ANSWERING REVIEWERS

August 3, 2017

Dear Editor,

Please find enclosed the edited the full-text manuscript in Word format

Journal: World Journal of Gastroenterology

Manuscript NO: 35107

Title: Safe and large bloc biopsy for submucosal tumor with reversible mucosa opened by a hinged double doors method

Author: Hirohito Mori, Yu Guan, Hideki Kobara, Noriko Nishiyama, Yasuhiro Goda, Nobuya Kobayashi, Tsutomu Masaki

The manuscript has been improved according to the suggestions of reviewers:
1. Format has been updated
2. Revision has been made according to the suggestions of the reviewer
3. References and typesetting were corrected
All responses to comments are as following pages.

Sincerely yours,

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REVIEWER #1 (00069066)

COMMENT

Dear author, I agree with the authors that we often have difficulty obtaining sufficient samples in submucosal tumor cases. So the sampling technique offered can be an alternative. But I see in the manuscript the explanation of the technique presented is less clear. So the author needs to make a more detailed explanation about this method.

RESPONSE

I agree with you. There was no detail description about this technical explanation.

Therefore, I revised (Page 6, line 96- 108) and added Figure 1 as the technical procedures with illustrations as follows:

As the tumor located in the fornix where EUS-FNA was unable to puncture its needle due to maximum bended endoscope position and STB was also difficult to create submucosal tunnel under maximum bended endoscope position, it was difficult to obtain sufficient tissue sample of this tumor (Schema ①) (Figure 1). A 5- 10mm straight incision was made on the top of the SMT by Dual knife (KD-650L, OLYMPUS Co., Tokyo, Japan) (Schema ②) (Figure 2). After a 5-mm ring-shaped thread was delivered by grasping forceps and clipped on the left side mucosa of the incision edge (Schema ③), second clip was hooked the ring-shaped thread (Schema ④) and moved to be tied up the left gastric wall.

The same procedures were performed on the right side of the incision mucosa (Figure 3) making a straight incision like an oval-shaped incision (Figure 4). With more insufflation, both ring threads expanded the oval incision to a round-shaped incision from which the tumor capsule was clearly recognized (Figure 5). An approximately 5 mm incision of the tumor capsule by Dual knife made it possible to confirm the tumor itself which had abundant tumor vessels (Figure 5) (Schema ⑤). A 5-mm piece of tumor tissue was obtained by cutting the tumor surface with a Dual knife. After both sides of the ring threads were detached, the opened mucosa was closed by hemoclips to restore it back to the original mucosa (Figure 6) (Schema ⑥).

REVIEWER #2 (01441415)

COMMENT

General comments This case report by Mori H et al. presented a new biopsy method for GIST of the stomach. The authors demonstrate clearly that 'reversible hinged double doors method' is useful to obtain large tissue sample. This method may certainly be of use for tough case even if we use EUS-FNA. This manuscript is well-written in terms of language and seems to be informative to the readers. My evaluation is that the paper is publishable with minor scientific revisions Specific comments

1. I fail to understand why authors judged '1-cm' linera incision is appropriate. Is it possible to cut shorter incision if operators add counter traction by clip or ring-shaped thread? This interpretation is not supported by any demonstration. Please comment this fact.

RESPONSE

Thank you for your informative comment. I agree with you. As you mentioned, more strong traction force made it possible to cut less incision as 5- 10 mm incision.

Therefore, I revised (Page 6, line 97) as follows;

A 5- 10mm straight incision was made on the top of the SMT by Dual knife (KD-650L, OLYMPUS Co., Tokyo, Japan) (Figure 1-②) (Figure 3).

2. This 'reversible hinged double doors method' may be hard for general endoscopist. Authors mentioned that 'it is difficult for ordinary endoscopist to perform STB' and 'only ESD experts could perform STB'. The technical criteria of endoscopist to perform this method needs to be addressed in detail (ex. the number of ESD operation, et al.).

RESPONSE

I agree with you. There was no detail description about the technical criteria of endoscopist to perform STB.

I revised (Page 8, line 137- 139) as follows;

As STB was safely performed using flexible endoscopic knives, only ESD experts could perform STB. It is difficult for ordinary endoscopists to perform STB[13], because making appropriate size and location of mucosal incision suitable for creating submucosal tunnel was very difficult for ESD beginner. And creating submucosal tunnel to correct direction and adjusting correct depth of submucosal dissection within the submucosal tunnel were more difficult than conventional gastric ESD.

3. I'm not at all familiar with the term 'TBB' (p.6, 2nd paragraph, 2nd line). Is it STB? Please explain and cite or remove.

RESPONSE

I am sorry that I made a mistake the word "STB" not "TBB" (Page 6, line 96). I revised this part.

I also cited about STB in REFERENCE section as follows;

6. Kobara H, Mori H, Rafiq K, Fujihara S, Nishiyama N, Chiyo T, Matsunaga T, Ayaki M, Yachida T, Kato K, Kamada H, Fujita K, Morishita A, Oryu M, Tsutsui K, Iwama H, Kushida Y, Haba R, Masaki T. Analysis of the amount of tissue sample necessary for mitotic count and Ki-67 index in gastrointestinal stromal tumor sampling. *Oncol Rep* 2015; **33**: 215-222 [PMID: 25405369 DOI: 10.3892/or.2014.3608].

REVIEWER #3 (00074961)

COMMENT

The text is too simplified and it is difficult to understand all the steps of the technique. Could you describe how you made the incision, how you got the 5-mm ring-shaped threads, how you clipped them, how you hooked them, how you detached them…? It would be interesting if you include a drawing.

RESPONSE

I agree with you. There was no detail description about this technical explanation, and it is difficult to understand all the steps of the technique.

Hence, as you recommended, I explained the technical procedures and added illustrations.

I revised (Page 6, line 96- 108) and added Figure 1 as the technical procedures with illustrations as follows:

As the tumor located in the fornix where EUS-FNA was unable to puncture its needle due to maximum bended endoscope position and STB was also difficult to create submucosal tunnel under maximum bended endoscope position, it was difficult to obtain sufficient tissue sample of this tumor (Schema ①) (Figure 1). A 5- 10mm straight incision was made on the top of the SMT by Dual knife (KD-650L, OLYMPUS Co., Tokyo, Japan) (Schema ②) (Figure 2). After a 5-mm ring-shaped thread was delivered by grasping forceps and clipped on the left side mucosa of the incision edge (Schema ③), second clip was hooked the ring-shaped thread (Schema ④) and moved to be tied up the left gastric wall.

The same procedures were performed on the right side of the incision mucosa (Figure 3) making a straight incision like an oval-shaped incision (Figure 4). With more insufflation, both ring threads expanded the oval incision to a round-shaped incision from which the tumor capsule was clearly recognized (Figure 5). An approximately 5 mm incision of the tumor capsule by Dual knife made it possible to confirm the tumor itself which had abundant tumor vessels (Figure 5) (Schema ⑤). A 5-mm piece of tumor tissue was obtained by cutting the tumor surface with a Dual knife. After both sides of the ring threads were detached, the opened mucosa was closed by hemoclips to restore it back to the original mucosa (Figure 6) (Schema ⑥).

Thank you for your informative comment.

REVIEWER #4 (02531403)

COMMENT

Dear authors, I read with interest manuscript n. 35107 about "hinged double doors method" to sample submucosal tumour. I have some remarks: - It should be better to define the method in a less confusing way: "sampling after incision and direct visualization", for example - The manuscript is well written and illustrated, however it should be useful to make a scheme together with the images –

RESPONSE

I agree with you. There was no description with regard to this technical explanation, and it is difficult to understand all the steps of the technique.

Hence, I explained the technical procedures and added illustrations as Figure 1.

I also agree with you that this new method had better to be named as "sampling after incision and direct visualization" not "hinged double doors method".

I revised this method's name (Page 1, line 4- 7) as follows;

"Oval mucosal opening bloc biopsy after incision and widening by ring thread traction for submucosal tumor"

and

Running title as "Mori H et al. Oval mucosal opening biopsy"

Thank you for your informative comment.

COMMENT

It should be useful to insert the image of the recovered mucosa 3 weeks after the procedure –

RESPONSE

I agree with you. Although the image of the recovered mucosa after the procedure was

useful for readers, we managed to find out only 1 endoscopic picture [I am sorry that endoscopic image was low resolution compared with pre-operation endoscopic images (GIF H260Z) due to endoscope (GIF Q260J) equipped in operation room] when laparoscopy and endoscopy cooperative surgery (LECS) was performed six week after oval mucosal opening bloc biopsy.
We added this figure 7 with legend and (Page 7, line 112-113) as follows;
An endoscopic image revealed that straight incision on the top of the SMT was completely scarred and closed (yellow ring) (Figure 7) when laparoscopy and endoscopy cooperative surgery (LECS) was performed six week after oval mucosal opening bloc biopsy.

COMMENT
In the discussion, the authors should be draw their conclusion more cautiously, since: 1. It is impossible to adfirm that the technique does not show false negative since it is reported only one case
RESPONSE
I agree with you. I mentioned a little too much about this sentence.
I revised and deleted (Page 4, line 62- 63) and (Page 8, line 143).

COMMENT
2. It is impossible to adfirm "without cell dissemination" since the neoplasm that was analyzed did not presented a malignant potential!
RESPONSE
I agree with you. I also mentioned a little too much about this sentence.
I revised and deleted (Page 4, line 63) and (Page 8, line 144).

REVIEWER #5 (00035938)
COMMENT
General comments: Mori et colleagues present a case report to introduce a novel technique to obtain tissue for further characterization of submucosal tumours. The method is based on an incisional cut which is then widened to an oval opening by fixing both margins from the middle of the cut to the adjacent gastric wall using threads, clips and insufflation. The method appears quite complicated but has been performed in this case in 10 minutes. Naming the procedure “reversible hinged double doors opening biopsy (R-HDD)” is confusing; “biopsy after incision and widening” might be an exacter description.
RESPONSE
I totally agree with you that naming the procedure “reversible hinged double doors opening biopsy (R-HDD)” was confusing.
Thank you for your recommendation “biopsy after incision and widening”.
Then, I revised the title, short title and abbreviation (R-HDD) (Page1, line 4- 7) as follows;
“Oval mucosal opening bloc biopsy after incision and widening by ring thread traction for submucosal tumor”
and
“Mori H et al. Oval mucosal opening biopsy”
Thank you for your informative comments.

COMMENT

Compared to de-roofing by EMR, the advantages of the introduced method is that the defect is easier closed again after taking the biopsy which likely will reduce the bleeding risk. A cartoon illustrating the technique step by step would be helpful for the reader.

RESPONSE

I agree with you that there were some illustrations explaining the procedures. I revised (Page 6, line 96- 108) and added Figure 1 as the technical procedures with illustrations as follows:

As the tumor located in the fornix where EUS-FNA was unable to puncture its needle due to maximum bended endoscope position and STB was also difficult to create submucosal tunnel under maximum bended endoscope position, it was difficult to obtain sufficient tissue sample of this tumor (Schema ①) (Figure 1). A 5- 10mm straight incision was made on the top of the SMT by Dual knife (KD-650L, OLYMPUS Co., Tokyo, Japan) (Schema ②) (Figure 2). After a 5-mm ring-shaped thread was delivered by grasping forceps and clipped on the left side mucosa of the incision edge (Schema ③), second clip was hooked the ring-shaped thread (Schema ④) and moved to be tied up the left gastric wall.

The same procedures were performed on the right side of the incision mucosa (Figure 3) making a straight incision like an oval-shaped incision (Figure 4). With more insufflation, both ring threads expanded the oval incision to a round-shaped incision from which the tumor capsule was clearly recognized (Figure 5). An approximately 5 mm incision of the tumor capsule by Dual knife made it possible to confirm the tumor itself which had abundant tumor vessels (Figure 5) (Schema ⑤). A 5-mm piece of tumor tissue was obtained by cutting the tumor surface with a Dual knife. After both sides of the ring threads were detached, the opened mucosa was closed by hemoclips to restore it back to the original mucosa (Figure 6) (Schema ⑥).

Thank you for your informative comment.

COMMENT

Regarding the conclusion, I would consider it misleading to report on “no false negative results” in only one single case. You cannot conclude on any diagnostic yield after only one case.

RESPONSE

I agree with you. I mentioned a little too much about this sentence.

I revised and deleted (Page 4, line 62- 63).

COMMENT

Specific comments: -TBB –please explain the abbreviation where it appears first.

RESPONSE

I am sorry that I made a mistake. I should have mentioned submucosal tunneling bloc biopsy (STB) not TBB.

COMMENT

- What is the size of the thread loops? How do you advance them into the stomach? Are they already loaded onto a clip? - Please describe in more detail how the threads are fixed to the gastric wall and how they are solved again later.

RESPONSE

I agree with you that there were some illustrations explaining the procedures. I revised (Page 6, line 96- 108) and added Figure 1 as the technical procedures with illustrations.

Sincerely yours,

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