Author’s response to reviews

Title: Long-term outcomes and significance of preoperative lymphocyte-to-monocyte ratio as a prognostic indicator in patients with invasive pancreatic neoplasms after repeat pancreatectomy

Authors:

Shigetsugu Takano (stakano@faculty.chiba-u.jp)
Hideyuki Yoshitomi (yoshitomi@faculty.chiba-u.jp)
Shingo Kagawa (kagawas@chiba-u.jp)
Katsunori Furukawa (k-furukawa@umin.ac.jp)
Tsukasa Takayashiki (takayashiki@hospital.chiba-u.jp)
Satoshi Kuboki (kuboki@faculty.chiba-u.jp)
Daisuke Suzuki (d-kun@dai.vip.co.jp)
Nozomu Sakai (sakain@chiba-u.jp)
Takashi Mishima (takashimishima@khe.biglobe.ne.jp)
Eri Nakadai (erinakadai@hotmail.com)
Masaru Miyazaki (masaru@faculty.chiba-u.jp)
Masayuki Ohtsuka (otsuka-m@faculty.chiba-u.jp)

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Dear Dr. Yuliya Pylayeva-Gupta,
Editor of BMC Cancer

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Title: Long-term outcomes and significance of preoperative lymphocyte-to-monocyte ratio as a prognostic indicator in patients with invasive pancreatic neoplasms after repeat pancreatectomy.

Thank you for your letter inviting a revised manuscript. To that end, we enclose by Takano et al. "Long-term outcomes and significance of preoperative lymphocyte-to-monocyte ratio as a prognostic indicator in patients with invasive pancreatic neoplasms after repeat pancreatectomy".
We note the general enthusiasm by the reviewers and provide a point-by-point response to the helpful comments and insights. We added and analyzed the information about the nature of relapse and the detail of medical treatments before repeat pancreatectomy. We hope this revised manuscript is deemed meritorious for publication as we believe the topic of repeat pancreatectomy for isolated tumor recurrence in the remnant pancreas is timely, engendering broad appeal to the community of gastroenterological oncology and the BMC Cancer readership.

Sincerely yours.

Masayuki Ohtsuka M.D. Ph.D.,
Professor and Chairman
Department of General Surgery
Chiba University, Graduate School of Medicine
E-mail: otsuka-m@faculty.chiba-u.jp

Reviewer 1

We greatly appreciate your constructive comments to improve our manuscript.

1- section Methods: repeat pancreatectomy was performed in 29 patients, but 26 out of 28 underwent repeat complete pancreatectomy in this cohort. It is not clear how many patients were included in the study. What means "complete" pancreatectomy?

[Authors' reply for 1] We agree with the reviewer’s comment. To avoid a confusion and clarify the number of participants, we added the term “of this study” in Results section, line 5, page 6. Furthermore, we promptly corrected “complete” to “completion” pancreatectomy in the revised manuscript (Results section, line 8, page 6).

2- What means local recurrence after repeat pancreatectomy?

[Authors' reply for 2] We apologize the inadequate term. We amended “local recurrence” to “local recurrence at pancreatic bed” in the revised manuscript (Results section, line 2, page 7) and (Figure legend section, Figure 3b).

3- Authors stated that median cancer specific survival time was 61 months showing favorable outcomes. However, no comparison was made with other populations, i.e not resected patients, patients treated with chemotherapy, etc.

[Authors' reply for 3] We appreciate this suggestion so much. This is a really important point which is also suggested by the other reviewer. We analyzed the survival outcome of patients who were treated with chemotherapy instead of repeat pancreatectomy in this same period (July 2006 and July 2016). Since we actively attempted to undergo repeat pancreatectomy (RP) for the patients with the isolated local recurrence after initial pancreatectomy, only 6 patients who received chemotherapy only were found as the comparable candidates. Despite of the limited number, the Kaplan-Meier analysis showed a significant difference of survival between the RP group and the chemotherapy group (P < 0.0001; Figure 4a). We included this additional data in the revised manuscript (Results section, line 13-15, page 7).
4- Which treatment should be suggested for those patients with isolated pancreatic recurrence and low preoperative LMR?

[Authors' reply for 4] According to the additional analysis for the survival, no significant difference on survival was observed between low preoperative LMR group and chemotherapy group (revised Figure 4c). We added the result (Results section, line 4-6, page 8) and discussion (Discussion section, line 2-3, page 11) in the revised manuscript.

Reviewer 2

We sincerely thank the reviewer so much for giving us the meaningful and important suggestions.

1) To specify whether the relapse was a local recurrence in continuity with the primary tumor previously resected or a new cancer in the remnant pancreas. You should differentiate the two situations and if the numerosity is adequate you could consider also this parameter in the analysis.

[Authors' reply for (1)] We thank to the reviewer’s comments. To specify these two situations in the remnant pancreas as the reviewer indicated above, we assessed whether the location of tumor relapse was at the margin of initial resection or not. In the cohort of this study, there was no difference of survival between these two types of tumor recurrence. This parameter was included in the univariate analysis of the revised Table 2.

2) Did the patients have any chemo or radiotherapy after initial diagnosis of recurrence? if yes did they have any impact on survival after recurrence resections? which kind of therapy did they receive before surgical exploration?

[Authors' reply for (2)] As the reviewer pointed out, we assessed whether chemo or radiotherapy after initial diagnosis of recurrence had any impact on survival of the patients who underwent repeat pancreatectomy. Eight patients received chemotherapy (S-1 for 4 patients, gemcitabine for 2 patients, and gemcitabine plus S-1 for 2 patients) and 1 patient received carbon-ion radiotherapy before repeat pancreatectomy. There was no difference of patients’ survival between surgery first and neoadjuvant therapy prior to RP. This information and result were added in the revised manuscript (the first paragraph of Results section and the univariate analysis of the revised Table 2).

3) Do you have a cohort of recurrent patients who were not suitable for operation even after chemo or radiotherapy? which was the impact of LMR in this subgroup? Actually, the survival after resection for Patients who have LMR<3,3 is still interesting and probably better if compared with medical treatment. Could you add some informations about that? This could help a lot the Clinicians whether to operate or not based upon LMR.

[Authors' reply for (3)] We appreciate this great suggestion. As the reviewer recommended, we attempted to find the patients who were administrated chemotherapy for isolated local recurrence in the remnant pancreas after initial pancreatectomy, instead of second operation. In the same period, only 6 patients who received chemotherapy without operation were found. We compared the survival of patients between surgical treatment and medical treatment in the Kaplan-Meier analysis (in the revised Figure 4a). We also compared the survival between LMR < 3.3 group and medical treatment group in the revised Figure 4c, and there was no significant difference between these two groups. We added the data (Results section, line 13-15, page 7 and line 4-6, page 8) and discussion (Discussion section, line 2-3, page 11) in the revised manuscript.