

Response to Reviewers' Comments

Editorial Board Member comments:

We would like to express our sincere appreciations to the editors and the reviewers for identifying areas of corrections or modifications in our manuscript. We have made the necessary revisions in the manuscript and provided a point-by-point responses to the comments of the reviewers in the attached. The revisions are indicated with yellow highlights. We were unable to upload the highlighted version of manuscript because the manuscript was generated automatically in website and there was no place we could upload the file.

EDITORIAL OFFICE'S COMMENTS

Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response

Thank you for your review. We have provided decomposable Figures in a single PowerPoint file. All the included tables have currently been aligned with the journal requirements.

Reviewer Comments:

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors:

1. Was white light used for adenoma inspection and recurrence or NBI was also used?

Response

All authors claim they routinely use both white light and NBI for the thorough inspection of recurrence, but some studies neither contain written form concerning NBI usage nor image of NBI, especially in those without recurrence. Therefore, we could not include our opinion concerning use of NBI in our paper due to the retrospective design of the study. If the reviewer/editor suggests its appropriate to include, we will include the sentence regarding use of NBI in limitation section.

2. Was pathology slides read by gastrointestinal pathologist or general pathology?

Response

All pathology slides were read by gastrointestinal pathologist in each hospital. We have added the following sentence in method section. (page 6, line 27-28)

“The specimen was reviewed by a gastrointestinal pathologist and one or more residents in each hospital.”

3. Also, bias could be also on different experience of endoscopist on how well they are trained in these procedures. Seven different endoscopist may have different outcome.

Response

We totally agree that there could be a bias as the reviewer suggested. Although we compared the outcomes of endoscopists and hospitals, we could not conclude that the outcomes of EP are similar between different endoscopists. We have added the following sentence to the Discussion section. (page 15, line 8)

“Further studies with larger number of patients are needed to support our suggestion.”

4. Also, how many pathologist were involved? different readers can contribute to bias especially with low grade dysplasia

Response

It depends on the hospital setting, but each of the enrolled hospitals have a gastrointestinal pathologist, and the specimen was reviewed with the GI pathologist and at least one or more resident in training.

We have added a statement on this as we responded to question 2 above.

(page 6, line 27-28)

The specimen was reviewed by a gastrointestinal pathologist and one or more residents in each hospital.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors:

The authors have evaluated 119 patients with endoscopic papillectomy for malign ampullary lesions. Briefly, they have found that 81(76.4%) underwent curative resection, 99 (93.4%) had endoscopic success, showing most patients with non-curative resection were successfully managed with endoscopy. 16 patients (15.1%) had piecemeal resection, 22 patients (20.8%) had shown positive resection margin, 11 patients (16.1%) had an early recurrence, 13 patients (10.4%) had a late recurrence, and 6 patients (12.3%) had a re-recurrence. In multivariate analysis, a positive margin (OR 4.023, p = 0.048) and piecemeal resection (OR 6.610, p = 0.005) were significant risk factors for early and late recurrence, respectively. Piecemeal resection was also a significant risk factor for non-curative resection (OR 5.424, p = 0.007). 26 patients experienced adverse events (24.5%).

Abstract: Please clarify the endoscopic success

Introduction: well written

Materials and methods: well organized

Results: The authors have written the results very well

Discussion: All the results have been discussed.

Response

We have re-defined the endoscopic success in the Methods paragraph of abstract, with further clarification of the definition. (page 3, line 16-17)

“endoscopic success: treatment of ampullary adenoma with endoscopy without surgical intervention;”

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

1. In this study, how was an unclear margin case treated? According to Table 2, margin status was classified into only 2 categories: positive or negative.

Response

Many endoscopic papillectomy studies evaluated the margin as positive or negative. As of other studies that separated the margin into 3 categories, they evaluated the margin with 2 categories: negative vs. positive/uncertain(unevaluable).^[1-3]

In the previous version of our paper, unless it is negative, we included an uncertain lesion as a positive lesion. For clarification, we have included the following sentence in the Outcome measures subsection of the Method section: (page 8, line 2-4)

“Resection margins were categorized into 3 groups, negative, positive, and uncertain, and they were analyzed as positive/uncertain group and negative group”

And in the discussion: (page 14, line 11-12)

“Also, many previous studies do not clearly state how they analyzed the lesion with uncertain margin.”

We separated positive into positive and uncertain in Table 2, changed the word positive to positive/uncertain in all areas.

Positive -> Positive/Uncertain

Resection margin	
Negative	84 (79.2)
Positive/Uncertain	22 (20.8)

Positive	19 (17.9)
Uncertain	3 (2.8)

2. Authors analyzed the risk factors for pancreatitis after EP, and multivariate logistic regression analysis revealed that thermal ablation and pancreatic ductal stent insertion (PDS) were independent significant risk factors. How do authors interpret this result? It seems quite strange that PDS is an independent risk factor for pancreatitis after EP.

Response

In Table 7, multivariate analysis was performed for the risk factor of pancreatitis. Thermal ablation and PDS were significant, and their OR were 4.128 and 0.205, respectively. Therefore, thermal ablation group is likely to experience pancreatitis than non-ablation group, and PDS group is less likely to experience the pancreatitis than non-PDS group.

For clarification, we have revised the sentence in the Results section. (page 11, line 15-19)

“FAP, pancreatogram, thermal ablation, and PDS were significant risk factors for pancreatitis in univariate analysis, and in multivariate analysis, thermal ablation (OR 4.128; 95% CI 1.005-17.128; $p = 0.048$) was a positive risk factor, while PDS (OR 0.205; 95% CI 0.044-0.945; $p = 0.042$) was a negative risk factor for pancreatitis.”

Although there is an ongoing debate on this, it has been widely studied, with several studies advocating for the insertion of PDS as prophylaxis for pancreatitis.^[4-6]

We inserted the following sentence in the discussion section: (page 15, line 22-24)

“The role of PDS is still under debate, but results of several studies, including ours, advocate the use of PDS for prophylaxis of pancreatitis.”

In this study PDS was performed in 78 cases (73.6%). In what kind of cases was PDS performed? Was there any criterion?

Response

Insertion of PDS was attempted in most cases, but because it is not mandatory, the procedure was performed at the discretion of the endoscopist. We have stated this as a limitation. (Page 17, Line 7-9)

“Moreover, due to the lack of guidelines on the optimal EP technique, several decisions made during the procedure were at the discretion of the endoscopist.”

3. Multivariate analysis revealed that piecemeal resection was a risk factor for bleeding. How do authors explain causal relationship?

Response

Thank you for pointing out this important point for discussion. We have included the following paragraph in the Discussion section. (page 15, line 26-page 16, line 5)

“Also, our result showed that piecemeal resection was the only significant risk factor for delayed bleeding. Piecemeal resection was performed for lesions where en-bloc resection was impossible, therefore, the lesions with piecemeal resection tend to be larger^[7]. A previous study did not show the correlation between piecemeal resection and bleeding, based on the small number of piecemeal resection cases, but colonic lesions with piecemeal resection show significant bleeding during endoscopic mucosal resection^[8]. Further research is needed to support the role and adverse events of piecemeal resection in endoscopic papillectomy.”

We believe that these revisions have significantly improved our manuscript and hope that it is now suitable for publication in your esteemed journal.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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