

Peer Review File

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Review comments

Reviewer A

I read with great interest the ESD Review.

Very well written, but I have a few questions and corrections. Thank you in advance.

1. Colorectal ESD

P4, Even though these lesions are considered to have a high risk, the risk of covert invasive cancer is estimated to be 3.7%–15.3% (16).

Comment)

In Japan, where JNET and Pit diagnoses are routinely performed, the diagnostic accuracy is extremely high when SM2 is diagnosed reliably by endoscopy, and ESD for T1b cancer is usually not performed only when SM1 or SM2 is in doubt.

Please provide an additional explanation as this is misleading.

Reply: Thank you for this comment - we recognize that in Japan JNET and pit diagnoses are routinely performed, but in western countries pit pattern diagnosis is not routine practice. In Western countries, it is not standard of care for us to perform ESD on T1B lesions. Given this is a review of standard U.S. practices for ESD, this is what we decided to focus on despite slight disparities in practice pattern.

P4, line 90

the periphery of the lesions, 3-5 mm outside the lesion borders, is marked circumferentially with thermal dots using the tip of the ESD knives.

Comment)

I believe that marking is not usually performed in the colorectum. I think marking would be done only when the boundary is unclear in 0-IIc or LST-NG.

Reply: Thank you for the comment and this is a good point - we would not necessarily need to mark all the lesions if the boundaries are clear. We have modified the language to reflect that this is optional.

Following submucosal injection, a mucosal incision is performed circumferentially using a specialized ESD knife. See Table 1 for a list of commercially available devices for colorectal ESD (21–28).

⇒Comment)

Also, recently, partial incision => SM dissection => partial incision => SM dissection repeated, or bridge formation method (similar to PCM) is the most common method for colorectal ESD, instead of full circumferential resection first.

Please comment on this.

Reply: Although the bridge method is very interesting, the only literature that I could find on pubmed on the bridge method is Abe et al. 2023: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10099846/#den14453-bib-0005>, that describe the technique but does not comment necessarily on outcomes. Although they cite in the study they have treated 1300 patients, the reference they used does not comment on outcomes of those patients nor does it reference the bridge technique at all. Given the lack of published literature on this topic, we feel it would be better served to not comment on the bridge technique at this time until additional literature is published on this technique. If there are other more extensive literature on the BFM that we are not aware of, such as in the Japanese literature, please let us know and we are happy to reference it.

P5 line 109-110

Coagulation with a soft coagulation current is then performed using hemostatic forceps on any exposed, non-bleeding, visible vessels or areas of bleeding (35).

⇒Comment) I think it is not common to coagulate the exposed vessel too much in the colon, except usually in the rectum.

Reply: In our institution we do perform coagulation even in exposed vessels in the proximal colon, in particular those with large penetrating arteries, and there is literature on this. Given this may not be routine at other practices, we have toned down the language and added "at the endoscopist's discretion" in the main text.

P7, 155- p98, 157,

Hybrid ESD and Precutting EMR (not precut EMR) should use the same terminology as JGES GL.

『Similarly, a technique wherein snaring is carried out without dissecting the SM layer after incising the circumference of the lesion alone, by using a knife for ESD or the tip of a snare, is defined as “precutting EMR”.¹¹⁴ Finally, a technique wherein the SM layer is dissected and snaring is carried out after the ESD procedure (mucosal incision + SM dissection), by using a knife for ESD or the tip of a snare, is defined as “hybrid ESD” 』

Reply: Thank you for the comment and clarification. We have changed all mentions of the word "precut" to "precutting" to meet the same terminology as JEGS GL.

P8, 167

1.4 Outcomes

Reply: Not sure what this comment is referencing - the title 2.4 outcomes should be correct

P9, 182

on multivariable analysis,

⇒Comment) on multivariate analysis,

Reply: Thank you - this has been changed to multivariate

P9, 193

Ref. (51–57).

⇒Please also add complication rate data from a recent Japanese multicenter prospective study.

Kobayashi N, Takeuchi Y, Ohata K, et al. Outcomes of endoscopic submucosal dissection for colorectal neoplasms: Prospective, multicenter, cohort trial. *Dig Endosc.* 2022 Jul;34(5):1042-1051.

Results: ESD was performed for 1883 patients (1965 lesions). The mean procedure time was 80.6 min; en bloc and curative resections were achieved in 1759 (97.0%) and 1640 (90.4%) lesions, respectively, in epithelial lesions ≥ 20 mm. Intra- and postprocedural perforations occurred in 51 (2.6%) and 12 (0.6%) lesions, respectively, and emergency surgery for adverse events was performed in nine patients (0.5%).

Reply: Thank you for the comment and reference. We have added an additional part reflecting this reference. We separated it from the rest of the references as it provided additional info on intra- and post-procedure perforation rate and emergency surgery risk. "...(51-57), with one study out of 1883 patients separating intra- and postprocedural perforation rate at 2.6% and 0.6% respectively as well as 0.5% patients requiring emergency surgery post procedure (58)."

P9, 195

1.5 Interpretation of Pathological Findings

Could you add that it is important for the endoscopist to advise the pathologist on where to cut the resected specimen and how many mm wide to divide the tissue?

Reply: In the US, we do not routinely advise pathologists and have not run into any particular issues. We added a sentence in section 2.5 and mentioned that "the ESD specimens should be appropriately processed for accurate histopathological diagnosis as described in the Japanese ESD guideline (69)."

P20 Table 1

IT knife 2 is a device for gastric ESD. Please change to IT knife nano for colorectal ESD

Reply: Thank you for the correction - it has been made.

Reviewer B

Decisive comments to editors: The paper is well written and of interest to the community, especially to interventional endoscopists.

Comments to the authors:

General comments:

It is a very interesting review that intends to support best practice in endoscopic therapeutics for the removal of early colorectal neoplasia by ESD. I enjoyed reading this paper. The study includes a meticulous review of clinical application of colorectal ESD, that will increase the interest of endoscopists in the West. Congratulations for this review. Several constructive comments below.

Specific comments:

ABSTRACTS:

38 line: "...and that are difficult to remove en bloc due to submucosal fibrosis ". I do not agree with this sentence. Underwater EMR has emerged as an alternate technique for en-bloc resection of larger lesions, including for the removal of lesions with submucosal fibrosis. Probably authors should change to (or similar): "or lesions for which previous EMR had failed or was not possible. Please rephrase

Reply: Thank you for this comment. We appreciate the suggested text and have incorporated in our edits to the PDF file.

TEXT:

88 line: "Figure 3" Please ,this typo should be changed (Figure 2).

Reply: Yes thank you will adjust - I believe our figure order was swapped slightly on the revised version hence the discrepancy.

91 line: " ... circumferentially with thermal dots using the tip of the ESD knives"

Most of the Japanese expert authors do not recommend routine marking for CR-ESD. I believe that this protocol would help us to facilitate resection where the procedure is of a prolonged duration or where vision may be compromised. Please rephrase.

Reply: Thank you for this comment - another reviewer made a similar suggestion. We have modified the language to reflect that this step is optional for boundaries that may be unclear and does not need to be routinely performed for all.

133,134 lines: "However, this difference was not observed in a randomized controlled 134 trial (RCT), as en bloc and R0 resection rates in both groups were 100% (41)".

I suggest including detailed information on the efficacy and safety of the underwater method with the creation of a submucosal pocket described in this study. In addition, the underwater method improved dissection speed and procedure time compared to standard ESD. Please rephrase.

Reply: Thank you for this comment. Details regarding the cited study have been included.

166 line: 2.3 Variations of the ESD technique.

I do appreciate the authors efforts to collect the data of variations of the ESD technique. However, the authors do not present data of other strategies. Please complete this review with a paragraph describing the underwater ESD technique. It could be interesting to discuss the role of other techniques in difficult situations (severe fibrosis, fatty tissue or tattoo in the submucosal layer). Cite for example:

Tattoo:

- Successful endoscopic submucosal dissection of colon cancer with severe fibrosis after tattooing. Clin J Gastroenterol. 2017 Oct;10: 426-430. doi: 10.1007/s12328-017-0770-z. Epub 2017 Aug 7. PMID: 28785991.

- Tissue retractor system-assisted endoscopic submucosal dissection of a large rectal tumor with significant fibrosis from direct tattooing. VideoGIE. 2019 Jan 11;4(2):84-86. doi: 10.1016/j.vgie.2018.10.008. PMID: 30766951; PMCID: PMC6362363.

Reply: Included this as part of the traction ESD technique

- "Trans-tattoo in immersion" method for the removal of a recurrent, previously tattooed adenoma using endoscopic submucosal hydrodissection. Endoscopy. 2020 Nov;52(11):E408-E410. doi: 10.1055/a-1147-1206. Epub 2020 Apr 24. PMID: 32330953.

Reply: This one seems to be similar to underwater ESD so deferred to comment below

Underwater:

- Usefulness of underwater endoscopic submucosal dissection in saline solution with a monopolar knife for colorectal tumors (with videos). Gastrointest Endosc 2018; 87: 1345–1353. doi:10.1016/j.gie.2017.11.032. PMID: 29242059

- "Underwater" endoscopic submucosal dissection: a novel method for resection in saline with a bipolar needle knife for colorectal epithelial neoplasia. Surg Endosc 2018; 32: 5031–5036. doi:10.1007/s00464-018-6278-x

- Novel approach to endoscopic submucosal dissection of a cecal lesion with nonlifting sign by submucosal fatty tissue with use of selective-regulation high-pressure water-jet method and immersion in saline solution. VideoGIE 2020; 5: 116–119. doi:10.1016/j.vgie.2019.11.009

- Safety and efficacy of water pressure endoscopic submucosal dissection for colorectal tumors with submucosal fibrosis (with video). Gastrointest Endosc. 2021 Sep;94(3):607-617.e2. doi: 10.1016/j.gie.2021.03.026. Epub 2021 Mar 30. PMID: 33798542.

Reply: Thank you for this comment and bringing to our attention the underwater ESD Technique. We have included a paragraph on this to highlight the technique with citations as listed.

163 line: As the authors know, it is difficult to obtain the necessary technical skills in colorectal EDS in western countries. The use of the snare to finish the ESD is an interesting discussion point. It should also be noted that most of the time hybrid ESD is a rescue technique that is applied if difficulties are encountered during ESD (mostly

during the learning curve) and most data report poorer technical outcomes than conventional ESD. Finishing the ESD with snare is a necessary alternative in daily practice and is often pragmatic in situations involving a high risk of complications. Please include in this paragraph with the different aspects of training for colorectal ESD, for example

- Efficacy of hybrid endoscopic submucosal dissection (ESD) as a rescue treatment in difficult colorectal ESD cases. *Dig Endosc* 2017; 29: (Suppl. 02): 45– 52.

doi:10.1111/den.12863

- Safety and efficacy of colorectal endoscopic submucosal dissection by the trainee endoscopists. *Dig Endosc* 2012; 24 (Suppl 1):154–158.

- Risk factors for conversion to snare resection during colorectal endoscopic submucosal dissection in an expert western center. *Endoscopy* 2019; 51:152–160

- Feasibility and learning curve of unsupervised colorectal endoscopic submucosal hydrodissection at a Western Center. *Eur J Gastroenterol Hepatol* 32:804–812.

<https://doi.org/10.1097/MEG.0000000000001703>

-Learning curve of endoscopic submucosal dissection (ESD) with prevalence-based indication in unsupervised Western settings: a retrospective multicenter analysis. *Surg Endosc* 37, 2574–2586 (2023). <https://doi.org/10.1007/s00464-022-09742-5>

Reply: Thank you for this insightful comment. We have included an additional sentence to reflect these points in the specified paragraph with citations

194 line (2.4 Outcomes):

As we know, a third of the world’s population is currently overweight or obese. These patients may be more at risk of presenting submucosal fatty tissue in colon during ESD procedure. This phenomenon may be more relevant in West, given obesity is prevalent in the occidental population, such as the US. Colorectal ESD in obese patients can be technically challenging. Please include a paragraph on the impact of obesity on the performance of colorectal ESD.

Reply: Thank you so much for this comment and the citations. We dedicated a few sentences into the impact of obesity in the specified section with citations.

References:

- Dual red imaging maintains clear visibility during colorectal endoscopic submucosal dissection. *Dig Dis Sci* 2019; 64:224–231.

- The impact of submucosal fatty tissue during colon endoscopic submucosal dissection in a western center. *Eur J Gastroenterol Hepatol*. 2021 Aug 1;33(8):1063-1070. doi: 10.1097/MEG.0000000000002146. PMID: 33867446.

- Impact of obesity in colorectal endoscopic submucosal dissection: single-center retrospective cohort study. *BMC Gastroenterol* 21, 74 (2021).

<https://doi.org/10.1186/s12876-021-01652-5>

201 line: Please update reference 58 (Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy Guideline – Update 2022. *Endoscopy* 2022; 54: 591–622. doi:10.1055/a-1811-7025)

Reply: Thank you - updated

400 line: Table 1. Hybridknife. These knives have a central capillary that allows penetration of the regulated pressure waterjet through the mucosa and lifting of the submucosa without the need for needle puncture. Please include that Hybridknife has injection capability and in brackets (regulated pressure water jet)

Reply: Comment included into table

Reviewer C

Thank you very much for taking the time to submit your expertise and knowledge to contribute to this series. I very much enjoyed this review for its content, structure, and flow. The article will be a valuable resource to gastroenterologists and surgeons and addresses key elements required to understand the application of ESD in the colon.

A short dialog on safety helps incorporate the reviewer's suggestion (hybrid ESD w/snare, and conversion to EMR as "salvage rescue"). Essential for safe ESD is good tissue plane exposure, which is central to the incision-dissection, further incision then dissection approach (versus circumferential ESD and pocket).

*Please considering adding to your content the importance of recognizing the dependent (i.e., gravity) field when performing ESD. Gravity can guide the stepwise approach to ESD, including when turning the patient may expedite safe resection. Even with retraction devices, dependent areas will still pool fluid—which can affect exposure during ESD. Perhaps the water pressure/underwater ESD method is beneficial in dependent planes to maintain clear visualization and "float" the mucosal lesion upwards for exposure without turning the patient and without using a retraction device.

Reply: Thank you for this comment - this was also outlined by some of the other reviewers. We have dedicated a separate paragraph on the underwater ESD technique under the variations section with discussion as well on recognizing the dependent field when performing EGD.

Thank you for mentioning areas of increased difficulty for ESD (flexures, IC valve) due to unstable scope position. Please emphasize the importance of maintaining a straight scope position and describe the potential advantages of a pediatric colonoscope for colon ESD (maneuverability, retroflexion).

Reply: Thank you for this comment - we included a sentence in the paragraph introducing "variations of the ESD technique" to discuss this point

Consider briefly mentioning assist devices to maintain scope stability (overtube such as Pathfinder).

Reply: Thank you for the comment. We considered including this but given all the other major categories decided against it as to not overwhelm the reader with examples

Consider mentioning the Ovesco ESD knife and assist device for ESD.

Reply: Thank you for this comment. Unfortunately the Ovesco ESD knife is not commercially available in the US hence why we did not mention it. On review of our list though we did find that we failed to mention the Medtronic ESD knife and will include in our table. We have reached out to Medtronic for permission to include this in the book chapter.

<https://www.medtronic.com/covidien/en-us/products/therapeutic-endoscopy/prodigi-multi-functional-esd-knife.html>

Congratulations again on a well-written paper.