ORIGINAL ARTICLE

How To Handle Locally- Advanced Pancreatic Ductal Adenocarcinoma or the Intraoperative Incidental Finding of A Solitary Liver Metastasis: Do Patients Benefit from the Extended Resection?

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ABSTRACT

Introduction Only around 20% of patients are diagnosed with a primarily resectable pancreatic ductal adenocarcinoma. However, some of these patients show intraoperatively the incidental finding of a solitary, resectable liver metastasis (LM). Another 15- 20% of tumors are locally- advanced or involving surrounding organs at diagnosis. The objective of this study was to investigate first if the long- term survival of these patients can be improved by an extended resection (ER) and second to point out the strongest predictors for long- term survival. **Patients and methods** All patients with locally- advanced tumors or those with intraoperatively diagnosed, unexpected, solitary LM between January 2002 and December 2013 were analyzed retrospectively. The ER was defined as the simultaneous resection of adjacent organs or solitary LM. For statistical analyses, these patients´ long- term survival was compared with the one of patients who did not undergo oncological tumor resection in case of locally- advanced cancer. **Results** 40 patients (17 men, 23 women, age 68 ± 9.5 years) underwent ER and another 40 patient's only explorative laparotomy or palliative surgical treatment. After ER, patients had a significantly better long-term survival (10.8 ± 2.85 *vs.* 6.43 ± 2.43 months, p=0.02). The R0- resection and the application of a postoperative chemotherapy were the strongest predictors for long- term survival. **Conclusion** In case of locally- advanced ductal pancreatic adenocarcinoma or intraoperatively diagnosed, unexpected, solitary LM, selected patients can benefit from an extended resection in order to achieve clearness of tumor. The R0- resection and the use of postoperative chemotherapy are the strongest predictors for long- term survival.

INTRODUCTION

Pancreatic ductal adenocarcinoma is the most common type of pancreatic cancer [1] and it is the fourth leading cause of cancer related death [2, 3].

Surgery, and especially the R0- resection of pancreatic ductal adenocarcinoma, is the treatment of choice and the strongest predictor for long- term survival [4, 5, 6].

Due to surgical as well as peri-/postoperative improvements and therefore decreasing perioperative morbidity and mortality, the indications and feasibility for resections of pancreatic cancer extended [7, 8, 9, 10].

In this study we want to focus on these 15-20% of patients with locally- advanced pancreatic cancer at diagnosis or who show intraoperatively an unexpected, solitary liver metastasis [11].

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There is some evidence that even locally-advanced ductal adenocarcinoma of the pancreas can be safely resected in an extended pancreatectomy [12]. The non- contiguous liver resection for metastases is a well established part in the curative treatment not only for colorectal [13, 14, 15], but also non- colorectal, non-neuroendocrine neoplasms [16, 17] and, in the last few years, it is more and more reported in the setting of pancreatectomy [18].

In case of locally- advanced or metastatic disease, modern chemotherapies allow a median survival of 8.5 months and the response rate is only 23% [19]. On the other hand there are encouraging results which show that the survival after extended pancreatectomy in case of locally- advanced pancreatic cancer or after the simultaneous resection of a liver metastasis is superior to palliative treatment, especially if negative margins can be reached [18, 20, 21, 22, 23, 24].

The intention of this study is to compare the long-term survival of patients who underwent extended pancreatectomy or simultaneous liver resection in case of locally- advanced cancer or a solitary liver metastasis with the one of patients that underwent only explorative laparotomy or implementation of an internal bypass followed by a palliative chemotherapy. Second, we want

to investigate the strongest predictors for long- term survival after oncological tumor resection in these selected patients.

PATIENTS AND METHODS

Clinicopathological characteristics of the patients were derived from our own pancreaticobiliary database at the Department of General- and Visceral- Surgery, Saarland University Medical Center, Homburg/ Germany.

All patients with locally- advanced pancreatic ductal adenocarcinoma or those with intraoperatively diagnosed, unexpected, solitary and resectable liver metastases between January 2002 and December 2013 were analyzed retrospectively.

Extended resection was defined as either the simultaneous resection of adrenals, parts of the colon, kidneys or solitary liver metastases in case of pancreatoduodenectomy, independent of a pylorus preserving approach or not, or the simultaneous resection of parts of the colon or stomach, adrenals, kidneys or solitary liver metastases in case of distal pancreatectomy with splenectomy. The splenectomy itself in case of cancer of the pancreatic body or tail did not determine the classification as an extended resection. The simultaneous resection of an unexpected, solitary liver metastasis was only performed if the macroscopic R0- resection of the pancreatic tumor itself was possible. The extent of liver resection, depended on the size and the position of the metastasis, was divided into minor (segmentectomies or non- anatomic resections) or major resections (hemihepatectomy). The exclusive resection of parts of the portal as well as superior mesenteric vein or arterial reconstructions did not classify for extended resection.

Patients with extrahepatic metastatic disease including those with serosal implants or peritoneal disease and any pancreatic tumor other than ductal pancreatic adenocarcinoma were excluded from this study.

In order to assess the impact of extended resection of locally- advanced ductal pancreatic adenocarcinoma or unexpected, solitary liver metastases, these patients´ long- term survival was compared with the one of patients who underwent only explorative laparotomy or palliative surgical interventions, for example hepaticojejunostomy and/ or gastrojejunostomy in case of locally- advanced ductal pancreatic adenocarcinoma.

For both groups, demographic parameters, peri- and postoperative data, for example intraoperative blood-loss, duration of operation, intensive care unit (ICU) stay and hospitalization, intrahospital mortality and long- term survival were collected. Furthermore, the kind of postoperative or palliative therapy was recorded. Information about the stage of the tumor and its extension in relation to the specimen´s margin was taken from the final pathologic analysis.

STATISTICS

Data were reported as mean or median values, standard deviations and frequencies. Student T- Test was used for continuous variables if they were normally distributed and Mann-Whitney- U test if not. Chi- square test was applied in order to compare categorical variables. For all tests, two sided p value of ≤ 0.05 was considered statistically significant. Kaplan- Meier method was used in order to estimate long- term survival and the log rank test in order to analyze the difference between the two groups. Variables that showed a strong correlation with long- term survival in the univariate analysis were afterwards tested in multivariate model. SPSS software, version 23 was used for statistical analysis (SPSS Inc, Chicago, Ill).

RESULTS

Demographics

We identified a total of 40 patients (17 men, 23 women, age 68±9.5 years) with pancreatic ductal adenocarcinoma who underwent extended tumor resection in our institution within the 12- year time period from January 2002 to December 2013. In 22 patients (55.0%) the tumor was localized in the body or the tail of the pancreas, 18 patients had a ductal adenocarcinoma of the pancreatic head. One patient had a neoadjuvant chemoradiotherapy (45 Gy plus gemcitabine) before he underwent distal pancreatectomy. Altogether there were 13 patients with a preoperative bile drain, 10 of them (76.9%) had a cancer of the pancreatic head, three of the body and tail.

In the same period, another 40 patients (24 men, 16 women, age 69.5±8.5 years) with locally- advanced pancreatic ductal adenocarcinoma that did not undergo oncological resection could be found and served as control group. There were no statistically significant differences between the two groups with regard to age, sex and comorbidities.

Surgical Therapy

Among the 40 patients in the resection- group, 18 patients (45.0%) had their tumor localized in the pancreatic head. 11 patients of them (61.1%) underwent a pylorus preserving pancreatoduodenectomy and 7 the classical Whipple- procedure. The basic operation of the other 22 patients with a tumor in the body or tail of the pancreas was a distal pancreatectomy with splenectomy. There was no total pancreatectomy among the extended resections.

In case of pancreatoduodenectomy, 10 patients (55.6%) suffered from locally- advanced cancers; 8 patients had a liver metastasis (44.4%). One of the 10 patients with locally- advanced cancer of the pancreatic head underwent a simultaneous liver resection, but without the histological evidence of a metastasis. Among the 22 extended distal pancreatectomies, 3 patients underwent distal pancreatectomy (plus splenectomy) plus non-anatomic liver resection; a right hemihepatectomy was performed in one patient. In the other 18 patients, one or

more surrounding organs were resected within the extended approach, in 3 patients combined with the non- contiguous resection of a solitary liver metastasis **(Table 1)**.

Altogether, 15 patients underwent a non- anatomic liver resection (9 after pancreatoduodenectomy, 6 after distal pancreatectomy). One right hemihepatectomy was performed after distal pancreatectomy. With one exception, the clinically diagnosed metastases were confirmed histologically in all cases.

In order to achieve macroscopic negative margins if the cancer was locally- advanced, 9 right hemicolectomies, 5 left hemicolectomies and a resection of the transvers colon in three cases had to be performed. In addition, 7 patients underwent adrenalectomies, 1 patient a nephrectomy and 11 of the 22 patients with tumor localization in the pancreatic body or tail a partial (9 patients) or total gastrectomy (2 patients) combined with distal pancreatectomy.

A standard lymphadenectomy (defined as the lymphnode dissection of the compartment 1 and 2) was carried out in 28 patients (70.0%), the extended lymphadenectomy (levels 1-3) in 12 patients.

On final pathologic analysis, the overall rate of R0- resection was 70.0%, 13 patients after extended pancreatoduodenectomy, 15 after extended distal pancreatectomy. A microscopic involvement of the margin was found in 10 patients (25.0%), 4 patients after extended pancreatoduodenectomy and 6 after extended distal pancreatectomy. Two specimens were classified as Rx. None of the specimens had macroscopically positive margin **(Table 2)**.

In the control group, 11 patients (27.5%) only underwent laparotomy, the other 29 patients received an internal bypass (biliodigestive anastomosis and/ or gastroenterostomy).

When an extended resection was performed, the median operation time (234±77 min *vs.* 157±74 min, p<0.001) and the median intraoperative blood loss (661±516 ml *vs.* 17 ±311 ml, p<0.001) were significantly higher compared to the palliative surgical intervention. Furthermore, both the duration of intensive care unit- stay (4.9±8.5 d *vs.* 1.3±1.8 d, p<0.001) and the duration of hospitalization (22.8 ± 14.1 d *vs.* 12.7±5.4 d, p<0.001) were significantly longer after extended resection, but intrahospital mortality was not different between the two groups (1 patient died after extended resection, 2 after the palliative operation).

Among the 40 patients who underwent extended resection, 15 patients (37.5%) developed a pancreatic fistula: 3 patients after extended pancreatoduodenectomy, 12 after distal pancreatectomy. There was one grade C fistula among them. One patient developed a bile fistula after extended pancreatectomy. Among the 17 colectomies that were performed, there was one anastomotic leakage, which required an operative revision. 9 patients (22.5%) suffered from delayed gastric emptying, 7 after pancreatoduodenectomy and 2 after distal pancreatectomy. In the course of the hospitalization, 19 patients in total received a blood transfusion; the mean number of blood transfusions per patient was 3.

For additional information about morbidity after extended resection, we built matched pairs between the 18 patients who underwent extended pancreatoduodenectomy and another 18 patients after standard pancreatoduodenectomy. The patients in both groups did not differ with regard to age, sex, American Society of Anesthesiologist (ASA) Physical Status Classification. We used Student- T test and Mann-Whitney- U test or Chi- square test in order to compare both groups with regard to intraoperative blood loss, number of re- operations, incidence of a pancreatic fistula or delayed gastric emptying as well as the length of the stay on intensive care unit and in hospital. There were no

Table 1. Simultaneously resected organs within the extended pancreatoduodenectomy (PD) and extended distal pancreatectomy (DP); partial gastrectomy in case of PD and splenectomy in case of DP are not mentioned.

Standard operation	Partial gastrectomy	Total gastrectomy	Partial colectomy	Adrenalectomy	Nephrectomy	Hepatectomy	Number of patients
PD			x				9
PD						x	8 (non-anatomic)
PD			x			x	1
DP	x		x	x			3
DP	x					x	2
DP						x	3 non-anatomic, 1 hemihepatectomy
DP		x					2
DP				x			2
DP			x				2
DP	x			x			2
DP			x		x		1
DP	x						2
DP			x	x			1
DP				x		x	1
							40

Table 2. Surgical therapy.

		multivisceral pancreatoduodenectomy	multivisceral distal pancreatectomy	
n = 40		18	22	
	pylorus- preserving	11		
simultaneously resected organs				
colectomy		10	7	
	right hemicolon	9	0	
	transverse colon	1	2	
	left hemicolon	0	5	
adrenalectomy		0	7	
	right adrenal	0	0	
	left adrenal	0	7	
hepatectomy		9	7	
	non anatomic	9	6	
	right hemihepatectomy	0	1	
	histologically verified metastasis	8	7	
gastrectomy		(7)	11	
	partial gastrectomy	(7)	9	
	total gastrectomy	0	2	
nephrectomy		0	1	
	right kidney	0	0	
	left kidney	0	1	
lymphadenectomy lymphnodes pos./resected				
standard	patients (number) lymphnodes pos./resected (number)	9 3±3/14±9	19 3±3/12±7	
extended	patients (number) lymphnodes pos./resected (number)	9 2±2/22±12	3 4±6/25±13	
specimens´margin	R0	13	15	
	R1	4	6	
	R2	0	0	
	Rx	1	1	
intraoperative blood loss (ml)		644±451	675±574	*n.s. (p=0,85)*
blood transfusion intraop.	number of patients	4	4	
	number of erythrocyte concentrate/ patient	6,25	2,5	*n.s. (p=0,30)*
duration of operation [min]		258±64	214±81	*n.s. (p=0,06)*

statistically significant differences between the two groups with regard to the parameters mentioned above.

18 patients (45.0%) in the extended resection group and 21 patients (52.5%) in the control group received a postoperative chemotherapy (n.s.). A palliative chemoradiotherapy was offered to 2 patients in the control group and to 1 patient after oncological tumor resection. 1 patient received a chemotherapy plus SIRT because of the recurrence of a solitary liver metastasis after the initial simultaneous liver resection. 20 patients (50.0%) after extended resection and 17 patients (42.5%) of the palliative operated patients did not have any postoperative or palliative therapy.

Survival

The median postoperative survival of all patients that underwent extended resection, independent of the presence of solitary liver metastases or a locally- advanced cancer, was significantly longer than the one of the patients with the palliative surgical intervention in case of locally-advanced cancer (10.8±2.85 months *vs.* 6.43±2.43 months, p=0.019) **(Figure 1)**. Patients´ median survival after extended resection of locally- advanced cancer in absence of a liver metastasis was 15.7±5.2 months, which was statistically significantly longer than the median survival of patients with the palliative surgical intervention, too (p=0.027).

Within the extended resection group, in particular the R0- resection (median postoperative survival 14.6±3.89 months) **(Figure 2)** and the use of postoperative chemotherapy (median postoperative survival 17.3±0.88 months) **(Figure 3)** were associated with a favorable long- term survival, but only the R0- resection reached statistical significance. Patients without a liver metastasis had a better long- term survival than those with a solitary, intraoperatively diagnosed liver metastasis (15.7±5.2 months *vs.* 5.5±2.8 months), but without statistical significance **(Figure 4 and Table 3)**. Furthermore, demographic parameters like age, sex, cardio- pulmonary or vascular comorbidities, American Society of

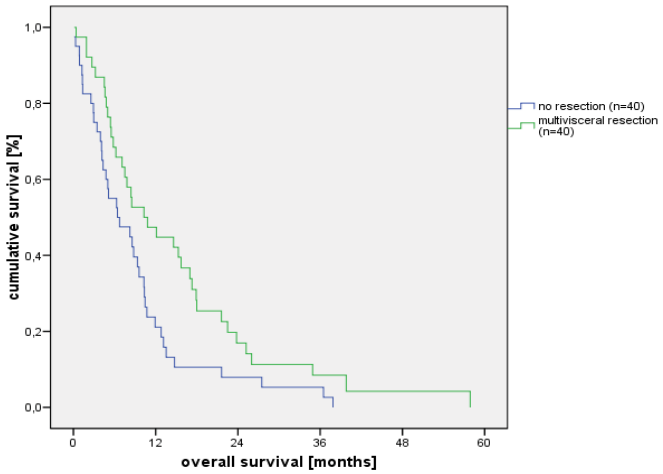

Figure 1. Long- term survival after multivisceral resection *vs.* no tumor resection (10.8 ± 2.85 *vs.* 6.43 ± 2.43 months, p=0.019).

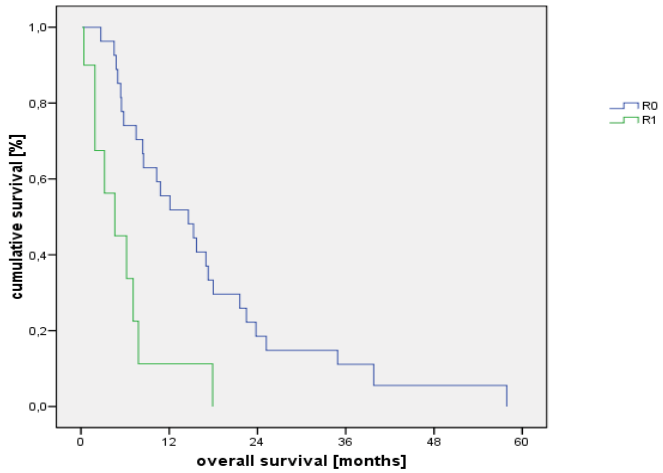

Figure 2. Long- term survival after multivisceral resection with regard to specimens´ margin (14.6±3,89 *vs.* 4.6±2.07 months, p=0.001).

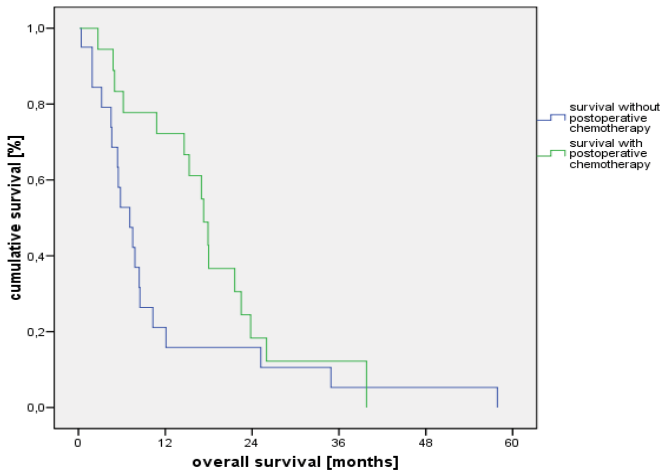

Figure 3. Long- term survival after multivisceral resection with regard to postoperative chemotherapy (17.3 ± 0.88 *vs.* 7.5 ± 1.79 months, p=0.052).

Anesthesiologist (ASA) Physical Status Classification, weight- loss or BMI, as well as duration of symptoms before operation, elevation of the tumor markers CEA and CA 19-9, oncological diseases or operations into the abdominal cavity in the past, number and kind of organs that were resected simultaneously, intraoperative blood loss or number of blood transfusions, duration of the operation, classification and differentiation of the tumor in the pathologist´s analysis, postoperative complications such as pancreatic fistula, cardio- pulmonary complications, delayed- gastric emptying, subsequent operations, duration of ICU- stay or hospitalization did not correlate significantly with long- term survival.

Within the group of patients that did not undergo tumor resection, the implementation of an internal bypass did not have any impact on patients´ survival in comparison to the explorative laparotomy alone.

Multivariate Analysis

The three factors with the strongest impact on long- term survival, R0- resection, absence of a solitary liver metastasis and application of a postoperative chemotherapy, were then analyzed in multivariate model: Cox multivariate regression analysis model revealed that only the R0- resection (HR 0.388, 95%CI 0.174-0.865, p=0,021) and the use of postoperative chemotherapy (HR: 0.424, 95%CI 0.205-0.880, p=0.021) correlated significantly with favorable long- term survival.

DISCUSSION

Pancreatic ductal adenocarcinoma is among the most common cancer related causes of death [2]. Neither today nor in the near future there will be any alternative curative therapy other than surgery and as the peri- and postoperative morbidity and mortality have decreased during the last decades, surgery even plays a more and more important role in the therapy of the pancreatic ductal adenocarcinoma and the indications for resection of the carcinoma were extended [7, 8, 9, 10].

As a result of this, venous resections, for example, are well established in these days and can be performed without an increased morbidity and mortality [25, 26].

Similar data can be found for locally- advanced tumors, that are involving surrounding organs: There are studies that support an extended resection in the treatment of a locally- advanced cancer as well. The investigations of Shrikhande *et al*., Hartwig *et al*. or Adham *et al*. confirm our findings which show that even in case of a locally-advanced cancer a long- term survival is possible, if the

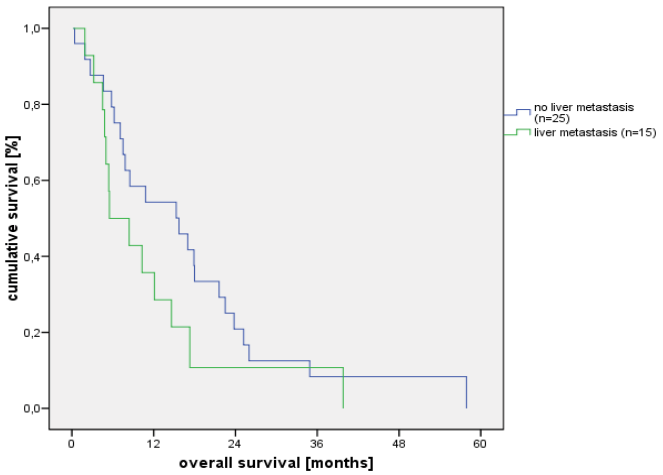

Figure 4. Long- term survival after multivisceral resection with regard to presence of a liver metastasis (15.7±5.2 *vs.* 5.5±2.8 months, p=0.144).

Table 3. Survival after extended pancreatectomy *vs.* palliative treatment and after extended pancreatectomy depending on the specimen´s margin, postoperative chemotherapy and presence of a solitary liver metastasis.

survival [months]	**extended resection (n=40)**	**palliative treatment (n=40)**	**p- value**
	10.8±2.85	6.43±2.43	*0.019*
survival [months]	**extended resection, R0 (n=28)**	**extended resection, R1 (n=10)**	**p- value**
	14.6±3.89	4.6±2.07	*0.001*
survival [months]	**extended resection, postoperative chemotherapy (n=18)**	**extended resection, without postoperative chemotherapy (n=20)**	**p- value**
	17.3±0.88	7.5±1.79	*0.052*
survival [months]	**extended resection, no liver metastasis (n=25)**	**extended resection, liver metastasis (n=15)**	**p- value**
	15.7±5.2	5.5±2.28	*0.144*

extended resection leads to an R0- situation [20, 21, 22]. So, microscopically negative margins are the highest and most important ambition. We found a median long- term survival of 14.6 months after R0- resection just as Hartwig *et al*. or Sasson *et al*. who reported that the long- term survival after R0- resection of a locally- advanced tumor is similar to the one after microscopically complete standard resection [23, 24].

Christein *et al*. have observed that at the time of surgery almost 35% of the carcinomas of the pancreatic body and tail involve surrounding structures. Intraoperatively it is often hard to decide if these are only inflammatory adhesion or, however, tumor infiltration [27]. So, these facts emphasize the importance and need for extended resections in order to reach definitely a microscopically complete tumor resection.

More controversially discussed even in these days is the question how to deal with preoperative not diagnosed, unexpected, solitary and resectable liver metastases: Should the operation be continued in a palliative intention, in order to create a palliative bypass for example, or even terminated as an explorative laparotomy, or should we follow the curative intention that means simultaneous resection of the liver metastasis if the R0- resection of the primary seems possible?

On the one hand the resection of liver metastases is an inherent part of the curative treatment of not only colorectal, but also non- colorectal and non- neuroendocrine metastases [16]. Critics disbelieve the benefit of resection pancreatic liver metastases even if there is a solitary one and refer to the extraordinary aggressiveness of the pancreatic ductal adenocarcinoma and the complexity and morbidity of the surgical procedure itself, especially the head resection. But particularly with regard to the point that was last mentioned, a lot of progress has been made over the time, as it is reported above.

Shrikhande *et al*. reported a group of eleven patients with synchronous resection of liver metastases and found a median survival of 11.4 months compared to 5.9 months in the control group with palliative bypass or just explorative laparotomy without a significant difference in morbidity and postoperative mortality [28].

A study from Michalski *et al*. supports these findings: They reviewed three case reports and 18 studies, altogether 103 patients, and reported a survival of patients with a complete resection of the primary and the metastasis similar to patients´ survival that do not have a metastatic disease. The morbidity and mortality rate ranged from 24.1 to 26% and from 0 to 4.3% - dimensions that are required and observed for standard resections as well [29].

These results confirm our findings: If the R0- resection of the pancreatic cancer itself and the metastasis succeeded, patients benefitted from a significantly better long- term survival compared to palliative bypass or explorative laparotomy alone (14.6 *vs.* 6.43 months). Therefore, in case of an intraoperatively diagnosed, solitary and resectable liver metastasis, we also favor the continuation of the operation in curative intent what means simultaneous resection of the primary and the metastasis.

Another point is the peri- and postoperative morbidity and mortality. Compared to the patients with palliative surgical intervention, patients after extended resection stayed significantly longer on intensive care unit and in hospital. One of the 40 patients that underwent extended resection died (2.5%). That represents a mortality rate similar to the one after standard resection [7, 30]. With regard to morbidity, investigations from Shrikhande *et al*. and Michalski *et al*. confirm the results of our matched- pair analysis: They found no statistically significant differences between standard and extended resections, as it is mentioned above [28, 29]. In opposite, Hartwig *et al*. and Brudelski *et al*. reported an increased morbidity after extended resections. Among the risk factors for morbidity they identified were the kind and number of organs that were resected additionally and the need of blood transfusions [21, 31]. Kleef *et al*. identified the extent of the resection, multivisceral versus conventional, as one of the main factors for increased overall morbidity after distal pancreatectomy [32].

For those who still complain about morbidity and mortality of extended resections or the simultaneous non- contiguous resection of a liver metastasis, it would be interesting to analyze the role of other local treatments, for example ablative technologies of the liver like RFA or microwave ablation that obtain good results in the therapy of both liver metastases of other primaries and liver own tumors [33, 34]. These procedures are known to be less invasive and show less morbidity and reach a similar oncological outcome in small metastases as the unexpected and preoperative not diagnosed pancreatic ones usually are.

There are some limitations of this study: It is a single center and a retrospective analysis. Although it is one of the largest single center studies that are reported, it is nevertheless a relatively small group of patients and therefore, the statistical power of this study is limited. Another point is that the current study does not assess other interesting endpoints such as quality of life after extended resection versus palliative bypass or, in case of no intestinal obstruction, just explorative laparotomy.

But, the results of our study demonstrate that both in case of locally- advanced pancreatic adenocarcinoma and in case of the intraoperatively incidental finding of a solitary liver metastasis in an otherwise resectable primery, patients benefit from the extended resection or the non- contiguous resection of the liver metastasis. The extended resection offers a significantly longer median survival (4 months) than palliative treatment. There is no doubt that surgery is the only curative option available for ductal pancreatic adenocarcinoma, and – according to our results – even if the cancer is locally- advanced or if there is a solitary liver metastasis.

Conflict of Interest

The authors declare that there is no conflict of interests.

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