



# Significance of staging laparoscopy in multidisciplinary treatment for pancreatic cancer: a narrative review

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**Background and Objective:** Accurate evaluation of resectability classification before treatment initiation is particularly important in recent treatment strategies for pancreatic cancer. The problem is to consider which pancreatic cancer patients should be evaluated for gross and microscopic peritoneal dissemination by staging laparoscopy (SL) before treatment initiation.

**Methods:** From January 2000 to December 2020, a literature about SL for pancreatic cancer search was performed using the PubMed database without language or geographic restriction to identify eligible studies. Titles and abstracts were screened to identify relevant articles, and evaluated for eligibility using predefined inclusion and exclusion criteria. Studies that mentioned peritoneal dissemination in reports examining the diagnostic performance of various therapies for distant metastases of pancreatic cancer were included. Articles were excluded if (I) they were not written in English, (II) relevant data could not be extracted, or (III) they were case reports, reviews, or letters to the editor.

**Key Content and Findings:** Previous reports have been mixed in their diagnosis and definition of peritoneal seeding, including gross and histopathological diagnosis by SL and experimental laparotomy, diagnosis by ascites cytology, and imaging diagnosis with consideration of the clinical course. Indications for SL were limited except in cases that were candidates for surgical treatment, and the inability to microscopically assess for peritoneal seeding limited the diagnosis of peritoneal seeding in pancreatic cancer based on imaging alone. About diagnosis of pancreatic cancer with peritoneal dissemination by SL, 21% to 25% of patients diagnosed as resectable (R) by imaging were found to be unresectable (UR) by SL. On the other hand, 5–18% of patients who underwent SL had UR lesions diagnosed at laparotomy. Looking at microscopic and gross peritoneal dissemination diagnosed at SL by resectability, peritoneal dissemination tended to increase with progression, ranging from 2.2% to 23.8% in R, 12.1% to 28.6% in borderline resectable (BR), and 19.0% to 49.1% in unresectable locally advanced (UR-LA). In particular, more than half of UR-LA pancreatic cancers were cytology (CY) positive for peritoneal dissemination, suggesting that it is difficult to diagnose peritoneal dissemination by existing imaging alone.

**Conclusions:** SL may contribute to more accurate pretreatment diagnosis, which in turn may lead to appropriate treatment based on early and appropriate resectability classification.

**Keywords:** Pancreatic cancer; staging laparoscopy (SL); peritoneal dissemination; cytology (CY); resectability

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## Introduction

Pancreatic cancer is a highly lethal malignancy and the seventh-most common cause of death worldwide (1). The presence of gross and microscopic peritoneal dissemination is important in the diagnosis and treatment of pancreatic cancer. The prognosis of pancreatic cancer with peritoneal dissemination is particularly poor, with the median survival time (MST) reported to be approximately 7 months (2). Based on an analysis of pancreatic cancer cases registered by the Japan Pancreatic Society, Tsuchida *et al.* reported that intraoperative cytology (CY)-positive cases had a poorer prognosis than negative cases (MST: 17.5 vs. 29.4 months) (3), even in resectable (R) pancreatic cancer cases. In recent pancreatic cancer treatment strategies, accurate evaluation of resectability classification before starting treatment is said to be particularly important.

Staging laparoscopy (SL) is a low-invasive procedure that can identify occult distant metastases, resulting in appropriate patient selection for chemotherapy or chemoradiation therapy. The clinical usefulness of SL has been reported in several kind of cancers (4-6).

The question arises as to which pancreatic cancer patients should be evaluated for gross and microscopic peritoneal dissemination (positive CY of peritoneal lavage) by SL prior to the start of treatment.

In this article, we review the significance of SL for the treatment of pancreatic cancer based on previous reports. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://ls.amegroups.com/article/view/10.21037/ls-22-37/rc>).

## Methods

### *Data sources and literature search*

A literature search was conducted from January 2000 to December 2020 without language or geographic restriction using the PubMed database to identify eligible studies. Titles and abstracts were screened to identify relevant articles, and potentially relevant articles were examined in full text to assess eligibility using predefined inclusion and exclusion criteria. The search terms were defined as “pancreatic neoplasms” or “pancreatic cancer” or “pancreas cancers” or “pancreatic ductal adenocarcinoma” or “pancreas cancer” or “pancreatic carcinoma” and “peritoneal metastasis” or “peritoneal dissemination” or “peritoneal carcinomatosis” or “carcinomatosis” or “malignant ascites” and “staging laparoscopy”. These database searches

were supplemented by manual searches of reference lists of included studies. These searches were performed on separate occasions by all co-authors, and consensus meetings were held to resolve any discrepancies.

### *Inclusion and exclusion criteria*

In addition to the above search terms, studies that mentioned peritoneal dissemination among the reports examining the diagnostic performance of various modalities for distant metastasis of pancreatic cancer were included in this review. Articles were excluded if: (I) not written in English; (II) relevant data could not be extracted; and (III) they were case reports, reviews, or letters to the editor.

An overview of the search method is shown in *Table 1*.

### **Limitations of the diagnostic performance of peritoneal dissemination of pancreatic cancer by imaging modalities alone**

Multidetector-row computed tomography (MDCT), ethoxybenzyl magnetic resonance imaging (EOB-MRI), positron emission tomography computed tomography (PET-CT), and endoscopic ultrasonography (EUS) are useful imaging modalities for the diagnosis of pancreatic cancer other than SL. We reviewed the literature describing peritoneal dissemination among the reports examining the diagnostic ability of various imaging modalities other than SL for distant metastasis of pancreatic cancer.

In the literature on contrast-enhanced CT reading regarding the diagnostic performance of peritoneal dissemination, there is a report comparing the diagnostic performance by three readers using 2.5 mm slice axial images and 6 mm slice 3D reconstructed images (7). The sensitivity of axial images reports by the three readers was 72%, 50%, and 51%, and that of reconstructive images was 69%, 42%, and 51%, suggesting that interreader discrepancies can occur and that both types of images may complement each other in diagnostic performance.

Three meta-analyses evaluating the diagnostic performance of abdominal MRI for distant metastasis of pancreatic cancer have been reported (8-10), with some reporting that MRI is superior to CT in diagnosing vascular invasion and distant metastasis, while others report that they are equivalent, and it is not clear whether one should be given priority. None of these reports mentioned the diagnosis of the presence of peritoneal dissemination, and the diagnostic performance of MRI for peritoneal dissemination,

**Table 1** The search strategy summary

Items	Specification
Date of search	1 April 2022
Databases and other sources searched	PubMed
Search terms used	“pancreatic neoplasms” or “pancreatic cancer” or “pancreas cancers” or “pancreatic ductal adenocarcinoma” or “pancreas cancer” or “pancreatic carcinoma” and “peritoneal metastasis” or “peritoneal dissemination” or “peritoneal carcinomatosis” or “carcinomatosis” or “malignant ascites” and “staging laparoscopy”
Timeframe	From January 2000 to December 2020
Inclusion and exclusion criteria	Inclusion criteria: in addition to the above search terms, studies that mentioned peritoneal dissemination among the reports examining the diagnostic performance of various modalities for distant metastasis of pancreatic cancer were included in this review  Exclusion criteria: (I) they were not written in English; (II) relevant data could not be extracted; (III) they were case reports, reviews, or letters to the editor
Selection process	Data were extracted from the included studies by all authors
Any additional considerations, if applicable	Discrepancies were resolved through a consensus meeting

including micrometastases, is unsatisfactory (11).

A meta-analysis compared PET-CT and CT in the staging of pancreatic cancer (9). The sensitivity and specificity of PET-CT for the diagnosis of distant metastasis were reported to be 67% and 100%, respectively. Compared with the sensitivity and specificity of CT, which are 57% and 91%, respectively, PET-CT is more specific and useful for the diagnosis of distant metastasis. However, there is no reference for the diagnosis of peritoneal dissemination, and its diagnostic ability is not clear.

A retrospective study of the validity of a staging protocol using CT, MRI, and PET-CT in 232 cases of pancreatic cancer has been reported (12). The positive findings of peritoneal dissemination by each modality were 57% for CT, 22% for MRI, and 26% for PET-CT, and the diagnostic performance of CT was considered good among these. However, the paper noted that in approximately 20% of cases, peritoneal seeding was first noted at laparotomy, suggesting a limitation in the diagnosis of peritoneal seeding by these imaging modalities.

One meta-analysis evaluated the diagnostic performance of EUS for the resectability of pancreatic cancer, but the diagnostic performance of EUS for peritoneal seeding has not been reported (13). EUS has high spatial resolution and is more capable of diagnosing the presence of ascites than CT, and EUS-fine needle aspiration (EUS-FNA) is capable of qualitative diagnosis of peritoneal seeding (14-16). EUS-FNA is a relatively invasive test with complications

reportedly occurring in 0.3% of cases (17), and the indication for EUS-FNA should be carefully considered.

Previous reports have mixed diagnoses and definitions of peritoneal seeding, including gross and histopathological diagnosis by SL or exploratory laparotomy, diagnosis by ascites CY, and imaging diagnosis taking into account the clinical course of the disease. Diagnostic performance may be overestimated because the indications for SL or exploratory laparotomy are limited except in cases that may be candidates for surgical treatment, and the presence of microscopic peritoneal dissemination cannot be evaluated. It is hoped that appropriately designed studies will validate the diagnostic value of imaging for peritoneal dissemination.

### **Diagnosis of pancreatic cancer with peritoneal dissemination by SL (meta-analysis and retrospective studies)**

Except in advanced situations where ascites effusion is evident, peritoneal seeding in pancreatic cancer is often a microscopic lesion, and the sensitivity of imaging modalities such as MDCT, MRI, PET-CT, and EUS is poor. In many cases, peritoneal dissemination is diagnosed at the time of laparotomy in pancreatic cancer patients scheduled for resection, resulting in an exploratory laparotomy. It has been reported that peritoneal dissemination was found in 7–19% of pancreatic cancer patients diagnosed as locally advanced by MDCT (18,19), indicating that MDCT has limitations in

**Table 2** Systematic review and meta-analysis of pancreatic cancer cases undergoing SL

Author	Year	Number of trials	Disease	n	Unresectable by SL	Unresectable at laparotomy
Allen VB, <i>et al.</i>	2016	16	Pancreatic and periampullary cancer	1,146	20%	18%
Ta R, <i>et al.</i>	2019	15	Pancreatic cancer	R: 1,756; UR-LA: 242	R: 20%; UR-LA: 36%	All: 5%
Hariharan D, <i>et al.</i>	2010	29	Pancreatic cancer and bile duct cancer	2,905	25.0%	14.4%

SL, staging laparoscopy; R, resectable; UR-LA, unresectable locally advanced.

**Table 3** Analysis of peritoneal dissemination in a retrospective study of pancreatic cancer cases undergoing laparoscopy

Author	Year	Resectability/stage	n	Peritoneal dissemination positive rate	CY positive rate	Unresectable at laparotomy
Shoup M, <i>et al.</i>	2004	UR-LA	100	7%	12%	–
Morak MJ, <i>et al.</i>	2009	UR-LA	68	3%	21%	–
Contreras CM, <i>et al.</i>	2009	R/UR-LA	R: 25; UR-LA: 33	8%; 21%	–; –	12%; –
Clark CJ, <i>et al.</i>	2010	UR-LA	202	3%	20%	–
Schnelldorfer T, <i>et al.</i>	2014	Stages I–III	136	2.2%	–	8.8%
Satoi S, <i>et al.</i>	2016	UR-LA	67	23.9%	23.9%	–
Peng JS, <i>et al.</i>	2017	BR	75	–	4%	–
Suker M, <i>et al.</i>	2019	UR-LA	91	12.1%	–	–
Takadate T, <i>et al.</i>	2021	R/BR/UR-LA	R: 42; BR: 49; UR-LA: 55	0%; 6%; 11%	24%; 22%; 38%	5.4%
Imamura T, <i>et al.</i>	2022	R/BR/UR-LA	48	13%	44%	–

CY, cytology; UR-LA, unresectable locally advanced; R, resectable; BR, borderline resectable.

diagnosing microperitoneal dissemination. Thus, peritoneal dissemination cannot be diagnosed by preoperative imaging of pancreatic cancer in many cases, and SL is useful for the diagnosis of peritoneal dissemination. Although SL requires general anaesthesia and is invasive, it has been reported to be more useful than other modalities for the diagnosis of peritoneal dissemination in terms of both sensitivity and positive diagnosis rate (18,19).

There are three systematic review and meta-analyses on the diagnosis of distant metastasis by SL, as shown in *Table 2*. Sixteen studies by Allen *et al.* for pancreatic or periampullary cancer in 1,146 patients (20), 15 studies by Ta *et al.* for R or unresectable (UR) pancreatic cancer in 1,998 patients (21), and Hariharan *et al.* analysed 29 studies (22), which consisted of 3,305 patients with pancreatic or bile duct cancer. In these analyses, 21%, 20%, and 25% of patients diagnosed as R by imaging were found to be UR by SL. On the other hand, among the patients who underwent SL, the percentages of UR lesions diagnosed at laparotomy

were 18%, 5%, and 14.4%.

*Table 3* shows the results of a retrospective cohort study examining the significance of SL in pancreatic cancer staging, with false-negative rates (2,23–31). There is also a report showing the diagnostic rate of peritoneal and/or microscopic dissemination (CY positive) for each resectability category of unresectable locally advanced (UR-LA), borderline resectable (BR), and resectable (R) cases (30). Although all the reports are retrospective studies, microscopic peritoneal dissemination was diagnosed in 4–44% of cases, and positive gross peritoneal dissemination was diagnosed in 2.2–23% of cases by SL for pancreatic cancer. On the other hand, 5.4–12% of cases were diagnosed as R by SL but were found to be UR due to distant metastasis or local invasion during subsequent laparotomy. Whether these cases progressed over time from the time the SL was performed to the time of laparotomy or whether the accuracy of SL itself was a problem is a matter of debate. At the very least, there are cases in which

the SL results in a change in the resectability classification to a more advanced one. When divided by resectability category, microscopic and gross peritoneal dissemination diagnosed by SL tended to increase from 2.2–23.8% in R, 12.1–28.6% in BR, and 19.0–49.1% in UR-LA lesions, with an increasing trend towards peritoneal dissemination as the disease progressed. Especially in UR-LA pancreatic cancer, more than half of the cases were microscopically positive for peritoneal dissemination, suggesting that it is difficult to diagnose peritoneal dissemination by existing imaging techniques alone. Although careful judgement is required to discuss these cases together because of the different publication dates and patient backgrounds, SL may be useful in the diagnosis of peritoneal dissemination. In particular, if peritoneal dissemination cannot be ruled out when radical resection is planned, SL before treatment is initiated is likely to avoid unnecessary exploratory laparotomy. As described above, peritoneal dissemination is highly probable in locally advanced lesions. Therefore, it is important to reevaluate patients who have responded to chemotherapy and are being considered for resection by SL prior to radical resection.

### **Cost-effectiveness of laparoscopy and selection of eligible patients (selection of high-risk group for peritoneal dissemination)**

If unnecessary laparotomy can be avoided by SL, postoperative pain can be reduced, hospital stay can be shortened, and patients can be transferred to effective treatment such as chemotherapy earlier, thereby extending prognosis (2). On the other hand, postoperative complications from SL have been observed, although they are not frequent. In the meta-analysis by Hariharan *et al.* described above, the frequency of postoperative complications was 0.4% (15 of 3,305 patients), and the mortality rate was 0.03% (1 patient) (22). Of the 15 complications, bleeding requiring laparotomy (20%) and port site infection (20%) were the most common.

In terms of cost, if an experimental laparotomy can be avoided by performing SL for cases with peritoneal dissemination, individual costs can be reduced by shortening the hospitalization period. However, performing SL for all patients with pancreatic cancer, including those who can be resected, would conversely increase medical costs. From this point of view, it is necessary to apply SL appropriately to patients at high risk of peritoneal dissemination.

There are few reports on risk factors for peritoneal

dissemination of pancreatic cancer. Patients with locally advanced pancreatic cancer are considered a high-risk group because peritoneal dissemination is diagnosed in 19–49.1% of patients by SL. In particular, peritoneal dissemination was diagnosed in 65% of patients with pancreatic caudal carcinoma exceeding 42 mm in diameter by laparoscopy (19). De Rosa *et al.* searched for the keywords “pancreatic cancer” and “staging” in articles published between 2000 and 2014 and reviewed 24 articles. They reviewed these studies and reported on a high-risk group for distant metastasis. In this review, the authors reported that CA19-9 >150 U/mL or tumour diameter >30 mm were risk factors for potential distant metastasis in patients who were considered R by CT and that SL should be performed for screening (32).

Based on the above, we believe that performing SL for pancreatic cancer patients who intend to undergo surgery is useful for improving the diagnosis rate of peritoneal dissemination and avoiding unnecessary exploratory laparotomies. On the other hand, considering cost and complications, it is appropriate to perform laparoscopy after selecting appropriate cases, and it is necessary to consider the establishment of a high-risk group for peritoneal dissemination positivity. Tumour size and tumour markers such as CA19-9 may be useful indicators. In addition, the positivity rate of peritoneal dissemination may differ depending on R, BR, and UR-LA cases, but there are few reports on them. A meta-analysis to establish a high-risk group for positive peritoneal dissemination using these markers and a prospective cohort study of the established high-risk group are warranted.

### **Conclusions**

SL is useful in the diagnosis of peritoneal dissemination, which is difficult to evaluate by imaging studies, and it is important to perform SL after appropriate patient selection, especially when surgery is planned but peritoneal dissemination cannot be ruled out.

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