Systematic Review and/or Meta-analysis

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Surgical treatment of synchronous liver-only oligometastatic pancreatic adenocarcinoma: a systematic review and meta-analysis of long-term outcomes

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Background The potential long-term survival benefits of surgical resection for synchronous liver-only metastases of pancreatic ductal adenocarcinoma (liver oligo-PDAC) remain controversial. This systematic review and meta-analysis aim to compare the current evidence on long-term survival outcomes between surgical treatment of liver oligo-PDAC and conventional systemic chemotherapy.

Materials and methods A systematic review and meta-analysis were conducted using the PubMed and Scopus databases to identify studies comparing surgery and systemic chemotherapy in terms of long-term survival in oligo-PDAC patients. The search included studies published up to October 2024. The meta-analysis was performed using the Jamovi software.

Results Eleven retrospective studies were selected for a total of 897 patients: 565(63%) underwent synchronous resection of liver metastases and the primary tumor, while 332(37%) received conventional chemotherapy. The majority of patients presented a pancreatic head tumor, and the median number of liver metastases ranged between 1 and 3 in the surgical cohort and 1 and 2 in the nonsurgical cohort. The rate of major surgical complications was 14.4% while the cumulative incidence of postoperative mortality was 2.8%. The median overall survival(OS) in the surgical group ranged from 7.6 to 18.4 months, while a lower value comprised between 6 and 9.9 months was evidenced in the nonsurgical cohort. Six studies were included in the meta-analysis for the OS evaluation, showing significantly better survival outcomes in the surgical group (OR: 0.286, 95% CI: 0.100–0.409; $P < 0.0001$). According to the Q-test, there was no significant heterogeneity in the true outcomes ($Q = 4.063$, $P = 0.541$, $I^2 = 0$ %). A sensitivity analysis, conducted by excluding one study at a time, confirmed the robustness of the meta-analysis findings.

Conclusions Surgical resection of oligo-PDAC may represent a valuable treatment option with potential long-term survival benefits. However, prospective randomized trials are required to further validate these findings.

Keywords: liver metastases, oligometastasis, pancreatic adenocarcinoma, pancreatic surgery

Introduction

Pancreatic ductal adenocarcinoma (PDAC) currently represents the fourth leading cause of cancer-related death and is expected to become the second by 2030[1,2]. Despite the recent advancements in multimodal treatments and surgical techniques, PDAC prognosis remains dismal with reported 5-year and 10-year survival rates of 8.1% and 3%, respectively[3]. Radical surgery remains the only potentially curative treatment.

HIGHLIGHTS

- A systematic review and meta-analysis were conducted to evaluate the potential long-term survival benefits of surgery for synchronous liver-only metastases of pancreatic ductal adenocarcinoma (oligo-PDAC) compared to conventional chemotherapy.
- Surgical resection of oligo-PDAC was shown to be a safe and feasible procedure, with acceptable rates of major postoperative complications and mortality.
- Surgery for oligo-PDAC demonstrated a survival advantage over conventional chemotherapy alone.
- Randomized controlled trials and well-defined inclusion criteria for the surgical treatment of oligo-PDAC are necessary to further validate these findings.

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However, only up to 20% of patients affected by PDAC are considered eligible for surgical resection, while almost 50–60% present with unresectable or metastatic disease at the time of diagnosis, with the liver being the most common site of synchronous metastases[4]. According to current guidelines, systemic chemotherapy—including cytotoxic chemotherapy, targeted therapy, and immunotherapy—remains the cornerstone of treatment for this subset of patients[5].

In this scenario, an intermediate stage between localized and widespread metastatic disease, defined as oligometastatic disease, was first introduced in 1995 by Hellmann and Weichselbaum and defined as a limited metastatic spread[6]. Despite surgery is progressively becoming part of the standard of care for certain oligometastatic solid tumors, such as neuroendocrine tumors, colorectal cancer, breast cancer, and prostate cancer[7-10], the role of surgical resection in oligometastatic PDAC remains controversial. This is mainly due to the well-known biological aggressiveness of the disease, its consequent poor prognosis (especially in stage IV patients), and the high morbidity and mortality rates, which would be even higher in the case of a combined resection of metastatic sites. Nevertheless, increasing interest has recently been noted in evaluating the prognostic role of surgery as a treatment option for oligometastatic PDAC in comparison to chemotherapy alone[11,12]. To date, no randomized controlled trials (RCT) have been conducted on this topic, and current evidence is only based on retrospective studies with limited study cohorts. While the majority of authors documented significant long-term survival advantages for the combined resection of the primary tumor and liver metastatic sites over chemotherapy alone[13-18], others did not evidence significant differences between the compared cohorts[19-21].

Based on these premises, the aim of this systematic review and meta-analysis is to evaluate the current state-of-the-art regarding the surgical treatment of PDAC with synchronous liver-only oligometastatic disease (liver oligo-PDAC), with a particular focus on its potential survival benefits compared to the conventional chemotherapy.

Materials and methods

Data sources, search strategy, and selection criteria

The systematic review was prospectively registered in International Prospective Register of Systematic Reviews (PROSPERO database). The work has been reported in line with AMSTAR (Assessing the methodological quality of systematic reviews) guidelines[22]. The literature research was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[23] and performed on PubMed and Scopus databases from January 2011 to October 2024. Only studies evaluating the prognostic role of surgical resection in liver oligo-PDAC were included in the analysis.

The search terms “pancreatic cancer,” “liver metastasis,” and “surgery” were adapted for each database. The final research was ((“pancreatic neoplasms”[MeSH Terms] OR “pancreatic neoplasm” OR “pancreatic cancer” OR “pancreatic carcinoma” OR “pancreatic tumor” OR “pancreatic tumour” OR “pancreatic malignancy” OR “pancreatic ductal adenocarcinoma” OR “pancreatic ductal carcinoma” OR “pancreas neoplasm” OR “pancreas cancer” OR “pancreas carcinoma” OR “pancreas tumor” OR “pancreas tumour” OR “pancreas malignancy” OR “pancreas ductal adenocarcinoma” OR “pancreas ductal carcinoma”) AND (“hepatectomy”[MeSH Terms] OR “hepatectomy”[All Fields] OR (“liver”[All Fields] AND “resection”[All Fields]) OR “liver resection”[All Fields] OR (“hepatectomy”[MeSH Terms] OR “hepatectomy”[All Fields] OR “hepatectomies”[All Fields]) OR “pancreatectomy”[MeSH Terms] OR “pancreatectomy “[tw] OR “pancreaticoduodenectomy”[MeSH Terms] OR “pancreaticoduodenectomy”)) AND (“liver”[MeSH Terms] OR “liver”[All Fields] AND (“metastasi”[All Fields] OR “neoplasm metastasis”[MeSH Terms] OR (“neoplasm”[All Fields] AND “metastasis”[All Fields]) OR “neoplasm metastasis”[All Fields] OR “metastasis”[All Fields]) OR “liver neoplasms”[MeSH Terms] OR (“liver”[All Fields] AND “neoplasms”[All Fields]) OR “liver neoplasms”[All Fields]). The references of included articles were also manually searched, and further articles were included if appropriate. Duplicate references were semi-automatically removed using RAYYAN platform (https://www.rayyan.ai/).

Eligibility criteria

Inclusion criteria were retrospective, cohort, prospective, RCT studies reporting the evaluation of long-term outcomes after surgical resection of liver oligo-PDAC, published in the English and including only adult patients aged 18 years and older.

Exclusion criteria

Exclusion criteria included non-English articles, review articles, editorials, opinion statements, animal studies, case reports and studies on metachronous liver metastases or metastases in sites other than the liver.

Data extraction

The articles were uploaded into the SYSTEMATIC REVIEW ACCELLERATOR (www.sr-accelerator.com), a web-based screening tool. Abstracts and titles were screened independently on SYSTEMATIC REVIEW ACCELLERATOR by 2 reviewers and assessed for inclusion or exclusion. Any issue or disagreement was resolved with the input of a senior author. Study characteristics including article title, year of publication, first author, study type, number of patients, level of evidence and data related to the defined outcome were extracted and reported on an electronic database.

Study risk-of-bias assessment

The Newcastle-Ottawa classification[24] was independently used by two authors for the assessment of study quality. Grading was based on a scale 0 to 9 according to the following domains:

S1: representativeness of the exposed cohort; S2: selection of the non-exposed cohort; S3: ascertainment of exposure; S4: demonstration that outcome of interest was not present at start of the study; C: comparability; O1: assessment of outcome; O2: sufficient length of follow-up for outcomes to occur; O3: adequacy of follow-up.

Outcomes of interest

The primary outcome was to perform a systematic review and meta-analysis on the long-term survival of patients with liver-only oligo-PDAC who underwent synchronous surgical resection of the primary tumor and metastatic sites compared to conventional chemotherapy. Secondary outcomes included 1-, 2-, 3- and 5-year survival rates in both comparison cohorts as well as the evaluation of the Clavien–Dindo ≥ 3 complication rates and perioperative mortality in the surgical group.

Statistical analysis

The meta-analysis was conducted using Jamovi software (version 2.4.11.0). The analysis was carried out using the log odds ratio (ORs) as the outcome measure. The ORs and 95% confidence intervals (95% CI) were calculated to estimate the association between binary factors and AL. A fixed-effects model and a random-effects model were fitted to the data. Furtheremore, the Q-test for heterogeneity (Cochran 1954) and the I^2 statistic were reported. Studentized residuals and Cook's distances were used to examine whether studies may be outliers and/or influential in the context of the model. Studies with a studentized residual larger than the $100 \times (1–0.05/(2 \times k))$ th percentile of a standard normal distribution were considered potential outliers (i.e., using a Bonferroni correction with two-sided alpha = 0.05 for k studies included in the meta-analysis). Studies with a Cook's distance larger than the median plus six times the interquartile range of the Cook's distances were considered to be influential. Finally, the rank correlation test and the regression test, using the standard error of the observed outcomes as predictor, were used to check for funnel plot asymmetry.

Sensitivity analysis (excluding one study at a time) was conducted to test the stability of the pooled results.

Results

Studies selection and patients' characteristics

The systematic research identified 9934 studies. After screening titles and abstracts, 9834 studies were removed due to ineligibility or duplication. Of the remaining 100 studies, 89 were excluded due to inappropriate study population, outcome analysis, and/or study design (Fig. 1). Finally, 11 (13–18, 24–28) studies met the inclusion criteria and were included in the systematic review. Among them, six[13-18] conducted a comparative analysis between surgery and chemotherapy for liver oligo-PDAC treatment and were, therefore, included in the meta-analysis. All included studies were non-randomized retrospective cohort studies (Table 1). Table 2 reports the quality assessment of the studies.

As a whole, 897 patients with liver oligo-PDAC were included in the systematic review: 565 (63%) underwent surgery with synchronous resection of liver metastatic sites, while 332 patients (37%) received palliative chemotherapy and constituted the nonsurgical group. Demographic, biochemical, and oncological characteristics of the surgical and non-surgical populations are reported in Table 3. Detailed information on PDAC location was available in 8 out of 11 studies (344 patients) for the surgical group[13,15-18,25,26,28] and in 5 out of 6 studies (195 patients) for the nonsurgical group[13,15-18]. In both cohorts, the pancreatic head was the most common PDAC location, reported in 229 (66.6%) in the surgical group and 161 (82.6%) in the non-surgical group. The median number of liver metastases ranged from 1 to 3 in the surgical cohort, compared to a median range of 1 to 2 in the non-surgical group.

Overall, data on neoadjuvant/adjuvant treatments in the surgical population were reported in 9 out of 11 studies[13,15-18,25-28] for a total of 432 patients (Table 4). Specifically, 165 (45%) patients underwent neoadjuvant therapy and 267 (72.9%) received adjuvant treatment. Data on neoadjuvant regimes were available in only 7 studies (124 patients)[13,15,17,18,25,26,28], with FOLFIRINOX being the most commonly used chemotherapy regimen (70 patients—56.4%) followed by Gemcitabine + NAB-Paclitaxel (19 patients—15.3%) and Gemcitabine alone (15 patients—12.1%). Among the 267 patients who received adjuvant therapy, 73 (27.3%) were treated with Gemcitabine alone, 7 (2.6%) with FOLFIRINOX, and 3 (1.1%) with Gemcitabine followed by second-line FOLFIRINOX.

Eight out of 11 studies[13,16-18,25-28] provided detailed information on the pancreatic surgical procedure for a total of 331 patients. A pancreaticoduodenectomy was performed in 213 (64.3%), a total pancreatectomy in 13 cases (3.9%) and a distal pancreatectomy in 105 patients (31.7%). Seven out of 11 studies[13,17,18,25-27,29] including 328 patients described the type of liver resection performed. Specifically, an atypical resection was conducted in 296 (90.2%) patients, a major hepatectomy in 18 cases (5.5%) and a segmentectomy in the remaining 14 patients (4.3%).

Only 6 studies[17,18,25-28] for a total of 263 patients reported the rate of postoperative surgical complications with a Clavien–Dindo ≥3 grade observed in 38 (14.4%) patients. Perioperative mortality was reported in eight studies[15,17,18,25-29] with a cumulative incidence rate of 2.8% (10 out of 360 patients).

Data on surgical procedures and postoperative courses are summarized in Table 5.

Limited data were available on the chemotherapy regimens used in the nonsurgical group (2 out of 6 studies[17,18]—100 patients) with Gemcitabine being the most frequently administered agent (49 patients—49%%) followed Gemcitabine-S1 (14 patients—14%%), Gemcitabine + Nab-Paclitaxel (4 patients—4%), and FOLFIRINOX (4 patients—4%). Two patients (2%) received Gemcitabine followed by second-line FOLFIRINOX.

Long-term outcomes analysis and meta-analysis of OS in the surgical and nonsurgical groups

The median OS in the surgical group ranged from 7.6 to 18.4 months, whereas a lower OS, between 6 and 9.9 months, was observed in the nonsurgical cohort.

One-year survival was reported in seven studies[13,15,16,18,25,26,28] with values ranging from 34.3% to 100% in the surgical group, compared to 19.3–29% in the nonsurgical cohort. No patients in the nonsurgical group survived at 5 years, whereas in the surgical group, the 5-year survival rate ranged from 5.8% to 27.7% (Table 6).

Six studies[13-18] comparing OS between the surgical and the nonsurgical groups were included in the metanalysis for a total of 664 patients: 332 in the surgical group and 332 in the nonsurgical group. The analysis, conducted using both the random-effects model (Fig. 2A) and fixed-effects model (Fig. 2B), demonstrated superior survival outcomes in the surgical group (OR: 0.286,

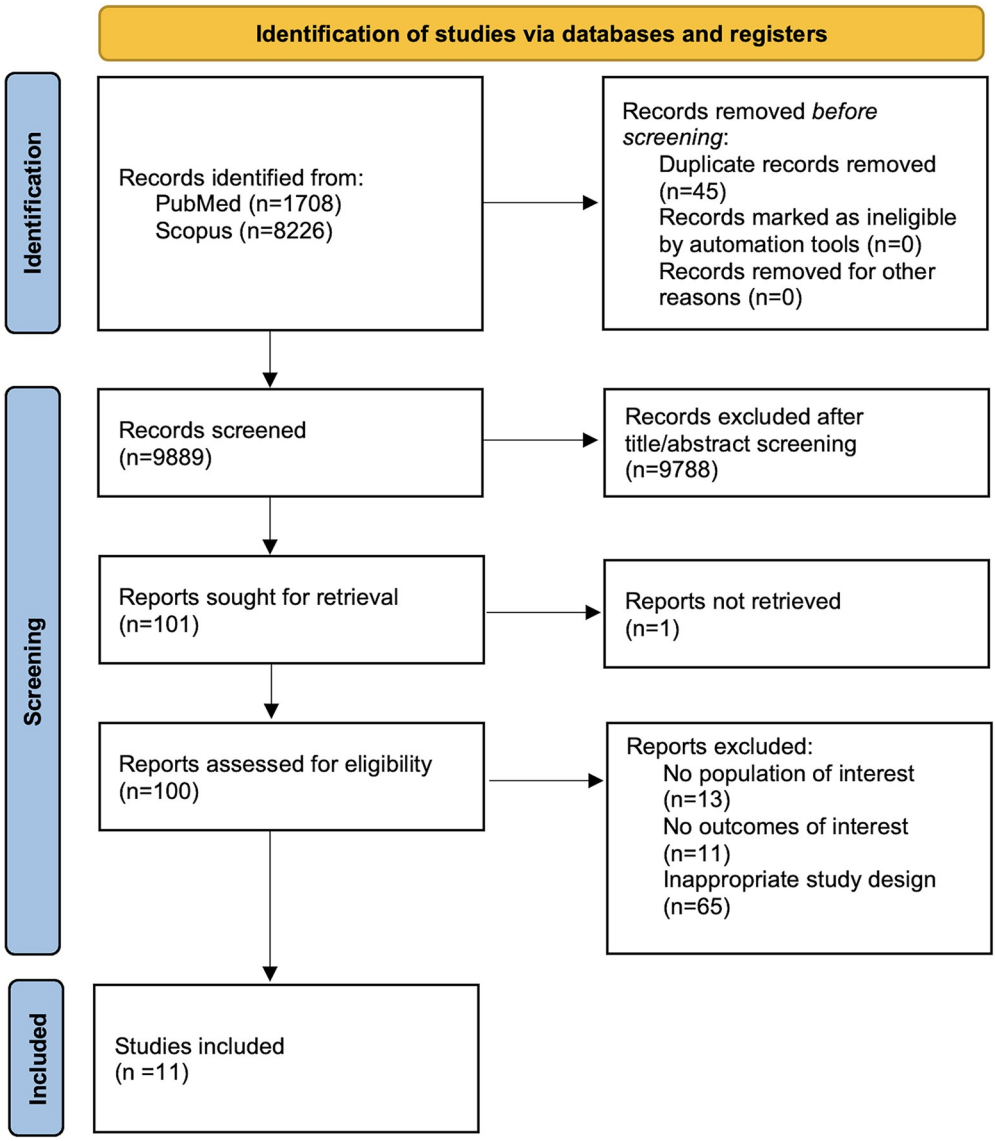

Figure 1. Prisma flowchart for studies selection.

95% CI: 0.100–0.409; P <0.0001). According to the Q-test, no significant heterogeneity was detected in the true outcomes (Q = 4.063, P = 0.541, I^2 = 0%). A sensitivity analysis was also performed to assess the robustness of this statistically significant result. As shown in Figure 3, the sensitivity analysis, conducted by excluding one study at a time, confirmed the previously mentioned finding, showing a survival advantage for the surgical group over the nonsurgical approach (OR: 0.286, 95% CI: 0.199–0.409; P < 0.0001).

Discussion

Oligometastatic disease is defined as an intermediate oncological state between localized and widely disseminated disease[6]. In several cancers, surgical treatment of the primary tumor and limited metastatic sites has demonstrated long-term survival benefits compared to chemotherapy alone. Among these, hepatic resection for metastatic colorectal cancers has progressively gained general acceptance as a valuable treatment option, offering survival advantages over chemotherapy alone[7]. Similarly, favorable prognostic outcomes have been demonstrated in cases of combined surgical resection of various neuroendocrine tumors and their metastastic sites[8].

On the other hand, the well-known biological aggressiveness of pancreatic cancer and its unfavorable prognosis have traditionally discouraged the surgical treatment of oligo-PDAC. Current available guidelines do not recognize surgical resection as a viable treatment option for this subset of patients[30,31]. However, the recent introduction and effectiveness of novel multimodal preoperative treatments have led to an increasing number of patients achieving tumor regression or complete response to chemotherapy[32]. This brought to increasing interest in investigating the potential survival benefits of surgical treatment for oligo-PDACs compared to chemotherapy alone. Preliminary studies[19-21] contraindicated hepatic resection for PDAC patients with liver metastases, given

Table 1

Characteristics of the studies included in the systematic review and meta-analysis

Author	Year	Study design	Surgical group, *n*	Nonsurgical group, *n*	Endpoint	Oligometastatic disease definition
Klein *et al* [25]	2012	R	22	-	Assessment of surgical outcomes and long-term survival	Intraoperative detection of a single liver metastasis (15 patients) or multiple metastases susceptible of segmentectomy (7 patients)
Tachezy *et al* [17]	2016	R	69	69	Comparative analysis of long-term survival and assessment of surgical outcomes	Distant metastases to a single or limited number of organs and a number of metastases consistent with high potential for a complete resection[6]
Hackert *et al* [26]	2016	R	62	-	Assessment of surgical outcomes and long-term survival	1 to 3 liver metastases that could be easily resected by atypical resection (intention-to-treat).
Hamad *et al* [14]	2020	R—PSM	137	137	Comparative analysis of long-term survival	NR
Yang *et al* [18]	2020	R	23	31	Comparative analysis of long-term survival and assessment of surgical outcomes	Distant metastases to a single or limited number of organs and a number of metastases consistent with high potential for a complete resection[6]
Shao *et al* [16]	2020	R—PSM	50	50	Comparative analysis of long-term survival and assessment of surgical outcomes	3 or less liver metastases
Safi *et al* [15]	2021	R	35	14	Comparative analysis of long-term survival and assessment of surgical outcomes	Resectable hepatic metastases isolated in one hepatic lobe, accessible only via an atypical resection, and independent on size and amount of metastases.
Bachellier *et al* [27]	2023	R	92	-	Assessment of surgical outcomes and long-term survival	Limited non-anatomical subscapular lesions and/or small deep metastases with diameter less than 3 cm
Takeda *et al* [24]	2023	R	10	-	Assessment of long-term survival	3 or less liver metastases
Nagai *et al* [28]	2023	R	47	-	Comparative analysis of long-term survival and assessment of surgical outcomes	Up to 4 resected metastases
Satoi *et al* [13]	2023	R	18	31	Comparative analysis of long-term survival and assessment of surgical outcomes	3 or less liver metastases

R: retrospective; PSM: propensity score matching; NR: not reported

the surgical complexity of the procedure, high rates of morbidity and perioperative mortality, and uncertain survival benefits. Conversely, more recent evidence has demonstrated potential long-term advantages of combined resection of metastatic sites and primary PDAC. Yasuda *et al*[33] in a comprehensive review documented a favorable long-term survival, particularly in patients with a good response to preoperative chemotherapy, reporting a median survival time ranging from 25.5 to 54.6 months. Additionally, patients who underwent surgery for oligometastatic liver metastases had significantly longer OS than those who received chemotherapy alone. The study identified postchemotherapy normalization of Ca19-9 levels and a good radiological response as independent prognostic factors for a more prolonged survival. Similarly, Giuliante *et al*[11] and Crippa *et al*[34], in systematic reviews, reported that surgical resection of oligo-PDACs is a safe and effective procedure, potentially associated with improved survival. Comparable results were also reported in the first meta-analysis by Yu *et al*[12] in 2017, which found that hepatic resection of metastatic sites was associated with potential 1-year and 3-year survival benefits.

Despite these encouraging results, current studies have significant limitations that hinder the generalizability of the findings. Firstly, the available evidence is based solely on retrospective cohort studies with a limited number of patients and short

Table 2

Quality assessment of the included studies according to the Newcastle–Ottawa scale

	Selection					Outcome			
Authors	1	2	3	4	Comparability	1	2	3	Total
Klein et al[25]	*	*	*	*	*	*	*	*	8
Tachezy et al[17]	*	*	*	*	*	*	*	*	8
Hackert et al[26]	*	*	*	*	*	*	*	*	8
Hamad et al[14]	*	*	*	*	**	*	*	*	9
Yang et al[18]	*	*	*	*	*	*	*	*	8
Shao et al[16]	*	*	*	*	*	*	*	*	9
Safi et al[15]	*	*	*	*	*	*	*	*	8
Bachellier et al[27]	*	*	*	*	*	*	*	*	8
Takeda et al[24]	*	*	*	*	*	*	*	*	8
Nagai et al[28]	*	*	*	*	*	*	*	*	8
Satoi et al[13]	*	*	*	*	*	*	*	*	8

Table 3

Demographic, biochemical, and oncological features of the surgical and nonsurgical groups

Surgical group characteristics

Author	*N*	Age, median (range)	Male/Female, *n*	Tumor localization (Ph/Pb-Pt), *n*	Number of metastases, median (range)	Ca 19-9 level at the diagnosis, median U/ml (range)
Klein *et al* [25]	22	57.5 (31–78)[a]	14/8	NR	NR	8427.6 ± 25 812.9[b]
Tachezy *et al* [17]	69	65 (31–83)	39/30	44/25	2 (1–11)	NR
Hackert *et al* [26]	62	NR	NR	NR	NR	191 (33–532) [c]
Hamad *et al* [14]	137	NR	NR	NR	NR	NR
Yang *et al* [18]	23	61.8 ± 10.4[b]	13/10	12/11	NR	NR
Shao *et al* [16]	50	63 (40–81)	30/20	50/0	NR	1451 (2–12 000)
Safi *et al* [15]	35	67 (45–80)	20/15	27/8	1 (1–4)	NR
Bachellier *et al* [27]	92	63.5 (32–82)	57/35	54/38	3 (1–21)	126 (1–18 160)
Takeda *et al* [24]	10	62 (38–77)	8/2	5/5	2 (1–2)	704.5 (4–9953)
Nagai *et al* [28]	47	62 (54–67)[c]	14/33	26/21	2 (0–4)	NR
Satoi *et al* [13]	18	64 (46–84)	9/9	11/7	3 (1–10)	569 (2–5668)

Nonsurgical group characteristics

Author	*N*	Age, median (range)	Male/Female	Tumor localization (Ph/Pb-Pt)	Number of metastases, median (range)	Ca 19-9 level at the diagnosis, median U/ml (range)
Tachezy *et al* [17]	69	62 (34–83)	48/21	58/11	2 (1–8)	NR
Hamad *et al* [14]	137	NR	NR	NR	NR	NR
Yang *et al* [18]	31	61.1 (±8) [b]	23/8	16/15	NR	NR
Shao *et al* [16]	50	63 (47–81)	37/13	50/0	NR	2912 (2–12 000)
Safi *et al* [15]	14	71.5 (51–87)	7/7	13/1	1 (1-2)	NR
Satoi *et al* [13]	31	72 (51–82)	16/15	24/7	NR	168 (1–15 380)

[a]Mean (range).
[b]Mean (± standard deviation).
[c]Median (interquartile rank).
Ph: pancreatic head; Pb-Pt: pancreatic body-pancreatic tail; NR: not reported

follow-up periods. Secondly, there is currently no uniform consensus on the definition of oligo-PDAC in terms of number of metastases, metastatic size, and location. Moreover, and more importantly, a substantial number of authors evaluated the potential survival benefits of surgical resection regardless of the time of onset (synchronous or methacronous) and location (liver or pulmonary).

Based on these premises and given the aforementioned limitations of current studies, we conducted a meta-analysis with a sensitivity analysis specifically focused on the role of surgery in the combined treatment of primary PDAC and synchronous liver-only metastases. The aim was to define the potential long-term benefits of surgery in this specific subset of patients.

According to our pooled analysis, surgical resection of liver oligo-PDAC was associated to a significant improvement in long-term survival (OR: 0.286, 95% CI: 0.100–0.409; $P < 0.0001$). This result was further confirmed in the sensitivity analysis, conducted by excluding one study at a time (OR: 0.286, 95% CI: 0.199–0.409; $P < 0.0001$). Overlooking the survival data, surgical treatment of liver oligo-PDAC was associated to a 1-year survival rate ranging from 34.4% to 100%, compared to 19.3–29% in the conventional chemotherapy group. Notably, the 5-year survival rate reached a value of 27.7% in the surgical cohort as compared to 0% in the non-surgical population. Additionally, an evaluation of postoperative surgical outcomes documented an acceptable rate of major complications (14.1%) and mortality (2.8%), supporting the hypothesis that the combined surgical approach may be considered safe and feasible when performed in high-volume centers.

Although our findings support the long-term advantages of surgery over palliative chemotherapy, several issues need to be highlighted. Firstly, there was no unanimous definition of oligo-PDAC across the studies. According to a recent review on the management of metachronous liver metastases from PDAC[35], which analyzed 34 studies, nearly 60% did not include a definition of oligometastic disease, while the remaining studies reported inconsistent definitions. Similarly, the narrative review by Giuliante *et al*[11] highlighted a similar lack of consensus even for synchronous oligo-PDACs. This finding was further confirmed in our pooled cohort, where no uniform definition was used by the authors and one study[14] did not report the criteria for classifying the disease as oligometastic. As a consequence, the number of treated synchronous metastases varied significantly across the studies, with the highest value (up to 21 lesions) reported by Bachellier *et al*[26]. It is, thus, implicit the need for a standardized oligo-PDAC definition, especially in light of the prognostic impact of the number of metastases. This was demonstrated by Crippa *et al*[36] who found significantly longer survival in patients with a single metastasis compared to those with more than five lesions. A significant contribution to this field was recently made by Leonhardt *et al*[32] aiming to objectively define oligo-PDACs. The authors conducted a systematic review on 22 studies, including a total of 692 patients, and reported a consensus (100% agreement) on defining liver oligo-PDAC as the presence of three or fewer secondary lesions. This may

Table 4

Neoadjuvant and adjuvant chemotherapy regimens in the surgical group

Neoadjuvant regimes

Author	No. of NAT/No patients, *n* (%)	Gemcitabine, *n* (%)	FOLFIRINOX, *n* (%)	Gemcitabina + NAB-Paclitaxel, *n* (%)	Others, *n* (%)
Tachezy *et al* [17]	9/69 (13)	3 (33.3)	4 (44.4)	0	2 (22.3)
Yang *et al* [18]	2/23 (8.7)	0	0	2 (100)	0
Shao *et al* [16]	41/50 (82)	NR[a]	NR[a]	NR[a]	NR[a]
Safi *et al* [15]	4/35 (11.4)	0	4 (100)	0	0
Bachellier *et al* [27]	52/92 (56.5)	7 (13.4)	44 (84.6)	0	0
Takeda *et al* [24]	10/10 (100)	0	2 (20)	7 (70)	1 (10)
Nagai *et al* [28]	32/47 (68)	0	14 (43.7)	4 (12.6)	14 (43.7)
Satoi *et al* [13]	15/18 (83.3)	5 (33.4)	2 (13.3)	6 (40)	2 (13.3)

Adjuvant regimens

Author	No of AT/No patients, (%)	Gemcitabine, *n* (%)	FOLFIRINOX, *n* (%)	Gemcitabine + FOLFIRINOX, *n* (%)	Others, *n* (%)
Klein *et al* [25]	22/22 (100)	22 (100)	0	0	0
Tachezy *et al* [17]	43/69 (62.3)	35 (81.3)	3 (7)	3 (7)	2 (4.7)
Yang *et al* [18]	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
Shao *et al* [16]	47/50 (94)	NR[a]	NR[a]	NR[a]	NR[a]
Safi *et al* [15]	26/35 (74.3)	15 (57.7)	4 (15.4)	0	7 (26.9)
Bachellier *et al* [27]	78/92 (84.8)	NR	NR	NR	NR
Takeda *et al* [24]	7/10 (70)	NR	NR	NR	NR
Nagai *et al* [28]	28/47 (60)	NR	NR	NR	NR
Satoi *et al* [13]	16/18 (88.9)	1 (6)	0	0	15 (94)

NAT: neoadjuvant therapy; AT: adjuvant therapy; NR: not reported

[a]Shao *et al*: treatment strategies included FOLFIRINOX or gemcitabine-based chemotherapy.

[b]Yang *et al*: the authors declared that data regarding postoperative therapy are incomplete. Gemcitabine, Gemcitabine + Oxaliplatin, Gemcitabine + S-1, Gemcitabine + Nab-paclitaxel were the most common regimens.

potentially pave the way for the standardized adoption of a universally accepted definition in the near future.

Another debated topic is the optimal timing for the surgical treatment of oligo-PDAC. An international consensus meeting on the surgical management of metastatic pancreatic cancer, held in conjunction with the Joint Congress of the 26th Meeting of the International Association of Pancreatology (IAP) and the 53rd Annual Meeting of the Japan Pancreas Society (JPS) in Kyoto[37], gathered expert opinions on the treatment approach for synchronous liver-metastatic PDAC. The expert panel proposed two major strategies: the surgery-first and chemotherapy-first approaches. The surgery-first approach consists of the simultaneous resection of liver metastases and the primary PDAC, performed only in cases of oligo-metastatic disease where margin-negative resections can be ensured. On the other hand, the chemotherapy-first approach involves surgical resection of the primary tumor and metastatic lesions following a major response to preoperative chemotherapy.

Table 5

Surgical procedures and postoperative outcomes of the surgical population

Author	No. of patients	Surgical procedure (PD/DP/TP), *n* (%)	Liver surgical procedures (AT/SEG/HP), *n* (%)	Vascular resection, *n* (%)	Clavien–Dindo ≥3 complications, *n* (%)	Reoperation, *n* (%)	Perioperative mortality, *n* (%)	pN1-2, *n* (%)	R0, *n* (%)
Klein *et al* [25]	22	17/1/4	15/7/0	NR	4 (18)	2 (9)	0	18 (82)	7 (32)
Tachezy *et al* [17]	69	42/25/2	69/0/0	18 (26)	6 (8.7)	4 (6)	1(1.4)	48 (70)	40 (58)
Hackert *et al* [26]	62	NR	59/2/1	NR	NR	2 (3.2)	1 (1.6)	NR	NR
Hamad *et al* [14]	137	NR	NR	NR	NR	NR	NR	NR	NR
Yang *et al* [18]	23	12/11/0	21/2/0	NR	3 (13%)	0	0	NR	23 (100)
Shao *et al* [16]	50	50/0/0	NR	NR	NR	1 (2%)	NR	34 (68)	46 (92)
Safi *et al* [15]	35	NR	NR	12 (34.3)	NR	NR	3 (8.5)	28 (80)	17 (48.6)
Bachellier *et al* [27]	92	49/38/5	91/0/1	66 (71.7)-33 (35.8)[a]	14 (15.2)	1 (1.08)	5 (5.4)	79 (85.8)	46 (50)
Takeda *et al* [24]	10	6/3/1	NR	2 (20)	3 (30)	NR	0	NR	10 (100)
Nagai *et al* [28]	47	27/20/0	41/3/3	2 (4.2)	8 (17)	NR	0	34 (72.3)	38 (81)
Satoi *et al* [13]	18	10/7/1	NR/NR/13	10 (55.5)	NR	0	NR	10 (55.5)	NR

PD: pancreaticoduodenectomy; DP: distal pancreatectomy; TP: total pancreatectomy; AT: atypical resection; SEG: segmentectomy; HP: hepatectomy;
NR: not reported

[a]66 venous resections and 33 arterial resections

Table 6

Survival outcomes of surgical and no-surgical groups

Surgical group

Author	No. of patients	Median OS, months, median (95% CI)	1-year survival rate, %	2-year survival rate, %	3-year survival rate, %	5-year survival rate, %
Klein *et al* [25].	22	7.6	NR	5	NR	0
Tachezy, *et al* [17]	69	14.5 (10.8–18.2)	NR	23.2[b]	15.9[c]	5.8
Hackert *et al* [26]	62	10.6	NR	NR	NR	NR
Hamad *et al* [14]	137	15.6	NR	NR	NR	NR
Yang *et al* [18]	23	16.1	43.5	8.7	4.3	0
Shao *et al* [16]	50	16 (14.7–17.3)	63.8	29	6.7	NR
Safi *et al* [15]	35	10.3 (7.2-13.4)	34.3	5.7	2.9	0
Bachellier *et al* [27]	92	18.2 (14.7-22.7)	70	NR	10	0
Takeda *et al* [24]	10	54.6	100	90	50	10
Nagai *et al* [28]	47	21.9	72.3	38.3	21.3	0
Satoi *et al* [13]	18	18.4 (6.6–122.3)[a]	83.3	44.4	33.3	27.7

Nonsurgical group

Author	No. of patients	Median OS, months, median (95% CI)	1-year survival rate, %	2-years survival rate, %	3-years survival rate, %	5-years survival rate, %
Tachezy *et al* [17]	69	7.5 (4.9–10.2)	NR	0[b]	0	0
Hamad *et al* [26]	137	8.1	NR	NR	NR	NR
Yang *et al* [18]	31	7.6	19.3	0	0	0
Shao *et al* [16]	50	6 (4.7–7.3)	24	2	0	0
Safi *et al* [15]	14	NR	28.6	0	0	0
Satoi *et al* [13]	31	9.9 (8.3–10.9)	29	6.4	0	0

[a]Median value (range).
[b]Value at 20 months.
[c]Value at 40 months.

Although no consensus has yet been established on the optimal treatment approach, it is undeniable that preoperative chemotherapy and its corresponding regimen play a fundamental role in enabling an adequate surgical management of oligo-PDAC. This is particularly relevant given the recent oncological advancements in the treatment of pancreatic tumors. According to the ESPAC-5 randomized clinical trial[38], the preoperative administration of FOLFIRINOX improved 1-year OS to 84% compared to immediate surgery (39%) in borderline resectable PDAC. Similarly, gemcitabine plus capecitabine and capecitabine-based chemotherapy resulted in 1-year OS of 78% and 60%, respectively. In this context, the response to NAT may potentially serve as a selection criterion for surgical treatment of oligo-PDACs. Indeed, several authors[33,39-41] have already demonstrated better survival outcomes in patients with a major response to treatment compared to those with a poor response. This approach would likely allow for the appropriate selection of patients initially diagnosed with stage IV disease who could benefit from surgical intervention following NAT. However, there is currently insufficient data in the literature regarding the optimal chemotherapy regimen for oligo-PDAC patients, and no comparative analysis has been conducted to determine the effectiveness of one regimen over another. This is further confirmed in our analysis, where only seven studies[15,17,18,25,26,28,37] reported information on the type of neoadjuvant treatment used, with no comparative analysis of different regimens in terms of long-term survival.

There are several limitations to the present systematic review and meta-analysis. The effects estimated in the model are primarily based on limited retrospective observational studies and are therefore subject to biases and confounding factors that may have influenced our estimates. In addition, the retrospective study designs inevitably contributed to the population

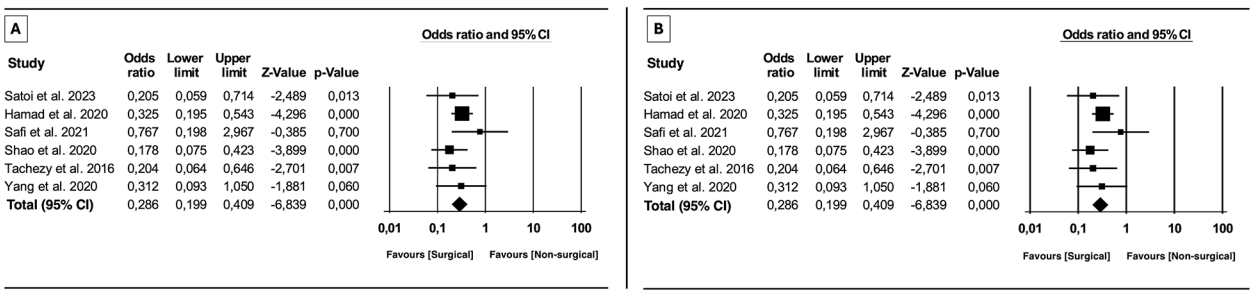

Figure 2. Forest plots of the meta-analysis comparing OS between surgical and nonsurgical groups using the random-effects model (A) and the fixed-effects model (B).

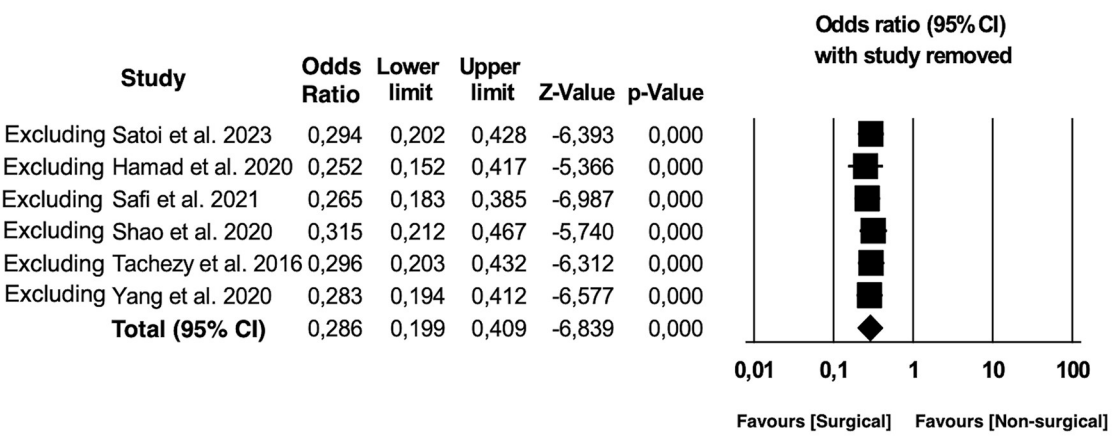

Figure 3. Sensitivity analysis on OS between surgical and non-surgical groups.

heterogeneity, particularly due to the consistent lack of information regarding primary tumor resectability, the number of metastatic lesions, and their exact location. Moreover, insufficient data were reported on the potential influence of metastasis size and the need for more extended hepatic resections on short- and long-term outcomes. Furthermore, data on neoadjuvant and adjuvant chemotherapy regimens were heterogenous, introducing a significant bias in drawing solid conclusions. More importantly, the absence of a standardized definition of oligo-PDAC considerably limits the generalization of our findings. Ultimately, the authors provided no information on the decision-making process or the volume of the centers where surgery was performed. Given the importance of the multidisciplinary approach and the experience of the institutions in the outcomes of patients with complex diseases[42-45] such as oligo-PDAC, the lack of these data further represents a substantial limitation.

Conversely, our study represents the first meta-analysis in the literature specifically focused on the role of surgery in the treatment of synchronous liver oligo-PDAC, reporting promising results despite the limited number of patients included and the retrospective study designs.

In conclusion, the surgical treatment of liver oligo-PDAC may potentially provide survival advantages over conventional chemotherapy. However, there is an undeniable need for a standardized definition of oligo-PDAC, along with the establishment of specific criteria for the accurate selection of patients who may benefit from a surgical approach. In this context, major radiological response to chemotherapy and a significant post-chemotherapy reduction of Ca 19.9 levels have been widely demonstrated as indicator of less aggressive disease[33] and, thus, may serve as potential selection criteria for the surgical treatment of oligo-PDACs. Nonetheless, there remains a clear need for prospective randomized trials to validate our findings and further support surgery as a potential treatment option for selected liver oligo-PDAC patients.

Ethical approval

Not applicable since the study is a systematic review and meta-analysis of the literature.

Consent

Not applicable since the study is a systematic review and meta-analysis of the literature.

Author contributions

Conceptualization: Giuseppe Quero, Lodovica Langellotti. Methodology: Claudio Fiorillo, Beatrice Biffoni, Teresa Mezza. Formal analysis and investigation: Roberta Menghi, Davide De Sio; Chiara Lucinato; Edoardo Panza. Writing - original draft preparation: Giuseppe Quero, Giuseppe Daloiso; Maria Carmen Puzzangara. Writing - review and editing: Giuseppe Massimiani. Supervision: Sergio Alfieri, Vincenzo Tondolo.

Conflicts of interest disclosure

None declared.

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