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ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

The impact of neoadjuvant therapy in patients with left-sided resectable pancreatic cancer: an international multicenter study

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Background: Left-sided pancreatic cancer is associated with worse overall survival (OS) compared with right-sided pancreatic cancer. Although neoadjuvant therapy is currently seen as not effective in patients with resectable pancreatic cancer (RPC), current randomized trials included mostly patients with right-sided RPC. The purpose of this study was to assess the association between neoadjuvant therapy and OS in patients with left-sided RPC compared with upfront surgery.

Patients and methods: This was an international multicenter retrospective study including consecutive patients after left-sided pancreatic resection for pathology-proven RPC, either after neoadjuvant therapy or upfront surgery in 76 centers from 18 countries on 4 continents (2013-2019). The primary endpoint was OS from diagnosis. Time-dependent Cox regression analysis was carried out to investigate the association of neoadjuvant therapy with OS, adjusting for confounders at the time of diagnosis. Adjusted OS probabilities were calculated.

Results: Overall, 2282 patients after left-sided pancreatic resection for RPC were included of whom 290 patients (13%) received neoadjuvant therapy. The most common neoadjuvant regimens were (m)FOLFIRINOX (38%) and gemcitabine-nab-paclitaxel (22%). After upfront surgery, 72% of patients received adjuvant chemotherapy, mostly a single-agent regimen (74%). Neoadjuvant therapy was associated with prolonged OS compared with upfront surgery (adjusted hazard ratio 0.69, 95% confidence interval 0.58-0.83) with an adjusted median OS of 53 versus 37 months ($P = 0.0003$) and adjusted 5-year OS rates of 47% versus 35% ($P = 0.0001$) compared with upfront surgery. Interaction analysis demonstrated a stronger effect of neoadjuvant therapy in patients with a larger tumor ($P_{interaction} = 0.003$) and higher serum carbohydrate antigen 19-9 (CA19-9; $P_{interaction} = 0.005$). In contrast, the effect of neoadjuvant therapy was not enhanced for splenic artery ($P_{interaction} = 0.43$), splenic vein ($P_{interaction} = 0.30$), retroperitoneal ($P_{interaction} = 0.84$), and multivisceral ($P_{interaction} = 0.96$) involvement.

Conclusions: Neoadjuvant therapy in patients with left-sided RPC was associated with improved OS compared with upfront surgery. The impact of neoadjuvant therapy increased with larger tumor size and higher serum CA19-9 at diagnosis. Randomized controlled trials on neoadjuvant therapy specifically in patients with left-sided RPC are needed.

Key words: pancreatic adenocarcinoma, pancreatic body/tail, resectable, neoadjuvant therapy, CA19-9, tumor size

INTRODUCTION

Pancreatic ductal adenocarcinoma (hereafter: pancreatic cancer) presents in the pancreatic body/tail in about 30% of the patients, as then known as 'left-sided pancreatic cancer'.[1] Left-sided pancreatic cancer is associated with worse overall survival (OS) compared with tumors located in the pancreatic head, neck, or uncinate process (i.e. right-sided).[2,3] This poor prognosis is probably related to a more aggressive tumor biology of left-sided pancreatic cancer at the time of diagnosis, which is typically diagnosed later than right-sided tumors because of limited symptoms without jaundice due to bile duct obstruction.[4-6]

Although anatomical, biological, and conditional (A-B-C) parameters are increasingly used for staging of localized pancreatic cancer,[7-10] anatomical resectability criteria still have a prominent role in clinical decision making for upfront surgery versus chemotherapy first.[11-13] Because resection of the spleen is part of a standard left-sided pancreatic resection, involvement of the splenic vasculature does not influence the resectability status. However, several observational studies have found that radiological or pathological tumor involvement of the splenic vessels is associated with worse OS.[14-21] This raises the hypothesis that patients with left-sided pancreatic cancer might benefit more from neoadjuvant therapy in comparison to patients with pancreatic head cancer, especially for patients with specific A-B-C characteristics.

To date, randomized trials (e.g. NORPACT-1, PREOPANC) investigating the value of neoadjuvant therapy for upfront resectable pancreatic cancer (RPC) have not universally shown a benefit in OS.[22-24] However, only about 25% of patients included in these trials had a left-sided tumor, leaving little room for meaningful sub-analyses.[24,25] Also, the observational evidence on the value of neoadjuvant therapy in left-sided pancreatic cancer is sparse, mostly limited by outdated chemotherapy regimens and the inclusion of borderline resectable and locally advanced tumors.[26,27]

Therefore, the present international observational multicenter study aimed to investigate the potential survival benefit of neoadjuvant therapy over upfront surgery in patients with left-sided RPC, thereby investigating different anatomical, biological, and conditional characteristics as potential indications for neoadjuvant therapy.

PATIENTS AND METHODS

This retrospective observational international multicenter study was carried out in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline[28] and was approved by the ethical committee from the Amsterdam UMC (reference number: W22_027 # 22.056), Sahlgrenska University Hospital (reference number: DNR 2022-00575-01), and the University of Colorado (reference number: COMIRB 22-1531). The need for informed consent was waived.

Study design

Centers for pancreatic surgery with an average annual volume of $\geq$20 pancreatic resections during the study period were considered eligible for participation.[29]

All consecutive adult patients (age $\geq$18 years) diagnosed with radiologically defined primary resectable left-sided pancreatic ductal adenocarcinoma[12] were included who underwent an open or minimally invasive (i.e. laparoscopic and robotic) left-sided pancreatic resection,[30] either after neoadjuvant chemotherapy ($\pm$ radiotherapy) or using upfront surgery in the period from January 2013 until June 2019. Pancreatic ductal adenocarcinomas arising from cystic precursors were also included. The definition of resectable disease was solely based on cross-sectional imaging, without incorporating biological criteria for resectability.[31]

Exclusion criteria were (i) radiological involvement of the superior mesenteric artery, celiac axis, hepatic artery, portal vein, superior mesenteric vein, and/or inferior mesenteric vein; (ii) left-sided pancreatic resection with concomitant major vascular resection other than splenic artery/vein (e.g. superior mesenteric artery, any hepatic artery, celiac axis, portal vein, superior mesenteric vein, and/or inferior mesenteric vein); (iii) distant metastatic disease present before and/or at the time of surgical resection; and (iv) subtypes of pancreatic adenocarcinoma other than pancreatic ductal adenocarcinoma (e.g. acinar cell carcinoma, squamous cell carcinoma, mixed neuroendocrine adenocarcinoma). Lastly, patients with missing data on the day of diagnosis and/or last follow-up were excluded, as well as patients who received preoperative radiotherapy alone. Although the National Comprehensive Cancer Network (NCCN) guideline allows $\leq$180° portomesenteric venous contact in the definition of RPC,[12] these patients were excluded to increase the homogeneity.[32]

The primary endpoint was OS from the time of diagnosis. Patients alive at the end of follow-up were censored observations.

Definitions

Patients' comorbidity and conditional status at the time of diagnosis were defined, using the Charlson Comorbidity Index and Eastern Cooperative Oncology Group (ECOG) performance status, respectively. The American Society of Anesthesiologists Physical Status (ASA-PS) classification was used to estimate the patients' physical status at the time of surgery.

The date of diagnosis concerned either the moment of imaging- or pathology-based diagnosis. No distinction was made between tumors located in the pancreatic body versus tail due to the lack of standardized anatomical criteria. Radiological tumor involvement of the splenic vein and artery was defined as the presence of complete loss of a fat plane between the tumor and the vessel, vessel wall irregularity, and/or thrombosis or obliteration. If these criteria were not clearly described in the radiology report, the tumor involvement was re-assessed by an experienced local radiologist

(i.e. no central review was done). The eighth edition of the TNM (tumor—node—metastasis) classification was used for both clinical and pathological disease staging.[33]

Radiological response evaluation was defined in accordance with the criteria.[34] Serum tumor markers carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) were collected preoperatively and, if applicable, before neoadjuvant therapy. CA19-9 $\geq$37 U/ml and CEA $>$5 ng/ml were considered as elevated.

Extended resections were defined in accordance with the International Study Group for Pancreatic Surgery (ISGPS) definition.[35] Radicality was classified following either the 0 mm rule (i.e. R0: $\geq$0 mm margin; R1: $<$0 mm margin clearance), 1 mm rule (i.e. R0: $\geq$1 mm margin; R1: $<$1 mm margin clearance), or the variant 1 mm rule (i.e. R0: $\geq$1 mm margin; R1: $<$1 mm margin clearance; R1: direct margin involvement).[36] In-hospital major morbidity was defined as Clavien-Dindo grade $\geq$IIIa.[37] Histopathological response after neoadjuvant therapy graded following the College of American Pathologists (CAP), Evans classification, or MD Anderson classification was categorized into pathological complete response (i.e. CAP grade 0/Evans grade 4 or 4M/MD Anderson grade 0), near-complete response (i.e. CAP grade 1/Evans grade 3 or 3M/MD Anderson grade 1), and partial to no response (i.e. CAP grade 2-3/Evans grade 1-2/MD Anderson grade 2).[38] Major morbidity related to pancreatic surgery-specific complications were presented, including delayed gastric emptying, post-operative pancreatic fistula, post-pancreatectomy hemorrhage, and chyle leak.[39-42]

The calculation of adjuvant treatment duration was not possible since this information was missing in most patients. In case of disease recurrence, the first site of disease recurrence (i.e. locoregional, distant, or both) was registered. Locoregional disease recurrence was defined as suspected recurrence at the operation site and/or locoregional lymphadenopathy.

Statistical analyses

Data analyses were carried out by statistician M.A., using R, version 4.3.2 (R Foundation for Statistical Computing), and Stata version 17 (StataCorp, College Station, TX). Statistical significance was considered as a two-tailed *P* value of $<$0.05.

Categorical variables are presented as percentages and frequencies and analyzed using Pearson's chi-square test. Continuous variables are presented as medians with interquartile ranges (IQRs) and compared with the Mann—Whitney *U* test. The reverse Kaplan—Meier method was used to calculate the median follow-up. Unadjusted OS was estimated by the Kaplan—Meier method, measured from date of diagnosis. Differences between neoadjuvant therapy and upfront surgery were assessed with the log-rank test.

Cox regression analysis was used to investigate the association of neoadjuvant therapy with OS, adjusted for known confounders at the time of diagnosis: age; sex; ECOG performance status; Charlson Comorbidity Index; imaging-based solid tumor size and splenic vein, splenic artery, multivisceral, and retroperitoneal involvement; serum CA19-9; serum CEA; year of surgery; and the continent. Of note, no correction was made for the clinical lymph node status considering its limited reliability.[43] Moreover, only solid tumor size was used and not the total tumor size, because of the collinearity between these two parameters. Serum CA19-9 at the time of diagnosis was transformed into a logarithmic scale. The proportional hazard assumption was checked using visual inspection of Schoenfeld residuals and the Grambsch—Therneau test. Patients with missing data on the date of diagnosis were excluded from the model. A time-dependent Cox regression model was used for OS to account for immortal time bias caused by the neoadjuvant therapy, with left-truncation for the time between diagnosis and resection. Results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). A sensitivity analysis was carried out to adjust for the center where patients underwent surgery. A competing risk model was used to investigate the association of neoadjuvant therapy and upfront surgery with the risk of recurrence, adjusting for the same confounders as in the main Cox regression model and treating death as a competing risk.

Interactions between the use of neoadjuvant chemotherapy and parameters at the time of diagnosis were analyzed. Interactions were tested in multivariable Cox regression models for OS adjusted for the covariates as used in the main multivariable Cox proportional hazards model. A likelihood ratio test was used to calculate the *P* value of each interaction. Multiple imputation was used to account for missing data in the multivariable Cox regression analyses (50 imputed datasets after 30 burn-in iterations). In addition, flexible parametric survival models and regression standardization were used to estimate absolute survival probabilities and median survival times for patients treated with neoadjuvant therapy versus upfront surgery (see Supplementary Material, available at https://doi.org/10.1016/j.annonc.2024.12.015).[44-46] All continuous variables were winsorized at the 2nd and 98th percentile to reduce the influence of extreme values, and were modelled using restricted cubic splines with three knots, to account for potential nonlinear relationships with OS.[47]

Sensitivity analyses were carried out to investigate the impact of single-agent chemotherapy on the study outcome. Firstly, a sensitivity analysis was carried out excluding patients who received single-agent adjuvant and no adjuvant therapy. Thus, only patients receiving multi-agent adjuvant therapy remained. Secondly, a sensitivity analysis was carried out excluding patients who received single-agent neoadjuvant chemotherapy. Thus, in the neoadjuvant group only patients receiving multi-agent neoadjuvant therapy remained.

RESULTS

Overall, 2282 patients after left-sided pancreatic resection for pancreatic cancer were included of whom 290 patients (13%) received neoadjuvant therapy. Patients originated from 76 centers in Europe (12 countries; 51 centers: 1102 patients), Asia (3 countries; 14 centers: 807 patients),

United States (9 centers: 353 patients), and Australia (2 centers: 20 patients).

Clinicopathological details at diagnosis

Patients treated with neoadjuvant therapy were younger compared with patients treated with upfront surgery [median 68 years (IQR 62-73 years) versus 70 years (IQR 63-77 years); $P = 0.0002$]. Clinical tumor characteristics were unfavorable among patients in the neoadjuvant therapy group, including a larger solid tumor size [median 30 mm (IQR 21-41 mm) versus 25 mm (IQR 18-36 mm); $P < 0.0001$]; higher rates of splenic artery (52% versus 28%; $P < 0.0001$), splenic vein (58% versus 38%; $P < 0.0001$), and multivisceral involvement (21% versus 9%; $P < 0.0001$); cN1-2 (17% versus 12%; $P = 0.026$); and a higher serum CA19-9 [median 103 U/ml (IQR 27-400 U/ml) versus 54 U/ml (IQR 15-263 U/ml); $P = 0.0005$]. See Table 1 for the baseline characteristics.

Neoadjuvant and adjuvant chemotherapy

The most common neoadjuvant chemotherapy regimens were (m)FOLFIRINOX (38%) and gemcitabine-nab-paclitaxel (22%). Neoadjuvant chemotherapy was combined with radiotherapy in 33% of patients. See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.

Table 1. Baseline characteristics at diagnosis

	Neoadjuvant therapy ($n = 290$)		Upfront surgery ($n = 1992$)		*P* value
Age, median, years (IQR)	68	(62-73)	70	(63-77)	**0.0002**
Female sex, *n* (%)	152	(52)	895	(45)	**0.017**
BMI, median, kg/m^2 (IQR)	24	(21-27)	24	(22-27)	0.15
Missing, *n* (%)	4	(1)	62	(3)	
Charlson Comorbidity Index, median (IQR)	4	(3-5)	4	(3-6)	**0.030**
Missing, *n* (%)	4	(1)	34	(2)	
ECOG, *n* (%)					0.99
0-1	172	(59)	1356	(68)	
≥2	28	(10)	220	(11)	
Missing	90	(31)	416	(21)	
Total tumor size, mm, *n* (%)					
Median (IQR)	30	(21-41)	25	(18-36)	**<0.0001**
≤20	69	(24)	671	(34)	
21-40	144	(50)	938	(47)	
>40	72	(25)	325	(16)	
Missing	5	(2)	58	(3)	
Solid tumor size, mm, *n* (%)					
Median (IQR)	30	(21-40)	25	(18-35)	**<0.0001**
≤20	70	(24)	698	(35)	
21-40	144	(50)	920	(46)	
>40	71	(24)	282	(14)	
Missing	5	(2)	92	(5)	
Involvement splenic artery, *n* (%)	152	(52)	553	(28)	**<0.0001**
Impossible to assess	16	(6)	103	(5)	
Missing	1	(<1)	2	(<1)	
Involvement splenic vein, *n* (%)	167	(58)	766	(38)	**<0.0001**
Impossible to assess	13	(4)	100	(5)	
Missing	1	(<1)	3	(<1)	
Multivisceral involvement, *n* (%)	60	(21)	175	(9)	**<0.0001**
Missing	17	(6)	71	(4)	
cN stage, *n* (%)					**0.026**
N0	229	(78)	1659	(83)	
N1-2	50	(17)	237	(12)	
Nx	10	(3)	95	(5)	
Missing	1	(<1)	1	(<1)	
CA19-9, U/ml, *n* (%)					
Median (IQR)	103	(27-400)	54	(15-263)	**0.0005**
<37	80	(28)	688	(35)	
≥37 to <150	70	(24)	432	(22)	
≥150 to <500	52	(18)	273	(14)	
≥500	54	(19)	279	(14)	
Missing	34	(12)	319	(16)	
CEA, ng/ml, *n* (%)					
Median (IQR)	4	(2-5)	3	(2-5)	0.24
Normal	131	(45)	918	(46)	
>5 to ≤20 ng/ml	45	(16)	235	(12)	
>20 ng/ml	10	(3)	68	(3)	
Missing	104	(36)	771	(39)	

A bold *P* value indicates statistical significance (i.e. $P < 0.050$).
BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

2024.12.0151, for details about neoadjuvant therapy. The median neoadjuvant treatment duration was 9 weeks (IQR 5-16 weeks). Radiological response after neoadjuvant therapy occurred in 34% and serum CA19-9 normalized in 34% of patients. See Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.12.015, for the details about disease response.

Administration rates of adjuvant chemotherapy were similar in patients treated with neoadjuvant therapy and those who underwent upfront surgery (72% versus 72%; $P = 0.32$). In both groups, a single-agent adjuvant chemotherapy regimen was given in most patients [$n = 137/209$ (66%) versus $n = 1050/1428$ (74%); $P = 0.016$] with a higher rate among patients treated with upfront surgery. In the neoadjuvant therapy group, adjuvant (m)FOLFIRINOX was administered more often than after upfront surgery [$n = 31/209$ (15%) versus $n = 88/1428$ (6%); $P < 0.0001$]. See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.12.015, for details about the adjuvant regimens.

Surgical outcome and histopathology

Following neoadjuvant therapy, open surgery was more frequently carried out compared with patients treated with upfront surgery (78% versus 63%; $P < 0.0001$). The rates of a radical antegrade modular pancreatosplenectomy (RAMPS) procedure (65% versus 39%; $P < 0.0001$) and multivisceral resection(s) (36% versus 21%; $P < 0.0001$) were higher in the neoadjuvant group compared with the upfront surgery group.

Histopathological tumor characteristics were more favorable in the neoadjuvant therapy group compared with the upfront surgery group, including a smaller median tumor size [26 mm (IQR 19-36 mm) versus 30 mm (IQR 20-42 mm); $P = 0.0002$], higher rate of regional lymph node-negative disease (59% versus 43%; $P < 0.0001$), and higher rates of R0 resections (84% versus 73%; $P < 0.0001$). See Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.12.015, for details about the surgical and histopathological outcome.

Oncological outcome

The median follow-up was 61 months (IQR 46-82 months). During follow-up, 1354 patients (59%) died. Neoadjuvant therapy was independently associated with a lower risk of recurrence (adjusted HR 0.83, 95% CI 0.70% to 0.99%). See Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2024.12.015, for the unadjusted and adjusted recurrence risks and Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2024.12.015, for the locations of disease recurrence.

The median OS in patients treated with neoadjuvant therapy was 49 months (95% CI 44-59 months) with 1-, 3-, and 5-year OS rates of 92% (95% CI 89% to 96%), 62% (95% CI 56% to 68%), and 42% (95% CI 36% to 49%), respectively, versus a median OS of 38 months (95% CI 35-41 months) with a 1-, 3-, and 5-year OS of 86% (95% CI 85% to 88%), 51% (95% CI 49% to 54%), and 36% (95% CI 34% to 39%) in patients who underwent upfront surgery ($P = 0.009$), respectively. See Figure 1A for the unadjusted OS curves.

Parameters associated with overall survival

See Table 2 for the time-dependent Cox regression analysis. After adjusting for baseline characteristics known at the time of diagnosis, neoadjuvant therapy was associated with longer OS (HR 0.69, 95% CI 0.58-0.83). Neoadjuvant therapy was associated with longer OS independent of omission or use of concomitant radiotherapy. See Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2024.12.015, for the Cox regression analysis with stratification for the additional value of radiotherapy. The adjusted median OS after neoadjuvant therapy was 53 months (95% CI 43-64 months) versus 37 months (95% CI 35-39 months) ($P = 0.003$), with adjusted 5-year OS rates of 47% (95% CI 41% to 52%) versus 35% (95% CI 34% to 38%), respectively ($P = 0.0001$). See Figure 1B for the adjusted OS curves.

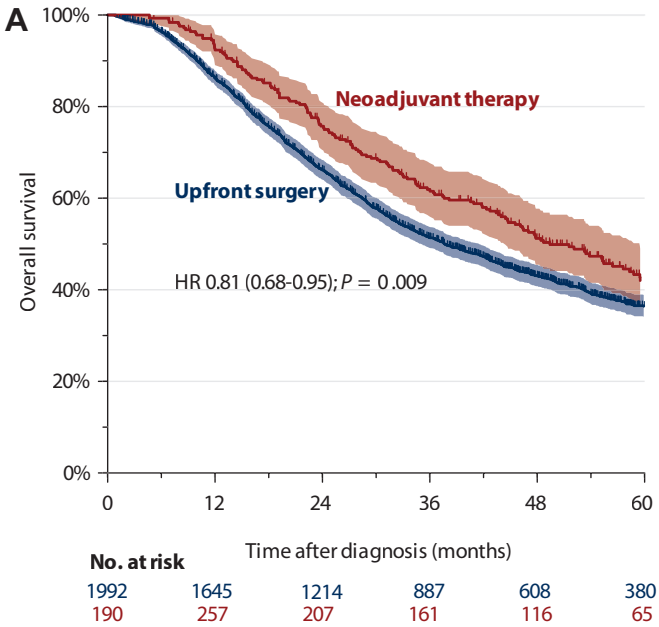
In the multivariable analysis, anatomical disease characteristics associated with shorter OS were a larger solid tumor size on imaging at diagnosis (HR per 10 mm increase 1.12, 95% CI 1.07-1.17), whereas other anatomical parameters known at the time of diagnosis were not significantly associated with OS: splenic vein involvement (HR 1.05, 95% CI 0.91-1.21), splenic artery involvement (HR 1.08, 95% CI 0.93-1.25), retroperitoneal involvement (HR 1.14, 95% CI 0.96-1.37), and multivisceral involvement (HR 0.95, 95% CI 0.78-1.16). From the biological parameters known at the time of diagnosis, serum CA19-9 elevation of $\geq$150-500 U/ml (HR 1.69, 95% CI 1.43-2.00) and $\geq$500 U/ml (HR 1.81, 95% CI 1.52-2.16) were associated with shorter OS in the multivariable analysis, compared with a CA19-9 level $<$37 U/ml ($P < 0.0001$). See Table 2 for the Cox regression analysis and Figure 2 for the variety in association strength of the different A-B-C parameters. Results were similar in a sensitivity analysis that included adjustment for the center where patients underwent surgery.

The interaction analysis and forest plot showed that the benefit of neoadjuvant therapy was stronger in patients with a larger solid tumor ($P_{interaction} = 0.003$) and higher serum CA19-9 ($P_{interaction} = 0.005$) at the time of diagnosis. In contrast, there was no evidence for a difference in the effect of neoadjuvant therapy in patients with or without splenic artery ($P_{interaction} = 0.43$), splenic vein ($P_{interaction} = 0.30$), multivisceral ($P_{interaction} = 0.96$), or retroperitoneal ($P_{interaction} = 0.84$) involvement. See Figure 3 for the forest plot and Supplementary Table S7 and Supplementary Figure S1 available at https://doi.org/10.1016/j.annonc.2024.12.015, for the adjusted survival estimates and interaction analysis among different subgroups.

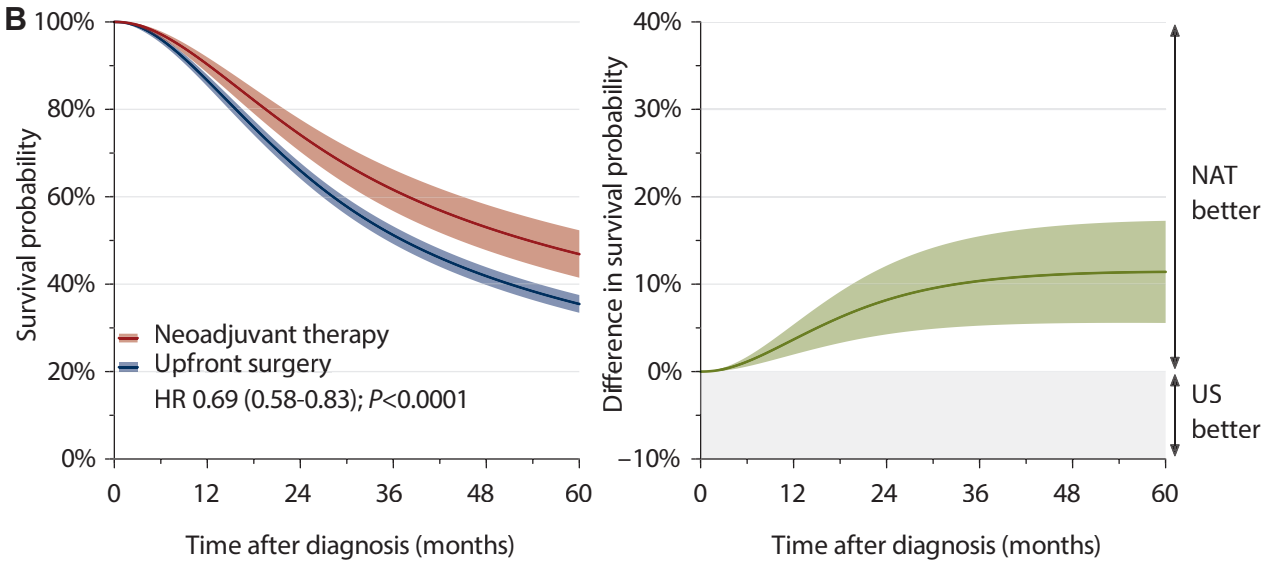
The association of neoadjuvant therapy with prolonged OS after adjustment remained in the sensitivity analysis with adjustment for the centers (HR 0.72, 95% CI 0.59-0.87).

Sensitivity analysis

In the first sensitivity analysis excluding patients treated with adjuvant single-agent and no adjuvant chemotherapy,



Median OS: 49 months (44-59) versus 38 months (35-41); difference: 12 months (4-20) ($P = 0.005$)
1-year OS: NAT = 92% (89-96) versus US = 86% (85-88); difference: 6% (1-11) ($P = 0.027$)
3-year OS: NAT = 62% (56-68) versus US = 51% (49-54); difference: 11% (4-17) ($P = 0.001$)
5-year OS: NAT = 42% (36-49) versus US = 36% (34-39); difference: 6% (–1-12) ($P = 0.11$)



Median OS: NAT = 53 months (43-64) versus US = 37 months (35-39); difference 16 months (6-27) ($P = 0.003$)
1-year OS: NAT = 90% (88-92) versus US = 87% (85-88); difference: 4% (2-5) ($P < 0.0001$)
3-year OS: NAT = 62% (57-66) versus US = 51% (49-53); difference: 10% (5-15) ($P < 0.0001$)
5-year OS: NAT = 47% (41-52) versus US = 35% (33-38); difference: 11% (6-17) ($P = 0.0001$)

Figure 1. Survival. (A) Unadjusted overall survival. (B) Adjusted overall survival estimates. See Table 2 for the adjusted hazard ratios.
HR, hazard ratio; NAT, neoadjuvant therapy; OS, overall survival; US, upfront surgery.

the independent association of neoadjuvant therapy with prolonged OS compared with upfront surgery remained (HR 0.63, 95% CI 0.40-0.99) in the 60 patients treated with neoadjuvant therapy and the 323 patients treated with upfront surgery.

In the second sensitivity analysis excluding patients treated with neoadjuvant single-agent chemotherapy, the independent association of neoadjuvant therapy with prolonged OS compared with upfront surgery remained (HR 0.67, 95% CI 0.55-0.82) in the 220 patients treated with

https://doi.org/10.1016/j.annonc.2024.12.015

Table 2. Cox regression models for associations between risk factors and mortality

Variables	*n*/total		Univariable analysis HR (95% CI)		*P* value	Multivariable analysis HR (95% CI)		*P* value[a]
Neoadjuvant chemotherapy					**0.009**			**<0.0001**
No	1992	(87)	(Referent)			(Referent)		
Yes	290	(13)	0.81	(0.68-0.95)		0.69	(0.58-0.83)	
Geographic region					**<0.0001**			**<0.0001**
Europe	1102	(48)	(Referent)			(Referent)		
United States	353	(15)	0.78	(0.67-0.91)		0.79	(0.67-0.92)	
Oceania	20	(<1)	1.39	(0.84-2.32)		1.27	(0.74-2.16)	
Asia	807	(35)	0.58	(0.51-0.66)		0.66	(0.58-0.76)	
Age (per 5 years increase)	2282	(100)	1.08	(1.05-1.11)	**<0.0001**	1.06	(1.03-1.10)	**0.004**
Sex					0.078			0.11
Female	1047	(46)	(Referent)			(Referent)		
Male	1234	(54)	1.10	(0.99-1.23)		1.10	(0.99-1.23)	
ECOG-PS					**0.0003**			0.090
0-1	1528	(67)	(Referent)			(Referent)		
≥2	248	(11)	1.35	(1.15-1.59)		1.16	(0.98-1.38)	
Solid tumor size at diagnosis (per 10 mm increase)	2282	(100)	1.22	(1.18-1.27)	**<0.0001**	1.12	(1.07-1.17)	**<0.0001**
Charlson Comorbidity Index (per 1 point increase)	2282	(100)	1.12	(1.09-1.15)	**<0.0001**	1.05	(1.02-1.09)	0.059
Splenic vein involvement					**<0.0001**			0.87
No	1232	(54)	(Referent)			(Referent)		
Yes	933	(41)	1.31	(1.17-1.46)		1.05	(0.91-1.21)	
Impossible to assess	113	(5)	1.45	(1.14-1.84)		1.19	(0.71-1.98)	
Splenic artery involvement					**<0.0001**			0.61
No	1455	(64)	(Referent)			(Referent)		
Yes	705	(31)	1.35	(1.20-1.51)		1.08	(0.93-1.25)	
Impossible to assess	119	(5)	1.40	(1.11-1.77)		0.92	(0.56-1.51)	
Multivisceral involvement					**0.003**			0.99
No	1959	(86)	(Referent)			(Referent)		
Yes	235	(10)	1.30	(1.10-1.54)		0.95	(0.78-1.16)	
Retroperitoneal involvement					0.19			0.19
No	1639	(72)	(Referent)			(Referent)		
Yes	346	(15)	1.10	(0.96-1.27)		1.14	(0.96-1.37)	
CA19-9 at diagnosis, U/ml					**<0.0001**			**<0.0001**
<37	768	(34)	(Referent)			(Referent)		
≥37-<150	502	(22)	1.20	(1.03-1.39)		1.14	(0.97-1.32)	
≥150-<500	326	(14)	1.86	(1.59-2.18)		1.69	(1.43-2.00)	
≥500	333	(15)	2.09	(1.79-2.44)		1.81	(1.52-2.16)	
CEA at diagnosis, ng/ml					**0.0007**			0.57
Normal	1049	(46)	(Referent)			(Referent)		
>5-≤ 20 ng/ml	78	(3)	1.22	(1.04-1.43)		0.98	(0.82-1.17)	
>20 ng/ml	280	(12)	1.63	(1.24-2.15)		1.12	(0.83-1.50)	

A bold *P* value indicates statistical significance (i.e. $P < 0.050$).
$n = 12$ patients were excluded from the model because of missing data from the date of diagnosis.
CI, confidence interval; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG-PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio;.
[a]The hazard ratio with 95% CI is based on the Cox regression model in which continuous variables are modelled as presented in the table (i.e. CA19-9, CEA, and tumor size are categorized) to increase the interpretability. The *P* values are derived from the final Cox regression model in which all continuous variables are non-linearly modelled. See Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2024.12.015, for the nonlinear association of continuous variables with overall survival.

multi-agent neoadjuvant chemotherapy and the 1982 patients treated with upfront surgery.

DISCUSSION

This international multicenter retrospective study including 2282 patients after left-sided pancreatic resection for RPC, of whom 290 patients (13%) received neoadjuvant therapy, found a strong association between neoadjuvant therapy and prolonged OS, with an adjusted median OS of 53 versus 37 months (Δ +16 months) and 5-year OS rates of 47% versus 35% (Δ +11%) compared with upfront surgery. The effect remained in the two sensitivity analyses excluding (i) patients receiving adjuvant single-agent and no adjuvant chemotherapy, and (ii) excluding patients receiving single-agent neoadjuvant chemotherapy. The effect of neoadjuvant therapy was stronger for larger tumors and for patients who had elevated serum CA19-9 levels at diagnosis. In contrast, splenic vein, splenic artery, multivisceral, and retroperitoneal involvement were not associated with OS or with the effect of neoadjuvant therapy.

Two previous studies have investigated the value of neoadjuvant therapy in patients with left-sided pancreatic cancer.[26,27] An observational national study (2006-2015) using the National Cancer Database (United States) compared neoadjuvant therapy versus upfront surgery in 5003 patients who underwent a left-sided pancreatic resection for stage cT1-3 pancreatic cancer, using propensity score matching ($n = 353$ versus $n = 353$).[26] The median OS from diagnosis was longer in the neoadjuvant therapy group compared with the upfront surgery group (33 versus 27 months), but no adequate adjustment was made for the

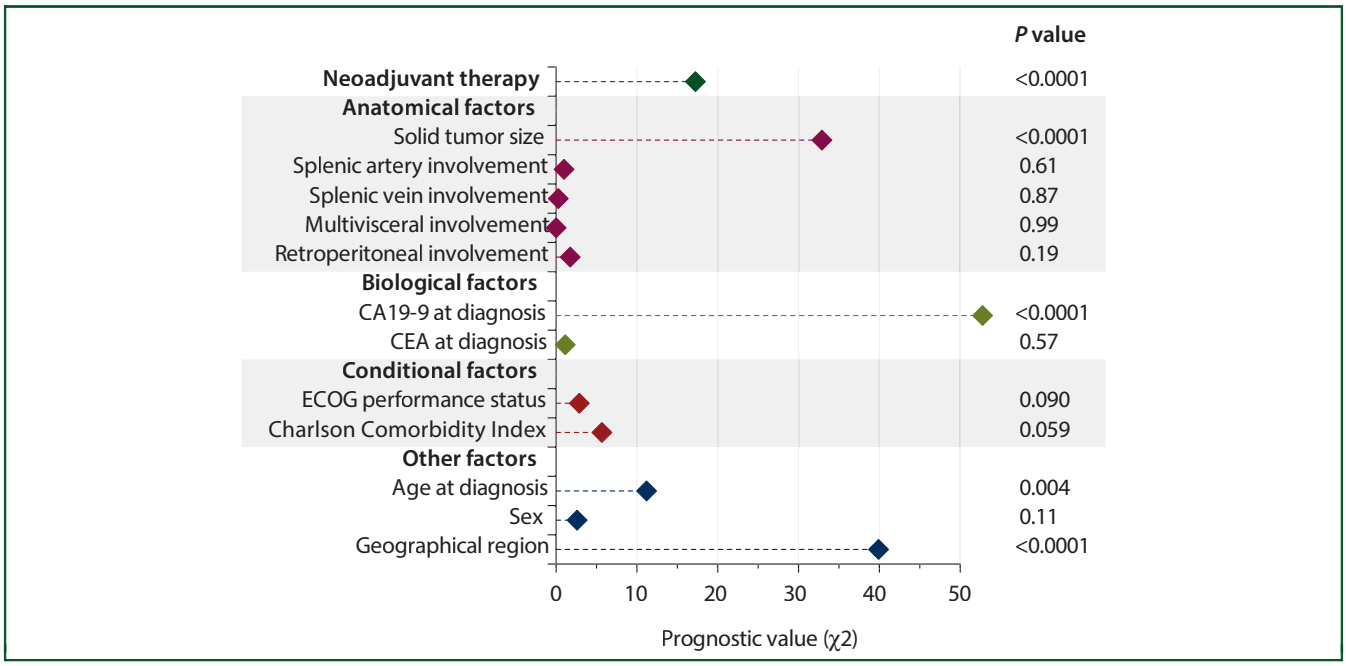


Figure 2. Strength of associations from A-B-C parameters with survival. The x-axis represents the prognostic value of a variable, with higher values indicating a stronger association with overall survival in the full multivariable model. *P* values and chi-square values were obtained from likelihood ratio tests for the full multivariable Cox regression model across multiple imputed datasets. Note that the *P* value of the likelihood ratio test is dependent on the prognostic value and the degrees of freedom of a variable; i.e. two variables with the same prognostic value can have different *P* values if one variable is modelled in a more complex manner than the other variable (e.g. if one variable consists of three categories and the other consists of two categories).
CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group.

immortal time bias caused by neoadjuvant treatment.[26] Moreover, anatomical and biological disease characteristics (e.g. tumor size, involvement of vasculature and organs, serum CA19-9) were not available,[26] in contrast to the present study. Another international multicenter study (2007-2015), including 1236 patients with localized pancreatic cancer [i.e. (borderline) resectable and locally advanced] who underwent a left-sided pancreatic resection, showed no difference in median OS between preoperative therapy versus upfront surgery (27 versus 31 months; $P = 0.277$) after propensity score matching ($n = 94$ versus $n = 94$).[27] However, the median OS was longer after preoperative therapy compared with upfront surgery among patients with involvement of the splenic vessels (36 versus 20 months; $P = 0.049$), but this was an unmatched comparison.[27] The fact that neoadjuvant therapy did not result in prolonged OS in that series could have been caused by the lower rate of modern multi-agent chemotherapy regimens ($\leq$38%) compared with the current study (74%).[27]

The current study is the first, to the best of our knowledge, to have investigated the effect of neoadjuvant therapy in left-sided RPC while adjusting for anatomical and biological disease characteristics at the time of diagnosis. The favorable effect of neoadjuvant chemotherapy was particularly seen in patients with a larger tumor and/or elevated serum CA19-9 levels. In contrast, other anatomical parameters including splenic artery, splenic vein, retroperitoneal, or multivisceral involvement were not associated with the effect of neoadjuvant therapy. Several observational single-center studies suggested that radiological involvement of the splenic vasculature is associated with impaired OS after upfront surgery, after adjusting for perioperative confounders. Based on these findings, they hypothesized on the potential value of neoadjuvant therapy in these patients.[16-20] While in the present study the involvement of the splenic vein and artery and multivisceral involvement were associated with OS in the univariable analysis, only the association of the solid tumor size remained in the multivariable analysis. This might be caused by the collinearity between tumor size and the other anatomical parameters. After all, larger tumors have a higher likelihood of involving the splenic vessels and other organs.

The splenic artery is a same-grade branch from the celiac axis as the common hepatic artery. However, the common hepatic artery is one of the determinants in the definition of resectability whereas the splenic artery is not. The lack of association of splenic artery involvement with OS is in line with the ongoing paradigm shift that resectability of pancreatic cancer should be based on a combination of A-B-C parameters instead of focusing on vascular involvement alone.[7-9] Solid tumor size seems to be the only relevant anatomical parameter in left-sided RPC, according to this study. Hypothetically, larger tumors existed for a longer period with possibly a higher load of micro-metastatic disease, having therefore more benefit from neoadjuvant therapy. Of note, the biological parameter serum CA19-9 had a stronger association with OS than solid tumor size. Since serum CA19-9 is not elevated at diagnosis in about one-third of patients with localized pancreatic cancer,[48] serum carcinoembryonic antigen (CEA) is considered as an alternative tumor marker.[49] However, elevated serum CEA

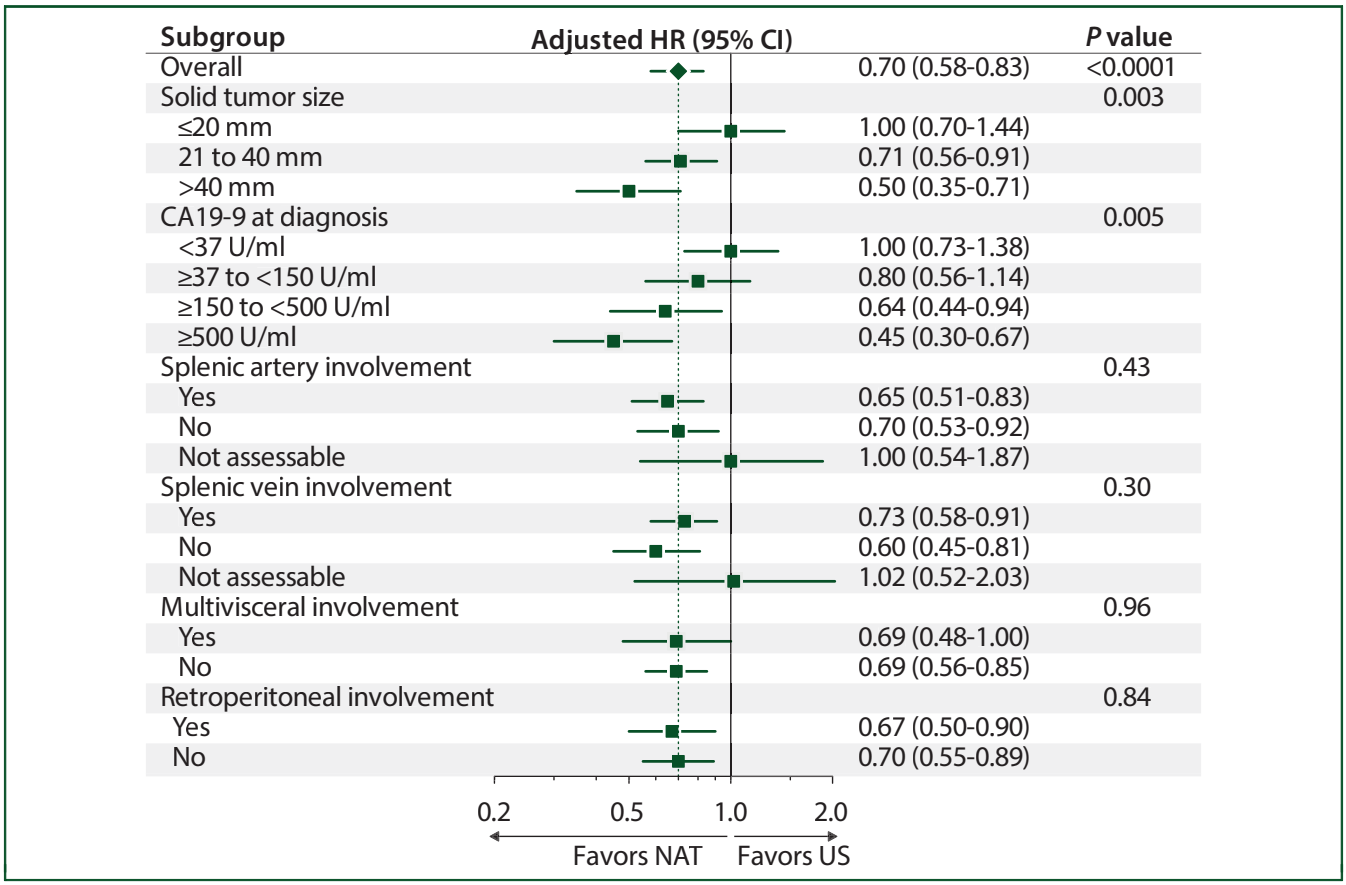


Figure 3. Forest plot of the association of neoadjuvant therapy on mortality in subgroup analyses. The average treatment effect is represented by the diamond and dotted line, and the hazard ratio in each subgroup is represented by the squares. In the interaction analyses, CA19-9 and solid tumor size were analyzed as continuous variables to calculate interaction P values.
CA19-9, carbohydrate antigen 19-9; CI, confidence interval; HR, hazard ratio; NAT, neoadjuvant therapy; US, upfront surgery.

at diagnosis was not associated with OS, illustrating the need for more reliable tumor markers.[50]

In the setting of pancreatoduodenectomy for pancreatic cancer, it is known that the rates of post-operative pancreatic fistula and postpancreatectomy hemorrhage are decreased by neoadjuvant therapy.[51,52] This might be related to the use of concomitant radiotherapy and larger tumors in the neoadjuvant therapy group, leading to more fibrotic pancreas parenchyma.[53] This mechanism is different in left pancreatectomy as is confirmed by the present study wherein no benefit of neoadjuvant therapy was seen in terms of post-operative pancreatic fistula and post-pancreatectomy hemorrhage.

The findings from the current study need to be interpreted in the light of several limitations. Firstly, this study only included patients who underwent resection, therefore lacking an intention-to-treat analysis. An intention-to-treat analysis was considered not feasible and unreliable in this international multicenter setting. The prolonged OS in patients treated with neoadjuvant therapy might therefore have been influenced by the test-of-time effect from neoadjuvant therapy, leading to a selected group of patients who underwent surgery. This was not only due to the neoadjuvant therapy itself, but also to delays in receiving neoadjuvant therapy (i.e. requiring biopsies for pathology confirmation). Of note, in patients with left-sided pancreatic cancer there are no delays caused by biliary drainages with the risk for pancreatitis and cholangitis. One can argue that the test-of-time effect is a positive phenomenon as it might reduce the risk for futile surgery. However, the test-of-time effect is limited due to the relatively short neoadjuvant treatment duration of about 2-3 months, both in this observational study as well as in completed randomized controlled trials on RPC.[23,25,54,55] This is underlined by the similar resection rates in those trials, ranging from 68% to 82% in the neoadjuvant therapy arms and from 72% to 89% in the upfront surgery arms.[23,25,54,55] Secondly, 74% of patients in the neoadjuvant group received a modern multi-agent neoadjuvant regimen (i.e. FOLFIRINOX, gemcitabine-nab-paclitaxel, gemcitabine-S1), whereas only 16% of patients in the upfront surgery group received a modern multi-agent adjuvant regimen (i.e. FOLFIRINOX, gemcitabine-capecitabine, gemcitabine-S1, gemcitabine-nab-paclitaxel). This might have contributed to the association of neoadjuvant therapy with prolonged OS.[56] Stratification of the neoadjuvant therapy into multi-agent and single-agent regimens was not feasible because of the small number of patients treated with a single-agent regimen. Nevertheless, the two sensitivity analyses showed that the association of neoadjuvant therapy with

prolonged OS remained after (i) excluding patients treated with single-agent adjuvant and no chemotherapy, and after (ii) neoadjuvant single-agent chemotherapy. Importantly, the effect estimates in the first sensitivity analysis could have been distorted by immortal time bias due to insufficient data on time between surgery and start of adjuvant chemotherapy. Of note, the high rate of single-agent adjuvant chemotherapy use in this study can be explained by the fact the vast majority of the study period was before publication of the PRODIGE 24-ACCORD trial.[57] Thirdly, the involvement of the splenic vessels was not divided based on the extent of involvement and occlusion, which might be relevant.[18,58] Fourthly, neoadjuvant therapy is not the standard of care for patients with RPC, illustrated by its rarity of 13% in this study cohort. Therefore, it is likely that a substantial number of included patients was treated with neoadjuvant therapy in the setting of a clinical trial. However, the impact of the selection from often-times fit patients in clinical trials is probably limited in this study due to the adjustment for comorbidity and performance status. The limited sample size of the neoadjuvant therapy group could have made this group vulnerable for heterogeneity. Fifthly, the continent where a patient underwent surgery was associated with OS. Hypothetically, this could have been related to patient selection for surgery and/or by differences in tumor biology between different races. However, no data were available about patients' ethnicity.[59] Sixthly, it is likely that there have been differences in surgical approaches between centers regarding indications and use of minimally invasive surgery and RAMPS procedure, and local pathology protocols, which should be standardized in the design of future trials.[60,61] Seventhly, data on the number of cycles of (neo)adjuvant chemotherapy were not presented due to the amount of missing data. Eighthly, possibly some patients in the upfront surgery group would not have been a candidate for neoadjuvant therapy, as the indication for surgery was intraductal papillary mucinous neoplasm with worrisome features without preoperative proof of pancreatic adenocarcinoma, which could be a reason for the relatively satisfying OS in the upfront surgery group.[62] Ninthly, it is likely that various post-operative surveillance strategies were used,[63] particularly since patients treated with neoadjuvant therapy were most likely treated within clinical trials. This could be the reason that the unadjusted risk on recurrence did not differ between neoadjuvant therapy and upfront surgery. Nevertheless, the major strength of this study is the international multicenter design involving both moderate- and high-volume centers from four continents, with a homogeneous cohort by exclusion of borderline resectable and locally advanced tumors, and being the first study that investigated the value of neoadjuvant therapy in specific subgroups of patients with left-sided RPC. The large sample size made it possible to investigate differences in treatment effect across subgroups.

Even though this study demonstrated an association of neoadjuvant therapy with longer OS compared with upfront surgery, a randomized controlled trial remains required to draw the definite conclusions, as illustrated by the general discrepancy between previous observational studies and randomized trials on RPC in general.[22,64] This is particularly underlined by the randomized NORPACT-1 trial which even suggested worse OS after neoadjuvant therapy compared with upfront surgery in patients with pancreatic head cancer.[23] Notably, this trial randomized patients before pathology confirmation. As a result, the downsides of therapeutic delay and complications related to obtaining biliary drainage and pathology confirmation were included in the neoadjuvant treatment arm. The relevant disease parameters such as tumor size and serum CA19-9 could be considered when designing this trial. Furthermore, the use of other tumor markers should be considered (e.g. circulating tumor DNA).[65,66] In the light of the preliminary results from the PREOPANC-2 trial wherein no difference was found in OS between neoadjuvant regimens FOLFIRINOX versus gemcitabine with radiotherapy in 368 patients with (borderline) RPC,[67] one could argue that different neoadjuvant chemotherapy regimens could be used in such a trial. Of note, the possibility for switch to a second-line neoadjuvant chemotherapy in case of insufficient disease response or disease progression should be taken into account.[68] After all, the limited number of patients with left-sided RPC requires an international design, leading to different standards in chemotherapy regimens. Based on the present study, adding radiotherapy to neoadjuvant chemotherapy seems not to result in prolonged OS compared with neoadjuvant chemotherapy alone, which is in line with the literature[69] although gemcitabine with conventional radiotherapy has equal OS outcome compared with FOLFIRINOX in the PREOPANC-2 trial.[67]

Conclusion

In conclusion, neoadjuvant therapy was associated with prolonged OS compared with upfront surgery in patients with left-sided RPC who underwent a resection. Particularly patients with larger tumors and patients with increased serum CA19-9 at diagnosis may benefit most from neoadjuvant therapy. In contrast, the effect of neoadjuvant therapy was not enhanced in case of splenic vein/artery, retroperitoneal, or multivisceral involvement. Randomized controlled trials are needed to confirm the value of neoadjuvant therapy specifically in patients with left-sided RPC.

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DISCLOSURE

MDC has been awarded with an industry grant (Haemonetics, Inc.) to conduct a multicenter study to evaluate the prognostic implications of TEG in pancreatic cancer. MDC is co-principal investigator of a Boston Scientific-sponsored international multicenter study on the use of intraoperative pancreatoscopy of patients with IPMN. ER received a grant from Bengt Ihre's Fond. TFS, MGB, JWW, and CHJvE are granted by Dutch Cancer Society (KWF) and

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