Original Article

Late recurrences of pancreatic cancer in patients with long-term survival after pancreaticoduodenectomy

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Background: Pancreatic cancer remains a relevant clinical problem due to poor prognosis. Even after curative pancreaticoduodenectomy tumor recurrences occur in up to 80%. Risk factors for postoperative tumor recurrences have been identified before, but data on risk factors for tumor recurrences in patients with long-term-survival is scarce.

Methods: In this retrospective study consecutive long-term survival-patients (defined as at least 60 months survival) undergoing pancreaticoduodenectomy for pancreatic cancer from 2007–2014 were identified in the 2nd largest pancreatic surgery center in Germany. Clinical, pathohistological and laboratory values were analyzed to identify risk factors for tumor recurrence.

Results: Thirty-four of one-hundred-sixty-seven patients were identified as long-term-survival-patients in the study period. Of those, 10 patients (29.4%) suffered from tumor recurrence. Lymph vessel invasion was identified as an independent risk factor (P=0.031, hazard ratio 13.127, 95% confidence interval: 1.270–135.698). Median postoperative time to tumor recurrence in long-term-survival-patients was 49 months. Overall survival after diagnosis of tumor recurrence was 33 months. 80% (N=8) of the patients were asymptomatic. Half of the patients (N=5) suffered from local disease, with 40% undergoing curative tumor resection. CA 19-9 levels were significantly elevated at 57 U/mL (normal <27 U/mL).

Conclusions: Tumor recurrence in long-term-survival-patients is typically asymptomatic. Especially long-term-survival-patients with lymph vessel invasion are more likely to develop tumor recurrence. Therefore, a structured follow-up program including CT-scans and CA 19-9 surveillance must be continued in all patients undergoing pancreaticoduodenectomy even in cases of long-term-survival.

Keywords: Pancreatic cancer (PC); pancreatic ductal adenocarcinoma; pancreaticoduodenectomy; recurrence; long-term survival

Submitted Oct 09, 2020. Accepted for publication Jan 17, 2021.
doi: 10.21037/jgo-20-433
View this article at: http://dx.doi.org/10.21037/jgo-20-433

Introduction

Pancreatic cancer (PC) remains a devastating diagnosis for patients due to a poor prognosis. Unfortunately, PC is often diagnosed too late due to late development of symptoms. Surgical resection—the most important treatment modality for cure—is in general feasible in only less than 20% of patients at time of diagnosis (1-4). Despite technical, surgical, and oncological advances, pancreatic cancer is still ranked as the 4th leading cancer related death and will soon be ranked 2nd (5). Tumor related characteristics such as a large tumor, a high tumor grade, lymph-node metastases, a high level of carbohydrate antigen 19-9 (CA 19-9) and a cancer cell positive resection margin have been identified as negative prognostic factors for the overall postoperative survival (4).

International consensus guidelines recommend adjuvant chemotherapy following curative resection in most cases (6-8). Recent developments in oncologic treatment have shown significant improvement in overall postoperative survival of 28–54 months (9,10). Postoperative long-term survival (LTS) in PC is typically defined as a minimum survival of 60 months and is achieved in approximately 20% of patients after curative treatment (6,11-13).

Thus, up to 80% of all patients with PC suffer from tumor recurrence (TR) after resection with fatal outcome (14-16). They often present as local recurrences, or liver-, peritoneal-, or lung metastases with or without local recurrence (4,17,18).

Despite an increasing amount of reports about improved overall survival following pancreaticoduodenectomy (PD), there is lacking information in literature about risk factors for TR in patients with LTS.

In this study we investigated the overall incidence and risk factors for tumor recurrence in PC-patients with LTS following PD. We present the following article in accordance with the STROBE reporting checklist (available at: http://dx.doi.org/10.21037/jgo-20-433).

Methods

In this study, we retrospectively investigated data of all patients undergoing PD due to pancreatic ductal adenocarcinoma of the pancreatic head from January 2007 to December 2014 from the second largest pancreatic surgery center in Germany (St. Josef Hospital, Ruhr-University Bochum). Patients diagnosed with other pancreatic cancer types like intraductal papillary mucinous neoplasia (IPMN)—associated carcinomas or acinar cell carcinomas were excluded. LTS was defined as a postoperative survival of at least 5 years (60 months). Primary endpoint was tumor recurrence of LTS patients. Secondary endpoint was overall survival of LTS-patients with TR. These patient data were compared to those of LTS-patients without TR (control group).

Follow-up to evaluate LTS in all patients was performed until August 2020. Patient data was gathered from our prospective database.

Discharge letters and all relevant documents were obtained from other institutions or from the patients' general practitioner if the treatment and follow-up was continued elsewhere. Last, all patients or their relatives underwent a phone-interview to evaluate the overall duration of postoperative survival.

Surgical approach

The standard surgical approach in resectable pancreatic head cancer is a pylorus-preserving pancreaticoduodenectomy. Further, the standard type of pancreatic anastomosis is a double-layered end-to-side duct-to-mucosa pancreaticojejunostomy as described by Warren and Catell (19).

Statistical analysis

Data were expressed as percentages and the median with interquartile range. Comparison of LTS-patients with TR to those without TR was performed using a two-tailed chi-square test, a Fisher's exact test, or a Mann-Whitney U test, as appropriate. A binary logistic regression model was applied for multivariate analysis to identify risk factors for TR in LTS-patients. All variables being significant in univariate analysis were entered in the multivariate analysis. Statistical significance was present in the case of P values <0.05. Statistical analysis was performed with SPSS 21.0 (IBM Corp., Armonk, NY, USA).

Ethical statement

This study has been approved by the institutional review board of the Ruhr-University of Bochum (NO: 19-6771-BR). Because of the retrospective nature of the study, the requirement for informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Table 1 Epidemiologic data of all long-term survival patients and all patients with or without tumor recurrences

	All patients	Recurrence	No recurrence	P value
Total	34 (100%)	10 (29.4%)	24 (71.6)	–
Survival of all LTS patients (months, median, IQR)	102 (80–142)	79 (65–92)	–	–
Time of recurrence (months)	–	49 (30–68)	–	–
Time of late recurrence (months)	–	68 (56–68)	–	–
Survival after detection of rec. (months)	–	33 (15–43)	–	–
Age at time of primary surgery, median (%)				
≤65	18 (53%)	–	–	–
>65	16 (47%)	–	–	–
Sex				
Men	12 (35.3%)	3 (30%)	9 (37.5%)	0.681
Women	22 (64.7%)	7 (70%)	15 (62.5%)	
ASA score				
I	5 (14.7%)	2 (20%)	3 (12.5%)	0.376
II	15 (44.1%)	5 (50%)	10 (41.7%)	
III	14 (41.2%)	3 (30%)	11 (45.8%)	
IV				
Additional potential risk factors				
Diabetes mellitus	12 (35.3%)	3 (30%)	9 (38%)	0.681
Cardiovascular diseases	16 (47.1%)	2 (20%)	14 (58%)	0.044
Nicotine consumption	9 (26.5%)	3 (30%)	6 (25%)	0.767
Alcohol consumption	2 (5.88%)	1 (10%)	1 (4.2%)	0.516
Exocrine pancreatic insufficiency	12 (35.3%)	3 (30%)	9 (38%)	0.681
Body mass index, median (IQR)	25.0 (23.0–29.0)	21 (19–21)		
Preoperative stenting of the CBD	25 (73.5%)	7 (70%)	18 (75%)	0.767
Preoperative laboratory values				
Initial CA 19-9 U/mL, median (IQR)	73.0 (20.0-163)	88.5 (20–182)	73 (19–173)	0.880
CA 19-9 at time of recurrence	–	57 (17–176)	–	–

LTS, long-term survival; IQR, interquartile range; ASA, American Society of Anesthesiologists; CBD, common bile duct; CA 19-9, carbohydrate antigen 19-9.

Results

Thirty-four out of 167 patients were identified as LTS-patients following PD (20.4%) in the study period. Of those 10 patients (29.4%) suffered from TR (*Table 1*). Median time to TR was 49 months (IQR: 30–68, *Figure 1*), whereas median time to late-recurrence, i.e., TR after postoperative month 60, was 68 months. Overall survival after detection of recurrent disease was 33 months [15–43]. Male to female ratio was 0.43 (P=0.681). No significant differences in LTS-patients with or without TR in terms of comorbidities were observed (P=0.376) except for cardiovascular diseases, being more common patients without TR (P=0.044). CA 19-9 levels were significantly elevated at time of TR (median level: 57 U/mL, normal <27 U/mL).

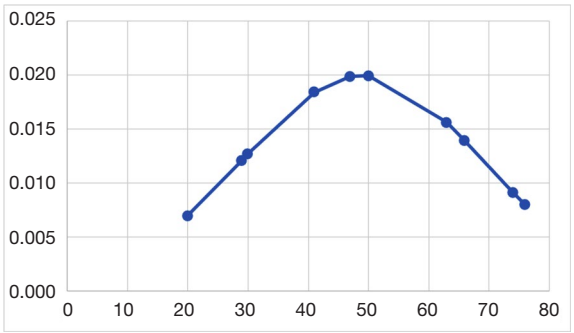

Figure 1 Graph demonstrating the normal distribution of tumor recurrences of patients who underwent pancreaticoduodenectomy due to pancreatic cancer. Y-axis: normal distribution function. X-axis: postoperative months following pancreaticoduodenectomy.

Location of tumor recurrence and treatment

Tumor recurrence in LTS-patients was mainly diagnosed in routine follow-up studies without symptoms (80%, N=8). Only 2 patients (20%) presented with symptoms due to small bowel obstruction or TR at the pancreaticojejunostomy.

Half of the patients suffered from local TR (50%, *Table 2*). The other half suffered from liver- (N=4), lung- (N=2) or peritoneal (N=2) metastases. Surgical treatment was performed in 60%. Forty percent underwent curative surgery in terms of a completion pancreatectomy (20%), a Re-Do-pancreaticoduodenectomy (10%) or a liver segment resection (10%). Palliative surgery was performed twice (20%) due to small bowel obstruction.

Chemotherapy was either adjuvant (40%) and gemcitabine- or fluorouracil—based or palliative (40%) and FOLFIRINOX-[folinic acid ([leucovorin], fluorouracil, irinotecan, and oxaliplatin) or gemcitabine—based. Twenty percent received no chemotherapy.

Table 2 Location of tumor recurrence and treatment

	TR patients [%]
Location of tumor recurrence	
Local tumor recurrence	5 [50]
Local recurrence + anywhere	3 [30]
Metastases, no local recurrence	5 [50]
Liver	4 [40]
Peritoneum	2 [20]
Lung	4 [40]
Surgical treatment	6 [60]
Curative intention	4 [40]
Completion pancreatectomy	2 [20]
Atypical liver resection	1 [10]
Re-Do pancreaticoduodenectomy	1 [10]
Palliative surgery	2 [20]
Chemotherapy	
Adjuvant	4 [40]
Gemcitabine	1 [10]
Gemcitabine + oxaliplatin	1 [10]
5 Fluorouracil	1 [10]
5 Fluorouracil, oxaliplatin	1 [10]
Palliative	4 [40]
FOLFIRINOX	2 [20]
Gemcitabine	1 [10]
Gemcitabine + orlitinib	1 [10]
No chemotherapy	2 [20]

TR, tumor recurrence.

Histopathological features

Patients with lymph vessel invasion suffered significantly more often from TR compared to other patients (P=0.019, *Table 3*). Furthermore, those patients had higher rates of venous and perineural invasion. However, statistically significant differences were not present. All patients with TR were classified T3 compared to 83.3% in the control group (P=0.176), in which 4 patients were classified T1 or T2. R0 resection was achieved in 80% (N=8), whereas 20% (N=2) were classified R1. No differences in terms of AJCC-stage (American Joint Committee on Cancer), resection margin or grading were observed.

Tumor re-recurrence

Two out of ten patients (20%) with TR suffered from re-recurrence following curative surgery (*Table 4*). Median interval between surgery and re-recurrence was 33 months. Overall median survival was 83.5 months (*Figure 2*). One patient underwent palliative chemotherapy with oxaliplatin and fluorouracil. The other one received best supportive care only. Median CA 19-9 was 285 U/mL.

Table 3 Histopathological features

	All patients	Recurrence	No recurrence	P value
Number of patients	34	10		
T				0.176
1	1 (2.9%)	–	1 (4.2%)	
2	3 (8.8%)	–	3 (12.5%)	
3	30 (88.2%)	10 (100%)	20 (83.3%)	
4	0	–	–	
Lymph node invasion				0.827
N0	18 (52.9%)	5 (50%)	13 (54.2%)	
N1	16 (47.1%)	5 (50%)	11 (45.8%)	
Lymph node ratio				0.803
0	18 (52.9%)	5 (50%)	14 (58.3%)	
≤0.2	10 (29.4%)	5 (50%)	5 (20.8%)	
≤0.5	6 (17.6%)	–	5 (20.8%)	
>0,5	0	–	–	
Metastases				0.519
M0	33 (97.1%)	10 (100%)	23 (95.8%)	
M1	1 (2.9%)	-	1 (4.2%)	
Lymph vessel invasion				0.019
L0	14 (41.2%)	1 (10%)	13 (54.2%)	
L1	20 (58.8%)	9 (90%)	11 (45.8%)	
Venous invasion				0.138
V0	17 (50.0%)	3 (30%)	14 (58.3%)	
V1	17 (50.0%)	7 (70%)	10 (41.7%)	
Perineural invasion				0.114
pN0	10 (29.4%)	1 (10%)	9 (37.5%)	
pN1	24 (70.6%)	9 (90%)	15 (62.5%)	
AJCC				0.678
Ia	1 (2.9%)	–	1 (4.2%)	
Ib	2 (5.9%)	–	2 (8.3%)	
IIa	15 (44.1%)	5 (50%)	10 (41.7%)	
IIb	15 (44.1%)	5 (50%)	10 (41.7%)	
III	0	–	–	
IV	1 (2.9%)	–	1 (4.2%)	
Resection margin				0.417
R0	30 (88.2%)	8 (80%)	22 (91.7%)	
R1	2 (5.9%)	2 (20%)	–	
R2	2 (5.9%)	–	2 (8.3%)	
Tumor grade				0.499
G1	3 (8.82%)	0	3 (12.5%)	
G2	30 (88.2%)	10 (100%)	20 (83.3%)	
G3	1 (2.9%)	0	1 (4.2%)	
G4	0	0		

AJCC, American Joint Committee on Cancer.

Table 4 Data of patients with tumor re-recurrences

	TRR
Re-recurrences, N	2
Postoperative time of TR from after primary surgery	49 (30–68)
Time of TRR after TR	33 (15–33)
Survival, (months)	83.5 (79–83.5)
Surgery	0 (0%)
CTx (N=1)	Oxaliplatin + 5 Fluorouracil
CA 19-9	546 (42–546)
CA 19-9 with TRR	285 (28–285)

TR, tumor recurrence; TRR, tumor re-recurrence; CTx, chemotherapy; CA, carbohydrate antigen.

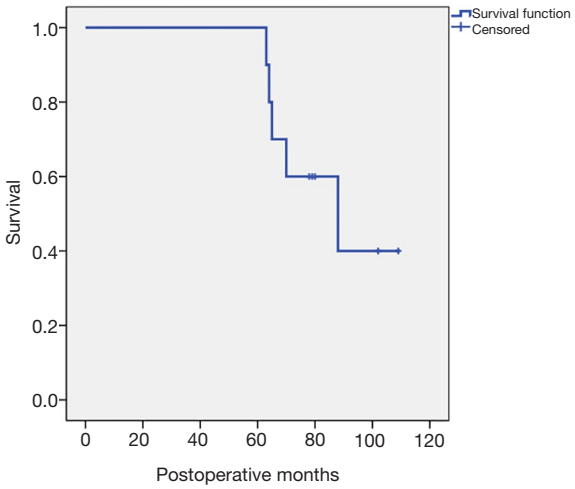

Figure 2 Kaplan-Meier curve demonstrating overall survival of long-term survival patients with tumor recurrence.

Table 5 Binary logistic regression analysis for multivariate analysis

	Hazard ratio	95% confidence interval	P value
Lymph vessel invasion	13.127	1.270–135.698	0.031
Cardiovascular diseases	0.141	0.021–0.963	0.046

Multivariate analysis

Binary logistic regression analysis was performed for multivariate analysis (*Table 5*). Lymph vessel invasion and cardiovascular diseases were significant in univariate analysis and thus entered in the multivariate model. Lymph vessel invasion was identified as an independent risk factor for TR in patients with LTS (P=0.031, hazard ratio 13.127, 95% confidence interval: 1.270–135.698). Cardiovascular diseases were also identified as influencing factors (P=0.046, hazard ratio 0.141, 95% confidence interval: 0.021–0.963).

Discussion

This study demonstrates that PC remains a serious disease which patients and physicians should always stay aware of even in cases of LTS.

Unfortunately, up to 80% of the patients with PC suffer from TR which often leads to patient demise within 2 years of curative resection (15,16,18,20,21). Our data demonstrate that even LTS patients are not spared from TR which occurs in approximately 30%. Undetected micrometastases are typically too small for detection with radiographic imaging and can evolve undetected over time (22). Therefore, even pathologic complete response following neoadjuvant treatment in patients with PD can unfortunately be followed by TR (1,23-25). Thus, pancreatic cancer must be considered a systemic disease even at a stage of local resectability (18). According to international guideline recommendations the combination of curative resection and additional chemotherapy treatment is crucial (4,18). Median disease-free survival is 12–13 months and can nowadays be increased up to 21.6 months with modified FOLFIRINOX treatment (10,18).

Most LTS-patients (80%) tend to be asymptomatic at the time of TR compared to non-LTS patients. The latter group tends to suffer in 76% from symptoms compared to 20% in LTS-patients (15). This can be explained by the more aggressive growth pattern of PC in non-LTS patients with an increased amount of lymph node-, venous- or perineural invasion as well as higher tumor gradings (4). Treatment rates in case of recurrent cancer are unequally reported in literature. Daamen *et al.* report a 35% treatment rate compared to a best supportive care rate of 65%: main causes were the patient's wish (40%) and poor overall performance status (30%) (15). However, another study by Gbolahan *et al.* investigating data of 435 patients showed a 63% chemotherapy rate and a 32% best supportive care rate (26).

Relevant risk factors for local TR are a negative resection

margin as well as existence and extension of lymphogenous metastasis (20,22,27,28). Further relevant factors affecting the overall survival were perioperative treatment by chemotherapy or radiotherapy (26).

In our study, we identified lymph vessel invasion as an independent risk factor for TR in patients with LTS. Presence of cardiovascular diseases was associated with longer survival. However, we believe this effect occurred only by chance due to the low case number as there is no indication in literature for this effect.

Isolated TR allowing surgical resection was present in 40% in our cohort and higher than in literature (20–30%) (18,22). Resection of local TR is technically demanding due to adhesions, local tumor mass and modified anatomical surrounding. In those cases, surgery should be performed in high-volume pancreatic surgery centers which then is associated with a lower grade of morbidity (18–29%). Treatment options comprise completion pancreatectomy, Re-Do-pancreaticoduodenectomy or liver segment resection and can finally lead to a significant improvement of overall survival compared to single chemotherapy or radiotherapy (26 *vs.* 14 months) (21,29,30). Isolated resection of pancreatic TR leads to median overall survival of 16–32 months (21,30-32). Importantly, according to international guidelines, resection of recurrent disease is not considered a standard-approach. Other local treatment options being discussed in literature are radiotherapy and irreversible electroporation in selected patients (20,33).

Commonly, surgical resection cannot be performed in patients with TR, because half of the patients already suffer from multilocular disease or distant metastases, which are present in up to 62% (15,28). As a meta-analysis by Tanaka *et al.* investigating data of 17,313 patients demonstrated, liver metastases occur in 26.5%, lung metastases in 11.4% and peritoneal metastases in 13.5% following curative resection (22). Typically, liver and lung metastases are associated with a shorter recurrence free survival as well as a shorter overall survival. Daamen *et al.* described in a large nationwide Dutch study with 836 patients a significant increase of overall survival in patients with tumor recurrence who received additional treatment underlining the results of Tzeng, Tjaden and Nordby (15,34-36). Furthermore, those studies demonstrated an increase of life quality compared to patients receiving best supportive care only. Typical chemotherapy regimens are FOLFIRINOX (68%) followed by gemcitabine ± nab-paclitaxel (15).

Our data present significant higher post-recurrence survival rates compared to current survival data in the literature. Median survival period after detection of TR was 33 months compared to a median of 7 months reported in the literature due to delayed diagnosis of TR (26). In cases of a low overall performance status, patients receive best supportive care only. Median survival has been reported to be 3 months, comparable to patients being primary diagnosed with an advanced pancreatic cancer with either brain or umbilical metastases (37,38). These data underline the aggressive growth pattern and common multifocal recurrences of PC.

One important requirement for additional treatment is a good ECOG performance status (39). Therefore, a timely detection of tumor recurrence is crucial for patient survival. As our results demonstrate, most tumor recurrences in LTS patients are asymptomatic (80%). Only 20% of the patients were complaining of abdominal pain. Currently, the German guideline on pancreatic cancer does not recommend regular postoperative follow up investigations (7). However, patients with structured follow up survive 25 months compared to 15 months in patients who received symptomatic follow up only (15). Additionally, to the study group of Daamen, an increasing number of clinicians suggest a structured postoperative surveillance (22,34,35). Focusing on clinical symptoms without routine imaging commonly leads to diagnosis of TR at an advanced stage with a decreased chance for successful secondary treatment (40). A cost-effectiveness study by Tzeng *et al.* demonstrated that a surveillance every 6 months is the most cost-effective strategy (41).

As most TR in our LTS-cohort occurred relatively late at the 49th postoperative month, we strongly recommend a continuous follow-up program for all patients undergoing curative resection for PC to detect TR in time for surgical and/or chemotherapeutical treatment. Late recurrences appearing after 5 years of uneventful courses exist as well as re-recurrences following curative tumor resection of a recurrent tumor. This emphasizes the hazardous nature of pancreatic cancer. Most importantly, even in patients with LTS, the surveillance should be continued after the fifth year. One important problem in radiographic findings—especially in asymptomatic patients—is that TR cannot always be differentiated from unspecific postoperative tissue alterations. Our structured follow-up program consists of abdominal CT-scans every 6 months, abdominal ultrasounds every 3 months and testing of CA 19-9 levels every 3 months for the first five postoperative years. As Azizian *et al.* demonstrated, our data confirm that CA 19-9 is the most important laboratory value indicating

TR and must be monitored regularly (42). If no tumor recurs within five years, the radiographic control interval can be prolonged to every 12 months but should never be discontinued. The CA 19-9 surveillance should be continued every 6 months.

This study is limited by the small cohort of LTS-patients with TR, because LTS by itself is relatively rare. Furthermore, no standardized adjuvant treatment was given.

Future studies should enroll a larger number of patients to identify further risk factors for tumor recurrence. Furthermore, analysis of the impact and best chemotherapy regimen in patients with TR is required. Decrease of tumor load as well as the lowest level of medical side-effects are the main goals.

In conclusion, our data shows that tumor recurrence in LTS-patients is common (especially in patients with lymph vessel invasion) and typically asymptomatic. Therefore, we suggest a structured follow up of CA 19-9, abdominal ultrasound, and CT-scans even after the fifth postoperative year.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at: http://dx.doi.org/10.21037/jgo-20-433

Data Sharing Statement: Available at: http://dx.doi.org/10.21037/jgo-20-433

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at: http://dx.doi.org/10.21037/jgo-20-433). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study has been approved by the institutional review board of the Ruhr-University of Bochum (No: 19-6771-BR). Because of the retrospective nature of the study, the requirement for informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Luu AM, Belyaev O, Höhn P, Praktiknjo M, Janot M, Uhl W, Braumann C. Late recurrences of pancreatic cancer in patients with long-term survival after pancreaticoduodenectomy. J Gastrointest Oncol 2021;12(2):474-483. doi: 10.21037/jgo-20-433

