ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2024.106.1.51
Annals of Surgical Treatment and Research

Radical resection benefits patients suffering pancreatic ductal adenocarcinoma with liver oligometastases

Qingyan Kong, Fei Teng, Hang Li, Zheyu Chen

Division of Hepatic Surgery, Department of General Surgery, West China Hospital, Sichuan University, Chengdu, China

Purpose: Whether patients suffering liver oligometastases from pancreatic ductal adenocarcinoma (LOPDA) should undergo surgical treatment remains controversial.

Methods: PubMed and Embase databases were systematically reviewed until 2023 June. Survival data were collected from the Kaplan-Meier curves. Safety and survival were evaluated using primary outcomes such as 1-year, 3-year, and 5-year survival rates, and 30-day mortality and morbidity. A subgroup meta-analysis was conducted to compare survival rates post-synchronous resection and resection post-neoadjuvant chemotherapy in LOPDA.

Results: Our analysis of 15 studies involving 1,818 patients (surgical group, 648 and nonsurgical group, 1,170) indicates that radical hepatectomy for LOPDA notably improved 1-year (odds ratio [OR], 3.24; 95% confidence interval [CI], 2.45–4.28; $P < 0.001$), 3-year (OR, 5.74; 95% CI, 3.36–8.90; $P < 0.001$), and 5-year (OR, 4.89; 95% CI, 2.56–9.35; $P < 0.001$) overall survival (OS) rates. A separate analysis of 6 studies with 750 patients demonstrated the safety of LOPDA surgery, with no increase in postoperative complications ($P = 0.26$ for overall morbidity and $P = 0.99$ for mortality) compared to the patients with no metastatic disease from the pancreatic ductal adenocarcinoma (NMPDA) group. The NMPDA group showed superior 1-year and 3-year OS rates, but not 5-year OS rates compared to the LOPDA group.

Conclusion: Surgical treatment apparently offers a survival advantage to LOPDA by comparing with nonsurgical groups in 1-, 3-, and 5-year OS rates. Radical resection for LOPDA is a safe treatment without more postoperative complications than NMPDA.

[Ann Surg Treat Res 2024;106(1):51-60]

Key Words: Hepatectomy, Liver neoplasms, Meta-analysis, Neoplasm metastasis, Pancreatic neoplasms

INTRODUCTION

Among all causes of cancer death, pancreatic cancer ranks seventh in both sexes worldwide. There is evidence that pancreatic cancer will overtake breast cancer as the third leading cause of cancer death by 2025 in a study of 28 European countries [1]. Pancreatic ductal adenocarcinoma (PDAC) is the most common pathological type of pancreatic cancer, with an overall 5-year survival rate of approximately 8.5% [2]. Distant metastases contribute to poor prognosis, with liver metastases accounting for approximately 80% of PDAC cases with distant metastases [3]. Currently, PDAC with distant metastases is considered unresectable, and systemic chemotherapy, including cytotoxic chemotherapy, immunotherapy, and targeted therapy, is the mainstay of treatment [4]. Yet, as the only treatment that can achieve cure, surgery is increasingly considered for the improvement of preoperative systemic therapy and surgical safety. Patients presenting with clinically significant oligometastatic status, as proposed by Hellman and Weichselbaum [5], with distant metastases to a single or

Received August 11, 2023, **Revised** October 16, 2023,
Accepted November 15, 2023

Corresponding Author: Zheyu Chen
Division of Hepatic Surgery, Department of General Surgery, West China Hospital, Sichuan University, 37 Guoxue Ln, Wuhou District, Chengdu 610041, Sichuan, China
Tel: +86-15567018468, **Fax:** +86-28-8542-2114
E-mail: kqydoctor@163.com
ORCID: https://orcid.org/0009-0009-7131-0173

limited number of organs and a high likelihood of complete surgical resection of the metastases should be suitable for curative therapeutic strategies [5,6]. With improved accuracy in identifying oligometastatic disease, particularly for isolated liver metastases, several studies have investigated surgery and shown that surgery of the primary tumor and metastatic disease are associated with better overall survival (OS). For liver metastases from pancreatic, periampullary, and biliary cancers, Lee et al. [7] reached a conclusion based on a meta-analysis that resection could provide a survival advantage without compromising the safety and quality of life in a select group of patients. Yu et al. [8] concluded that extended surgery benefits the medium term (less than 3 years). The limitations of these studies, however, are the small number of patients, the studies published a long time ago, and the adulteration to other pathological types. For liver oligometastases from PDAC (LOPDA), published studies fail to supply sufficient evidence-based medicine to conclude convincingly that radical resection benefits patients. Whether or not to perform radical resection for LOPDA remains undetermined.

This meta-analysis with a stronger adequate number of studies and patients is much more reliable compared to other relevant reviews. In addition, this study introduces the concept of oligometastases. No systematic reviews or meta-analyses have focused on LOPDA with radical resection in recent years. This study analyzed the impact of radical resection compared with nonsurgical resection on the survival and safety of LOPDA radical resection compared with patients with no metastatic disease from PDAC (NMPDA) to maximize patient benefit and make a cure possible for a greater number of patients. The purpose of this study is to assist clinical surgery decisions in strict LOPDA selection.

METHODS

This study was reviewed by the Ethics Committee of West China Hospital of Sichuan University (No. 2022-1774).

Search strategy and data sources

This study performed a literature electronic search using PubMed from 1989 to 2023 and Embase from 1974 to 2023. Languages mainly included English and other languages such as Chinese, Japanese, and German. The retrieval strategy covered free words and key words. The search terms were "pancreatic cancer," "pancreatic ductal adenocarcinoma," "pancreatic neoplasm," "hepatic metastases resection," "liver metastases resection," "synchronous hepatectomy," "simultaneous hepatectomy," "synchronous hepatic resection," "synchronous liver resection," "simultaneous liver resection," "simultaneous hepatic resection," and "simultaneous liver resection," in MeSH terms. According to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, the search flowchart is listed in Fig. 1. Meanwhile, this study has been registered at PROSPERO (registration ID. 297926).

Inclusion and exclusion criteria

The inclusion criteria in this study were as follows: (1) all patients were diagnosed with pancreatic ductal adenocarcinoma (PDAC) with less than 3 liver metastases; (2) patients in the surgical group with liver metastases were suitable for surgery with or without (neo)adjuvant chemotherapy/radiation therapy; (3) survival rates can be collected in the literature; and (4) Newcastle-Ottawa Scale (NOS) score of ≥7. The exclusion criteria were as follows: (1) neuroendocrine neoplasm and other pathological types; (2) studies without a control group; (3) fewer than 5 surgical patients; and (4) published in the form of systematic reviews and meta-analyses, animal experiments, letters, comments, and case reports.

Data extraction and tabulation

Two authors (QK and ZC) performed the basic data collection independently by a data extraction form that included patient characteristics (age, sample size, gender, country, treatment methods, and surgical treatment details) and study information (first author, published year, and NOS score). Major outcomes (perioperative mortality, morbidity, and 1-, 3-, and 5-year OS) are displayed in the form and forest plot. Disagreements reached a consensus with a third author (FT). All tables, texts, and figures were the targets for data extraction.

Quality assessment

The quality of the included studies was evaluated in the form of the Newcastle-Ottawa Quality Assessment Scale (NOS System) for cohort or case-control studies. We focused on the selection of the exposed cohort, the comparability of cohorts, the basis of the analysis of design, and the follow-up time long enough at least 1 year. Most of the included studies with NOS scores ≥8 belonged to high-quality literature.

Statistical analysis

According to Cochrane recommendations, following the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines, meta-analysis was performed by using RevMan ver. 5.3 software (Cochrane Collaboration). Due to the heterogeneity between the research design and the research object, I^2 and P-values were calculated to represent statistical heterogeneity. The pooled effect was chosen using either the fixed effects model or the random effects model based on a threshold of 75%, with significance being set at a P-value of <0.05 and I^2 of $>75\%$. A fixed effects model was applied in all analyses due to little heterogeneity. Survival outcomes such as 1-, 3- and 5-year OS rate data were analyzed by dichotomous

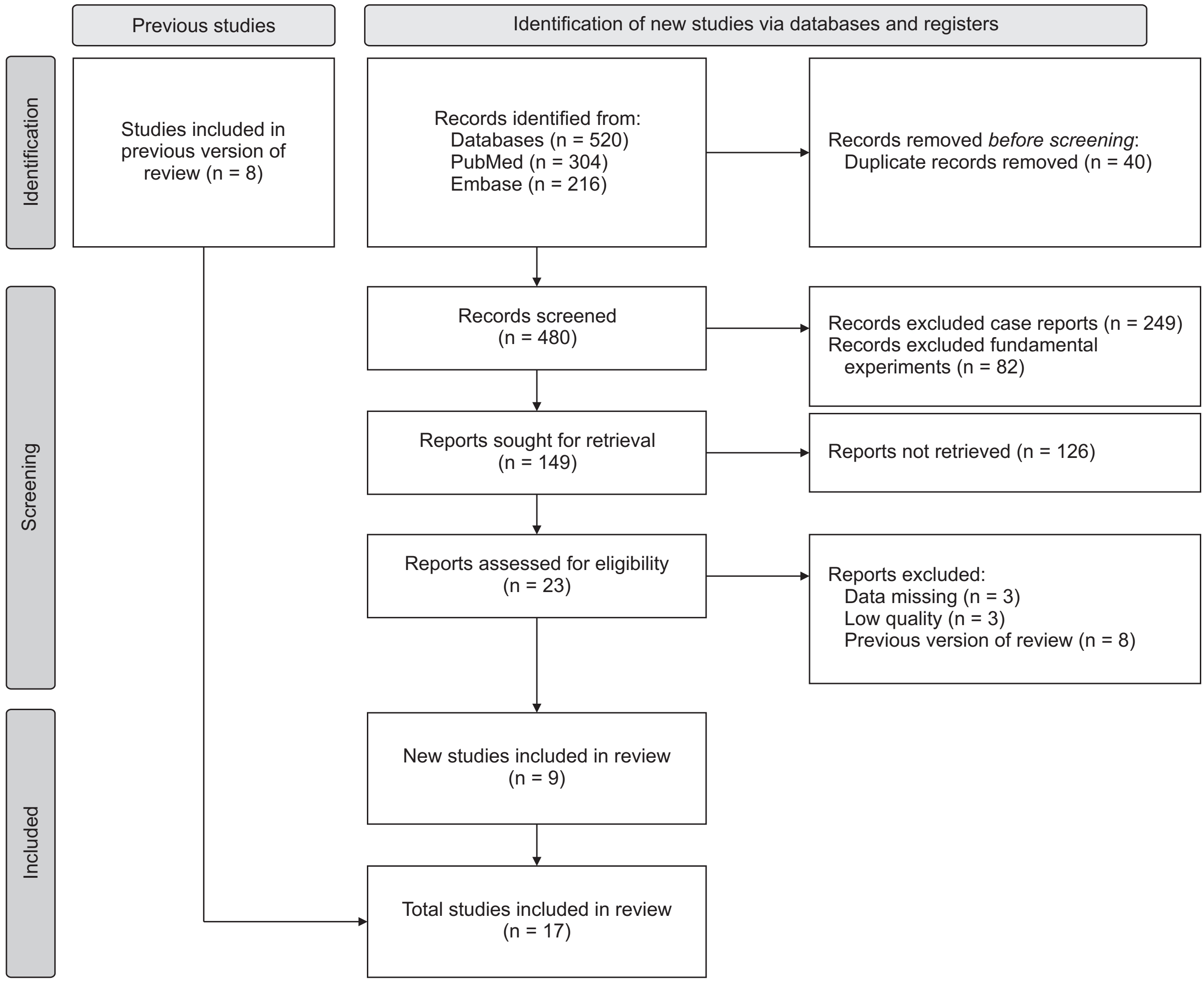

Fig. 1. Search strategy in the flow diagram.

variables with estimation of odds ratios (ORs) together with 95% confidence intervals (CIs), which were calculated using the number of events and the total number. Overall morbidity and 30-day perioperative mortality were also pooled in this way. Survival means the time of resection of the hepatic metastases in the surgical group and the time of diagnosis of pancreatic cancer with hepatic metastases in the nonsurgical group. To evaluate publication bias, funnel plots were generated. Excluding some studies or changing the effects model can test sensitivity of total studies.

RESULTS

Study selection

The initial literature search strategy identified a total of 520 unique articles. After the exclusion of case reports, reviews, fundamental experiments, and duplications, 26 studies were screened to assess potential relevance. After further screening, this study finally included 17 articles. Among them, 11 studies involved clinical research on the choice of surgical and nonsurgical treatment in PDAC. Details are displayed in Table 1. The number of patients was 1,929 in this meta-analysis. To demonstrate the advantage of surgery in PDAC, 659 patients underwent hepatic resection as the surgical group, and the nonsurgical group included 1,192 patients. The number of included studies and patients ensured the authenticity of this study. The pathological type of all studies was pancreatic ductal adenocarcinoma. Five studies mentioned the quantity of hepatic metastases (solitary/multiple) [9-14]. Meanwhile, 5 articles were clinical studies of surgical treatment for LOPDA and NMPDA [9,13,15-17]. To confirm the effects of surgery, this study compared OS rates, postoperative complications, and mortality between LOPDA and NMPDA.

Seven studies compared metachronous and synchronous liver resection [12,14,18-22]. Reasons for metachronous liver resection included neoadjuvant chemotherapy followed

Table 1. Basic study characteristics of included studies on the surgical group and the nonsurgical group for LOPDA

Study	Year	Country	Time period	No. of patients	Age (yr)[a]		Sex ratio, male: female	Hepatic resection, yes/no	Chemotherapy, nonsurgical/ surgical	Radiotherapy	Surgical hepatic metastases		No. of metastases tumor, nonsurgical/ surgical	Lymph node disease, nonsurgical/ surgical	NOS score
					Nonsurgical	Surgical					Solitary/ multiple	Synchronous/ metachronous			
Gleisner et al. [9]	2007	America	1995–2005	88	67.2 ± 11.6	67.4 ± 11.4	44:44	22/66	NR/7	NR	20/2	NR	NR	57/19	9
Shrikhande et al. [10]	2007	Germany	2001–2005	129	65 (60–74)		NR	11/118	NR	NR	7/3	NR	NR	NR/9	7
Dünschede et al. [18]	2010	Germany	1996–2008	23	52.5 (42–78)	51 (39–81)	13:10	13/10	10/4	NR	NR	9/4	NR	NR	8
de Jong et al. [14]	2010	America	1993–2009	40	63.0 ± 10.6		24:16	40/0	NR	NR	34/6	27/13	NR	NR	8
Ouyang et al. [19]	2015	China	2000–2012	497	NR	NR	321:176	22/475	NR	NR	NR	17/5	NR	NR	7
Zanini et al. [20]	2015	Italy	2003–2014	15	NO	55 (52–64)	8:7	15/0	NR	NR	NR	11/4	NR	NR	7
Tachezy et al. [6]	2016	Europe	1994–2014	138	62 (34–83)	65 (31–83)	87:51	69/69	49/43	1/138	NR	NR	2 (1–8)/2 (1–11)	38/48	9
Crippa et al. [25]	2016	Italy	2003–2013	127	65.0 ± 7.3	65.0 ± 5.4	76:51	11:116	NR	2/9	NR	NR	NR	NR	8
Shi et al. [15]	2016	China	2007–2015	69	63.0 ± 10.4	62.2 ± 10.0	37:32	30:39	39/NR	NR	NR	NR	NR	NR/14	9
Hackert et al. [21]	2017	Germany	2001–2014	128	62.7	60.4	62:66	85/43	NR	NR	NR	62/23	NR	0/43	9
Yang et al. [11]	2019	China	2012–2017	89	NR	NR	57:32	48/41	31/38	NR	23/25	NR	NR	NR	8
Mitsuka et al. [12]	2020	Japan	2005–2015	17	65 (43–74)	66 (41–74)	NR	9/8	8/6	NR	6/3	1/8	7 (4–15)/1 (1–3)	NR	8
Schwarz et al. [22]	2020	Austria	2004–2015	33	69 (64–73)	64 (57–70)	14:19	25/8	8/22	NR	NR	0/25	2 (2–2.3)/1 (1–2)	NR	9
Shao et al. [13]	2020	China	NR	100	63 (47–81)	63 (40–81)	67:33	50/50	NR/41	NR	50/50	NR	NR	NR	9
Su et al. [23]	2021	China	NR	325	65.0 ± 9.5	65.0 ± 6.4	180:145	93/232	133/31	18/325	NR	NR	NR	NR	8

LOPDA, liver oligometastases from pancreatic ductal adenocarcinoma; NOS, Newcastle-Ottawa Scale; NR, not recorded; NO, not nonsurgical.
[a]Values are presented as mean ± standard deviation or median (interquartile range).

by resection of liver metastases and the discovery of liver metastases after surgery. This study compared the 3-year OS rate with synchronous resection and resection following neoadjuvant chemotherapy [9,13,15-17]. Six studies especially introduced chemotherapy treatment. The median chemotherapy rates in the surgical group and the nonsurgical group were 64% (range, 31%–88%) and 87.5% (range, 57%–100%), respectively [6,11,12,18,22,23]. Nine articles clarified the types of

Table 2. Results of the meta-analysis comparing the surgical group and the nonsurgical group for LOPDA

Outcome of interests	No. of study	No. of events for surgical	No. of events for nonsurgical	OR (95% CI)	P-value	Heterogeneity P-value and I^2	Meta-analysis model
1-year OS	11	215/390	322/1,222	3.24 (2.45–4.28)	<0.0001	<0.0001, 76%	Fixed
3-year OS	11	61/392	37/1,114	5.74 (3.36–8.90)	<0.0001	0.50, 0%	Fixed
5-year OS	5	29/348	15/573	4.89 (2.56–9.35)	<0.0001	0.79, 0%	Fixed

LOPDA, liver oligometastases from pancreatic ductal adenocarcinoma; OR, odds ratio; CI, confidence interval; OS, overall survival.

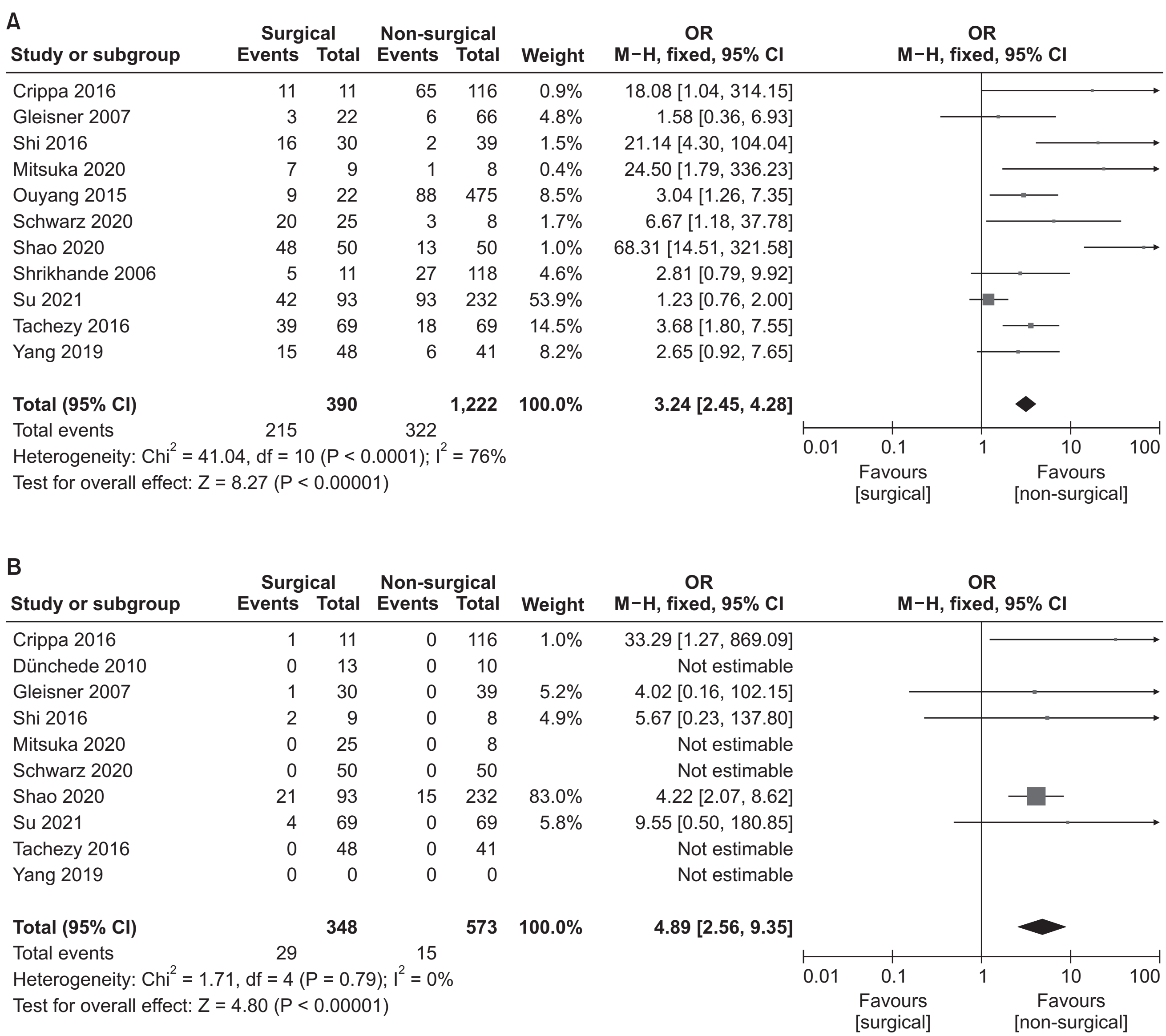

Fig. 2. (A) Forest plot of the meta-analysis of the 1-year (A) and 5-year (B) overall survival (OS) rate between the surgical and nonsurgical groups. For all patients included in the pool, the surgical group was associated with a significantly improved OS rate (1-year: odds ratio [OR], 3.24; 95% confidence interval [CI], 2.45–4.28; P < 0.001; 5-year: OR, 4.89; 95% CI, 2.56–9.35; P < 0.001).

chemotherapy drugs; the details are shown in Supplementary Table 1.

Meta-analysis of primary outcomes

The primary meta-analysis outcomes of 11 studies on the surgical group and nonsurgical group from PDAC are summarized in Table 2. For the surgical group, the median 1-, 3-, and 5-year survival rates were 55.1%, 15.6%, and 8.3%, respectively. For the nonsurgical group, the median 1-, 3-, and 5-year survival rates were 26.4%, 3.3%, and 2.6%, respectively. For the 1-year OS rate, a meta-analysis of the 11 studies illustrated that radical resection for LOPDA was associated with a significantly improved 1-year OS rate (OR, 3.24; 95% CI, 2.45–4.28; P < 0.001) (Fig. 2A). However, there was significant heterogeneity in the 1-year OS meta-analysis (I^2 = 76%, P < 0.0001). Through sensitivity analysis, we found that the main source of heterogeneity came from 2 studies [13,23]. A short observation time and low-quality research may be the reasons. For the 3-year OS rate, a meta-analysis of the 11 studies illustrated that radical resection for LOPDA was associated with a significantly improved 3-year OS rate (OR, 5.74; 95% CI, 3.36–8.90; P < 0.001) (Fig. 3), without heterogeneity (I^2 = 0%, P = 0.50). For the 5-year OS rate, a meta-analysis of the 5 studies illustrated that radical resection for LOPDA was associated with a significantly improved 5-year OS rate (OR, 4.89; 95% CI, 2.56–9.35; P < 0.001), without heterogeneity (I^2 = 0%, P = 0.79) (Fig. 2B).

The primary meta-analysis outcomes of 6 studies on surgical resection for LOPDA and NMPDA are summarized in Table 3. The median morbidity of surgical resection of LOPDA was 63% (range, 50%–68%), and the median 30-day postoperative mortality was 1.4% (range, 0%–9.1%). The evaluation of postoperative complications was based on the Clavien-Dindo evaluation system. Comparing the overall morbidity of the two groups, no significant difference was observed (OR, 1.26; 95% CI, 0.85–1.87; P = 0.26). Regarding the 30-day mortality: there was also no significant difference observed between the 2 groups (OR, 1.01; 95% CI, 0.24–4.26; P = 0.99). This further illustrated that the safety of pancreatic cancer surgery with or without liver metastases was comparable. For the 1-year OS rate,

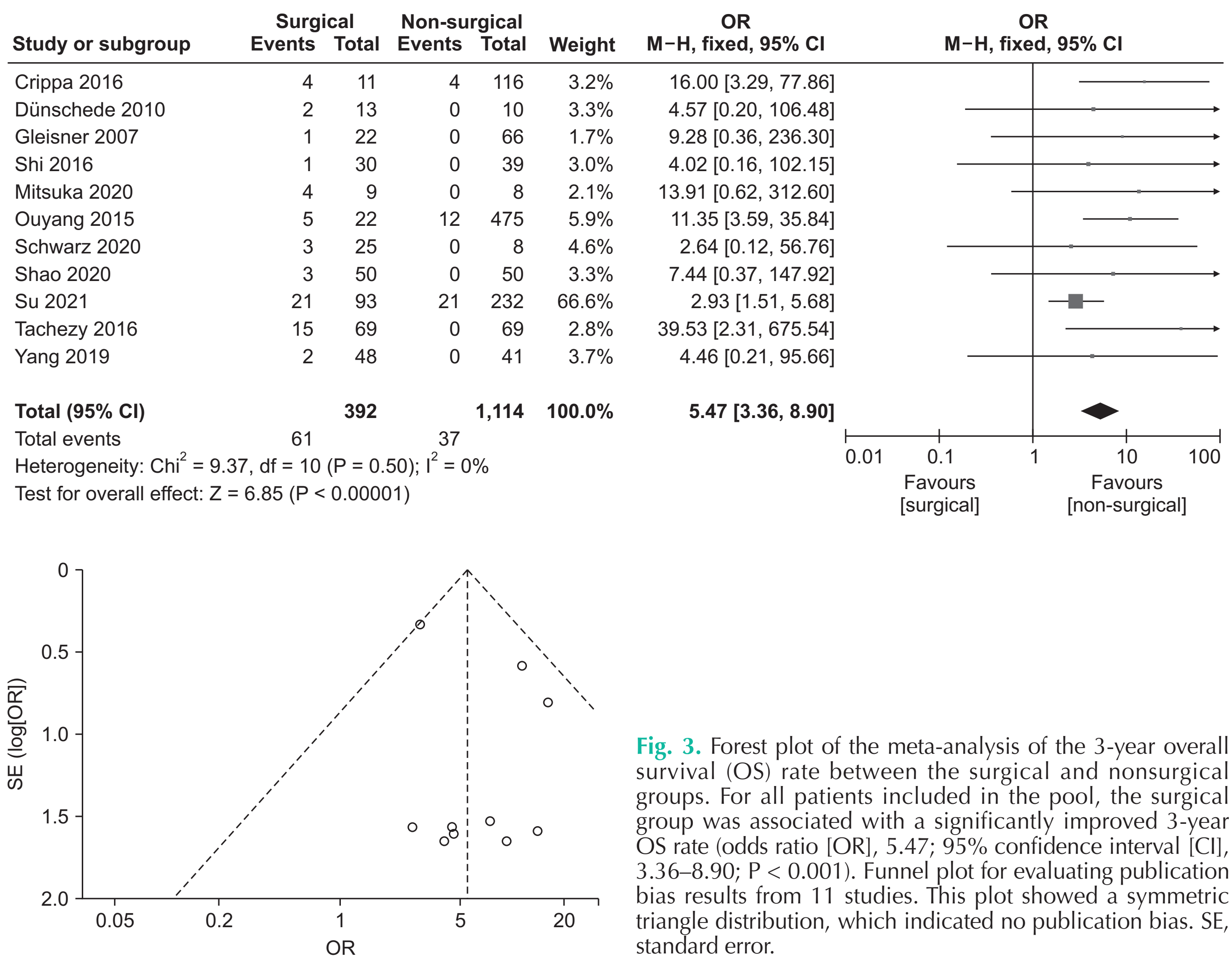

Fig. 3. Forest plot of the meta-analysis of the 3-year overall survival (OS) rate between the surgical and nonsurgical groups. For all patients included in the pool, the surgical group was associated with a significantly improved 3-year OS rate (odds ratio [OR], 5.47; 95% confidence interval [CI], 3.36–8.90; P < 0.001). Funnel plot for evaluating publication bias results from 11 studies. This plot showed a symmetric triangle distribution, which indicated no publication bias. SE, standard error.

Table 3. Results of the meta-analysis comparing LOPDA with NMPDA in surgical resection

Outcome of interests	No. of study	No. of events for LOPDA	No. of events for NMPDA	OR (95% CI)	P-value	Heterogeneity P-value and I^2	Meta-analysis model
Overall morbidity	6	75/167	218/583	1.26 (0.85–1.87)	0.26	0.07, 51%	Fixed
Perioperative mortality	4	2/103	15/513	1.01 (0.24–4.26)	0.99	0.30, 6%	Fixed
1-year OS	5	64/138	218/296	0.24 (0.14–0.39)	<0.0001	0.31, 17%	Fixed
3-year OS	5	7/138	46/296	0.22 (0.10–0.53)	0.0006	0.94, 0%	Fixed
5-year OS	3	2/74	13/226	0.39 (0.10–1.48)	0.17	0.14, 50%	Fixed

LOPDA, liver oligometastases from pancreatic ductal adenocarcinoma; NMPDA, no metastatic disease from pancreatic ductal adenocarcinoma; OR, odds ratio; CI, confidence interval; OS, overall survival.

a meta-analysis of the 5 studies illustrated that radical resection for NMPDA was associated with a significantly improved 1-year OS rate (OR, 0.24; 95% CI, 0.14–0.39; P < 0.0001). For the 3-year OS rate, a meta-analysis of the 5 studies illustrated that radical resection for NMPDA was associated with a significantly improved 3-year OS rate (OR, 0.22; 95% CI, 0.10–0.53; P = 0.0006). Because the tumor stage in the LOPDA group was later than that in the NMPDA group, the survival rate was better in line with expectations. Surprisingly, for the 5-year OS rate, no significant difference was observed (OR, 0.39; 95% CI, 0.10–1.48; P = 0.17). Pancreatic cancer itself has a low survival rate, and a small amount of literature may have contributed to this result.

Meta-analysis of subgroups

Four studies [6,12,20,21] (163 participants) focused on synchronous resection and resection after neoadjuvant chemotherapy (RANC) of LOPDA (Supplementary Fig. 1). In the synchronous resection group, the patients were diagnosed with pancreatic cancer with liver oligometastases before surgery. In the RANC group, patients were those who were found to have liver oligometastases during the chemotherapy period 1 month after pancreatic cancer surgery. In the RANC group, the neoadjuvant chemotherapy drugs were gemcitabine or 5-fluorouracil [21], S-1 or gemcitabine [12], gemcitabine or FOLFIRINOX (folinic acid, 5-FU, irinotecan, oxaliplatin) [6,20]. For 3-year OS, no significant difference was observed between synchronous resection and RANC (OR, 1.04; 95% CI, 0.41–2.69). This provides a clinical decision framework for prioritizing surgical treatment in LOPDA. However, due to the limited number of reported studies, further support from high-quality research with larger sample sizes is still needed.

Additionally, we conducted a subgroup analysis based on the demographic characteristics of each study, dividing the research into 2 subgroups: Western countries and Asian countries. The subgroup analysis results indicate that despite some variations in research outcomes across different regions, radical resection is closely associated with improved 1-year (Supplementary Fig. 2A) and 3-year (Supplementary Fig. 2B) OS rates for LOPDA. The subgroup analysis results are consistent with the previous findings, further enhancing the credibility and reliability of the main research outcomes.

Sensitivity analysis and bias exploration

This study performed a sensitivity analysis using postoperative chemotherapeutic agents in 6 studies [6,11,12,18,22,23]. The results were consistent with the initial outcomes (1-year OS rate: OR, 2.07; 95% CI, 1.46–2.95; P < 0.001; 3-year OS rate: OR, 4.55; 95% CI, 2.58–8.02; P < 0.001; and 5-year OS rate: OR, 4.63; 95% CI, 2.35–9.11; P < 0.001). This study was confirmed to have good stability by omitting each study to analyze the general sensitivity. Funnel plots of the studies were used in the meta-analysis. This study showed little publication bias in funnel plots. Due to the strict requirements on the general conditions of patients who underwent surgical resection, there may be selection bias in this paper. All studies were with homogenous control groups. The selection bias of patients could be reduced by setting up controls.

DISCUSSION

Hellman and Weichselbaum [5] proposed the state of oligometastases in which the metastasis of the tumor is limited in number and location. Distinct from micrometastases, the facility for metastatic growth is not fully developed and the site of it is confined. Cure strategies that may be considered include surgery and ablation. For a single liver metastasis ≤5 cm, or ≤3 tumors, each ≤3 cm, Hua et al. [24] concluded that RFA plus gemcitabine-based chemotherapy may prolong survival in selected patients. Four earlier studies [9,10,14,20] suggested that surgery does not bring a significant survival benefit to LOPDA and is often not recommended. Due to the improvements in pre-, peri-, and postoperative management, as well as appropriate patient selection, surgical safety has improved [13,22]. The safety of surgery has prompted more studies willing to operate on PDAC patients. In recent years, more studies have shown that surgery for pancreatic cancer with oligometastases can provide survival benefits [6,11,13,18,23,25]. The meta-analysis of mortality included only 4 studies due to missing information on the control group. However, in terms of surgical safety, the reported studies [10-12,15,18,22] included 88 patients with a 30-day mortality rate of 0%. One study was 9.1% (n = 22) [9] and the other was 1% (n = 69) [6]. More importantly, the mortality for radical LOPDA resection was 0% in the last 3 years [11,12,22]. Combined with the results of the meta-analysis in this article, the safety of surgery for LOPDA can be well illustrated.

In 2 RCTs on modern chemotherapy regimens for metastatic pancreatic cancer, survival was significantly improved (1- and 3-year OS of FOLFIRINOX group were 36% and 1%, gemcitabine groups were 16% and 1%, respectively [26]; 1- and 3-year OS of nab-paclitaxel–gemcitabine group were 6% and 0%, gemcitabine group were 2% and 0%, respectively [27]). One study had a 5-year OS of 0% [27] and another had a follow-up of less than 5 years [26]. Chemotherapy regimens alone may have influenced the improved survival rate. However, in this meta-analysis, the median 1- and 3-year OS rates of the surgical group were 53.3% and 15.0%, respectively. Meanwhile, the median 1- and 3-year OS survival rates of the nonsurgical group were 22% and 0%, respectively. Table 1 and Supplementary Table 1 show the number of patients who received chemotherapy and the type of chemotherapeutic drugs mentioned in the study. The majority of patients in this study were given chemotherapy drugs in both the surgical group and the nonsurgical group. The chemotherapy regimen in this study was similar to that in the 2 RCTs, and this study included more patients than 2 RCTs. The 1- and 3-year OS rates were almost indiscriminate between the nonsurgical group and the FOLFIRINOX group. By removing the effects of chemotherapy, this study reliably concluded that surgery still significantly improves survival in LOPDA, especially long-term survival. Surgery combined with chemotherapy has become a potential option for multidisciplinary treatment [19,25].

Certainly, limited lymph node metastases are considered a special form of oligometastases, which are treated through surgery [5]. Nevertheless, few studies have evaluated the impact of surgical treatment of patients with oligometastases on long-term survival. There were no unified, specific, observed criteria for the number and size of oligometastases in the liver. Some of the included studies explained the specific number of liver metastases ≤3 [9,11-13,22,25]. These studies were published in the last 2 years, as developments in imaging have made it possible to identify patients with oligometastases [28].

Several limitations may impact this meta-analysis. Firstly, the number of included studies is not large enough and no randomized controlled trials are included due to the small number of original studies addressing radical resection of LOPDA. And this would have increased selection bias. Secondly, the source of heterogeneity is a limitation. Primary tumors in various positions present different metastatic patterns and may affect the OS rate in each study. In addition, for metastatic pancreatic cancer, FOLFIRINOX is recommended as a systemic therapy for first-line treatment with good performance. Different chemotherapy regimens in each study have different effects on OS. Four studies [6,12,20,21] (163 participants) used neoadjuvant chemotherapy and Lee et al. [7] obtained significantly higher OS rates in patients who responded well to neoadjuvant chemotherapy. In addition, the time from diagnosis to operation also affects OS. Unfortunately, this has not been documented in most studies. Finally, the LOPDA in the surgical group were patients who had been carefully screened. The number and size of metastases, patient requirements, and physical conditions influence whether surgery should be performed. This would lead to selective bias.

Due to the small number of patients undergoing surgery for liver metastasis from pancreatic cancer, and the wide distribution of research over different time periods, we stratified the included studies by year to exclude differences attributable to time period. The results are shown in Supplementary Fig. 3. As can be inferred from the results, there were differences between the studies conducted prior to 2010 and the findings of this current study. However, studies conducted after 2011 have still shown that surgical resection for LOPDA provides patients with 1-year and 3-year survival benefits. Meanwhile, in order to ensure comparability between the surgical and nonsurgical groups, we collected data on the size of the primary tumor and the number of metastatic tumors in each group from various studies to reflect consistent tumor burden, as shown in Supplementary Table 2. According to reports from various studies, we found that in the majority of studies, there was no significant difference in tumor burden between the 2 groups ($P > 0.05$).

This review shows that surgery delivers greater survival benefits to LOPDA compared to chemotherapy. However, pharmacological chemotherapy is the first recommendation for metastatic pancreatic cancer such as FOLFIRINOX and gemcitabine plus nab-paclitaxel [29]. This has led to the existence of some chemotherapy patients who could live longer through surgical treatment. Therefore, it is important to establish criteria and to select LOPDA accurately. This review provides evidence-based medical rationales for future studies on surgical resection of LOPDA.

In conclusion, radical resection offers a survival advantage to LOPDA in 1-, 3-, and 5-year OS rates with low heterogeneity in comparison to the nonsurgical group. Meanwhile, LOPDA is similar to NMPDA in the safety of surgery with low mortality and without more postoperative complications. This study shows that LOPDA can benefit from radical resection and surgery is safe. These findings suggest that surgery as a more curative and beneficial choice should be generally considered in LOPDA. Nevertheless, there are no well-accepted criteria for the surgery indications of LOPDA, and more studies, especially prospective ones, are urgently needed.

SUPPLEMENTARY MATERIALS

Supplementary Tables 1, 2, and Supplementary Figs. 1–3 can be found via https://doi.org/10.4174/astr.2024.106.1.51.

ACKNOWLEDGEMENTS

Fund/Grant Support
None.

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

ORCID iD
Qingyan Kong: https://orcid.org/0000-0001-9979-5453
Fei Teng: https://orcid.org/0009-0002-8808-1417
Hang Li: https://orcid.org/0009-0001-2406-0118
Zheyu Chen: https://orcid.org/0009-0009-7131-0173

Author Contribution
Conceptualization: All authors
Formal Analysis: FT
Data curation: ZC
Investigation: HL, QK
Writing – Original Draft: QK
Writing – Review & Editing: All authors

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49.
2. Duggan MA, Anderson WF, Altekruse S, Penberthy L, Sherman ME. The surveillance, epidemiology, and end results (SEER) program and pathology: toward strengthening the critical relationship. Am J Surg Pathol 2016;40:e94-102.
3. Noda Y, Tochigi T, Baliyan V, Kordbacheh H, Kambadakone A. Hepatobiliary contrast uptake patterns on gadoxetic acid-enhanced MRI in liver metastases from pancreatic ductal adenocarcinoma: can it predict prognosis? Eur Radiol 2021;31:276-82.
4. Varghese AM, Lowery MA, Yu KH, O'Reilly EM. Current management and future directions in metastatic pancreatic adenocarcinoma. Cancer 2016;122:3765-75.
5. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995;13:8-10.
6. Tachezy M, Gebauer F, Janot M, Uhl W, Zerbi A, Montorsi M, et al. Synchronous resections of hepatic oligometastatic pancreatic cancer: disputing a principle in a time of safe pancreatic operations in a retrospective multicenter analysis. Surgery 2016;160:136-44.
7. Lee RC, Kanhere H, Trochsler M, Broadbridge V, Maddern G, Price TJ. Pancreatic, periampullary and biliary cancer with liver metastases: Should we consider resection in selected cases? World J Gastrointest Oncol 2018;10:211-20.
8. Yu X, Gu J, Fu D, Jin C. Dose surgical resection of hepatic metastases bring benefits to pancreatic ductal adenocarcinoma? A systematic review and meta-analysis. Int J Surg 2017;48:149-54.
9. Gleisner AL, Assumpcao L, Cameron JL, Wolfgang CL, Choti MA, Herman JM, et al. Is resection of periampullary or pancreatic adenocarcinoma with synchronous hepatic metastasis justified? Cancer 2007;110:2484-92.
10. Shrikhande SV, Kleeff J, Reiser C, Weitz J, Hinz U, Esposito I, et al. Pancreatic resection for M1 pancreatic ductal adenocarcinoma. Ann Surg Oncol 2007;14:118-27.
11. Yang J, Zhang J, Lui W, Huo Y, Fu X, Yang M, et al. Patients with hepatic oligometastatic pancreatic body/tail ductal adenocarcinoma may benefit from synchronous resection. HPB (Oxford) 2020;22:91-101.
12. Mitsuka Y, Yamazaki S, Yoshida N, Yan M, Higaki T, Takayama T. Time interval-based indication for liver resection of metastasis from pancreatic cancer. World J Surg Oncol 2020;18:294.
13. Shao Y, Feng J, Hu Z, Wu J, Zhang M, Shen Y, et al. Feasibility of pancreaticoduodenectomy with synchronous liver metastasectomy for oligometastatic pancreatic ductal adenocarcinoma: a case-control study. Ann Med Surg (Lond) 2021;62:490-4.
14. de Jong MC, Tsai S, Cameron JL, Wolfgang CL, Hirose K, van Vledder MG, et al. Safety and efficacy of curative intent surgery for peri-ampullary liver metastasis. J Surg Oncol 2010;102:256-63.
15. Shi HJ, Jin C, Fu DL. Preoperative evaluation of pancreatic ductal adenocarcinoma with synchronous liver metastasis: diagnosis and assessment of unresectability. World J Gastroenterol 2016;22:10024-37.
16. Klein F, Puhl G, Guckelberger O, Pelzer U, Pullankavumkal JR, Guel S, et al. The impact of simultaneous liver resection for occult liver metastases of pancreatic adenocarcinoma. Gastroenterol Res Pract

2012;2012:939350.
17. Seelig SK, Burkert B, Chromik AM, Tannapfel A, Uhl W, Seelig MH. Pancreatic resections for advanced M1-pancreatic carcinoma: the value of synchronous metastasectomy. HPB Surg 2010;2010:579672.
18. Dünschede F, Will L, von Langsdorf C, Möhler M, Galle PR, Otto G, et al. Treatment of metachronous and simultaneous liver metastases of pancreatic cancer. Eur Surg Res 2010;44:209-13.
19. Ouyang HH, Pan ZY, Ma WD, Zhao LJ, Zhang T, Liu F, et al. [Multidisciplinary treatment and survival analysis for 497 cases of pancreatic cancer with liver metastases]. Zhonghua Yi Xue Za Zhi 2016;96:425-30. Chinese.
20. Zanini N, Lombardi R, Masetti M, Giordano M, Landolfo G, Jovine E. Surgery for isolated liver metastases from pancreatic cancer. Updates Surg 2015;67:19-25.
21. Hackert T, Niesen W, Hinz U, Tjaden C, Strobel O, Ulrich A, et al. Radical surgery of oligometastatic pancreatic cancer. Eur J Surg Oncol 2017;43:358-63.
22. Schwarz C, Fitschek F, Primavesi F, Stättner S, Margonis GA, Weiss MA, et al. Metachronous hepatic resection for liver only pancreatic metastases. Surg Oncol 2020;35:169-73.
23. Su BB, Bai DS, Yu JQ, Zhang C, Jin SJ, Zhou BH, et al. Can patients with pancreatic cancer and liver metastases obtain survival benefit from surgery? A population-based study. J Cancer 2021;12:539-52.
24. Hua YQ, Wang P, Zhu XY, Shen YH, Wang K, Shi WD, et al. Radiofrequency ablation for hepatic oligometastatic pancreatic cancer: an analysis of safety and efficacy. Pancreatology 2017;17:967-73.
25. Crippa S, Bittoni A, Sebastiani E, Partelli S, Zanon S, Lanese A, et al. Is there a role for surgical resection in patients with pancreatic cancer with liver metastases responding to chemotherapy? Eur J Surg Oncol 2016;42:1533-9.
26. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.
27. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691-703.
28. Litjens G, Rivière DM, van Geenen EJ, Radema SA, Brosens LA, Prokop M, et al. Diagnostic accuracy of contrast-enhanced diffusion-weighted MRI for liver metastases of pancreatic cancer: towards adequate staging and follow-up of pancreatic cancer. DIA-PANC study: study protocol for an international, multicenter, diagnostic trial. BMC Cancer 2020;20:744.
29. Sohal DP, Kennedy EB, Cinar P, Conroy T, Copur MS, Crane CH, et al. Metastatic pancreatic cancer: ASCO guideline update. J Clin Oncol 2020;38:3217-30.