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REVIEW ARTICLE

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Essential updates 2021/2022: Surgical outcomes of oligometastasis in pancreatic ductal adenocarcinoma

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Abstract

Oligometastatic disease has been proposed as an intermediate state between localized and polymetastatic disease that can benefit from multimodal treatment, including surgery. There is a growing concern about performing surgery for oligometastatic pancreatic ductal adenocarcinoma, although there is still little evidence. We reviewed articles published between 2021 and 2022, focusing mainly on surgical outcomes. Furthermore, we summarized the current status of surgery in the multidisciplinary treatment of oligometastatic pancreatic cancer and discuss future perspectives. In liver oligometastasis, multimodal treatment including surgery achieved favorable long-term survival, especially in patients with good responses to preoperative chemotherapy, with a median survival time from 25.5 to 54.6 months. In addition, the data from the National Cancer Database in the United States showed that patients who underwent surgery for oligometastatic liver metastases had a significantly longer overall survival than those who received chemotherapy alone. Prognostic biomarkers were identified, including carbohydrate antigen 19–9 (CA19-9) levels at diagnosis and preoperative chemotherapy with normalization of CA19-9 levels or favorable radiological response. Patients with lung oligometastasis had a more favorable long-term prognosis than those with other recurrence sites, and the updated literature further confirmed the previous studies. Overall survival was favorable, with 84 months after initial surgery and 29.2 months after metastasectomy, and a 5-year survival rate of 60.6% was also reported. In peritoneal oligometastasis, the results of conversion surgery after good responses to preoperative treatment with intraperitoneal therapy or systematic chemotherapy were reported, and the conversion rate and long-term prognosis were favorable. There is a growing concern about performing surgery for oligometastatic pancreatic ductal adenocarcinoma. We reviewed articles published between 2021 and 2022, focusing mainly on surgical outcomes. Furthermore, we summarize the current status of surgery in multidisciplinary treatment of oligometastatic pancreatic cancer and discuss future perspectives.

KEYWORDS
liver metastasis, lung metastasis, oligometastasis, pancreatic ductal adenocarcinoma, peritoneal metastasis

1 | INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is highly aggressive and still one of the most intractable human malignancies.[1,2] Curative resection in combination with systemic chemotherapy offers the best chance of survival; however, only approximately 20% of newly diagnosed patients are eligible for surgical resection. Approximately 50% of patients are diagnosed with metastatic PDAC (mPDAC), with a median survival time (MST) of 3–6 months and a 5-year survival rate of less than 10%.[1,3,4] Current clinical guidelines for PDAC with distant metastases recommend systematic chemotherapy but not surgical resection, as a first-line treatment.[5,6]

Oligometastatic disease, usually defined as fewer than five distant metastases in an organ, has been considered an intermediate state between localized and polymetastatic disease.[7,8] Patients with oligometastatic disease may potentially benefit from multimodal treatment. However, in contrast to some malignancies, such as colorectal cancer or neuroendocrine tumors, mPDAC is generally contraindication to surgical resection, even if a few visible metastatic lesions are limited to one organ.[9] This is simply because a number of previous studies have shown no surgical benefit on patient survival.

However, recent advancements in the treatment of pancreatic cancer, especially the introduction of potent chemotherapeutic regimens, such as combination chemotherapy with 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX: FFX) and gemcitabine plus nab-paclitaxel (GnP), have significantly changed the therapeutic concept and strategy for advanced pancreatic cancer, including oligometastatic pancreatic cancer. In fact, it has been widely accepted that conversion surgery for initially unresectable locally advanced pancreatic cancer may provide long-term survival or even complete cure in selected patients.[10] In contrast, conversion surgery for oligometastatic pancreatic cancer is still challenging and controversial. However, increasing attention has been paid to surgical treatment of PDAC with oligometastasis, especially after a favorable response to systemic chemotherapy.[11–14]

There are many unsolved clinical questions regarding surgery for patients with oligometastatic PDAC. For example, the optimal indication and timing of surgical treatment, as well as that reliable biomarkers should be investigated and clarified. In this review, we summarized and updated the current status of surgical treatment for oligometastatic PDAC and discussed future perspectives.

2 | METHODS

A literature search was conducted using PubMed (MEDLINE), Cochrane Library, Google Scholar, and Web of Science from January 2021 to October 2022. The following search keywords were used in every possible combination: “pancreatic cancer”, “pancreatic adenocarcinoma”, “pancreatic ductal adenocarcinoma”, “PDAC”, “cancer of the pancreas”, “metastasis”, “oligometastasis”, “liver metastasis”, “lung metastasis”, “peritoneal metastasis”, “peritoneal dissemination”, “distant metastasis”, “oligometastatic”, “surgery”, “surgical treatment”, “resection”, “metastasectomy”, “pancreaticoduodenectomy”, “pancreatoduodenectomy”, “distal pancreatectomy”, “pancreatic resection”, and “distal pancreatic resection”.

The reference lists of all the included studies were also searched to identify other potentially relevant studies. Two independent authors (S.Y. and M.S.) evaluated the available literature, and the authors resolved discrepancies by consensus. Inclusion criteria were original articles with more than five patients, written in English, and reporting on patients with metastatic PDAC who underwent surgery. Articles that lacked necessary data, including survival information, were excluded from this review. Abstracts, letters, expert opinions, and case reports were also excluded. A qualitative assessment of the included studies was conducted using the Newcastle–Ottawa Scale (NOS). Each study was assessed based on its evaluation of the three sections of this scale (selection, comparability, and outcome).

3 | OLIGOMETASTASIS OF PDAC

A definition of oligometastasis in PDAC has not yet been established. Previous studies have shown that surgical treatment results differ according to the metastatic site. Therefore, it is critical to evaluate the surgical outcomes and consider the optimal therapeutic strategy for oligometastatic PDAC according to the type of oligometastasis.

4 | LIVER OLIGOMETASTASIS

4.1 | Summary up to 2020 and update 2021/2022

It is generally known that the liver is the most common metastatic site of PDAC. There is no evidence that surgical resection for liver metastases of PDAC improves survival. However, up to 2020, several studies have reported a favorable effect on postoperative survival, with MST ranging from 21.9 to 56 months.[11–14] In contrast, several clinical questions, including appropriate biomarkers to predict the efficacy of treatment and determine surgical indications in oligometastatic PDAC, remain controversial. Six studies were published between 2021 and 2022 (Table 1).[15–20] Among them, five were retrospective cohort studies,[15–19] while one was a case–control study from a single institution.[20]

4.2 | Safety of surgery

The safety of simultaneous resection of the pancreas and liver is one of the most important issues because the complication rate of pancreatectomy is inherently high. The overall morbidity after simultaneous hepatic resections has been reported to range between 8% and 62%, while the mortality was lower than 5%.[12,13,21–23]

TABLE 1 Studies on surgery of synchronous liver oligometastasis in PDAC

First author (year)	Study design	Study period	Country	No. of patients	Definition of oligometastasis	No. of metastases	Resection rate	Preoperative therapy	Adjuvant therapy	OS from initial treatment (mo)	Morbidity (CD ≥ 3)	Mortality
Takeda[15] (2022)	RCS Single center	2013–2020	Japan	10	≤3 liver metastases	1 (30%) 2 (70%)	11.8%	100% of Pts. GnP: 70% mFFX: 20% SIROX: 10%	70% of Pts. S-1: 100%	54.6	23.0%	0
Hank[16] (2022)	RCS Single center	2006–2019	Germany	64	N/A	N/A	50.8%	100% of Pts. FFX or Gem-based regimen	N/A	19.2[a]	N/A	N/A
Bachellier[17] (2022)	RCS Single center	2008–2020	France	92	N/A	3 (1–21) 50% had one metastasis	N/A	56.5% of Pts. FFX: 87%	84.8% of Pts.	18.26 1/3/5-years OS 70/10/0%	40.2%	90 day 5.43%
Hamad[18] (2022)	RCS NCDB	2010–2015	USA	137	N/A	N/A	15.4%	67.2% of Pts.[b]	N/A	15.6	N/A	N/A
Safi[19] (2021)	RCS Single center	2006–2019	Germany	35	Resectable, isolated in one hepatic lobe, accessible via an atypical resection, independent on size and amount of metastasis	1 (1–4) 60% had one metastasis	73.1%	11.4% of Pts. FFX: 100%	85.7% of Pts. Gem: 50% FFX: 26.7% Gem-based: 6.7% CRT: 16.7%	10.3 5-years OS: 0%	N/A	30 day 7.9%
Shao[20] (2021)	CCS Single center	2009–2018	China	50	≤3 liver metastases	N/A	N/A	82% of Pts.	76% of Pts.	16	N/A	0

Abbreviations: CCS, case control study; CD, Clavien-Dindo; CRT, chemoradiotherapy; FFX, FOLFIRINOX; Gem, gemcitabine; GnP, gemcitabine + nab-paclitaxel; mFFX, modified FOLFIRINOX; N/A, not available; NCDB, National Cancer Database; OS, overall survival; Pts, patients; RCS, retrospective cohort study; SIROX, S-1, Irinotecan, Oxaliplatin.

[a]From pancreatic and liver surgery.

[b]Patients received either neoadjuvant or adjuvant chemotherapy.

Additionally, other studies have reported no significant increase in perioperative morbidity or mortality after pancreatectomy with simultaneous hepatic resection.[24,25]

In recent studies, severe complications were evaluated in two articles (23% and 40.2%),[15,17] and the mortality rate was between 0% and 7.9%.[15,17,19,20] As the updated literature showed, preoperative chemotherapy or simultaneous resection of the pancreas and liver were confirmed not to be associated with increased complication or mortality rates.

4.3 | Prognostic impact of surgery

To date, there is no evidence that synchronous or metachronous resection of liver metastases in PDAC improves survival. However, multiple studies suggested a positive effect on survival after surgery, with MSTs ranging between 6 and 56 months.[11–14,21,25–30] Some of those studies claimed the importance of favorable responses to preoperative chemotherapy[11–14] or metachronous liver resection.[22,23]

Furthermore, some studies have reported relatively better survival after surgery for metachronous liver metastases in comparison with hepatectomy for synchronous metastases.[22,23,31] However, since those studies included only a few cases, it seems difficult to reach a consensus regarding indication and efficacy of hepatectomy for metachronous liver oligometastasis.

Recently updated studies have demonstrated a favorable effect on long-term survival,[15–20] especially patients with favorable responses to preoperative chemotherapy with MST from 25.5 to 54.6 months.[15,16] In addition, Hamad et al.[18] reviewed the prognosis of 47 785 pancreatic cancer patients with liver-only metastasis in the National Cancer Database in the United States. After propensity score matching, 137 (0.3%) patients who received multimodality treatment, including surgery for oligometastatic liver metastases, had a significantly longer median overall survival (OS) compared to those who received chemotherapy alone (15.6 vs. 8.1 months). Metachronous liver oligometastasis was not reviewed in this study, since there was no updated literature on the subject.

4.4 | Surgical indication and biomarker

The surgical indication for liver oligometastasis remains undetermined and is currently under investigation. In most previous reports, surgery was performed for less than five oligometastases. However, in some studies, major hepatectomy was performed for multiple liver metastases.[22,23,31] In general, resection of hepatic oligometastases should be considered only with R0 resection of the primary tumor, good performance status (PS), and no extrahepatic metastases.

In updated studies, the actual number of resected metastases ranged from one to three, single metastasis was the most frequent, and resection rates were between 11.8% and 73.1%.[15,16,18,19] Takeda et al.[15] reported that biological and pathological factors should be included in the new definition of oligometastatic disease. They proposed four preoperative biological and conditional factors as prognostic factors: carbohydrate antigen 19–9 (CA19-9) <1000 U/ml, PS of 0, modified Glasgow prognostic score of 0, and age < 70 years.[15] When patients with three or four of these factors were treated with chemotherapy, and if CA19-9 was normalized and radiological response was confirmed, a significantly excellent prognosis of 54.6 months in OS was achieved. Among the 85 patients with oligometastatic PDAC, 10 (11.8%) patients underwent surgical resection.[15] Similarly, Bachellier et al.[17] proposed CA19-9 < 500 U/ml as a biological factor at diagnosis. Furthermore, Hank et al.[16] reported CA19-9 < 400 U/ml and adjuvant chemotherapy as well as ypM0 as significant prognostic factors in the resection group for metastatic, including liver PDAC.

4.5 | Multidisciplinary treatment

A standard treatment strategy for PDAC patients with oligometastatic liver disease has not yet been established. However, preoperative and postoperative adjuvant chemotherapy seem essential for long-term survival. The median duration from diagnosis to surgical treatment is likely to be prolonged, ranging between 9.7 and 12 months.[11–13]

Preoperative chemotherapy was administered in 11.4% to 100% of patients,[15–20] and as expected, GnP or FFX were most frequently used in recent studies.[15,17,19] Adjuvant chemotherapy, including S-1, gemcitabine, FFX, and chemoradiotherapy, was administered to 70%–85.7% of the patients.[15,17,19,20] Further studies to solve the above many unsolved clinical questions are clearly required.

5 | LUNG OLIGOMETASTASIS

5.1 | Summary up to 2020 and update 2021/2022

Previous studies have suggested that patients with lung oligometastasis had a more favorable long-term prognosis than those with other recurrence sites. Studies on lung oligometastasis entirely focused on metachronous metastasis. There were three retrospective cohort studies on lung oligometastatic PDAC published in 2021 and 2022 (Table 2).[32–34]

5.2 | Safety of surgery

Lung resection has been reported to be safe with minimal complications, and mortality has rarely been reported.[35,36] Most patients underwent wedge resection, while lobectomy was performed only in a few cases.[36,37]

TABLE 2 Studies on surgery of metachronous lung oligometastasis in PDAC

First author (year)	Study design	Study period	Country	No. of patients	Definition of oligometastasis	No. of metastases	Preoperative therapy for lung metastasis	Adjuvant therapy after lung resection	OS from initial treatment (months)	OS from lung resection (months)	DFS from lung resection (months)
Homma[32] (2022)	RCS Multiple centers	2010–2014	Japan	32	Lung only metastasis	1 (75%) 2 (12.5%) 3 (6.3%) ≥ 4 (6.3%)	21.9% of Pts. S-1: 71.4% GnP: 14.3% GS: 14.3%	75% of Pts. S-1: 66.7% GS: 12.5% Gem: 12.5% GnP: 8.3%	84[a]	29.2[b]	25.0
Yun[33] (2022)	RCS Single center	2007–2018	Korea	15[c]	N/A	N/A	N/A	84.6% of Pts.	5-yr OS 60.6%	N/A	N/A
Mashiko[34] (2021)	RCS Single center	2006–2018	Japan	6	N/A	2 (83.3%) 3 (16.7%)	33.3% of Pts.	16.7% of Pts.	Not reached (observation period 57.0)	Not reached (observation period 14.5)	24.0

Abbreviations: DFS, disease free survival; Gem, gemcitabine; GnP, gemcitabine + nab-paclitaxel; GS, gemcitabine + S-1; N/A, not available; OS, overall survival; Pts, patients; RCS, retrospective cohort study.

[a]From pancreatic surgery.

[b]From diagnosis of lung metastasis.

[c]Including two synchronous cases.

5.3 | Prognostic impact of surgery

Previous studies have suggested that patients with lung-only metastases had more favorable OS and post-recurrence survival than those with other recurrence sites.[38,39] Furuse et al.[40] reported that patients with oligometastasis with a solitary or a few lesions, especially in the lung, can benefit from surgery. The median OS after initial therapy and lung resection was reported to range from 52 to 121 months and from 27 to 47 months, respectively.[36,37,39,41,42] Thomas et al.[41] reported that the median OS after initial treatment was significantly longer for patients with lung recurrence than those with liver recurrence among patients with surgery (92.3 vs. 32.5 months).

The updated literatures further corroborated the previous studies. Homma et al.[32] have reported a nationwide survey from multi-centers in Japan, which is the largest study to date. In addition, Yun et al.[33] analyzed data from the National Cancer Database and found that OS was significantly better for patients who had resected lung metastases. Overall survival was quite favorable, with 84 months after initial surgery and 29.2 months after metastasectomy,[32] and a 5-year survival rate of 60.6% was also reported.[33]

For the first time, we have recently demonstrated that lung metastasis was an immunologically "hot" tumor with increased tumor-infiltrating lymphocytes and PD-L1 expression, which could potentially contribute to a favorable prognosis.[43] Furthermore, our study also suggested that immune checkpoint inhibitor might be effective to such immunologically hot tumors, i.e., lung metastasis.

5.4 | Surgical indication and biomarker

Lung resection for oligometastasis of PDAC can be considered if the lung metastasis with no additional lesions in the other organs are thought to be completely resected.[36,37,39] Additionally, resection for lung metastasis can be conducted for patients with a relatively long interval from initial pancreatic resection to a diagnosis of lung metastasis.[36,37,41] Serum CA19-9 level before lung resection and single lung metastasis have been reported to predict favorable prognosis.[32]

In the updated studies, lung resection and metastases of five or fewer were one of the prognostic factors.[32,33]

5.5 | Multidisciplinary treatment

In previous reports, adjuvant chemotherapy after pulmonary resection was administered in 20% to 88% of patients, mainly a gemcitabine-based combination.[37,41,42,44] In the latest study, Homma et al.[32] reported that postoperative chemotherapy after pulmonary resection was significantly associated with the recurrence after pulmonary resection. In contrast, preoperative chemotherapy before lung resection was not generally evaluated. Therefore, the efficacy of perioperative chemotherapy in patients who undergo pulmonary resection should be evaluated in the future.

6 | PERITONEAL OLIGOMETASTASIS

6.1 | Summary up to 2020 and update 2021/2022

In patients with peritoneal metastatic PDAC, the conversion rate and long-term survival have been reported to be unfavorable[28,29,45]; however, patients with intraperitoneal (IP) therapy who underwent conversion surgery had achieved remarkable outcomes.[46,47] Three reports were published on peritoneal mPDAC in 2021 and 2022 (Table 3).[16,48,49] Yamada et al. reported a summary of two previous prospective studies on IP therapy for peritoneal mPDAC, focusing on conversion surgery.[48] Yamamoto et al.[49] compared patients with IP treatment and conventional chemotherapy, of whom 12 underwent conversion surgery. Whereas Hank et al.[16] administered preoperative systemic chemotherapy for patients with peritoneal mPDAC and planned to perform conversion surgery for those who had a good response to preoperative therapy.

6.2 | Safety of surgery

Surgery for PDAC with peritoneal metastases has been reported to be safely performed.[28,29,46]

6.3 | Prognostic impact of surgery

In peritoneal mPDAC, most studies focused on synchronous metastasis, and the rate of conversion surgery and OS have been reported to be unfavorable, with a prognosis between 5.3 and 12.9 months.[28,29,45] In contrast, Satoi et al.[46] reported the remarkable outcomes of patients with peritoneal metastasis, with an MST of 27.8 months, among those who underwent conversion surgery in a prospective clinical study. Satoi et al. are conducting a prospective study (SP study).[50]

In updated studies, the conversion rate after IP therapy for peritoneal mPDAC was 20.3%, and the OS from the initial treatment was 32.5 months.[48] Yamamoto et al.[49] compared 43 patients with IP treatment and 49 patients treated with conventional chemotherapy and found that IP treatment significantly increased the conversion rate compared with systemic chemotherapy (23% vs. 4%). Additionally, the conversion surgery group had a significantly better prognosis with an MST of 27.4 after initial treatment compared to 11.3 months in the nonsurgery group.

As described above, Hank et al.[16] reported an MST of 19.4 months after recent systemic chemotherapy and conversion surgery for peritoneal mPDAC. At this point, there is very limited evidence to support conversion surgery for patients with peritoneal oligometastatic PDAC.

6.4 | Surgical indication and biomarker

In the above prospective study, the eligibility criteria for IP treatment were histologically or cytologically proven PDAC, peritoneal

TABLE 3 Studies on surgery of synchronous peritoneal oligometastasis in PDAC

First author (year)	Study design	Study period	Country	No. of patients	No. of metastases	Preoperative therapy	Adjuvant therapy	OS from initial treatment (mo)	OS from surgery (mo)	DFS from surgery (mo)
Yamada[48] (2021)	Clinical trial Two centers	2012–2019	Japan	16	11: peritoneal metastasis with otherwise R PDAC 5: CY(+) with UR-LA PDAC	100% of Pts. IV and IP PTX with S-1: 41.8% IV Gem + nab-PTX with IP PTX: 58.3%	N/A	32.5	N/A	9.2
Yamamoto[49] (2022)	RCS Single center	2007–2018	Japan	12	6: peritoneal metastasis with otherwise R PDAC 6: CY(+) with UR-LA PDAC	100% of Pts. IV and IP PTX with S-1: 50% IV Gem + nab-PTX with IP PTX: 25% IV Gem and IP PTX with S-1: 8.3% RT + GS: 8.3% RT + S-1: 8.3%	IP PTX with S-1 Gem	27.4	18.3	8.4
Hank[16] (2022)	RCS Single center	2006–2019	Germany	11	N/A	100% of Pts. FFX or Gem-based regimen	N/A	N/A	19.4	N/A

Abbreviations: CY, peritoneal washing cytology; DFS, disease free survival; FFX, FOLFIRINOX; Gem, gemcitabine; GS, gemcitabine + S-1; IP, intraperitoneal; IV, intravenous; N/A, not available; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; Pts, patients; PTX, paclitaxel; R, resectable; RCS, retrospective cohort study; RT, radiotherapy; UR-LA, unresectable locally advanced.

TABLE 4 Ongoing clinical trials of surgery for oligometastasis of PDAC

Registration number	Study name	Objective	Definition of oligometastasis	Treatment arm	Primary endpoint	Phase	Country	Start of study
NCT03398291	CSPAC-1[51]	PDAC with liver oligometastasis	≤3 liver metastases Irrespective of their distribution within the liver lobes	Arm 1: Simultaneous resection of the primary tumor and liver metastasis after conversion chemotherapy Arm 2: Standard chemotherapy	Real OS (from diagnosis to death)	III	China	2019
NCT04617457	HOLIPANC[52]	PDAC with liver oligometastasis	≤5 liver metastases Potentially resectable or treatable by ablative procedures	NAC with liposomal irinotecan combined with oxaliplatin and 5-FU	OS-res (OS after R0/R1 resection)	II	Germany	2021
UMIN000027229/ jRCTs051180199	SP Study[50]	PDAC with peritoneal metastasis	Inclusion criteria Macroscopic peritoneal dissemination with otherwise R PDAC Microscopic peritoneal dissemination with UR-LA PDAC	Arm1: Intravenous and intraperitoneal paclitaxel with S-1 Arm2: Gemcitabine plus nab-paclitaxel	OS	III	Japan	2020

Abbreviations: 5-FU, 5-fluorouracil; NAC, neoadjuvant chemotherapy; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; R, resectable; UR-LA, unresectable locally advanced.

metastasis in patients with otherwise resectable cancer, and positive peritoneal washing cytology in patients with unresectable locally advanced cancer. The surgical criteria were as follows: good PS, marked tumor shrinkage, decrease of tumor marker levels, cytology turned negative, and disappearance of peritoneal deposits on staging laparoscopy.[46,47] As a biomarker, serum CA19-9 might allow decision-making following a patient's biological response and can offer improved outcomes.[16,49]

In a recent study, conversion surgery after systemic chemotherapy was performed when the partial or complete response of metastatic lesions was observed in combination with biological tumor response (decrease in CA19-9 and carcinoembryonic antigen levels). In addition, for patients with unclear lesions, positron emission tomography-computed tomography was used. In that study, the conversion rate was about 35%.[16]

6.5 | Multidisciplinary treatment

It remains unknown whether there are different biological mechanisms between peritoneal and other types of metastases in PDAC. Peritoneal metastasis is generally thought to be a form of systemic metastasis with no indication for surgery. However, if intensive local therapy specific for peritoneal metastasis is effective in highly selected cases, patients may benefit from individualized treatment. Considering the aggressive oncological behavior of PDAC, perioperative chemotherapy is likely to be essential for long-term survival or a complete cure. Based on previous studies and clinical practice experience, GnP may be a key drug for peritoneal oligometastatic PDAC. However, information regarding the optimal treatment strategy remains limited. Therefore, further studies are warranted.

7 | ONGOING RANDOMIZED CONTROLLED TRIALS (RCTS)

To date, there has been no evidence from RCTs to determine the impact of surgery on oligometastatic PDAC. Three prospective studies are currently ongoing, including two RCTs (Table 4).[50–52] There are two prospective clinical trials on the efficacy of surgery after chemotherapy for PDAC with liver oligometastasis. The CSPAC-1 is a multicenter prospective phase III RCT that demonstrates the efficacy of simultaneous resection after systemic chemotherapy compared to systemic chemotherapy without surgery in pancreatic cancer with liver oligometastases.[51] The study started in 2019, and the results of this trial are planned to be released in 2025. The HOLIPANC is a single-arm phase II trial to assess the efficacy of neoadjuvant chemotherapy followed by complete resection in patients with hepatic oligometastatic PDAC.[52] As described above, there is another phase III RCT to confirm the superiority of IP paclitaxel therapy compared to conventional systemic chemotherapy for peritoneal mPDAC and conversion surgery will also be evaluated (SP study).[50] These results are expected to provide valuable evidence for improving the clinical

guidelines and enhancing the prognosis of patients with oligometastatic PDAC.

8 | CONCLUSION

Recent studies on the surgical treatment of oligometastases of PDAC are reviewed and important points are summarized. Advances in multidisciplinary treatment, including combination chemotherapy and appropriate selection of patients with favorable response to chemotherapy have occasionally led to a long-term prognosis, even for oligometastatic PDAC, which is generally thought to have a dismal prognosis. However, because only a limited number of patients benefit from surgery, optimal biomarkers need to be established to evaluate tumor response and determine surgical indications. Furthermore, further efforts should be made to provide patients with this fatal disease with more effective multimodality treatment, combining surgery with chemotherapy, immunotherapy, and radiotherapy.

AUTHOR CONTRIBUTIONS

Masayuki Sho devised the project, main conceptual ideas, and proof outline. Satoshi Yasuda selected and reviewed the references and wrote the manuscript's initial draft. Minako Nagai, Taichi Terai, and Yuichiro Kohara contributed to the review of the references and assisted with the presentation of the manuscript. All authors have reviewed the manuscript.

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CONFLICT OF INTEREST

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Registry and the Registration No. of the study/trial: N/A.
Animal Studies: N/A.

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