

January, 2021

World Journal of Gastroenterology

Manuscript No: 61160

We would like to thank you for reviewing our manuscript. We appreciate the opportunity to revise the manuscript according to the recommendations of the reviewers. Please find below our responses to those comments, together with any corrections. We have reorganized the manuscript after due consideration of the recommendations. Please contact me if you have any questions.

Sincerely,

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Reviewer #1:

Specific Comments to Authors: This case report focused on a patient with locally advanced HER2-positive gastric cancer invading the pancreatic head, which was successfully treated with PD after neoadjuvant chemotherapy and anti-HER2 therapy. This manuscript is interesting, and it suggests that these patients might benefit from radical resection with PD after neoadjuvant chemotherapy plus trastuzumab. Here are some questions or advice:

1. Diagnosis of pancreatic head invasion is very important, and it is hard to distinguish cancerous invasion from desmoplastic reaction before surgical operation. For desmoplastic or inflammatory reaction, it is obviously unnecessary to perform PD that may cause fatal complications. Is it feasible to diagnose pancreatic head invasion through intraoperative pathological examination? If feasible, how to extract the tissue sample?

Thank you for your important comments.

It is impossible to diagnose pancreatic head invasion from an intraoperative pathology examination. If the head of the pancreas and surrounding tissue (fatty tissue, lymph nodes, fibrotic tissue, etc.) are in one mass, as in this case, the duodenum cannot be cut because the duodenum cannot be encircled. Thus, pancreaticoduodenectomy is required to secure the distal end of the gastrectomy, regardless of whether the tissue mass is infiltrated with a malignant tumor or has undergone benign inflammatory changes. Therefore, pancreaticoduodenectomy cannot be avoided based on the results of rapid pathology. In addition, in the case of pancreatic head infiltration, since no sample can be collected from the dissected cross-section for intraoperative rapid pathology, the presence or absence of cancer cannot be determined promptly during the operation.

2. To show pancreatic invasion by cancer cells clearly, a pathological figure with high magnification should also be provided.

Thank you for your advice. We have added a high-magnification figure showing pancreatic invasion.

3. For gastric cancer patients, how many people have pancreatic invasion, and how many of them are free of non-curative factors? It seems necessary to discuss these issues to specify the clinical significance of PD and neoadjuvant chemotherapy in gastric cancer.

Thank you for your important comments. According to a report from a high-volume national cancer center in Japan, 195 (2.1%) of 9349 cases of gastric cancer were suspected of having pancreatic head infiltration clinically. Of these, 23 (0.2%; 23/9349) underwent pancreaticoduodenectomy (PD). Among

those patients, eight (35%; 8/23) were diagnosed as pathologically incurable (para-aortic lymph node metastasis, lavage cytology positive, and peritoneum dissemination). Furthermore, according to a Japanese report, 120 (0.1%) of 120,202 surgical cases of gastric cancer required PD. Therefore, there are cases in which curable resection can be considered with PD, at a rate of about 1 in 500 to 1000 cases, and about one third of these may have intractable factors. Combining neoadjuvant chemotherapy may reduce the proportion of incurable cases and increase the rate of radical resection with PD.

We added this information to discussion.

Reviewer #2:

Specific Comments to Authors: The manuscript entitled ‘Pancreaticoduodenectomy after neoadjuvant chemotherapy for gastric cancer invading the pancreatic head: A case report. The results showed that radical resection with PD after neoadjuvant chemotherapy plus trastuzumab is an option for locally advanced HER2-positive gastric cancer invading the pancreatic head in the absence of non-curative factors. This paper is of scientific interest; however, there are several minor issues that if addressed would significantly improve the manuscript.

1. This is a single case report. The sample size is small. How to avoid selective bias?

Thank you for your important comments.

Because it is a case report, selection bias cannot be eliminated. The effect of preoperative trastuzumab chemotherapy on advanced gastric cancer will be revealed with the results of ongoing randomized controlled trials (JCOG1301). Until then, whether similar chemotherapy should be extrapolated for cases of pancreatic head infiltration will depend on the facility or case. As the number of case reports increases, neoadjuvant chemotherapy combined with trastuzumab may become widespread as a general medical option for advanced gastric cancer with pancreatic head invasion.

2. What is the safety of trastuzumab in the treatment of gastric cancer, especially in combination with other anti-tumor drugs? How to avoid side effects in combination therapy?

Thank you for your important comments.

The ToGA study, which is clinical trial examining the initial treatment of unresectable advanced recurrent gastric cancer and unresectable advanced esophagogastric junction cancer, found no difference in adverse events between the two groups, except for Grade 3/4 diarrhea (chemotherapy + trastuzumab 9% vs. chemotherapy 4%). The frequency of cardiovascular complications was similar. In the ToGA study,

hypertension, pruritus, rash, urticaria, chills, headache, joint pain, muscle pain, infusion-related reactions, fatigue, asthenia, drowsiness, malaise, nausea, vomiting, coughing, dyspnea, bronchospasm, hypotension, hypertension, tachycardia, and dizziness that occurred within 24 hours were all defined as infusion reactions. Based on this definition, Grade 3/4 infusion reactions occurred in 8% of the chemotherapy group and 6% of the chemotherapy + trastuzumab group, with no difference between the groups. Thus, there are no additional drugs to use when used with trastuzumab. As appropriate, aprepitant, 5-HT3 inhibitor, long-acting corticosteroid, etc., are actively used as antiemetics with reference to the guidelines for the proper use of antiemetics..

3. The author provided the time on the CT image in figure 2 and 5.

Thank you for your comments.

The exact date and time of CT imaging is not stated from the viewpoint of personal information protection. The figure legends states that Figure 2 is the initial CT and Figure 5 is the CT after neoadjuvant chemotherapy.

4. Scale bar is needed in figure 3 and 7.

Thank you for your advice. We added the scale bar to figure 3 and 7.

5. The references should be revised.

Thank you for your comments. We revised the references according to the guidelines.