Peer Review File

Article Information: https://dx.doi.org/10.21037/jgo-23-545

Reviewer A

General Comments 1

- There is a significant body of literature on this topic that has been overlooked/uncited by the authors. To name a few, an assessment of the clinicopathologic features of remnant gastric cancer (RGC), PMID: 34797185; a systematic review of the literature, PMID: 26667370; a meta-analysis with findings of no significant difference in histology and the TNM stage, PMID: 32253109; pathologic findings, PMID: 24895831. Even an extremely cursory literature review reveals that a significant volume of literature has been published on this topic. It would strengthen the manuscript significantly to talk about what is already known about RGC instead of repeatedly, and incorrectly, claiming that little is known.

Reply 1

We appreciate your thoughtful suggestion. As you mentioned, we excessively focused on the risk factors and did not mention the RGC features. According to your excellent comment, we have rewritten the Introduction section and cited the references you suggested.

Changes in the text:

(Before)

In the last few decades, male sex (4,9), old age (9), differentiated type (4), tumor depth (9), and synchronous multiple GC (6,10,11) have been reported to be associated with RGC development in previous reports. However, because only a few studies involving a small number of cases have described the risk factors for RGC development, the risk factors of RGC remain unclear. (Lines 110–114)

(After)

Male sex (7,10), old age (10), differentiated type GC (7,10), tumor depth (10), and synchronous multiple GC (9,11,12) have been reported to be associated with RGC development. However, these risk factors that have been previously identified were from studies that included only a small number of cases and had not been not fully understood. (Lines 107–112)

Radical surgery remains the only curative treatment for RGC; however, because of intraabdominal adhesions and different lymphatic structures in RGC, surgical treatment is complex and remains to be associated with relatively high rates of morbidity and mortality (2,13). Moreover, the reported 5-year

survival rates after gastrectomy were worse in cases of stage III RGC than in proximal primary gastric cancer cases (14). Moreover, ESD of the remnant stomach is technically difficult because of the limited working space, particularly for lesions that involve the suture line or anastomosis, which contains staples and may have severe fibrosis (15). However, the indications of ESD for primary gastric cancer can be applied to RGC (16). Compared with surgical treatment, ESD is considered a minimally invasive treatment even for early GC in the remnant stomach, based on the reported favorable long-term outcomes (15). Therefore, endoscopic surveillance of the gastric remnant for early detection of RGC that can be treated with ESD is extremely important. (Lines 113–125)

General Comments 2

- It is necessary to comment on the surgical margins. Such information is necessary to this topic/the manuscript and should be both discussed and included in Table 2.

Reply 2

Thank you for your excellent suggestion. To distinguish between cancer recurrence and newly developed GC, we excluded patients with positive surgical margins. According to your comment, we described the surgical margins in Table 2; the median proximal and distal margins were not significantly different between the groups. Moreover, we discussed the margin status and the reasons for excluding patients with positive margins.

Changes in the text:

(After)

The surgical margin status was not significantly different between the RGC and no RGC group (Table 2). (Lines 215–216)

RGC has been defined to encompass all cancers that arise from the remnant stomach after partial gastrectomy (2,3). This definition includes local recurrence in the gastric stump, synchronous GC that was not detected during preoperative endoscopic examination, and new GC arising from the gastric remnant. In the present study, we excluded patients with positive surgical margins during the primary operation in order to exclude local recurrence. Because the mechanism completely differs between local recurrence and newly developed cancer, inclusion of patients who developed local recurrence was not suitable for this investigation of the risk factors. Differentiating between missing synchronous GC and metachronous GC was difficult, although we thought that this was not clinically essential, because both lesions require similar treatment. Therefore, we defined RGC as GC in the remnant stomach, excluding recurrent cancer lesions after the initial curative resection. In the present study, surgical margin status was not significantly different between the RGC and no RGC groups. Therefore, short surgical margin was not associated with the

development of RGC. (Lines 250–263)

Table.2

(After)

Proximal margin, mm, median(range)	38(0.2-245)	30(0.6-90)	0.26‡
Distal margin, mm, median(range)	45(1-195)	47(13-170)	0.76‡

General Comments 3

- Can you comment on the average intervals between EGD surveillance in the RGC and nonRGC groups? Were any recurrences first noted by rising laboratory values versus EGD?

Reply 3

We appreciate that you pointed out that we did not mention the average intervals of the EGD surveillance in the RGC and nonRGC groups. According to your comment, we added information on endoscopic surveillance in Table 1. There were no RGC cases that were suspected for cancer recurrence based on increasing tumor marker levels.

Changes in the text:

(After)

The median endoscopic surveillance interval was 12 months, and no significant difference was observed between the RGC and no RGC groups (Table 1). (Lines 207–209)

All 11 RGC cases were detected by follow-up endoscopy. No RGC case was suspected for new recurrence based on increasing tumor marker levels. (Lines 226–227)

Table.1

(After)

Endoscopic interval, months, median(range)	12(1-70)	12(8-39)	0.11

Specific Comment 1

- Line 91: “RGC develops due to duodenal fluid regurgitation.” This statement requires a citation and/or should be qualified. “is thought to develop” or “is hypothesized to develop.”

Reply 1

Thank you for your thoughtful suggestion. According to your comment, we added the citation and revised

this sentence.

Changes in the text:
(Before)
RGC develops due to duodenal fluid regurgitation. (Lines 107–108)

(After)
RGC had been thought to develop secondary to duodenal fluid regurgitation (26). (Lines 287–288)

Specific Comment 2
- Lines 95–96: “because only a few studies involving a small number of cases have described the risk factors for RGC development, the risk factors of RGC remain unclear.” As above, there is a significant body of published literature on RGC. Risk factors have been identified, as cited. Perhaps you mean to say that risk factors are understudied, or not fully understood, or are an area of continuing investigation.

Reply 2
We appreciate your thoughtful comment. As you mentioned, there had been published systematic reviews and meta-analyses on RGC, and some risk factors have been identified. According to your comment, we revised our manuscript.

Changes in the text:
(Before)
However, because only a few studies involving a small number of cases have described the risk factors for RGC development, the risk factors of RGC remain unclear. (Lines 112–114)

(After)
However, these risk factors that have been previously identified were from studies that included only a small number of cases and had not been not fully understood. (Lines 110–112)

(Before)
In summary, the risk factors of RGC remain unclear. (Line 123)

(After)
In summary, the risk factors for RGC had been understudied. (Line 134)

Specific Comment 3

- Line 129: Misspelling of the word differentiated.

Reply 3

Thank you for your comment, and we apologize for our mistake. We corrected the spelling.

Changes in the text:

(Before)

differntiated types GC (Line 154)

(After)

differentiated types GC (Line 165)

Specific Comment 4

- Line 135: Is this the universally accepted definition? Would be helpful to include the universally accepted definition in the Introduction.

Reply 4

We appreciate your comment and the opportunity to clarify this point. In general, previous literature has defined RGC as all cancers arising from the remnant stomach after partial gastrectomy. Our definition was slightly different, because we thought that the mechanism of developing GC was different between local recurrence and a new lesion arising from the remnant stomach. To focus on the mechanism of developing GC arising from the remnant stomach, we excluded patients with positive surgical margins. To explain these, we mentioned the previously published definition and described the difference in our definition in the Discussion section.

Changes in the text:

(After)

The term RGC has been used to define all cancers arising from the remnant stomach after partial gastrectomy, regardless of the initial disease or operation (2,3). (Lines 95-97)

Specific Comment 5

- Line 247: instead of “considered” do you mean to say that you recommend intensive endoscopic surveillance?

Reply 5

We thank you for this comment. We wanted to convey that the patients who underwent DG for differentiated GC required intensive endoscopic surveillance. Therefore, we revised this word.

Changes in the text:

(Before)

Hence, we consider endoscopic surveillance even more than 5 years after curative resection. (Lines 261–262)

(After)

Therefore, we recommend endoscopic surveillance, even after more than 5 years of the curative resection. (Lines 302–303)

(Before)For patients who underwent a DG for differentiated type GC, we considered intensive endoscopic surveillance. (Lines 294–295)

(After)

For patients who underwent a DG for differentiated type GC, we recommended intensive endoscopic surveillance. (Lines 328–329)

Tables/Figures:

- Table 1: Misspelling of the work habitual

Reply

Thank you for your comment, and we apologize for our mistake. We corrected our spelling.

Changes in the text:

(Before)

habital-drinker	138 (52.3%)	5 (62.5%)

(After)

habitual-drinker	138 (52.3%)	5 (62.5%)

- Table 3: Should clarify that this is treatment of the RGC
- Table 3: Could include y/n associated with rise in CEA/CA19-9

Reply

We thank you for this comment. We revised Table 3 in order to clarify that this was the treatment for RGC. In all 11 cases, RGC was detected by follow-up EGD. No patients had increasing CA19-9 or CEA levels before the detection of RGC.

Changes in the text:

(Before)

Case	Age*	Sex	Pathology of initial GC	Reconstruction	Durations$	Intervals$$	Treatment	Pathology of RGC
1	84	M	Intestinal	R-Y	11 year	13 month	ESD	Intestinal
2	76	M	Intestinal	B-I	1 year	13 month	ESD	Intestinal
3	77	M	Intestinal	R-Y	4 year	12 month	ESD	Intestinal
4	68	M	Intestinal	B-I	1 year	12 month	ESD	Intestinal
5	73	M	Diffuse	B-I	2 year	13 month	Gastrectomy	Diffuse
6	72	M	Intestinal	B-I	4 year	13 month	Chemotherapy	Intestinal
7	49	F	Intestinal	R-Y	6 year	7 month	ESD	Intestinal
8	79	F	Intestinal	R-Y	5 year	19 month	ESD→ Gastrectomy	Intestinal
9	76	M	Intestinal	R-Y	3 year	40 month	Follow-up	Intestinal
10	68	M	Intestinal	R-Y	1 year	17 month	ESD	Intestinal
11	71	M	Diffuse	R-Y	1 year	13 month	ESD	Diffuse

* age at RGC documented.

§ Durations mean duration from initial operation for gastric cancer to diagnosis for RGC

§§Intervals mean intervals of endoscopic examination between detection of RGC and previous examination.

RGC ; remnant gastric cancer. M; male. F; female.

B-I; Billroth-I. R-Y; Roux-en Y. ESD; endoscopic submucosal dissection.

(After)

Case	Age*	Sex	Pathology of initial GC	Reconstruction	Durations$	Intervals$$	Treatment for RGC	Pathology of RGC	TNM of RGC
1	84	M	Dif	R-Y	11 year	13 month	ESD	DIf	T1aN0M
2	76	M	Dif	B-I	1 year	13 month	ESD	Dif	T1bN0M
3	77	M	Dif	R-Y	4 year	12 month	ESD	Dif	T1aN0M
4	68	M	Dif	B-I	1 year	12 month	ESD	Dif	T1aN0M
5	73	M	Und	B-I	2 year	13 month	Gastrectomy	Und	T1aN0M
6	72	M	Dif	B-I	4 year	13 month	Chemotherapy	Dif	T3N0M1(
7	49	F	Dif	R-Y	6 year	7 month	ESD	Dif	T1aN0M
8	79	F	Dif	R-Y	5 year	19 month	ESD→ Gastrectomy	Dif	T1bN0M
9	76	M	Difl	R-Y	3 year	40 month	Follow-up	Dif	T1aN0M
10	68	M	Dif	R-Y	1 year	17 month	ESD	Dif	T1aN0M
11	71	M	Und	R-Y	1 year	13 month	ESD	Und	T1bN0M

* age at RGC documented.

§ Durations mean duration from initial operation for gastric cancer to diagnosis for RGC

§§Intervals mean intervals of endoscopic examination between detection of RGC and previous examination.

‡ According to the Japanese Classification of Gastric Carcinoma 15th Edition

RGC; remnant gastric cancer. M; male. F; female.

Dif；differentiated type. Und; undifferentiated type

B-I; Billroth-I. R-Y; Roux-en Y. ESD; endoscopic submucosal dissection.

Reviewer B

This is a good study that evaluates the occurrence of remnant gastric cancer (RGC) following gastrectomy for gastric cancer. Overall, the study has been well executed, and despite the evaluation of a limited number of recurrence cases, it has offered some valuable insights.

However, the readability of the text could be improved. Several sentences contain grammatical and concordance errors (e.g., lines 38, 73, 129), making it challenging to understand the intended meaning. Additionally, there are editing errors (e.g., line 90), and inconsistencies throughout the text, which may suggest a lack of attention from the authors.

I have a few questions and suggestions for the authors:

Comment 1
In line 81, what is meant by "important cancer"? Please clarify the intended meaning.

Reply 1
We appreciate this comment. Because of the higher incidence of gastric cancer in Eastern Asia than in other regions, discussing gastric cancer was more meaningful. Therefore, we revised the term “important cancer” to “serious health problem.”

Changes in the text:
(Before)
The incidence rates are the highest in Eastern Asia, and GC is considered an important cancer, especially in those regions (1). (Lines 95–96)

(After)
In Eastern Asia, the incidence of GC is the highest among the other regions and is a serious health problem(1). (Lines 94–95)

Comment 2
Regarding the statement in line 88 about the nontumorous mucosa in primary GC potentially being the cancer-causing region for RGC, it would be beneficial to elaborate on this concept. Since your research results appear to be linked to this idea, further development and discussion are warranted. Additionally, in lines 229–234, it is important to provide more comprehensive evidence for the concept of carcinogenic mucosa and explain why it may remain undetectable for an extended period without developing into cancer

or other histological alterations.

Reply 2

We appreciate your thoughtful comment. Based on our study, we speculated that after DG for GC, RGC developed from an atrophic mucosa. Although the remnant stomach was affected by bile reflux, the mechanism was similar to the development of primary cancer. We identified differentiated type GC as a risk factor for RGC development; the atrophic gastric mucosa was considered a carcinogenic tissue on which differentiated type GC could develop. According to your comment, we explained this in detail in the Discussion section.

Changes in the text:

(Before)

Therefore, we speculated that RGC after gastrectomy for GC developed in the remnant stomach from the already formed carcinogenic tissue and bile reflex had no effect. (Lines 278–280)

(After)

Similar to the pathophysiology of primary GC, we speculated that after gastrectomy for GC, RGC developed from an atrophic gastric mucosa (i.e., carcinogenic tissue) in the remnant stomach. (Lines 295-297)

Comment 3

Could you explain the rationale behind not searching for and/or treating H. pylori in your service?

Reply 3

We thank Reviewer B for pointing this out. The relationship between GC development and metachronous GC prevention after ESD is proven. However, *H. pylori* eradication in patients who have undergone gastrectomy for GC has not been shown to prevent GC recurrence and prolong OS; we cited the pertinent article (i.e., *Cancer Res Treat*. 2016;48:1020–1029).

Changes in the text:

(Before)

however, a survival benefit from *H. pylori* eradication in patients who underwent gastrectomy for GC has not been shown. (Lines 286–287)

(After)

However, a previous study reported no survival benefit from *H. pylori* eradication in patients who have

undergone gastrectomy for GC (33). (Lines 320–321)

Comment 4

Furthermore, all tables require editing and improvement, including the addition of information such as tumor size (in millimeters), and if the continuos values are mean or median.

Reply 4

We appreciate your comment. According to your suggestion, we added detailed information in the tables.

Changes in the text:

Table.1

(Before)

Age, years (range)	68 (36-89)	71 (43-74)	0.63‡

(After)

Age, years, median (range)	68 (36-89)	71 (43-74)	0.63‡

Table.4

(Before)

Age
Tumor size of main lesion

(After)

Age, years
Tumor size of main lesion, mm