

May 2, 2020

Na Ma, Company Editor-in-Chief, Editorial Office

World Journal of Gastrointestinal Oncology

Dear Editor:

We wish to resubmit our manuscript for publication in *World Journal of Gastrointestinal Oncology* after incorporating the revisions suggested by the reviewers.

The title has been revised to “Endoscopic mucosal resection vs. endoscopic submucosal dissection for superficial non-ampullary duodenal tumors.”

The manuscript ID is 53678 and the invited manuscript ID is 0487607.

We wish to thank you and the reviewers for your careful review of our manuscript. The manuscript has benefited immensely from these insightful suggestions. We hope that this revised version of the manuscript is now suitable for publication in the *World Journal of Gastrointestinal Oncology*.

The manuscript has been rechecked and the necessary changes, which are indicated in yellow, have been made in accordance with your and the reviewers’ suggestions. We have also provided point-by-point responses to all the comments.

Thank you again for your efforts in reviewing our manuscript. We look forward to hearing from you.

Sincerely yours,

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Response to Reviewer #1

Reviewer's comments

1. It would be better if more details could be shown about the difference of en bloc/complete resection rate between EMR and ESD. Whether this difference has any effect on the long-term outcomes? Besides, a detailed description of any potential limitation of EMR and ESD would be of help.

Response: Thank you very much for your valuable comments.

As you pointed out, long-term outcomes might show the differences in the efficacies of EMR and ESD. Therefore, we have added such data including local recurrence rate, distant recurrence rate, follow-up duration, and 1-year follow-up rate even though this was not a main outcome of the study. The local recurrence rate was 2.1% (3/142), distant recurrence rate was 0% (0/142), the median follow-up period was 24.5 months, and the 1-year follow-up rate was 81.0% (115/142). The details are presented in Table 3 and supplemental Table 1. Three local recurrences occurred in patients treated with EMR treated by piecemeal resection. However, all recurrent lesions were successfully treated by salvage endoscopic resection, and no distant metastasis occurred. Citing these data, we emphasize the importance of en bloc resection and the acceptability of EMR in the revised manuscript. Higher follow-up rates and longer follow-up periods are required to reflect the curative potential of endoscopic resection in future studies; we have included this in the limitations in the revised manuscript.

Therefore, we have revised the manuscript as follows:

Revised Manuscript

(page 5, lines 11–22)

We analyzed the treatment outcomes, including the rates of en bloc/complete resection, procedure time, adverse event rate, hospital stay, and local or metastatic recurrence.

RESULTS: Twenty-eight pairs of patients were created. The characteristics of patients between the two groups were similar after matching. The EMR group had a significantly shorter procedure time and hospital stay than those of the ESD group (median procedure time [interquartile range]: 6 [3–10.75] min vs. 87.5 [68.5–136.5] min, $P < 0.001$, hospital stay: 8 [6–10.75] days vs. 11 [8.25–14.75] days, $P = 0.006$). Other outcomes were not significantly different between the two groups (en bloc resection rate: 82.1% vs. 92.9%, $P = 0.42$; complete resection rate: 71.4% vs. 89.3%, $P = 0.18$; and adverse event rate: 3.6% vs. 17.9%, $P = 0.19$, local recurrence rate: 3.6% vs. 0%, $P = 1$; metastatic recurrence rate: 0% in both).

Revised Manuscript

(page 11-12, lines 11–1)

Clinical outcomes

We analyzed the short-term outcomes of endoscopic resection, such as the rates of en bloc resection and complete resection, procedure time, and incidence of adverse events, including delayed bleeding and intraprocedural or delayed perforation. In addition, we analyzed the local and metastatic recurrences during the follow-up period after endoscopic treatment. The procedure time was defined as the time from the start of mucosal injection to the completion of tumor resection. En bloc resection was defined as resection in a single piece in contrast to piecemeal resection. Complete resection was defined as en bloc resection with horizontal and vertical margins that were free of the tumor. Intraprocedural perforation was identified as a visible break in the duodenal wall confirmed via endoscopy during endoscopic resection. Delayed perforation was diagnosed as the presence of free air confirmed on radiography or computed tomography scans after endoscopic resection without intraprocedural perforation. Delayed bleeding was defined as the clinical evidence of bleeding after endoscopic resection that required endoscopic hemostasis or transfusion. Local recurrent was defined as tumor relapse from the treatment scar, which was diagnosed by endoscopy or biopsy during the follow-up period. Metastatic recurrence was defined as tumor relapse in the lymph nodes and/or other organs, which was diagnosed by computed tomography during the follow-up period.

Revised Manuscript

(page 13–14, lines 15–7)

Treatment outcomes before propensity score matching

The treatment outcomes before propensity score matching are shown in Supplemental Table 1. In the EMR group, the median procedure time was 5 [3.5–10] min and the rates of en bloc and complete resection were 87.4% and 71.3%, respectively. The rate of adverse events in the EMR group was 4.6% (observed in 4 of 87 patients); delayed bleeding occurred in 4.6% of the patients (4/87), and neither intraoperative nor delayed perforation was observed in any patient. The median hospital stay in the EMR group was 7.0 [6–9] days. In contrast, in the ESD group, the median procedure time was 90 [67–134.5] min, and the rates of en bloc and complete resection were 94.5% and 83.6%, respectively. The rate of adverse events in the ESD group was 18.2% (observed in 10 of 55 patients); delayed bleeding occurred in 1.8% of the patients (1/55), intraoperative perforation in 12.7% (7/55), and delayed perforation in 3.6% (2/55). The median hospital stay in the ESD group was 11 [9–14] days. In fact, only one patient with intraoperative perforation in the ESD group required emergency surgery immediately after ESD. Nevertheless, none of the patients in either group died due to adverse events.

Follow up duration and 1-year follow-up rate were not significantly different between the two groups: median follow-up duration, 24.5 [15–53.75] months; 1-year follow-up rate, 81.0% (115/142). Three cases of local recurrence occurred in EMR, which were successfully managed by salvage endoscopic treatment. No metastatic recurrence occurred in either groups.

Revised Manuscript

(pages 14–15, lines 18–4)

Treatment outcomes after propensity score matching

The treatment outcomes of patients in the EMR and ESD groups after propensity score matching are summarized in Table 3. The procedure time was significantly shorter in the EMR group than in the ESD group (6 [3–10.75] min vs. 87.5 [68.5–136.5] min, $P < 0.001$). Furthermore, the median hospital stay was significantly shorter in the EMR group than in the ESD group (8 [6–10.75] days vs. 11 [8.25–14.75] days, $P = 0.006$). There were no significant differences in en bloc resection and curative resection rates between both groups (en bloc resection rate: 82.1% vs. 92.9%, $P = 0.42$; complete resection rate: 71.4% vs. 89.3%, $P = 0.18$). There was also no significant difference in the rate of adverse events between both groups (3.6% vs. 17.9%, $P = 0.19$). Delayed bleeding in the EMR group was successfully managed using a conservative approach without surgery. Only one patient with intraoperative perforation in the ESD group required emergency surgery immediately after ESD. None of the patients in either group died due to adverse events. As for recurrence events, only one local recurrence was observed in EMR group, and no metastatic recurrence was seen during follow-up period.

Revised Manuscript

(page 15, lines 6–16)

Discussion

To the best of our knowledge, the current study is the first to compare the efficacy and safety of EMR with those of ESD for SNADETs using propensity score matching. Although ESD tended to result in a higher complete resection rate than did EMR, ESD was a significantly longer procedure and required longer hospital stay with a tendency of having a higher adverse event rate. In fact, one patient in the ESD group required emergency surgery for a perforation. Local recurrent lesions in EMR were successfully treated by endoscopic resection. Therefore, although ESD was more effective than EMR, all SNADETs cannot be treated with ESD because of the possible risk of adverse events and higher cost of hospitalization.

Revised Manuscript

(page 16–17, lines 14–4)

ESD resulted in an extremely high curability rate in the current study; the en bloc resection rate was >90%, and the complete resection rate also reached approximately 90%. These outcomes are similar to or better than those of previous studies^[28-31]. In addition, although the curability of EMR in the current study seemed to be lower than that of ESD, the difference was not significant. In previous studies, piecemeal resection was required during EMR for lesions that were >10–15 mm in diameter. In fact, the en bloc resection rate exceeded 80%, and the complete resection rate was approximately 70% in the current study, both of which are higher than those reported in previous studies^[32]. The advancements in the endoscopic devices and the electro-surgical power unit, as well as advancements in the skill of the endoscopists, might have contributed to the better treatment outcomes. During follow-up, three local recurrences before matching (one local recurrence after matching) were observed only in the EMR group, although no recurrence was observed in the ESD group. All recurrent lesions were attributed to the piecemeal resection but could be managed by salvage endoscopic treatment. Furthermore, no metastatic lesion was observed in either group during the follow-up period. The high rate of en bloc resection in the EMR group might contribute to comparably low rate of local recurrence as that in ESD group. Accordingly, the curative potential of EMR in the current study seems to be acceptable, even though the follow-up duration was short.

Revised Manuscript

(page 18, lines 23–27)

Fourth, the follow-up period in this study was insufficient to evaluate long-term outcomes. Median follow-up duration was 24.5 (15–53.75) months, and the 1-year follow up rate was 81.0% (115/142). Longer follow-up will be required to evaluate the accurate curative potential of endoscopic resection.

Response to Reviewer #2

Reviewer's comments

2. The main drawback is the retrospective nature of the work.

Thank you very much for the valuable comments. As you have pointed out, the retrospective nature of the study is one of its limitations. The selection of treatment methods might depend on the preference of endoscopists. Thus, a prospective randomized control trial is required to accurately compare the treatment outcomes of the two methods. We have now revised the limitations of this study in the latter part of discussion as follows:

Revised Manuscript

(page 18, lines 9–23)

The current study had some limitations. **First, this was a retrospective study and did not include a randomized population.** Although propensity score matching reduced the confounding biases, not all biases, such as the endoscopists' preference of EMR or ESD, could be eliminated. There was a possibility of selection bias because lesions that could be easily snared were selected for EMR. Second, lesions treated with EMR tended to include adenomas, mucosal lesions, and small lesions. These rates among two groups were similar after matching, but the comparison of treatment outcomes was limited primarily to such lesions. Therefore, it is questionable whether these findings could be generalized to adenocarcinomas, submucosal invasive lesions, or large lesions. Third, the sample size was relatively small owing to propensity score matching, even though this was a multi-center study. Therefore, the differences in the effectiveness and safety between EMR and ESD are unclear for SNADETs. **A prospective study with a larger randomized population is expected to be conducted in the future.**

Response to Reviewer #3

Reviewer's comments

3. The lesion was superficial, so ESD was too over. I don't think GI-endoscopist will change their treatment preference after reading this paper.

Thank you very much for the valuable comments. As you pointed out, in this study, all the included lesions were superficial non-ampullary duodenal tumors. ESD seems to have a higher risk of procedure-related complications than does EMR. Over half of SNADETs, 11–20 mm in diameter, were treated by ESD according to our study and a previous study. As you pointed out, the preference of endoscopists is an important factor in the selection of the treatment methods for SNADETs. On the basis of our findings in this study, EMR might be promoted as the optimal treatment method for such lesions, considering safety and total medical cost with similar curative potential to that of ESD. We have made the following revision in the manuscript:

Revised Manuscript

(page 19, lines 6–10)

In conclusion, the results of our study demonstrated that EMR required a significantly shorter procedure time and hospital stay than did ESD, with comparable curative potential and a lower risk of adverse events. Therefore, EMR should preferably be selected as a local treatment for SNADETs, especially for adenomas, mucosal lesions, and small lesions.

Response to Reviewer #4

Reviewer's comments

4. The oncological results of EMR and ESD are controversial. Authors concluded in this paper that the EMR was curative treatment method in the treatment of SNADETs with some advantages of procedure time. On the other hand, the study does not contain any result about SNADETs patients. It cannot be made a decision about curation with this information. It must be re-written after evaluation of oncologic outcomes of SNADETs to make a conclusion about curation of methods.

Thank you very much for the valuable comments. As you pointed out, curability should be assessed by including long-term outcomes. Therefore, we added such data including the local recurrence rate, distant recurrence rate, follow-up duration, and 1-year follow-up rate; the local recurrence rate was 2.1% (3/142), the distant recurrence rate was 0% (0/142), the median follow-up period was 24.5 months, and the 1-year follow-up rate was 81.0% (115/142). The details are presented in Table 3 and supplemental Table 1. Three cases of local recurrence were observed in patients treated with EMR, who underwent piecemeal resection; the cases of local recurrence were successfully treated by salvage endoscopic resection, and no distant metastasis occurred. Although the follow-up rate and follow-up period were insufficient to demonstrate the accurate curability of EMR and ESD, we have emphasized the importance of en bloc resection and the acceptability of EMR, in the revised manuscript. Higher follow-up rate and longer follow-up period are required in future studies; we have included this as the limitations of the study. To clarify this point, we have revised the manuscript as follows: (The same revisions were made as the reviewer #1)

Revised Manuscript

(page 5, lines 11–22)

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vs. 0%, $P = 1$; metastatic recurrence rate: 0% in both).

Revised Manuscript

(page 11-12, lines 11–1)

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