Reviewer 00504445

Confidential comments to the Managing Editor

Thank you for your invitation of reviewing the paper submitted to World Journal of Gastrointestinal Endoscopy. In the present study, the authors presented Colorectal endoscopic submucosal dissection: "For safe and successful procedures" recent advances and perspectives in techniques using various devices. This paper is well-written and is useful for endoscopists who try to perform ESD. I suggest this article is valuable for the publication of WJGE. I have several suggestions for this paper as it is accepted by lots of endoscopists in the world.

Comments to the Author

Thank you for your invitation of reviewing the paper submitted to World Journal of Gastrointestinal Endoscopy. In the present study, the authors presented Colorectal endoscopic submucosal dissection: "For safe and successful procedures" recent advances and perspectives in techniques using various devices. This paper is well-written and is useful for endoscopists who try to perform ESD. I have several suggestions for this paper as it is accepted by lots of endoscopists in the world.

We would like to thank you very much for your careful review of our manuscript, for the high evaluation that you provided, and for your important

and valuable suggestions to help us improve our manuscript. We believe our revised manuscript has been significantly improved on the basis of your expert input. Our responses to your suggestions and the changes that were made to the manuscript are provided below.

1) The length of paper is a little long. 10-20% reduction of the length are useful for better understanding of readers.

Thank you very much for this helpful suggestion. We have shortened our manuscript as much as possible as you requested, but it was impossible to reduce the length by 10%–20%. Although we deleted a substantial number of words, phrases, and sentences, we had to add additional text, tables, figures, and references to respond to and appropriately address your comments. In addition, our manuscript includes wide-ranging topics relevant to colorectal ESD because the journal editors invited us to submit our manuscript without a word limit. To help readers more easily understand the content of our article, we believe it would be difficult to further reduce the length of the text in our revised manuscript. We sincerely hope that you can understand our opinion.

2) In the abstract, authors used the word “mucosal flap”. I think the explanation of “mucosal flap” should be described in the abstract.

Thank you very much for this valuable comment. As you described, we have modified the sentence in the abstract as follows. “To prevent complications such as perforation and unexpected bleeding, it is crucial to ensure good visualization of the submucosal layer by creating a mucosal flap, which is an exfoliated mucosa for inserting the tip of the endoscope under it.”

3) Authors indicated the importance of mucosal flap. Making schemas about mucosal flap are expected for better understanding of readers.

Thank you very much for this excellent suggestion. As you recommended, we have created a schema of the mucosal flap to aid the readers’ understanding. Please refer to the new Figure 3.

4) In the section named “Indication for colorectal ESD”, uses of pit pattern and NBI should be written.

Thank you very much for this valuable comment. As you described, pit pattern and image-enhanced endoscopy, including NBI or BLI, are useful in determining the indication for colorectal ESD. We have added the following sentence and references to the section INDICATION FOR COLORECTAL ESD. “Magnifying chromoendoscopy for pit pattern observation [23] and magnifying image-enhanced endoscopy (narrow band imaging [24,25] or blue laser imaging

[26], etc.) are useful for preoperative differential diagnosis of adenoma, intramucosal cancer, and submucosal invasive cancers."

5) In the section named "preparation", general method for appropriate preparation should be also written though authors wrote their original methods.

Thank you very much for this important suggestion. We have not only quoted the article written by Prof. Yahagi, who is an authority on colorectal ESD (reference 11) but we have also added a few procedures that have been adopted at our institution, as you expected. We have deleted and modified the relevant sentences as follows and have also quoted an article written by endoscopists from Western nations.

"Bowel preparation is required for adequate visualization of the operative field and as prophylaxis against bacterial peritonitis in case of perforation. Patients are restricted to a low-fiber diet on the day before colorectal ESD and are instructed to orally consume 10 mL picosulfate after the last meal on the day before the procedure. Two–four liters of an electrolyte solution is orally administrated before the procedure [11,29]."

6) In the section named "selection of endoscope", H290I is wrong and HQ290I is correct.

Thank you for your careful and detailed reading of our manuscript. We selected either PCF-290HI or CF-H290I but not CF-HQ290I. CF-H290I is thinner and newer than CF-HQ290I; Therefore, we guess that CF-290HI is more suitable for ESD than CF-HQ290I. Please refer to
http://www.info.pmda.go.jp/ygo/pack/180590/224ABBZX00107000_A_01_04/
for support of our opinion.

7) Authors used the word “distal attachments” and “hood”. I think the word should be unified.

Thank you very much for this valuable comment. As you described, we have combined these terms as much as possible. We primarily use “distal attachment” in this manuscript; however, we still use “transparent hood” only in the explanation of “ST-hood” because of its trade name.

8) Authors should write the detain setting of ESG100 or ESG400 who are made by Olympus. Because some countries use only Olympus’s high frequency generators.

Thank you very much for this valuable comment on high-frequency generators.

As you described, the settings for multiple high-frequency generators need to be defined to help expand the worldwide use of ESD, although we suspect that VIO300D is a comparatively an excellent instrument. Furthermore, we have also described the settings for ICC-200, which is less expensive than VIO300D. To address your comment, we have added the following sentence and modified Table 1.

"ICC-200 (Erbe) and ESG-100 (Olympus) is also used for colorectal ESD. The settings on each instrument when using short-needle knives (FlushKnife BT, DualKnife) and hemostatic forceps (FD-410LR, FD-411QR; Olympus) are shown in Table 1 [11,50,59]."

9) In the section named "strategies for improving safety and efficacy of ESD", authors used the word "proximal aspect" in the first sentence. The meaning of "proximal aspect" is used for anal side in this part. But, I think this is confusing. "Proximal" may be changed "anal".

Thank you very much for your insightful comment. As you described, the readers may misunderstand the meaning of "proximal". Thus, we have provided explanations for the two ways by which the procedure is initiated, namely "from the anal side in a forward direction or from the oral side in retroflexion" at the beginning of the section "Strategies for improving safety and efficacy of ESD."

Conversely, the method selection used by endoscopists largely depends on the

institution's procedures and lesion location. Thus, we added "In either case, it is important to start dissecting the submucosa immediately proximal to the tip of the endoscope to avoid complications, such as perforation and unexpected bleeding, caused by blind procedures." after we describe the preceding two approaches.

10) Authors enhanced the usefulness of the clip flap method. I think they should write which hood is better for the clip flap method.

Thank you very much for this helpful suggestion.
As we described in our manuscript, we predominantly use a slightly tapered-type distal attachment, but various types of distal attachments can be used with the clip-flap method. Therefore, we added the following sentence "Furthermore, various types of distal attachments, including a tapered type, can be used in the clip-flap method".

11) Authors may describe the schedule of patients receiving colorectal ESD. When do patients start oral takes? When do they discharge?

Thank you for requesting these important points of clarification. Your suggestions will be helpful for the readers of this article. We have added the following sentence and references to "Preparation and Oral intake" in the

section METHOD FOR SAFE AND SUCCESSFUL ESD:

"In contrast, no food or drink is allowed on the day of the procedure or the following day. Provided that there are no signs or symptoms of complications, patients will begin drinking water on day 1 and have light meals (rice porridge) on day 2. Meals are upgraded to normal food with alcohol excluded from day 2 until day 3–5 or the date of hospital discharge [30-32]."

In addition, we also referred to the association between hospital stay and adverse events, including electrocoagulation syndrome after ESD in the section "SUCCESS RATES AND COMPLICATIONS." The revisions are as follows.

"Abdominal pain or fever due to electrocoagulation syndrome after ESD is occasionally observed, particularly in the proximal colon, and when conservatively managed [96]. The occurrence of adverse events may cause an extension in hospital stay [31,32,97]."

12) In the section named "Success rates and complications", authors should write the recurrence rates of ESD compared to the rates of EMR.

Thank you very much for this important suggestion. As you mentioned, not only for short-term outcomes but also for long-term outcomes, recurrence rates following ESD compared with the rates after EMR are important for demonstrating ESD efficacy. We have added the following sentence to the text and have modified Table 3 to include the recurrence rates of ESD compared with the rates of EMR. "In contrast, some studies have compared the local

recurrence rates after EMR and ESD for large colorectal tumors (Table 3) [91-95]. Those studies demonstrated that local recurrence rates after ESD were significantly lower than after EMR because of the high *en bloc* resection rates with ESD despite the larger tumor sizes compared with EMR [91,92,94,95]. Oka *et al*. [95] reported that piecemeal resection was the most important risk factor for local recurrence regardless of EMR or ESD in a large multicenter prospective study. Most local recurrences of mucosal lesions may be addressed with additional endoscopic treatment; however, close follow-up colonoscopy is required to detect local recurrence after piecemeal resection [91-95], even with ESD."

Reviewer 01469554

We would like to thank you for reviewing our manuscript and for the helpful comments that you shared. We believe our revised manuscript has been significantly improved by the revisions that you suggested. Our responses to your comments and the revisions that were made to the manuscript are provided below.

1) As EMR in Piecemeal resection 20 mm or more lesions can tolerating. Please cite attached paper, and add adaptation, please.

Thank you for this insightful comment. As you described, we have modified some sentences and added the sentence regarding EMR in the section titled INDICATION FOR COLORECTAL ESD. In addition, we have now cited the attached article. As you recommended, we expanded and added greater detail to the description of the indication for colorectal ESD as follows.

"Basically, the indications for ESD are colorectal tumors for which endoscopic *en bloc* resection is required but *en bloc* resection with EMR is difficult to apply. The primary objective lesions are large colorectal tumors, such as the laterally spreading tumor non-granular type (LST-NG) or the laterally spreading tumor granular type (LST-G) with a large nodule [20,21], which are suspected to be intramucosal or with slightly invaded submucosal cancers >20 mm in diameter

in the preoperative examinations. Large, protruding lesions are also indications for colorectal ESD [18,19]. However, an abundance of caution is required to treat large protruding lesions because even experienced endoscopists sometimes cannot avoid discontinuation of submucosal dissection due to severe submucosal fibrosis and retracted muscle [22]."

"In contrast, the technical simplicity of EMR can permit its utilization for colorectal tumors >20 mm in diameter when the preoperative diagnosis is adenoma or mucosal cancer in adenoma [18-20], although piecemeal mucosal resection includes the problem of a high local recurrence rate [20]. Magnifying chromoendoscopy for pit pattern observation [23] and magnifying image-enhanced endoscopy (narrow band imaging [NBI] [24,25] or blue laser imaging [BLI] [26], etc.) are useful for preoperative differential diagnosis of adenoma, intramucosal cancer, and submucosal invasive cancers."

2) Add on in what way are (including use of glucagon etc) for patients whom butylbromide can not use to preparation.

Thank you very much for your valuable suggestion. As you pointed out, it is very important to reduce bowel movements and ensure the stability of the operative field, even with patients for whom butylbromide scopolamine is contraindicated. Intravenous administration of glucagon is useful for such patients except when this too is contraindicated. In addition, previous studies have reported that intraluminal peppermint oil reduces colonic spasm.

Therefore, we have added the following sentence to the manuscript.
"Administration of intravenous glucagon [39] or intraluminal peppermint oil [40] may be useful for patients who are contraindicated for scopolamine."

3) Please more emphasize usefulness of carbon dioxide.

Thank you very much for this valuable suggestion. As you mentioned, the CO_2 insufflation system is extremely useful for colorectal ESD. Therefore, we have modified the relevant paragraph as follows and have also added supporting references.
"Use of a carbon dioxide (CO_2) insufflation system (UCR; Olympus Co., Tokyo, Japan) is extremely helpful for reducing the patient's discomfort and risk of peritonitis in case of perforation [35-37]. Excessive air present during the procedure decreases the endoscope maneuverability, but carbon dioxide can be quickly absorbed [35-37]. Yoshida et al. reported that CO_2 insufflation during colorectal ESD was safe even for patients with obstructive ventilator disturbance [38]."

4) This is a review paper, so as a major devise, please add B-knife in figure2. Mucosectome , too, in addition to figure2.

Thank you for these helpful comments. We agree that both B-knife and

Mucosectom are important endoknives for colorectal ESD. A photograph of a Mucosectom-short blade was previously included in Figure 2 of the original manuscript. To address your concern, we have added two additional photographs of a Jet B-knife and a Mucosectom-long blade to Figure 2.

5) MucoUp is at being hyaluronate solution of 0.4% those that is sold in only Japan. So, please note if using in overseas, another solution, after coordinated the concentration of hyaluronate solution, for example Suvenyl, and/or Artz are useful.

Thank you very much for your excellent suggestions. As you mentioned, it is important to show several injections to the many worldwide readers of this journal. Therefore, we have modified the relevant paragraph as follows.
"Saline, 0.4% sodium hyaluronate solution (MucoUp; Johnson & Johnson, Tokyo, Japan) (Sigmavisc; Hyaltech Ltd., Livingston, UK), or 10% glycerin with a small amount of indigo carmine dye and 0.001% epinephrine are usually used as the injected solution [11,41,47,61]. Sodium hyaluronate solution is the most long-acting agent that can be locally injected for colorectal ESD [62]. Suvenyl (2% hyaluronate, Chugai, Tokyo, Japan) or Artz (1% hyaluronate, Seikagaku Corp. Tokyo, Japan) may be used after coordinating their concentrations [4,47,62]."

6) Please note in time of fibrosis, what devices you recommend and the reason.

Thank you very much for this important recommendation. We predominantly use Flushknife BT even for cases of submucosal fibrosis because additional submucosal injection of solution not only widens the gap between the exfoliated mucosa and muscle layer but also enables us to check the translucency of the submucosal layer immediately after the submucosal injection, potentially enhancing the safety of the submucosal dissection. Takeuchi et al. [67] reported that a short needle knife with a water jet function was effective, particularly for LST-NG and large lesions when colorectal ESD was performed by two experienced endoscopists. They also suggested that LST-NG requires repeated submucosal solution injections because LST-NG is often accompanied by submucosal fibrosis, and when sufficient submucosal space is created by injecting hyaluronate, it can easily collapse and will not stay patent for long. We regard a water jet function as being very effective and safe when submucosal fibrosis is present, but the use of a short-needle knife may require skill and experience in those suboptimal situations. It may be easier for unexperienced endoscopists to use a scissor-type endoknife or HookKnife in those situations, and the choice of the endoknives will likely also be affected by the endoscopist's skill and the institution's established procedures.

We had already described the effectiveness of using a short needle knife with a water jet function for cases of submucosal fibrosis in the original manuscript, which is as follows. "A short needle knife with a water-jet function, such as Flushknife BT, is very useful in these situations because it enables repeated submucosal injection without changing the injection needle [12,51,66,67].

Therefore, we have added the following sentence to the revised text. "A HookKnife or scissor-type endoknife, which enable the endoscopists to resect the submucosal tissue while pulling up on it, may also be useful in those situations [55]".

7) Please write reason why you choozed EZ clip HX-610-135.

Thank you very much for your valuable comment. The addition of this explanation may be very helpful for our readers. We have added the following sentence to the revised text.
"We use the EZ clip in the clip-flap method because it can be easily rotated, and it has a joint between the metal prongs and sheath, most of which is made of plastic. The joint may be utilized as a step difference with which to hook it to the distal attachment. A long endoclip may be inappropriate because it can be a hindrance in a narrow lumen."

8) ESD in Single balloon assist is described already. Because it is a paper-refference 31 Ohya reported, clarify as for citations, please.

Thank you very much for this helpful suggestion. As you pointed out, we had described the publication by Ohya et al. We have added the following sentence to the revised text.

"Ohya *et al*. [44] reported that a short-type single-balloon overtube through which a thin conventional endoscope can be introduced was useful for colorectal ESD, particularly for poor endoscope maneuverability in the proximal colon."