

Peer Review File

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Reviewer A

This manuscript has been described some patients showed long OS who received ip PTX plus S-1/PTX followed by conversion surgery. Is there a new fact or recommendation in this manuscript comparing previous reports?

#1. Sample size in this retrospective study is small.

We appreciate the reviewer's comment.

Generally, CS (+) and CS (-) are compared in order to evaluate the usefulness of CS. However, this comparison takes into account the effects of chemotherapy and is not a valid evaluation. Although the number of cases in this study is small, it is the only result comparing responders who received the same chemotherapy with or without surgery. Additionally, the concept of this study has described in the introduction part: "Several retrospective studies have reported the long-term survival in selected patients after CS (10,11,12), but as yet, the role of CS is unclear. Because these previous studies have evaluated the significance of CS for the chemotherapy responder group compared with the chemotherapy non-responder group, it is difficult to identify whether these results are caused by the effect of chemotherapy or the effects of surgery.

A prospective randomized controlled trial is necessary to verify the efficacy of CS for responders to chemotherapy. However, undertaking such a randomized study to evaluate the safety and efficacy of CS might be difficult in this patient population, and so we conducted a retrospective study making use of updated our preliminary and phase II trial data (7,9), " (see Page 4, line 63-72).

#2. In patients with no target lesions, did author evaluate the antitumor effects based

*on the wall thickness of the primary tumor even for the patients with non-type 4?
Is it correct?*

We appreciate the reviewer's question.

Type 4 gastric cancer with no target lesions was evaluated based on the wall thickness. To clarify your point, we added the distribution of type 4 and non-type 4 in Table 1.

#3. Table 1 should include distribution of type 4 and non-type 4 because this variable was used in multivariate analysis.

We appreciate the reviewer's suggestion.

We added the distribution of type 4 and non-type 4 in Table 1.

#4. Table 3 should include univariate analysis at the same time. If multivariate analysis performed using 5 variables in only 31 patients, it should be incorrect as statistical method. In only 31 sample size, 3 variables should be appropriate.

We appreciate the reviewer's important suggestion.

We added the data of univariate analysis and we performed multivariable analysis only for two variables that showed significantly difference in univariate analysis in Table 3.

Reviewer B

Shinkai and Imano present a paper regarding patients with gastric cancer and PM. Since the study population is so small, it should preferably, be described as a case series.

As a reviewer, one wonders why such historical material, time period 2003-2008, is used? Are there no newer data? So the last patient was treated 13 years ago?

Follow-up is not defined in any clear way. Presumably all patients are dead?! But yet, you write that they were followed up until death, or last follow-up. When was the last follow-up? You mention that some lived more than five years, but if some were alive at the last follow up, they should have survived nearly 13 years.

We appreciate the reviewer's question.

The concept of this study using these historical material has described in the introduction part: "Several retrospective studies have reported the long-term survival in selected patients after CS (10,11,12), but as yet, the role of CS is unclear. Because these previous studies have evaluated the significance of CS for the chemotherapy responder group compared with the chemotherapy non-responder group, it is difficult to identify whether these results are caused by the effect of chemotherapy or the effects of surgery. A prospective randomized controlled trial is necessary to verify the efficacy of CS for responders to chemotherapy. However, undertaking such a randomized study to evaluate the safety and efficacy of CS might be difficult in this patient population, and so we conducted a retrospective study making use of updated our preliminary and phase II trial data (7,9), " (see Page 4, line 63-72).

As newer data, we updated the long-term prognosis of conversion surgery patients. The final follow-up of the date was May 2020, and we identified two recurrence-free patients more than 12 years after conversion surgery.

To clarify your point, we added the following to the main text: "And at the time of analysis (May 2020) two patients still alive over 12 years after CS, " (see Page 12, line 207-208).

Inclusive language, instead of male/female (which commonly refers to reproductive animals), it is advisable to use men/women.

We thank the reviewer for pointing out this error. This has been corrected to men/women.

The definition of median survival time (MST)? Why this abbreviation? Do you use OS interchangeably with MST?

The median survival time (MST) defines a period of time when the proportion of survivors in the treated population is exactly 50%.

We listed MST and OS together, not compatible.

We had described the survival data as follows in the main text: “OS of the two groups is shown in Fig. 2. At the time of analysis, the MST of the CTx group was 15.8 months and the 1-year, 2-year, and 5-year OS rates were 66.7%, 26.7% and 6.7%, respectively.

In the CSI group, the MST was 21.3 months and the 1-year, 2-year, and 5-year OS rates were 68.6%, 45.7% and 13.7%, respectively. Regarding survival rates, a significant difference was not observed among the two groups ($p=0.14$; 95% CI, 0.3016–1.197).

OS rates were analyzed in the two groups, taking into account differences in chemotherapy response and surgery. In the CTx group who have responded to chemotherapy, the 1-year, 2-year and 5-year OS rates were 77.7%, 22.2% and 11.1%, respectively, and the MST was 15.8 months. In the CSI group who underwent surgery, the 1-year, 2-year and 5-year OS rates were 77.2%, 59.1% and 21.8%, respectively, and the MST was 29.8 months. There was no significant difference in OS between the two groups in chemotherapy-responders ($p=0.059$; 95% CI, 0.1473–1.039) (Fig. 3).

However, four patients in the CSI group have survived >5 years. And at the time of analysis (May 2020), two patients still alive over 12 years after CS. Additionally, the MST of the chemotherapy non-responders in the CTx group was 15.4 months, and the 1-year and 2-year OS rates were 50.0% and 33.3%, respectively. The chemotherapy non-responders in the CSI group who did not undergo surgery demonstrated 1-year and 2-year OS rates of 53.8% and 15.3%, respectively, with MST of 14.7 months. There were no significant differences in OS between the two groups of chemotherapy non-responders ($p=0.957$; 95% CI, 0.383–2.758) (Fig. 4), (see Page 11-12, line 193-213).

The authors conflate multivariate with multivariable. The procedure that has been

performed is multivariable cox regression analyses. (See Hidalgo ‘Multivariate or multivariable regression?’)

We thank the reviewer for pointing out this error. This has been corrected to multivariable.

P 10. ‘curative total gastrectomy’ and ‘curative’ pancreaticoduodenectomy and ‘curative’ distal gastrectomy, how can this have been performed given the fact that there were peritoneal metastasis present? If so, how is this defined by the authors?

We appreciate the reviewer’s question.

We performed conversion surgery on the patients who were confirmed P0 and CY0 by second-look laparoscopy. We had mentioned the indication of conversion surgery in the main text: “In other words, when the response to chemotherapy was complete response, partial response or >30% improvement in wall thickness, we performed second-look laparoscopy. If negative conversion in the PM and negative peritoneal cytology findings were confirmed, we performed gastrectomy with D2 lymph node dissection, “(see Page 8, line 127-131).

P 10. An explanatory note on complications need to be included, and defined. The fact that only two patients had complications, despite these surgical procedures is very uncommon, unless the definition is not according to Clavien Dindo.

We appreciate the reviewer’s question.

We had described about complications in the main text: “Intraoperative and postoperative complications were reported according to the Clavien-Dindo classification,“ (see page 8, line 131-132).

And to clarify your point, we added the following to the main text: “Complications were defined by National Cancer Institute Common Toxicity Criteria Version 4.0 [17] and

recorded, “ (see Page 8, line 132-133).

P 12. “Unfortunately” there were no differences. Value judgments should be avoided.

We appreciate the reviewer’s important suggestion.

As reviewer pointed out, the word “unfortunately” has been deleted in the text.

p. 23 KM need to include numbers at risk. At the time line, x axis, need to be truncated. The four outliers, can be addressed in the main text.

We appreciate the reviewer’s important suggestion.

We added the data of numbers at risk in Figure 2.3.4 and 5.

How is anastomotic leakage defined? And Pancreatic fistula?

We appreciate the reviewer’s question.

To clarify your point, we added the following to the main text: ”Complications were defined by National Cancer Institute Common Toxicity Criteria Version 4.0 [17] and recorded” (see Page 8, line 132-133).

And we added reference 17 (U.S. Department of Health and Human Services, National Events (CTCAE) version 4.0, 2009) to the revised manuscript.

There are no reflections on the limitations of the study?

We appreciate the reviewer’s suggestion.

We added the following to the main text: “This study has several limitations.

First, this was a single-center, small-scale, retrospective study. Second, advances and

improvement in treatments and perioperative management may have impacted our results because the study period was old. These limitations might have affected several results; therefore, large validation studies are required to evaluate the role of CS for advanced GC with PM,” (see Page 16, line 279-283).

The most obvious limitation is the limited study population, where two heterogeneous groups are compared. The fact that there are a few long term survivors, makes me interested to know more about these specific patients. What was the final histopathological report for them? Was it a special form of cancer? No cancer? Any specific genetic alternations?

We appreciate the reviewer’s question.

To clarify your point, we added the following to the main text:” four patients who have survived > 5 years were ypN0 cases and one patient obtained pathological CR in the primary tumor, “ (see Page 15, line 260-262).

Where the patients discussed in a MDT conference? Where they considered to be palliative from the outstart? Since patients are retrospectively studied, it seems that they did not follow a pre determined study protocol. What was the reasoning when one decided to undergo surgery? Was it solely based on response on chemotherapy?

We appreciate the reviewer’s question.

We decided the treatment policy of each patient through the MDT conference.

Additionally, we had explained why we decided to undergo surgery in the introduction section: “However, no patients underwent surgery in our preliminary study, and the most common progression onset region was the primary tumor, not malignant ascites. These patients had obstructed stomachs owing to the increased size of the primary lesions (7). Based on these results, we considered that gastrectomy might improve the prognosis of the patients for whom our new regimen was effective. Therefore, in our

next phase II trial, we performed gastrectomy, termed conversion surgery (CS) (8) on patients who exhibited a response to combination chemotherapy”, (see Page 3-4, line 54-60).

To my mind, the present manuscript suggest that for a very small number of patients, CSI + chemo is possible. However, to compare results between the two arms is not really possible because (1) small numbers in each arm (will be more evident with numbers at risk); (2) the groups constitute different sets of patients. Patients that undergo resection is already a selected group.

My advice to the authors, is rephrase the ambitions of the manuscript, and instead present it as a case series with a few patients with long overall survival despite a palliative diagnosis.

We appreciate the reviewer’s suggestion.

We have submitted this manuscript as a mini review with updated clinical data, following JGO kind invitation to contribute to the focus issue dedicated to the 12th Peritoneal Surface Oncology Group International (PSOGI) Conference.