

Peer Review File

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Reviewer A:

1) The article does not (clearly) state what the outline of the research question is for this review article. What is the novelty of this review article compared to the Cochrane article published in 2016?

Reply 1: A Cochrane article published in 2016 recommends SL to reduce unnecessary laparotomies that are not curatively resectable.

In this review, we would like to emphasize that SL can lead to more accurate pretreatment diagnosis and appropriate treatment based on early and appropriate resectability classification. The abstract of this article has been changed.

2) The authors state peritoneal and cytological metastasis. However, they do not include liver metastasis found by SL. This should be taken into account in the search of the value of SL in pancreatic cancer, and should be included in the results of this review.

Reply 2: As you pointed out, the SL provides partial information on liver metastasis in addition to cytology (CY) and peritoneal dissemination (P), but it can only point out the presence or absence of liver surface metastasis, not all liver metastasis. In this article, I would like to discuss the significance of SL focusing on CY and P.

3) line 97: CT was superior to PET-CT in terms of diagnostic performance ($p=0.072$). This p-value is not significant? So if this was the case the author can not state that CT was superior to PET-CT.

Reply 3: No significant difference as you indicated. The wording of the statement has been changed.

Changes in the text:

~~although there was no significant difference between MRI and PET-CT ($p=0.94$), CT was superior to PET-CT in terms of diagnostic performance ($p=0.072$).~~

→ the diagnostic performance of CT was considered good among these.

4) Table 2 : Suker et al is stated that the patients were staged as Borderline Resectable. That is not correct to my knowledge, the article states that the patients included were UR-LA

Reply 4: The relevant section in Table.2 has been changed from "BR" to "UR-LA".

5) Table 2: Cytology results are shown. Cytology is still much debated in SL of pancreatic cancer. The added value is not proven. Could the authors state what the yield is of cytology above biopsies in SL in the articles that performed cytology during SL .

Reply 5: The fact that the percentage of positive peritoneal washing cytology is higher

than that of positive peritoneal dissemination suggests that the process of peritoneal dissemination is preceded by a situation in which cancer cells are first spilled into the peritoneal cavity.

Reviewer B:

This paper is a review article dealing with the clinical usefulness and indication of staging laparoscopy (SL) for pancreatic cancer.

With the recent development of multimodality treatment for pancreatic cancer, accurate staging by SL is important. The present review article presented provide important clinical implications.

I have some questions and comments about this manuscript.

Major comments

1. In surgery for pancreatic cancer, the factors that lead to unresectable after laparotomy include micro liver metastases and distant lymph node metastases (para-aortic lymph nodes) in addition to P and CY factors. Considering the usefulness of SL, the identification of micro liver metastases by observation of the liver surface should be discussed.

Reply 6: As you pointed out, the SL provides partial information on liver metastasis in addition to cytology (CY) and peritoneal dissemination (P), but it can only point out the presence or absence of liver surface metastasis, not all liver metastasis. In this article, I would like to discuss the significance of SL focusing on CY and P.

2. As shown in the TABLE 2, there are unresectable cases at laparotomy even after SL. The authors mentioned the possible influence of the accuracy of SL; the items and techniques to be searched for during SL should be discussed. Several questions are raised as to what techniques are recommended. How many and where is the lavage ascites fluid collected from? Whether do you perform echoes, lymph node and peritoneal nodule sampling?

Reply 7: In general, SL is performed using the following techniques.

Staging laparoscopy is performed with the patient supine under general anesthesia. After creating a 12 mm port at the umbilicus, pneumoperitoneum was established and maintained at 10 mmHg. An endoscope was used to fully view the abdominal cavity, and two additional 12-mm ports were placed in the left abdomen. After the small intestine was moved cephalad with the patient in the Trendelenburg position, peritoneal lavage cytology with 100 ml of saline was collected. The small intestine and mesentery from the end of the ileum to the proximal jejunum were then carefully observed to confirm the presence of peritoneal seeding. The omental bursa was not opened. Finally, the presence or absence of liver nodules was confirmed by direct visualization and/or laparoscopic ultrasonography. Patients with nodular lesions suspected of metastasis underwent excisional biopsy.

However, we believe that there are differences in technique between institutions and that the items to be evaluated by laparoscopy for each case may differ. We believe that peritoneal nodules with suspected metastases should be aggressively evaluated, but we do not recommend lymph node sampling in all patients who do not have such nodules.

3. NAC will be the standard treatment for resectable pancreatic cancer. The appropriate timing of SL is important as clinical information: before or after NAC? Treatment strategy in case of positive unresectable factors (CY, P, or liver metastases) should also be discussed.

Reply 8: As you have pointed out, appropriate timing of SL is important, especially now that NAC has become the standard of care for resectable pancreatic cancer. We believe that review laparoscopy should be performed prior to the start of all treatment, as accurate evaluation of resectability classification prior to the start of treatment is essential, except from the perspective of cost-effectiveness. In addition, a positive unresectability factor should be treated as UR-M.

Minor comments

1. In the Table 2, does "peritonitis" mean peritoneal dissemination?

Reply 9: Changed description to "Peritoneal dissemination positive rate".

2. In the Table 2, the year of publication by Takadate is different between the Table 2 (2020) and Reference (2021). Which is true?

Reply 10: The year 2021 is correct and has been unified with 2021.

3. Prof. Fujii who is listed as the last authors is one of famous pancreatic surgeon. Is the corresponding author OK with the current status?

Reply 11: The corresponding author was changed to Tsutomu Fujii.

4. I recommend several recent papers (Pancreatology. 2022 Jun;22) should be listed in the Table 2.

Reply 12: This paper was added to Table 2.

Reviewer C

The authors described the significance of staging laparoscopy in multidisciplinary treatment for pancreatic cancer.

I read it with interest, but I found it difficult to decide whether SL is really useful. I have several questions.

1. On page 5, line 97, "However, the paper noted that less than half of the cases of peritoneal seeding..."

Please check if the description is correct. Is "less than half of the cases" right, not

"more than..."?

Reply 13: Since the cited reference states that 24 of 113 cases (21.2%) were first noted to have peritoneal dissemination at laparotomy, we changed the wording to "about 20% of cases".

2. On page 7, line 155, the authors described, "it is important to reevaluate patients who have responded to chemotherapy and are being considered for resection by SL prior to radical resection."

Is there actually any literature on SL before radical resection after response to chemotherapy?

Reply 14: Although SL for accurate staging and resectability classification has already been reported as mentioned above, the literature on SL for determining treatment efficacy is scarce, and this item is a subject for future study.

3. In order to determine the usefulness of SL in terms of cost-effectiveness, etc., it would be necessary to include cases in which peritoneal dissemination was not detected as a result of SL, or cases in which peritoneal dissemination was first detected during laparotomy after SL.

Has the true efficacy of SL been clarified for the high-risk cases of peritoneal dissemination you mentioned?

Reply 15: Sensitivity and specificity in detecting peritoneal dissemination are always an issue when performing SL. Since performing SL on all patients, including those who are resectable, will increase medical costs, we believe that it is necessary to appropriately apply SL to those at high risk for peritoneal dissemination, such as those with large tumor diameters and high tumor markers.