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ORIGINAL ARTICLE

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Intention to treat outcomes among patients with pancreatic cancer treated using International Study Group on Pancreatic Surgery recommended pathways for resectable and borderline resectable disease

Sivesh K. Kamarajah,* Nikolaos Chatzizacharias,* James Hodson,† Francesca Marcon,* Marit Kalisvaart,* Pankaj Punia,‡ Yuk Ting Ma,‡ Bobby Dasari,* Ravi Marudanayagam,* Robert P. Sutcliffe,* Paolo Muiesan,* Darius F. Mirza,* John Isaac* and Keith J. Roberts*§

*Department of Pancreatic Surgery, Queen Elizabeth Hospital Birmingham, Birmingham, UK
†Institute of Translational Medicine, University of Birmingham, Birmingham, UK
‡Department of Oncology, Queen Elizabeth Hospital Birmingham, Birmingham, UK and
§Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK

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Correspondence
Mr Keith J Roberts, Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham B15 2TH, UK. Email: j.k.roberts@bham.ac.uk

S. K. Kamarajah MBChB; **N. Chatzizacharias** FRCS; **J. Hodson** BSc; **F. Marcon** MD; **M. Kalisvaart** MD; **P. Punia** MRCP; **Y. Ting Ma** PhD; **B. Dasari** FRCS; **R. Marudanayagam** FRCS; **R. P. Sutcliffe** FRCS; **P. Muiesan** PhD; **D. F. Mirza** FRCS; **J. Isaac** FRCS; **K. J. Roberts** PhD.

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Abstract

Background: The International Study Group on Pancreatic Surgery recommends upfront surgery for resectable pancreatic cancer or borderline resectable-venous (BR-V) disease and neoadjuvant therapy (NAT) among those with arterial involvement (BR-A or locally advanced, LA). Though neoadjuvant therapy (NAT) is a promising strategy, outcomes are rarely reported on intention-to-treat (ITT) basis. This study presents ITT outcomes where pathways to surgery were in line with International Study Group on Pancreatic Surgery guidelines.

Methods: Patients recommended for potentially curative treatment with PDAC between 2012 and 2017 (n = 345) were classified as resectable, BR-A/BR-V or LA, according to NCCN criteria. The primary outcome was overall survival. Secondary outcomes were resection rates, positive margins and toxicity among patients receiving NAT.

Results: At surgery, the resection rates were 78% (172/221), 65% (35/54) and 54% (21/39) for those with resectable, BR-V and BR-A/LA disease, respectively ($P < 0.0001$). The median survival of those resected in the BR-A/LA cohort was 31 months. However, on an ITT basis, there was no significant difference in survival between resectable, BR-V and BR-A/LA disease (median: 19 versus 15 versus 19 months; $P = 0.585$). On review, some 31 (44%) patients of the BR-A/LA cohort either did not receive or did not complete NAT.

Conclusion: To realize benefits of NAT, more patients need to complete NAT and to undergo resection. Upfront resection for BR-V disease is associated with equivalent outcomes to upfront surgery for resectable disease or NAT for BR-A/LA disease. Strategies to increase the proportion of patients who complete NAT and undergo resection are needed.

Introduction

Only a small group of patients with pancreatic ductal adenocarcinoma (PDAC) are 'resectable' at diagnosis. A further group has local vascular involvement, divided into borderline resectable-venous (BR-V), arterial (BR-A) or locally advanced (LA) subgroups.[1] When venous resection is performed, survival outcomes are reported to be equivalent to those patients with resectable disease undergoing a surgery-first approach[2–11] and, as such, the International Study Group on Pancreatic Surgery (ISGPS) position is that BR-V patients should be treated with a surgery-first approach.[1] However, arterial resection has not gained widespread acceptance, given the poor outcomes of up

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front surgery in this cohort,[12] and is not supported by the ISGPS.[1] The use of neoadjuvant therapy (NAT) for BR-A and LA disease has been widely reported[13]. NAT is associated with reduced rates of disease within lymph nodes or at resection margins.[13,14]

There is much debate regarding optimal pathways to surgery for patients with resectable or BR disease. Indeed, in selected patients with resectable and BR cancers identified from the US National Cancer Database (NCDB), Mokdad *et al*. demonstrated that those receiving NAT have superior survival to those receiving upfront surgical resection.[15]

However, since not all patients who receive NAT proceed to surgery, reporting survival among those patients who are resected is problematic due to selection bias. Resection rates among published cohorts are typically low, reflecting a lack of efficacy of various NAT regimes and associated toxicity.[13] A further complicating factor is that pancreatic cancer typically affects elderly patients, whilst current NAT regimes are typically confined to younger patients with minimal comorbidity. As a result, a proportion of patients who are recommended NAT are unlikely to actually receive it. As such, to accurately understand the impact of treatment strategies on survival, analyses need to be performed on an intention-to-treat basis.

With a lack of level 1 evidence, there is thus uncertainty as to the efficacy of NAT. Hence, this study aimed at evaluating overall survival, on an intention-to-treat basis, using the ISGPS recommended pathways for upfront surgery (resectable and BR-V) or NAT (BR-A).

Methods

This was a single centre retrospective analysis of patients with non-metastatic pancreatic cancer in the head of pancreas discussed at the specialist multidisciplinary meeting (MDT) between August 2012 and August 2017 at the Queen Elizabeth Hospital Birmingham, UK. Patients with PDAC were included in the study if the MDT recommended potentially curative treatment, whether that was surgery-first or surgery after NAT. Patients with cancers of the bile duct, ampulla of Vater or duodenum were excluded, as were those that were deemed unresectable with or without NAT. Patients who received FOLFIRINOX with palliative intent were also excluded. Only those patients with tumours of the pancreatic head were included to keep the cohort homogenous.

Patient groups

Patients were stratified by extent of disease at the time of diagnosis as resectable, borderline resectable (BR-V and BR-A for BR venous and arterial disease respectively) or locally advanced (LA), according to the NCCN criteria.[1] In line with the ISPGS consensus statement, those patients with resectable disease or BR-V disease were treated with a surgery-first approach and those patients with BR-A disease were treated with NAT. Other selected patients with LA disease were offered NAT if it was thought that surgery would be possible after chemotherapy. Therefore, for the purposes of this study, the following groups are defined, based upon the anatomical distribution of tumour, as defined by the ISGPS: (i) resectable, (ii) BR-V, consisting of those patients with BR-V disease and (iii) the combination of BR-A and LA, as there is considerable homogeneity within this group, in terms of burden of disease and treatment pathways, and to avoid having small groups of patients.

Patient pathway

Six cycles of FOLFIRINOX without radiotherapy was the standard regime for NAT. Patients deemed too frail for FOLFIRINOX or who had complications that prevented further therapy received gemcitabine-based regimens. Re-staging CT scans were performed following completion of NAT, to allow assessment of resectability. For patients proceeding directly to surgery, since 2015 those with jaundice have primarily been treated without placing a biliary drain, otherwise preoperative biliary drainage was used among the remaining jaundiced patients. All patients undergoing surgery were referred for adjuvant chemotherapy in line with contemporaneous existing practice within the UK.

Resection and bypass surgery

Pylorus-preserving pancreatoduodenectomy was the standard operation, with a Kausch Whipple procedure performed when deemed appropriate on oncological grounds. A standard lymphadenectomy was performed to include dissection of the common hepatic artery from the splenic artery origin to the origins of the hepatic arteries. Perineural tissue and lymph nodes along the common bile duct, station 8 nodes along the hepatic artery, posterior and anterior pancreaticoduodenal nodes, nodes along the superior mesenteric vein and right lateral wall of the superior mesenteric artery were removed. If a vein resection was required, the preferred reconstruction was circumferential resection with end to end anastomosis; if the defect was too extensive for primary closure, a cadaveric iliac interposition vein graft was used. The splenic vein was re-implanted when possible. Arterial resection was not practiced routinely. The technique of pancreato-enteric anastomosis was performed at the operating surgeons' discretion. All specimens were reviewed by dedicated pancreatic specialist pathologists. The resection margins that were consistently examined were the pancreatic neck transection margin, the superior mesenteric artery surface, proximal bile duct margin, proximal duodenal margin and distal duodenal margin. If a patient was found to be unresectable, then single gastrojejunostomy was performed, with biliary bypass more latterly confined to those patients without pre-existing metal biliary stent.

Outcomes

The primary outcome was overall survival, defined as the time from diagnosis at presentation to death, with patients being censored at the final follow-up appointment. Secondary outcomes were resection rates, rates of positive margins and toxicity in patients receiving NAT.

Statistical analysis

Initially, comparisons across the disease groups were performed using one-way ANOVA for normally distributed continuous variables, Kruskal-Wallis tests for non-normal and ordinal variables and Fisher's exact tests for nominal variables. Patient survival was compared between groups using Kaplan–Meier curves and Cox regression models and reported as estimated median survival times and hazard

ratios (HRs). A multivariable analysis was also performed, to identify significant independent predictors of patient survival. Continuous variables were divided into categories, prior to analysis, where poor model fit was detected. The extent of disease, use of NAT and patient demographics were then considered for inclusion in a multivariable Cox regression model, with a backwards stepwise approach used for variable selection. Where the extent of disease was not selected for inclusion in the final model, this factor was included in a new model, alongside the factors identified by the stepwise procedure.

The subgroup of BR-A/LA patients was then analysed in further detail, to assess the differences in survival between the types of surgery performed (i.e. none, bypass or resection). Initially, this analysis treated the type of surgery as a fixed covariate in a Cox regression model. However, this was subject to survivorship bias as, by definition, patients in the surgical groups had to survive for a sufficient period from diagnosis to receive surgery, artificially inflating the survival benefit in these groups. As a result, the analysis was also repeated with the type of surgery treated as a time-dependent covariate. In this model, the whole cohort commenced follow up in the non-surgical group, moving to either the bypass or resection groups at the time that surgery was performed.

All analyses were performed using IBM SPSS 22 (IBM Corp, Armonk, NY, USA), with $P < 0.05$ deemed to be indicative of statistical significance throughout.

Results

Patient demographics and treatment

Of 345 patients, at the time of diagnosis, 64% ($n = 221$) had disease that were classified as resectable, 16% ($n = 54$) as BR-V and 20% ($n = 70$) as BR-A/LA (Table 1). Patients in the BR-A/LA cohort were significantly younger ($P < 0.001$), with lower rates of jaundice ($P = 0.006$) and preoperative biliary drainage ($P = 0.014$) than the other two groups.

Treatment of patients differed significantly between the groups (Table 2). NAT was received by the majority of patients with BR-A/LA disease (79%), compared to 4% of BR-V (two patients developed post-ERCP pancreatitis and so received NAT as a temporizing measure whilst they recovered from pancreatitis), and none of the resectable patients ($P < 0.001$).

Resection rates

At surgery, some 78% (172/221), 65% (35/54) and 54% (21/39) of those patients with resectable, BR-V and BR-A/LA disease, respectively ($P = 0.003$), were resected. However, among the BR-A/LA cohort, a further 31 patients who did not receive or complete NAT due to rapid disease progression or progression of frailty and did not undergo any attempt at resection. Therefore, the ITT resection rate among the BR-A/LA group was 30%.

NAT in BR-A/LA disease

Some 55/70 (79%) received NAT which comprised 87% (48/55) receiving FOLFIRINOX, 11% (6/55) gemcitabine and 2% (1/55) gemcitabine/abraxane. Some 60% of these patients developed at least one symptom of toxicity (Table S1).

Thus 15 (21%) of this cohort who were referred for NAT never began treatment. Patients who received NAT were significantly younger (mean 62.6 versus 67.9 years, $P = 0.021$), less likely to

Table 1 Baseline demographics of patients with pancreatic adenocarcinoma stratified by extent of disease at diagnosis

		Extent of disease at diagnosis			
	N	Resectable ($n = 221$)	BR-V ($n = 54$)	BR-A/LA ($n = 70$)	*P*-value
Patient demographics					
Age at presentation (years)	345	68.0 ± 8.8	65.3 ± 8.9	63.7 ± 7.9	**<0.001**
Gender (% male)	345	116 (52%)	23 (43%)	36 (51%)	0.428
Body mass index (BMI, kg/m^2)	337	25.9 ± 4.8	26.7 ± 5.0	25.7 ± 4.1	0.446
Smoker	345	18 (8%)	5 (9%)	4 (6%)	0.735
Preoperative jaundice	345	173 (78%)	44 (81%)	42 (60%)	**0.006**
Back pain	345	11 (5%)	5 (9%)	5 (7%)	0.409
Preoperative biliary drainage	345	146 (66%)	27 (50%)	35 (50%)	**0.014**
Charlson Co-morbidity Index	345				0.160†
2		109 (49%)	22 (41%)	41 (59%)	
3		67 (30%)	18 (33%)	17 (24%)	
4		33 (15%)	10 (19%)	8 (11%)	
5		8 (4%)	3 (6%)	3 (4%)	
6		4 (2%)	1 (2%)	1 (1%)	
Past medical history					
Diabetes	345	51 (23%)	20 (37%)	18 (26%)	0.119
Cerebrovascular accidents	345	8 (4%)	1 (2%)	3 (4%)	0.834
Asthma	345	18 (8%)	4 (7%)	3 (4%)	0.654
Cardiac/angina/coronary	345	19 (9%)	1 (2%)	5 (7%)	0.238
Chronic obstructive pulmonary disease	345	9 (4%)	5 (9%)	0 (0%)	**0.024**
Hypertension	345	95 (43%)	19 (35%)	20 (29%)	0.082
Renal failure	345	5 (2%)	3 (6%)	1 (1%)	0.330
Myocardial infarction	345	9 (4%)	0 (0%)	0 (0%)	0.104

Data are reported as mean ± SD, with *P*-values from one-way ANOVA or as *n* (%), with *P*-values from Fisher's exact tests, unless stated otherwise.

†*P*-value from a Kruskal-Wallis test, since the factor was ordinal. Bold *P*-values are significant at $P < 0.05$.

BR-V/BR-A, borderline resectable with local veins/arteries involved; LA, locally advanced.

Table 2 Treatment and tumour-related factors stratified by extent of disease at diagnosis

		Extent of disease at diagnosis			
	N	Resectable (*n* = 221)	BR-V (*n* = 54)	BR-A/LA (*n* = 70)	*P*-value
Treatment					
Neoadjuvant chemo.	345	0 (0%)	2 (4%)	55 (79%)	**<0.001**
IRE	345	0 (0%)	0 (0%)	3 (4%)	**0.012**
Radiotherapy	345	0 (0%)	0 (0%)	3 (4%)	**0.012**
Type of surgery	345				**<0.001**
None		0 (0%)	0 (0%)	31 (44%)	
Bypass		49 (22%)	19 (35%)	18 (26%)	
Resection		172 (78%)	35 (65%)	21 (30%)	
Venous resection	228	23 (13%)	34 (97%)	14 (67%)	**<0.001**
Arterial resection	228	0	0	0	-
		Resectable (*n* = 172)	**BR-V (*n* = 35)**	**BR-A/LA (*n* = 21)**	
Disease-related factors (in resected patients: *N* = 228)					
Tumour size (mm)	228	29.1 ± 9.2	33.1 ± 11.0	30.0 ± 11.4	0.087
Tumour grade	227				0.387†
Well		6 (4%)	1 (3%)	2 (10%)	
Moderate		125 (73%)	23 (66%)	15 (71%)	
Poor		40 (23%)	11 (31%)	4 (19%)	
T-stage	227				0.789†
T0		1 (1%)	0 (0%)	0 (0%)	
T1		1 (1%)	0 (0%)	0 (0%)	
T2		4 (2%)	1 (3%)	0 (0%)	
T3		164 (96%)	34 (97%)	21 (100%)	
T4		1 (1%)	0 (0%)	0 (0%)	
N-stage (% N1)	228	147 (85%)	32 (91%)	13 (62%)	**0.013**
Margin status (% R1)	228	60 (35%)	18 (51%)	7 (33%)	0.179
Total nodes	228	18 ± 7	19 ± 4	19 ± 6	0.740
Positive nodes	228	4 (1–7)	5 (2–7)	1 (0–4)	**0.008**
Lymph node ratio	228	0.22 (0.07–0.37)	0.26 (0.08–0.40)	0.08 (0.00–0.21)	**0.012**
CA19-9, IU/L‡	192	150 (44–565)	278 (87–2332)	136 (16–960)	0.137
Perineural invasion	228	143 (83%)	31 (89%)	17 (81%)	0.677
Perivascular invasion	228	138 (80%)	26 (74%)	15 (71%)	0.489
Duodenal invasion	228	88 (51%)	16 (46%)	7 (33%)	0.284
Bile duct invasion	228	88 (51%)	24 (69%)	8 (38%)	0.067
Pancreatic invasion	228	52 (30%)	13 (37%)	9 (43%)	0.390
Fatty tissue invasion	228	150 (87%)	34 (97%)	18 (86%)	0.217
Adjuvant chemotherapy	228	119 (69%)	24 (69%)	16 (76%)	0.794

Data are reported as mean ± SD, with *P*-values from one-way ANOVA, median (IQR), with *P*-values from Kruskal-Wallis tests, or as *n* (%), with p-values from Fisher's exact tests, unless stated otherwise. Bold *P*-values are significant at $P < 0.05$.

†*P*-value from a Kruskal-Wallis test, since the factor was ordinal.

‡CA19-9 levels measured prior to surgery.

BR-V/BR-A, borderline resectable with local veins/arteries involved; IRE, irreversible electroporation; LA, locally advanced.

have a history of cerebrovascular accidents (0% versus 20%, $P = 0.008$) and had a significantly lower rate of preoperative jaundice (51% versus 93%, $P = 0.003$) than those that did not receive the treatment (Tables S2 and S3). A further 16 (23%) patients begun NAT but did not proceed to surgery due to progression of disease and/or frailty. NAT was not found to be significantly associated with post-diagnosis survival in those treated with resections (HR 0.39, 95% CI 0.06–2.37, $P = 0.305$).

Pathologic variables among resected patients

There were significant differences between patients with resectable, BR-V and BR-A/LA disease with respect to N-staging ($P = 0.013$), numbers of positive nodes ($P = 0.008$) and the LN ratio ($P = 0.012$), all of which tended to be highest in the BR-V cohort, and lowest in the BR-A/LA cohort. There was no significant difference in the rates of R1 resection in patients with resectable, BR-V and BR-A/LA disease (35% versus 51% versus 33%, $P = 0.179$) (Table 2) and overall rates of surgical complications were also similar in the three groups (38% versus 37% versus 14%, $P = 0.123$, Table 3).

Overall survival

Survival was greatest among those patients who had received NAT and were resected (median survival 31 months). However, when considering all patients who begun a treatment pathway and including those patients who either did not undergo surgery or were unresectable at surgery, overall survival from diagnosis was similar in the three cohorts (Fig. 1, $P = 0.585$), with median survival of 18.8, 14.9 and 19.0 months in patients with resectable, BR-V and BR-A/LA disease, respectively. Relative to the resectable cohort, HRs were 1.14 (95% CI 0.77–1.70, $P = 0.512$) and 0.89 (95% CI 0.61–1.28, $P = 0.514$) for the BR-V and BR-A/LA disease groups, respectively.

Table 3 Postoperative complications in resected patients

	Extent of disease at diagnosis			
	Resectable (n = 172)	BR-V (n = 35)	BR-A/LA (n = 21)	P-value
Clavien-Dindo Grade				0.123†
0	107 (62%)	22 (63%)	18 (86%)	
1	18 (10%)	3 (9%)	0 (0%)	
2	33 (19%)	8 (23%)	3 (14%)	
3A	3 (2%)	2 (6%)	0 (0%)	
3B	5 (3%)	0 (0%)	0 (0%)	
4A	2 (1%)	0 (0%)	0 (0%)	
5	4 (2%)	0 (0%)	0 (0%)	
Pancreatic fistula				0.489†
No	165 (96%)	32 (91%)	20 (95%)	
Grade A	5 (3%)	0 (0%)	1 (5%)	
Grade B/C	2 (1%)	3 (9%)	0 (0%)	
Bile leak	5 (3%)	0 (0%)	0 (0%)	0.749
Wound infection	16 (9%)	4 (11%)	1 (5%)	0.731
Chest infection	5 (3%)	0 (0%)	0 (0%)	0.749
Renal	1 (1%)	3 (9%)	0 (0%)	**0.016**
Delayed gastric emptying	12 (7%)	3 (9%)	1 (5%)	0.902
GDA/pseudoaneurysm	0 (0%)	1 (3%)	0 (0%)	0.246
Gastrointestinal bleeding	11 (6%)	2 (6%)	1 (5%)	1.000
Intra-abdominal collection	8 (5%)	6 (17%)	0 (0%)	**0.015**
ARDS	5 (3%)	0 (0%)	0 (0%)	0.749

P-values are from Fisher's exact tests, unless stated otherwise, and bold P-values are significant at $P < 0.05$.

†P-value from a Kruskal-Wallis test, as the factor is ordinal.

ARDS, adult respiratory distress syndrome; BR-V/BR-A, borderline resectable with local veins/arteries involved; GDA, gastroduodenal artery; LA, locally advanced.

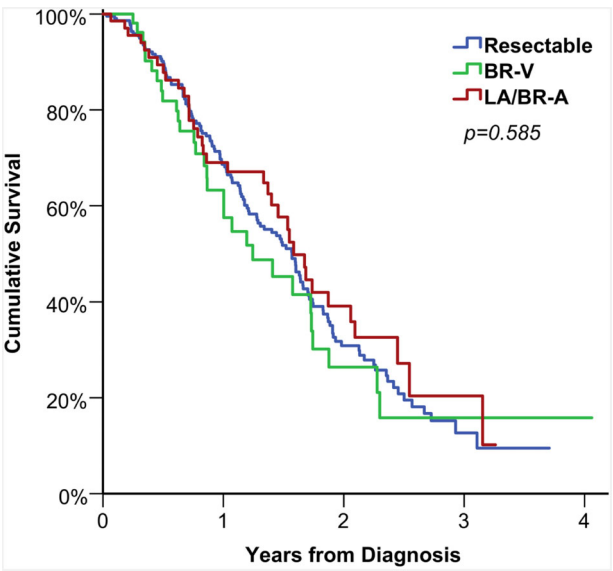

Fig. 1. *Intention to treat* survival analysis among patients stratified by their extent of local disease at diagnosis.

On multivariable analysis (Table S4) that accounted for the patient demographics and use of NAT, the difference between the cohorts remained non-significant (P = 0.661), with HRs of 1.03 (95% CI 0.69–1.55, P = 0.869) and 0.84 (0.57–1.25, P = 0.395) for BR-V and BR-A/LA disease, respectively, relative to the resectable cohort. Analyses were then performed to assess how the patient survival differed by the type of surgery. Within the resectable cohort, patients who received bypass surgery had significantly shorter survival than those who received resections (Fig. 2a), with median survival of 8.8 versus 20 months (HR 3.39, 95% CI 2.33–4.94, $P < 0.001$). A similar trend was observed in the BR-V patients (Fig. 2b), with median survival of 10.1 versus 27.3 months in resection versus bypass surgeries (HR 3.91, 95% CI 1.78–8.63, $P < 0.001$).

Survival analysis in the BR-A/LA group was more complex. In this cohort, 44% (31/70) of patients did not proceed to surgery. Hence, comparing survival between these groups would be subject to survivorship bias, since some patients in the non-surgical group did not survive long enough to have the opportunity to undergo surgery. As such, the analysis was performed using two different approaches to assess and mitigate the impact of this bias (Table 4). The unadjusted analysis (Fig. 3a) found patients in the non-surgical group to have the shortest survival, at a median of 12.4 months. After accounting for survivorship bias in the adjusted analysis, this increased to a median of 16.8 months (Fig. 3b). Adjusted analyses demonstrated the greatest survival among those undergoing resection (median: 30.5 months, HR 0.29, 95% CI 0.11–0.79, P = 0.015 versus no surgery). Patients undergoing bypass surgery had a median survival of 20.2 months, which was not a significant improvement over those that did not receive surgery (HR 0.93, 95% CI 0.41–2.07, P = 0.853) and was significantly shorter than those undergoing resection (HR 3.35, 95% CI 1.20–9.37, P = 0.021).

Discussion

This was a retrospective cohort study among patients with pancreatic cancer who were considered for potentially curative treatment, with patients treated in line with the ISGPS recommended treatment

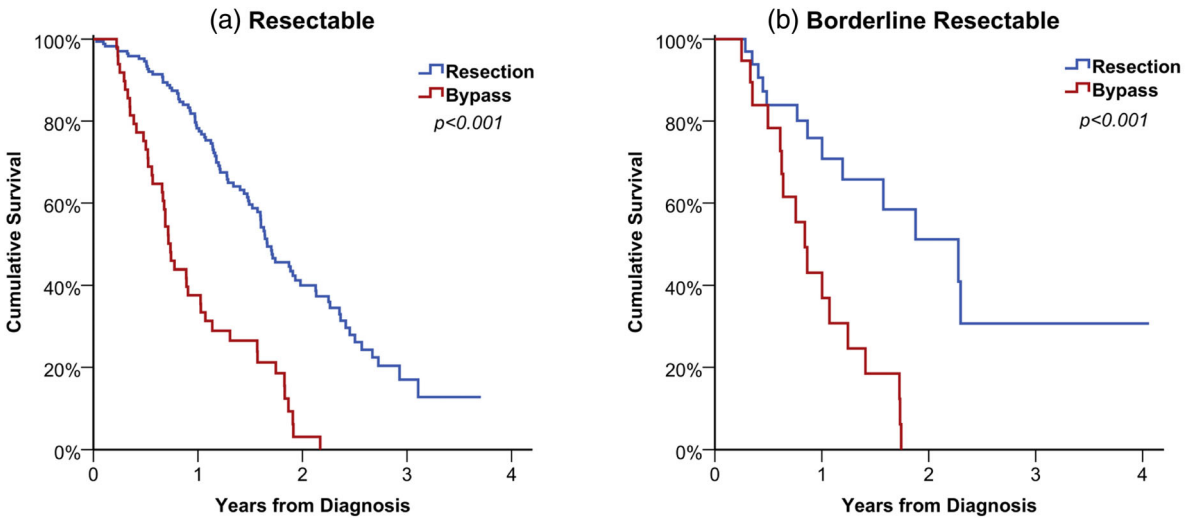

Fig. 2. Kaplan–Meier curves of survival by type of surgery in the (a) resectable and (b) borderline resectable (BR-V) cohorts.

Table 4 Survival analysis in the BR-A/LA (borderline resectable-arterial and locally advanced) subgroup

	Median survival (months)	HR (95% CI)	*P*-value
A. Surgery as fixed covariate (all patients, *n* = 70)			
Surgical group			**<0.001**
None	12.4	-	-
Bypass	20.2	0.50 (0.23–1.09)	0.081
Resection	30.5	0.15 (0.06–0.38)	**<0.001**
B. Surgery as time-dependent (all patients, *n* = 70)			
Surgical group			**0.041**
None	16.8	-	-
Bypass	20.2	0.93 (0.41–2.07)	0.853
Resection	30.5	0.29 (0.11–0.79)	**0.015**
C. Surgery as fixed covariate (neoadjuvant chemo. patients, *n* = 55)			
Surgical group			**<0.001**
None	12.4	-	-
Bypass	20.2	0.45 (9.17–1.22)	0.116
Resection	>39.1†	0.13 (0.04–0.38)	**<0.001**
D. Surgery as time-dependent (neoadjuvant chemo. patients, *n* = 55)			
Surgical group			0.076
None	17.0	-	-
Bypass	20.1	0.94 (0.33–2.68)	0.907
Resection	30.2	0.26 (0.08–0.85)	0.026

Median survival is a Kaplan–Meier estimate. Hazard ratios (HRs) are from univariable Cox regression models. Models A and C assigned patients to their surgical group at the beginning of follow-up. Models B and D treated the surgical group as a time-dependent covariate; hence, all patients were initially assigned to the non-surgical group, before moving into one of the surgical groups at the time that the surgery was performed. Bold *P*-values are significant at $P < 0.05$.

†Survival was >50% at the final follow-up (50.6%); hence, the quoted value is the longest observed follow-up time.

pathways. The intended pathway was upfront resection among those with resectable or BR-V disease and neoadjuvant therapy prior to surgery among patients with BR-A/LA cancer. The study was conducted to assess survival against the background of increasing interest and use of NAT. Indeed, among those patients who received NAT and underwent resection there was significantly greater survival (31 months) than those treated with upfront resection. However, nearly half (44%) of the patients who were referred for NAT never reached surgery due to disease progression and/or because of perceived frailty. The resectable and BR-V cohorts were almost exclusively treated with a surgery-first approach, in line with ISGPS recommendations. The main finding of this study is therefore on an intention-to-treat basis, there appears no significant difference in overall survival between patients with resectable, BR-V and BR-A/LA disease treated within recommended pathways.

One potential advantage of NAT is the avoidance of unnecessary surgery – assuming that no survival advantage is offered by surgical resection in the setting of disease recurrence – the so-called test of biological behaviour. However, this is a simplistic view that does not account for the potential differences in the rates and severities of complications of surgery and NAT, both of which are significant, but have not yet been compared in a randomized trial.[14,16–19] In the present study, complications were more frequent after NAT than

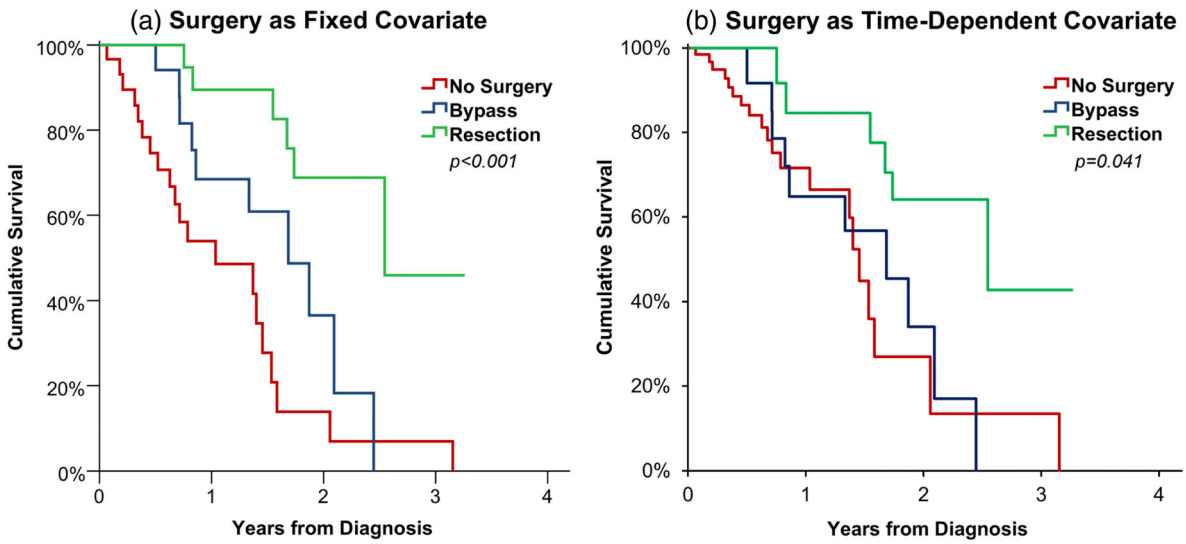

Fig. 3. Kaplan–Meier curves of survival in the locally advanced and borderline resectable - arterial (BR-A/LA) subgroup. Part (a) is a standard Kaplan–Meier curve that assigned patients to their surgical group at the beginning of follow-up. Part (b) is a modified Kaplan–Meier curve that treats the surgical group as a time-dependent covariate. Hence, all patients were initially assigned to the non-surgical group, before moving into one of the surgical groups at the time that the surgery was performed.

after surgery, although the definitions are not the same, and so direct comparison is not possible. Furthermore, surgery is commonly performed on elderly patients, although experience with NAT among elderly patients is generally lacking, given the ages of treated surgical[20] and NAT[14–16] cohorts.

Outcomes among cohorts presented in this study are therefore in line with existing data[14,16–19,21] meaning that our data are generalizable. The key observation here is that although neoadjuvant therapy is associated with very encouraging duration of survival among those who undergo resection, many patients referred for NAT either do not complete or even begin this treatment. As surgeons, we rightly focus upon surgical outcomes. However, we typically recommend treatment at multidisciplinary/cancer board meetings. It is therefore important that we understand what is likely to happen when patients are recommended NAT.

These findings raise an important question whether neoadjuvant FOLFIRINOX could also benefit patients with resectable and BR-V pancreatic cancers in improving long-term survival, recurrence rates and oncological outcomes. Recently, Mokdad *et al.* demonstrated NAT with resection was associated with significantly longer survival compared to patients receiving upfront resection and lower rates of positive resection margins.[15] However, in that study every patient in the NAT cohort had completed NAT and so there was selection bias and when the survival analysis was adjusted reflect this the there was no survival benefit. Such studies perpetuate beliefs that NAT is superior to an upfront surgery strategy. This may not be the case and other factors, such as quality of life and patient experience should also be considered when reviewing optimal pathways. Patients undergoing upfront surgery can avoid preoperative biliary drainage and its associated risks[22]; this cannot be said for NAT, where jaundiced patients must undergo preoperative biliary drainage. A further complicating factor is that comparing NAT with adjuvant therapy is not only comparing treatment pre- or post-surgery, but it is comparing two different chemotherapy regimes. NAT typically consists of therapies that are more effective in other settings of pancreatic cancer treatment than gemcitabine-based therapies.[23] Thus, any survival advantage of NAT may be strongly influenced by the chemotherapy and not timing of its delivery relative to surgery. The addition of capecitabine to gemcitabine yielded a major step forward in survival following resection of pancreatic cancer[24] with further benefit of FOLFIRINOX in this setting.[25] To return to the Mokdad study, which reported better survival among those resectable patients who received NAT, patients were 250% more likely to have received multiagent chemotherapy if they received NAT compared to upfront surgery and then adjuvant therapy.

An interesting observation in this study is the relatively low rates of R0 margins among patients who had received NAT. This is at variance with other non-randomized[26] and randomized data.[27] It is however in keeping with a recent multicentre observational cohort study conducted across 31 European/African centres.[28] Strict criteria for inclusion within randomized trials and intraoperative pathologic assessment of margins with abandoned resection in the setting of positive margins ('Involved arterial structures or narrowing of venous structures should be approached via serial frozen-section biopsies before attempted resection. If biopsies are positive, resection should be abandoned because an R1 or R2 resection is associated with a poor OS')[14] may go some way to explain the discrepancy. This variation is not well understood and requires further work.

There are limitations to this study. Firstly, as this study is non-randomized with a retrospective design, the risks of selection bias are clear and compensating for these is not possible, given the different stages of disease at presentation. Whilst the BR-A/LA cohort

were younger and with less comorbidity, they had more advanced disease. However, findings from this study will allow design of better randomized controlled trials in the future to help answer further questions on NAT for PDAC. There is also likely to be an under-reporting of toxicity outcomes, as not all complications may have been identified, particularly since some patients received treatment in local centres (although these data were sought for every patient). Despite this, the main strength of this study is the reporting of outcomes in all patients with PDAC, that is those with resectable, BR-V and BR-A/LA disease on an intention-to-treat basis, an approach that has been lacking in previous studies reporting FOLFIRINOX in BR-A/LA disease.

Conclusion

In summary, when analysed using an intention-to-treat approach, no significant difference in survival was identified between patients with resectable, BR-V or BR-A/LA disease, treated in line with ISGPS guidance. If response rates and/or tolerance of NAT can improve, then NAT may be associated with improved survival; similarly FOLFIRINOX in the adjuvant setting may also improve outcomes. Future randomized studies are thus urgently needed to identify the optimal timing and nature of chemotherapy. There must also be appropriate consideration of complications, patients experience and generalizability of treatments.

AUTHOR CONTRIBUTIONS

Conceptualization; data curation; formal analysis; methodology; writing-original draft; writing-review and editing. **Nikolaos Chatzizacharias:** Conceptualization; formal analysis; writing-review and editing. **James Hodson:** Formal analysis. **Francesca Marcon:** Writing-review and editing. **Marit Kalisvaart:** Writing-review and editing. **Pankaj Punia:** Writing-review and editing. **YUk Ting Ma:** Writing-review and editing. **Bobby Dasari:** Writing-review and editing. **Ravi Marudanayagam:** Writing-review and editing. **Robert Sutcliffe:** Writing-review and editing. **Paolo Muiesan:** Writing-review and editing. **Darius Mirza:** Writing-review and editing. **John Isaac:** Writing-review and editing.

Conflicts of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Rates of toxicity grades among the 55 patients in the LA/BR-A subgroup (locally advanced and borderline resectable-arterial) receiving neoadjuvant therapy.
Table S2. Baseline demographics of the LA/BR-A subgroup (locally advanced and borderline resectable-arterial) stratified by NAT.
Table S3. Treatment and tumour-related factors of the LA/BR-A subgroup (locally advanced and borderline resectable-arterial) stratified by NAT.
Table S4. Multivariable analysis of overall survival.