Timing But Not Patterns of Recurrence Is Different Between Node-negative and Node-positive Resected Pancreatic Cancer

HHS Public Access

Author manuscript

Ann Surg. Author manuscript; available in PMC 2020 July 18.

Timing but not patterns of recurrence are different between node-negative and node-positive resected pancreatic cancer

Kim C. Honselmann, MD[1,3], **Ilaria Pergolini, MD**[1], **Carlos Fernandez-del Castillo, MD**[1], **Vikram Despande, MD**[1], **David Ting, MD**[2], **Martin S Taylor, MD, PhD**[1], **Louisa Bolm, MD**[3], **Motaz Qadan, MD**[1], **Ulrich Wellner, MD**[3], **Marta Sandini, MD**[1], **Dirk Bausch, MD**[3], **Andrew L. Warshaw, MD**[1], **Keith D. Lillemoe, MD**[1], **Tobias Keck, MD**[3], and **Cristina Ferrone, MD**[1]

[1]Department of Gastrointestinal Surgery & Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, USA

[2]MGH Cancer Center, Massachusetts General Hospital and Harvard Medical School, Boston, USA

[3]Department of Surgery, University Medical Center Schleswig-Holstein, Campus Luebeck, Luebeck, Germany

Abstract

Objective: Our aim was to evaluate recurrence patterns of surgically resected PDAC patients with negative (pN0) or positive (pN1) lymph nodes.

Summary Background Data: Pancreatic ductal adenocarcinoma (PDAC) is predicted to become the second leading cause of cancer death by 2030. This is mostly due to early local and distant metastasis, even after surgical resection. Knowledge about patterns of recurrence in different patient populations could offer new therapeutic avenues.

Methods: Clinicopathologic data were collected for 546 patients who underwent resection of their PDAC between 2005 and 2016 from two tertiary university centers. Patients were divided into an upfront resection group (n=394) and a neoadjuvant group (n=152).

Results: Tumor recurrence was significantly less common in pN0 patients as compared to pN1 patients, (upfront surgery: 55% vs. 77%, p<0.001 and 64% vs. 78%, p=0.040 in the neoadjuvant group). In addition, time to recurrence was significantly longer in pN0 versus pN1 patients in the upfront resected patients (median 16 mo pN0 vs. 10 mo pN1 p<0.001), and the neoadjuvant group (pN0 21 mo vs. 11 mo pN1, p<0.001). Of the patients who recurred, 62 % presented with distant metastases (63% of pN0 and 62% of pN1, p=0.553), 24 % with local disease (27% of pN0 and 23% of pN1, p=0.672) and 14% with synchronous local and distant disease (10% of pN0 and 15% of pN1, p=0.292). Similarly, there was no difference in recurrence patterns between pN0 and pN1 in the neoadjuvant group, in which 68% recurred with distant metastases (76% of pN0 and 64% of pN1, p=0.326) and 18% recurred with local disease (pN0: 22% and pN1: 15%, p=0.435).

Correspondence: Cristina R. Ferrone, Associate Professor of Surgery, Department of Surgery, Massachusetts General Hospital/ Harvard Medical School, 55 Fruit Street, Boston, MA 02114, Cferrone@partners.org.
(Keck and Ferrone shared last author)

Conclusion: Time to recurrence was significantly longer for pN0 patients. However, patterns of recurrence for pN0 vs. pN1 patients were identical. Lymph node status was predictive of time to recurrence, but not location of recurrence.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is currently the fourth most common cause of cancer death and is predicted to become the second leading cause of cancer death by 2030[1]. Although only surgical resection offers a potential cure, just 10–15% of patients are surgical candidates at presentation. Of resected patients, 19–22% of patients survive 5 years[2, 3] due to local or distant recurrence. While many patients recur at distant sites, 12% to 40% of patients demonstrate a destructive local recurrence pattern[4–6].

To date, various prognostic factors for recurrence and overall survival have been identified including lymph node/ lympho-vascular- and perineural involvement, tumor grade, portal vein and mesenteric artery involvement, positive resection margins, and genomic characteristics. Similar to other cancers, lymph node metastasis is a strong indicator of more advanced disease[7–10]. Several studies have demonstrated that cancers with lymph node-positive disease are more likely to recur[8]. However, patterns of recurrence in lymph node positive versus lymph node-negative patients have not been studied.

Neoadjuvant therapy in locally advanced and borderline resectable PDAC has shown both prolonged survival and a significant decrease in the rate of lymph node-positivity on resected specimens compared to the rate in the absence of neoadjuvant therapy[11,12,13]. However, the effect on the recurrence pattern (local versus distant) has also not been studied.

The aim of this study was to explore the timing and nature of recurrence of node-negative compared with node-positive PDAC. The study was stratified for patients who underwent upfront resection versus those who received neoadjuvant treatment followed by resection. We hypothesized that patients with lymph node-negative disease would recur locally first, while lymph node-positive patients would recur distantly first, suggesting that lymph node negative patients may benefit from more aggressive local therapy including adjuvant radiation.

Methods

Consecutive patients undergoing surgical resection of their pancreatic ductal adenocarcinoma (PDAC) between January 1, 2005 and December 31, 2016 in the Department of Gastrointestinal Surgery at the Massachusetts General Hospital and between January 1, 2013 and December 31, 2016 in the Department of Surgery of the University Medical Center Schleswig-Holstein, Campus Luebeck, Germany were included. Patients with either a minimum of 6 months follow-up or evidence of recurrence were included in the study. Patients who died of peri-operative complications within 90 days were excluded. The study was approved by the institutional IRBs.

Data were collected from prospectively maintained databases at the respective institutions. Clinicopathologic variables collected included age at operation, gender, preoperative

chemotherapy, CA19–9 levels, tumor size, nodal status, number of resected and positive lymph nodes, tumor grade, lymphovascular and perineural invasion (according to the 7th and 8th edition of the AJCC), R-status according to the "1mm rule" by the British Royal college of Pathologists[14], and type of operation (pancreatoduodenectomy, distal or total pancreatectomy). Standard lymphadenectomy was performed in both institutions. Postoperative outcomes and treatments including hospital length of stay (days), postoperative chemotherapy and radiation therapy, date of first recurrence, site of first recurrence, and overall survival.

Patients were staged according to the AHPBA/SSO/SSAT consensus guidelines[15]. Resectable patients were included in the upfront resection group. They did not receive preoperative chemotherapy or radiation. Patients in the neoadjuvant therapy group were only treated at MGH and included resectable, borderline resectable, and locally advanced patients. Short-course proton radiation (5Gy × 5 days) with Capecitabine ± Hydroxychloroquine was administered neoadjuvantly to resectable patients (These patients were all part of phase I and II clinical trials published elsewhere[16,17]).

Borderline resectable and locally advanced patients received eight cycles of FOLFIRINOX or Gemcitabine plus 50.4 Gy radiation and 5-FU.

Locoregional recurrence was defined by radiographic or pathological evidence of recurrent disease in the remnant pancreas, pancreatic bed, retroperitoneum, along the SMA/SMV, porta hepatis, or celiac axis. Distant recurrence was tumor spread outside of the loco-regional area (extra-regional lymph nodes, peritoneum, lungs, and liver). We separately listed "hematogenous metastasis" (liver and lung) from "Other" (extraregional lymph nodes and peritoneum and other rare distant locations such as small intestine). Disease-free survival (DFS) and overall survival (OS) were calculated from the date of operation to the date of recurrence or death, respectively (event), or to the date of last follow-up (censored). Date of death was obtained from the medical records or from the Social Security Death Index.

Patients with pancreatic cancer arising in an IPMN, mucinous adenocarcinoma, adenosquamous carcinoma, chronic pancreatitis, acinar cell carcinoma and acinar cystadenocarcinoma were excluded due to differing tumor biology.

Disease-free survival and overall survival (DFS and OS) were calculated as the median of actual survival from the time of diagnosis. Differences in survival were tested by the log-rank test. Multivariate analyses for local and distant recurrence were calculated with a logistic regression model using the forward conditional approach. Criteria for inclusion were significance on univariate analysis and clinical relevance (age, sex). Propensity score matching was performed with the R-add-on for SPSS Version 21 for all patients without neoadjuvant chemo-radiation. Pathologic node-positive (pN1) and pathologic node-negative (pN0) patients were matched for age, gender, tumor size and T-stage. P values less than 0.05 were considered statistically significant. All tests used were two-tailed. Statistical analysis was performed with the IBM SPSS Statistics software for Mac, Version 21.0 (IBM Corp., Armonk, NY).

Results

Demographics and Clinical Data

Of the 715 patients who underwent surgical resection of their PDAC at the two academic centers within the study period, 546 patients met the inclusion criteria (Figure 1). Upfront resection was performed in 394 patients and 152 patients underwent neoadjuvant therapy followed by resection. Median follow-up of the entire cohort was 18 (10–34) months. For the upfront resected group follow up was 18 months (10–34) and 21 months (9–35) for the neoadjuvant group. Separate analyses of these two cohorts, as well as a propensity score matching, were performed (n=188).

Upfront resection group

For the upfront resection group, in both the pN0 (n=109, 28%) and pN1 (n=285, 72%) cohorts, 47 % were female and the median age was 68 years with 21% of patients older than 75 years (Table 1). Median preoperative CA19–9 levels were significantly lower in lymph node-negative patients (pN0 65 vs. pN1 140 U/ml, p=0.045).

Surgical and Pathological outcomes

The most common operation was pancreaticoduodenectomy (75%) (Table 1). Patients undergoing distal pancreatectomy were more likely to have node-negative disease. No patient in this group had combined arterial and venous resection. Median length of operation and hospital stay (330 minutes and 8 days) did not differ between the lymph node cohorts. Ninety-day postoperative mortality was 1.7%.

In the upfront resection group, 109 patients were pN0 and 285 were pN1 (Table 1). The majority (63%) of tumors were grade 2 (moderately differentiated), but pN0 patients displayed lower tumor grading than pN1 patients. Patients with pN1 disease had slightly larger cancers (median 32 mm vs. 29 mm, p=0.012) and were more likely to have a positive resection margin than patients with pN0 disease (59% vs. 31%, p< 0.001). Perineural invasion and lympho-vascular invasion were also more frequent in pN1 cancers (pN1 93% vs. pN0 73%, p<0.001 and pN1 73% vs. pN0 37%, respectively p<0.001). In both cohorts, the majority of patients received adjuvant treatment (pN0 72% and pN1 75%, p=0.328). Chemotherapy alone and chemoradiation were the most common type of adjuvant therapy (48% and 51%), whereas radiation alone was only given to two patients (1%) total (Table 1).

Survival

Median OS for all patients was 18 months (10–34). Median OS for the pN0 patients was significantly longer (median 25 months, range 11–45) than the pN1 patients (median 16 months, range 10–29) (p<0.001). Figure 2 illustrates the significant difference in overall survival.

Recurrence

Overall median DFS was 11 months (6–23). Patients with pN0 disease had a significantly longer DFS of 16 months (7–36), as compared to 10 months (5–20) in patients with pN1 disease (p<0.0001). Tumor recurrence was significantly less common in pN0 patients as

compared to pN1 patients, (55% vs. 77%, p<0.001). On multivariate analysis, both lymph-node ratio and lymph-node status were significantly associated with recurrence (OR: 1.415–16.398, p=0.012 and OR: 1.349–4.496, p= 0.003).

Patterns of recurrence between pN0 and pN1 patients were similar. Locoregional recurrence occurred in 27% of pN0 and 23% of pN1 patients (p=0.672). Distant recurrence occurred in 63% of pN0 and 62% of pN1 patients (p=0.553) (Figure 2 and Table 2). This was also true for the new lymph node staging system (8th AJCC), where local recurrence occurred in 25% of pN0 patients, in 21% in pN1 and in 26% in pN2, p=0.594. Distant recurrence was found in 58% of pN0, 60% of pN1 and 64% of pN2, p=0.795. Specific sites of distant recurrence were also similar, with 49% of distant metastases to the liver and 22% to the lung in pN0 patients, whereas pN1 patients metastasized in 36% to the liver and in 25% to the lung. Multivariate logistic regression analysis revealed R1 resection as the only independent risk factor for local recurrence (OR: 1.040–3.307, p=0.033). An R1 resection was independently associated with a decreased prevalence of distant recurrence (OR: 0.311–0.963, p=0.037) (Table 2). Importantly, lymph node status and lymph node ratio were not independently associated with local versus distant recurrence (Table 2).

Propensity-Score Matching

Due to the differences between pN0 and pN1 patients, propensity-score matching was performed (see methods) (Table 3). Clinical characteristics such as age, diabetes, CCI and pathologic factors such as tumor size and tumor grade did not differ between the groups in propensity-score matching. Despite similar clinicopathologic characteristics, patients with pN0 disease had a longer actual median disease-free survival than patients with pN1 disease (14 vs. 10 months, p=0.001). Patterns of recurrence, however, were still similar: 14–23% recurred locally and 60–72% recurred distantly (p=0.214 and p= 0.329) (Table 3 and Figure 2). In multivariate analysis, a preoperative CA-19–9 score more than 37 U/L was the only independent predictor for the occurrence of local or distant metastasis (OR 1.620–10.892, p=0.003).

Neoadjuvant Patient Group

There were 152 patients who received neoadjuvant treatment at the MGH from January 1st, 2009 until December 31st, 2014. The most common neoadjuvant regimen consisted of chemotherapy plus radiation (90%), twelve patients received chemotherapy alone (Table 4). Adjuvant therapy was less common than in the upfront resection group with 65% of neoadjuvant patients receiving any type of regimen. Here chemotherapy alone was the most frequent administered therapy (50%), 75 of the 137 (55%) patients who received neoadjuvant chemoradiation were administered adjuvant chemotherapy alone. This cohort was 55% female, but patients were significantly younger (median 64 years, p<0.001) and had lower pre-resection CA19–9 levels (median 51 U/ml) than those in the upfront resection group. Pathologically patients receiving neoadjuvant therapy had smaller cancers, a lower pN1 rate, and a lower rate of PNI and LVI, than the upfront resectable group. There was one patient who had a combined arterial and venous resection.

Interestingly these trends remained true when comparing patients with pN0 and pN1 disease in the neoadjuvantly treated cohort. Patients with pN0 cancers after receiving neoadjuvant therapy had smaller tumors (median 22 vs. 30 mm, $p<0.001$), less lympho-vascular invasion (24% vs. 65% $p<0.001$) and perineural invasion (73% vs. 95% $p<0.001$) (Table 4) than pN1 patients.

Actual median OS for this cohort from the time of diagnosis was 24 months (13–41). Median OS for the pN0 patients was significantly longer than for the pN1 patients (33 months (range 20–44) vs. 17 months (range 10–30), $p=0.003$). DFS was also significantly longer for pN0 patients than pN1 patients (21 months (range 11–38) vs. 11 months (range 5–20), respectively).

Similar to patients who did not receive neoadjuvant therapy patterns of recurrence were similar between pN0 and pN1 patients. Distant recurrence continued to be the most common first site of disease progression (pN0 76% and pN1 64% ($p=0.326$)). There was also no difference in specific site of distant recurrence with 38% to the liver and 24% to the lung in pN0 patients and 44% to the liver and 27% to the lung in pN1 patients, respectively. Local recurrence as first site of disease progression occurred in 22% of pN0 patients vs. 15% of pN1 patients ($p=0.435$). Interestingly, clinicopathological parameters were not different between patients who recurred and who did not, as was true for local versus distant metastasis in the neoadjuvant group, therefore no multivariate analysis was performed (Table 3).

Discussion

This is the first report to demonstrate recurrence patterns in resected pN0 versus pN1 PDAC patients who were treatment naive or received neoadjuvant therapy. Unadjusted and adjusted, patterns of recurrence between either upfront resection and those receiving neoadjuvant treatment were strikingly similar, irrespective of nodal involvement, with 60–76% presenting with distant metastasis and 14–27% with local recurrence (not statistically significant).

Even when pN0 and pN1 patients were matched for clinicopathologic factors, time to recurrence and overall survival continued to be significant between pN0 and pN1 patients, but patterns of recurrence were similar. The basis of this observation is not certain. One possibility is that tumor characteristics (smaller tumor size, lower CA19–9 levels, less perineural invasion and less lympho-vascular invasion) in the pN0 patients may reflect earlier detection. This could represent merely a shift to the right in the curves for recurrence and survival (Figure 2b). Our neoadjuvant data may support this hypothesis, in that those tumors were significantly down-staged (48% Stage IIa vs. 28% Stage IIa or I), but again the patterns of recurrence continued to be similar. While pN0 patients may have been resected earlier in the biology of the disease, the same proportion of patients presented with symptomatic disease in both the pN0 and pN1 groups. This may highlight that the clinical course does not always represent the true biology of the disease/

An alternate explanation is that patients with pN0 cancers have a different tumor biology than patients with pN1 cancers. Although pN0 tumors were only slightly smaller, they exhibited less aggressive properties such as perineural and lympho-vascular invasion, lower Ca19–9 levels as well as a longer time to metastasis. However, since patients with lung metastases tend to have a more indolent course one would expect that pN0 patients would more commonly present with lung metastases, which they did not.

The results of our upfront resection group is similar to the 692 PDAC patient cohort from Johns Hopkins Hospital who had not received neoadjuvant treatment[6]. Patients presented with distant metastases (58%) more often than isolated local (24%) recurrences as their first site of disease recurrence.

A Japanese study investigated the impact of a positive resection margin (1mm-rule) on recurrence in 117 PDAC patients. Similar to our data, resection margin and nodal status were independent risk factors for a shorter DFS[18]. The authors also reported a significant difference in distant recurrence rates for patients with a positive resection margin. However, the data was not adjusted for confounding variables, and percentages of recurrence were calculated differently.

While nodal disease did not seem to be a good surrogate marker for patterns of recurrence in our patient cohort, our data clearly demonstrates that distant recurrence is the most frequent site of recurrence irrespective of the patient's tumor stage. Even in patients with node negative disease more than half of the patients recur at a median of 16 months. This suggests that PDAC is a systemic disease, which needs to be controlled with effective chemotherapy, and that local modalities such as an operation or radiation therapy are not sufficient to control the disease. While positive resection margins were an independent risk factor for local recurrence in our upfront resected group, it failed to have any impact in our neoadjuvant group. However, the neoadjuvant group did receive upfront radiation therapy. Based on these results, as well as other published data, our group has moved to administering effective neoadjuvant chemotherapy, followed by radiation therapy for borderline resectable disease, followed by surgical resection of the PDAC.

Our study has several limitations. This is a retrospective study and recurrences were identified radiologically, without pathological verification. Since the patients were not phase III clinical trial patients, there was some provider variability regarding post operative imaging. Most patients were evaluated and had a CA19–9 level every 3 months, and underwent imaging every 6 months, A change in Ca19–9 value or symptoms, depending on the provider, did increase the frequency of imaging. The timing of post-operative imaging does affect the detection of recurrence. This should be taken into consideration, when evaluating the results.

Our study is the largest multi-institutional study to examine patterns of recurrence after potentially curative resection of PDAC in lymph node-positive and -negative patients. Although the time to recurrence and overall survival were significantly longer for pN0 as compared to pN1 cancers, there was no corresponding difference in site of first recurrence. The implications for clinical practice are two-fold. Irrespective of nodal involvement, an R1

resection was independently associated with an increased likelihood of local recurrence, suggesting a possible benefit of local tumor therapy in addition to systemic therapy. Second, both pN0 and pN1 patients are more likely to present with distant metastatic disease. These findings emphasize the need for potent systemic therapy in the peri-operative setting. Pancreatic adenocarcinoma continues to be best treated with multi modality therapy.

Acknowledgments

Parts of this manuscript were presented at the American Pancreatic Association 2016 and the German Pancreasclub meeting 2017. KCH was supported by the German Research Foundation (DFG: HO 5737/1–1)

Literature

1. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014; 74(11):2913–21. [PubMed: 24840647]
2. Ferrone CR, Brennan MF, Gonen M, et al. Pancreatic adenocarcinoma: the actual 5-year survivors. J Gastrointest Surg 2008; 12(4):701–6. [PubMed: 18027062]
3. Ferrone CR, Pieretti-Vanmarcke R, Bloom JP, et al. Pancreatic ductal adenocarcinoma: long-term survival does not equal cure. Surgery 2012; 152(3 Suppl 1):S43–9. [PubMed: 22763261]
4. Crane CH, Varadhachary GR, Yordy JS, et al. Phase II trial of cetuximab, gemcitabine, and oxaliplatin followed by chemoradiation with cetuximab for locally advanced (T4) pancreatic adenocarcinoma: correlation of Smad4(Dpc4) immunostaining with pattern of disease progression. J Clin Oncol 2011; 29(22):3037–43. [PubMed: 21709185]
5. Winter JM, Tang LH, Klimstra DS, et al. Failure patterns in resected pancreas adenocarcinoma: lack of predicted benefit to SMAD4 expression. Ann Surg 2013; 258(2):331–5. [PubMed: 23360922]
6. Groot VP, Rezaee N, Wu W, et al. Patterns, Timing, and Predictors of Recurrence Following Pancreatectomy for Pancreatic Ductal Adenocarcinoma. Ann Surg 2017.
7. Valsangkar NP, Bush DM, Michaelson JS, et al. N0/N1, PNL, or LNR? The effect of lymph node number on accurate survival prediction in pancreatic ductal adenocarcinoma. J Gastrointest Surg 2013; 17(2):257–66. [PubMed: 23229885]
8. Riediger H, Keck T, Wellner U, et al. The lymph node ratio is the strongest prognostic factor after resection of pancreatic cancer. J Gastrointest Surg 2009; 13(7):1337–44. [PubMed: 19418101]
9. Wellner UF, Krauss T, Csanadi A, et al. Mesopancreatic Stromal Clearance Defines Curative Resection of Pancreatic Head Cancer and Can Be Predicted Preoperatively by Radiologic Parameters: A Retrospective Study. Medicine (Baltimore) 2016; 95(3):e2529. [PubMed: 26817896]
10. Lapshyn H, Bronsert P, Bolm L, et al. Prognostic factors after pancreatoduodenectomy with en bloc portal venous resection for pancreatic cancer. Langenbecks Arch Surg 2016; 401(1):63–9. [PubMed: 26739620]
11. Itchins M, Arena J, Nahm CB, et al. Retrospective cohort analysis of neoadjuvant treatment and survival in resectable and borderline resectable pancreatic ductal adenocarcinoma in a high volume referral centre. Eur J Surg Oncol 2017; 43(9):1711–1717. [PubMed: 28688722]
12. Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg 2015; 261(1):12–7. [PubMed: 25599322]
13. Shrestha B, Sun Y, Faisal F, et al. Long-term survival benefit of upfront chemotherapy in patients with newly diagnosed borderline resectable pancreatic cancer. Cancer Med 2017; 6(7):1552–1562. [PubMed: 28639410]
14. Campbell F, Smith RA, Whelan P, et al. Classification of R1 resections for pancreatic cancer: the prognostic relevance of tumour involvement within 1 mm of a resection margin. Histopathology 2009; 55(3):277–83. [PubMed: 19723142]

15. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol 2009; 16(7):1727–33. [PubMed: 19396496]

16. Hong TS, Ryan DP, Blaszkowsky LS, et al. Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head. Int J Radiat Oncol Biol Phys 2011; 79(1):151–7. [PubMed: 20421151]

17. Hong TS, Ryan DP, Borger DR, et al. A phase 1/2 and biomarker study of preoperative short course chemoradiation with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma. Int J Radiat Oncol Biol Phys 2014; 89(4):830–8. [PubMed: 24867540]

18. Nitta T, Nakamura T, Mitsuhashi T, et al. The impact of margin status determined by the one-millimeter rule on tumor recurrence and survival following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. Surg Today 2017; 47(4):490–497. [PubMed: 27677294]

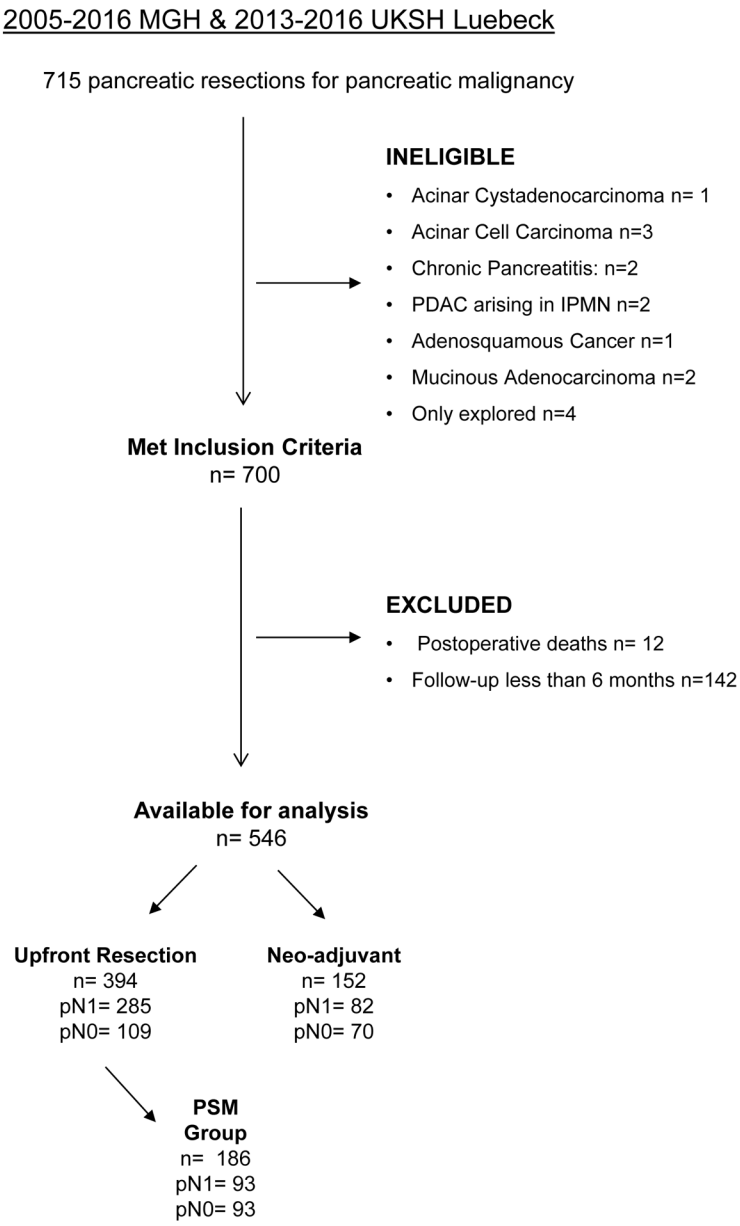

Figure 1:
Flowchart of study population

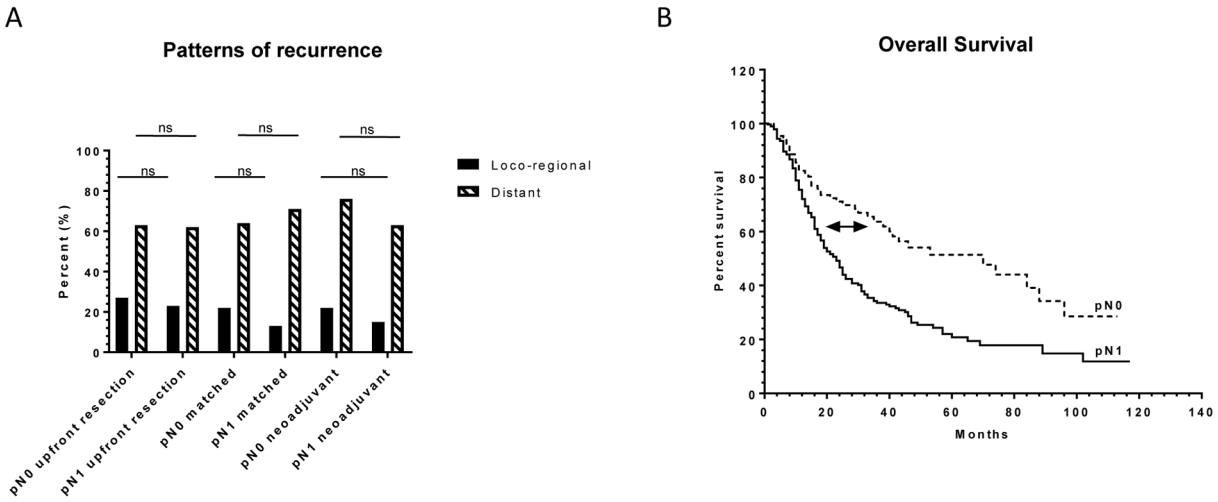

Figure 2:

A Patterns of recurrence of all study populations. Ns non significant (p>0.05) B Overall survival of upfront surgery group divided in pN1 and pN0

Table 1:

Baseline characteristics of the Upfront Surgery Group

	Total N= 394		pN0 N=109 (28%)		pN1 N=285 (72%)		*Univariate*
	Upfront Surgery Group						
	Median/N	**IQR/%**	**Median/N**	**IQR/%**	**Median/N**	**IQR/%**	**p**
Age in years	*68*	*(61–75)*	*70*	*(62–76)*	*68*	(60–75)	0.300
Gender							
Male	208	(53%)	59	(54%)	149	(52%)	0.742
Female	186	(47%)	50	(46%)	136	(48%)	
Preoperative CA 19–9	125	(27–456)	65	(19–363)	140	(39–588)	0.045
Type of Surgery							0.063
Whipple	294	(75%)	71	(65%)	223	(78%)	
Distal pancreatectomy	81	(21%)	32	(29%)	49	(17%)	
Total pancreatectomy	13	(3%)	4	(4%)	9	(3%)	
Other	4	(1%)	2	(2%)	2	(1%)	
OR duration, min	330	(253–410)	314	(242–404)	333	(263–411)	0.105
LOS, days	8	(6–13)	8	(6–13)	8	(6–13)	0.326
Complications	255	(65%)	67	(62%)	188	(66%)	0.403
Tumorgrade							0.302
G1	25	(6%)	7	(6%)	18	(6%)	
G2	249	(63%)	76	(70%)	173	(61%)	
G3	118	(30%)	26	(24%)	92	(32%)	
G4	2	(1%)	0	(0%)	2	(1%)	
T-stage							0.000
0	0	(0%)	0	(0%)	0	(0%)	
T1	10	(3%)	9	(8%)	1	(1%)	
T2	32	(8%)	20	(18%)	12	(4%)	
T3	338	(86%)	78	(72%)	260	(91%)	
T4	14	(4%)	2	(2%)	12	(4%)	
Tumor size (mm)	30	(24–40)	29	(20–40)	32	(25–40)	0.012
Positive lymph nodes	2	(0–4)	0	(0–0)	3	(2–6)	0.000
Total lymph nodes	18	(13–24)	15	(10–21)	20	(14–25)	0.000
Lymphatic invasion	249	(63%)	40	(37%)	209	(73%)	0.000
Perineural invasion	345	(87%)	80	(73%)	265	(93%)	0.000
Positive margins (≤1mm)	202	(51%)	34	(31%)	169	(59%)	0.000
Adjuvant therapy	292	(74%)	78	(72%)	214	(75%)	0.328
Chemotherapy alone	136	(48%)	40	(54%)	96	(46%)	0.473
Chemoradiation	145	(51%)	34	(46%)	111	(53%)	
Radiation alone	2	(1%)	0	(0%)	2	(1%)	

Table 2:

Outcome data and multivariate analysis of Upfront Surgery Group

	Total N= 394		pN0 N=109		pN1 N=285		*Univariate*
FOLLOW-UP DATA-UPFRONT SURGERY GROUP							
	Median/N	**IQR/%**	**Median/N**	**IQR/%**	**Median/N**	**IQR/%**	**p**
Overall Survival	18	(10–34)	25	(11–45)	16	(10–29)	0.000
Disease free survival	11	(6–23)	16	(7–36)	10	(5–20)	0.000
Recurrence	278	(71%)	60	(55%)	218	(77%)	0.000
Local	66	(24%)	16	(27%)	50	(23%)	0.672
Distant	172	(62%)	37	(63%)	135	(62%)	0.553
Lung only	42	(24%)	8	(22%)	34	(25%)	0.718
Liver only	67	(39%)	18	(49%)	49	(36%)	
Lung & Liver	11	(6%)	1	(3%)	10	(7%)	
Other/multiple distant sites	52	(30%)	10	(27%)	42	(32%)	
Both	38	(14%)	6	(10%)	32	(15%)	0.292

RECURRENCE

univariate (Chi-square)		**Multivariate (Logistic regression)**	
Factor	**p**	**OR**	**p**
Age	0.136		0.730
Sex	0.103		0.203
Type of Pancreatectomy	0.976		not included
pN1	0.000	**1.349–4.496**	**0.003**
Lymph-node ratio <0.3	0.004	**1.415–16.398**	**0.012**
Preoperative CA 19–9 <37U/ml	0.043		0.061
T-status	0.022		0.464
R0	0.014		0.203
Adjuvant Chemoradiation	0.143		not included
Adjuvant Chemotherapy alone	0.759		not included

LOCAL RECURRENCE

Univariate (Chi-square)		**Multivariate (Logistic regression)**	
Factor	**p**	**OR**	**p**
Age	0.372		0.221
Sex	0.259		0.225
Type of Pancreatectomy	0.649		not included
pN1	0.548		not included
Lymph node rate <0.3	0.503		not included
Preoperative CA 19–9 <37 U/ml	0.795		not included
T-status	0.456		not included
R0	0.035	**1.040–3.307**	**0.033**
Adjuvant Chemoradiation	0.810		not included
Adjuvant Chemotherapy alone	0.742		not included

DISTANT RECURRENCE

Univariate (Chi-square)		Multivariate (Logistic regression)	
Factor	**p**	**OR**	**p**
Age	0.863		0.912
Sex	0.459		0.853
Type of Pancreatectomy	0.646		not included
pN1	0.971		not included
Lymph node rate <0.3	0.793		not included
Preoperative CA 19–9 <37 U/ml	0.548		not included
T-status	0.436		not included
R0	**0.005**	**0.306–0.958**	**0.005**
Adjuvant Chemoradiation	0.626		not included
Adjuvant Chemotherapy alone	0.467		not included

Table 3:

Baseline characteristics and outcome parameters of the Propensity Matched Group

	Total N= 186		pN0 N= 93		pN1 N=93		*Univariate*
BASELINE CHARACTERISTICS of Upfront Resection Propensity Matched Group							
	Median/N	**IQR/%**	**Median/N**	**IQR/%**	**Median/N**	**IQR/%**	**p**
Age at operation, years	*70*	*(62–77)*	*71*	*(63–76)*	*68*	(62–78)	0.537
Gender (Male)	102	(55%)	49	(53%)	53	(57%)	0.556
Type of Surgery							0.086
Whipple	133	(72%)	60	(65%)	73	(78%)	
Distal pancreatectomy	42	(23%)	28	(30%)	14	(15%)	
Total pancreatectomy	6	(3%)	2	(2%)	4	(4%)	
Other	4	(2%)	2	(2%)	2	(2%)	

TUMOR PATHOLOGY							
Grade							0.262
1	9	(5%)	5	(5%)	4	(5%)	
2	125	(66%)	67	(72%)	58	(62%)	
3	52	(29%)	21	(23%)	32	(34%)	
4	0	(0%)	0	(0%)	0	(0%)	
T-stage							0.850
1	3	(2%)	2	(2%)	1	(1%)	
2	25	(13%)	14	(15%)	11	(12%)	
3	*154*	*(83%)*	75	(81%)	79	(85%)	
4	*4*	*(2%)*	2	(2%)	2	(2%)	
Tumor size (mm)	30	(20–40)	26	(20–40)	30	(21–40)	0.266
Lymphatic invasion	94	(51%)	34	(37%)	60	(65%)	0.000
Perineural invasion	160	(86%)	73	(79%)	87	(94%)	0.003
Positive margins (≤1mm)	62	(33%)	23	(24%)	39	(44%)	0.013
Adjuvant Therapy	127	(68%)	66	(71%)	61	(66%)	0.387
Chemotherapy alone	70	(55%)	39	(59%)	31	(51%)	0.634
Chemoradiation	57	(45%)	27	(41%)	30	(49%)	
Radiation alone	0	(0%)	0	(0%)	0	(0%)	

	Total N= 186		pN0 N= 93		pN1 N= 93		*Log-rank Test*
FOLLOW-UP							
Factor	**Median/N**	**95%KI/%**	**Median/N**	**95%KI /%**	**Median/N**	**95%KI/%**	**p**
Overall Survival	17	(10–34)	25	(11–45)	15	(10–26)	**0.000**
Disease free survival	12	(7–27)	14	(7–34)	10	(6–18)	**0.001**
Recurrence	119	(64%)	53	(57%)	66	(71%)	0.077
Local	21	(18%)	12	(23%)	9	(14%)	0.214
Distant	79	(66%)	33	(60%)	46	(72%)	0.329
Both	17	(14%)	7	(8%)	9	(10%)	0.920

RECURRENCE

Univariate Analysis (Chi-square)		Multivariate Analysis (Logistic Regression)	
Factor	**p-value**	**OR**	**p-value**
Age	0.503		0.337
Sex	0.093		0.223
Type of Pancreatectomy	0.909		not included
pN1	**0.016**		0.142
Lymph node rate <0.3	0.068		not included
Preoperative CA 19–9 >37 U/ml	**0.002**	**1.620–10.892**	**0.003**
T-status	0.528		not included
R1	0.305		not included
Adjuvant Chemoradiation	0.566		not included
Adjuvant Chemotherapy alone	0.420		not included

Table 4:

Baseline characteristics and outcome parameters of the neoadjuvant group. Preop. Preoperative;OR operation;LOS length of stay

	Total N= 152		pN0 N=70 (46%)		pN1 N=82 (54%)		*Univariate*
	NEOADJUVANT GROUP						
	Median/N	**IQR/%**	**Median/N**	**IQR/%**	**Median/N**	**IQR/%**	**p**
Age, years	64	(57–72)	64	(58–71)	64	(57–73)	0.996
Gender							0.465
Male	70	(46%)	30	(43%)	40	(49%)	
Female	82	(54%)	40	(57%)	42	(51%)	
Preop. CA 19–9	51	(14–120)	36	(14–96)	69	(13–208)	0.219
OR duration, min	353	(296–423)	357	(296–431)	346	(295–420)	0.426
LOS, days	7	(6–9)	6	(5–9)	7	(6–8)	0.670
Grade							0.005
0	2	(1%)	2	(3%)	0	(0%)	
G1	8	(5%)	5	(7%)	3	(4%)	
G2	89	(59%)	45	(64%)	44	(54%)	
G3	45	(30%)	10	(14%)	35	(43%)	
X	8	(5%)	8	(11%)	0	(0%)	
T-stage							0.004
0	3	(2%)	3	(4%)	0	(0%)	
T1	10	(6%)	9	(13%)	1	(1%)	
T2	21	(14%)	11	(16%)	10	(12%)	
T3	118	(78%)	47	(67%)	71	(87%)	
T4	0	(0%)	0	(0%)	0	(0%)	
Tumor size (mm)	25	(20–35)	22	(15–31)	30	(23–38)	0.000
Positive lymphn.	1	(0–3)	0	(0–0)	2	(1–4)	0.000
Total lymph nodes	19	(15–23)	18	(14–22)	19	(15–25)	0.174
Lymphatic invasion	71	(46%)	17	(24%)	54	(65%)	0.000
Perineural invasion	131	(85%)	52	(73%)	79	(95%)	0.000
Positive margins	53	(35%)	24	(34%)	29	(35%)	0.889
Adjuvant therapy	100	(65%)	40	(40%)	60	(60%)	0.056
Chemo alone	77	(78%)	33	(83%)	45	(75%)	0.077
Chemoradiation	19	(19%)	5	(13%)	14	(23%)	
Radiation alone	1	(1%)	1	(3%)	0	(0%)	
Neoadjuvant regimen	152	(100%)	70	(100%)	82	(100%)	0.075
Chemotherapy alone	12	(8%)	6	(10%)	6	(4%)	
Chemoradiation	137	(90%)	63	(88%)	74	(89%)	
Radiation alone	0	(0%)	0	(2%)	0	(0%)	

	Total N= 152		pN0 N=70		pN1 N=82		*univariate*
FOLLOW-UP DATA							
	Median/N	**IQR/%**	**Median/N**	**IQR/%**	**Median/N**	**IQR/%**	**p**
Overall Survival	24	(13–41)	33	(20–44)	17	(10–30)	0.003
Disease free survival	15	(9–27)	21	(11–38)	11	(5–20)	0.000
Recurrence	110	(72%)	45	(64%)	64	(78%)	0.040
Local	20	(18%)	10	(22%)	10	(15%)	0.435
Distant	75	(68%)	34	(76%)	41	(64%)	0.326
Lung only	19	(25%)	8	(24%)	11	(27%)	0.568
Liver only	31	(41%)	13	(38%)	18	(44%)	
Lung &Liver	3	(4%)	2	(6%)	1	(2%)	
Other/Multiple sites	22	(29%)	11	(32%)	11	(27%)	
Local and Distant	13	(12%)	1	(2%)	12	(18%)	0.014

RECURRENCE	**LOCAL RECURRENCE**	**DISTANT RECURRENCE**
Univariate (Chi-square)		
Factor	**p**	**p**	**p**
Age	0.339	0.653	0.727
Sex	0.943	0.115	0.508
Type of Pancreatectomy	0.913	0.873	0.624
pN1	0.060	0.381	0.202
Lymph-node ratio <0.3	0.443	0.335	0.884
Preoperative CA 19–9 <37U/ml	0.572	0.381	0.391
T-status	0.199	0.932	0.771
R0	0.451	0.172	0.279
Adjuvant Chemoradiation	0.808	0.381	0.444
Adjuvant Chemotherapy alone	0.454	0.205	0.222