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Surgical treatment of metastatic pancreatic ductal adenocarcinoma: A review of current literature

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ABSTRACT

Background: There is no international consensus concerning the role of surgical treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC), but favorable prognoses can be expected for highly selected patients.
Methods: A comprehensive literature search of the PubMed and Cochrane databases was conducted using combinations of keywords to 4 July 2018. Eligible studies were those reporting on patients with histologically confirmed mPDAC undergoing surgery with curative intent. We excluded case reports with fewer than five patients, insufficient descriptions of survival data, and palliative or cytoreductive surgery as well as studies that assessed para-aortic lymph node metastasis or peritoneal washing cytology.
Results: Thirteen studies were deemed eligible, and six studies were identified from their references. The studies involved 428 patients who underwent surgical resection for liver metastases (n = 343), lung metastases (n = 57), and peritoneal dissemination (n = 28). Median overall survival (OS) in patients with synchronous liver metastases who underwent conversion surgery following favorable response to initial chemotherapy was 27 or 34 months, and peritoneum metastases was 28 months. Median OS after the initial treatment was varied from 51 to 121 months in metachronous lung metastasis and from 24 to 40 months in metachronous liver metastasis, respectively.
Conclusion: Encouraging OS was indicated in patients with synchronous mPDAC of liver and peritoneum who underwent conversion surgery. Metastasectomy for metachronous lung and liver oligometastases could be considered a practical treatment option.

Background

Pancreatic ductal adenocarcinoma (PDAC) currently presents the third leading cause of cancer mortality in the United States, and projections to 2030 estimate that the disease will become the second leading cancer-related cause of death [1–3]. Considering that the incidence of PDAC is equal to its mortality, virtually 100% of diagnosed patients will die from the disease irrespectively from the therapeutic approach. Therefore, even resected patients will recur with loco regional or, most likely, metachronous distant metastasis [4]. Moreover, majority of patients has synchronous metastatic disease on an initial presentation. Unlike other cancer types such as colon, for which the resection of distant metastasis has been included into the therapeutic algorithm [5], for PDAC there is not proved evidence regarding a possible benefit of metastasectomy, which therefore does not represent, so far, the standard of care. A recent guideline for metastatic pancreatic ductal adenocarcinoma (mPDAC) recommends intensive chemotherapy regimens such as FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) or gemcitabine plus nanoparticle albumin-bound paclitaxel (GEM/nab-PTX) as first-line treatments [6]. In randomized controlled trials for patients with mPDAC treated by FOLFIRINOX [7] and GEM/nab-PTX [8], the median overall survival (OS) was 11.1 and 8.5 months, respectively. Although long-term survival remains unsatisfactory, these intensive chemotherapies have the potential to

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convert unresectable disease to resectable disease. Moreover, in line with what reported in the adjuvant setting, the median OS was significantly impacted by chemotherapy regimens including FOLFIRINOX [9]. Nevertheless, the long-term prognosis of conversion surgery and/or metastasectomy for mPDAC has not been sufficiently investigated. There is no international consensus concerning the role of surgical management for patients with mPDAC, but favorable prognoses can be expected for highly selected patients under certain circumstances [10]: (i) conversion surgery, which can be defined as additional surgical resection after favorable response to anti-cancer treatments in patients with initially unresectable PDAC and (ii) resection with only a few metastases (so-called oligometastases, which can be defined as distant metastases to a single or limited number of organs and a number of metastases consistent with a high potential for a complete operative resection [11]). The aim of this study was to evaluate the survival of patients with mPDAC who have undergone surgical resection of the disease.

Methods

Search strategy and data sources

Identification of eligible studies was performed through a search of the PubMed (MEDLINE) and Cochrane databases until 4 July 2018. The following algorithm was applied: "(metastasis of pancreatic ductal adenocarcinoma OR metastasis of pancreatic cancer) AND (pancreatectomy OR metastasectomy OR resection)." Two independent reviewers (T.S. and K.T.) screened the available literature, and discrepancies were resolved by team consensus. Finally, the reference lists of eligible studies were manually assessed to detect any potentially relevant articles ("snowball" procedure).

Inclusion and exclusion criteria

Eligible studies were those reporting on patients with histologically confirmed mPDAC undergoing surgery with curative intent with or without (neo)adjuvant chemotherapy/radiation therapy. The exclusion criteria were as follows: (1) irrelevant studies, (2) reviews and meta-analyses, (3) editorials and letters to the editors, (4) non-English articles, (5) case reports including fewer than five patients, (6) uncertain tumor histology, (7) insufficient description of survival data, (8) studies involving surgery without curative intent (palliative or cytoreductive surgery), (9) studies that assessed metastasectomy of para-aortic lymph nodes (PALN) as a result of extended lymphadenectomy, (10) studies that recognized metastases only in peritoneal washing cytology, and (11) studies involving treatment mainly by ablative technologies.

Data extraction and tabulation

One author (T.S.) conducted data extraction. Variables of interest included general study characteristics (e.g., study period, type of study, number of patients and metastatic organs), regimens of (neo)adjuvant treatment and percentages of patients who received the therapy, interval from diagnosis to pancreas surgery, interval from prior pancreas surgery to metastasectomy, disease-free interval (DFI) defined as the interval from prior pancreas surgery and the first recurrence, disease-free survival (DFS) defined as the interval from metastasectomy and the recurrence, OS after metastasectomy, OS after initial treatment, and type of operation.

Data were tabulated when possible. Discordant judgment was resolved by discussion and consensus.

Results

Article selection and study demographics

Following initial algorithm and the successive steps of the selection process, including screening of the titles and abstracts, 65 studies were retrieved for full-text evaluation. Finally, 13 studies were deemed eligible and 6 were identified from their references. These 19 studies comprised the analytic cohort. Overall, the studies included 428 patients who underwent surgical resection for liver metastases (n = 343), lung metastases (n = 57), and peritoneal dissemination (n = 28).

Liver

Fourteen studies described the outcomes of surgical management for synchronous and/or metachronous liver metastases (Table 1) [12–25]. Two studies focused on clinical outcome of conversion surgery after favorable response to anti-cancer treatments [12,13]. Frigerio et al. [12] described the outcomes of patients with liver oligometastases underwent pancreatic resection as a result of complete resolution of liver metastases after a course of chemotherapy. Chemotherapeutic regimens such as FOLFIRINOX, GEM/nab-PTX or GEM alone were induced. Curative resection of the primary lesion followed by preoperative chemotherapy was successful in 24 patients (4.5%). The median interval from diagnosis to surgery, DFS and OS was 10, 27 and 56 months, respectively. Wright et al. [13] focused on primary tumor resection with or without metastasectomy as a result of a favorable response to chemotherapy, including a FOLFIRINOX or GEM-based regimen with a median of nine cycles prior to surgical treatment. Criteria for surgical resection were disappearance of liver metastasis on radiological examination, and normalization or significant reduction of serum cancer antigen (CA) 19-9 level. High performance status and strong personal motivation of candidates were necessary to make final decision of surgery. Surgical resection was subsequently performed for 15 patients (2.0%). The median interval from diagnosis to surgery, DFS, and OS were 9.7, 8.6, and 34.1 months, respectively.

Eleven studies focused on synchronous resection of pancreas and liver metastases [14–24]. Main eligibility criteria of surgery for patients in their studies were as follows: (1) oligometastases [14,15,22] or occult liver metastases which were not diagnosed in the preoperative evaluation [15,18]; (2) no evidence of extrahepatic disease [17,19]; (3) a high probability to obtain R0 resection with low surgical risk [17,19,20,22]; (4) patient in good clinical condition [17,20,22]. A relatively small ratio (3%–16%) of patients received multimodal therapy in four studies [14,15,20,22]. The extent of hepatectomy was minor (wedge or bi-segmental resection) in majority of patients (67%–100%) [14,15,17–20,23,24]. More than half patients received adjuvant chemotherapy in five studies [13,15,17,20,22]. The median OS varied from 5.9 to 15.7 months.

Four studies focused on metachronous liver metastases [14,17,19,25]. The median interval from pancreas surgery to hepatectomy, OS after hepatectomy, and OS after initial treatment varied from 7.6 to 18.4, from 11.4 to 31.0, and from 24.5 to 40 months, respectively.

Lung

Six studies focused on the outcomes of surgical management for metachronous lung metastases (Table 2) [25–30]. Robinson et al. suggested criteria for pulmonary metastasectomy with the expectation of potential therapeutic benefits: the primary cancer is resected; a limited number of metastases occur in the lungs

Table 1
Characteristics of studies including patients who have undergone surgery for synchronous liver metastasis through conversion surgery or combined pancreas and metastasis resection or who have undergone surgery for metachronous liver metastasis.

Synchronous pancreas and liver resection

Author (year)	Reference number	Study period	Study design	Country	No. of patients	Neoadjuvant therapy	Operation for primary lesion	Operation for metastases	Adjuvant therapy	DFS (month, median)	OS (month, median)
Frigerio (2017)	[12]	2007-2015	Case series, two centers	Italy	24	For all Pts. *FOLFIRINOX (66.7%)* *GEM (20.8%)* *GEM plus NAB-PTX (12.5%)*	PD (58%) DP (42%)	0%	For 63% of Pts.	27	56
Wright (2016)	[13]	2008-2013	Case series, two centers	USA	15	For all Pts. *FOLFIRINOX (61%)* *GEM-based regimens (39%)*	PD (65%) DP (35%)	For 48% of Pts.	For 52% pf Pts.	8,6	34,1

Synchronous pancreas and liver resection

Author (year)	Reference number	Study period	Study design	Country	No. of patients	Neoadjuvant therapy	Operation for primary lesion	Operation for metastases	Adjuvant therapy	DFS (month, median)	OS (month, median)
Hackert (2017)	[14]	2001-2014	Case series, single center	Germany	62	For 16% of Pts.	PD (43%) DP (41%) TP (17%)	Minor hepatectomy (98%) Major hepatectomy (2%)	For 74% of Pts. GEM (80%) 5-FU (8%) others (12%)	*Not described*	10,6
Tachezy (2016)	[15]	1994-2014	RCS, six centers	Germany, Italy, France, Greece	69	For 14% of Pts. *GEM-based regimens (40%)* *FOLFIRINOX (40%)* *others (20%)*	PD (60%) DP (36%) TP (3%)	Minor hepatectomy (100%)	For 80% of Pts. *GEM (81%)* *FOLFIRINOX (7%)* *GEM, following FOLFIRINOX (7%)* *others (5%)*	*Not described*	14,5
Shi (2016)	[16]	2007-2015	Case series, single center	China	30	*Not described*	PD (37%) DP (60%) TP (3%)	*Not described*	*Not described*	*Not described*	15,7
Zanini (2015)	[17]	2003-2014	Case series, single center	San Marino	11	0%	PD (55%) DP (27%) TP (18%)	Minor hepatectomy (75%) Major hepatectomy (25%)	For all Pts.	4	8,3
Klein (2012)	[18]	2004-2009	Case series, single center	Germany	22	*Not described*	PD (78%) DP (5%) TP (18%)	Minor hepatectomy (100%)	*Not described*	*Not described*	7,6
Dünschede (2010)	[19]	1996-2008	RCS, single center	Germany	9	*Not described*	PD (67%) DP (33%)	Minor hepatectomy (67%) Major hepatectomy (33%)	*Not described*	*Not described*	8
Seelig (2010)	[20]	2004-2007	Case series, single center	Germany	14	For 10% of Pts.	N.D.	Minor hepatectomy (100%)	For all Pts.	*Not described*	11
Yamada (2009)	[21]	1981-2007	RCS, single center	Japan	11	0%	PD (55%) DP (36%) TP (9%)	*Not described*	For 46% of Pts GEM (60%). others (40%)	*Not described*	10,1

Shrikhande (2007)	[22]	2001-2005	RCS, single center	Germany	11	For 3% of Pts.	PD (36%) DP (55%) TP (9%)	*Not described*	For 79% of Pts.	*Not described*	11,4
Gleisner (2007)	[23]	1995-2005	RCS, single center	USA	17	*Not described*	PD (68%) DP (32%)	Minor hepatectomy (95%) Major hepatectomy (5%)	For 32% of Pts. GEM (43%) 5-FU (43%) others (14%)	*Not described*	5,9
Takada (1997)	[24]	1981-1995	RCS, single center	Japan	11	*Not described*	PD (100%)	Minor hepatectomy (100%)	*Not described*	*Not described*	6

Metachronous pancreas and liver resection

Author (year)	Reference number	Study period	Study design	Country	No. of patients	Neoadjuvant therapy	Operation for primary lesion	Adjuvant therapy after pancreatectomy	Operation for metastases	Adjuvant therapy after hepatectomy	Interval between pancreas surgery and hepatectomy (month, median)	OS after hepatectomy (month, median)
Hackert (2017)	[14]	2001-2014	Case series, single center	Germany	23	For 16% of Pts.	PD (43%) DP (41%) TP (17%)	*Not described*	Minor hepatectomy (74%) Major hepatectomy (26%)	For 74% of Pts. GEM (80%) 5-FU (8%) others (12%)	18,4	14,8
Zanini (2015)	[17]	2003-2014	Case series, single center	San Marino	4	0%	PD (100%)	For all Pts.	Minor hepatectomy (100%)	*Not described*	9	11,4
Thormas (2012)	[25]	1992-2010	RCS, single center	USA	6	*Not described*	*Not described*	For 76% of Pts. *	Resection (33%) Ablation therapy (67%)	For 29% of Pts.	7,6	*Not described*
Dünschede (2010)	[19]	1996-2008	RCS, single center	Germany	4	*Not described*	*Not described*	For 50% of Pts.	Minor hepatectomy (100%)	*Not described*	9 †	31 ‡

DFS = Disease free survival; OS = Overall survival; RCS = Retrospective cohort study; * = Neoadjuvant therapy against recurrence; † = Until the diagnosis of liver metastases; ‡ = Since detection of liver metastases.

Table 2
Characteristics of studies including patients who have undergone surgery for metachronous lung metastasis.

Author (year)	Reference number	Study period	Study design	Country	No. of patients	Neoadjuvant therapy	Operation for primary lesion	Adjuvant therapy after pancreatectomy	Operation for metastases	Adjuvant therapy after lung resection	DFI (month, median)	OS after lung resection (median, month)	OS after initial treatment (median, month)
Yasukawa (2017)	[26]	2004–2016	Case series, single center	Japan	12	For 50% of Pts.	PD (50%) DP (42%)	For all Pts. *GEM-based regimen (100%)*	Wedge resection (83%) Lobectomy (16%)	For all Pts.	*Not described*	47	121
Okui (2017)	[27]	2008–2015	Case series, single center	Japan	5	For 20% of Pts.	PD (60%) DP (40%)	For all Pts. *GEM (60%)* *S-1 (40%)*	Wedge resection (60%) Lobectomy (20%)	For 20% of Pts.	26	38,3	85,9
Downs-Canner (2016)	[28]	2000–2010	RCS, single center	USA	8	*Not described*	*Not described*	For 63% of Pts. (neo-adj)	Stereotactic radiotherapy (50%)	For 88% of Pts.	*Not described*	27	67,5
Robinson (2016)	[29]	1996–2015	RCS, single center	USA	16	For 19% of Pts. GEM-based regimen (100%)	*Not described*	For 88% of Pts. *GEM (71%)* *5FU (36%)*	Wedge resection (63%) Segmentectomy (6%) Lobectomy (31%)	For 63% of Pts.	24,0	28	52
Thormas (2012)	[25]	1992–2010	RCS, single center	USA	7	*Not described*	*Not described*	For 76% of Pts.*	*Not described*	For 29% of Pts.	52,4	21 †	92,3
Arnaoutakis (2011)	[30]	1996–2009	RCS, single center	USA	9	*Not described*	PD (100%)	*Not described*	*Not described*	*Not described*	29	18.6 ‡	51

DFI = Disease free interival from pancreas surgery to first recurrence; * = Neoadjuvant therapy for reoperation; † = Disease free survival after lung resection; ‡ = Survival after relapse.

(usually ≤5); all lung metastases can be removed; the patient can tolerate the necessary lung resection(s); no evidence indicates that metastases occur outside of the lungs [29]. Pre-operative chemotherapy was performed for 19%–50% of patients in three studies [26,27,29]. Adjuvant chemotherapy after pancreatic surgery was performed in 63%–100% of patients in five studies [25–29]. More than half of patients underwent wedge resection of the lung, but in one study, 50% of patients underwent stereotactic radiotherapy [28]. Adjuvant chemotherapy after lung resection was performed for 20%–100% of patients in five studies [25–29]. The median DFI, OS after lung resection and OS after initial treatment varied from 24.0 to 52.4, from 18.6 to 38.3, from 51.0 to 85.9 months.

Peritoneum

Four studies focused on the outcomes of surgical management for synchronous peritoneal metastases (Table 3) [20–22,31]. Satoi et al. [31] performed a prospective multicenter phase II trial of intravenous and intraperitoneal paclitaxel combined with oral S-1 for 33 patients with peritoneal mPDAC, including eight patients (24% of resectability) who underwent conversion surgery. Surgical indication was reduction of tumor marker, possible R0 resection of the primary tumor, surgically-fit, negative cytology, no peritoneal dissemination and at least 8 months after initial treatment. Among these eight patients, R0 resection was achieved in six, and median OS was 27.8 months. The other three studies reported the outcomes of synchronous pancreas and peritoneal metastatic resection [20–22]. Most patients in this group had occult metastases to be considered in a good condition with a high probability of R0 resection [22]. Only 2–10% of patients received pre-operative chemotherapies. The median OS varied from 5.3 to 12.9 months only.

Prognosis according to the surgical procedures and chemotherapy regimens

Survival data according to the surgical procedures for pancreatic tumor or tumor locations are summarized in Table 4. Based on the reported data from Frigerio et al. [12], median OS was significantly longer in patients who underwent pancreaticoduodenectomy compared to those who underwent distal pancreatectomy (37.0 vs 23.0 months, $p = 0.031$). However, no significant differences of OS or DFS between the surgical procedures have been recognized in other reports. Furthermore, no reports compared the prognosis according to the induced regimens of chemotherapy.

Discussion

We have herein reviewed studies including more than four patients with a focus on liver, lung, and peritoneal metastases of histologically confirmed PDAC treated by surgical management with curative intent. Due to the high heterogeneity in reporting of outcomes among eligible studies, no cumulative statistical analysis or meta-analysis was attempted. The benefits and risks of surgical management for PALN metastasis have long been discussed among pancreatic surgeons worldwide. However, we did not examine this issue in the present review because most retrospective studies that assessed the influences of PALN metastasis obtained their data from extended lymphadenectomy, which is basically a preventive maneuver with clinical significance that differs from both conversion surgeries as a part of multimodal treatment and resection for oligometastases with curative intent. Studies of metastasis to other organs (e.g., brain and skin) were excluded because the number of patients in each report included less than 5 patients.

In 2008, Michalski et al. [32] performed a systematic review of

Table 3
Characteristics of studies including patients who have undergone surgery for synchronous peritoneal metastasis through conversion surgery or combined pancreas and metastasis resection.

Conversion surgery										
Author (year)	Reference number	Study period	Study design	Country	No. of patients	Neoadjuvant therapy	Operation for primary lesion	Adjuvant therapy	Disease free survival (median, month)	Overall survival (median, month)
Satoi (2017)	[31]	2012-2015	Non-randomized prospective trial, seven centers	Japan	8	For all Pts.PTX (i.v./i.p.)/S-1(p.o)	RAMPS (25%) DP-CAR (25%) DP (25%) TP (13%) PD (13%)	0%	*Not described*	27,8

Synchronous pancreas and metastasis resection										
Author (year)	Reference number	Study period	Study design	Country	No. of patients	Neoadjuvant therapy	Operation for primary lesion	Adjuvant therapy	Disease free survival (median, month)	Overall survival (median, month)
Seelig (2010)	[20]	2004-2007	Case series, single center	Germany	5	For 10% of Pts.	PD (40%) DP (60%)	For all Pts.	*Not described*	5,3
Yamada (2009)	[21]	1981-2007	RCS, single center	Japan	6	0%	TP (33%) PD (33%) DP (33%)	For all Pts.	*Not described*	9,6
Shrikhande (2007)	[22]	2001-2005	RCS, single center	Germany	9	For 2% of Pts.	PD (56%) DP (33%)	For 79% of Pts.	*Not described*	12,9

Table 4
Survival data according to the surgical procedures for pancreatic tumor or tumor locations

Author	Reference number		PD	DP	P value
Frigerio	[10]	OS(M)	37.0	23.0	0.031
		DFS(M)	26.5	21.0	0.13
Tachezy	[13]	OS(M)	14,5	14,0	-
Shi	[14]	OS(M)	7,0	7,1	-
Zanini	[15]	OS(M)	8,0	9,0	0,66
Seelig	[18]	OS(M)	13,9	10,6	0,37
Shrikhande	[20]	OS(M)	9,6	12,1	0,66
Yasukawa	[24]	OS(M)	72.0	62.0	0.33
		DFS(M)	27.0	34.0	0.74
Okui	[25]	OS(M)	85.9	90.0	0.87
		DFS(M)	36.2	43.0	0.52

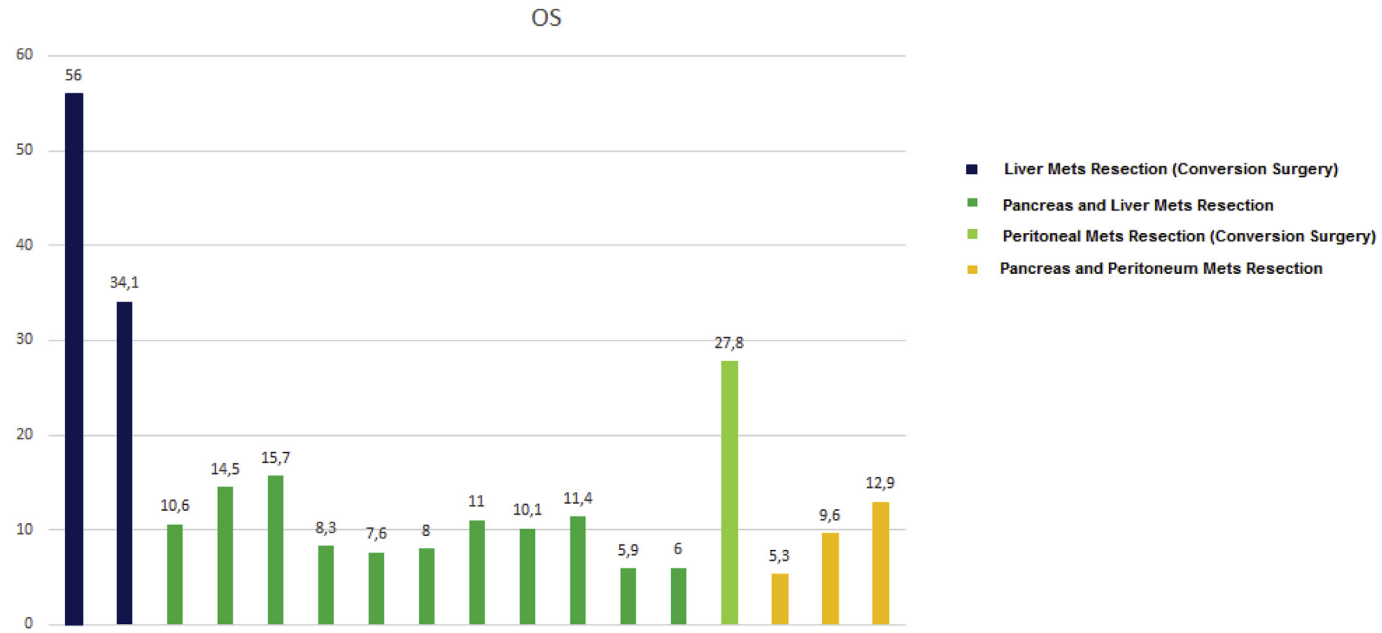

Fig. 1. Overall Survival (OS) after resections for synchronous metastatic disease, divided by site and surgical timing.

resection of primary PDAC and liver metastases. This study comprised 103 patients, but only 2 studies included more than 10 patients. The median OS reportedly ranged from 5.8 to 11.4 months.

A decade later, our study comprised 331 patients with liver metastasis, and 12 studies included more than 10 patients. Among them, two studies reported the outcomes of conversion surgery for

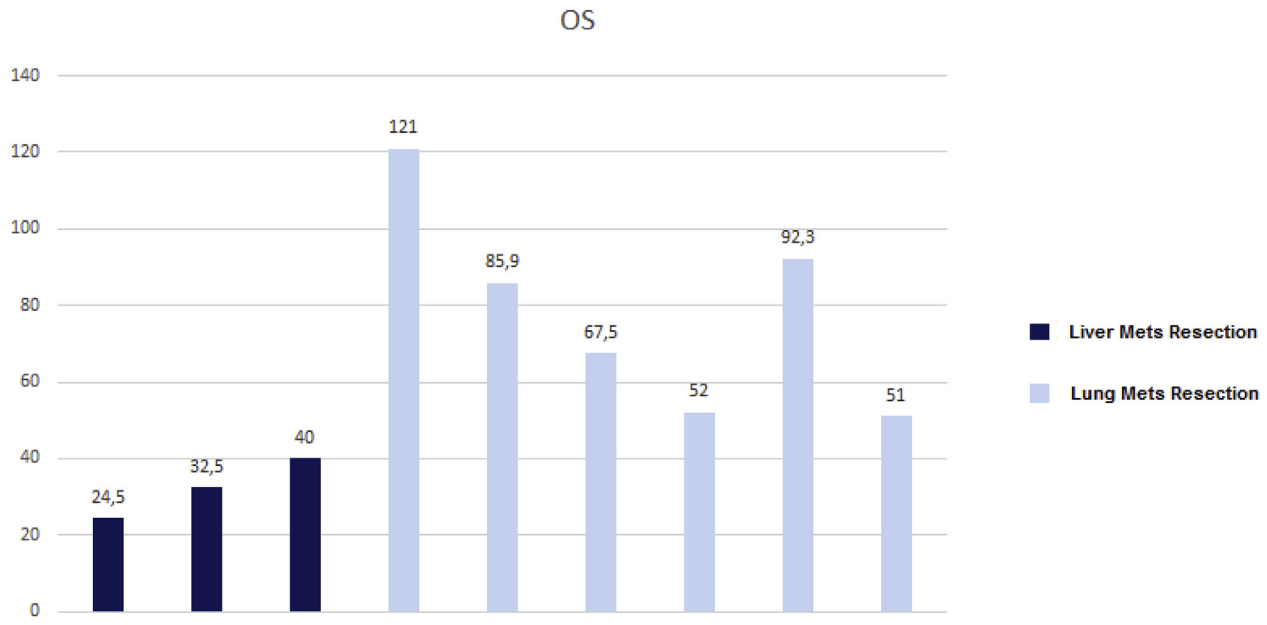

Fig. 2. Overall Survival (OS) after resections for metachronous metastatic disease, divided by site and surgical timing.

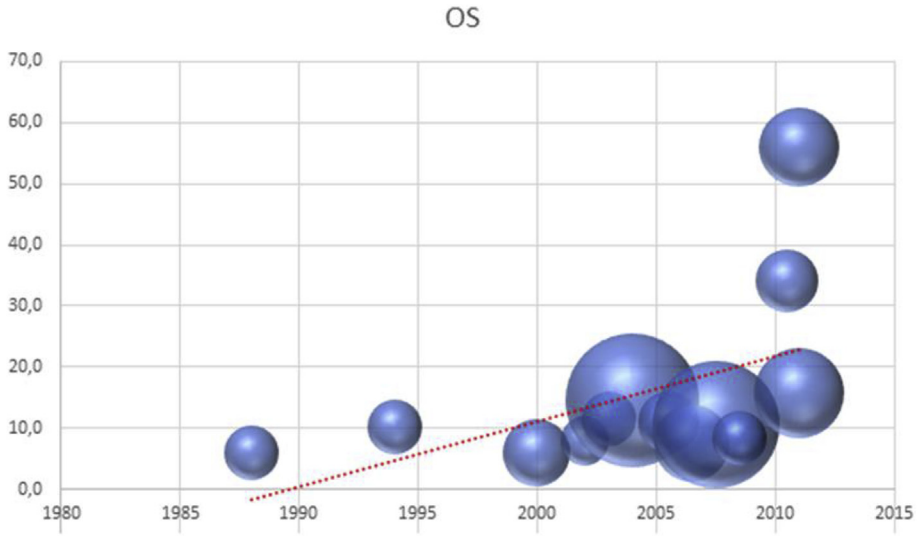

Fig. 3. The graph shows the reported overall survival (OS) after resection of synchronous liver metastasis with the volume of the spheres reflecting the number of included patients in each study. The red line shows a linear and progressive improvement of prognosis during the last decades, possibly reflecting the appearance of new and more effective systemic treatments.

liver metastases with an encouraging median OS (56 [12] and 34.1 [13] months) and DFS (27 [12] and 8.6 [13] months). Although the survival benefit of conversion surgery for liver metastases remains obscure because both of them lacked control groups for comparison, conversion surgery could play an important role in multimodal therapy for patients with initially unresectable PDAC. In 2013, the Japanese Society of Hepato-Biliary-Pancreatic Surgery reported a significant survival benefit of conversion surgery following anticancer treatments with a favorable response during a 6-month period. In totally 58 patients who underwent conversion surgery with initially unresectable PDAC (including 13 patients with liver metastases and one patient with peritoneal metastases), the median OS from the initial treatment and after surgical resection was 39.7 and 25 months, respectively. Moreover, the obvious survival benefit was found especially in patients who received initial treatment for more than 240 days prior to surgery [33].

The survival benefit of synchronous resection of liver metastases without pre-operative treatment still remains unclear. Among six studies compared the median OS of patients who underwent surgery with that of patients who underwent palliative treatment alone [15,19,21–24], two studies demonstrated significant improvement of the median OS (14.5 vs. 7.5 months [15], and 11.4 vs. 5.9 months [22], respectively), but a very strong potential for selection bias would exist. The extent of hepatectomy was decided only on a case-by-case basis in most studies; thus, we could not recognize precisely what kind of metastatic statuses (number, size, location, etc.) had affected the surgical indication and prognosis. However, considering the remarkable superiority in OS of patients

underwent conversion surgery [12,13], it is assumed that a certain strategy of pre-operative chemotherapy and appropriate patients' selection could contribute to the improvement of prognosis. Fig. 1 summarizes the overall survival (OS) after resections for synchronous metastatic disease, divided by site and surgical timing and showing how conversion surgery is suggested to possibly positively affect survival both in liver and peritoneal metastatic patients.

Hepatectomy for metachronous liver metastases was performed in four studies as a relatively small subgroup. The median OS after hepatectomy of metachronous metastases (11.4–31 months) surpassed the data of synchronous metastases (8–10.6 months) in each study [14,17,19]. Dünschede et al. [19] concluded that hepatectomy improved survival for carefully selected patients with metachronous liver metastases of PDAC. Hackert et al. mentioned that the interval between the initial and the consecutive operation might be useful as an additional criterion for patient selection. In general, from the clinical experience, a time interval of 12 months could probably be regarded as a reference, although not based on high-level evidence [14].

Although the great majority of patients operated for PDAC will recur with liver metastasis, around 17% will display the occurrence of isolated lung metastasis [34]. Such kind of patients displays a more favorable OS and survival from recurrence than patients with other primary recurrence sites [35]. We selected six studies of lung resection for mPDAC. All of them focused on metachronous metastases followed by resection of primary lesions. Lung resections were intended to remove all nodules present in the lungs and they were safely performed with minimal morbidity, and the outcomes were successful [30]. Thomas et al. [25] reported that among patients selected for reoperation, the median OS after initial treatment was significantly longer for patients who developed an initial lung recurrence (92.3 months) than for those who developed an initial liver recurrence (32.5 months). Also, among patients who underwent reoperation, OS after initial treatment was significantly longer in those who had a median DFI of >20 than <20 months. The available data suggest that lung metastasectomy should be considered for patients with a relatively long DFI with favorable response to systemic therapy [27].

Fig. 2 shows the overall survival (OS) after resections for metachronous metastatic disease, divided by site and surgical timing. We identified four studies with contrasting outcomes concerning surgical management for peritoneal mPDAC. Yamada et al. stated that surgery was considered to be contraindication for patients with peritoneal mPDAC because of the dismal prognosis [21]. Three studies reported that synchronous pancreatic and peritoneal resection resulted in dismal prognosis of 5.3–12.9 months. In contrary, Satoi et al. [31] reported the remarkable outcomes of patients (median OS of 27.8 months) who underwent conversion surgery. Considering the results of these four studies, the survival benefit of surgical management for peritoneal mPDAC might be restricted to patients who have favorably responded to initial systemic therapy and/or are expected to achieve an R0 status with confirmation of no visual peritoneal dissemination and negative cytology even if aggressive surgeries are required.

Our review comprised studies with relatively small and highly selected populations, and most studies were retrospective. Although a definitive regimen was not clearly obtained from the previous publications, FOLFIRINOX has a potential to increase the proportion of candidates for conversion surgery. Fig. 3 shows the linear and progressive improvement of prognosis during the last decades, possibly reflecting the appearance of new and more effective systemic treatments.

We must be aware that though metastasectomy was performed safely without increased mortality and morbidity, it should be done with great caution by experienced surgeons in specialized centers. Wright et al. sounded the alarm of 30.4% of an early disease recurrence <6 months after surgical resection for patients with liver metastasis [13]. In this situation, there was no clinical benefit of surgical resection, and therefore, surrogate marker for predicting early recurrence and appropriate surgical indication should be explored in the near future.

It would be impossible to suggest definitive criteria of surgical indication for patients with mPDAC from the current review, so that, in practice, it should be decided in multidisciplinary meeting, and representative surgeons must provide adequate informed consent to patients before surgery.

Prospective randomized studies are needed to confirm the survival benefits of surgical management of mPDAC. Future studies should assess which combinations of perioperative multimodal treatments would be suitable among patients with different oncological backgrounds. In addition, the optimal interval between initial treatment and surgical resection, an accurate method to evaluate tumor remission, and the type/duration of adjuvant treatment regimen should be investigated.

Conclusion

The present review indicates substantial survival benefits of conversion surgery for patients with synchronous mPDAC of the liver and peritoneum who responded favorably to initial chemotherapy for a certain period of time. In addition, metastasectomy for metachronous lung and liver oligometastases with a relatively long interval between initial resection and relapse with favorable response to systemic therapy could be considered a practical treatment option.

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