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Radical surgery of oligometastatic pancreatic cancer

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Abstract

Background: In metastatic disease (M1), chemotherapy (expected survival: 6–10 months) is considered the only treatment option. The aim of this study was to evaluate the outcome of curative M1 PDAC resections.
Methods: Prospective data of all patients undergoing primary tumour and metastasis resection for stage IV PDAC during a 12-year period was analysed regarding localisation (liver or distant interaortocaval lymph nodes; ILN), morbidity and survival. Patients were stratified with regard to syn- or metachronous metastases resection.
Results: Patients (n = 128) undergoing PDAC and metastases resection (intention-to-treat, oligometastatic stage; liver n = 85; ILN n = 43) were included. Surgical morbidity and 30-day mortality after synchronous resection of M1 tumours were 45% and 2.9%, respectively. Overall median survival after M1 resection was 12.3 months in both groups. Long-term outcome showed a 5-year survival of 8.1% after surgery for both liver metastases and 10.1% following ILN resection.
Conclusions: The present collective is the largest series of resected metastatic PDAC and shows that resection of liver or ILN metastases can be done safely and should be considered as it may be superior to palliative treatment, and it is associated with long-term survival of 10% in selected patients. Further studies to stratify patients for these procedures are warranted.

Keywords: Liver metastasis; PDAC; Pancreatic cancer; Para-aortal lymph nodes; M1; Surgery

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains a challenging disease with a poor prognosis[1]. Despite improved medical treatment options and the significant impact of adjuvant chemotherapy, surgery remains the only basis on which long-term survival can be achieved[2]. Surgery is limited to patients presenting with localised disease, and metastatic spread is generally regarded as a contraindication for resection, regardless of whether it is synchronously or metachronously observed[3]. Despite this, metastases resection or local therapy is occasionally performed by centres around the world based on individual decisions without existing evidence regarding patient selection or the extent of metastatic spread[4–8]. Most commonly, PDAC metastases are present in the liver, interaortocaval lymph nodes (ILN) or the peritoneum. As peritoneal metastases are intraoperatively found to be diffusely spread in most cases, no surgical approach is possible in most patients. In contrast, a resection of liver metastases is often possible without major surgical trauma, e.g. for subcapsular lesions that are found during intraoperative exploration. In addition, ILN metastases – currently defined as distant metastases – are regarded as an indication to stop resection when proven positive in an intraoperative frozen section[9,10], although evidence on the prognostic value of these lymph nodes remains controversial[11] and resection is not technically challenging.

The aim of the present study was to analyse the impact of resection therapy in stage IV PDAC patients with limited metastases located in the liver or the interaortocaval lymph nodes in terms of surgical outcome and long-term survival.

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Methods

Prospectively collected data of all patients undergoing surgery for PDAC at the Department of Surgery, University of Heidelberg, between October 2001 and May 2014 were analysed. Patients who underwent primary tumour and metastasis resection for stage IV PDAC with metastatic spread to the liver or within the interaortocaval lymph nodes were extracted. They were investigated regarding the following: localisation of metastases (liver or interaortocaval lymph nodes; ILN); primary tumour resection; time point of metastases resection (synchronous vs. metachronous); perioperative morbidity and mortality; prognostic parameters; survival. Patients undergoing surgery for metastatic pancreatic neuroendocrine tumours were excluded from the analysis. Oligometastatic PDAC was defined as 1–3 liver metastases that could be easily resected by atypical resection (intention-to-treat) or ILN metastases. This study was approved by the Institutional Review Board (Ethic votum S-127/2015) and is in accordance with the Helsinki Declaration.

SAS software (Release 9.1, SAS Institute, Inc., Cary, NC) was used for statistical analysis. Data were analysed using the Mann–Whitney U-test and Fisher's exact test depending on data characteristics. Overall survival from the date of pancreatic and/or metastases resection was calculated using a Kaplan–Meier estimate. All deaths from any cause were included in the survival analysis. Median survival times are presented. The log-rank test was performed to compare survival curves. Patients alive at the last follow-up were censored. Two-sided p-values were calculated and a difference was considered statistically significant at $p < 0.05$.

Results

Baseline characteristics

One hundred and twenty-eight patients undergoing surgery for stage IV PDAC with spread to the liver or the ILN were identified in the observation period, with a mean age of 61 years; 48% of the patients were male. Regarding the subgroups of liver and ILN metastases, no differences in these parameters were found. Furthermore, there were no differences regarding preoperative body mass index or American Society of Anesthesiologists' (ASA) classification between the groups (Table 1).

All patients underwent pancreatic and metastases resection, 43 of these for ILN metastases and 85 for liver metastases. Twenty of the patients had previously undergone neodadjuvant treatment. All ILN resections were performed synchronously with the pancreatic resection. In the patients with liver metastases, 72.9% of the liver resections were carried out at the time of the pancreas resection, whereas 22.4% of the patients underwent liver resections following prior PDAC surgery at an average time of 18.4 (range 1–58) months after the index operation. In four patients (4.7%), liver metastases were removed during an initial exploration, followed by chemotherapy and resection of the primary pancreatic tumour (Table 2).

Table 1
Patient characteristics and operative procedures during pancreas resection.

	Liver met. (n = 85)	ILN met. (n = 43)
Age (mean)	60.4	62.7
Male/female	47/38	15/28
BMI		
<20	3	6
20–25	70	35
>25	5	2
n/a		
ASA classification		
I	3	0
II	48	27
III	23	16
IV	0	0
n/a		
Pancreatic resection		
pr/pp PD	36	30
TP	14	8
DP	34	5
Histopathology		
R0	16	15
R1	51	24
Rx	18	4
ypT0 N0	2	–
ypT3 N0	9	–
ypT3 N1	8	1
pT3 N0	10	2
pT3 N1	55	40
pT4 N1	1	–

Surgical procedures

All types of oncological pancreatic resections were performed, including pancreato-duodenectomy, distal pancreatectomy and total pancreatectomy with splenectomy (Table 1).

In the patients with extended lymphadenectomy, lymph nodes of the interaortocaval space were always included in the dissection (position 16 according to the Japanese Surgical Society classification). Extended other ILN resections

Table 2
Types and timing of hepatic resections.

Liver resection	Overall	Synchronous	Metachronous
1× atypical	55 (64.7%)	43	12
2× atypical	15 (17.7%)	14	1
3× atypical	1 (1.1%)	–	1
4× atypical	2 (2.4%)	2	–
Bisegmentectomy	2 (2.4%)	1	1
Bisegmentectomy & 1× atypical	3 (3.5%)	1	2
Right hepatectomy	6 (7.1%)	1	5
Extended right hepatectomy	1 (1.1%)	–	1
	85 (100%)	62	23

were performed in five patients where lymph nodes of the right and left perirenal right area were dissected. In average, seven ILN were harvested, with an average of 3.4 positive lymph nodes in the final histopathology.

Resection of liver metastases

In the majority (86%) of patients with liver metastases, atypical resections of one to four subcapsular lesions were performed. The remaining patients (14%) received formal resections, including bisegmentectomies, and right and extended right hepatectomies. The majority of major hepatic resections were carried out metachronously (Table 2). With regard to the diameter of the largest resected metastasis in each patient, diameters of <1 cm (43.0%), followed by lesions measuring between 1 and 2 cm (31.7%), were most commonly found. The overall number of metastases in the resected specimen was up to three in 96.4% of all patients, and only three patients finally displayed more than three metastases in the pathological workup.

Postoperative morbidity and mortality

Surgical morbidity and 30-day mortality after synchronous resection of M1 tumours were 45.0% and 2.9%, respectively. After metachronous resection for liver metastases, surgical morbidity was 21.7% and 30-day mortality was 4.3%. Table 3 summarises the surgical outcome.

Tumour markers

The preoperative values of CA 19-9 showed no significant difference between patient groups with different M1 localisations. Median preoperative CA 19-9 levels were 165 U/ml (interquartile range (IQR) 29–558 U/ml) in patients with liver metastases and 212 U/ml (IQR 40–606) in patients with ILN metastases (p = 0.866). Preoperative CA 19-9 levels for liver metastases resected syn- or metachronously were not significantly different with a median level of 191 (IQR 33–532) U/ml and 165 (IQR 30–530) U/ml, respectively (p = 0.990).

Using 1000 U/ml as a cut-off level for preoperative CA 19-9, this was exceeded by a significantly different proportion of patients in each group (ILN metastases 11.6%, liver metastases 19.0%; p = 0.294).

Table 3
Perioperative outcome grouped according to the specific procedures.

	Pancreas resection with ILN resection	Pancreas resection with liver resection	Liver resection alone
Patients (n)	43	62	23
Wound infection	3 (7.0%)	9 (14.5%)	2 (8.6%)
POPF B/C	3 (7.0%)	6 (9.7%)	–
DGE B/C	5 (11.6%)	6 (9.7%)	–
Lymphatic fistula	2 (4.7%)	5 (8.1%)	–
Bleeding	–	4 (6.4%)	1 (4.3%)
Bilioma	–	–	2 (8.6%)
Percutaneous drainage	2 (4.7%)	7 (11.3%)	2 (8.6%)
ERCP & stent	–	2 (3.2%)	–
PTCD	–	1 (1.6%)	–
Re-operation	–	2 (3.2%)	1 (4.3%)
30-Day mortality	2 (4.7%)	1 (1.6%)	1 (4.3%)

Adjuvant and palliative postoperative therapy

Data on adjuvant chemotherapy were completely available for 95/128 patients (74.2%). Among these, 73 patients completed adjuvant therapy, including gemcitabine as the most commonly administered drug (79.5%) followed by 5-FU (8.2%) and other schemes (12.3%).

Survival

From the time point of liver resection (syn- or metachronously), median survival was 12.3 months, which was similar to the ILN resection patients (12.3 months, Fig. 1). In addition, 5-year survival after resection of liver metastases was 8.1% and after ILN resection was 10.1% (p = 0.773). The actual 5-year survival for liver or ILN metastases was 5.9% and 7.0%, respectively. Regarding the timing of liver resection, there was no significant difference between the syn- and metachronously resected patients when survival was analysed from the time of liver resection (p = 0.210; Fig. 2). There was no survival difference observed after neoadjuvant treatment in both M1 liver and M1 ILN (M1 liver: p = 0.287; M1 liver metachronous: p = 0.224; M1 liver synchronous: p = 0.105). Also, the tumour localisation (head/body/tail) had no impact on survival in patients with liver metastases (p = 0.770).

Neither number (one vs. two vs. three or more metastases; p = 0.589), size of liver metastases (0–1 cm vs. ≥1 cm; p = 0.713) nor preoperative CA 19-9 levels (p = 0.456) showed a significant influence on survival.

Discussion

The present study includes the largest collective of patients resected for stage IV PDAC to date and shows a survival benefit for selected patients with liver or ILN metastases compared to reported survival times after palliative treatment alone. Importantly, 5-year survival was 10% of the patients in both groups, which has never been reported following any type of chemotherapy regimen alone.

According to international guidelines and widespread clinical practice, stage IV PDAC patients are generally referred to palliative treatment by chemotherapy[3,12]. With the administration of modern chemotherapy regimens, a median survival of 11 months can be achieved in a palliative setting[13]. However, these regimens are often associated with severe side effects that can impair patients' quality of

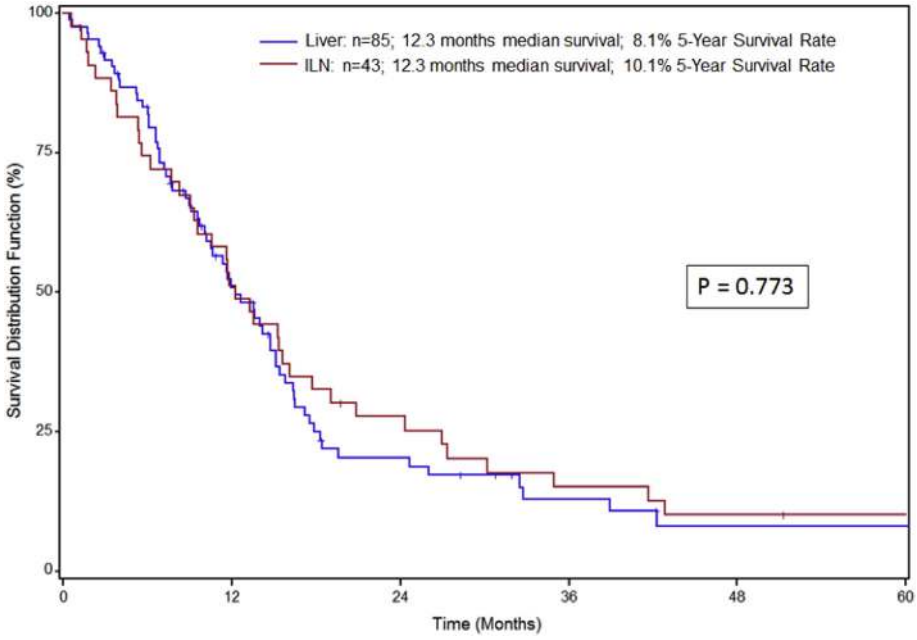

Figure 1. Overall survival, entire patient collective (n = 128).

life[14,15] and no long-term survivors have been reported. Although it remains unquestionable that PDAC with diffuse tumour spread to the liver, peritoneum or the lung is a situation in which surgery is not indicated, the approach of a surgical resection or liver-directed therapies in oligometastatic situations has been performed in a limited number of studies in the past[4–7,16,17] with partly conflicting results.

An older meta-analysis published in 2007[18] showed no clear benefit for resection of metastases; however, the study was based on small case series and, therefore, the evidence was highly limited whereas in a recently published retrospective multi-center analysis of six European centers simultaneous resection of pancreatic cancer and singular liver metastases was associated with prolonged survival[19].

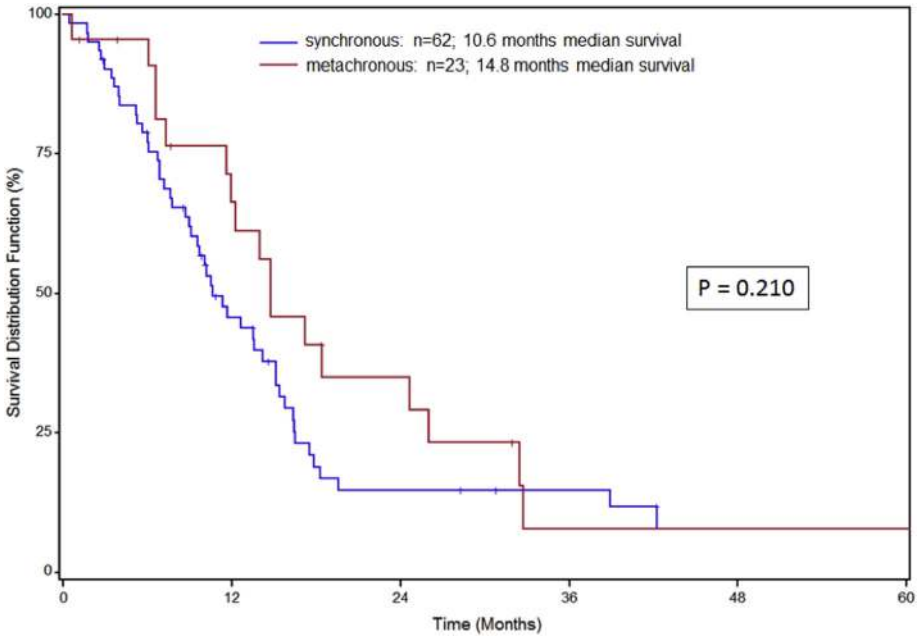

Figure 2. Survival according to the time of liver resection in patients undergoing syn- and metachronous resection of liver metastases. M1 group: synchronous resection at the time of pancreas resection (n = 62), M0 group: metachronous resection after initial pancreas resection without evidence for metastases (n = 23).

Probably the most challenging topic is the appropriate selection of patients with stage IV PDAC who may be candidates for a resection. Clinical and translational experience shows that there are prognostically relevant parameters in PDAC patients beyond macroscopically visible tumour lesions, including genetic alterations that cannot be specified preoperatively[20]. This observation supports the hypothesis that syn- or metachronous resection of limited metastases might be more beneficial in selected patients than primary tumour resection in other stage II patients who show extensive and immediate tumour progression postoperatively despite no metastases being found at the time of the operation. These clinical observations are attributed to currently unknown mechanisms of tumour biology leading to a more or less aggressive growth pattern. Currently, stratification of patients that belong to either group cannot be done sufficiently. Tumour markers, such as CA 19-9, can serve as a prognostic parameter and cut-off levels of 100, 200 or 1000 U/ml have been defined as prognostic thresholds for resectability or early recurrence after resection[21–26]. This underlines the potential usefulness of CA 19-9 for stratification, but does not yet allow the definition of valid cut-off levels for clinical decision-making.

With regard to the present results, it has to be differentiated between liver metastases and ILN metastases. Considering liver metastases resection, surgery –and its potential morbidity and mortality – has to be weighed against other therapeutic options, especially chemotherapy and locally targeted approaches that have been reported in selected patients[6,7]. We could demonstrate a median survival of 12 months, which is clearly superior to recently reported survival times of ~6–7 months following palliative standard chemotherapy (e.g. gemcitabine). Although this survival time may be expanded by modern chemotherapy regimens, this is achieved at the price of high toxicities with a considerable impairment of quality-adjusted lifetime. In contrast, the additional resection of liver metastases did not have an influence on postoperative morbidity resulting in reduced quality of life. In addition and most importantly, in contrast to the palliative setting, the combination of surgery and adjuvant chemotherapy can give the perspective of a long-term survival as we could demonstrate a 5-year survival of 10% patients, which is impossible without surgery in stage IV PDAC.

Regarding the presence of ILN metastases, the present study shows that resection of these lymph nodes in combination with the primary tumour seems to be feasible and specific complications such as lymphatic fistulas do not seem to adversely affect outcome. In part, this conflicts with the current guideline recommendation that an extended lymphadenectomy of this compartment should not be routinely performed as it has not proven useful and was associated with an increased morbidity in older studies[27]. In contrast to a routine extended lymphadenectomy, a subcollective of patients with positive lymph nodes in this localisation seems to benefit from this approach in terms of survival. This seems to justify ILN resection, especially when these lymph nodes are intraoperatively found to be the only extrapancreatic tumour manifestation, even though morbidity may be increased. Other recent studies investigating patients with ILN metastases have shown conflicting results with regard to the potential oncological benefit[10,28–31]. Consequently, a recent consensus statement by the International Study Group on Pancreatic Surgery[32] has addressed this controversy and underlined the lack of high-level evidence regarding surgery despite the presence of metastases in these lymph nodes. The results of the present study, therefore, make an important contribution to the current discussion. However, a recommendation for routine ILN dissection in all patients undergoing PDAC surgery cannot be made.

As mentioned above, the proper patient selection of surgical candidates with stage IV PDAC seems to be crucial. The present study underlines this challenge as no clear cut-off levels in tumour markers or number and size of liver metastases can currently be defined, which can be attributed to the overall limited number of patients, as well as the retrospective character. Clearly, this study has several limitations such as retrospective and single-center design. The selection of patients was considered an individual approach in a vast majority of the cases. Furthermore there is no matched group to compare the results with palliative chemotherapy, alone. In other studies focusing on this topic, no valid serum markers or clinical criteria have yet been identified[4–7]. In the future, neoadjuvant chemotherapy may serve as a useful tool for patients presenting at an oligometastatic stage to select appropriate candidates for surgery as only patients that respond to the neoadjuvant treatment might also benefit from an aggressive resection strategy.

In patients with metachronous liver metastases resection, the interval between the initial and the consecutive operation may be useful as an additional criterion for patient selection, and probably best reflects the tumour biology and potential prognosis of the individual patient. In general, from the clinical experience, a time interval of 12 months can probably be regarded as a reference, although not based on high-level evidence. As this observation period cannot be used for synchronous resection of liver metastases, the decision for surgery in this situation remains even more challenging and additional studies and markers are warranted for prognostic patient stratification.

In conclusion, the present study shows that resection of liver or ILN metastases can be done safely. It should be considered as an individual approach as it may be superior to palliative treatment in selected patients and offers long-term survival in 10% of the patients. Further studies to stratify patients for these procedures and to define prognostic markers that allow an accurate selection are warranted.

Conflict of interest statement

The authors have no disclosures.

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