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Resection of Primary Pancreatic Cancer and Liver Metastasis: A Systematic Review

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Key Words
Pancreatic cancer · Liver metastasis · Metastasis resection

Abstract
Resection of liver metastases for locally resectable pancreatic cancer has rarely been performed. Recently, promising results regarding morbidity and mortality as well as long-term survival have been shown. Thus, we conducted a systematic review of the literature on pancreatic cancer resection with associated liver metastasis resection. There are 3 case reports and 18 studies including less than 10 patients. Only three studies are larger series with 10 or more patients in whom pancreatic resections and hepatic metastasectomies were performed. Here, morbidity and mortality ranged from 24.1 to 26% and from 0 to 4.3%, respectively. Median survival was reported to be between 5.8 and 11.4 months. In total, all identified studies included 103 patients in whom a metastasis resection was performed. Liver metastasis resection for locally resectable pancreatic cancer can be performed in selected cases with low morbidity and mortality. Overall survival in cases with one or few liver metastases which are concomitantly resected seems to be comparable to cases without evidence of metastasis. Therefore, randomized controlled clinical trials will have to be initiated to determine the value of such resections and to identify factors which will allow for selection of patients in whom the extension of the resectability criteria might confer a survival benefit.

Introduction

The extension of the resectability criteria for pancreatic cancer is currently controversially discussed. Several radical approaches such as extended lymphadenectomy and arterial resections have been shown not to be superior to standard resections [1–4]. At the same time, a less radical approach such as the pylorus-preserving variant of the partial pancreaticoduodenectomy is oncologically comparable to the classical Whipple's resection [5]. However, regarding distal pancreatic resections, Strasberg et al. [6, 7] have demonstrated that a more radical resection – the so-called radical antegrade modular pancreatosplenectomy – might be superior to the classical left resection. The data on portal vein/superior mesenteric vein/confluence resection for tumor infiltration detected during pancreaticoduodenectomy is also promising [8]. A number of studies have demonstrated that R0 resections achieved through venous resection (with or without interposition of a graft) lead to comparable results as R0

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resections where venous resection was not necessary; however, other groups report that venous invasion should be regarded as a sign of local advancement and should thus be seen as a criterion for unresectability [9]. Recently, we have demonstrated that resection for recurrent pancreatic cancer might confer a survival benefit in those patients in whom the time until (local) recurrence of the tumor is longer than 9 months pointing to the importance of tumor biology and of the correct selection of patients [10]. We have also shown that re-operations/explorations of patients who had initially been deemed unresectable can be beneficial in selected cases [11]. However, the value of metastasis resection and particularly of resection of metastatic disease of the liver remains a matter of intense and controversial discussion. Furthermore, it is unclear whether combinations of extensive surgery and novel treatment concepts might confer a survival benefit particularly in younger and fitter patients. Although there is only a limited number of case reports and smaller studies on metastasectomy during pancreatic resection for cancer, we performed a systematic review of the literature and subsequently combined the available data on morbidity, mortality and survival for a more reliable overview on the results of such an extension of pancreatic resections.

Materials and Methods

Search Strategy

Three authors (C.W.M., M.E., N.H.) independently performed a systematic literature search of the following databases as previously described [1], without language restriction: National Center for Biotechnology Information, National Library of Medicine (PubMed; January 1966–May 2008) and the Cochrane Central Register of Controlled Trials, with the last search on May 19, 2008. The Internet and the authors' libraries were also searched. The following medical subject headings were used: pancreatic cancer, liver metastasis, lymph node metastasis, metastasectomy, metastasis resection, pancreaticoduodenectomy, Whipple's operation, distal pancreatic resection, extended pancreatic resection. Abstracts and relevant articles were retrieved according to the consensus of the investigators. Additional relevant articles were identified by cross-searching bibliographies. Study titles, abstracts and full texts were analyzed for the study. No further stratification was applied since there were no randomized trials available.

Data Extraction

The investigators analyzed the studies according to the type of resection of the primary tumor (pancreaticoduodenectomy, left/distal pancreatic resection) and the overall mortality and morbidity. Data collection and assessment of methodological quality were conducted following recently published protocols [1]. Heterogeneity of studies was evaluated by analyzing comparability of the following items: number of patients, grade or stage of disease, type of surgery performed, type of adjuvant treatment applied.

Inclusion and Exclusion Criteria

Relevant retrieved studies (case reports, single-center analyses and retrospective studies) were included in the systematic review.

Results

A literature search identified 3 case reports and 21 studies addressing the indications and use of an aggressive surgical approach – for the most part with major or segmental hepatic resection – as primary treatment modalities for hepatic metastases from pancreatic cancer. However, most of the identified 'studies' included far less than ten patients in whom liver resection for pancreatic cancer has been performed; mostly, these studies describe liver resections for cancer of different origins, among these, pancreatic cancer metastasectomies have been rarely performed. The first report in the literature on metastasectomy for pancreatic cancer dates from 1982 and has been published within a larger series on metastasectomies by Morrow et al. [12]. Since then, only three larger studies (with 10 or more patients) have been published on metastasis resections for pancreatic cancer (fig. 1).

Evidence from Case Reports

The first case report on a patient with an invading, advanced pancreatic carcinoma, in whom a hepatic metastasis was successfully resected together with a pancreatic resection, was described by Takamori et al. [13] in 1994. We identified 2 additional case reports on resection of pancreatic tumors with concomitant metastasectomy in the literature (table 1). Due to different treatment modalities and the specific history of cancer in each of these highly selected patients (table 1), clear conclusions could not be drawn. In general, these authors call for resection of localized liver metastases and of infiltrated abdominal organs to improve the chances for long-term survival, except in cases with distant, widespread metastasis [13–15].

Evidence from Case Series

Although the literature provides no clear indications for hepatectomy for noncolorectal or nonendocrine liver metastases, there have been increasing numbers of published articles presenting the adequacy of resecting pan-

Table 1. Case reports

Year [ref.]	First author	Age years	Primary tumor	Therapy	Histology	Site of metastasis	Survival
1994 [13]	Takamori	70	neck of pancreas	no adjuvant therapy	moderately differentiated PDAC (pT3N1M0)	segment VI: metachronous	>6 years (alive)
		58	head of pancreas	adjuvant CTx	moderately differentiated PDAC (pT3N1M0)	segment VI: metachronous segment VI: right lung	2 years, 6 months (died)
2001 [14]	Ko	69	head of pancreas	not specified	well-differentiated PDAC (pN0)	segment VI: metachronous	2 years, 5 months (died)
2004 [15]	Shimada	44	tail of pancreas	adjuvant CTx	moderately differentiated PDAC (pN0)	anterior/inferior segment: synchronous	>7 years (alive)

creatic cancer metastases in selected patients. In total, we identified 18 studies with less than 10 patients and three larger series on metastasectomy for pancreatic cancer (table 2). In total, data on 103 patients has been presented in these studies. Some studies included curative and palliative resections [16–18]. Generally, most authors conclude that due to advances in surgical techniques and in the postoperative management, aggressive hepatectomy for synchronous or metachronous metastases in combination with pancreatic resections is a safe procedure and carries a low intra-/perioperative mortality (0–20% [12, 16–25]); the reported morbidity rates (minor and major postoperative complications) ranged from 8 to 38% [12, 20–25] and are thus within the range of morbidity rates for pancreaticoduodenectomy without metastasis resections. In studies by Yamada et al. [20], Hemming et al. [26] and Harrison et al. [18], the site of the primary tumor and the curative resection of liver metastases itself were independent prognostic factors after hepatectomy. Furthermore, some studies showed that a shorter disease-free interval was associated with a worse prognosis [18, 20, 22, 27], whereas Hemming et al. [26] demonstrated that a disease-free interval of (more than) 36 months was not predictive of the outcome. Interestingly, survival was not influenced by age, sex, number, size and location of metastases, type of hepatectomy or blood transfusions [22, 28].

Up to now, only three larger series [19, 29, 30] have been published that evaluate the outcome and use of pancreatic resections with concomitant metastasectomies. In the study by Takada et al. [19], hepatic resection with pancreatoduodenectomy was performed on 11 patients with metastatic pancreatic head carcinomas. This study revealed no significant differences in the outcome compared with patients who underwent a palliative bypass surgery for the same disease. All patients died from multiple recurrent liver metastases within 1 year. By performing a resection for metastases from pancreatic or ampullary carcinoma, Klempnauer et al. [29] have shown a median survival of 8.3 months after synchronously (n = 16) and 5.8 month after metachronously, curatively (n = 7) resected hepatic metastases (fig. 2). Regarding the curative intent, R0 resections were performed in 18 patients (69% of synchronously and 100% of metachronously resected metastases). The procedures were carried out with low morbidity and mortality (26 and 4.3%). Thus, Klempnauer et al. [29] concluded that such extended resections can be carried out safely, but that it will be necessary to establish criteria upon which patients can be selected who most likely benefit from hepatic resection for metastasized pancreatic cancer. Recently, the Heidelberg group has published their experience on pancreatic resections with resection of liver metastases [30]. Survival

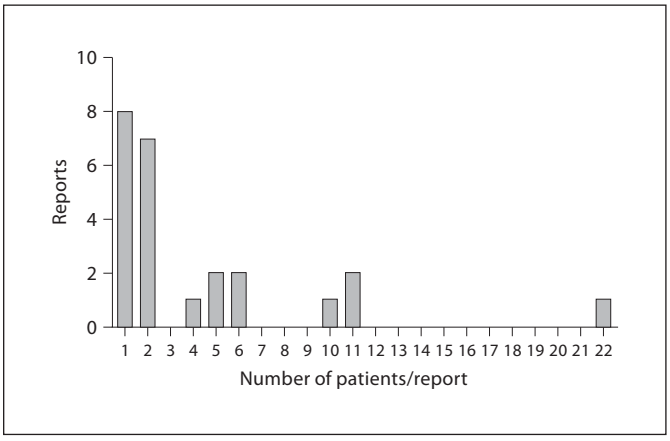

Fig. 1. Number of patients included in the published case reports and case series.

Table 2. Case series and studies

Year [ref.]	First author	Patients with PDAC/ total patients	Histology	Survival for pancreatic carcinoma	Morbidity/ 30-day mortality rates %	Liver metastasis	Study design	Additional therapy for pancreatic carcinoma
1982 [12]	Morrow	1/64	not specified	not specified	19/20 (all patients)	overall 30 synchronous 34 metachronous	retrospective	not specified
1983 [25]	Thompson	1/138	not specified	not specified	38/10.9 (all patients)	not specified	retrospective	not specified
1986 [21]	Ekberg	1/81	not specified	>13 months (alive)	33/4.9 (all patients)	not specified	retrospective	not specified
1987 [23]	Sesto	1/128	papillary cystic adeno-carcinoma	>1.5 years (alive)	≈20/7 (all patients)	not specified	retrospective	not specified
1995 [36]	Schildberg	5/227	not specified	median 7 months 3 years 0%	not specified/ 2.4 (all patients)	not specified	retrospective	not specified
1996 [29]	Klempnauer	22/22	12× moderately differen-tiated PDAC 7× poorly differentiated PDAC 2× undifferentiated PDAC 1× well-differentiated PDAC	8.3 ± 0.6 (synchronous, R0) 5.8 ± 2.3 (metachronous, R0) 7.7 ± 0.2 (synchronous, all) 5.8 ± 2.3 (metachronous, all)	26/4.3 (only pancreatic patients)	16 synchronous 7 metachronous	retrospective	6× adjuvant CTx 2× palliative CTx
1997 [18]	Harrison	2/96	papillary cystic adeno-carcinoma	>8 months (alive) >28 months (alive)	not specified/0	overall 22 synchronous 74 metachronous	retrospective	not specified
1997 [37]	Howard	10/10	not specified	median 11 months 5–30 months	not specified/0	not specified	retrospective	adjuvant RCTx
1997 [19]	Takada	11/109	not specified	median 6 months 2–10 months	0/9.1	synchronous	retrospective	not specified
1998 [28]	Lindell	2/32	not specified	0.8 months 5 months	16/9 (all patients)	not specified	retrospective	not specified
1998 [16]	Berney	2/34	pancreatic cystadenocarcinoma	>22 months (alive) >70 months (alive)	20.6/0 (all patients)	overall 12 synchronous 22 metachronous	retrospective	not specified
1998 [17]	Elias	1/147	undifferentiated PDAC	not specified	not specified/2 (all patients)	not specified	prospective	not specified (CTx pre- or postoperatively in all patients
2000 [24]	Benevento	1/20	PDAC	11 months	35/0 (all patients)	synchronous metachronous overall	retrospective	not specified
2000 [26]	Hemming	2/37	2× papillary cystic carcinoma	>9 months (alive) 26 months	not specified/0 (all patients)	14 synchronous 23 metachronous	retrospective	not specified
2001 [22]	Laurent	2/39	2× PDAC	not specified	8/0 (all patients)	overall 6 synchronous 33 metachronous	retrospective	not specified
2001 [38]	Takada	2/14	adenosquamous carcinoma, moderately differentiated PDAC	7 months 22 months	not specified	1 synchronous 1 metachronous overall 6 synchronous 8 metachronous	retrospective	not specified

Table 2 (continued)

Year [ref.]	First author	Patients with PDAC/ total patients	Histology	Survival for pancreatic carcinoma	Morbidity/ 30-day mortality rates %	Liver metastasis	Study design	Additional therapy for pancreatic carcinoma
2001 [20]	Yamada	6/33	not specified	not specified	17/0 (all patients)	overall 19 synchronous 14 metachronous	retrospective	not specified
2003 [39]	Pawlik	4/172	not specified	not specified	19.8/2.3 (all patients)	not specified	prospective	partially RFA of hepatic metastases
2005 [27]	Weitz	5/141	3× papillary solid/cystic carcinoma 1× cystadenocarcinoma 1× mucinous cystadenocarcinoma	not specified	33/0 (all patients)	overall 39 synchronous, 102 metachronous	prospective	not specified
2006 [40]	Yamada	6/33	4× PDAC 1× adenosquamous carcinoma 1× cystadenocarcinoma	4–56 months posthepatectomy (5 patients) >5 years (alive) 1-, 3-, and 5-year survival 67%, 33%, 17%	33/0 (only pancreatic patients)	overall 5 synchronous 1 metachronous	retrospective	not specified
2007 [30]	Shrikhande	11/29	18× pancreatic head 9× pancreatic body and tail 2× advanced pancreatic head	overall median 13.8 months R0/R1M1 11.4 R0/R1M0 5.9 months	24.1/0 (only pancreatic patients)	synchronous liver metastases (n = 11)	retrospective	1× neoadjuvant RCTx 1× adj. RCTx 13× gemcitabine 6× fluorouracil 2× tumor devascularization

PDAC = Pancreatic ductal adenocarcinoma; CTx = chemotherapy; RCTx = chemoradiation; RFA = radiofrequency ablation; patients with PDAC = patients with liver metastasis from PDAC; total patients = patients with metastases from all origins.

rates were significantly better when comparing pancreatic resections plus resection of liver metastases (R0/R1 M1) with explorative laparotomy plus – if applicable – a (double) bypass (M1/no resection). Median survival was 11.4 months in the R0/R1 M1 group compared to 5.9 months in the M1/no resection group (p = 0.038; fig. 3). The 1-year overall survival rate was 45% with no significant difference between patients who received adjuvant treatment and those who did not. At the same time, morbidity and mortality were comparable between the R0/R1 M1 and R0/R1 M0 groups (including resections for peritoneal metastasis and interaortocaval lymph node metastases). Thus, the authors concluded that irrespective of the limitations of their study (i.e. small patient numbers), aggressive surgery might be justified in a select group of patients and that justification of this approach will depend on the results of (to be conducted) randomized controlled clinical trials.

Discussion

In the last decades, there have been a number of reported attempts on clarifying the value of hepatic metastasis resection in pancreatic cancer. The large majority of these reports includes less than 10 patients and is thus considered more or less anecdotal. Recently, two relatively larger studies have been published showing at least favorable results following hepatic metastasis resection for pancreatic cancer in a highly selected cohort of patients. However, these had been retrospectively conducted. Therefore, we systematically reviewed the literature in an effort to combine the available data to identify whether there is any scientific evidence in favor or against metastasectomy. Unavoidably, our results are influenced mostly by the two larger reports stemming from tertiary referral centers. Both studies were conducted with the argument that in some patients with a

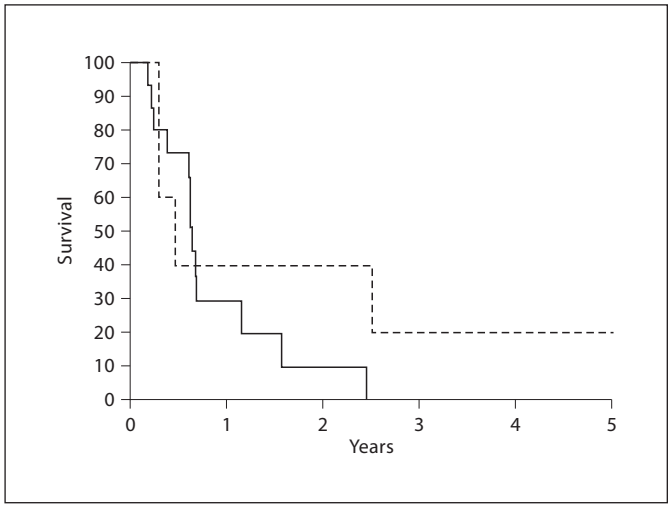

Fig. 2. Survival curves in the study by Klempnauer et al. [29]. Survival after synchronous resection of the pancreatic primary tumor and the liver metastasis (—; n = 15) and after metachronous resection of liver metastases of pancreatic cancer (– – – –; n = 7). Reprinted with permission from *Der Chirurg*, 1996.

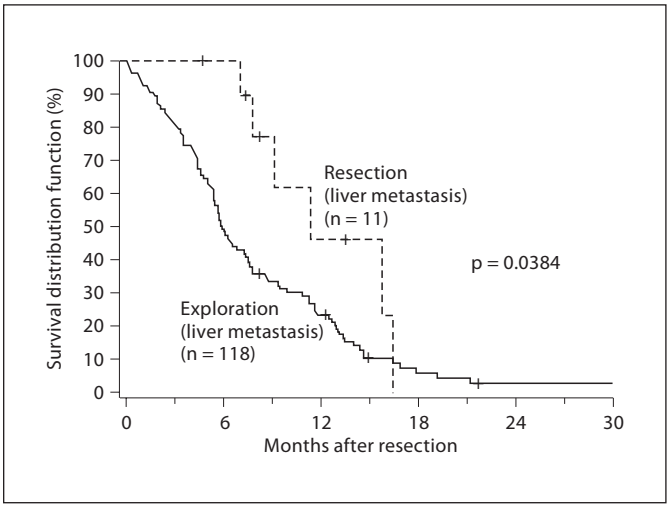

Fig. 3. Survival curve of the patients with liver metastasectomies in the study by Shrikhande et al. [30]. Kaplan-Meier curve comparing survival curve of R0/R1M1 (liver metastases) with survival curve of patients with liver metastasis who did not undergo resection, but exploration or palliative bypass procedures. Patients alive at the last follow-up are censored and indicated. Reprinted with permission from *Annals of Surgical Oncology*, 2007.

more 'favorable' tumor biology, metastasis resection versus conventional palliative (chemo-)therapy might confer a survival benefit by reducing the tumor load. These studies also showed that this kind of surgery can be safely performed – with low morbidity and mortality – in specialized centers for hepato-pancreato-biliary diseases. Since these studies lack control groups, it cannot be determined whether these patients would have also been better responders in standard palliative chemotherapy regimens. Thus, the main conclusion which can be drawn from the literature so far is that metastasectomy for pancreatic cancer is technically feasible and – upon careful selection of fit patients, i.e. normal liver function, no disseminated liver metastasis, no peritoneal carcinosis and no additional metastatic sites – can be performed with a low operative risk.

The main rationale for extending the resectability criteria is that pancreatic cancer surgery is in most cases not curative yet offers the best possible palliation: more than 80–90% of the few patients that can be resected with curative intent die within the course of the disease. This is because at the time of surgery, occult systemic spread is often present and most pancreatic cancer resections are R1 resections at a closer look [31]. However, not only is surgery the best possible palliation, but no effective alternative therapies are available and only resection of the tumor offers a – though still small – chance for cure. In this respect, Bilimoria et al. [32] have recently shown that in stage I pancreatic cancer, surgery prolongs the median survival by approximately one year. However, only about one third of all patients diagnosed with stage I pancreatic cancer are offered surgery at all. Taking into consideration that resection is superior even in advanced (in this case locally invasive) cancers when comparing surgery versus radiochemotherapy – as shown by Imamura et al. [33] who demonstrated a survival benefit of more than 6 months in the cohort of resected patients – it seems reasonable to think about alternatives to 'standard' medical treatment with gemcitabine. Particularly, since such a drug with a 5–10% response rate and – at most – a 1–3-month increase in median survival as compared to best supportive care is considered to be 'effective' [34, 35]. Therefore, the aim of modern pancreatic cancer surgery should not be the selection of patients with the greatest chance for cure but rather the selection of patients in whom resection of the tumor provides the greatest chance for longer survival and better quality of life. Increasing the rates of resection might also include M1 resections in selected patients. If one roughly approximates the number of pancreatic cancer resections having been performed in the last 30 years (the time period since the first patients have been resected for M1 disease), there are 103

cases of reported metastasectomies in the literature as compared to probably more than 150,000 pancreatic cancer resections worldwide. Thus, the general concern should not be that in a few cases boundaries are crossed, but that in a much larger number (as highlighted by Bilimoria et al. [32]) opportunities for prolonged survival and better quality of life are lost.

However, it will be necessary to conduct adequately powered studies with appropriate control arms to determine whether the benefit shown in the above-mentioned studies of liver metastasis resection is derived from surgery or whether it is a result of a different tumor biology and thus of patient selection. Nevertheless, 'conventional' (chemo-)therapies do not offer a better alternative which justifies extending the resectability criteria within a larger randomized controlled trial, similar to the one currently being carried out by Langrehr and coworkers at the Humboldt University Berlin, Germany (ISRCTN20060588).

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