Author's response to reviews

Title: Successful surgical approach for a patient with encapsulating peritoneal sclerosis after hyperthermic intraperitoneal chemotherapy: a case report and literature review

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RESPONSE TO REVIEWER:

We wish to express our appreciation to the Reviewer for his or her insightful comments, which have helped us improve the paper.

Reviewer 1

Reviewer's report:

The authors describe their experience in surgical treatment of a patient with encapsulating peritoneal sclerosis occurring 15 months after HIPEC.

Comments:

#1. The rationale for hyperthermic IP 5-FU is unclear as minimal drug penetration of only 0.2 mm and no thermal enhancement has been reported suggesting that 5-FU is not effective in the context of HIPEC but maybe normothermic or bidirectional regimens.

Response: We reported in vitro study that hyperthermia at 42°C significantly enhanced the sensitivity of 5-FU to the antitumor agents, compared to normothermia (37°C) [reference 3]. Thus, we used 5-FU for HIPEC protocol in our institute.

#2: The indication for HIPEC in this patient should be discussed. A patient with an UICC stage II cancer without lymph node infiltration and without peritoneal
disease does not seem to be at high risk for developing PM.

Response: The indication for HIPEC at our institute is at high risk for developing PM, including, serosal invasive cancer, cytology positive case. Present case was indicated at serosal invasive advanced cancer. In this manuscript, it is noted at first sentence in section “case presentation”. In addition, the number of dissected nodes was noted as follows: [The number of dissected lymph nodes was 10 at this operation.] (line 55-56)

#3: Most reports show sclerosis after several applications of IPC corresponding to the effect seen during CAPD. The possible reasons for EPS after singular HIPEC application might be discussed. Where there any risk factors in this patient? Where there any signs of (subclinical) peritonitis during the postoperative course or follow-up?

#4: A sclerosing effect of doxorubicin is well known if doses higher than 15 mg/sqm body surface are used. Thus, the dependence of EPS on the drug regimen should be discussed.

Response to comment #3 and #4: In accordance with the reviewer’s comment, we revised the sentence concerning the cause of EPS and the role of chemotherapy as follows.

[Most of the cases developing EPS underwent intraperitoneal chemotherapy including platinums. One of the possible causes of EPS in patients undergoing CAPD is related to the low pH of the dialysate [7]. The incidence of EPS decreases in response to agents that neutralize the pH of the dialysate [7]. In our method, the optimal pH for Oxaliplatin ranges from approximately 4.0 to 7.0 [4], and this acidity might contribute to the development of EPS.] (line 95-99)

In next paragraph, we revised and discussed the correlation between developing EPS and influence of singular HIPEC.

[Shindo et al. reported that peritoneal damage was not dissimilar between patients given HIPEC and those given continuous normothermic peritoneal perfusion using 37.0°C perfusate [12]. However, hyperthermia induced intracellular acidosis [13] and may accelerate instability in intracellular pH. Thus, we consider hyperthermia may be a cause of EPS.] (line 102-105)

And we could not find out the especial risk factor or unusual postoperative course in this patient.

#5: page 7, line 96f: This sentence does not make sense and should be revised.

Response: In accordance with the reviewer’s comment, we have revised this sentence. [Previous reports have described EPS occurred even among patients treated by normothermia [8, 10].] (line 101-102)
#6: page 7, line 89: There are great series including a French clinical trial with programmed surgical revision and 2nd or 3rd CRS/HIPEC procedures showing no higher rates of EPS. Thus, this sentence should be deleted from the revised manuscript as 30-40% is definitely too high.

Response: In accordance with the reviewer’s comment, we deleted this sentence.

Page 8, line 108: Did you mean overall morbidity rate?
Response: As reviewer pointed out, we corrected mortality to morbidity.(line 113)

Page 4, line 27: This trial has been published as a phase I NOT phase II study.
Response: As reviewer pointed out, we corrected it. (line 26)

Page 4, line 30: There are numerous publications regarding overall morbidity and mortality after CRS/HIPEC. The morbidity rates of about 30% and the presence of numerous reports should be mentioned in the revised manuscript.

Response: In accordance with the reviewer’s comment, we have added the next sentences about complications after HIPEC.

[Several report showed the morbidity rates after HIPEC were 20.8-53.3% [6]. Major complications may include nephrotoxicity, hemotoxicity, postoperative hemorrhage, anastomotic leakage, intestinal perforation, and wound complications [6]. EPS is a rare surgical complication that can occur after HIPEC.] (line 87-90)

Reviewer 2

Reviewer’s report:
- Major Compulsory Revisions
  1: there is no the “discussion” section but only the case presentation.

Response: Accordingly to this journal instruction, we structured our article as follows: Background, Case presentation, Conclusion. The discussion is included in the section of case presentation.

2: the discussion is too fragmented and the review of the literature might be more accurate; you should base your discussion on the role of chemotherapy in developing EPS
Response: In accordance with the reviewer’s comments, we deleted too accurate sentence about the literature review. And we revised the sentence concerning the cause of EPS and the role of chemotherapy as follows.

[Most of the cases developing EPS underwent intraperitoneal chemotherapy including platinums. One of the possible causes of EPS in patients undergoing CAPD is related to the low pH of the dialysate [7]. The incidence of EPS decreases in response to agents that neutralize the pH of the dialysate [7]. In our method, the optimal pH for Oxaliplatin ranges from approximately 4.0 to 7.0 [4], and this acidity might contribute to the development of EPS.] (line 95-99)

3: at line 83 you report the number of cases in the literature but you’re not exhaustive and you don’t cite the casuistic reported in the line 87. The table is incomplete: you report only the cases treated with surgery; you should make a more exhaustive table of EPS after intraperitoneal chemotherapy;

Response: As reviewer pointed out, we added the case noted in reference [11] in Table 1.

Best of our knowledge, in EPS after intraperitoneal chemotherapy, the cases treated by conservative treatment such as steroid therapy were not reported previously.

- Discretionary Revisions

1: you may report with more detail the hipec procedure with more detail in the postoperative course.

Response: In accordance with the reviewer’s comment, we have revised the procedure of HIPEC as next sentences.

[Briefly, the laparotomy incision was closed until an 18-cm opening. An Alexis Wound Retractor (Applied Medical Resource, CA, USA) and plastic cylinder were used to make a waterbath space for HIPEC. A perfusate of 5 L saline solution (Otsuka Pharmaceutical Factory, Tokushima, Japan) was circulated at flow rate of 500-750 mL / min by using the CP-3000 system (Tonokura, Tokyo, Japan).] (line 44-49)

And we added the sentences about postoperative course.

[There were no postoperative complications, and 4 days after the operation, he started oral intake. He was discharged from hospital on the 8th postoperative day.] (line 56-58)

2: how many day after the hospital admission and the initial conservative treatment the patient were operated? You should describe how was the medical treatment, which dosage? For how many days?
Response: In accordance with the reviewer’s comment, we have added the details of the treatment before operation.

[After admission, we diagnosed as EPS based on these data. He was treated with decompression via long intestinal tube and with intravenous betamethasone administration. After 3 days, intestinal obstruction did not improve with such conservative treatments.] (line 66-69)

- "Minor issues not for publication"

Line 87, the name of the author cited is wrong (baraly#braly)

Response: In accordance with another reviewer’s comment, the sentence including this name was deleted it.

Reviewer 3

The Authors report a single case of successful surgical treatment of encapsulating peritonitis due to HIPEC.

This clinical case is not so rare, nor the presented surgical solution is original nor it adds data to the actual management of patients with EPS. Furthermore, many criticisms have to be made, as follows.

Major Compulsory Revisions

• Is iv steroid therapy useful for EPS? Are there some data in the Literature?

Response: Reference 15 showed that EPS after CAPD was relieved in 3 of 18 patients.

• In the abstract and in the text the diagnosis made by CT are different

Response: We revised the sentence in Abstract section similarly to that of text:

[Abdominal computed tomography showed a dilated small intestine enveloped by a thickened membrane.] (line 10-11)

• The duration of the intervention should be mentioned

Response: In accordance with reviewer’s comment, we added next sentence.

[After admission, we diagnosed as EPS based on these data. He was treated with decompression via long intestinal tube and with intravenous betamethasone administration. After 3 days, intestinal obstruction did not improve with such conservative treatments.] (line 66-69)

• Why a first laparoscopic, diagnostic approach was not envisaged?
Response: We selected laparotomy rather than laparoscopic approach for avoiding bowel injury.

• 18 post-operative days are quite long for an uneventful course; please comment
Response: In our case, the meal was gradually given. And we considered that hospital stay is largely affected by local social traditions, the health care system, and the patients’ housing condition. We added the detail of postoperative course.

[Seven days after the operation, he started oral intake. He was discharged from hospital on the 18th postoperative day.] (line 77-79)

• English style should be revised
Response: In accordance with the reviewer’s comment, we revised the sentence in our manuscript.

• Grammar should be checked
Response: Our manuscript was carefully checked by native-English speaker.

Minor Essential Revisions
• In many Centers HIPEC is run for more than 30 minutes, as You did. Please Comment
Response: Several reports showed that HIPEC was run for 30-120 minutes. The appropriate time of peritoneal perfusion is unclear. However, we considered that more than 30 minutes were necessary until the peritoneum kept the temperature at hyperthermic therapeutic effect we expect.

• The number of nodes harvested in the first operation would be interesting (for determining the prognosis)
Response: Present case is at high risk for developing peritoneal metastasis, based on serosal invasive caner. The number of dissected lymph nodes was 10 at first operation.

We added the sentence in case presentation.

[The number of dissected lymph nodes was 10 at this operation.] (line 55-56)

• The adjuvant chemotherapy course was a little bit quick (3 months); there was a particular reason not to performing the classical 6-months schedules?
Response: He felt abdominal discomfort since starting adjuvant chemotherapy. So he did not wish to continue adjuvant chemotherapy.
Follow-up should be reported in the abstract Response: In accordance with the reviewer’s comment, we have added this sentence in Abstract. [Seven months after surgery, he is well with no recurrence.] (line 14)

Reviewer 4

Minor Essential Revisions:

Line 26: remove the words peritoneal metastasis and the brackets to the abbreviation PM.

Response: In accordance with the reviewer’s comment, we have replaced “peritoneal metastasis” to “PM”.

Line 77: insert the term CONCLUSION Response: Accordingly to this journal instruction, we structured our article as follows: Background, Case presentation, Conclusion. The section “Conclusion” was placed in line 125.