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Recurrence after neoadjuvant therapy and resection of borderline resectable and locally advanced pancreatic cancer

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ABSTRACT

Introduction: The incidence, timing, and implications of recurrence in patients who underwent neoadjuvant treatment and surgical resection of borderline resectable (BRPC) or locally advanced (LAPC) pancreatic cancer are not well established.

Materials and methods: Patients with BRPC/LAPC who underwent post-neoadjuvant resection between 2007 and 2015 were included. Associations between clinicopathologic characteristics and specific recurrence locations, recurrence-free survival (RFS), and overall survival from resection (OS) were assessed using Cox regression analyses.

Results: For 231 included patients, median survival from diagnosis and resection were 28.0 and 19.8 months, respectively. After a median RFS of 7.9 months, 189 (81.8%) patients had recurred. Multiple-site ($n = 87$, 46.0%) and liver-only recurrence ($n = 28$, 14.8%) generally occurred earlier and resulted in significantly worse OS when compared to local-only ($n = 52$, 27.5%) or lung-only recurrence ($n = 18$, 9.5%). Microscopic perineural invasion, yN1-yN2 status and elevated pre-surgery CA 19-9 >100 U/mL were associated with both local-only and multiple-site/liver-only recurrence. R1-margin was associated with local-only recurrence (HR 2.03). yN1-yN2 status and microscopic perineural invasion were independent predictors for both poor RFS and OS, while yT3-yT4 tumor stage (HR 1.39) and poor tumor differentiation (HR 1.60) were only predictive of poor OS. Adjuvant therapy was independently associated with both prolonged RFS (HR 0.73; median 7.0 vs. 10.9 months) and OS (HR 0.69; median 15.4 vs. 22.7 months).

Conclusion: Despite neoadjuvant therapy leading to resection and relatively favorable pathologic tumor characteristics in BRPC/LAPC patients, more than 80% of patients experienced disease recurrence, 72.5% of which occurred at distant sites.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is associated with poor survival. In recent years, more aggressive utilization of potent neoadjuvant therapy regimens has increasingly allowed patients with borderline resectable (BRPC) or locally advanced (LAPC) pancreatic cancer to undergo curative-intent pancreatectomy [1–5]. In these patients, meta-analyses indicate that rates of R0-resection and survival can be achieved similar to those of patients with initially resectable disease [6–11]. However, as with primary resected PDAC, disease recurrence remains the principal cause of limited survival in resected BRPC/LAPC patients.

Treatment of BRPC/LAPC requires a patient-tailored and multidisciplinary approach [12–14]. A comprehensive understanding of PDAC recurrence can provide valuable insight when contemplating appropriate strategies regarding adjuvant treatment, oncologic surveillance, and management following recurrence. However, the incidence, timing, and implications of disease recurrence in patients undergoing post-neoadjuvant resection of BRPC/LAPC are not well established. Furthermore, it is unknown if specific

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Abbreviations

AJCC	American Joint Committee on Cancer
BRPC	Borderline Resectable Pancreatic Cancer
CA 19-9	Carbohydrate Antigen 19-9
CI	Confidence Interval
HR	Hazard Ratio
IQR	Interquartile Range
LAPC	Locally Advanced Pancreatic Cancer
NCCN	National Comprehensive Cancer Network
OS	Overall Survival
PDAC	Pancreatic Ductal Adenocarcinoma
RFS	Recurrence-Free Survival

clinicopathological features and treatment factors are associated with distinct patterns of recurrence in these patients.

Therefore, the aim of this single-institution cohort study was to accurately report on different aspects of PDAC recurrence in BRPC/LAPC patients who underwent neoadjuvant treatment followed by surgical resection. These aspects include the patterns and timing of recurrence, clinical factors associated with distinct recurrence locations and implications of recurrence on survival outcomes. Additionally, we sought to identify predictors of recurrence-free survival (RFS) and overall survival (OS) in this unique cohort of post-neoadjuvant resected PDAC patients.

2. Methods

2.1. Patient selection

This study included patients with BRPC or LAPC who underwent neoadjuvant treatment followed by resection at the Johns Hopkins Hospital between 2007 and 2015. Resectability and staging were based on computed tomography (CT) imaging and assessed conform the National Comprehensive Cancer Network (NCCN) guidelines [15]. Further imaging studies to exclude distant metastases, such as magnetic resonance imaging (MRI) and/or positron-emission tomography/computed tomography (PET/CT) scans were performed on individual patient basis, based on recommendations of the pancreatic multidisciplinary clinic. Similarly, utilization of diagnostic laparoscopy was decided based on individual assessment. Excluded were patients with metastatic disease at the time of diagnosis or surgery, or those who experienced 90-day post-resection mortality. Also excluded were patients with <12 months of follow-up (in which neither recurrence nor death had occurred), or patients with incomplete follow-up records.

2.2. Data collection

Demographics, clinicopathologic and treatment characteristics were extracted from a prospective single-institution pancreatectomy database. Neoadjuvant chemotherapy regimens were chosen at the discretion of the treating medical oncologist, and predominantly included gemcitabine-based regimens, 5-fluorouracil–based regimens such as FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan), or a combination of the two. After completion of neoadjuvant treatment, patients were re-evaluated with CT and those without evidence of local disease progression or distant metastasis were offered operative exploration.

Thirty-day morbidity was graded using the Clavien–Dindo classification system [16]. Tumor staging was reported according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for pancreatic cancer [17]. Treatment effect was measured using the College of American Pathologists (CAP) Cancer Protocol [18]. When available, pre-neoadjuvant and pre-surgery carbohydrate antigen (CA) 19-9 values were documented. CA 19-9 values acquired more than 1 month before start of neoadjuvant treatment or date of surgery were not included for analysis. Based on receiver operating characteristics curves, cut-offs of 150 and 100 U/ml were utilized for pre-neoadjuvant and pre-surgery CA 19-9 values, respectively.

2.3. Follow-up and recurrence

Post-pancreatectomy follow-up methodology at our institution has been described previously and is performed according to the NCCN guidelines [15,19]. Follow-up data were retrieved through November 2018. The first location of disease recurrence was documented using five mutually exclusive groups: “local-only”, “liver-only”, “lung-only”, “multiple-site” and “other”. Multiple-site recurrence included patients with recurrence at multiple distant sites (i.e. lung and liver), patients with carcinomatosis, and/or patients with simultaneous first recurrence at local and distant sites.

2.4. Survival outcomes and statistical analysis

RFS was defined as the time interval between the date of surgery and the date of recurrence. OS and post-recurrence survival were defined as the time from the date of resection (OS) or the date of recurrence (post-recurrence survival) to either death or last follow-up. Kaplan-Meier curves were used to estimate median survival outcomes with a corresponding 95% confidence interval (CI), and the log-rank test was used for subgroup comparison. Univariable Cox-proportional hazard regression analyses were performed to describe associations between clinicopathologic characteristics and specific patterns of recurrence, RFS, and OS. A stepwise, backward approach using the Akaike information criterion (AIC) was used to select covariates for inclusion in multivariable Cox models predicting RFS and OS. A two-tailed *P*-value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS v25.0 (IBM Corporation, Armonk, NY, USA) and R v3.3.3 (R Foundation, Vienna, Austria).

3. Results

3.1. Patient cohort

A total of 272 BRPC/LAPC patients underwent neoadjuvant treatment followed by a pancreatectomy between 2007 and 2015. From this cohort, 7 patients (2.6%) with 90-day mortality were excluded. Also excluded were 34 patients (12.5%) with <12 months of follow-up or with incomplete follow-up reports. Consequently, 231 patients (84.9%) were included in the final study cohort. At last follow-up, 57 patients (24.7%) were alive after a median follow-up of 44.9 months (95% CI 39.8–50.0) from the time of diagnosis and 37.3 months (95% CI 31.2–44.4) from the date of surgery. Disease recurrence was documented in 189 patients (81.8%) after a median RFS of 7.9 months (Table 1).

3.2. Cohort and treatment characteristics

Complete demographic, clinicopathologic, and treatment characteristics are shown in Table 1. All patients underwent neoadjuvant chemotherapy with significant variations noted in their corresponding regimens (Suppl. Table 1). The majority of patients ($n = 180$, 77.9%) also underwent neoadjuvant radiotherapy, either with conventional external beam radiotherapy ($n = 81$), intensity-

Table 1
Demographic, clinicopathologic, and treatment characteristics of included patients.

Variable	All patients (n=231)	No recurrence (n=42)	Recurrence (n=189)	P-value
Male, *n* (%)	128 (55.4%)	23 (54.8%)	105 (55.6%)	0.925
Caucasian, *n* (%)	204 (88.3%)	36 (85.7%)	168 (88.9%)	0.562
Age, mean years (SD)	62.7 (9.4)	62.6 (9.6)	62.8 (9.4)	0.905
Disease stage, *n* (%)				0.975
Borderline resectable	138 (59.7%)	25 (59.5%)	113 (59.8%)	
Locally advanced	93 (40.3%)	17 (40.5%)	76 (40.2%)	
Neoadjuvant therapy *n* (%)				0.477
Chemotherapy	51 (22.1%)	11 (26.2%)	40 (21.2%)	
Chemotherapy & radiotherapy	180 (77.9%)	31 (73.8%)	149 (78.8%)	
Chemotherapy regimen, *n* (%)				
FOLFIRINOX-based	98 (42.4%)	20 (47.6%)	78 (41.3%)	0.155
FFX-Gem combination	44 (19.0%)	11 (26.2%)	33 (17.5%)	
Gemcitabine-based	89 (38.5%)	11 (26.2%)	78 (41.3%)	
Time of CHT administered, median months (IQR)	4 (2–5)	4 (2–5)	3 (2–5)	0.380
Neoadjuvant radiotherapy modality, *n* (%)				0.706
Conventional	81 (45.0%)	13 (41.9%)	68 (45.6%)	
IMRT/SBRT	99 (55.0%)	18 (58.1%)	81 (54.4%)	
Time from diagnosis to resection, median months (IQR)	8 (6–10)	8 (6–10)	7 (5–9)	0.214
Pre-neoadjuvant CA 19-9, median U/ml (IQR)[a]	170 (68–554)	103 (39–294)	184 (79–587)	**0.018**
Pre-surgery CA 19-9, median U/ml (IQR)[b]	39 (21–85)	27 (20–38)	47 (24–97)	**0.010**
Type of operation, *n* (%)				0.765
Pancreatoduodenectomy	164 (71.0%)	30 (71.4%)	134 (70.9%)	
Distal pancreatectomy	42 (18.2%)	9 (21.4%)	33 (17.5%)	
Total pancreatectomy	12 (5.2%)	1 (2.4%)	11 (5.8%)	
DP-CAR	13 (5.6%)	2 (4.8%)	11 (5.8%)	
Vascular resection, *n* (%)	91 (39.4%)	15 (35.7%)	76 (40.2%)	0.590
Morbidity, *n* (%)				0.516
≤ Clavien-Dindo grade II	190 (82.3%)	36 (85.7%)	154 (81.5%)	
≥ Clavien-Dindo grade III	41 (17.7%)	6 (14.3%)	35 (18.5%)	
R0 margin (>1.0 mm), *n* (%)	180 (77.9%)	36 (85.7%)	144 (76.2%)	0.178
Tumor size, mean cm (SD)	2.5 (1.5)	2.4 (1.5)	2.5 (1.5)	0.629
T-stage (AJCC 8th edition), *n* (%)				0.092
yT0-yT2	127 (55.0%)	28 (67.7%)	99 (52.4%)	
yT3-yT4	104 (45.0%)	14 (33.3%)	90 (47.6%)	
N-stage (AJCC 8th edition), *n* (%)				**0.011**
yN0-status	140 (60.6%)	34 (81.0%)	106 (56.1%)	
yN1-status	72 (31.2%)	6 (14.3%)	66 (34.9%)	
yN2-status	19 (8.2%)	2 (4.8%)	17 (9.0%)	
Tumor differentiation, *n* (%)				0.353
Well/moderate	162 (70.1%)	32 (76.2%)	130 (68.8%)	
Poor	69 (29.9%)	10 (23.8%)	59 (31.2%)	
Micr. perineural invasion, *n* (%)	133 (57.6%)	16 (38.1%)	117 (61.9%)	**0.005**
Micr. lymphovascular invasion, *n* (%)	91 (39.4%)	12 (28.6%)	79 (41.8%)	0.113
CAP score treatment response, *n* (%)				0.190
Complete (grade 0)	15 (6.5%)	4 (9.5%)	11 (5.8%)	
Extensive (grade 1)	43 (18.6%)	8 (19.0%)	35 (18.5%)	
Moderate (grade 2)	75 (32.5%)	18 (42.9%)	57 (30.2%)	
Poor (grade 3)	98 (42.4%)	12 (28.6%)	86 (45.5%)	
Adjuvant chemotherapy, *n* (%)				0.425
None	93 (40.3%)	20 (47.6%)	73 (38.6%)	
Chemotherapy	109 (47.2%)	16 (38.1%)	93 (49.2%)	
Chemotherapy & radiotherapy	29 (12.6%)	6 (14.3%)	23 (12.2%)	
Survival, median months (95% CI)				
Recurrence-free survival	9.8 (8.3–11.3)	NA	7.9 (7.1–8.8)	NA
Post-recurrence survival	NA	NA	8.4 (7.3–9.6)	NA
Overall survival	19.8 (17.3–22.4)	Not reached	18.0 (16.4–19.5)	**<0.001**
Survival from diagnosis	28.0 (25.5–30.5)	Not reached	26.1 (24.3–27.9)	**<0.001**

AJCC, *American Joint Committee on Cancer*; CA, *carbohydrate antigen*; CAP, *College of American Pathologists*; CHT, *chemotherapy*; CI, *confidence interval*; DP-CAR, *distal pancreatectomy with celiac axis resection*; FFX, *FOLFIRINOX*; GEM, *gemcitabine*; IMRT, *intensity-modulated radiation therapy*; IQR, *interquartile range*; Micr, *microscopic*; NA, *not applicable*; SBRT, *stereotactic body radiation therapy*; SD; *standard deviation*.

[a] 149 patients had documented pre-neoadjuvant CA 19-9 values, of whom 11 patients were Lewis-antigen negative and excluded.

[b] 149 patients had documented pre-operative CA 19-9 values, of whom 11 patients were Lewis-antigen negative and excluded.

modulated radiotherapy ($n = 17$) or stereotactic body radiotherapy ($n = 82$). After resection, 138 patients (59.7%) received additional adjuvant treatment, consisting of either chemotherapy alone ($n = 109$, 47.2%) or chemotherapy and radiotherapy ($n = 29$, 12.6%) (Suppl. Table 1).

3.3. Pattern of recurrence

Of the 189 patients (81.8%) with recurrent PDAC, 62 patients (32.8%) had pathologic confirmation of recurrence with a tissue biopsy while the other patients were diagnosed based on imaging evidence alone. Most patients first recurred at multiple sites ($n = 87$, 46.0%) (Fig. 1A). Of these 87 patients, 57 had simultaneous first recurrence at local and distant sites (Suppl. Table 2). Isolated local recurrence occurred in 52 patients (27.5%). Isolated distant recurrence was most often seen in the liver ($n = 28$, 14.8%) or in the lungs ($n = 18$, 9.5%). Four patients (2.1%) recurred at less common distant sites, specifically: the abdominal wall, the left ovary, the

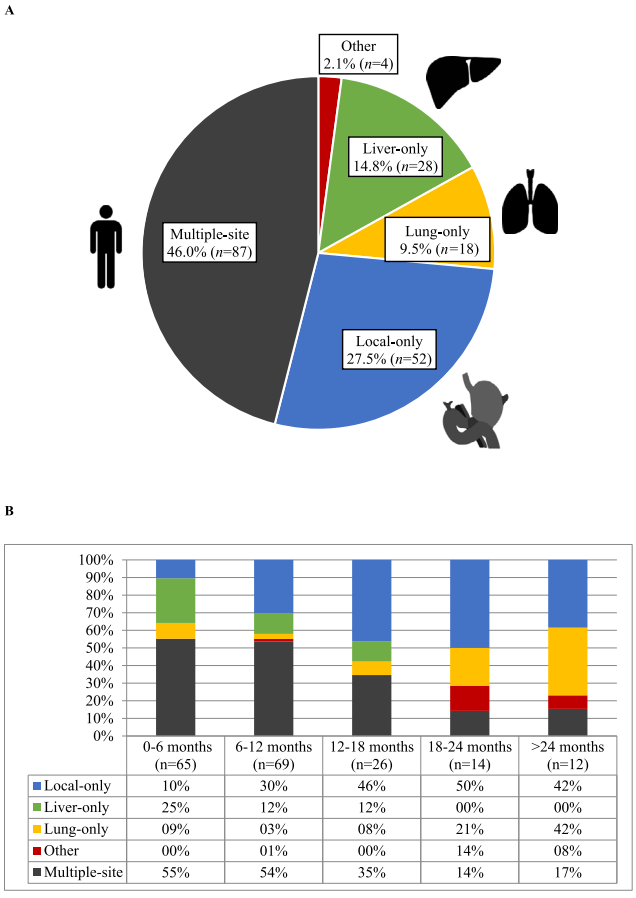


Fig. 1. A) Distribution of recurrence patterns and B) distribution of recurrence pattern at different time points.

uterus and the right calf muscle. The proportion of different recurrence locations at successive time intervals is displayed in Fig. 1B. The rate of recurrence for patients with pre-neoadjuvant BRPC (81.9%) and LAPC (81.7%) was nearly identical ($P = 0.975$). Additionally, recurrence patterns did not differ between patients with initial BRPC or LAPC ($P = 0.622$). Specifically, the fraction of local recurrence for BRPC (35/113; 31.0%) and LAPC (17/76; 22.4%) did not significantly differ ($P = 0.194$).

An historical cohort of primary resectable patients undergoing upfront resection at our institution between 2000 and 2013, which has been extensively described previously, was utilized to compare recurrence patterns and outcomes (Table 2) [20,21]. The current cohort of post-neoadjuvant BRPC/LAPC patients had significantly lower pre-surgery CA 19-9 and more favorable pathologic tumor characteristics than patients with primary resectable PDAC. However, overall recurrence rates (81.8% vs 78.6%; $P = 0.291$) and median survival from diagnosis (28.0 vs. 26.1 months; $P = 0.371$) for post-neoadjuvant BRPC/LAPC and primary resectable patients were similar. While survival from diagnosis per recurrence location did not differ for the two patient cohorts, liver-only recurrence occurred less frequent in the post-neoadjuvant patients (Table 2).

3.4. Timing of recurrence

At 6 months after resection, 67 of 189 patients with recurrence (35.4%) had recurred, and 136 (72.0%) had done so within 12 months (Fig. 2). No recurrences were documented more than 5 years post-surgery. Forty-two patients (18.2%) had no sign of recurrence after a median follow-up of 42.5 months (95% CI 35.2–49.8) after diagnosis and 32.2 months (95% CI 24.9–39.5) after resection. Fig. 2 further demonstrates that nearly 90% of liver-only recurrences occurred in the first 12 months. Similarly, 95.3% of multiple-site recurrences transpired in the first 18 months. Median RFS of the specific recurrence patterns with pairwise comparison are presented in Suppl. Fig. 1A. The high cumulative early recurrence rates of liver and multiple-site recurrence are further illustrated by their relatively short median RFS of 4.2 months and 6.7 months, respectively. Local-only, lung-only, and other recurrence generally occurred later, reflected by their median RFS exceeding 10 months.

3.5. Implications of recurrence pattern and timing on survival

Median survival outcomes for all patients and per different recurrence location are presented in Suppl. Table 3. Median OS was not yet reached at 108 months in 42 patients without recurrence, compared to a median OS of 18.0 months for patients with recurrence ($P < 0.001$). Pairwise comparison of specific recurrence patterns revealed that median post-recurrence survival and OS varied significantly based on recurrence location (Suppl. Fig. 1B–C). Patients with liver-only or multiple-site recurrence had a median post-recurrence survival of 6.6 and 8.0 months, resulting in relatively limited median OS of 11.9 and 15.7 months, respectively. Similar to the observed differences in RFS, lung-only, local-only and other recurrence were all associated with considerably longer median post-recurrence survival and OS.

The timing of recurrence was strongly correlated with subsequent survival after recurrence. Using the log-rank test and a minimum *P*-approach [20], the optimal length of RFS to distinguish between early and late recurrence, based on subsequent post-recurrence survival, was 9 months ($P = 6.30 \times 10^{-5}$). Median post-recurrence survival in the early (RFS <9 months) recurrence cohort ($n = 108$, 57.1%) was 7.9 months (95% CI 6.9–8.8). Patients with recurrence after 9 months ($n = 81$, 42.9%) had a median post-recurrence survival of 13.8 months (95% CI 10.2–17.4). Patients with early recurrence had 1- and 2-yr post-recurrence survival rates of 21.9% and 7.0% compared with 54.3% and 25.4% for the late recurrence group (both $P < 0.001$).

3.6. Factors associated with patterns of recurrence

On univariable Cox regression analysis, several clinicopathologic and treatment variables were associated with distinct recurrence locations (Table 3). Based on observed survival outcomes, recurrence patterns were grouped in local-only ($n = 52$), multiple-site/liver-only ($n = 115$) and lung-only/other ($n = 22$). Microscopic perineural invasion and yN1-yN2 status were correlated with both local and multiple-site/liver recurrence. An R1-margin was only associated with local recurrence (Hazard Ratio [HR] 2.03, $P = 0.019$), while poor tumor differentiation (HR 1.85, $P = 0.002$) and yT3-yT4 tumor stage (HR 1.46, $P = 0.042$) correlated with multiple-site/liver recurrence. Whereas lung/other recurrence occurred less in males (HR 0.34, $P = 0.025$), no other associations were found.

There was no significant difference observed in the rate of local recurrence between patients who received radiotherapy in either the neoadjuvant or adjuvant setting (43/201; 21.4%), and those who did not receive any radiation treatment (9/30; 30.0%) ($P = 0.292$). Gemcitabine-based neoadjuvant therapy was associated with a higher likelihood of multiple-site/liver recurrence when compared to FOLFIRINOX-based regimens (HR 1.52, $P = 0.042$). Alternatively, adjuvant therapy was associated with a decreased likelihood of multiple-site/liver recurrence (HR 0.61, $P = 0.008$). A pathologic complete response (CAP score 0) was significantly associated with a

Table 2
Comparison of clinicopathologic characteristics, recurrence patterns and survival outcomes between the study cohort of resected post-neoadjuvant patients and an historical cohort of patients who underwent upfront resection.

Variable	Post-neoadjuvant (n=231)	Upfront surgery (n=957)	P-value
Male, *n* (%)	128 (55.4%)	501 (52.4%)	0.403
Caucasian, *n* (%)	204 (88.3%)	821 (85.8%)	0.317
Age, mean years (SD)	62.7 (9.4)	65.8 (10.5)	**<0.001**
Pre-surgery CA 19-9, median U/ml (IQR)	39 (21–85)[a]	130 (50–398)[b]	**<0.001**
Type of operation, *n* (%)			**<0.001**
Pancreatoduodenectomy	164 (71.0%)	798 (83.4%)	
Distal pancreatectomy	42 (18.2%)	125 (13.1%)	
Total pancreatectomy	12 (5.2%)	34 (3.6%)	
DP-CAR	13 (5.6%)	0 (0%)	
R0 margin (>1.0 mm), *n* (%)	180 (77.9%)	658 (68.8%)	**0.006**
Tumor size, mean cm (SD)	2.5 (1.5)	3.2 (1.5)	**<0.001**
T-stage (AJCC 8th edition), *n* (%)			**<0.001**
T0-T2	127 (55.0%)	99 (52.4%)	
T3-T4	104 (45.0%)	90 (47.6%)	
N-stage (AJCC 8th edition), *n* (%)			**<0.001**
N0-status	140 (60.6%)	238 (24.9%)	
N1-status	72 (31.2%)	400 (41.8%)	
N2-status	19 (8.2%)	319 (33.3%)	
Positive lymph node ratio, median (IQR)	0.00 (0.00–0.08)	0.11 (0.02–0.25)	**<0.001**
Tumor differentiation, *n* (%)			**<0.001**
Well/moderate	162 (70.1%)	591 (61.8%)	
Poor	69 (29.9%)	366 (38.2%)	
Micr. perineural invasion, *n* (%)	133 (57.6%)	859 (89.8%)	**<0.001**
Micr. lymphovascular invasion, *n* (%)	91 (39.4%)	544 (56.8%)	**<0.001**
Adjuvant chemotherapy, *n* (%)			**<0.001**
None	93 (40.3%)	307 (32.1%)	
Chemotherapy	109 (47.2%)	207 (21.6%)	
Chemotherapy & radiotherapy	29 (12.6%)	443 (46.3%)	
Recurrence, *n* (%)	189 (81.8%)	753 (78.6%)	0.291
Recurrence pattern, *n* (%)			
Lung-only	18 (9.5%)	106 (14.1%)	0.098
Local-only	52 (27.5%)	190 (25.2%)	0.521
Multiple-site	87 (46.0%)	253 (33.6%)	**0.001**
Liver-only	28 (14.8%)	184 (24.4%)	**0.005**
Other	4 (2.1%)	20 (2.7%)	0.674
Overall survival (from diagnosis), median months (95% CI)			
Lung-only	31.5 (12.6–50.5)	43.5 (32.3–54.8)	0.992
Local-only	34.6 (30.3–39.0)	27.8 (24.5–31.2)	0.297
Multiple-site	23.8 (22.6–25.0)	19.1 (17.4–20.8)	0.193
Liver-only	17.8 (9.5–26.2)	16.2 (14.3–18.1)	0.766
Other	64.2 (0-not reached)	34.9 (19.6–50.1)	0.114
Survival outcomes, median months (95% CI)			
Recurrence-free survival (from resection)	9.8 (8.3–11.3)	15.2 (14.0–16.4)	**<0.001**
Post-recurrence survival	8.4 (7.3–9.6)	7.5 (6.8–8.2)	0.403
Survival from diagnosis	28.0 (25.5–30.5)	26.1 (24.5–27.7)	0.371
Overall survival (from resection)	19.8 (17.3–22.4)	24.8 (23.3–26.3)	**0.015**

AJCC, American Joint Committee on Cancer; CA, carbohydrate antigen; CI, confidence interval; DP-CAR, distal pancreatectomy with celiac axis resection; IQR, interquartile range; Micr, microscopic; SD; standard deviation.
[a] 149 patients had documented pre-operative CA 19-9 values, of whom 11 patients were Lewis-antigen negative and excluded.
[b] 398 patients had documented pre-operative CA 19-9 values, of whom 65 patients were Lewis-antigen negative and excluded.

decreased chance of multiple-site/liver recurrence (HR 0.35, $P = 0.038$) when compared to moderate/poor treatment effect.

3.7. Association of CA 19-9 with recurrence and survival

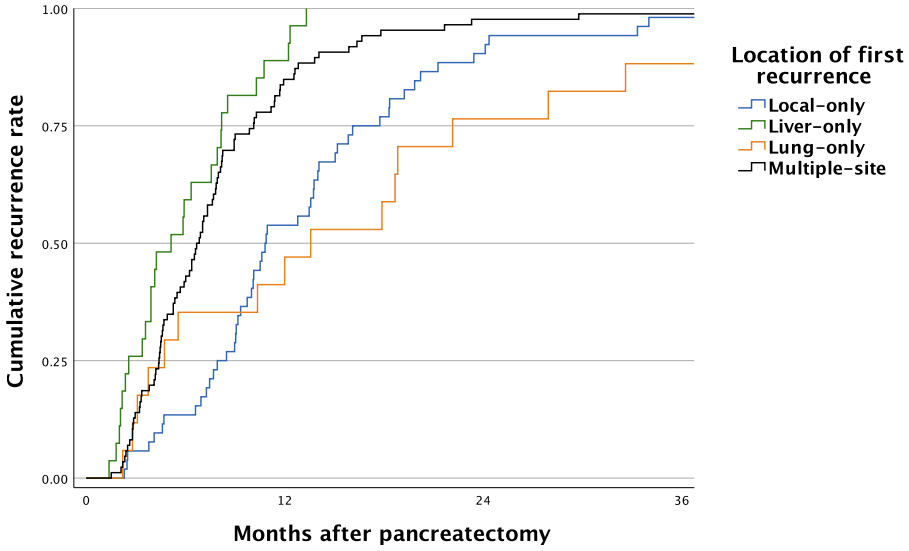
In both the pre-neoadjuvant and pre-surgery setting, 138 patients had CA 19-9 values available for analysis. Median CA 19-9 before start of neoadjuvant treatment was 170 U/ml (interquartile range [IQR] 68–554), with a decrease to 39 U/mL (IQR 21–85) before surgery. Elevated pre-neoadjuvant CA 19-9 >150 U/mL correlated with multiple-site/liver recurrence (HR 1.84, $P = 0.016$), yet displayed no association with local or lung/other recurrence (Table 3). Elevated pre-surgery CA 19-9 >100 U/mL was associated with both local (HR 2.61, $P = 0.028$) and multiple-site/liver recurrence (HR 2.61, $P < 0.001$).

Patients with pre-neoadjuvant elevated CA 19-9 >150 U/mL had significantly decreased survival from PDAC diagnosis (24.0 vs. 34.7 months; $P = 0.015$), RFS (7.9 vs. 13.7 months; $P = 0.005$) and OS (15.9 vs. 25.0 months; $P = 0.020$) (Suppl. Fig. 2). Similarly, patients with pre-operatively elevated CA 19-9 >100 U/mL had worse RFS (4.6 vs. 10.9 months; $P < 0.001$) and OS (11.2 vs. 20.9 months; $P = 0.001$) (Suppl. Fig. 3).

3.8. Factors associated with recurrence-free and overall survival

Median survival outcomes for patients with and without recurrence, and for different recurrence patterns are shown in Table 1 and Suppl. Table 3. For all 231 patients, 1-yr, 2-yr and 5-yr rates of RFS and OS were 40%, 21%, 9% and 76%, 43%, 15%, respectively.

Table 4 shows the results of univariable and multivariable Cox regression analyses for RFS and OS. On univariable analysis, several pathologic features were associated with both decreased RFS and OS. On multivariable analysis, yN1-yN2 status (HR 1.68, $P = 0.003$)



Recurrence patterns	*0-6 months*	*6-12 months*	*12-18 months*	*18-24 months*	*24-48 months*	*48-60 months*
Local only (*n*=52)	13.5% (*n*=7)	53.8% (*n*=28)	76.9% (*n*=40)	90.4% (*n*=47)	98.1% (*n*=51)	100% (*n*=52)
Liver only (*n*=28)	60.7% (*n*=17)	89.3% (*n*=25)	100% (*n*=28)	100% (*n*=28)	100% (*n*=28)	100% (*n*=28)
Lung only (*n*=18)	33.3% (*n*=6)	44.4% (*n*=8)	55.6% (*n*=10)	72.2% (*n*=13)	94.4% (*n*=17)	100% (*n*=18)
Multiple-site (*n*=87)	42.5% (*n*=37)	85.1% (*n*=74)	95.34% (*n*=83)	97.7% (*n*=85)	98.9 % (*n*=86)	100% (*n*=87)
Other (*n*=4)	0.0% (*n*=0)	25.0% (*n*=1)	25.0% (*n*=1)	75.0% (*n*=3)	75.0% (*n*=3)	100% (*n*=4)
All recurrence (*n*=189)	35.4% (*n*=67)	72.0% (*n*=136)	85.7% (*n*=162)	93.1% (*n*=176)	97.9% (*n*=185)	100% (*n*=189)

Fig. 2. Cumulative recurrence rate per specific recurrence pattern as a function of time.

and microscopic perineural invasion (HR 1.43, $P = 0.041$) were independent predictors for reduced RFS. Independent prognostic factors for poor OS were yT3-yT4 tumor stage (HR 1.39, $P = 0.046$), yN1-yN2 status (HR 1.91, $P = 0.0024$), poor tumor differentiation grade (HR 1.60, $P = 0.006$) and microscopic perineural invasion (HR 1.48, $P = 0.041$). Furthermore, adjuvant therapy was independently associated with both prolonged RFS (HR 0.73, $P = 0.043$) and OS (HR 0.69, $P = 0.025$). Estimated median RFS and OS for patients who received adjuvant therapy were 10.9 and 22.7 months respectively, while median RFS and OS for patients who did not receive adjuvant therapy were 7.0 and 15.4 months.

Patients with a pathologic complete response did not have a significantly lower recurrence rate (11/15; 73.3% vs. 178/216; 82.4% ($P = 0.378$)), although a near significant difference in median RFS was observed (21.3 months (95% CI 12.5–30.0) vs. 9.1 months (95% CI 7.8–10.4); $P = 0.051$). The 11 patients who recurred after a complete response did have significantly extended post-recurrence survival (24.8 months (95% CI 8.7–40.9) vs. 8.3 months (95% CI 7.5–9.1); $P = 0.003$). Notably, patients with a complete response had significantly improved OS (46.8 months (95% CI 0-not reached) vs. 19.2 months (95% CI 17.1–21.2); $P = 0.002$).

4. Discussion

Patients initially diagnosed with BRPC/LAPC who underwent post-neoadjuvant resection represent a growing cohort of importance in pancreatic cancer care. While low rates of R1-margin and lymph node positivity were observed in this study, PDAC recurrence nevertheless occurred in more than 80% of patients. Furthermore, 72.5% of recurrences occurred at distant sites, suggesting that despite a radiographic progression-free period leading to resection, viable micrometastatic PDAC can persist after systemic neoadjuvant treatment. Additionally, similar to primary resectable PDAC, different recurrence patterns were found to be associated with unique survival curves, with liver and multiple-site recurrence resulting in particularly poor outcomes. Lastly, several clinicopathologic and treatment features were found to be associated with distinct recurrence locations and patient survival. This detailed knowledge on the timing, pattern and factors associated with disease failure may help clinicians with important decisions regarding the challenging multimodality care of these patients with advanced localized disease.

Few studies on BRPC/LAPC have studied disease recurrence following resection as a primary outcome of interest. Therefore, currently published recurrence rates differ considerably. For instance, seven large contemporary studies that included data on recurrence after resection of BRCP/LAPC reported overall recurrence rates ranging from 38% to 65% [12,22–27]. However, one of the first prospective randomized trials reported a recurrence rate of 88% in 17 BRPC patients undergoing post-neoadjuvant resection; more similar to the 82% found in the current study [28]. The discrepancies in the published recurrence rates can likely be attributed to a combination of multiple factors, including variations in neoadjuvant treatment regimen and differences in both follow-up strategies and length. To reduce these potential biases in this retrospective study, we utilized a large, contemporary single-institution cohort and excluded patients with incomplete follow-up records. In the near future, further prospective clinical trials

Table 3
Univariable Cox regression analysis for the identification of clinicopathologic and treatment characteristics associated with different recurrence patterns.

Clinical characteristics	Local-Only (n=52)			Multiple-site/Liver-Only (n=115)			Lung-Only/Other (n=22)	
	HR	95% CI	P	HR	95% CI	P	95% CI	P
Gender								
Male vs. female	1.42	0.81–2.48	0.223	1.24	0.86–1.80	0.249	**0.13–0.87**	**0.025**
Race								
Caucasian vs. all others	1.30	0.51–3.26	0.583	1.00	0.57–1.75	0.992	0.29–5.45	0.754
Age at surgery (years)*	1.02	0.99–1.05	0.204	1.00	0.98–1.02	0.850	0.92–1.01	0.140
Disease stage at diagnosis								
LAPC vs. BRPC	0.72	0.40–1.29	0.268	1.29	0.90–1.86	0.170	0.24–1.49	0.274
Tumor location								
Body/tail vs. head/uncinate	0.76	0.38–1.51	0.431	1.17	0.79–1.75	0.437	0.38–2.57	0.976
Neoadjuvant therapy								
CHRT vs. CHT	0.80	0.44–1.46	0.473	1.36	0.86–2.17	0.192	0.64–7.39	0.213
Neoadjuvant regimen								
Gem-based vs. FFX-based	0.74	0.40–1.38	0.342	**1.52**	**1.02–2.26**	**0.042**	0.45–3.22	0.705
Gem-FFX vs. FFX-based	0.72	0.34–1.53	0.388	0.97	0.57–1.67	0.917	0.37–3.52	0.815
CA 19-9 pre-neoadjuvant[a]								
>150 U/mL vs. <150 U/mL	1.58	0.78–3.21	0.207	**1.84**	**1.12–3.01**	**0.016**	0.51–4.02	0.499
CA 19-9 pre-surgery[b]								
>100 U/mL vs. <100 U/mL	**2.61**	**1.11–6.13**	**0.028**	**2.61**	**1.56–4.37**	**<0.001**	0.53–3.36	0.268
Vascular resection								
Yes vs. no	0.72	0.40–1.31	0.283	1.25	0.86–1.80	0.240	0.47–2.59	0.820
Resection margin status								
R1 (≤1.0 mm) vs. R0 (>1.0 mm)	**2.03**	**1.12–3.66**	**0.019**	1.15	0.75–1.79	0.524	0.22–2.48	0.614
T-stage (AJCC 8th edition)								
yT3-yT4 vs. yT0-yT2	1.27	0.74–2.20	0.391	**1.46**	**1.01–2.12**	**0.042**	0.77–4.33	0.169
N-stage (AJCC 8th edition)								
yN1-yN2 vs. yN0	**2.18**	**1.25–3.81**	**0.006**	**1.88**	**1.30–2.71**	**0.001**	0.85–5.35	0.106
Tumor differentiation grade								
Poor vs. well/moderate	1.20	0.63–2.31	0.580	**1.85**	**1.26–2.70**	**0.002**	0.48–3.74	0.571
Micr. lymphovascular invasion								
Yes vs. no	1.26	0.72–2.21	0.413	1.36	0.94–1.97	0.098	0.68–3.92	0.271
Micr. perineural invasion								
Yes vs. no	**1.98**	**1.12–3.44**	**0.019**	**1.75**	**1.20–2.56**	**0.004**	0.67–3.68	0.297
CAP score treatment response								
0 vs. 2/3	0.90	0.35–2.29	0.818	**0.35**	**0.13–0.94**	**0.038**	0.15–2.77	0.546
1 vs. 2/3	1.36	0.70–2.62	0.364	0.86	0.53–1.38	0.523	0.11–1.97	0.292
Adjuvant therapy								
Any vs. none	1.64	0.86–3.14	0.133	**0.61**	**0.42–0.88**	**0.008**	0.27–1.46	0.277

AJCC, American Joint Committee on Cancer; BRPC, borderline resectable pancreatic cancer; CA, carbohydrate antigen;; CAP, College of American Pathologists; CHRT, chemoradiotherapy; CHT, chemotherapy; CI, confidence interval; FFX, FOLFIRINOX; GEM, gemcitabine; HR, hazard ratio; LAPC, locally advanced pancreatic cancer; Micr, microscopic.
*Continuous variable.
[a] 149 patients had documented pre-neoadjuvant CA 19-9 values, of whom 11 patients were Lewis-antigen negative and excluded.
[b] 149 patients had documented pre-operative CA 19-9 values, of whom 11 patients were Lewis-antigen negative and excluded.

on BRPC and LAPC, such as the ALLIANCE and SCALOP-2 trials, might provide more accurate recurrence and survival data for resected BRPC/LAPC patients [29]. Several studies have attempted to compare recurrence outcomes between neoadjuvant- and surgery-first strategies. A recent meta-analysis by Schorn et al. has suggested that the overall recurrence rate is lower in patients who received neoadjuvant therapy (Risk Ratio 0.82; $P < 0.001$) [30]. Additionally, less hepatic metastases were observed in the neoadjuvant patients (20% vs. 29% ($P = 0.02$)). The current study also found a decreased rate of liver-only recurrence in patients who underwent post-neoadjuvant resection when compared to upfront resection. Prospective trials that randomize patients to neoadjuvant and surgery-first arms, such as the PREOPANC-trial, ought to provide a better understanding of differences in patterns and rates of recurrence between these two treatment-sequence strategies [31].

While the clinical advantage of a neoadjuvant-first approach is still being intensely debated, multiple studies have shown that neoadjuvant treatment can lead to reduced tumor size, lower N-stage and R1-rates, and decreased frequency of microscopic perineural and lymphovascular invasion [6,32]. However, published predictive values of these historic pathologic risk factors vary significantly, with only post-neoadjuvant N-stage being fairly consistently associated with poor survival [1,4,33–38]. In this study, yN1-yN2 and yT3-yT4 status, poor tumor differentiation and microscopic perineural invasion were independent predictors for decreased OS. However, these associations were relatively weak, suggesting that conventional pathologic characteristics might have less prognostic value in post-neoadjuvant patients. Recent studies indicate that liquid biopsies in the form of circulating tumor cells or circulating tumor DNA show promise as potential novel biomarkers in cancer patients [39,40]. For instance, in patients undergoing resection of PDAC, a recent study from our institution found that the pre-operative presence of circulating tumor cells was the only predictors of early recurrence within 12 months from surgery in both chemo-naive and post-neoadjuvant patients [41]. Novel approaches to accurate prognostic stratification in PDAC patients undergoing neoadjuvant treatment and resection are warranted, as these could help to select patients for surgery and guide further treatment in the adjuvant setting.

Additional adjuvant treatment was associated with less multiple-site/liver recurrence and was an independent predictor for both improved RFS and OS. However, these results should be interpreted with caution as there was significant heterogeneity in

Table 4
Univariable and multivariable Cox regression analysis for recurrence-free and overall survival.

Clinical Characteristics	Recurrence-free survival						Overall Survival					
	Univariable Analysis			Multivariable Analysis			Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Gender												
Male vs. female	1.12	0.84–1.50	0.209	–			1.23	0.91–1.66	0.186	1.27	0.93–1.73	0.136
Race												
Caucasian vs. all others	1.10	0.70–1.73	0.691	–			1.19	0.73–1.94	0.489	–		
Age at surgery (years)*	1.00	0.99–1.02	0.951	–			1.01	0.99–1.03	0.094	–		
Disease stage at diagnosis												
LAPC vs. BRPC	0.02	0.76–1.37	0.902	–			1.03	0.76–1.39	0.873	–		
Tumor location												
Body/tail vs. head/uncinate	1.02	0.73–1.41	0.918	–			0.98	0.70–1.37	0.897	–		
Neoadjuvant therapy												
CHRT vs. CHT	1.22	0.86–1.72	0.276	1.40	0.97–2.03	0.071	1.16	0.81–1.66	0.429	1.42	0.96–2.08	0.076
Neoadjuvant regimen												
Gem-based vs. FFX-based	1.19	0.86–1.63	0.290	–			1.31	0.94–1.82	0.114	1.29	0.92–1.81	0.140
Gem-FFX vs FFX-based	0.89	0.59–1.35	0.590	–			0.94	0.61–1.44	0.769	0.86	0.55–1.33	0.496
CA 19-9 pre-neoadjuvant[a]												
>150 U/mL vs. <150 U/mL	1.70	1.17–2.48	**0.006**	NA[1]			1.60	1.07–2.39	**0.021**	NA[1]		
CA 19-9 pre-surgery[b]												
>100 U/mL vs. <100 U/mL	2.30	1.49–3.55	**<0.001**	NA[1]			2.12	1.34–3.35	**0.001**	NA[1]		
Vascular resection												
Yes vs. no	1.08	0.80–1.44	0.630	–			1.02	0.75–1.38	0.912	0.78	0.55–1.09	0.142
Resection margin status												
R 1 vs. R0	1.31	0.94–1.83	0.126	–			1.36	0.96–1.93	0.087	–		
T-stage (8th)												
yT3-yT4 vs. yT0-yT2	1.45	1.09–1.94	**0.012**	–			1.53	1.13–2.06	**0.006**	**1.39**	**1.01–1.92**	**0.046**
N-stage (8th)												
yN1-yN2 vs. yN0	1.93	1.44–2.59	**<0.001**	**1.68**	**1.19–2.38**	**0.003**	1.91	1.41–2.59	**<0.001**	**1.50**	**1.06–2.13**	**0.024**
Tumor differentiation grade												
Poor vs. well/moderate	1.69	1.23–2.31	**0.001**	1.37	0.98–1.89	0.062	1.97	1.43–2.71	**<0.001**	**1.60**	**1.14–2.23**	**0.006**
Micr. lymphovascular invasion												
Yes vs. no	1.34	1.00–1.79	**0.050**	–			1.52	1.13–2.06	**0.006**	–		
Micr. perineural invasion												
Yes vs. no	1.78	1.32–2.40	**<0.001**	**1.43**	**1.02–2.01**	**0.041**	1.87	1.36–2.55	**<0.001**	**1.48**	**1.02–2.15**	**0.041**
CAP score												
0 vs. 2/3	0.54	0.29–1.00	0.051	NA[2]			0.28	0.12–0.64	**0.002**	NA[2]		
1 vs. 2/3	0.93	0.65–1.35	0.717	NA[2]			0.89	0.60–1.31	0.548	NA[2]		
Adjuvant therapy												
Any vs. none	0.76	0.56–1.02	0.067	**0.73**	**0.54–0.99**	**0.043**	0.76	0.56–1.03	0.072	**0.69**	**0.50–0.95**	**0.025**

AJCC, American Joint Committee on Cancer; BRPC, borderline resectable pancreatic cancer; CA, carbohydrate antigen; CAP, College of American Pathologists; CHRT, chemoradiotherapy; CHT, chemotherapy; CI, confidence interval; FFX, FOLFIRINOX; GEM, gemcitabine; HR, hazard ratio; LAPC, locally advanced pancreatic cancer; Micr, microscopic; NA, not applicable.
*Continuous variable.
[1]Pre-neoadjuvant and pre-surgery CA 19-9 were not considered for inclusion in the multivariable models due to significant amount of missing values.
[2]Treatment response (CAP score) was not considered for inclusion in the multivariable models due to significant correlation with other pathologic tumor characteristics.
[a] 149 patients had documented pre-neoadjuvant CA 19-9 values, of whom 11 patients were Lewis-antigen negative and excluded.
[b] 149 patients had documented pre-operative CA 19-9 values, of whom 11 patients were Lewis-antigen negative and excluded.

the length and regimen of received treatments based on patient and clinician preference, potentially introducing substantial selection bias. In the current literature, data on adjuvant therapy after neoadjuvant therapy and resection in BRPC/LAPC patients are limited and often contradictory. In a recent study of 1375 patients, no difference in median OS was found based on the receipt of additional adjuvant therapy (28 vs. 27 months, $P = 0.541$) [42]. On the other hand, a different study showed survival benefit with added adjuvant treatment, albeit only in patients with a positive lymph node ratio <0.15 [43]. Due to the ostensible limitations of retrospective studies, many questions on the addition of adjuvant treatment currently remain unanswered. Hopefully, future prospective trials will provide more insights concerning the right indications and strategies for adjuvant therapy in these patients.

This retrospective study has several important limitations. Most importantly, both neoadjuvant and adjuvant treatment regimens and length varied considerably. Therefore, the associations between treatment factors and recurrence and survival outcomes should be interpreted cautiously, as selection bias could play a significant role. Additionally, a substantial number of patients did not have pre-neoadjuvant and/or pre-surgery CA 19-9 available, prohibiting the inclusion of this potentially important risk factor in the multivariable models. Lastly, diagnosing disease recurrence with radiographic imaging can be challenging, especially since neoadjuvant or adjuvant radiotherapy can lead to localized fibrosis at the pancreatectomy site, possibly resulting in over-estimation of the incidence of local recurrence [44].

5. Conclusions

In summary, this study offers a comprehensive understanding of the different aspects of disease recurrence in BRPC/LAPC patients, including the identification of specific clinicopathologic factors associated with distinct recurrence locations. Despite neoadjuvant therapy leading to resection and relatively favorable pathologic tumor characteristics, more than 80% of patients experienced disease recurrence, 72.5% of which occurred at distant sites. These findings suggest that systemic disease continues to exist in BRPC/LAPC patients after neoadjuvant treatment, highlighting the need to improve systemic treatment options and identify occult disease

prior to surgery. Future prospective studies should focus on finding the optimal treatment sequence and regimens to reduce recurrence rates and consequently improve survival in these patients.

Conflicts of interest

The authors have no financial disclosures and no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.04.007.

References

[1] He J, Blair AB, Groot VP, Javed AA, Burkhart RA, Gemenetzis G, et al. Is a pathological complete response following neoadjuvant chemoradiation associated with prolonged survival in patients with pancreatic cancer? Ann Surg 2018;268:1–8. https://doi.org/10.1097/SLA.0000000000002672.

[2] Castillo CFF. A changing landscape in pancreatic cancer. Ann Surg 2018;268:9–10. https://doi.org/10.1097/SLA.0000000000002755.

[3] Katz MH, Kim MP, Tzeng C-W, Lee JE. Preoperative chemoradiation for borderline resectable pancreatic cancer: the new standard? Ann Surg 2018;268:223–4. https://doi.org/10.1097/SLA.0000000000002783.

[4] Gemenetzis G, Groot VP, Blair AB, Laheru DA, Zheng L, Narang AK, et al. Survival in locally advanced pancreatic cancer after neoadjuvant therapy and surgical resection. Ann Surg 2018;1. https://doi.org/10.1097/SLA.0000000000002753.

[5] Javed AA, Wright MJ, Siddique A, Blair AB, Ding D, Burkhart RA, et al. Outcome of patients with borderline resectable pancreatic cancer in the contemporary era of neoadjuvant chemotherapy. J Gastrointest Surg 2019;23:112–21. https://doi.org/10.1007/s11605-018-3966-8.

[6] Gillen S, Schuster T, Meyer Zum Buschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med 2010;7:e1000267. https://doi.org/10.1371/journal.pmed.1000267.

[7] Petrelli F, Coinu A, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, et al. FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: a meta-analytical review of published studies. Pancreas 2015;44:515–21. https://doi.org/10.1097/MPA.0000000000000314.

[8] Tang K, Lu W, Qin W, Wu Y. Neoadjuvant therapy for patients with borderline resectable pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. Pancreatology 2016;16:28–37. https://doi.org/10.1016/j.pan.2015.11.007.

[9] Rombouts SJ, Walma MS, Vogel JA, van Rijssen LB, Wilmink JW, Mohammad NH, et al. Systematic review of resection rates and clinical outcomes after FOLFIRINOX-based treatment in patients with locally advanced pancreatic cancer. Ann Surg Oncol 2016;23:4352–60. https://doi.org/10.1245/s10434-016-5373-2.

[10] Dhir M, Malhotra GK, Sohal DPS, Hein NA, Smith LM, O'Reilly EM, et al. Neoadjuvant treatment of pancreatic adenocarcinoma: a systematic review and meta-analysis of 5520 patients. World J Surg Oncol 2017;15:183. https://doi.org/10.1186/s12957-017-1240-2.

[11] Versteijne E, Vogel JA, Besselink MG, Busch ORC, Wilmink JW, Daams JG, et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. Br J Surg 2018;105:946–58. https://doi.org/10.1002/bjs.10870.

[12] Katz MHG, Pisters PWT, Evans DB, Sun CC, Lee JE, Fleming JB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg 2008;206:833–46. https://doi.org/10.1016/j.jamcollsurg.2007.12.020.

[13] Loehrer AP, Ferrone CR. Treatment of locally advanced pancreatic ductal adenocarcinoma. Dig Surg 2016;33:343–50. https://doi.org/10.1159/000445020.

[14] Toesca DAS, Koong AJ, Poultsides GA, Visser BC, Haraldsdottir S, Koong AC, et al. Management of borderline resectable pancreatic cancer. Int J Radiat Oncol 2018;100:1155–74. https://doi.org/10.1016/j.ijrobp.2017.12.287.

[15] Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, et al. Pancreatic adenocarcinoma, version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 2017;15:1028–61. https://doi.org/10.6004/jnccn.2017.0131.

[16] Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187–96. https://doi.org/10.1097/SLA.0b013e3181b13ca2.

[17] Allen PJ, Kuk D, Castillo CF-D, Basturk O, Wolfgang CL, Cameron JL, et al. Multi-institutional validation study of the American Joint commission on cancer (8th edition) changes for T and N staging in patients with pancreatic adenocarcinoma. Ann Surg 2017;265:185–91. https://doi.org/10.1097/SLA.0000000000001763.

[18] Kakar S, Shi C, Adsay NV, Fitzgibbons P, Frankel WL, Klimstra DS, et al. Protocol for the examination of specimens from patients with carcinoma of the pancreas; PancreasExocrine 4.0.0.0. Coll Am Pathol 2017:1–16. http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution_Folders/WebContent/pdf/cp-pancreas-exocrine-17protocol-4000.pdf. [Accessed 20 May 2018].

[19] Groot VP, Rezaee N, Wu W, Cameron JL, Fishman EK, Hruban RH, et al. Patterns, timing, and predictors of recurrence following pancreatectomy for pancreatic ductal adenocarcinoma. Ann Surg 2018;267:936–45. https://doi.org/10.1097/SLA.0000000000002234.

[20] Groot VP, Gemenetzis G, Blair AB, Rivero-Soto RJ, Yu J, Javed AA, et al. Defining and predicting early recurrence in 957 patients with resected pancreatic ductal adenocarcinoma. Ann Surg 2018. https://doi.org/10.1097/SLA.0000000000002734.

[21] Groot VP, Gemenetzis G, Blair AB, Ding D, Javed AA, Burkhart RA, et al. Implications of the pattern of disease recurrence on survival following pancreatectomy for pancreatic ductal adenocarcinoma. Ann Surg Oncol 2018;25:2475–83. https://doi.org/10.1245/s10434-018-6558-7.

[22] Kadera BE, Sunjaya DB, Isacoff WH, Li L, Hines OJ, Tomlinson JS, et al. Locally advanced pancreatic cancer. JAMA Surg 2014;149:145. https://doi.org/10.1001/jamasurg.2013.2690.

[23] Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg 2015;261:12–7. https://doi.org/10.1097/SLA.0000000000000867.

[24] Pietrasz D, Marthey L, Wagner M, Blanc J-F, Laurent C, Turrini O, et al. Pathologic major response after FOLFIRINOX is prognostic for patients secondary resected for borderline or locally advanced pancreatic adenocarcinoma: an AGEO-French, prospective, multicentric cohort. Ann Surg Oncol 2015;22(Suppl 3):S1196–205. https://doi.org/10.1245/s10434-015-4783-x.

[25] Sherman WH, Chu K, Chabot J, Allendorf J, Schrope BA, Hecht E, et al. Neoadjuvant gemcitabine, docetaxel, and capecitabine followed by gemcitabine and capecitabine/radiation therapy and surgery in locally advanced, unresectable pancreatic adenocarcinoma. Cancer 2015;121:673–80. https://doi.org/10.1002/cncr.29112.

[26] Mellon EA, Jin WH, Frakes JM, Centeno BA, Strom TJ, Springett GM, et al. Predictors and survival for pathologic tumor response grade in borderline resectable and locally advanced pancreatic cancer treated with induction chemotherapy and neoadjuvant stereotactic body radiotherapy. Acta Oncol (Madr) 2017;56:391–7. https://doi.org/10.1080/0284186X.2016.1256497.

[27] Kim HS, Jang J-Y, Han Y, Lee KB, Joo I, Lee D-H, et al. Survival outcome and prognostic factors of neoadjuvant treatment followed by resection for borderline resectable pancreatic cancer. Ann Surg Treat Res 2017;93:186. https://doi.org/10.4174/astr.2017.93.4.186.

[28] Jang J-Y, Han Y, Lee H, Kim S-W, Kwon W, Lee K-H, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. Ann Surg 2018;268:215–22. https://doi.org/10.1097/SLA.0000000000002705.

[29] Katz MHG, Shi Q, Ahmad SA, Herman JM, Marsh R de W, Collisson E, et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer. JAMA Surg 2016;151:e161137. https://doi.org/10.1001/jamasurg.2016.1137.

[30] Schorn S, Demir IE, Samm N, Scheufele F, Calavrezos L, Sargut M, et al. Meta-analysis of the impact of neoadjuvant therapy on patterns of recurrence in pancreatic ductal adenocarcinoma. BJS Open 2018;2:52–61. https://doi.org/10.1002/bjs5.46.

[31] Versteijne E, van Eijck CHJ, Punt CJA, Suker M, Zwinderman AH, Dohmen MAC, et al. Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC trial): study protocol for a multicentre randomized controlled trial. Trials 2016;17:127. https://doi.org/10.1186/s13063-016-1262-z.

[32] Schorn S, Demir IE, Reyes CM, Saricaoglu C, Samm N, Schirren R, et al. The impact of neoadjuvant therapy on the histopathological features of pancreatic ductal adenocarcinoma - a systematic review and meta-analysis. Cancer Treat Rev 2017;55:96–106. https://doi.org/10.1016/j.ctrv.2017.03.003.

[33] Estrella JS, Rashid A, Fleming JB, Katz MH, Lee JE, Wolf RA, et al. Post-therapy pathologic stage and survival in patients with pancreatic ductal adenocarcinoma treated with neoadjuvant chemoradiation. Cancer 2012;118:268–77. https://doi.org/10.1002/cncr.26243.

[34] Takahashi H, Ohigashi H, Ishikawa O, Gotoh K, Yamada T, Nagata S, et al. Perineural invasion and lymph node involvement as indicators of surgical

outcome and pattern of recurrence in the setting of preoperative gemcitabine-based chemoradiation therapy for resectable pancreatic cancer. Ann Surg 2012;255:95–102. https://doi.org/10.1097/SLA.0b013e31823d813c.
[35] Roland CL, Yang AD, Katz MHG, Chatterjee D, Wang H, Lin H, et al. Neoadjuvant therapy is associated with a reduced lymph node ratio in patients with potentially resectable pancreatic cancer. Ann Surg Oncol 2015;22:1168–75. https://doi.org/10.1245/s10434-014-4192-6.
[36] Fischer LK, Katz MH, Lee SM, Liu L, Wang H, Varadhachary GR, et al. The number and ratio of positive lymph nodes affect pancreatic cancer patient survival after neoadjuvant therapy and pancreaticoduodenectomy. Histopathology 2016;68:210–20. https://doi.org/10.1111/his.12732.
[37] de Geus SWL, Kasumova GG, Sachs TE, Ng SC, Kent TS, Moser AJ, et al. Neoadjuvant therapy affects margins and margins affect all: perioperative and survival outcomes in resected pancreatic adenocarcinoma. HPB (Oxford) 2018;20:573–81. https://doi.org/10.1016/j.hpb.2017.12.004.
[38] Nurmi A, Mustonen H, Parviainen H, Peltola K, Haglund C, Seppänen H. Neoadjuvant therapy offers longer survival than upfront surgery for poorly differentiated and higher stage pancreatic cancer. Acta Oncol 2018;57:799–806. https://doi.org/10.1080/0284186X.2017.1415458.
[39] Husain H, Velculescu VE. Cancer DNA in the circulation: the liquid biopsy. J Am Med Assoc 2017;318:1272–4. https://doi.org/10.1001/jama.2017.12131.
[40] Corcoran RB, Chabner BA. Application of cell-free DNA analysis to cancer treatment. N Engl J Med 2018;379:1754–65. https://doi.org/10.1056/NEJMra1706174.
[41] Gemenetzis G, Groot VP, Yu J, Ding D, Teinor JA, Javed AA, et al. Circulating tumor cells dynamics in pancreatic adenocarcinoma correlate with disease status. Ann Surg 2018;268:408–20. https://doi.org/10.1097/SLA.0000000000002925.
[42] de Geus SWL, Kasumova GG, Eskander MF, Ng SC, Kent TS, James Moser A, et al. Is neoadjuvant therapy sufficient in resected pancreatic cancer patients? A national study. J Gastrointest Surg 2018;22:214–25. https://doi.org/10.1007/s11605-017-3541-8.
[43] Roland CL, Katz MHG, Tzeng C-WD, Lin H, Varadhachary GR, Shroff R, et al. The addition of postoperative chemotherapy is associated with improved survival in patients with pancreatic cancer treated with preoperative therapy. Ann Surg Oncol 2015;22:1221–8. https://doi.org/10.1245/s10434-015-4854-z.
[44] Balaj C, Ayav A, Oliver A, Jausset F, Sellal C, Claudon M, et al. CT imaging of early local recurrence of pancreatic adenocarcinoma following pancreaticoduodenectomy. Abdom Radiol 2016;41:273–82. https://doi.org/10.1007/s00261-015-0564-z.