal of diminutive polyps, especially adenomas (≤3 mm); however, evidence for the efficacy of CBP is lacking.[15] A recent study demonstrated the adequacy of resection of diminutive polyps and identified predictors for complete resection using CBP. It was concluded that CBP may be adequate for the resection of the majority of diminutive polyps if no residual tissue is left behind.[7]

Draganov *et al.*[16] introduced jumbo biopsy forceps designed with a greater capacity for removing larger tissue samples (Radial Jaw™ 4 Jumbo Biopsy Forceps; Boston Scientific, Marlborough, MA, USA) (Fig. 1) and reported advantages of its use, such as a higher complete histological eradication rate for removing diminutive polyps and shorter withdrawal time in the colonoscopy procedure than standard forceps. The Japanese authors of the present review also conducted a multicenter prospective study to evaluate the efficacy of jumbo biopsy forceps for the removal of 223 diminutive polyps.[17] The rate of one-bite polypectomy was 85% and included 100%, 100%, 96%, 88% and 70% for lesions 1 mm, 2 mm, 3 mm, 4 mm and 5 mm in diameter, respectively (Table 1). No significant differences were found in the one-bite rate based on macroscopic type between flat and polypoid lesions, no differences were found in endoscopists' experience and no adverse complications, such as post-polypectomy bleeding or perforation were reported (Fig. 2).

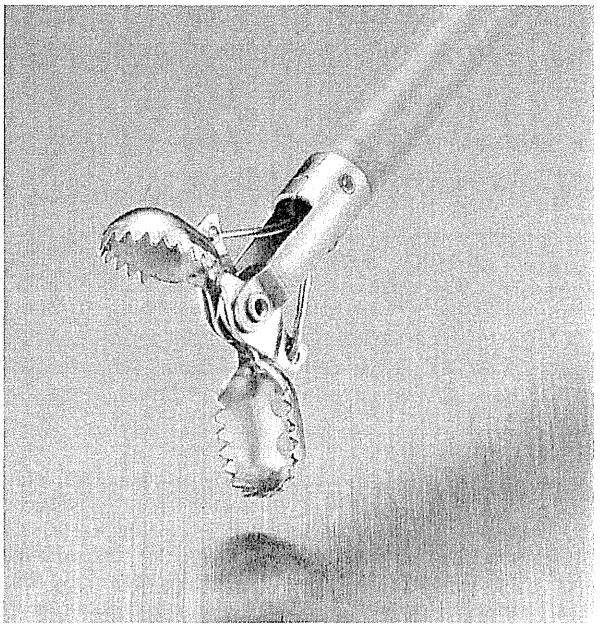

Figure 1 Radial Jaw™ 4 Jumbo Biopsy Forceps (Boston Scientific, Marlborough, MA, USA).

Table 1 Rate of one-bite polypectomy using jumbo biopsy forceps† according to lesion size

Lesion size (mm)	Rate of one-bite polypectomy
1	100% (4/4)
2	100% (31/31)
3	96% (103/107)
4	88% (45/51)
5	70% (21/30)
	Overall rate
	91% (204/223)

†Radial Jaw™ 4 Jumbo Biopsy Forceps (Boston Scientific, Marlborough, MA, USA).

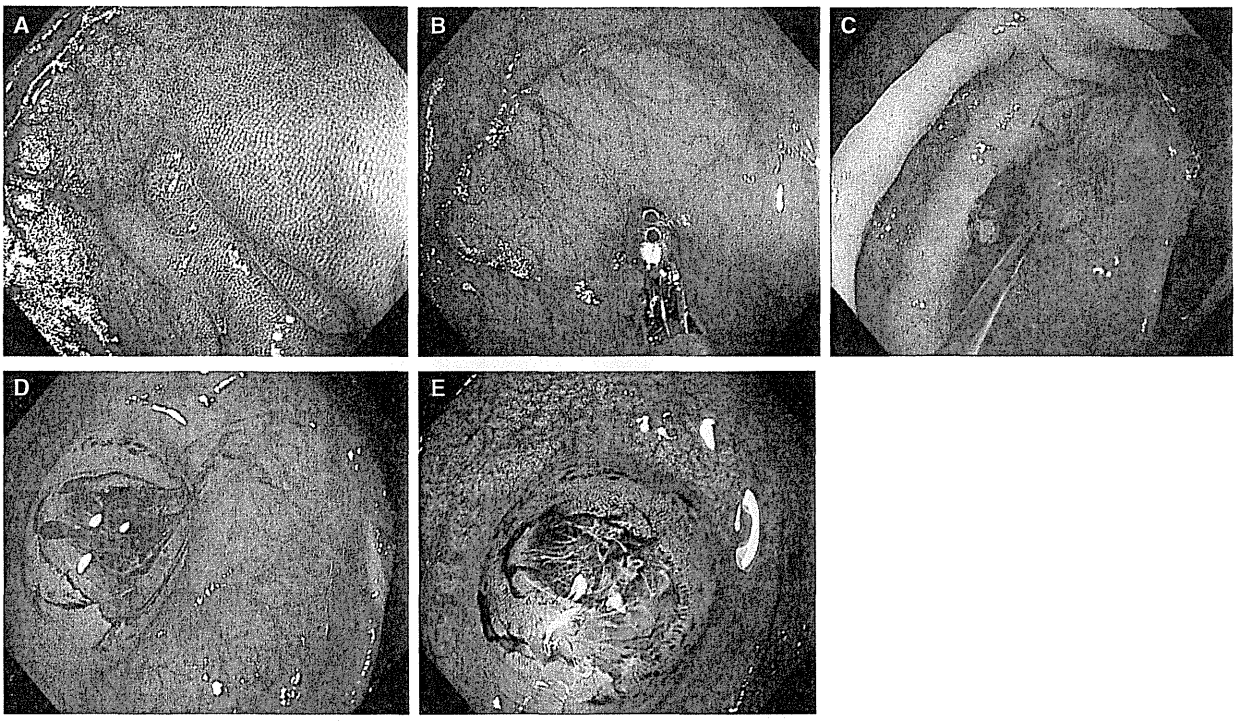

Figure 2 (A) Five-mm polyp Type 0-Is, narrow band imaging view (NBI). (B) Half-opening Radial Jaw™ 4 Jumbo Biopsy Forceps (Boston Scientific, Marlborough, MA, USA). (C) Post-one-bite polypectomy site with mild oozing. (D) Submucosal swelling as a result of forced water irrigation over the exposed base to create a submucosa tamponade. (E) NBI with closed view revealed no residual tissue.

Based on these studies, CBP using jumbo biopsy forceps is a simple and safe technique that can also retrieve all resected specimens for histological assessment.

Cold snare polypectomy

Cold snare polypectomy (CSP) has not only demonstrated the same efficacy as the hot snare technique,[15,18] but it requires a shorter procedure time and eliminates concerns associated with electrocautery-related tissue damage and post-polypectomy cautery syndrome. It results in en-bloc resection with histological verification, as some studies have reported advanced-type histology in these polyps, although the incidence is low. Therefore, this technique eliminates the concern for residual polyp and its progression to interval cancers. Even though the CSP technique is becoming more widely acceptable, particularly with Western endoscopists, it is used infrequently in Japan and other parts of Asia. However, recent studies from this region show an evolving adaptation of this technique.

With some evidence showing advanced-type histology in diminutive polyps as high as 8.7% in polyps <5 mm,[19] complete resection should be the goal for all intended polypectomies. This technique is simple, efficient, and cost-effective without the associated risks of standard snare cautery polypectomy.

Once the polyp is identified and the endoscope positioned adequately as for a standard polypectomy, the minisnare (SnareMaster 10 mm, Olympus Medical, Tokyo, Japan; Exacto 9 mm, US Endoscopy, Mentor, Ohio, USA; or Captivator Small Oval 13 mm, Boston Scientific) (Fig. 3) is advanced and opened over the polyp. Gentle suction is applied to reduce colonic distention while the tip of the endoscope is deflected down to facilitate a 'sink-in of the snare' in the surrounding desired mucosa, ensnaring approximately 2–3 mm of normal mucosa around the base of the polyp while the snare is closed assertively and the polyp is resected and suctioned (Fig. 4a–d). A self-limited oozing of blood and/or a small submucosal hematoma may form. In infrequent cases of ongoing bleeding, successful hemostasis is always achieved by the technique of positioning the endoscope 'en face' and close to the post-polypectomy base and with forced power water irrigation (equipped as standard on most current colonoscope), creating a 'pseudo' submucosal injection with the jet of water, which results in a submucosal cushion for tamponade (Fig. 4e).

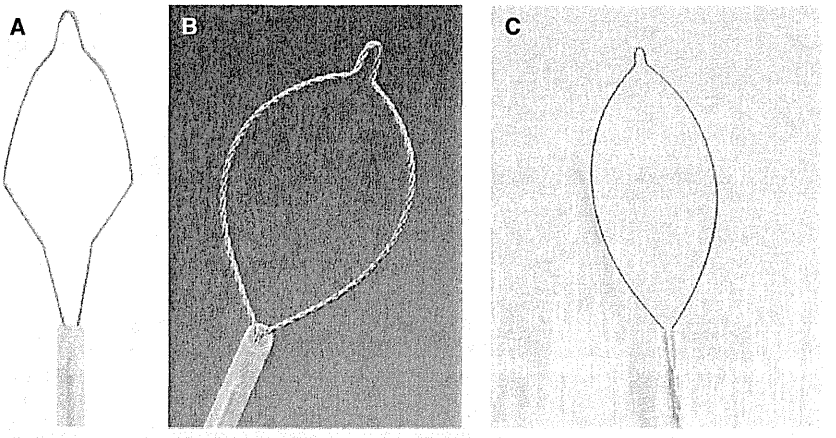

Figure 3 (A) Nine-mm Exacto cold snare; US Endoscopy, Mentor, Ohio, USA. (B) SnareMaster 10 mm; Olympus Medical, Tokyo, Japan. (C) Thirteen-mm Captivator Small Oval; Boston Scientific, Natick, MA, USA.

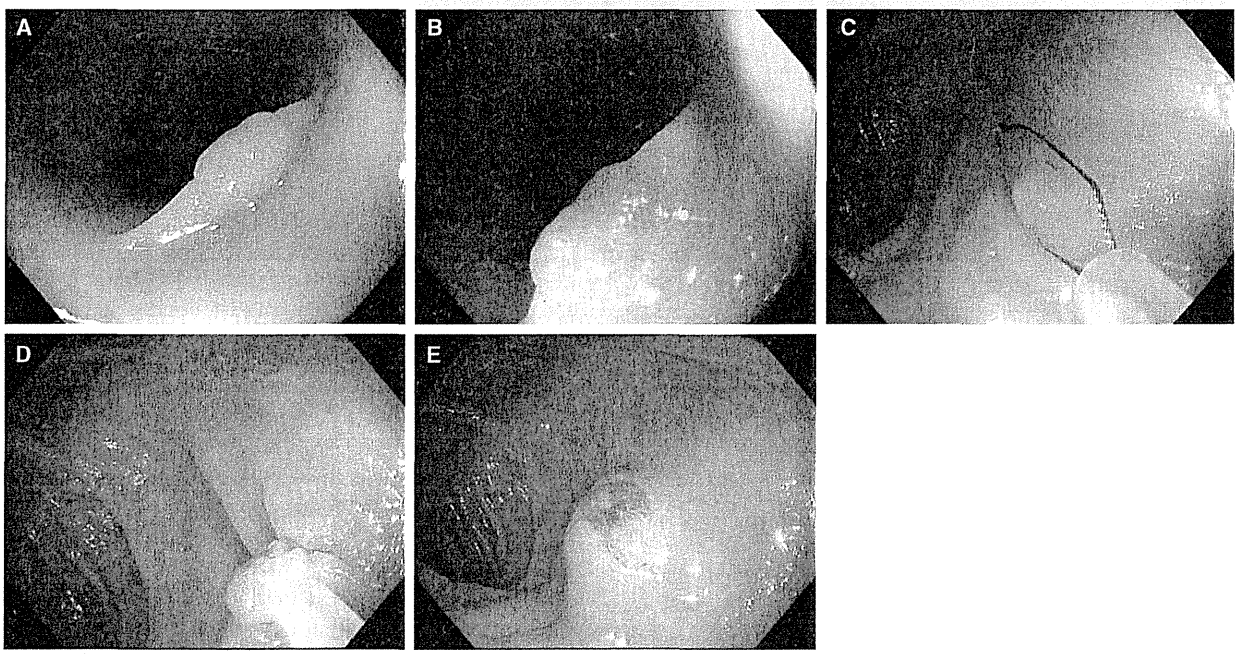

Figure 4 (A) Five-mm polyp Type 0-IIa, white light. (B) Narrow band imaging view. (C) Mini cold snare placed over the polyp which is positioned at approximately 5 o'clock with the working channel of the endoscope with a rim of normal surrounding mucosa (Exacto; US Endoscopy, Mentor, OH, USA). (D) Ensnaring and resection of the polyp while gentle suction is applied to deflate any distention of the colon ensuring complete en-bloc resection. (E) Post-polypectomy site without bleeding or exposed significant vessels. Note the submucosal swelling because of forced water irrigation over the exposed base to create a submucosa tamponade, which is usually done when there is oozing of blood.

Recently, other studies have demonstrated the safety and efficacy of CSP. One study from Japan found the results of CSP superior to those of conventional hot snare polypectomy. In this study, 14% of patients on anticoagulation therapy had delayed bleeding in the conventional polypectomy group whereas the CSP group had none.[20] Although this technique diverts from the current standard of practice in patients that are high risk for bleeding while on antiplatelet and anticoagulation therapy, it provokes discussion of the need for further prospective studies to clarify whether this would be a new and safer approach for polypectomy, particularly in patients who may have increased risk if their

antithrombotics are discontinued. Additionally, another prospective randomized study from South Korea found CSP a preferable technique in comparison to CBP for diminutive polyps when assessed for completeness of resection, as assessed by histological eradication.[21]

A disadvantage of using CSP in the resection of diminutive polyps is fragmentation of the polyps preventing retrieval after suctioning, particularly with poor bowel preparation.[18] However, the American co-author of the present review has adopted this technique and, in his personal anecdotal experience, based on retrospective review of prospectively collected data as part of his quality metrics for screening colonoscopy, he has observed no clinically significant post-polypectomy bleeding after CSP in approximately 3000 cases of polyps ≤10 mm.

CONCLUSIONS

COMPLICATIONS RELATED WITH polypectomy can occur even with proper technique; however, adverse effects should be avoided especially for removing diminutive polyps that have a low risk of colorectal cancer progression. Cold polypectomy techniques such as CBP using jumbo biopsy forceps and CSP must be effective and minimize complications. Whereas CBP and CSP have been found to be particularly advantageous techniques as a result of their decreased risk of bleeding and perforation, there is a need for prospective clinical trials to continue evaluating the safety, efficacy and utilization of this practice for diminutive polyps. Additionally, comparative studies of a variety of techniques, such as cold jumbo biopsy forceps removal, and snare with or without electrocoagulation (monopolar and bipolar), are warranted to also evaluate their utility, efficacy and safety.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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The Japanese Society of Gastroenterology

SPECIAL ARTICLE

Evidence-based clinical practice guidelines for management of colorectal polyps

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Abstract
Background Recently in Japan, the morbidity of colorectal polyp has been increasing. As a result, a large number of cases of colorectal polyps that are diagnosed and treated using colonoscopy has now increased, and clinical guidelines are needed for endoscopic management and surveillance after treatment.
Methods Three committees [the professional committee for making clinical questions (CQs) and statements by Japanese specialists, the expert panelist committee for rating statements by the modified Delphi method, and the evaluating committee by moderators] were organized. Ten specialists for colorectal polyp management extracted the specific clinical statements from articles published between 1983 and September 2011 obtained from PubMed and a secondary database, and developed the CQs and statements. Basically, statements were made according to the GRADE system. The expert panel individually rated the clinical statements using a modified Delphi approach, in which a clinical statement receiving a median score greater than seven on a nine-point scale from the panel was regarded as valid.
Results The professional committee created 91CQs and statements for the current concept and diagnosis/treatment of various colorectal polyps including epidemiology, screening, pathophysiology, definition and classification, diagnosis, treatment/management, practical treatment, complications and surveillance after treatment, and other colorectal lesions (submucosal tumors, nonneoplastic polyps, polyposis, hereditary tumors, ulcerative colitis-associated tumor/carcinoma).
Conclusions After evaluation by the moderators, evidence-based clinical guidelines for management of colorectal polyps have been proposed for 2014.

Keywords Colorectal polyp · Colorectal tumor · Polyposis · GRADE system

The original version of this article appeared in Japanese as "Daicho Polyp Sinryo Guidelines 2014" from the Japanese Society of Gastroenterology (JSGE), published by Nankodo, Tokyo, 2014. Please see the article on the standards, methods, and process of developing the Guidelines (doi: 10.1007/s00535-014-1016-1). The members of the Working Committee are listed in the Appendix in the text.

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Introduction

In Japan, following the westernization of eating habits and with aging of the population, the morbidity of colorectal carcinoma and associated mortality are both increasing. Indeed, it has been said that the 21st century is the era of the large intestine. As the number of cases of colorectal polyps that are diagnosed and treated via colonoscopy has now increased, clinical guidelines are needed for endoscopic management and surveillance after treatment. In April 2012, the National Health Insurance system began offering coverage for expenses incurred for colorectal endoscopic submucosal dissection (ESD). Accordingly, appropriate selection between ESD and endoscopic

mucosal resection (EMR) has become more important. In this regard, the Japanese Society of Gastroenterology (JSGE) has established "evidence-based clinical guidelines for management of colorectal polyps" (hereafter referred to as "the Guidelines"). Although the title of the Guidelines mentions colorectal polyps, they include all types of localized colorectal lesions, including superficial neoplastic lesions, early carcinoma, and polyposis.

The Guidelines Creation Committee and Evaluation Committee were established prior to drafting the Guidelines. The Japanese Gastroenterological Association, Japanese Society of Gastrointestinal Cancer Screening, the Japan Gastroenterological Endoscopy Society (JGES), the Japan Society of Coloproctology (JSCP), and the Japanese Society for Cancer of the Colon and Rectum (JSCCR), which are cooperative societies, recommended members to be assigned to these two committees.

In the creation of the Guidelines, the Guidelines Creation Committee drafted clinical questions (CQs) that covered: (1) epidemiology; (2) screening; (3) pathophysiology, definition, and classification; (4) diagnosis; (5) treatment and management; (6) practical treatment; (7) complication and surveillance after treatment; and (8) other colorectal lesions (submucosal tumors, nonneoplastic polyps, polyposis, hereditary tumors, ulcerative colitis-associated tumor/cancer). The Evaluation Committee evaluated the drafts of the CQs, and 91 CQs were established. For each CQ, a document retrieval style was created, and systematic document retrieval was performed by searching PubMed and Igaku Chuo Zassi for articles published between January 1983 and September 2011. For insufficient or unobtainable documents, manual searching was also performed. Subsequently, a structured abstract was created, and both a statement and an explanation were written. The Guidelines Creation Committee determined the grades of recommendations and the levels of evidence after deliberation using the Delphi method. As mentioned in a previous publication [1], the Guidelines were created in accordance with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. This draft was evaluated and amended by the Evaluation Committee, which was then presented to members of the JSGE. After obtaining public comments, these comments were discussed, and a final version of the Guidelines was created.

The contents on tumor diagnosis and endoscopic treatment described in the Guidelines partially overlap with those of the previously published 2014 JSCCR Guidelines for the Treatment of Colorectal Cancer [2] and the Colorectal ESD/EMR Guidelines (JGES) [3]. In addition, the committees for these three guidelines closely cooperated with each other to ensure their consistency. Concerning the contents of the Guidelines, this paper mainly introduces CQs for the treatment of colorectal polyps.

Clinical questions (CQ) and statements

CQ. What are the indications for endoscopic resection with respect to the size of adenomas?

- Endoscopic resection should be used for lesions ≥6 mm in size (Recommendation 2 [100 %], level of evidence C). However, endoscopic resection should also be used for diminutive lesions ≤5 mm, flat and depressed lesions, as well as for those indistinguishable from carcinoma (Recommendation 2 [100 %], level of evidence D).

Comment: It is strongly recommended that endoscopic resection be used for lesions ≥6 mm in size because the incidence of carcinoma is higher in lesions ≥6 mm than in those ≤5 mm, and because it is often difficult to distinguish between benign adenomas and carcinomas by colonoscopy alone [4, 5].

According to a study in the UK, if the relative risk for carcinoma in lesions ≤5 mm is considered 1, it increases to 7.2, 12.7, and 14.6 in lesions sized 6–10 mm, 11–20 mm, and >20 mm, respectively. Therefore, all colonic lesions ≥6 mm should be either resected or ablated [4]. From the results of meta-analyses, polypectomy [4] and EMR [6]/ESD [7] can be considered the preferred less invasive treatments for colorectal neoplasia [8, 9]. However, for flat and depressed lesions, endoscopic resection is recommended, since the incidence of carcinoma is even higher in lesions that are ≤5 mm in size than in polypoid lesions [6, 10].

CQ. How should diminutive adenomas that are ≤5 mm in size be managed?

- Diminutive polypoid lesions should be followed up (Recommendation 2 [100 %], level of evidence C). However, endoscopic resection should be performed for diminutive flat and depressed lesions that are difficult to distinguish from adenomas or carcinomas (Recommendation 2 [100 %], level of evidence D).

Comment: Hyperplastic diminutive lesions ≤5 mm in size are acceptable for being followed up by colonoscopy. In diminutive polypoid adenomas ≤5 mm, at least in principle, follow-up is acceptable in the absence of colonoscopic findings suggestive of carcinoma. Flat and depressed lesions suspected of being adenoma or carcinoma on colonoscopy are preferably treated by endoscopic resection. Colonoscopic findings suspicious for carcinoma include the following: (1) expansive appearance (protrusion and overextension of the lesion and/or surrounding normal mucosa such as a submucosal tumor); (2) depressed surface; (3) rough appearance (rough surface without shine); (4) normal mucosa of the border of the tumor in

sessile lesions; and (5) type V pit pattern (irregular or disappearance of surface structure). To confirm these findings, chromoendoscopy or magnifying colonoscopy is recommended [11, 12]. Diminutive lesions should be followed up with annual colonoscopy for 3 years [13, 14].

A cohort study on diminutive colorectal lesions reported that there is little change in either the size or shape of lesions after 2–3 years of follow-up [13]. The incidence of carcinoma in diminutive colorectal lesions in Western countries is reported to range from 0.03 to 0.05 %. According to a large-scale cohort study, the overall incidence of polypectomy-related complications is 0.7 % with a perforation rate of 0.1 % (one per 1,000 resections). In addition, to decrease unnecessary risks for healthy individuals and lower overall costs, endoscopic resection should not be performed for all diminutive colorectal lesions ≤5 mm [15, 16].

After resection of colorectal neoplasia, yearly follow-up by colonoscopy is recommended until all colorectal polyps including diminutive lesions have been completely excised, and every 3 years thereafter [14, 17].

CQ. How should hyperplastic polyps be managed?

- Follow-up is recommended for hyperplastic polyps ≤5 mm detected in the recto-sigmoid region (Recommendation 2 [100 %], level of evidence D). Endoscopic resection should be performed for lesions ≥10 mm detected in the right side of the colon, as they are difficult to discriminate from sessile serrated adenoma/polyps (SSA/P) (Recommendation 2 [100 %], level of evidence D).

Comment: Typical hyperplastic polyps presenting as whitish flat lesions ≤5 mm in the recto-sigmoid region should be followed up, as there have been no reports on the association of these lesions with adenoma [18, 19]. Colonoscopy every 10 years is recommended in the case of hyperplastic polyps according to the guidelines of the AGA/ASGE. Endoscopic resection should be used for lesions ≥10 mm in size in the right side of the colon, as they are difficult to distinguish from SSA/P; the incidence of carcinoma in such lesions has been reported to be 9.4 % [20].

According to the results of 1,800 cases in two large studies on chemoprevention, the risk of hyperplastic polyps is significantly higher (OR 3.67; $p < 0.001$) in patients with hyperplastic polyps detected at initial examination. Moreover, the risk of relapse of adenomatous polyps is also significantly higher (OR 2.08; $p < 0.01$) in patients with adenomatous polyps detected at initial examination. On the other hand, there is no correlation between the risk of adenoma and detection of hyperplastic polyps at initial examination or between adenomatous polyps and the presence of hyperplastic polyps [18, 19]. It has been hypothesized that adenomatous and hyperplastic polys may have different etiology, since the presence of the former has no correlation with the latter, and vice versa [18, 19].

However, one report has suggested that hyperplastic polyps in the recto-sigmoid region may indicate malignant lesions in the proximal colon, since *BRAF* mutations have been detected in hyperplastic polyps, although additional investigations are needed to clarify potential correlations between hyperplastic polyps and SSA/P [18, 19].

CQ. How should serrated lesions of the colorectum be treated?

- Serrated lesions of the colorectum include sessile serrated adenoma/polyp (SSA/P), traditional serrated adenoma (TSA), and hyperplastic polyp (HP). The former two lesions have potential to develop to adenocarcinoma and thus are recommended to treat (Recommendation 2 [100 %], level of evidence D).

Comment: Serrated lesions of the colorectum include SSA/P, TSA, and HP. SSA/P and TSA may undergo malignant transformation to adenocarcinoma and should thus be treated. SSA/P is associated with *BRAF* mutations and the CpG island methylator phenotype (CIMP), and is considered a precursor lesion of colorectal carcinoma with microsatellite instability [21]. Recent studies have reported that the rate of progression to carcinoma in SSA/P ranges from 1.5 to 20 % [22]. Aggressive resection should be performed for SSA/P [23].

TSA is a protruding lesion with distinct redness that is commonly found in the left side of the colon and rectum. Histologically, TSA is considered to potentially progress to carcinoma, similar to SSA/P. Treatment is therefore indicated for TSA, and resection is indicated for TSA ≥5 mm in diameter, similar to common adenomas. As for SSA/P, most studies recommend that lesions ≥10 mm in diameter should be resected [24–26]. HP may be a precursor lesion of SSA/P and/or TSA. Treatment is not indicated for HP ≤5 mm in diameter.

CQ. What therapy is indicated for laterally spreading tumors (LST)?

- The therapeutic choice between piecemeal EMR and ESD for a large LST should be based on the LST subtype, and use of magnifying endoscopy and endoscopic ultrasonography as appropriate (Recommendation 2 [100 %], level of evidence C).

Comment: LSTs are classified into two types according to morphology: granular type (LST-G) and non-granular type (LST-NG) [27]. Each type has two subtypes. The former consists of a "homogenous type" and a "nodular mixed type", while the latter consists of a "flat elevated type" and

a "pseudo-depressed type". Most LST-Gs are considered adenomatous lesions. Among homogenous-type LST-Gs, the incidence of carcinoma or submucosal invasion is extremely low [28, 29]. Large nodule in a nodular mixed-type LST-G, where submucosal invasion tends to be present [30], should be resected en bloc [31]. An adenomatous LST-G homogenous type can be resected by piecemeal EMR [32]. A flat elevated-type LST-NG should be treated according to preoperative diagnosis. For pseudo-depressed-type LST-NGs, en bloc resection should be performed, since these tumors have a high probability of multifocal submucosal invasion independent of their size or pit pattern [30, 31]. In summary, the indications for ESD or piecemeal EMR are based on the LST subtype; magnifying endoscopy and endoscopic ultrasonography are used as needed.

CQ. What are the indications for endoscopic resection of early colorectal carcinoma?

- An early colorectal carcinoma (Tis/T1) should be treated endoscopically when the possibility of lymph node metastasis is extremely low and en bloc resection is possible (Recommendation none, level of evidence level C).

Comment: There are no reports of lymph node metastasis in intramucosal (Tis) carcinomas, while lymph node metastasis occurs in approximately 10 % of submucosal invasive (T1) carcinomas [33, 34]. Therefore, endoscopic resection is recommended in a Tis or Tl carcinoma that has a low probability of lymph node metastasis. Endoscopic resection is both a therapeutic and important diagnostic method that can be used for total excisional biopsy. Complete resection with a negative vertical margin is indispensable for cure after endoscopic resection of a T1 carcinoma. Endoscopic resection of T1 carcinomas is associated with a risk of positive vertical margins. It is thus necessary to completely resect the carcinoma and ensure that horizontal and vertical margins are negative, enabling both precise pathological diagnosis and curative potential [2].

CQ. What pathological findings do indicate additional surgery after endoscopic resection for early colorectal carcinoma?

- T1 carcinoma with a tumor-positive vertical margin is an absolute indication. T1 carcinoma with an unfavorable histologic grade or submucosal invasion of $\geq$1,000 μm, or vascular invasion or grade 2/3 tumor budding should be considered for additional surgery with lymph node dissection (Recommendation none, level of evidence C).

Comment: Lymph node metastasis is found in 6.8–17.8 % of T1 carcinomas [2, 35, 36]. In principle, T1 carcinoma should be treated by surgery with lymph node dissection. The risk factors for lymph node metastasis in T1 carcinoma include depth of submucosal invasion [2, 35, 37–42], histological grade [2, 35, 37, 39–42], budding grade [2, 35, 36, 43], and vascular invasion [2, 35–44]. According to the 2014 guidelines by the JSCCR (Japanese Society for Cancer of the Colon and Rectum) for the treatment of colorectal carcinoma, among the carcinomas treated by endoscopic resection, T1 carcinomas with a tumor-negative vertical margin, favorable histologic grade with a submucosal invasion depth of <1,000 μm, and absence of vascular invasion with tumor budding grade 1 (low grade) could be followed up, while T1 carcinomas that do not meet these criteria should be considered for additional surgery with lymph node dissection. It may possible to reduce the number of patients undergoing unnecessary additional surgical resection considering the above risk factors [2, 37–39, 45, 46]. Even if the risk for lymph node metastasis after endoscopic treatment cannot be considered zero, a comprehensive assessment of the pathologic findings after endoscopic resection, patient age, physical activity levels, comorbidities, and any potentially undesirable consequences of the resection such as urinary and excretory disorders or the need for colostomy is needed.

CQ. In which types of colorectal tumors is it acceptable to perform piecemeal EMR?

- Definite adenoma or Tis carcinoma based on preoperative diagnosis are acceptable for piecemeal EMR. However, rates of local recurrence with piecemeal resection are high, and thus caution is advised (Recommendation 2 [100 %], level of evidence C).

Comment: In principle, en bloc resection should be used for suspicious or definite carcinoma, since the specimen obtained by complete en bloc resection should be pathologically examined in detail. On the basis of precise preoperative diagnosis with magnifying endoscopy, adenomatous lesions or focal carcinoma in adenomas $\geq$2 cm in diameter, for which en bloc snare EMR is not indicated, can be completely resected using deliberate piecemeal EMR to avoid segmentation of the carcinomatous area without compromising pathological diagnosis [2]. Although the local recurrence rate associated with piecemeal resection is high compared with that after en bloc resection [31, 32, 47–52], most local recurrent lesions are adenomas. Cure is possible with additional endoscopic treatment for local recurrent intramucosal lesions [47, 49, 52, 53]. In contrast, ESD allows complete en bloc resection regardless of lesion size. However, colorectal ESD is

technically more difficult and requires considerable experience.

CQ. What are the indications for endoscopic submucosal dissection?

- (1) Tumors requiring endoscopic en bloc resection, for which the snare technique is difficult to use; (2) intramucosal tumors accompanied by submucosal fibrosis, induced by biopsy or peristalsis of the lesion; (3) sporadic localized tumors that occur as a result of chronic inflammation; and (4) local residual early carcinoma after endoscopic resection are among the indications for ESD (Recommendation none, level of evidence C).

Comment: The Colorectal ESD Standardization Implementation Working Group proposed a draft entitled Criteria of Indications for Colorectal ESD [31]. It specifically states that colorectal ESD is indicated for tumors requiring endoscopic en bloc resection when it is difficult to use the snare technique, such as LST-NG (especially the pseudo-depressed type), tumors with a type VI pit pattern, shallow submucosal invasive carcinoma, large depressed tumors, and large elevated lesions that are probably malignant (large nodular lesions such as LST-G). Other lesions such as intramucosal tumors accompanied by submucosal fibrosis induced by biopsy or peristalsis of the lesion, sporadic localized tumors that occur as a result of chronic inflammation such as ulcerative colitis, and local residual early carcinoma after endoscopic resection, are also included in the indications for ESD. A cure rate of 83–88 % has been reported using ESD for local residual early carcinoma after endoscopic resection [54, 55]. In Japan, colorectal ESD has been covered by national health insurance since April 2012. It is indicated in early colorectal carcinomas, early carcinomas that are 2–5 cm in diameter. However, there were no significant differences in the outcome of colorectal ESD between lesions 2–5 cm in diameter and those $\leq$5 cm in diameter based on a prospective cohort study by the Japan Gastroenterological Endoscopy Society (JGES). Considering payments by national health insurance, no limitations on lesion size have been required for colorectal ESD.

CQ. Is biopsy essential for choosing the therapeutic strategy for colorectal lesions?

- This will depend on the characteristics of individual lesions. It is acceptable to decide a therapeutic strategy for colorectal lesions without biopsy (Recommendation 2 [100 %], level of evidence C).

Comment: Endoscopic procedures, especially magnifying endoscopy such as pit pattern diagnosis or image-enhanced endoscopy, avoid unnecessary biopsy for colorectal tumors. Biopsy should not be performed in polypectomy or EMR, as it increases medical expenses. In addition, it is clinically insignificant to randomly obtain biopsies for protruding lesions, as most are adenoma or carcinoma in adenoma. However, biopsy for a lesion suspected to be T1 carcinoma may acceptable, since histological information is helpful for planning the therapeutic strategy. Biopsy for superficial lesions (flat or depressed lesions) should not be performed prior to endoscopic resection, as it causes false-positive non-lifting signs due to submucosal fibrosis after injection during EMR [56]. It is important to understand whether the lesion is indicated for endoscopic resection through standard or magnifying endoscopic observation.

CQ. How is the choice made from among polypectomy, EMR, and ESD for colorectal tumors?

- Polypectomy is indicated for pedunculated or semi-pedunculated polyps, and EMR is indicated for sessile polyps or superficial lesions. ESD is indicated for lesions requiring endoscopic en bloc resection, although the lesions cannot be resected en bloc by snare techniques (Recommendation 2 [100 %], level of evidence C).

Comment: The choice of technique for endoscopic resection should be based on tumor morphology and size. Polypectomy is normally indicated for pedunculated or adenomatous semi-pedunculated polyps, while EMR is suitable for sessile, semi-pedunculated, or superficial tumors that are likely to be carcinoma [6, 57]. ESD allows complete en bloc resection regardless of the size of the lesion [28, 31, 58, 59]. Colorectal ESD is thus indicated for lesions requiring endoscopic en bloc resection when it is difficult to use the snare technique [31]. Moreover, en bloc resection is particularly indicated for depressed tumors or pseudo-depressed-type LST-NGs, as these tumors have a high incidence of submucosal invasion [28, 29]. In contrast, piecemeal EMR is acceptable for LST-G homogenous-type, since it is associated with a very low incidence of submucosal invasion [31]. EMR or ESD should be preferred over polypectomy for suspected submucosal invasive (T1) carcinoma.

CQ. Does colorectal carcinoma incidence decrease by endoscopic removal of colorectal adenoma?

- It is generally believed that the incidence of colorectal carcinoma decreases following endoscopic removal of colorectal adenomas, at least in Western countries, although there is limited data in Japan (Recommendation none, level of evidence B).

Comment: In 1993, the National Polyp Study (NPS) Workgroup reported that endoscopic removal of all

colorectal adenomatous polyps is associated with a decrease in the incidence of colorectal carcinoma from 76 to 90 % [60]. Since then, endoscopic removal of all adenomas during colonoscopy was strongly recommended in Western countries. In contrast, some Japanese endoscopists have reported that endoscopic polypectomy of all adenomas (especially for diminutive polyps) may not be effective in decreasing the incidence of colorectal carcinoma. Moreover, there is limited data in Japan. Regarding this CQ, two issues should be considered, namely the prevalence of carcinoma based on the size of the lesions and the interval of surveillance after endoscopic polypectomy. Regarding the former, in 1995, Sawada and Hiwatashi reported that the prevalence of carcinoma in patients with diminutive (<5 mm) polyps was 1.2 % (98.8 % were benign adenoma) [61]. While this proportion appears to be higher than that reported in Western countries (0.03–0.05 %), this discrepancy may be related to differences in pathological definitions. Nonetheless, the prevalence of carcinoma in patients with diminutive polyps is rather low. On the other hand, a single screening/surveillance colonoscopy session may not identify all polyps. Moreover, there are many reports concerning the clinical importance of de novo carcinoma. We note that a single colonoscopy with polyp removal is not a flawless procedure, and in particular, poor bowel preparation may be associated with a lower reported incidence of colorectal carcinoma [62–64]. Based on these points, it can be assumed that carcinoma can be prevented by endoscopic removal of polyps.

CQ. How should surveillance colonoscopy be planned after endoscopic removal of colorectal adenoma?

- Follow-up colonoscopy should be performed within 3 years after polypectomy (Recommendation 2 [100 %], level of evidence B).

Comment: The National Polyp Study (NPS) Workgroup recommended an interval of at least 3 years after colonoscopic removal of newly diagnosed adenomatous polyps and follow-up examination [65]. According to the European guidelines [66] and modified US guidelines [67], the most suitable interval for surveillance colonoscopy is recommended based on the number of adenomas, maximum size of polyps, and histopathological findings (including the presence of high-grade dysplasia) of resected lesions. As general guidance, patients with several (in European guidelines: <4, in US guidelines <9) small adenomas (low-grade dysplasia) <10 mm should undergo surveillance colonoscopy at 3 years following polypectomy. In contrast, patients with only one or two small low-grade adenomas should undergo routine screening (i.e., FOBT) according to the European guidelines, and surveillance colonoscopy after 5–10 years according to the US guidelines. Moreover, according to these guidelines, patients with many adenomas (>10) or high-grade dysplasia (known as intramucosal cancer in Japan) should undergo more intensive surveillance colonoscopy. In Japan, the decision to follow these guidelines is uncertain because management of diminutive adenoma (<5 mm) has not been established. In brief, endoscopists in the West attempt to remove all adenomas, whereas there is no uniform Japanese approach (removal or follow-up) for diminutive adenomas, and controversy remains in Japan [68–72]. The present guidelines, therefore, recommend the following based on data from a retrospective study carried out by the Japan Polyp Study Workgroup [73]: "Follow-up colonoscopy should be performed within 3 years after polypectomy."

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Appendix

Members of the Working Committee who created and evaluated the "Evidence-based clinical guidelines for management of colorectal polyps", JSGE

Director Responsible

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Vice-Chair: Yusuke Saitoh (Digestive Disease Center, Asahikawa City Hospital)

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ORIGINAL ARTICLE

An updated Asia Pacific Consensus Recommendations on colorectal cancer screening

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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

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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