

REVIEW ARTICLE

The surgical challenge of oligometastatic pancreatic cancer: A systemic review of the literature

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Summary

Purpose: We aim to review the available literature on surgical management of oligometastatic pancreatic ductal adenocarcinoma (PDAC), in order to assess the clinical outcomes and intraoperative parameters of the different strategies.

Methods: A systematic literature search was performed in PubMed database, in accordance with the PRISMA guidelines. Nine studies met the inclusion criteria incorporating 401 patients.

Results: Perioperative mortality was as low as 0%, regarding resection of pancreatic cancer combined with synchronous metastasectomy.

Conclusions: Currently, postoperative overall survival and progression-free survival have increased compared to previous trials. Nevertheless, the lack of precise operative indications delays the enhancement of survival rates. Well-designed, randomized controlled studies, assessing pancreatic surgery combined with metastasectomy, are necessary to further assess their clinical outcomes.

Key words: pancreatic malignancy, liver metastasis, pancreatic surgery

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies, fourth leading cause of cancer-related deaths in USA, with an overall survival (OS) of 6% [1,2]. Surgical resection remains the only chance for potential cure. However, at the time of diagnosis only 20-30% of cases can be surgically resected proving that the disease is not locally advanced [3]. Patients with more advanced disease, including peritoneal carcinomatosis, vascular involvement or distant metastasis are administered palliative therapeutic options [4]. Approximately 49.5% of patients with PDAC will present with metastatic disease at the

time of diagnosis [5], while liver is the main location of metastasis.

Despite the constant improvement regarding surgical techniques and perioperative medical care for patients with PDAC, metastasectomies with simultaneous resection of primary tumor have been performed in large tertiary centers [6]. However, several studies support contradicting data regarding surgical approach for oligometastatic PDAC. The main purpose of this review was to summarize the available data regarding the efficiency of metastasectomy combined with the resection of PDAC.

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Methods

A thorough systematic literature search was performed in Pubmed (Medline) database (last search: December 1st, 2020), in accordance with Prisma guidelines. We used the following terms in every possible combination: “pancreatic cancer”, “pancreatic adenocarcinoma”, “pdac”, “pancreatic tumor”, “oligometastatic”, “liver metastasis”, “distant metastasis”, “surgery”, “surgical treatment”, “resection”. Inclusion criteria were (1) original reports with ≥10 patients, (2) written in English, (3) published from 1970 to 2020, (4) conducted on human subjects and (5) reporting outcomes regarding surgical resection of synchronous or metachronous metastases on patients with PDAC.

Results

Baseline characteristics

The flow diagram of the literature search is presented in Figure 1. The characteristics of the included studies are summarized in Table 1. Nine

studies [7-15] were included in the present review. The majority of the studies (77.8%) [7-9,11-14] were retrospective. Two studies [10] were prospective. Totally, 401 patients were incorporated. The countries of origin of the included studies were France [7], USA [8,10,15] and Germany [9,11-14]. The included studies were published between 2006 and 2016. The median follow-up ranged from 1.75 to 8.7 months. The metastatic lesions were located in liver [7,9,10-15], lungs [8,15] and peritoneum [13,15].

Perioperative mortality

Eight studies [8-15] reported on perioperative mortality. Mortality was 0% in most studies [8,9,12,13,15]. In two recent studies [11,14] mortality was demonstrated to range between 1% and 2.9%.

1-, 2-, 3-, and 5-year overall survival

The outcomes regarding survival are presented in Table 2. The 1-year overall survival (OS) ranged from 13.3% [10] to 72.7% [15]. The 2-year

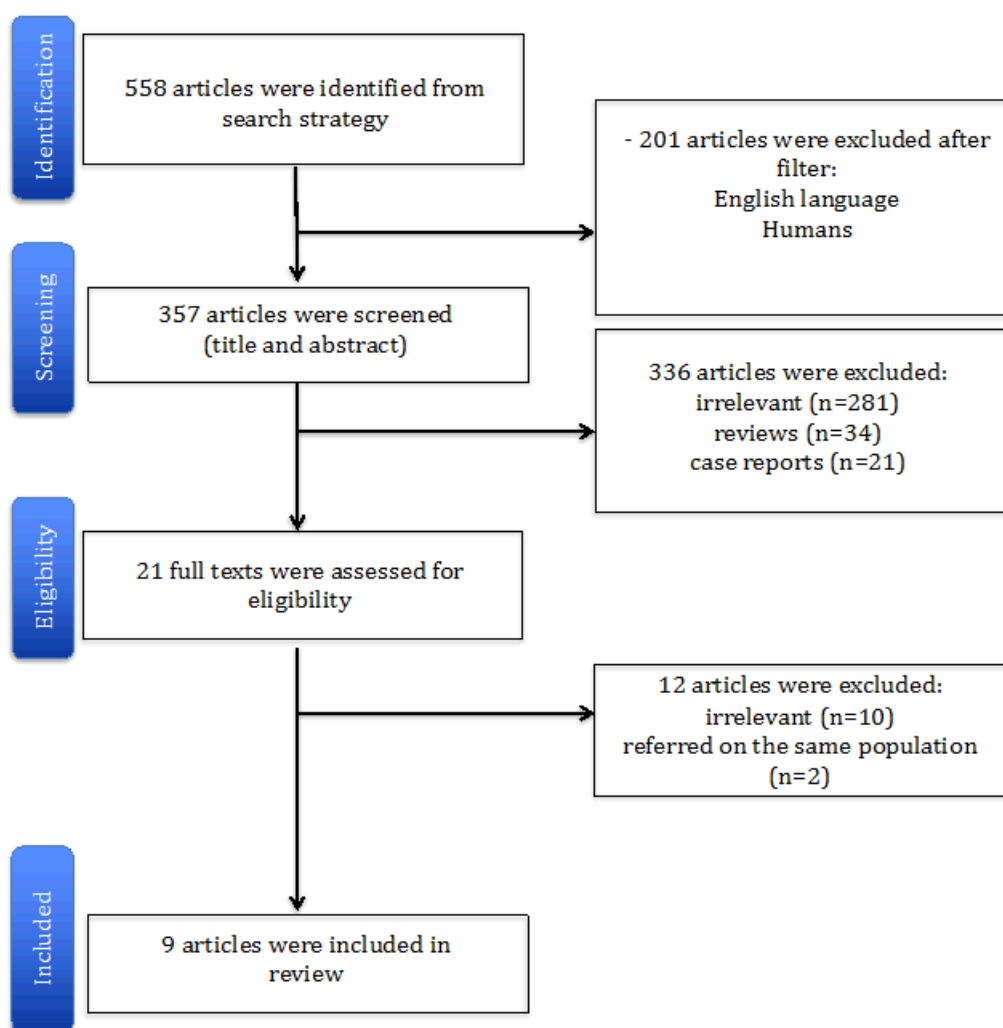


Figure 1. Trial flowchart.

Table 1. Characteristics of the studies that were finally included in the systematic review. Shown are the first author of every study along with the year of publication, the journals, the country of origin, the time period of the study, the location of metastases, the study design, the number of participants, the median follow-up, the minor resection and the major resection, along with the mortality

Study ID, Year	Journal	Country	Time period	Location of metastases	Type of study	Patients, n	Median follow-up, Months	Minor resection	Major resection	Mortality (%)
Adam et al., 2006 [7]	Ann Surg	France	1983-2004	Liver	R	41	N/A	N/R	N/R	N/R
Arnaoutakis et al., 2011 [8]	J Gastrointest Surg	USA	1996-2009	Lung	R	31	1.75	N/R	N/R	0
Dünschede et al., 2010 [9]	Eur Surg Res	Germany	1996-2008	Liver	R	23	N/A	10	3	0
Gleisner et al., 2007 [10]	Cancer	USA	2007	Liver	P	22	N/A	N/R	N/R	9.1
Hackert et al., 2017 [11]	EJSO	Germany	2017	Liver, ILN	P	128	N/R	N/R	N/R	2.9
Klein et al., 2012 [12]	Gastroenterology Research and Practice	Germany	2012	Liver	R	44	N/A	22	0	0
Seelig et al., 2010 [13]	HPB Surgery	Germany	2010	Liver, peritoneum, omentum majus	R	20	N/A	14	0	0
Tachezy et al., 2016 [14]	Surgery	Germany	2016	Liver	R	69	8.7	N/R	N/R	1
Wright et al., 2016 [15]	J Gastrointest Surg	USA	2016	Liver, lung, peritoneum	R	23	2.5	N/R	N/R	0

Abbreviations: N/R=Not Reported; N/A=Not Available; R=Retrospective; P=Prospective

Table 2. Postoperative outcomes of the included studies

Study ID, Year	1-Year OS (%)	2-Year OS (%)	3-Year OS (%)	5-Year OS (%)	Median OS	Median PFS
Adam et al., 2006 [7]	N/R	N/R	N/R	20	N/R	N/R
Arnaoutakis et al., 2011 [8]	N/R	40	N/R	N/R	51	29
Dünschede et al., 2010 [9]	N/R	N/R	N/R	N/R	8 (synchronous) 31 (metachronous)	N/R
Gleisner et al., 2007 [10]	13.3	6.7	N/R	N/R	5.9	N/R
Hackert et al., 2017 [11]	N/R	N/R	N/R	Liver: 8.1% ILN: 10.1%	12.3	N/R
Klein et al., 2012 [12]	32	5	5	0	7.6	0
Seelig et al., 2010 [13]	N/R	N/R	N/R	N/R	10.7	N/R
Tachezy et al., 2016 [14]	N/R	N/R	N/R	5.8	14.5	N/R
Wright et al., 2016 [15]	72.7	21.5	N/R	N/R	18.2	8.6

N/R=Not Reported; N/A=Not Available; OS=Overall Survival; PFS=Progression Free Survival

OS ranged between 5% [12] and 21.5% [15] regarding liver metastases. According to Arnaoutakis et al [8], the 2-year OS following resection of PDAC with contemporary lung metastasectomy was 40%. Only one study [12] reported on 3-year survival (5%). The 5-year survival ranged from 0% [12] to 20% [7].

Median overall survival and recurrence-free survival

Eight studies [8-15] reported on median overall survival (MOS). MOS ranged from 8% to 18.2% regarding synchronous liver metastases and 51% regarding lung metastases. Recurrence-free survival (RFS) ranged from 0% [12] to 8.6% [15] regarding hepatic metastases and 29% [8] regarding lung metastases.

Discussion

During the last decade, the advancements in surgical practice and the following expansion of operative indications regarding patients with oligometastatic PDAC have highlighted the modern debate on PDAC resection combined with metastasectomy. Two are the main approaches regarding the indication for combined pancreatic resection and metastasectomy. First, Tachezy et al [14] have reported a relation between small number of metastatic lesions with improved survival, thus proposing aggressive surgical treatment for oligometastatic disease without neoadjuvant chemotherapy. In contrast, Lu et al [16] proposed that combined resection would be the treating modality of choice only if a R0 pancreatic resection was anticipated, the patient was in good overall health and a favorable response to prior chemotherapy took place.

The progressive refinement of surgical and anesthetic techniques resulted in a significant reduction of perioperative mortality that almost reached 0% in a recent study [16]. Another possible explanation is the improvement in patient selection. Those advances have also led to improved OS. Three recent studies, reported on median OS that reached 12.3 [11], 14.5 [14] and 18.2 [15] months, while 10 years ago Gleisner et al [10] reported a median OS of 5.9 months. These encouraging and promising outcomes have failed to establish a new paradigm for oligometastatic PDAC, possibly due to the small study samples and the study design. In fact, most studies were retrospective and no randomized controlled study was identified.

A significant endpoint is to assess whether combined PDAC resection and metastasectomy en-

hances the oncological outcomes of the patients. Most included studies compared patients treated with PDAC with synchronous metastasectomy with either pancreatectomy alone or palliative therapy. In fact, two studies [9,14] compared simultaneous liver metastasectomy with palliative treatment. Moreover, Klein et al [12] reported on patients treated with pancreatectomy alone or with simultaneous hepatic resection.

Another interesting finding is the significant increase of 2-year OS, median OS and RFS in patients with metastatic pulmonary lesions compared to the rest of the cases with liver metastases. In fact, Arnaoutakis et al [8] demonstrated 51 months median OS and 29 months RFS. This interesting finding is crucial in order to plan the best treatment strategy for patients with oligometastatic pancreatic cancer.

The limitations of this review are related to the limitations of the included studies. Most studies were retrospective and no randomized controlled trials were identified. Moreover, the study sample is small and highly heterogeneous.

Conclusion

The present review indicates the lack of large data sets from well-designed randomized controlled studies that would enable the identification of prognostic factors in order to describe more precisely the operative indications regarding patients with oligometastatic PDAC. Given the lack of available randomized-controlled studies, the limited study population and the heterogeneity of the inclusion criteria among studies, the current study remains largely inconclusive. The identification of precise operative indications will facilitate the enhancement of survival rates. New randomized-controlled studies with specific inclusion criteria and primary endpoints are necessary to assess further the patient selection criteria and to establish higher standards regarding the surgical treatment of oligometastatic pancreatic cancer.

Author contributions

All authors contributed equally to this study in conception and design, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict of interests

The authors declare no conflict of interests.

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