

ANSWERING REVIEWERS

18th of June 2013

Dear Editor,



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

Title: Radical Excision of Barrett's Esophagus by Endoscopic Submucosal Dissection: compared with Radio-Frequency Ablation or Cryotherapy

Author: Hirohito Mori, Hideki Kobara, Kazi Rafiq, Noriko Nishiyama, Shintaro Fujihara, Maki Ayagi, Tatsuo Yachida, Kiyohito Kato, Tsutomu Masaki

ESPS Manuscript NO: 3724

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 response to comments are as following pages.

Sincerely yours,

Hirohito Mori, M.D, PhD

Department of Gastroenterology and Neurology,
Faculty of medicine, Kagawa Medical University Japan

e-mail: hiro4884@med.kagawa-u.ac.jp

Tel: +81-87-891-2156

Fax: +81-87-891-2158

REVIEWER #1 (58104)

This is a very interesting manuscript that describes two case reports of endoscopic submucosal dissection (ESD) application for the treatment of high grade dysplasia (HGD) Barrett's esophagus (BE) and Barrett's adenocarcinoma (BAC), with very promising results, and favorable outcomes. ESD is a recently considered approach as an option for the treatment of HGD BE and BAC. From this point of view, this manuscript offers additional information. The presentation and readability of the manuscript is good; however, needs revision (see specific comments section).

SPECIFIC COMMENTS

Title: The title should be reconsidered, since this is a presentation of two cases with no comparisons.

RESPONSE

As you pointed out, this is a presentation of two case reports of radical excision of Barrett's Esophagus and complete recovery of normal squamous epithelium by endoscopic submucosal dissection. We revised the title (Page 1, line 5-6) (RED FONT) as follows:

Radical Excision of Barrett's Esophagus and Complete Recovery of Normal Squamous Epithelium

COMMENT

Abstract: In the abstract, it is stated that the treatment approach has been made "in order to reduce healthcare expenditure"; however, there is no data according to the manuscript to support this.

RESPONSE

I agree with you. There is no data with regard to healthcare expenditure about treatment of Barrett's esophagus. We revised this sentence (Page 3, line8-10) (RED FONT) as follows:

We performed endoscopic submucosal dissection (ESD) as the once radically curable treatment procedure for BE with dysplasia, intestinal metaplasia and BAC.

COMMENT

Introduction: Authors might consider to add references regarding BE definition. Also, regarding consensus and guidelines, authors might consider to add more recent bibliography about treatment options of HGD BE and BAC.

RESPONSE

As you pointed out, there are no description regarding consensus and guidelines. We revised Introduction section (Page 4, line 6-21) and References considerably.

COMMENT

Discussion: Authors might consider to add references and discuss extensively about the outcomes of all other available treatments of BAC and HGD BE. Also, references regarding already published data about ESD should be added, and authors should comment on this before any final conclusions made.

RESPONSE

I agree with you. We should mention more about treatment of RFA and ESD. We revised and added (Page 7, line 8) more discussion and references as follows:

RFA is an established treatment for BE with dysplasia. Though short-term results of RFA have been ascertained, there have been concerns about recurrence of BE after RFA. It is reported that BE treated by RFA, 56% were in complete remission after 24 months. However, 33% of these patients had disease recurrence within the next 2 years [15, 16]. That is very higher recurrence rate. Therefore, as reported incidence rates of BAC vary widely and controversial, radical excision by ESD without recurrence and stenosis is best way as the once radically curative treatment procedure for BE with dysplasia, intestinal metaplasia and BAC. In Japan, ESD is recommend for Barrett's esophageal cancer after accurate diagnosis using narrow band imaging with magnifying endoscopy as its high curative rate. But the anatomical structure of the esophagus (the esophagus is a narrow organ), healing of an artificial ulcer that occupies two thirds or more of the circumference of the esophagus may result in the formation of a significant stricture. Recently, several studies have demonstrated the effectiveness of the local injection or oral administration of steroids for preventing strictures [17, 18]. We developed and reported new method for preventing post-ESD stricture by steroid application and permeation with balloon dilatation [10].

COMMENT

References: See comments regarding introduction and discussion sections. LANGUAGE EVALUATION Grade B: minor language polishing; Please, reconsider the use of the word "curable"; "curative" might be more meaningful. Also, the certificate of english editing documents a paper with different title than the title of this manuscript.

RESPONSE

As you pointed out, we revised the word "curable" to "curative".

REVIEWER #2 (45410)

The case report describes use of ESD in treating Barrett's esophagus in 2 patients. Combined with application of steroid gel to prevent stricture formation the authors suggest this technique as an alternative to RFA or cryotherapy.

COMMENT

Major comments: The authors need to justify ESD in short segment Barrett's. The report describes the procedure and its outcome in 2 patients only. It is premature to compare ESD with cryo or RFA. At best the authors can suggest that further studies are needed to compare the 3 techniques. For the same reason the title needs to be changed

RESPONSE

As you pointed out, this is a presentation of two case reports of radical excision of Barrett's Esophagus and complete recovery of normal squamous epithelium by endoscopic submucosal dissection. We revised the title (Page 1, line 5-6) (RED FONT) as follows:

Radical Excision of Barrett's Esophagus and Complete Recovery of Normal Squamous Epithelium

And we justified ESD in treatment of Short Segment Barrett's esophagus (SSBE) (Page, line) as follows:

It is reported that BE treated by RFA, 56% were in complete remission after 24 months. However, 33% of these patients had disease recurrence within the next 2 years [15, 16]. That is very higher recurrence rate. Therefore, as reported incidence rates of BAC vary widely and controversial, radical excision by ESD without recurrence and stenosis is best way as the once radically curative treatment procedure for BE with dysplasia, intestinal metaplasia and BAC. In Japan, ESD is recommend for Barrett's esophageal cancer after accurate diagnosis using narrow band imaging with magnifying endoscopy as its high curative rate. But the anatomical structure of the esophagus (the esophagus is a narrow organ), healing of an artificial ulcer that occupies two thirds or more of the circumference of the esophagus may result in the formation of a significant stricture. Recently, several studies have demonstrated the effectiveness of the local injection or oral administration of steroids for preventing strictures [17, 18].

COMMENT

The discussion section should describe the rationale of the procedure with focus on anatomy and the likely advantages. Currently the authors have described the genetics of development of cancer only. There should be greater details of the 2 cases.

RESPONSE

As you pointed out, we should describe the advantages of the procedures. Therefore, we revised and deleted (Page 6, line 18- Page 7, line 2).

REVIEWER #3(52339)

Radical Excision of Barrett's Esophagus by Endoscopic Submucosal Dissection: compared with Radio-Frequency Ablation or Cryotherapy Hirohito Mori, et al

COMMENT

What the authors would like to show is not focused in this report. What is new?

RESPONSE

As you pointed out, our manuscript should have been focused on the procedure of radical excision of Barrett's Esophagus and complete recovery of normal squamous epithelium by endoscopic submucosal dissection. We revised (Page 6, line 18 - Page 7, line 2) as follows:

RFA is an established treatment for BE with dysplasia. Though short-term results of RFA have been ascertained, there have been concerns about recurrence of BE after RFA. It is reported that BE treated by RFA, 56% were in complete remission after 24 months. However, 33% of these patients had disease recurrence within the next 2 years [12, 13]. That is very higher recurrence rate. Therefore, as reported incidence rates of BAC vary widely and controversial, radical excision by ESD without recurrence and stenosis is best way as the once radically curative treatment procedure for BE with dysplasia, intestinal metaplasia and BAC. In Japan, ESD is recommend for Barrett's esophageal cancer after accurate diagnosis using narrow band imaging with magnifying endoscopy as its high curative rate.

COMMENT

#1 Is the procedure of alcohol gel new?

RESPONSE

Yes, we reported this procedure [*Mori H, Rafiq K, Kobara H, Fujihara S, Nishiyama N, Oryuu M, Suzuki Y, Masaki T. Steroid permeation into the artificial ulcer by combined steroid gel application and balloon dilatation: prevention of esophageal stricture. Journal of Gastroenterol and Hepatol. 2013 in press*], so this procedure is new procedure to prevent the post-ESD stricture of esophagus. In this time, we used this procedure for prevention of radical circumferential Barrett's esophagus resection.

COMMENT

#2 Is ESD an appropriate treatment in case1 because of no high grade dysplasia in the tissue specimen?

RESPONSE

As you pointed out, in Case 1, we couldn't detect severe dysplasia by biopsies before ESD. But the patient whose mother died of BAC associated with BE strongly hoped radical resection of SSBE. Moreover, narrow band imaging magnified endoscopy revealed irregular microvascular pattern and irregular microsurface pattern. That's why we decided to perform ESD. We revised and add it (Page 5, line6).

COMMENT

#3 In discussion section, how p16 and p53 story are related to this report? If they would like to discuss this point they need immunohistochemistry.

RESPONSE

As you pointed out, p16 and p53 story were not related to this report. We deleted this sentences and revised Page 6, line18- Page 7, line 2.

Sincerely yours,

Hirohito Mori, M.D, PhD

Department of Gastroenterology and Neurology,
Faculty of medicine, Kagawa Medical University Japan

e-mail: hiro4884@med.kagawa-u.ac.jp

Tel: +81-87-891-2156

Fax: +81-87-891-2158