

February 24, 2023

Dr. Lian-Sheng Ma  
Company Editor-in-Chief  
*World Journal of Gastroenterology*

Dear Editor,

We are grateful for the feedback of the Reviewers that has helped us to improve the quality of the manuscript. We have carefully provided point-by-point responses to all concerns and comments and have modified the manuscript (in track changes) accordingly.

Reviewer #1:

**Specific Comments to Authors:**

I want to congratulate the authors for this well written and demonstrative mini-review. I believe abstract section may be more attractive if you can give details about recent advancements in EMR, ESD, and EFTR techniques and your proposed stepwise approach instead of background information.

**Response to Reviewer #1:**

**We would like to thank Reviewer#1. We were delighted to receive such magnificent feedback and did our best to address all your concerns. Please follow our modifications explained point-by-point.**

-I want to congratulate the authors for this well written and demonstrative mini-review. I believe abstract section may be more attractive if you can give details about recent advancements in EMR, ESD, and EFTR techniques and your proposed stepwise approach instead of background information.

**We agree with Reviewer#1. We revised the abstract section of the manuscript according to the reviewer's suggestion. We included detailed recent advancements in colorectal polypectomy and removed unnecessary background information (Pages 2, Lines 34-53).**

Reviewer #2:

**Specific Comments to Authors:**

This mini-review article summarizes the treatment strategy for difficult polyps, including the latest treatment methods. The content of the article is very well written and covers a wide range of topics from treatment selection to the latest equipment. As an additional note, I recommend that tip-in EMR for large lesions be included in the content of the report. Takada, Kazunori, Kinichi Hotta, Kenichiro Imai, Sayo Ito, Yoshihiro Kishida, Tatsunori Minamide, Yoichi Yamamoto, et al. 2022. "Tip-in EMR as an Alternative to Endoscopic Submucosal Dissection for 20- to 30-Mm Nonpedunculated Colorectal Neoplasms." *Gastrointestinal Endoscopy* 96 (5): 849–56.e3.

**Response to Reviewer #2:**

**We would like to thank Reviewer#2. We were delighted to receive such magnificent feedback and did our best to address all your concerns. Please follow our modifications explained point-by-point.**

-This mini-review article summarizes the treatment strategy for difficult polyps, including the latest treatment methods. The content of the article is very well written and covers a wide range of topics from treatment selection to the latest equipment. As an additional note, I recommend that tip-in EMR for large lesions be included in the content of the report. Takada, Kazunori, Kinichi Hotta, Kenichiro Imai, Sayo Ito, Yoshihiro Kishida, Tatsunori Minamide, Yoichi Yamamoto, et al. 2022. "Tip-in EMR as an Alternative to Endoscopic Submucosal Dissection for 20- to 30-Mm Nonpedunculated Colorectal Neoplasms." *Gastrointestinal Endoscopy* 96 (5): 849–56.e3.

**We agree with Reviewer#2. We added the tip-in EMR technique in the section of “selection of therapeutic modality for large colorectal polyps” as follows. “*Recently, Tip-in EMR was proposed as a promising modified EMR technique for resection of large nonpedunculated polyps.<sup>[17, 18]</sup> After the submucosal injection, the snare tip with a cut current was used to make a spot-shaped mucosal incision at the proximal side of the tumor. The small incision helps fix the snare tip in the submucosal layer during the snare placement; therefore, endoscopists could place the snare flexibly and repeatedly in the appropriate position. Takada et al.<sup>[19]</sup> compared Tip-in EMR with ESD for the resection of 20- to 30-mm nonpedunculated polyp using propensity score matching. They found that Tip-in EMR had a lower en-bloc resection (85% vs. 99%,  $P<0.001$ ) and R0 resection rates (63% vs. 91%,  $P<0.001$ ) than ESD; however, Tip-in had a shorter procedural time (8 vs. 60 mins,  $P<0.001$ ) and comparable local recurrence rate (2% vs. 0%,  $P=.386$ ). They concluded that Tip-in EMR could be a feasible alternative to ESD for 20- to 30-mm nonpedunculated polyps.*” (Pages 7, Lines 169-181).**

Reviewer #3:

**Specific Comments to Authors:**

General Impression In general, this is an interesting manuscript, and thank you for inviting me to review it. However, by thoroughly reading it, I came across several issues that need to be resolved prior to consider this manuscript for publication Major Revision 1) Weaknesses of the currently used classification systems when it comes to the assessment of submucosal invasion should be discussed. Please add 2) What is the risk of metastasis in polyps with submucosal invasion? Please add in text and make a table 3) ...However, the best modality for estimating the invasion depth in early colorectal lesions is magnifying chromoendoscopy with crystal violet.... The word “however” should be omitted and please explain the superiority of crystal violet 4) KUDO’s classification was developed for magnifying endoscopy. How correct is it to use this classification in non-magnifying dye-less chromoendoscopy? 5) When the SMSA criteria are used for the characterization of difficult polyps please also add morphology 6) Basic techniques of colorectal polypectomy? Are all those different techniques all basic steps for preparing the field for subsequent resection? Please review 7) The authors discriminate between morphology and endoscopic diagnosis. Why? Please discuss 8) Large pedunculated polyps. Please define 9) The authors classify LSTs in 2 categories. For me, they are classified into 3. Please review and discuss how the type affects our decision to resect. 10) Professional English editing is required throughout the manuscript and adaptation according to the guidelines for authors 11) Difficult polyps are for experts. Yes I agree. What makes an endoscopist expert? Please describe 12) The authors claimed that in this review they will describe helpful strategies and tips for dealing with difficult colorectal polyps. What are the strategies given? What are the tips? Please rewrite accordingly and amend figures 13) We have so many classification systems in the assessment of polyps mentioned and non mentioned in the manuscript. Please review and add a table that would make the comparison when appropriate for major clinical outcomes. 14) In the figure of scissor-type polypectomy, please describe the steps and make a collage of photos that is in line with these steps 15) The authors present several novel techniques such as EFTR. A graphical representation of the technique would save space from describing the technique in the body and concurrently would increase clarity 16) SMSA classification has been shown to be an accurate system that can help endoscopists estimate the complication risk associated with all sort of polypectomies. However it is not presented. It can be of value to be added in this review and concurrently the authors to inform the reader how the manage polyps with an increased SMSA score

**Response to Reviewer #3:**

**We would like to thank Reviewer#3. We were delighted to receive such constructive feedback and did our best to address all your concerns. Please follow our modifications explained point-by-point.**

1) Weaknesses of the currently used classification systems when it comes to the assessment of submucosal invasion should be discussed. Please add

**We agree with Reviewer#2. We added the limitation of the current methods of assessing submucosal invasion as follows. *“It should be noted that experienced examiners performed magnifying chromoendoscopy in this study; therefore, the effectiveness of magnifying chromoendoscopy should be revalidated in general endoscopists. Togashi et al.<sup>[18]</sup> reported a minimum experience of observing 200 lesions with magnifying chromoendoscopy is needed to understand pit***

*pattern diagnosis. Moreover, the limited availability of crystal violet outside Japan makes this approach difficult to apply in clinical practice.” (Pages 5, Lines 117-123).*

2) What is the risk of metastasis in polyps with submucosal invasion? Please add in text and make a table

**We agree with Reviewer#2. We added the detail about the risk of lymph node metastasis in submucosal cancers as follows. “Colorectal cancers with submucosal invasion have 7–14% risk of lymph node metastasis<sup>[11-14]</sup>. For submucosal cancers, it is crucial to differentiate between superficial (<1,000  $\mu\text{m}$ ) and deep submucosal invasive ( $\geq 1,000 \mu\text{m}$ ) cancer. Current evidence strongly supports the theory that superficial cancer with submucosal invasion <1,000  $\mu\text{m}$  without lymphovascular invasion, grade 2/3 tumor budding, or poorly differentiated component have no risk of lymph node metastasis<sup>[15, 16]</sup>. ” (Pages 5, Lines 104-109). We believe that the details in the texts are clear without the need for a table.**

3) ...However, the best modality for estimating the invasion depth in early colorectal lesions is magnifying chromoendoscopy with crystal violet.... The word “however” should be omitted and please explain the superiority of crystal violet

**We agree with Reviewer#2. We modified those sentences to “A Japanese study suggested that the best modality for estimating the invasion depth in early colorectal lesions is magnifying chromoendoscopy with crystal violet. Matsuda et al.<sup>[11]</sup> found that the diagnostic accuracy of the invasive pattern in magnifying chromoendoscopy with crystal violet to differentiate superficial (<1,000  $\mu\text{m}$ ) and deep submucosal invasive ( $\geq 1,000 \mu\text{m}$ ) cancers was 98.8%.” (Pages 5, Lines 109-114).**

4) KUDO’s classification was developed for magnifying endoscopy. How correct is it to use this classification in non-magnifying dye-less chromoendoscopy?

**Kudo’s classification was originally developed to characterize the polyp using dye and magnifying endoscopy. To characterize the polyp with non-magnifying dye-less chromoendoscopy, both vessel and surface patterns must be examined and classified using NICE classification. Using non-magnifying dye-less chromoendoscopy to diagnose pit patterns, as in Kudo’s classification, may not be possible.**

5) When the SMSA criteria are used for the characterization of difficult polyps please also add morphology

**We agree with Reviewer#2. We added the detail of the SMSA score as follows. “The SMSA (Size, Morphology, Site, Access) classification system has been proposed by Gupta et al.<sup>[19]</sup> for stratifying lesion complexity (Table 3). This stratifies polyps into 4 levels of difficulty, with level 1 being the easiest to resect by all endoscopists and level 4 being very difficult to resect. Longcroft-Wheaton et al.<sup>[20]</sup> validated the SMSA system in a prospective study of 220 lesions  $\geq 20 \text{ mm}$  in diameter. They found that lesions with SMSA level 4 had higher complication rates (8.6% vs. 0%,  $P=0.007$ ) and lower complete resection rates (87.5% vs. 97.5%,  $P=0.009$ ) than the lesions with SMSA level 2 and 3. European Society of Gastrointestinal Endoscopy guideline for colorectal polypectomy**

*and endoscopic mucosal resection recommends using the SMSA system to assess large and complex polyps. If the lesions have SMSA level 4, they should be resected by experts at a high-volume tertiary care center<sup>[21]</sup>.*” (Pages 5-6, Lines 130-140).

6) Basic techniques of colorectal polypectomy? Are all those different techniques all basic steps for preparing the field for subsequent resection? Please review

**Preparing the field for subsequent resection is a part of the basic techniques of colorectal polypectomy. To achieve successful polypectomy of simple or difficult colorectal polyps, the basic techniques that we mentioned should be implemented. Without these techniques, difficult polypectomy might be troublesome. We have already provided the detail of the basic techniques of colorectal polypectomy. Moreover, we provided Figure 1A-C to make readers easy to understand these techniques.**

7) The authors discriminate between morphology and endoscopic diagnosis. Why? Please discuss

**For difficult colorectal polyps, endoscopic diagnosis is critical to identify polyps with deep submucosal invasive cancer that should be resected by radical colectomy, not endoscopic resection. If the polyps could be resected endoscopically (adenoma or submucosal superficial cancer), morphology helps the endoscopist determine a suitable resection modality. We have provided the stepwise approach for difficult colorectal polyps in Figure 9.**

**In addition, endoscopic diagnosis is important for the selection of endoscopic treatment (EMR or ESD). For example, a LST was found at the ileocecal valve. If we diagnose it as adenoma, EMR is a possible treatment option. If we diagnose it as high-grade intramucosal neoplasia/superficial submucosal cancer, ESD should be performed. ESD allows accurate histopathologic diagnosis regarding the depth of invasion without segmentation of the carcinomatous part, which compromises the pathological diagnosis. This example is detailed in Figure 9.**

8) Large pedunculated polyps. Please define

**As I mentioned in the first paragraph of this section, the risk of bleeding after polypectomy of pedunculated polyps increases if the polyp size is > 17 mm and the stalk diameter is >5 mm. This should be the definition of large pedunculated polyps from our point of view. However, most previous studies included polyps >10 mm in diameter in their study to investigate the bleeding prophylaxis strategies. After recruitment of these studies, the mean polyp size in studies varied (Dobrowolski et al. = 16 mm, Lee et al. = 15 mm, Di Giorgio et al. = 22 mm, Kouklakis et al. = 26 mm, Paspatis et al. = 27 mm, Soh et al. median size = 15 mm). No current consensus defined how large should define as large pedunculated polyps.**

9) The authors classify LSTs in 2 categories. For me, they are classified into 3. Please review and discuss how the type affects our decision to resect.

**In the original study by Professor Kudo, LST is classified into 2 types, granular and nongranular type. The granular type is subclassified into homogeneous and nodular-mixed subtypes. The nongranular type is classified into elevated and pseudodepressed subtypes. (Gastrointest Endosc. 2008 Oct;68(4 Suppl): S3-47.) I have already mentioned how the type affect**

the decision to resect as follows. “These two types have different patterns of submucosal invasion. In a large retrospective cohort study by Yamada et al.<sup>[17]</sup>, 19% of the LST-G cases had submucosal invasion; the invasion site was the large nodule in 56%, the depression area in 28%, and multifocal in 16%. LST-NG showed 39% submucosal invasion, and the invasion site was 10% at submucosal mass-like elevation, 45% at depression, or 45% multifocal. Because of the substantial risk of multifocal submucosal invasion, ESD is warranted for LST-NG, and en bloc resection is required for large LST-G nodules.” (Pages 7, Lines 182-190).

10) Professional English editing is required throughout the manuscript and adaptation according to the guidelines for authors

**We have already used a Professional English editing service. However, we sent the revised manuscript to our English editing service to recheck again.**

11) Difficult polyps are for experts. Yes I agree. What makes an endoscopist expert? Please describe

**It is a difficult question. There are various polypectomy techniques, each needing its own learning curve. However, the most difficult technique for difficult colorectal polypectomy is ESD. Difficult ESD, such as a recurrent polyp, IC valve polyp, or polyp involving appendiceal orifice, need to be performed with the experts. We cannot specify how to make the endoscopist expert, but we know from the evidence that 80 procedures are required to gain proficiency in large polyp resection. (*Dig Endosc* 2010; 22: 302-306) We have mentioned this issue in the manuscript (Pages 7, Lines 166-169).**

12) The authors claimed that in this review they will describe helpful strategies and tips for dealing with difficult colorectal polyps. What are the strategies given? What are the tips? Please rewrite accordingly and amend figures

**We have already described the helpful strategies and tips for dealing with difficult colorectal polyps in Figure 9. In this figure, we summarized all tips and strategies in the manuscript as a stepwise approach.**

13) We have so many classification systems in the assessment of polyps mentioned and non mentioned in the manuscript. Please review and add a table that would make the comparison when appropriate for major clinical outcomes.

**We agree with Reviewer#2 that many classification systems have been proposed nowadays; therefore, we mentioned only well-known, standard systems. Since this minireview focused on how to resect difficult colorectal polyps, mentioning all diagnosis classification systems is out of the review scope and may make this review redundant and difficult to read.**

14) In the figure of scissor-type polypectomy, please describe the steps and make a collage of photos that is in line with these steps

We agree with Reviewer#2. We added the detail of the steps using a scissor-type knife *“With a scissor-type knife, the tissue and vessels could be grasped between two blades and pre-coagulated before cutting.”* (Pages 8, Lines 220-221). We also modified Figure 3 as suggested.

15) The authors present several novel techniques such as EFTR. A graphical representation of the technique would save space from describing the technique in the body and concurrently would increase clarity

We agree with Reviewer#2 that a graphical presentation is helpful to increase clarity; however, we endeavored to use the real endoscopic images in this manuscript to make it easy to understand and follow. We believe that descriptive texts and our figures will make it easy for audiences to understand. However, we cannot provide figures for all techniques, but we tried to provide as many as possible (a total of 9 figures in this manuscript).

16) SMSA classification has been shown to be an accurate system that can help endoscopists estimate the complication risk associated with all sort of polypectomies. However it is not presented. It can be of value to be added in this review and concurrently the authors to inform the reader how the manage polyps with an increased SMSA score

We agree with Reviewer#2. We added the detail of the SMSA score as follows. *“The SMSA (Size, Morphology, Site, Access) classification system has been proposed by Gupta et al.<sup>[19]</sup> for stratifying lesion complexity (Table 3). This stratifies polyps into 4 levels of difficulty, with level 1 being the easiest to resect by all endoscopists and level 4 being very difficult to resect. Longcroft-Wheaton et al.<sup>[20]</sup> validated the SMSA system in a prospective study of 220 lesions  $\geq 20$  mm in diameter. They found that lesions with SMSA level 4 had higher complication rates (8.6% vs. 0%,  $P=0.007$ ) and lower complete resection rates (87.5% vs. 97.5%,  $P=0.009$ ) than the lesions with SMSA level 2 and 3. European Society of Gastrointestinal Endoscopy guideline for colorectal polypectomy and endoscopic mucosal resection recommends using the SMSA system to assess large and complex polyps. If the lesions have SMSA level 4, they should be resected by experts at a high-volume tertiary care center<sup>[21]</sup>.”* (Pages 5-6, Lines 130-140).

Reviewer #4:

**Specific Comments to Authors:**

This manuscript submitted to World Journal of Gastroenterology with the title of “Difficult colorectal polypectomy: technical tips and recent advances” is a comprehensive overview. This article summarized the latest progress, treatment and technical points of difficult colorectal polyps. The quality of pictures and tables is also good. However, there are some common writing irregularities in the article. Please refer to the magazine's submission requirements for modification.

**Response to Reviewer #4:**

We would like to thank the Reviewer#4. We were delighted to receive such constructive feedback and did our best to address all your concerns. Please follow our modifications explained point-by-point.

-This manuscript submitted to World Journal of Gastroenterology with the title of “Difficult colorectal polypectomy: technical tips and recent advances” is a comprehensive overview. This article summarized the latest progress, treatment and technical points of difficult colorectal polyps. The quality of pictures and tables is also good. However, there are some common writing irregularities in the article. Please refer to the magazine's submission requirements for modification.

**We agree with Reviewer#4. To address the writing irregularities in our article, we sent the revised manuscript to our English editing service to correct this writing issue.**

We hope that a revised version of the manuscript is suitable and will be considered by *World Journal of Gastroenterology* for publication. Thank you for your suggestions and help.

Sincerely yours,



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Round 2

Dear Yu-Lu Chen, We would like to give a point-by-point response to the questions as follows.

**1. Specific Comments To Authors:** Happy with most of the changes made. 1.1) A final comment is for the authors to mention in the manuscript the debatable issues such as the definition of large polyps or the alternative classifications that can be used in cases where magnification is not available. ANS:

Thank you very much for the reviewer's suggestion. However, our manuscript focuses on "difficult colorectal polyps," which we have already mentioned the definition in the introduction. "Generally, difficult colorectal polyps are defined as any polyps that are technically challenging for endoscopic resection because of their size (>20 mm), morphology (pedunculated polyp with a thick stalk, laterally spreading tumor), or location (ileocecal valve, appendiceal orifice, dentate line)[5, 6]." Discussing the definition of "large" polyps is very subjective for each endoscopist. To date, no endoscopist proposed the width of polyps that should define as "large" polyps. We think it may not be critical to define "large" polyps, but the critical point is to define "difficult" polyps. Generally, non-magnifying colonoscopy is not preferable in diagnosing the histology of colorectal polyps in daily practice. The JGES guideline recommends magnifying colonoscopy with dye or IEE to be used for lesion assessment. We already mentioned the detail in the "lesion assessment" session. In addition, this minireview focused on how to resect difficult colorectal polyps; mentioning too many classification systems is out of the review scope and may make this review redundant and difficult to read. 1.2) The detailed description of the LSTs with special consideration when it comes to resection i believe that it would be of value for the reader so as to acquire a more complete picture for the management of these polyps. Please add. ANS: We have already provided a detailed description of the LSTs with management consideration in each type. "LST is classified as granular type (LST-G), which has a nodular surface, or non-granular type (LST-NG), which has a smooth surface. These two types have different patterns of submucosal invasion. In a large retrospective cohort study by Yamada et al[30], 19% of the LST-G cases had submucosal invasion; the invasion site was the large nodule in 56%, the depression area in 28%, and multifocal in 16%. LST-NG showed 39% submucosal invasion, and the invasion site was 10% at submucosal mass-like elevation, 45% at depression, or 45% multifocal. Because of the substantial risk of multifocal submucosal invasion, ESD is warranted for LST-NG, and en bloc resection is required for large LST-G nodules. Table 4 shows the indications for colorectal ESD suggested by the 2020 Japan Gastroenterological Endoscopy Society (JGES) guidelines for colorectal ESD and EMR[10]." 1.3) What about the use of non-ablative techniques in the management of colorectal polyps? Can be useful? and When? ANS: There is no non-ablative technique in managing difficult colorectal polyps. In addition, the non-ablative technique is not mentioned in any standard guidelines.

2. Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as "Manuscript No. -Figures.ppt" on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes. ANS:

We have attached the PowerPoint file with decomposable figures. Thank you very much. Sincerely yours, Sukit Pattarajierapan Surgical Endoscopy Colorectal Division, Department of Surgery, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand