



Impact of Surgery on Oligometastatic Pancreatic Cancer: Current Status and Future Perspectives

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Pancreatic cancer treatment has advanced. In particular, effective chemotherapy regimen development has fundamentally altered the therapeutic concept and strategy for pancreatic cancer treatment. Consequently, the prognosis of patients with pancreatic cancer has gradually improved. Conversion surgery for locally advanced pancreatic cancer may offer long-term survival or even a full recovery in some individuals. In contrast, metastatic pancreatic cancer has long been considered a surgical contraindication because aggressive surgical resection of the metastatic lesions does not prolong patient survival. Unexpectedly positive benefits of anticancer therapy in recent clinical experience were observed even with metastatic pancreatic cancer. To date, little evidence presented the success of surgical resection for metastatic pancreatic cancer treatment in such rare cases. However, hope and concern are growing that surgical intervention, even in patients with metastatic cancer, may result in favorable outcomes. Several studies suggested different surgical intervention effects depending on metastasis sites and patterns. Thus, this review summarizes the current status of surgery in the multidisciplinary treatment of oligometastatic pancreatic cancer and discusses future perspectives.

Key Words: Neoplasm metastasis; Pancreatic neoplasms; General surgery; Drug therapy; Biomarkers

INTRODUCTION

Pancreatic cancer is one of the most difficult human malignancies to treat. Surgery is generally contraindicated in advanced pancreatic cancer, even with one distant metastatic lesion [1]. However, recent advancements in the treatment of pancreatic cancer may change therapeutic concepts and strategies, even for metastatic pancreatic cancer. Even in cases of advanced pancreatic cancer, we occasionally see unexpectedly positive benefits of anticancer therapy in daily clinical practice. In such cases, surgical resection might result in long-term survival or even a complete cure.

Oligometastasis is considered an intermediate state between localized and polymetastatic disease [2]. Currently, the best treatment for oligometastasis in pancreatic cancer, despite being widely discussed, remains controversial. There

are several clinical questions regarding oligometastasis in pancreatic cancer. First, what is the definition of oligometastasis in pancreatic cancer? Second, does surgery play a significant role in the multidisciplinary treatment, even in patients with oligometastasis? Third, what is an appropriate biomarker to predict efficacy of treatment and determine surgical indications in oligometastatic pancreatic cancer?

In this review, we present an update on the current status of surgery in the multidisciplinary treatment of oligometastatic pancreatic cancer, and discuss future perspectives.

MAIN SUBJECTS

Definition of Oligometastasis

Although oligometastatic disease is usually defined as less



than five distant metastases in an organ, the definition of oligometastasis in pancreatic cancer is not yet established. While some published studies have focused on oligometastatic pancreatic cancer, the definition of oligometastasis varies [3-6]. Furthermore, previous studies have reported that the results of surgical treatment for oligometastasis differ depending on the metastatic site. Therefore, it is important to evaluate the results of surgery and consider the optimal therapeutic strategy for oligometastatic pancreatic cancer based on the metastatic site and organ.

Surgery for Oligometastasis of the Liver

The liver is well-known to be the most common metastatic site of pancreatic cancer. Liver oligometastasis is usually defined as the presence of less than three to five potentially resectable hepatic tumors. However, surgical resection of liver metastases from pancreatic cancer has not been proven to enhance survival in these select patients. However, some previous studies reported a favorable effect on postoperative survival, a range of 5.9 to 56 months for median survival

times (MSTs) (Table 1) [3-19].

Hamad et al. [19] recently published the prognosis of 47,785 patients with pancreatic cancer with liver-only metastasis in the National Cancer Database of the United States. This is the most extensive study to date. After propensity-score matching, patients who received multimodal treatment, including surgery for oligometastatic liver metastases, had significantly longer median overall survival (OS) than those who received chemotherapy alone (15.6 months vs. 8.1 months).

Preoperative chemotherapy [6,12-15] or metachronous hepatectomy [10,11] are likely to be important for long-term survival based on a review of previous studies. Takeda et al. [6] recently reported four preoperative biological and conditional prognostic factors: CA19-9 < 1,000 U/ml, a performance status of 0, a modified Glasgow prognostic score of 0, and patient’s age < 70 years [6]. If patients with three or four of these factors received chemotherapy, their CA19-9 was normalized, and the radiological response was confirmed, surgery would provide an excellent prognosis of 54.6 months in OS. In the study by Takeda et al. [6], 10 (11.8%)

Table 1. Studies on surgery for synchronous liver oligometastasis in PDAC

First author	Year	Country	No. of patients	OS from initial treatment (mo)
Takada et al. [7]	1997	Japan	11	6
Gleisner et al. [8]	2007	USA	17	5.9
Seelig et al. [9]	2010	Germany	14	11
Dunschede et al. [10]	2010	Germany	23 ^a	8 (synchronous) 31 (metachronous)
Zanini et al. [11]	2015	Italy	15 ^a	9.1
Wright et al. [12]	2016	USA	15	34.1
Tachezy et al. [3]	2016	Germany Italy, France	69	14.5
Crippa et al. [13]	2016	Italy	11	46
Frigerio et al. [14]	2017	Italy	24	56
Hackert et al. [4]	2017	Germany	85 ^a	12.3
Tanaka et al. [15]	2019	Germany	43	21.9
Safi et al. [5]	2021	Germany	35	10.3
Shao et al. [16]	2021	China	50	16
Takeda et al. [6]	2022	Japan	10	54.6
Hank et al. [17]	2022	Germany	64	19.2 ^b
Bachelier et al. [18]	2022	France	92	18.26
Hamad et al. [19]	2022	USA	137	15.6

^aIncluding metachronous resections

^bFrom pancreatic and liver surgery.

PDAC, pancreatic ductal adenocarcinoma; OS, overall survival; USA, United States of America.

of the 85 patients with oligometastatic pancreatic cancer underwent surgical resection. Furthermore, Hank et al. [17] recently demonstrated that patients with metastatic, including liver, pancreatic cancer, who underwent conversion surgery after recent systemic chemotherapy such as FOLFIRINOX and gemcitabine plus nab-paclitaxel had a favorable prognosis with an MST of 25.5 months, if complete pathological response of metastases (ypM0) was achieved. However, these proposed strategies should be evaluated in more extensive prospective studies.

Surgery for Peritoneal Oligometastasis

Peritoneal metastasis is generally considered a form of systemic metastasis that is not indicated for surgery. In pancreatic cancer, the definition of peritoneal oligometastasis has rarely been discussed and established. Previous studies have found that conversion surgery and OS rates in peritoneal metastatic pancreatic cancer were unfavorable, with a prognosis ranged from 5.3 to 12.9 months (Table 2) [9,17,20-24]. In contrast, Satoi et al. [22] reported remarkable outcomes in patients with peritoneal metastasis treated with conversion surgery after a favorable response to intravenous and intraperitoneal paclitaxel with S-1. The MST was 27.8 months in patients treated with the same regimen after surgery compared to 14.2 months in the patients treated with the same regimen without surgery. Yamamoto et al. [24] recently reported a study that compared 43 patients who received intraperitoneal chemotherapy to 49 patients who received conventional chemotherapy. They found that intraperitoneal treatment significantly increased the

conversion rate than systemic chemotherapy (23% vs. 4%). Furthermore, the conversion surgery group demonstrated a significantly better prognosis than the conventional systemic chemotherapy group, with an MST of 27.4 months vs. 11.3 months.

In the above-mentioned studies, the eligibility criteria for intraperitoneal treatment were peritoneal metastasis in patients with otherwise resectable cancer and positive peritoneal washing cytology in patients with unresectable locally advanced cancer. The criteria for surgery were good performance status, significant tumor shrinkage, decrease in tumor marker levels, negative cytology results, and the absence of peritoneal deposits on staging laparoscopy. Serum CA19-9 is one of the most potent biomarkers for determining conversion surgery indications.

However, there is currently insufficient evidence to support conversion surgery in patients with peritoneal oligometastatic pancreatic cancer. Furthermore, it is unknown whether peritoneal and other types of pancreatic cancer metastasis have distinct biological mechanisms. However, if intensive local therapy specific for peritoneal metastasis is effective, such selected patients may benefit from individualized treatment.

Surgery for Oligometastasis of the Lung

Unlike liver and peritoneal metastases, lung oligometastasis appears to have a better prognosis in pancreatic cancer (Table 3) [25-33]. Therefore, surgery for lung oligometastasis may play a more important role than surgery for other types of oligometastases. In addition, lung resection has

Table 2. Studies on surgery for synchronous peritoneal oligometastasis in PDAC

First author	Year	Country	No. of patients	OS from initial treatment (mo)
Shrikhande et al. [20]	2007	Germany	9	12.9
Yamada et al. [21]	2009	Japan	6	9.6
Seelig et al. [9]	2010	Germany	5	5.3
Satoi et al. [22]	2017	Japan	8	27.8
Yamada et al. [23]	2021	Japan	16	32.5
Yamamoto et al. [24]	2022	Japan	12	27.4
Hank et al. [17]	2022	Germany	11	19.4 ^a

^aFrom pancreatic and liver surgery.

PDAC, pancreatic ductal adenocarcinoma; OS, overall survival.

Table 3. Studies on surgery for metachronous lung oligometastasis in PDAC

First author	Year	Country	No. of patients	OS from initial treatment (mo)
Arnaoutakis et al. [25]	2011	USA	9	51
Thomas et al. [26]	2012	USA	7	92.3
Downs-Canner et al. [27]	2015	USA	8	67.5 (27 ^a)
Robinson et al. [28]	2016	USA	16	52 (28 ^a)
Yasukawa et al. [29]	2017	Japan	12	121 (47 ^a)
Okui et al. [30]	2017	Japan	5	85.9 (38.3 ^a)
Mashiko et al. [31]	2021	Japan	6	Not reached
Homma et al. [32]	2022	Japan	32	84 ^b (29.2 ^c)
Yun et al. [33]	2022	Korea	15*	5-year OS 60.6%

^aOS after lung metastasectomy.

^bFrom pancreatic surgery.

^cFrom diagnosis of lung metastasis.

PDAC, pancreatic ductal adenocarcinoma; OS, overall survival; USA, United States of America.

been reported to be safe with a few complications [29,34]. Most patients underwent wedge resection, whereas a few underwent lobectomy.

The median OS after initial anti-cancer therapy, including surgery or chemotherapy, and lung resection was ranged from 51 to 121 months and 27 to 47 months, respectively [25-30,32]. Thomas et al. [26] reported that the median OS after initial treatment was significantly longer in patients with lung oligometastasis recurrence than in those with liver oligometastasis recurrence among patients undergoing surgery. Recently, Homma et al. [32] conducted a nationwide survey in multiple centers in Japan. This is the most extensive study to date. OS was 84 months after the initial surgery and 29.2 months after metastasectomy. Furthermore, Yun et al. [33] analyzed data from the National Cancer Database and found that patients with resected lung metastasis had significantly better OS than those who received only chemotherapy or supportive care. A 5-year survival rate of 60.6% has been reported in 15 patients who underwent metastasectomy with chemotherapy.

If lung metastasis with no lesion in other organs is thought to be completely resected, pulmonary resection for lung oligometastasis in pancreatic cancer may be recommended. [25,29,30]. Additionally, resection for lung metastasis can be further considered in patients with a relatively long interval between initial pancreatic resection and the diagnosis of lung metastasis [26,29,30]. Serum CA19-9 levels before lung resection and single lung metastasis have been reported to

predict favorable prognosis [32].

Adjuvant chemotherapy was administered after pulmonary resection to 20–88% of the patients in previous reports [26,28,30]. Homma et al. [32] suggested that postoperative chemotherapy after pulmonary resection was significantly associated with recurrence. The evidence for perioperative chemotherapy in patients undergoing pulmonary resection should be evaluated.

The underlying mechanisms of the differences between lung and other types of pancreatic cancer metastases were previously unknown. We recently reported that lung metastasis had higher tumor-infiltrating lymphocytes and PD-L1 expression than other types of metastases, suggesting that lung metastasis was an immunologically “hot” tumor [35]. Such immune status could be associated with a better prognosis. Furthermore, our study suggests that immune-checkpoint inhibitors may effectively treat such immunologically hot tumors.

Ongoing Clinical Trial

To the best of our knowledge, three ongoing clinical trials (two randomized control trials and one prospective study) have evaluated surgical interventions for oligometastatic pancreatic cancer. Furthermore, two studies investigated the impact of surgery after chemotherapy for liver oligometastatic pancreatic cancer, and one aimed to clarify the surgical impact on patients with peritoneal oligometastasis.

The Chinese Study Group for Pancreatic Cancer-1 (Simultaneous Resection of Pancreatic Cancer and Liver Oligometastasis After Induction Chemotherapy: ClinicalTrials.gov Identifier: NCT03398291) was a multicenter prospective phase III trial conducted in China [36]. The presence of no more than three metastatic lesions in the liver was defined as liver oligometastasis. This study aimed to evaluate a treatment strategy for selecting patients who can benefit from synchronous resection of primary pancreatic cancer and liver oligometastasis after induction chemotherapy. In the first step, 1,000–1,200 patients with needle biopsy-confirmed pancreatic ductal adenocarcinoma with liver oligometastases were included in the study. Patients were then treated with first-line chemotherapy. In the second step, approximately 300 patients were randomly assigned in a 1:1 ratio to simultaneous resection of the primary pancreatic cancer lesion and liver oligometastases or standard chemotherapy. Half of those who met the eligibility criteria underwent surgery, while the other half continued to receive standard chemotherapy. The primary endpoint was OS. The study started in 2019, and the results of this trial were planned to be released in 2025.

Chemotherapy and Surgical Resection in Patients with Hepatic Oligometastatic Adenocarcinoma of the Pancreas (ClinicalTrials.gov Identifier: NCT04617457) was a single-arm phase II clinical trial conducted in Germany [37]. The efficacy of neoadjuvant chemotherapy followed by total resection in patients with oligometastatic liver pancreatic cancer was assessed in this study. Patients with liver-only metastasis, with a maximum of five metastases, were included. A combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil with folinic acid was administered as neoadjuvant chemotherapy. A total of 150 patients were enrolled with the aim of performing simultaneous resection of the primary pancreatic tumor and liver metastases in 55 patients.

Randomized phase III trial of intravenous and intraperitoneal paclitaxel with S-1 versus gemcitabine plus nab-paclitaxel for pancreatic ductal adenocarcinoma with peritoneal metastasis (Japan Registry of Clinical Trials jRCTs051180199) was conducted in Japan. This study aimed to confirm the

efficacy of intravenous and intraperitoneal paclitaxel with S-1 compared to conventional systemic chemotherapy with gemcitabine plus nab-paclitaxel for peritoneal metastatic pancreatic cancer [38]. The primary endpoint was OS. Conversion surgery was planned and evaluated in patients with negative peritoneal washing cytology and disappearance of peritoneal dissemination during chemotherapy.

These results are expected to provide important evidence on revising the clinical guidelines and improving the prognosis of patients with oligometastatic pancreatic cancer.

CONCLUSION

We reviewed recent studies on the surgical treatment of oligometastatic pancreatic cancer. We found that patient prognosis is gradually improving as multidisciplinary treatment of pancreatic cancer advances. Oligometastatic pancreatic cancer, which has long been considered a contraindication for surgery, can now be successfully treated with surgical resection in carefully-selected patients. However, to date, there is currently no information on how to perform surgery for oligometastatic pancreatic cancer. Nevertheless, as described in this review, some promising studies have been published, and a few exciting clinical trials are ongoing. Therefore, there is a strong hope for physicians to treat and cure potentially fatal disease. Further efforts should be made to identify reliable biomarkers, determine appropriate indications for surgery, and establish optimal multidisciplinary treatments for oligometastatic pancreatic cancer.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR’S CONTRIBUTIONS

Conceptualization: Masayuki Sho. Data acquisition: Satoshi Yasuda, Taichi Terai, Yuichiro Kohara. Formal analysis: Satoshi Yasuda, Minako Nagai, Kota Nakamura. Supervision: Satoshi Yasuda, Minako Nagai. Writing—original draft: Masayuki Sho. Writing—review & editing: Satoshi Yasuda, Minako Nagai, Kota Nakamura, Taichi Terai, Yuichiro Kohara.

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