

Peer Review File

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Reviewer A

We sincerely appreciate for your valuable comments and criticism for our manuscript. We will make point-by-point responses as shown in underlined sentences;

I read with interest a manuscript that is considered as a novel concept in pancreas cancer care and the results are interesting and important despite small sample size, which is but natural considering the patient selection for such aggressive treatment approach in advanced cases.

I have minor comments:

Comment 1. In Table 1 i see authors have calculated NLR PNI. But this is not included in discussion and i suggest to include some information of these variables in conversion surgery (if there is data) or their role in general in PDAC outcomes in BR or BRLA cases.

Reply 1; I added the following sentence; The neutrophil-to-lymphocyte ratio³⁰ and prognostic nutritional index as a nutritional parameter which can be correlated with prognosis in patients with PDAC did not differ among three groups in this study.

Changes in the text: the above sentence was added on Line 305, page 17.

Comment 2. I see in Table 1 patients are grouped in R : BR : UR groups. I am confused as you have grouped many patients in R = resectable group. In study method section you make it clear that only patients with liver mets were given conversion surgery allocation - than how can they have 5 patients in R group. I remain confused. Pls check and clarify or edit the data in all 3 columns for this variable.

Reply 1; Resectability status of PRIMARY TUMOR (R: BR: UR) was categorized in Table 1. “UR” in Table 1 was changed to “UR-LA” for easy recognition. The following sentence was added; “Resectability status of primary tumor such as R/BR/UR-LA was categorized in Table 1.”

Changes in the text: The above sentence was added on line 111, page 7 in Methods session. “UR” in Table 1 was changed to “UR-LA”

Comment 3. In Table 2 you have many patients given S1 chemotherapy. I see no mention about this in method or discussion section. I see Gemcitanine and folfirinox etc mentioned. Pls include some discussion of S1.

Reply 1; The sentence “in addition to Gemcitabine + S-1 as a key drug in Japan” was added in Discussion.

Changes in the text: It was added on Line 267, page 15.

Comment 4. I am very interested to see that conversion surgery improves OS but not RFS. What could be the reasons?

Reply 1; I agree with you. Firstly when the number of recruited patients who underwent conversions surgery increases, statistical significance of RFS seems to appear. At the moment, we mentioned on page 16 in Discussion that “the conversion surgery group contained super-responders to systemic chemotherapy before surgical resection; therefore, the early recurrence rate was relatively low and they received chemotherapy for a median (range) of 21 (16 to 57) months, even after disease recurrence, leading to the improved OS.”. Conversion surgery can make patients chemotherapy-free for a certain period. During this period, immuno-nutritional function may improve in these patients, resulting in longer time for chemotherapy. Since it is just a hypothesis, we will re-evaluate them in the future.

Changes in the text: none

Comment 5. If i understand correctly, a patient was un resectable due to liver mets, chemo was given, liver mets shrunk or disappeared, you then operated the patient and you removed liver met when it was evident on image and did not remove met when it disappeared. Is this correct? If so, this is different than our general guidance on colorectal liver mets where disappearing mets are many times also removed (the area of liver where disappearing mets reside is resected based on anatomical considerations). If my understanding is wrong - i suggest you to make an algorithm / flowchart in method section of the 3 included groups and omit/delete some text. Figure/algorithm may reduce confusion.

Reply 1; Your understanding is correct. In this study, a sample biopsy of the liver was done for confirming no liver metastasis when it disappeared in patients with multiple liver metastasis in bilateral lobes.

Changes in the text: Flow diagram was newly formed as Fig 1.

Comment 6. Title should include the "retrospective" study.

Reply 1; “in a retrospective study” was added in a title.

Changes in the text: “in a single-center retrospective study” was added in a title.

Comment 7. Abstract should include the ABC-LM concept that you have later discussed. See if you can do within the word count limit. It cannot than i leave it to you to add-include or omit or add-include with deleting something else.

Reply 1; AMC-LM concept (“**The surgical indication of conversion surgery was fixed as the ABC criteria, namely, Anatomical objective response of disappearance of liver metastases on imaging studies, Biological response of CA19-9 level decrease to \leq 150, and Conditional response of surgical fitness. In addition to the above ABC criteria, tumor disappearance at the liver was repeatedly confirmed using staging laparoscopy (laparoscopic response; L), and metabolic complete responses were confirmed using PET-CT (metabolic response; M).**”) was inserted in the abstract (word count; 300).

Changes in the text: It was added in the abstract on Line 46, page 3

Comment 8. metamorphic response by PET - is it dependent on biochemical response of CA19-9. Is it possible to omit doing PET if CA19-9 correlates with bright spots in PET IMAGES? Can discuss this. I mean if ALL positive pet scans can be known by raised ca19-9 than we dont have to do pet scan?

Reply 1; It is a very interesting and important issue. Generally, CA19-9 does not seem to correlate with bright spot in PET images in patients with PDAC because multiple occult metastasis or pancreatitis can affect on metabolic response. In this study, the number of patients was too small to discuss this issue. We would like to make the other research for solving this important clinical question. Thanks for your sharp pointing out.

Changes in the text: none

Comment 9. Add 1-2 lines more about ABC and ABC-LM concept. Some futuristic use.

Reply 1; We added the following sentences: Meeting ABC criteria may mean suitable general condition of a candidate for surgical resection. Meeting additional LM criteria may mean less activity of the tumor. As a result, meeting ABC-LM criteria may offer better surgical indication of conversion surgery in PDAC patients with liver metastasis.

Changes in the text: The above sentences were added on Line 289-296, page 16.

Comment 10. 2-3 practical tips to readers on how they can use these results to their practice.

Reply 1; The following sentences were added: Regardless of the number of liver metastases, conversion surgery may be considered if chemotherapy provides favorable responses meeting ABC-LM criteria to systemic chemotherapy. Liver resection may be avoided in patients showing no viable tumor with liver biopsy. Further study will be required for investigating necessity of liver resection in patients with PDAC.

Changes in the text: The above sentences were added on Line 322-5, page 18

Reviewer B

We sincerely appreciate for your valuable comments and criticism for our manuscript. We will make point-by-point responses as shown in underlined sentences;

Satoi et al. investigated 49 patients with pancreatic ductal adenocarcinoma with synchronous liver metastasis only between 2007 and 2022 and divided them into three groups based on conversion surgery, namely conversion surgery group, upfront surgery with or without short-term neoadjuvant chemotherapy (UpS/short NAC group) and chemotherapy group, To explore the effect of conversion surgery on patients with good anatomical, biological and conditioned response to systemic chemotherapy. The authors explored the median survival time (MST) between the three groups, which was 36.7 months (95% CI, 19.0-84.8) in the conversion therapy group versus 10.4 months (95% CI, 6.6-17.8) in the UpS/short NAC group and 9.9 months (95% CI, 19.0-84.8) in the chemotherapy group(95% CI, 8.3-10.9) had significant difference. The authors also compared relapse-free survival (RFS) in the conversion and UpS/short NAC groups, and found that one and three patients in the UpS/short NAC and

conversion groups achieved five-year survival, respectively, including two patients who initially had multiple liver metastases (≥ 10). These findings provide preliminary evidence for the beneficial effect of conversion surgery on survival in patients with PDAC synchronous liver metastasis.

Although some of these observations are well documented and persuasive, this study leaves much to be desired. As this study is a single-center retrospective study, small sample size and selection bias are major factors affecting the statistical accuracy. In addition, this paper does not have a clear explanation and definition of "good anatomy", "biology" and "conditioned response". Some of the other major issues are listed below. In order to represent a significant contribution, these observations should be addressed substantively.

Major points:

Comment 1. Page 2, 34: Comparison of Median survival time (MST) between the UpS/short NAC group and the chemotherapy group.

Reply 1; The following sentence was added in the abstract; [UpS/short NAC vs. chemotherapy, p=0.564.](#)

Changes in the text: the above sentence was added in the abstract.

Comment 2. Page 2, 36: The specific group of two patients who initially had multiple liver metastases was not explained.

Reply 1; The word of "[in the conversion surgery group](#)" was added.

Changes in the text: the above word was added in the abstract.

Comment 3. In the Introduction section, the author can introduce the existing studies on UpS/short NAC and MST chemotherapy for resectable or resectable recessive liver metastases.

Reply 1; In Introduction, we already introduced the excising studies. "Several studies have revealed that MST after synchronous resection of liver metastases with or without short-term neo-adjuvant therapy ranged from 5.9 to 15.7 months.³⁻⁹" We would be pleased if you could indicate detailed suggestions again. We apologize our misunderstandings if so.

Changes in the text: none

Comment 4. Page 7, 170: There is a grammatical error here, please remove the word "of".

Reply 1; We appreciate for your suggestion. It was deleted

Changes in the text: the word "of" was deleted.

Comment 5. Page 8,196,198: There are two grammatical errors. Please add the word "the" before "patients" and "efficacy".

Reply 1; We appreciate for your corrections. The word "the" before "patients" and "efficacy" were added.

Changes in the text: The corrections were added on Line 243 and 245, page 14.

Comment 6. Figure 1, Figure 2: The P-value of significant difference for comparison of survival

analysis between groups should be marked on Figure 1 and Figure 2.

Reply 1; We appreciate for your suggestions. The p-value was marked.

Changes in the text: The p-value was newly marked on Fig 1 and 2.

Comment 7. Table 1: A list of significant difference P-values for UpS/short NAC group comparison should be added to Table 1.

Reply 1; P-value between UpS/short NAC and chemotherapy groups was added in Table 1.

Changes in the text: P-value between UpS/short NAC and chemotherapy groups was added in Table 1.

Comment 8. General: The sample size was too small, and the number of patients alive after 24 months in the UpS/short NAC group and the chemotherapy group was very limited when comparing between groups, which may lead to limitations in the reliability of statistical analysis.

Reply 1; I agree with your suggestions. These issues are study limitation. The word “**and limitations in the reliability of statistical analysis**” was added.

Changes in the text: The above words were added on Line 327-8, page 18.

Comment 9. General: Lack of grouping with or without adjuvant chemotherapy to explore the effect of surgery with or without chemotherapy on the prognosis of PDAC.

Reply 1; Adjuvant chemotherapy was not administered in two patients who underwent surgical resection following short NAC because they suffered from post-operative complication and early recurrence within 6 months after surgical resection. The 16 out of 18 patients who underwent surgical resection received adjuvant chemotherapy. Therefore, clinical effectiveness of adjuvant chemotherapy cannot be evaluated in this study. Further study will be required.

Changes in the text: none

Comment 10. There are several articles relevant to your research, please add 2 references from the list below.

1) International assessment and validation of the prognostic role of lymph node ratio in patients with resected pancreatic head ductal adenocarcinoma (doi: 10.21037/hbsn-21-99. PMID: 36523941; PMCID: PMC9745624)

2) The microbiome as a potential diagnostic biomarker for pancreatic ductal adenocarcinoma (PDAC) (doi: 10.21037/hbsn-22-380. PMID: 36268252; PMCID: PMC9577974)

Reply 1; The above two references were added. “Other useful surrogate markers **such as circulating tumor cells²⁸ or DNA²⁹, Lymph node ratio³⁰, the microbiome³¹ and so on** for a complete response of liver metastasis should be explored in the future.”

Changes in the text: The above words were added on Line 265-6, page 15.

Reviewer C

We sincerely appreciate for your valuable comments and criticism for our manuscript. We will make point-by-point responses as shown in underlined sentences;

I have several queries and comments.

Comment 1. Control group includes the patients who received chemotherapy with occult liver metastasis diagnosed at operation (p4, Method). Primary tumor of these cases was not resected during treatment course? Or some of these cases converted after favorable response with chemotherapy (7 months or longer)? Please provide the flow diagram of this study as Figure, and define the study groups.

Reply 1; All patients in control group did not undergo surgical resection of the primary tumor as well as liver tumor. We newly provided the flow diagram of this study as Fig 1.

Changes in the text: The new Fig 1 was added.

Comment 2. Please show the duration of chemotherapy in Control group. If the duration was more than 7 months, selection bias would decrease in comparison of survival with Conversion group.

Reply 1; Median duration of chemotherapy of 6.1 months in the control group significantly shorter than 9.2 months in the conversion surgery group (p=0.011).

Changes in the text: none

Comment 3. In addition to regimen of systemic chemotherapy, treatment strategy might be changed during long study period. Please indicate that the resected cases in Table 2 was experienced in “latter or former” study period. This would also be mentioned as a limitation of this study in Discussion session.

Reply 1; Column of “latter or former” study period was added in Table 2. The sentence “**surgical resection in 15 out of 18 patients was performed in the latter phase (2015-2022) of this study, that may mean the changes in treatment strategy.**” was inserted in the study limitation.

Changes in the text: New column of study period was added in Table 1. The above sentence was added on Line 329-331, page 18.