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Original Article

International consensus on the management of large (≥20 mm) colorectal laterally spreading tumors: World Endoscopy Organization Delphi study

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DEN Digestive Endoscopy For Gastroenterologists and Endoscopic Surgeons

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Objectives: There have been significant advances in the management of large (≥20 mm) laterally spreading tumors (LSTs) or nonpedunculated colorectal polyps; however, there is a lack of clear consensus on the management of these lesions with significant geographic variability especially between Eastern and Western paradigms. We aimed to provide an international consensus to better guide management and attempt to homogenize practices.

Methods: Two experts in interventional endoscopy spearheaded an evidence-based Delphi study on behalf of the World Endoscopy Organization Colorectal Cancer Screening Committee. A steering committee comprising six members devised 51 statements, and 43 experts from 18 countries on six continents participated in a three-round voting process. The Grading of Recommendations, Assessment, Development and Evaluations tool was used to assess evidence quality and recommendation strength. Consensus was defined as ≥80% agreement (strongly agree or agree) on a 5-point Likert scale.

Results: Forty-two statements reached consensus after three rounds of voting. Recommendations included: three statements on training and competency; 10 statements on preresection evaluation, including optical diagnosis, classification, and staging of LSTs; 14 statements on endoscopic resection indications and technique, including statements on en bloc and piecemeal resection decision-making; seven statements on postresection evaluation; and eight statements on postresection care.

Conclusions: An international expert consensus based on the current available evidence has been developed to guide the evaluation, resection, and follow-up of LSTs. This may provide guiding principles for the global management of these lesions and standardize current practices.

Key words: Endoscopy, Endoscopic mucosal resection, Endoscopic resection, Endoscopic submucosal dissection, Gastrointestinal cancer, Neoplasia

INTRODUCTION

LARGE COLORECTAL LATERALLY spreading tumors (LSTs) ≥20 mm are immediate precursors to colorectal cancer (CRC). There are many perceived diverging paradigms on the optimal management of these lesions to prevent recurrence, eventual development of cancer, and metastasis, morbidity, and mortality. There have been significant advances in the management of these lesions, with novel resection techniques, increased uptake of en bloc resection methods in the Western world, and improved training. There is, however, a lack of clear consensus on the management of large nonpedunculated colorectal polyps, with significant geographic variability between Eastern and Western paradigms. Opinions surrounding training requirements, the use of chromoendoscopy, the selection of appropriate lesions for piecemeal resection, and appropriate follow-up remain controversial with a lack of a unified worldwide systematic approach. Two experts in interventional endoscopy spearheaded an evidence-based Delphi study on behalf of the World Endoscopy Organization Colorectal Cancer Screening Committee to spearhead an international consensus to better guide management and attempt to homogenize practices.

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METHODS

Steering committee and statement creation

WE PERFORMED A Delphi study conducted with an international panel of experts undergoing three rounds of anonymous voting on evidence-based statements. Two experts in endoscopic resection of LSTs (D.v.R., Y.S.) led the study and invited four additional members (D.K.R., R.D., H.M.C., N.F.) to join them in the study steering committee.

The steering committee deconstructed the management of large nonpedunculated colorectal polyps into five components: (i) training and competency; (ii) preresection evaluation; (iii) endoscopic resection indications and technique; (iv) postresection evaluation; and (v) postresection care. Initial statements were created within the five overarching categories through a combination of meetings and virtual exchanges, and all members approved the initial proposed statements for the first round of voting. A literature review was conducted for each proposed statement and evidence was assessed and rated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system and evidence was presented to experts during voting.[1] Consensus was predefined as ≥80% agreement (either Strongly Agree [SA] or Agree [A]) on a 5-point Likert scale (Strongly Agree [SA]; Agree [A]; Neither Agree nor Disagree [N]; Disagree [D]; Strongly Disagree [SD]).

Expert member selection and consensus process

Forty-three experts in varying aspects of advanced endoscopic tissue resection were selected by the steering committee. Experts were chosen based on international renown, quantity and impact of endoscopic resection-based research, as determined by expertscape ranking using the MEDLINE database, and by contacting professional societies for regions less represented in available publications (e.g., Africa) to ensure equity in expert selection. Careful consideration was given to select a diverse group of experts including both female and male members, pathologists, surgeons, and gastroenterologists to ensure the presence of a variety of opinion and experiences. Additional attention was given to balance North American, European, and Asian experts while also including experts from South America, Africa, and Oceania to promote a more international consensus and take into consideration the realities of practices in different regions of the world. After selection, the expert panel participated in three rounds of voting from January 2023 to May 2023 through an online survey platform. Voting was anonymized and voters were encouraged to submit anonymous comments for each presented statement to allow for further modifications and guide future rounds of voting. Anonymous opinions from the members of the expert voting panel were collected during round 1 of voting and the statements were heavily modified, reduced to core statements, and presented again for definitive voting from the expert panel during round 2. Remaining statements not reaching consensus were further modified and presented again during round 3.

RESULTS

FIFTY-ONE STATEMENTS WERE presented during round 1, with 25 reaching consensus by the expert panel. Statements were then modified taking into account anonymous comments from the expert panel, and 46 core statements were then presented during round 2, with 39 reaching consensus threshold. Removed statements had <50% agreement between experts and were judged unlikely to reach consensus even after modification. These statements included specific endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) case numbers to achieve and maintain competency and favoring the use of certain optical diagnosis classification systems over others. During round 3, five statements were presented for voting (four modified statements, one new statement), with three additional statements reaching consensus threshold.

Training, competency, pre-/postresection evaluation and care

Justification regarding endoscopic resection indications and technique are presented in this study as the complexities and number of factors to take into account before determining optimal resection method requires a nuanced and patient-centered approach (Table 1). Twenty-eight statements regarding training and competency, as well as postresection evaluation and histologic considerations, reached consensus threshold (Tables 2–5). Justification and explanatory text can be found in the Supplemental Section.

Endoscopic resection indications and technique

When determining the optimal resection method for LSTs, multiple factors could lead endoscopists to deviate from the statements presented. Endoscopists should take into account patient-related factors such as age, comorbidities, likelihood of benefitting from a given therapy, and patient perception of the risks and benefits of each procedure. This might lead to

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Table 1 Endoscopic resection indications and technique statements

Statement	Agreement	Strength	Quality of evidence
1.1. For lesions with serrated appearance on optical evaluation (e.g., JNET 1, WASP), either en bloc or piecemeal resection can be performed	83%	Conditional	Moderate
1.2. For lesions with serrated appearance on optical evaluation (e.g., JNET 1, WASP) with no suspicion of dysplasia, cold snare resection can be performed	88%	Conditional	Moderate
1.3. For lesions proximal to the rectum at low risk of containing cancer with superficial (<1000 μm) submucosal invasion (granular homogeneous type) and with no suspicion of invasive cancer on optical evaluation (JNET 2A), either en bloc or piecemeal resection can be performed	84%	Strong	Moderate
1.4. For lesions in the rectum at lower risk of containing cancer with superficial (<1000 μm) submucosal invasion (granular homogeneous type) and with no suspicion of submucosal invasion on optical evaluation (JNET 2A) an attempt at an en bloc resection should be made if feasible	85%	Strong	Moderate
1.5. When a piecemeal resection is performed, endoscopists should aim to resect lesions in as few pieces as possible when it is safe to do so	95%	Conditional	Low
1.6. For lesions with suspicion of superficial (<1000 μm) submucosal invasion on optical evaluation (JNET 2B), an en bloc method for tissue resection should be performed rather than piecemeal	95%	Strong	Moderate
1.7. For lesions proximal to the rectum at increased risk of superficial (<1000 μm) submucosal invasion (nongranular; granular mixed type with large dominant nodule; demarcated depressed areas), an en bloc method for tissue resection should be performed rather than piecemeal	83%	Strong	Moderate
1.8. For lesions in the rectum at increased risk of superficial (<1000 μm) submucosal invasion (nongranular; granular mixed type with large dominant nodule; demarcated depressed areas), an en bloc method for tissue resection should be performed rather than piecemeal	97%	Strong	Moderate
1.9. For lesions proximal to the rectum with suspicion of deep submucosal invasion on optical evaluation (JNET 3, Kudo V_N, Kudo V_I-severe with demarcated area), multidisciplinary evaluation should be performed to determine resection suitability and optimal modality	96%	Strong	Moderate
1.10. For lesions with suspicion of deep submucosal invasion on optical evaluation (JNET 3, Kudo V_N, Kudo V_I-severe with demarcated area) in the lower rectum and with staging negative for lymph node/distant metastasis, an en bloc method for tissue resection capable of resecting deeper tissue planes (e.g., EID, PAEM) can be considered in patients declining surgical resection after multidisciplinary team evaluation for resection suitability	88%	Conditional	Low
1.11. When an en bloc resection is necessary, ESD should be performed rather than EMR if en bloc resection is difficult to achieve with EMR	100%	Strong	Low
1.12. When an en bloc resection is necessary, ESD should be performed rather than EMR in the presence of submucosal fibrosis	88%	Strong	Low
1.13. When an en bloc resection is necessary, ESD should be performed rather than EMR when chronic inflammation is present (e.g., ulcerative colitis)	90%	Strong	Low
1.14. When ESD is required to achieve en bloc resection, adequate reimbursement mechanisms should be available given the longer procedure time and technical challenges associated with the technique with clinical benefit	100%	Strong	Moderate

EID, endoscopic intermuscular dissection; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; PAEM, peranal endoscopic myectomy.

preferential adoption of a different tailored resection strategy (e.g., piecemeal method of resection when en bloc is recommended). There is no consensus on what percentage constitutes a low, moderate, or high risk of submucosal invasion; therefore, discussion with patients and within multidisciplinary committees is highly encouraged. Additionally, the availability of resources at the referral center, time requirements of en bloc resection methods, and ESD volume capacity can also play a large role in the choice of resection methods. Centers can therefore choose to opt for piecemeal resection methods in some situations as an alternative to en bloc resection, to provide a larger number

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Table 2 Training and competency statements

Statement	Agreement	Strength	Quality of evidence
2.1. Training in image enhanced endoscopy and optical evaluation of polyp morphology and histology is required to perform resection of large laterally spreading tumors	97%	Strong	Moderate
2.2. Endoscopic resection should be performed by endoscopists trained in advanced tissue resection with adequate caseload to safely and effectively perform the selected technique	98%	Strong	Moderate
2.3. Endoscopists should monitor and audit their EMR and ESD performance (R0, curative resection, recurrence) and safety (perforation and bleeding rates) to ensure that competency is maintained	100%	Strong	Moderate

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

Table 3 Preresection evaluation statements

Statement	Agreement	Strength	Quality of evidence
3.1. All lesions should be evaluated using high-definition endoscopes	97%	Strong	High
3.2. All lesions should be evaluated using either virtual chromoendoscopy, dye-based chromoendoscopy, or both	83%	Strong	High
3.3. For all lesions, the Paris classification for morphology should be described and recorded	95%	Strong	High
3.4. For all nonserrated lesions, the laterally spreading tumors classification for morphology (granular homogenous, granular mixed, nongranular pseudodepressed, nongranular flat elevated) should be described and recorded	90%	Strong	High
3.5. For all lesions, a classification system capable of predicting the risk of submucosal invasion should be described and recorded	100%	Strong	Moderate
3.6. Optical diagnosis and evaluation of lesion morphology and submucosal invasion risk should be accounted for within procedure reimbursement as it is an essential component to evaluate resectability and selecting adequate resection technique	95%	Strong	High
3.7. For lesions with suspicion of superficial (<1000 μm) submucosal invasion on optical evaluation (JNET 2B) further stratification for deep submucosal invasion risk using the Kudo pit pattern classification (Kudo V_N, Kudo V_I-severe with demarcated area) can be considered	87%	Conditional	High
3.8. Evaluation of lesions using the Kudo pit pattern classification should be performed using optical magnification if available	86%	Strong	Moderate
3.9. Either magnetic resonance imaging or endoscopic ultrasonography should be performed for rectal lesions with suspicion of deep submucosal invasion on optical evaluation (JNET 3, Kudo V_N, Kudo V_I-severe with demarcated area)	95%	Strong	High
3.10. Complete staging for lymph node/distant metastasis should be performed for all lesions with suspicion of deep submucosal invasion on optical evaluation (JNET 3, Kudo V_N, Kudo V_I-severe with demarcated area)	90%	Strong	Low

of endoscopic resections and avoid situations in which surgery is performed for benign lesions because of long delays for en bloc resection. Attempting a piecemeal resection when en bloc is recommended should be preferred over surgery as first-line treatment for benign lesions. The following statements represent the current expert consensus on resection indications and techniques for LSTs, they assume that patient factors are favorable, and that all resources and expertise are readily available to perform the recommended techniques.

1.1. For lesions with serrated appearance on optical evaluation (e.g., JNET 1, WASP), either en bloc or piecemeal resection can be performed.

GRADE: Conditional recommendation, moderate-quality evidence.

SA (32%), A (51%), N (7%), D (10%), SD (0%). SA + A: 83%.

1.2. For lesions with serrated appearance on optical evaluation (e.g., JNET 1, WASP) with no suspicion of dysplasia, cold snare resection can be performed.

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Table 4 Postresection evaluation statements

Statement	Agreement	Strength	Quality of evidence
4.1. En bloc resection specimens should be pinned in the endoscopy room for histopathological evaluation	100%	Strong	Very low
4.2. Careful embedding of resection specimens as to produce well-oriented stained sections is required for accurate histologic assessment	100%	Strong	Very low
4.3. Resection specimens should be cut at 2–3 mm intervals throughout the specimen along parallel lines for histologic evaluation	95%	Strong	Very low
4.4. EMR and ESD resection specimens should be evaluated by experienced pathologists specialized in assessing gastrointestinal sections	100%	Strong	Moderate
4.5. In the case of submucosal invasion, histologic review by a second pathologist can be considered	93%	Conditional	Moderate
4.6. Immunohistochemistry staining for desmin to highlight the muscularis mucosa, lymphatic vessel endothelial antibody (D2-40) to assess lymphatic vessel invasion, and elastic fiber staining (such as Elastica van Gieson) to assess venous invasion, can be helpful and considered for specimens with submucosal invasion	83%	Conditional	Low
4.7. R0 resection is defined as the absence of neoplasia at the resection margins	98%	Conditional	Low

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

Table 5 Postresection care statements

Statement	Agreement	Strength	Quality of evidence
5.1. For lesions resected by EMR, same- day discharge without hospitalization is reasonable in the proper setting after observation in the postendoscopy care unit if no immediate complications are apparent	91%	Strong	High
5.2. Follow-up colonoscopy should be performed 6 months after piecemeal resection to detect recurrence	92%	Strong	Moderate
5.3. En bloc R0 resection of advanced lesions up to and including high-grade dysplasia/ intramucosal carcinoma should be deemed curative	100%	Strong	High
5.4. Follow-up colonoscopy can be considered 1–3 years after en bloc R0 resection of lesions without high-grade dysplasia and intramucosal carcinoma to detect synchronous and metachronous lesions	83%	Conditional	Low
5.5. Follow-up colonoscopy can be considered 1–3 years after en bloc R0 resection of lesions with high-grade dysplasia/intramucosal carcinoma to detect synchronous and metachronous lesions	85%	Conditional	Low
5.6. En bloc R0 resection of superficial submucosal invasive lesions without lymphovascular invasion, poor differentiation, or grade 2/3 tumor budding should be deemed curative	98%	Strong	High
5.7. After en bloc R0 resection of deep (≥1000 μm) submucosal invasive lesions without lymphovascular invasion, poor differentiation, or grade 2/3 tumor budding shared decision making between patients, endoscopists, pathologists, and surgeons should be performed to determine whether to undergo further resection or close follow-up	95%	Conditional	Low
5.8. En bloc R0 resection of deep (≥1000 μm) submucosal invasive lesions with either lymphovascular invasion, poor differentiation, or grade 2/3 tumor budding should be referred for surgical and oncologic evaluation for further treatment	95%	Strong	High

EMR, endoscopic mucosal resection.

GRADE: Conditional recommendation, moderate quality evidence.
SA (39%), A (49%), N (7%), D (3%), SD (2%). SA + A: 88%.

Multiple studies have retrospectively evaluated piecemeal cold snare resection of large sessile serrated lesions (SSLs) showing <5% recurrence at first and second follow-up colonoscopy.[2–6] En bloc resection of SSLs becomes less

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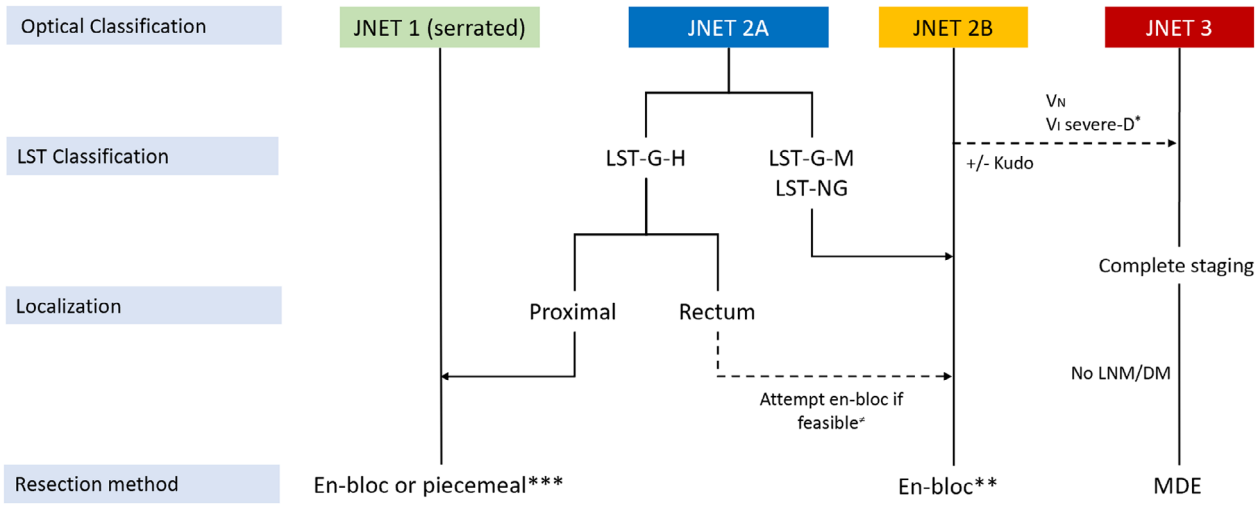

Figure 1 Flowchart for the management of large nonpedunculated colorectal polyps. *Kudo pit pattern V_I severe with demarcated area. **Endoscopic submucosal dissection if endoscopic mucosal resection is difficult, submucosal fibrosis, chronic inflammation. ***Cold snare if serrated without dysplasia. ≠If en bloc is not feasible, piecemeal resection can be performed. DM, distal metastasis; G-H, granular homogenous; G-M, granular mixed; LNM, lymph node metastasis; LST, laterally spreading tumor; MDE, multidisciplinary evaluation; NG, nongranular.

feasible with cold snares the larger the lesion. Current studies have shown no increased risk of adverse events or recurrence when using a piecemeal approach for SSLs although generalizability to nonexpert centers has not been evaluated.[2–5] A meta-analysis showed 4.7% (95% confidence interval [CI] 0.9–8.5) rates of local recurrence after cold snare resection of ≥20 mm SSLs.[7] This is in contrast with another meta-analysis showing that incomplete resection of 1–20 mm polyps was higher for SSLs (28.5%) when compared with adenomas (13.3%) when performed by a wide group of expert and nonexpert endoscopists.[8] Because SSLs can present with indistinctive borders, a piecemeal cold snare approach should be reserved for expert endoscopists trained in optical diagnosis and advanced tissue resection in which this approach could be highly advantageous because of its safety profile and efficacy. There are currently no data on the optimal approach for SSLs with an overt focus of dysplasia. A retrospective study found that SSLs with dysplasia had high rates of metachronous advanced lesions (22.2%).[9] However, recurrence after resection of SSLs with dysplasia is unclear. Current approaches involve either piecemeal or en bloc resection of the entire lesion or en bloc resection of the focus of dysplasia with piecemeal resection of the remaining lesion. Given the lack of evidence, no recommendation could be made on cold vs hot snare or en bloc vs piecemeal resection for these lesions (Fig. 1).

1.3. For lesions proximal to the rectum at low risk of containing cancer with superficial (<1000 µm) submucosal invasion (granular homogeneous type) and with no suspicion of invasive cancer on optical evaluation (JNET 2A), either en bloc or piecemeal resection can be performed.
GRADE: Strong recommendation, moderate quality evidence.
SA (30%), A (54%), N (0%), D (14%), SD (2%). SA + A: 84%.

A prospective study in 1712 LSTs with no overt signs of submucosal invasion found rates of submucosal invasive cancer (SMIC) in proximal granular homogenous type LSTs of 0.7%.[10] Another study found <1% submucosal invasion rates in large granular homogenous proximal LSTs.[11] Studies evaluating the diagnostic accuracy of JNET diagnosing adenoma without high-grade dysplasia or submucosal invasion have found high (91.0–98.3) positive predictive value (PPV) for JNET 2A (Fig. 2).[12–14] The findings of JNET 2A proximal granular homogenous LSTs signify a very low risk for submucosal invasion. Either piecemeal or en bloc resection of these lesions can therefore be performed safely, with very low risk of noncurative resection or missed covert submucosal invasion. Piecemeal EMR has been shown to lead to higher rates of recurrence, although recent advances including the addition of thermal ablation of the margins has led to <5% rates of recurrence in expert centers.[15–19] One study in 20 to 25 mm LSTs has

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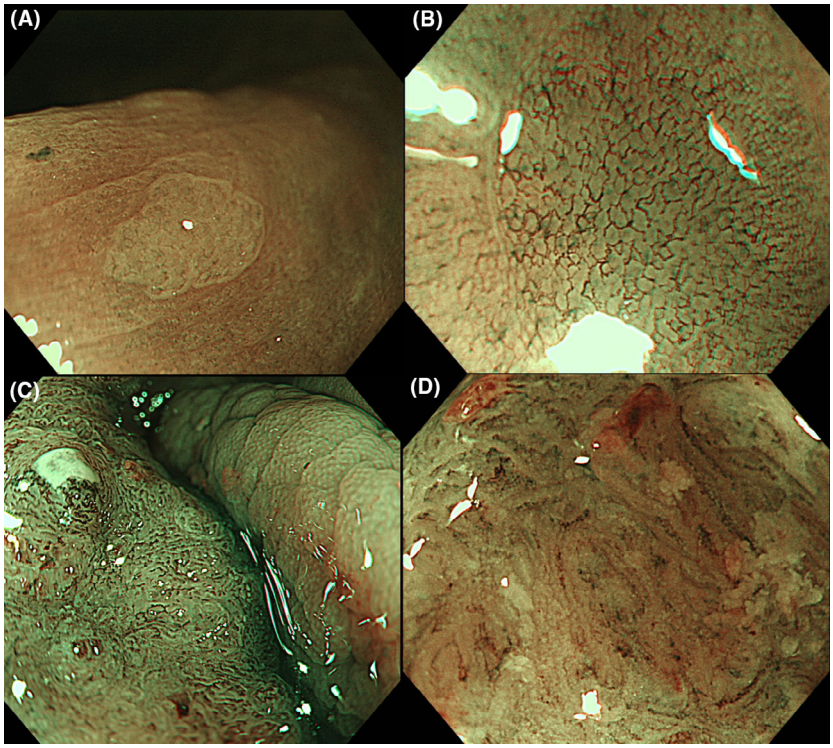

Figure 2 Optical findings for JNET classification. (A) JNET type 1. (B) JNET type 2A. (C) JNET type 2B. (D) JNET type 3.

shown that en bloc and piecemeal EMR had similar rates of long-term recurrence and low rates of surgery.[20] In one study including 3372 LSTs, of which 142 inadvertent piecemeal resection of submucosally invasive cancer occurred, no cases of residual cancer were observed for lesions with R0 deep margins.[21] Risk factors for lymph node metastasis were poor differentiation and lymphovascular invasion.[21] When recurrence does occur in LSTs, a large study of 1800 lesions with 213 recurrences undergoing long-term follow-up has shown that recurrences tended to be small and could be effectively and easily treated at follow-up with >90% success rates.[22] A recent randomized controlled trial from France reported that ESD is associated with fewer recurrences than EMR, even in the colon, and the rate of T1 cancers is significantly lower in EMR. Therefore, care should be taken not to miss covert T1 although infrequent (Fig. 3).

1.4. For lesions in the rectum at lower risk of containing cancer with superficial (<1000 μm) submucosal invasion (granular homogeneous type) and with no suspicion of submucosal invasion on optical evaluation (JNET 2A) an attempt at an en bloc resection should be made if feasible.

GRADE: Strong recommendation, moderate quality evidence.

SA (41%), A (44%), N (5%), D (7%), SD (3%). SA + A: 85%.

Given the difference in risk of covert submucosal invasion and the improved safety of en bloc resection methods in the rectum, these lesions are addressed separately from proximal LSTs in the statements. For granular homogenous JNET 2A rectal LSTs, expert consensus did not favor either a universal en bloc resection approach nor a universal piecemeal approach. A large study showed that granular homogenous LSTs in the rectum had a 1.2% rate of submucosal invasion risk when no overt signs of submucosal invasion were present.[10] Another retrospective study found no lesions with submucosal invasion in 75 granular homogenous LSTs.[11] However, studies have also shown that rectal lesions have more advanced histology and higher rates of submucosal invasion compared to proximal lesions.[23] Features such as sessile morphology, nongranular; granular mixed type with large dominant nodule; demarcated depressed areas incur higher risk of submucosal invasion in rectal lesions.[10,11,24] The potential effects of misdiagnosis of JNET 2B lesions as JNET 2A and the benefits of evaluating en bloc specimens in the rectum for

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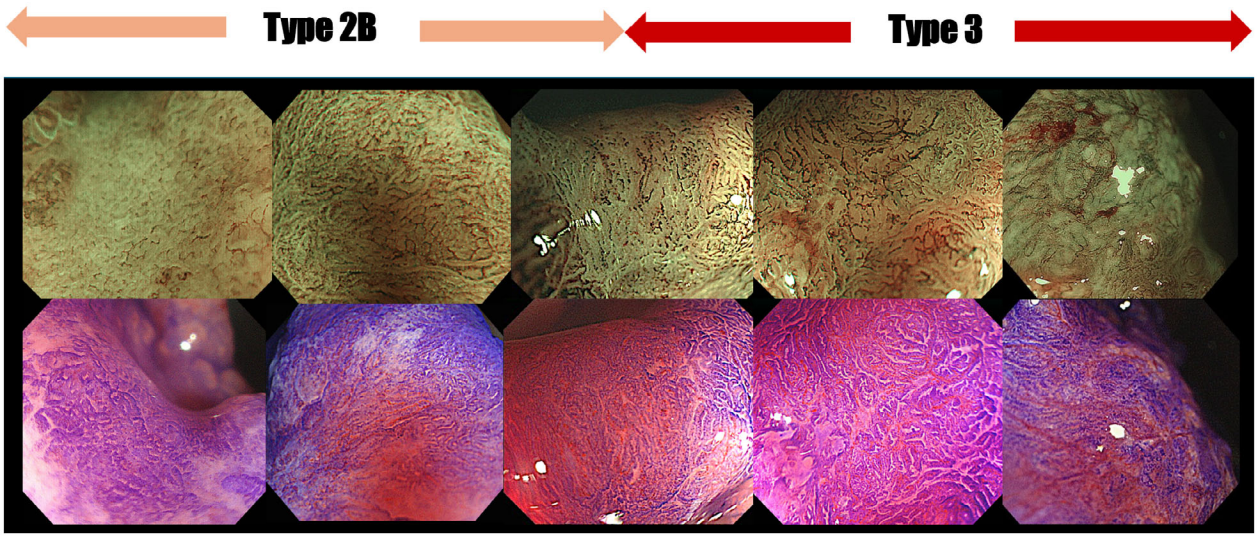

Figure 3 Optical findings for JNET type 2B and 3 laterally spreading tumors.

submucosal invasion in these cases were highlighted as reasons for considering attempting an en bloc resection if the time constraints and resources available at centers allow for it (Figs 1 and 2). One study evaluated a rectum-specific approach to 190 rectal LSTs in comparison to an EMR cohort of 240 lesions. The rectum-specific approach was based on lesion morphology and surface features. Piecemeal resection was performed in flat lesions without optical features of submucosal invasion and without a nodule >10 mm. ESD was performed in the remainder.[25] This approach resulted in 100% cure of all potentially curable superficially invasive SMIC. Thus centers with high expertise are equipped to safely attempt resection of rectal lesions using the methods they judge as most appropriate for each lesion.[25] All rectal LSTs should therefore be managed in expert centers where both ESD and EMR can readily be performed.

1.5. When a piecemeal resection is performed, endoscopists should aim to resect lesions in as few pieces as possible when it is safe to do so.

GRADE: Conditional recommendation, low quality evidence.

SA (44%), A (49%), N (2%), D (5%), SD (0%). SA + A: 93%.

One study showed that the risk of recurrence after EMR or ESD of >20 mm lesions increased with the number of pieces resected with 10% recurrence after three pieces and up to 25% recurrence after four pieces.[26] Local recurrence can originate from microscopic tissue remnants at the resection base and at the margins of the resection sites. A recent study using tissue sampling from the post-EMR resection base identified residual microscopic tissue in the margin of 19.5% of resection defects and within the base of 23.8% of resections.[27] Minimizing the number of resection pieces could theoretically reduce the number of regions within a resection base that do not completely overlap and thus are incompletely resected. Improving technique such as ensuring that resection pieces overlap to avoid creating bridges of residual lesion or ablating the resection base could also help in reducing recurrence.[28,29] Further, attempting to resect large pieces could potentially lead to increased adverse events, endoscopists should strive to resect larger pieces only when it is safe to do so. Piece size for cold snare resection is limited to a maximum of 8 mm as tissue transection fails in most instances above this size.

1.6. For lesions with suspicion of superficial (<1000 μm) submucosal invasion on optical evaluation (JNET 2B), an en bloc method for tissue resection should be performed rather than piecemeal.

GRADE: Strong recommendation, moderate quality evidence.

SA (68%), A (27%), N (3%), D (2%), SD (0%). SA + A: 95%.

Diagnosis of superficial submucosal invasion is difficult to differentiate from high-grade dysplasia without submucosal invasion on optical evaluation. A large retrospective study found 50.9% PPV for the diagnosis of high-grade dysplasia or submucosal invasion in JNET 2B lesions

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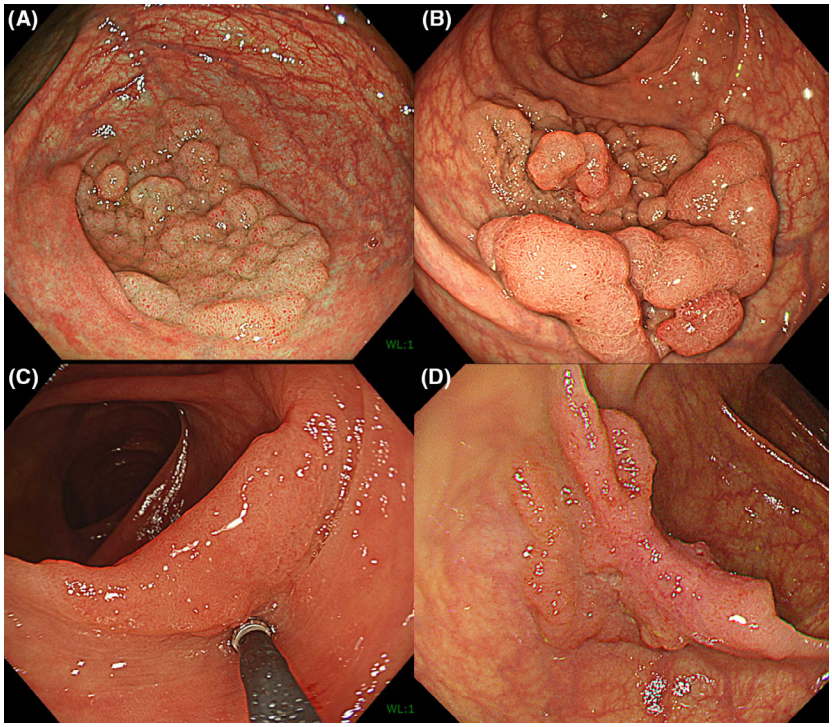

Figure 4 Examples of laterally spreading tumor classification. (A) Granular-homogenous; (B) granular-mixed; (C) nongranular-flat; (D) nongranular-pseudodepressed.

(Fig. 2).[12] In JNET 2B diagnosed lesions, superficial and deep submucosal invasion was present in 8% and 12%, respectively.[12] Another retrospective study found 30% PPV in JNET 2B lesions when performed by expert endoscopists.[13] However, 21% of JNET 2B lesions harbored deep submucosal invasion.[13] A multicenter prospective study found 8.6% superficial and 12.6% deep submucosal invasion in 397 JNET 2B lesions.[30] A retrospective study evaluating blue light imaging (BLI) and narrow band imaging (NBI) found 57.7% PPV for JNET 2B in the BLI group and 42.3% in the NBI group.[14] A total of 11.5% and 7.7% had superficial submucosal invasion in the BLI and NBI group respectively; 23.1% and 19.2% had deep submucosal invasion, respectively.[14] When there is reasonable suspicion of superficial submucosal invasion, an en bloc method of tissue resection should be performed to allow for adequate evaluation of horizontal and vertical margins for R0 resection and to adequately histologically assess the presence and depth of submucosal invasion. Techniques such as underwater EMR have been shown to increase en bloc resection rates; however, they are also limited in the maximum lesion size for which en bloc resection can be performed reliably.[31,32]

1.7. For lesions proximal to the rectum at increased risk of superficial (<1000 μm) submucosal invasion (nongranular; granular mixed type with large dominant nodule; demarcated depressed areas), an en bloc method for tissue resection should be performed rather than piecemeal.

GRADE: Strong recommendation, moderate quality evidence.

SA (54%), A (29%), N (0%), D (15%), SD (2%). SA + A: 83%.

En bloc resection of lesions at higher risk of submucosal invasion is important because it allows for adequate evaluation of horizontal and vertical margins for R0 resection. A large prospective study found rates of covert submucosal invasion ranging from 3.8% to 12.7% in proximal lesions presenting with nongranular or granular mixed morphologies.[10] In a large retrospective study of LSTs resected en bloc, 7.0% (nongranular, flat elevated), 12.8% (granular, mixed), and 39.7% (nongranular, pseudodepressed) of proximal LSTs were found to have submucosal invasion (Fig. 4).[11] A prospectively collected Italian database of granular mixed LSTs found 6.1% submucosal invasion rates in proximal lesions.[33] A third large cohort of Japanese patients undergoing ESD revealed 17.8%

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submucosal invasion in proximal nongranular large LSTs.[24] A total of 72.5% of submucosal invasion was superficial. Further, bulky proximal sessile non-LST lesions had 28.3% rate of submucosal invasion indicating that these lesions could also be considered for en bloc resection.[24] A meta-analysis showed 10.5% submucosal invasion in granular mixed-type LSTs, 4.9% in nongranular flat elevated, and 31.6% in nongranular pseudo-depressed LSTs.[34] Although this was not stratified by lesion location. Because these lesions have higher risk of submucosal invasion, the current expert consensus is to resect en bloc (Fig. 1). Other proposed strategies when en bloc resection is not feasible include full thickness or en bloc resection of high-risk areas (such as a large nodule) followed with piecemeal resection of low-risk areas. One analysis of 75 ≥ 25 mm nonlifting polyps undergoing hybrid endoscopic full thickness resection (EFTR)-EMR found 97.3% macroscopic complete resection.[35] There was a 11.4% rate of residual lesion at 8-month mean follow-up, all treated endoscopically.[35] In another retrospective study of 31 lesions treated with hybrid EFTR-EMR, clinical success rate was 89.5% and R0 resection was 89.7% among clinical successful interventions.[36] However, three studies evaluating the submucosal invasive pattern of LST granular mixed type found that between 56% and 83% of invasion can be found under the dominant nodule.[11,37,38] One study found 11.8% multifocal submucosal invasion in LST nongranular flat lesions and 46.9% in LST nongranular lesions.[11] The risk and benefits of these strategies should therefore be considered if they are attempted through shared decision-making with patients.

1.8. For lesions in the rectum at increased risk of superficial (<1000 μm) submucosal invasion (nongranular; granular mixed type with large dominant nodule; demarcated depressed areas), an en bloc method for tissue resection should be performed rather than piecemeal.

GRADE: Strong recommendation, moderate quality evidence.

SA (73%), A (24%), N (0%), D (3%), SD (0%). SA + A: 97%.

One large prospective study found consistently high rates (6.4–21.4%) of covert submucosal invasion in distal lesions presenting with granular mixed or nongranular morphologies.[10] Another large retrospective study found 19.8% (granular, mixed) and 20.5% (nongranular, flat elevated) submucosal invasion rates in LSTs.[11] A large database found 17.8% submucosal invasion rates in rectal granular mixed LSTs.[33] A large cohort of Japanese patients undergoing ESD revealed 29.4% submucosal invasion in rectal nongranular LSTs with 53.3% of these lesions with superficial submucosal invasion.[24] Further, bulky rectal sessile non-LST lesions had 22.6% rate of submucosal invasion indicating that en bloc resection may also be necessary for these lesions.[24] In one cohort study, attempting universal EMR in the rectum resulted in in 89% piecemeal resection and 5.7% curative resection in the 12% of lesions with superficial submucosal invasion.[25] Because the rates of submucosal invasion in these lesions are considerably high, an en bloc method for lesion resection should be performed to properly capture presence of submucosal invasion and to evaluate success of R0 resection (Fig. 4).

1.9. For lesions proximal to the rectum with suspicion of deep submucosal invasion on optical evaluation (JNET 3, Kudo V_N, Kudo V_I-severe with demarcated area), multidisciplinary evaluation should be performed to determine resection suitability and optimal modality.

GRADE: Strong recommendation, moderate quality evidence.

SA (54%), A (42%), N (2%), D (2%), SD (0%). SA + A: 96%.

Evaluation of lesions for risk of deep submucosal invasion has generally high specificity when performed by expert endoscopists; however, sensitivity can be low (35–58%) as many lesions such as bulky sessile lesions do not exhibit JNET 3 pattern at the surface.[13,39] A retrospective study of optically diagnosed lesions found 95.2% PPV and 96.6% negative predictive value for JNET 3 prediction of deep submucosal invasion.[12] A large retrospective analysis of prospectively collected data found 100% PPV and 98% negative predictive value for diagnosis of deep submucosal invasion in JNET 3 lesions when performed by experts (Fig. 3).[13] In both studies, 4% and 1% of JNET 3 lesions respectively had superficial submucosal invasion where endoscopic resection might have been curative. A prospective study found that Kudo V_I/V_N pit pattern was associated with an odds ratio of 79.4 (95% CI 24.6–256) for deep submucosal invasion; however, 8% of these lesions did not harbor deep submucosal invasion.[38] A large prospective multicenter Spanish study found >95% specificity in diagnosis of deep submucosal invasion using the NICE classification; however, the PPV was low (41%).[39] Additionally, a recent meta-analysis found that deep submucosal invasion is not an independent predictor of lymph node metastasis.[40] On the other hand, a recent analysis of more than 4600 cases of T1 cancer has identified a new risk of metastasis with the highest odds ratio of 2000 μm or deeper invasion.[41] One study evaluated performance of diagnostic ESD for patients with focal (<15 mm) deep invasive pattern on optical evaluation.[42] A total of 26.2% of resections were

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considered curative, potentially avoiding the need for unnecessary surgery.[42] The effect of magnetic resonance imaging or endoscopic ultrasound on diagnostic performance before performing diagnostic ESD on JNET 3 lesions has not yet been evaluated. In the case of noncurative resection, ESD samples can still provide high-quality pathology samples for diagnosis. EFTR has been performed for lesions with suspicion of submucosal invasion, with ≥80% technical success and ≥80% R0 resection in two large German and Dutch registries.[43,44] These methods do not prevent future definitive surgical treatment if definitive treatment is not achieved. Patients should be informed of the risks and benefits before resection is performed. Close follow-up must then be undertaken for patients with R0 resection of ≥Sm2 cancers. Because there is a lack of long-term data on nonsurgical approaches for these lesions, no formal recommendation on a specific technique can be made other than the need for discussion within colorectal multidisciplinary committees.

1.10. For lesions with suspicion of deep submucosal invasion on optical evaluation (JNET 3, Kudo V_N, Kudo V_I-severe with demarcated area) in the lower rectum and with staging negative for lymph node/distant metastasis, an en bloc method for tissue resection capable of resecting deeper tissue planes (e.g., endoscopic intermuscular dissection, peranal endoscopic myectomy) can be considered in patients declining surgical resection after multidisciplinary team evaluation for resection suitability.

GRADE: Conditional recommendation, low quality evidence.

SA (29%), A (59%), N (10%), D (0%), SD (2%). SA + A: 88%.

Total mesorectal excision (TME) has been the mainstay treatment for rectal cancer but can however be associated with adverse events and incomplete resection.[45,46] Transanal minimally invasive surgery is another treatment option for full thickness resection of rectal lesions. However, a meta-analysis showed lower quality mesorectal specimens and lower lymph node yields when completion TME is performed, likely because of fibrosis in the mesorectal plane.[47] Another meta-analysis showed 4% recurrence after completion TME when performed after local excision of rectal cancers with high risk features.[48] Novel endoscopic interventions targeting deeper resection planes without breaching into the mesorectum are being developed such as endoscopic intermuscular dissection (EID)/peranal endoscopic myectomy and endoscopic adventitial dissection. Only one study is currently available evaluating EID for rectal lesions, showing 96% technical success, 81% R0 resection, and 45% curative resection.[49] One study evaluated performance of diagnostic ESD for patients with focal (<15 mm) deep invasive pattern on optical evaluation achieved 26.2% curative resection.[42] These methods do not prevent future definitive surgical treatment if R0 resection is not achieved. However, these interventions must be discussed within colorectal multidisciplinary committees taking into account the location of the lesion (anterior vs. posterior) and local expertise (Fig. 1). Patients should be informed of the risks and benefits before resection is performed. One large study in patients with submucosal invasive CRC found higher risk of recurrence for rectal cancers treated with endoscopic resection compared to the proximal colon.[50] A recent analysis of more than 4600 cases of T1 cancer has also identified a new risk of metastasis with the highest odds ratio of 2000 μm or deeper invasion.[41] Close follow-up must therefore be undertaken for patients with R0 resection of cancers with ≥2000 μm submucosal invasion depth.

1.11. When an en bloc resection is necessary, ESD should be performed rather than EMR if en bloc resection is difficult to achieve with EMR.

GRADE: Strong recommendation, low quality evidence.

SA (66%), A (34%), N (0%), D (0%), SD (0%). SA + A: 100%.

1.12. When an en bloc resection is necessary, ESD should be performed rather than EMR in the presence of submucosal fibrosis.

GRADE: Strong recommendation, low quality evidence.

SA (46%), A (42%), N (0%), D (10%), SD (2%). SA + A: 88%.

1.13. When an en bloc resection is necessary, ESD should be performed rather than EMR when chronic inflammation is present (ex: ulcerative colitis).

GRADE: Strong recommendation, low quality evidence.

SA (46%), A (44%), N (7%), D (2%), SD (0%). SA + A: 90%.

1.14. When ESD is required to achieve en bloc resection, adequate reimbursement mechanisms should be available given the longer procedure time and technical challenges associated with the technique with clinical benefit.

GRADE: Strong recommendation, moderate quality evidence.

SA (71%), A (29%), N (0%), D (0%), SD (0%). SA + A: 100%.

There are many factors that can increase the difficulty of performing EMR. The presence of submucosal fibrosis can render EMR very challenging with the need to use adjunct methods such as forceps avulsion to achieve lesion

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clearance.[51] Resecting these lesions en bloc such as in the case of suspected cancer in patients with inflammatory bowel disease may not be possible with EMR. One study with 111 lesions with submucosal fibrosis showed 78.3% en bloc resection with 10% perforation rate.[52] Another case series of nine lesions with submucosal fibrosis achieved en bloc R0 resection in seven lesions.[53] In a larger multicenter cohort of 32 lesions of patients with inflammatory bowel disease, submucosal fibrosis was observed in 97% of lesions and en bloc resection was achieved in 91% with only one recurrence at follow-up.[54] There were no cases of perforation after ESD.[54] A retrospective study including two Japanese referral centers found 100% en bloc resection and 76% R0 resection for 25 lesions in patients with ulcerative colitis.[55] Only one perforation occurred in that cohort.[55] The utilization of traction devices may aid in improving ESD safety and success in the presence of submucosal fibrosis.[56–58] An attempt with ESD might therefore be preferable to the risks associated with surgery in patients with endoscopically curable lesions that may prove challenging or impossible with EMR. There should be adequate reimbursement mechanisms in place given the increased technical difficulty and time required to perform ESD or EID compared to EMR. In the setting of submucosal fibrosis when en bloc resection is not necessary, which constitutes the majority of encountered lesions, EMR can prove highly effective when accompanied with techniques such as cold forceps avulsion with adjuvant snare tip soft coagulation. Large studies have shown that these techniques can achieve successful lesion clearance in the vast majority of cases with no need for subsequent surgery.[51,59] Underwater EMR could also be a potential option to improve snare capture of the lesion in the presence of fibrosis.

DISCUSSION

THERE HAS BEEN a lack of clear international consensus on many aspects of management of LSTs. Differing regional practices and guidelines have led to the emergence of contrasting paradigms in lesion management. The current proposed statements underline the importance of adequate training for LST diagnosis and resection. They also highlight the importance of morphology-specific estimation of SMIC risk. Flat LSTs can be accurately characterized and SMIC risk correctly estimated in the vast majority of cases. A trend toward performing en bloc resection in a subset of bulky lesions that may be at risk of containing covert SMIC but do not express surface features of the same, particularly in the rectum, has emerged. The consensus also highlights the increasing importance of multidisciplinary management of advanced lesions and collaboration between endoscopists, pathologists, and surgeons to provide management that is tailored to each patient's individual circumstances.

There have been considerable advances in the management of complex lesions and controversies remain around topics where new data are emerging such as the significance of deep submucosal invasion in T1 CRCs without other high-risk features or the combination of en bloc or full thickness resection of suspicious areas (such as large nodules) combined with piecemeal resection of the remaining lesion. Less invasive techniques such as the advent of cold EMR, has sparked interest in studying their recurrence rates in LSTs with or without margin ablation. On the other hand, improvements in endoscopic techniques have pushed third space endoscopy toward the intermuscular and serosal planes. With these emerging techniques, training and adequate histologic evaluation and follow-up remain at the forefront of importance to ensure patient safety. The highly controversial nature of the topic of this consensus is evidenced by the fact that the majority of statements did not reach consensus after the first round of voting, which prompted significant modifications based on the anonymous comments provided. Some statements such as resection of granular homogenous rectal lesions were the subject of strong and healthy debate.

In conclusion, we present an international consensus on the management of large nonpedunculated colorectal polyps. Given the fast-paced and changing nature of research involving these lesions, we hope that this consensus can be used as a basis on which to guide current practice and as a template highlighting future areas of research. Future updates are planned.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Figure S1 Distribution of the expert voting panel by years of practice.

Figure S2 Geographic distribution of the expert voting panel (continent).

Figure S3 Distribution of the expert voting panel by sex.

Figure S4 Distribution of the expert voting panel by profession.

Table S1 Terminologies used by different societies in the columnar epithelium lined gastrointestinal (GI) tract. AJCC, American Joint Committee on Cancer; HGD, high-grade dysplasia; WHO, World Health Organization. *Pathologists outside Japan have difficulty in separating HGD from carcinoma in situ because the required criteria are missing in the Western literature.

Text S1 Consensus statements supplemental section.

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