

ANSWERING REVIEWERS



November 13, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5543-review.doc).

Title: Epstein-Barr virus-associated lymphoepithelioma-like early gastric carcinomas and endoscopic submucosal dissection: Case series

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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

Reviewer 00070894

COMMENT: Chapter introduction has to be improved. We need more focus on the treatment strategy of EBV-associated early LELC. Here is no sufficient describe of the standard treatment radical gastrectomy with extensive D2 LN dissection for LELC. You had better add the detailed efficacy and side effect of the past therapy.

ANSWER: According to your comment we added the following sentences to 'Introduction' part: "Nakamura et al.^[4] reported that the 5-year survival rate of LELC and conventional adenocarcinoma patients undergoing surgical treatment was 84% and 58%, respectively."

COMMENT: In our opinion , the diagnosis of the rare disease is critical for us .You had better give the diagnosis criteria for EBV-associated early LELC in introduction part.

ANSWER: In this study, LELC was defined according to the pathologic criteria shown in previous study from our group (Song HJ, et al. Gastroenterology 2010;139:84-92): (1) well defined tumor margin, (2) dense lymphocytic infiltration of a degree whereby the number of tumor infiltrating lymphocytes was greater than the tumor cells throughout the tumor, (3) indistinct cytoplasmic borders and a syncytial growth pattern with poorly formed glandular structures, and (4) no desmoplasia. We added this definition to the 'Introduction' part.

COMMENT: In the discussion part of the article , we also want to know the efficacy and side effect of ESD therapy, for example gastric cancer.

ANSWER: According to your comment we added the following sentences to 'Discussion' part: "ESD is an effective therapeutic strategy for early GC, and is recognized as the preferred method of treatment in

selected cases. Studies have demonstrated that the *en bloc* resection rate of ESD is greater than 90%, regardless of tumor size, and that the long-term survival rate following ESD is comparable to that of radical gastrectomy. The reported rates of postoperative bleeding and perforation range from 3.4 - 7.6% and 1.0 - 6.1%, respectively^[6]."

COMMENT: However, the number of cases is too small to make a conclusion that treatment of EBV-associated early LELC by ESD will get the favorable outcome.

ANSWER: According to your comment we added the following sentences to 'Discussion' part: "One shortcoming of this report is the limited number of cases; to confirm our findings, data from a larger number of case studies needs to be collected and analyzed."

Reviewer 00069394

COMMENT: This is the report of 4 cases of EBV-associated early lymphoepithelioma-like gastric carcinoma (LELC) treated by endoscopic submucosal dissection (ESD) with long-term outcome. However, the number of cases is too small to make a conclusion that treatment of EBV-associated early LELC by ESD will get the favorable outcome. Moreover, this cancer type has been reported to have a favorable prognosis compared with ordinary gastric carcinoma. Thus the result obtained may be similar to other treatment modalities, please discuss in more detail regarding this point.

ANSWER: The representative treatment modality for LELC is radical surgery. Previous studies consistently reported that the prognosis after surgery for LELC was significantly better than that of ordinary gastric carcinoma. We added the following sentence to the 'Discussion' part: "Nakamura et al.^[4] also reported that the 5-year overall survival rate following surgical treatment is significantly higher in patients diagnosed with LELC (84%) compared to those with conventional adenocarcinoma (58%)." we also added the following sentences to 'Introduction' part: "Nakamura et al.^[4] reported that the 5-year survival rate of LELC and conventional adenocarcinoma patients undergoing surgical treatment was 84% and 58%, respectively."

Reviewer 00034993

COMMENT: The pathologic review of ESD specimen revealed deep submucosal invasion more than 500 µm in all cases. In general, patients diagnosed as gastric cancer with deep submucosal invasion is not applicable for ESD treatment.

ANSWER: We agreed to your comment and we recommended the additional surgery for all cases as described in our original manuscript. In case 2,3, and 4, however, patients were medically followed up without additional surgery after ESD because of severe comorbidities or patients' refusal to undergo operation. Please refer to the 'Case series' and 'Abstract' part.

COMMENT: How did authors these patients as EBV-associated early lymphoepithelioma-like gastric carcinoma (LELC)?

ANSWER: In this study, LELC was defined according to the pathologic criteria shown in previous study from our group (Song HJ, et al. Gastroenterology 2010;139:84-92): (1) well defined tumor margin, (2) dense lymphocytic infiltration of a degree whereby the number of tumor infiltrating lymphocytes was greater than the tumor cells throughout the tumor, (3) indistinct cytoplasmic borders and a syncytial growth pattern with poorly formed glandular structures, and (4) no desmoplasia. We added this definition to the 'Introduction' part.

COMMENT: Major influenced factor of gastric cancer is H. pylori infection. Authors should add

information of *H. pylori* infection and gastric mucosal atrophy.

ANSWER: According to your comment we added the information on *H. pylori* infection status and gastric mucosal atrophy of each case to the 'Case series' part.

Case 1: A similar biopsy from background mucosa identified the presence of chronic atrophic gastritis and *Helicobacter pylori* infection.

Case 2: A similar pathological review of the background mucosa identified the presence of chronic atrophic gastritis and *H. pylori* infection.

Case 3: Chronic atrophic gastritis was found in the background mucosa. Unlike the previous cases, *H. pylori* infection was not detected.

Case 4: Chronic atrophic gastritis, but no *H. pylori* infection, was detected in the background mucosa.

COMMENT: Please show pictures of endoscopic findings/EUS/pathology in all four patients.

According to your comment, we added the images of the endoscopic and pathologic findings of case 2 and case 4. Please refer to Figure 2 and Figure 4.

Reviewer 00048752

COMMENT: This is a presentation of 4 cases of EB virus associated lymphoepithelioma-like early gastric cancer treated by ESD. Although this report is interesting, the number of the cases are small and it is difficult to compare clinical outcome to the ESD for non EB associated gastric cancer.

ANSWER: According to your comment we added the following sentences to 'Discussion' part: "One shortcoming of this report is the limited number of cases; to confirm our findings, data from a larger number of case studies needs to be collected and analyzed."

Reviewer 00503601

COMMENT: Fairly well written case series of 4 cases of EBV associated LELC which have shown good outcomes on follow up after ESD.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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