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Citation

Doppenberg, D., Dam, J. L. van, Han, Y., Bonsing, B. A., Busch, O. R., Festen, S., ... Koerkamp, B. G. (2023). Predictive value of baseline serum carbohydrate antigen 19-9 level on treatment effect of neoadjuvant chemoradiotherapy in patients with resectable and borderline resectable pancreatic cancer in two randomized trials. *British Journal Of Surgery*, 110(10), 1374-1380. doi:10.1093/bjs/znad210

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Note: To cite this publication please use the final published version (if applicable).

Predictive value of baseline serum carbohydrate antigen 19-9 level on treatment effect of neoadjuvant chemoradiotherapy in patients with resectable and borderline resectable pancreatic cancer in two randomized trials

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Abstract

Background: Guidelines suggest that the serum carbohydrate antigen (CA19-9) level should be used when deciding on neoadjuvant treatment in patients with resectable and borderline resectable pancreatic ductal adenocarcinoma (hereafter referred to as pancreatic cancer). In patients with resectable pancreatic cancer, neoadjuvant therapy is advised when the CA19-9 level is 'markedly elevated'. This study investigated the impact of baseline CA19-9 concentration on the treatment effect of neoadjuvant chemoradiotherapy (CRT) in patients with resectable and borderline resectable pancreatic cancers.

Methods: In this *post hoc* analysis, data were obtained from two RCTs that compared neoadjuvant CRT with upfront surgery in patients with resectable and borderline resectable pancreatic cancers. The effect of neoadjuvant treatment on overall survival was compared between patients with a serum CA19-9 level above or below 500 units/ml using the interaction test.

Results: Of 296 patients, 179 were eligible for analysis, 90 in the neoadjuvant CRT group and 89 in the upfront surgery group. Neoadjuvant CRT was associated with superior overall survival (HR 0.67, 95 per cent c.i. 0.48 to 0.94; $P = 0.019$). Among 127 patients (70, 9 per cent) with a low CA19-9 level, median overall survival was 23.5 months with neoadjuvant CRT and 16.3 months with upfront surgery (HR 0.63, 0.42 to 0.93). For 52 patients (29 per cent) with a high CA19-9 level, median overall survival was 15.5 months with neoadjuvant CRT and 12.9 months with upfront surgery (HR 0.82, 0.45 to 1.49). The interaction test for CA19-9 level exceeding 500 units/ml on the treatment effect of neoadjuvant CRT was not significant ($P = 0.501$).

Conclusion: Baseline serum CA19-9 level defined as either high or low has prognostic value, but was not associated with the treatment effect of neoadjuvant CRT in patients with resectable and borderline resectable pancreatic cancers, in contrast with current guideline advice.

Received: February 08, 2023. Revised: April 06, 2023. Accepted: June 13, 2023

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Introduction

Pancreatic ductal adenocarcinoma (pancreatic cancer) is known for its poor 5-year survival rate of 10 per cent¹. Only 20 per cent of patients are eligible for resection. Neoadjuvant therapy is increasingly being used in patients with primary resectable and borderline resectable pancreatic cancers. Possible advantages of a neoadjuvant approach include better selection of patients for surgery, more microscopically complete (R0) resections, and improved overall survival (OS)². It remains unknown whether all patients benefit from this approach.

Carbohydrate antigen 19-9 (CA19-9) is a sialylated Lewis blood group antigen, which was first described as a tumour marker in 1981³. A raised CA19-9 level is a known prognostic biomarker for worse OS⁴. CA19-9 is mainly used to determine treatment response and recurrence in addition to imaging. The 2019 American Society of Clinical Oncology (ASCO)⁵ and 2022 National Comprehensive Cancer Network (NCCN)⁶ guidelines recommend upfront surgery for resectable pancreatic cancer, and neoadjuvant therapy for borderline resectable pancreatic cancer. In addition, these guidelines^{5,6} recommend consideration of neoadjuvant therapy for patients with resectable pancreatic cancer with 'markedly elevated' CA19-9 levels, without specifying a cut-off value. However, the predictive value of CA19-9 when selecting patients for neoadjuvant therapy has not been investigated.

Two multicentre RCTs⁷⁻⁹ recently reported superior OS with neoadjuvant chemoradiotherapy (CRT) compared with upfront resection in patients with resectable and borderline resectable pancreatic cancers. The aim of the present study was to investigate the predictive impact of baseline CA19-9 levels on the treatment effect of neoadjuvant CRT in patients with resectable and borderline resectable pancreatic cancers.

Methods

Patients

This was a *post hoc* analysis of two RCTs^{7,9} that compared neoadjuvant CRT with upfront surgery in patients with resectable

pancreatic cancer and borderline resectable pancreatic cancer. Patients were included in the present analysis if the baseline serum CA19-9 level was available. Patients with a serum bilirubin concentration exceeding 5.85 mg/dl (100 µmol/l) at the time of CA19-9 measurement were excluded as obstructive jaundice may raise CA19-9 levels¹⁰. All patients provided written informed consent before participation in the trials.

Korean trial

In the trial reported by Jang *et al.*⁷ from Korea, 27 patients were randomized to receive neoadjuvant CRT and 23 to upfront surgery. Neoadjuvant CRT consisted of 45 Gy in 25 fractions and 9 Gy in 5 fractions (5 times a week for 6 weeks) combined with gemcitabine at 400 mg/m² administered at the start of each week. In the upfront surgery group, patients received adjuvant CRT in the same doses as the neoadjuvant group. Patients in both groups received adjuvant gemcitabine at 1000 mg/m² on days 1, 8, and 15 during four cycles with a duration of 4 weeks each.

Dutch PREOPANC trial

In the PREOPANC trial⁹, 119 patients were assigned to neoadjuvant CRT and 127 to upfront surgery. Neoadjuvant CRT consisted of three cycles of gemcitabine. The first and third cycles had a duration of 3 weeks, with gemcitabine on days 1 and 8 at 1000 mg/m². The second cycle had a duration of 4 weeks, with gemcitabine on days 1, 8 and 15, combined with 36 Gy radiotherapy in 15 fractions (5 times a week for 3 weeks). After surgery, patients in the neoadjuvant CRT arm received four cycles of adjuvant gemcitabine at 1000 mg/m² on days 1, 8, and 15 (4 weeks per cycle). Patients in the upfront surgery group received six cycles of adjuvant gemcitabine. Inclusion and exclusion criteria for both trials are summarized in Fig. 1, and the definitions used for resectable pancreatic cancer and borderline resectable pancreatic cancer are shown in Table 1.

Outcomes

The primary outcome was OS from the date of randomization. Secondary outcomes included resection rate, R0 resection rate,

	Jang <i>et al.</i> , trial	PREOPANC trial
Inclusion criteria	Aged ≥ 18 – 75 years	WHO performance status ≤ 1
	Radiological evidence of BRPC according to 2012 NCCN criteria (Table 1)	Radiological, evidence of RPC or BRPC according to DPCG 2012 criteria (Table 1)
	Pathologically confirmed PDAC	Pathologically confirmed PDAC
	No history of previous chemoradiotherapy	CT < 4 weeks before randomization
	Adequate hepatic, renal, and bone marrow function	Adequate haematological, renal, and hepatic function
Exclusion criteria	Concomitant or previous antitumour therapy*	Previous therapy or co-morbidity precluding surgery or radiochemotherapy
	Concomitant or previous malignancy, except cancer in complete remission for > 5 years	Previous malignancy within past 5 years before diagnosis of PDAC
	Uncontrolled systemic disease (infection or cardiovascular disease)	cT1 resectable tumour (< 2 cm, without vascular involvement) LAPC or unresectable tumour metastasis or N2 lymph node metastasis

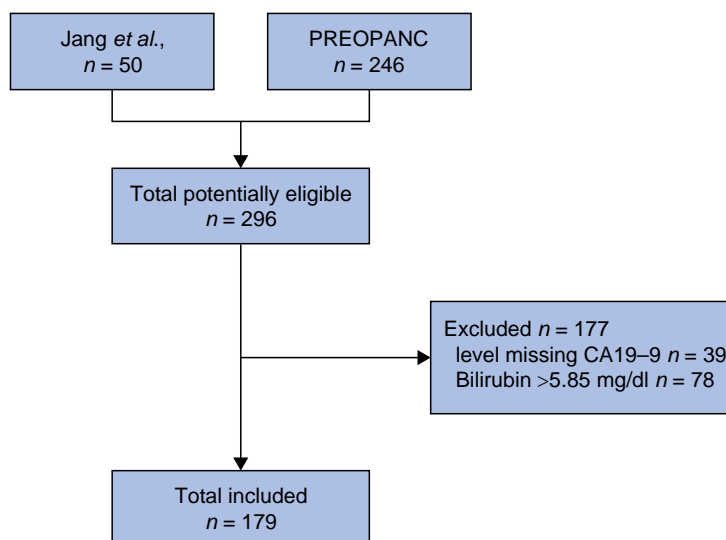
Fig. 1 Eligibility criteria in two randomized trials of neoadjuvant chemoradiotherapy in patients with (borderline) resectable pancreatic adenocarcinoma (pancreatic cancer)

*Chemotherapy, radiotherapy, immunotherapy. BRPC, borderline resectable pancreatic cancer; NCCN, National Comprehensive Cancer Network; PDAC, pancreatic ductal adenocarcinoma; RPC, resectable pancreatic cancer; DPCG, Dutch Pancreatic Cancer Group; LAPC, locally advanced pancreatic cancer.

Table 1 Definitions of primary resectable and borderline resectable pancreatic adenocarcinoma: degrees of vascular contact according to National Comprehensive Cancer Network 2.012 (Korean trial) versus Dutch Pancreatic Cancer Group (PREOPANC trial) criteria

		SMA	CA	CHA	SMV-PV	Comment
NCCN 2012	PR pancreatic cancer BR pancreatic cancer	No contact ≤180° contact	No contact No contact	No contact ≤90° contact*	No contact Contact or narrowing or occlusion†	- *No extension to CA †With possibility of allowing safe resection and replacement
DPCG 2012	PR pancreatic cancer BR pancreatic cancer	No contact ≤90° contact	No contact ≤90° contact	No contact ≤90° contact	≤90° contact ≤90–270° contact	All four required Minimally one required and no venous occlusion

SMA, superior mesenteric artery; CA, coeliac axis; CHA, common hepatic artery; SMV, superior mesenteric vein; PV, portal vein; NCCN, National Comprehensive Cancer Network; PR, primary resectable; BR, borderline resectable; DPCG, Dutch Pancreatic Cancer Group.

**Fig. 2 Study flow chart**

CA19-9, carbohydrate antigen 19-9.

and NO resection rate. A raised serum CA19-9 level was defined by a concentration exceeding 500 units/ml as this is a commonly used cut-off in the literature^{11,12}. As a sensitivity analysis, cut-offs of 180 and 1000 units/ml³ were tested.

Statistical analysis

Continuous variables are presented as median (i.q.r.) and categorical variables as counts with percentages. Continuous variables were compared using Mann-Whitney *U* test, and categorical variables using χ^2 test. OS was estimated using the Kaplan-Meier method and compared using the log rank test. The effect of a raised baseline CA19-9 level was investigated using Cox proportional hazards analysis. The interaction test was used to investigate whether the effect of neoadjuvant chemotherapy differed based on the CA19-9 level. $P < 0.050$ was considered to indicate statistical significance. Statistical analysis was undertaken using R software version 4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients and baseline characteristics

Of the 296 eligible patients, 39 had missing data on baseline CA19-9 and were excluded. The serum bilirubin concentration at the time of CA19-9 measurement was greater than 5.85 mg/dl

Table 2 Baseline characteristics

	Neoadjuvant CRT (n = 90)	Upfront surgery (n = 89)
Age (years), median (i.q.r.)	63 (57–70)	66 (60–72)
≥ 65	40 (44)	51 (57)
Sex ratio (M : F)	44 : 46	46 : 43
WHO performance status		
0	56 (58)	48 (52)
1	40 (42)	43 (46)
2	0 (0)	2 (2)
Tumour location in pancreas		
Head, n (%)	77 (80)	77 (83)
Body/tail, n (%)	19 (20)	16 (17)
Resectability status		
Primary resectable, n (%)	39 (43)	40 (45)
Borderline resectable, n (%)	51 (57)	49 (55)
Baseline CA19-9 (units/ml)		
≤ 500, n (%)	66 (73)	61 (69)
>500, n (%)	24 (27)	28 (31)

Values are n (%) unless indicated otherwise. CRT, chemoradiotherapy; CA19-9, carbohydrate antigen 19-9.

(100 μ mol/l) in 78 patients, resulting in the final inclusion of 179 patients (Fig. 2). Baseline characteristics are summarized in Table 2. The majority of patients (56 per cent) were staged as having borderline resectable pancreatic cancer, with 51 (57 per cent) in the neoadjuvant therapy group and 49 (55 per cent) in

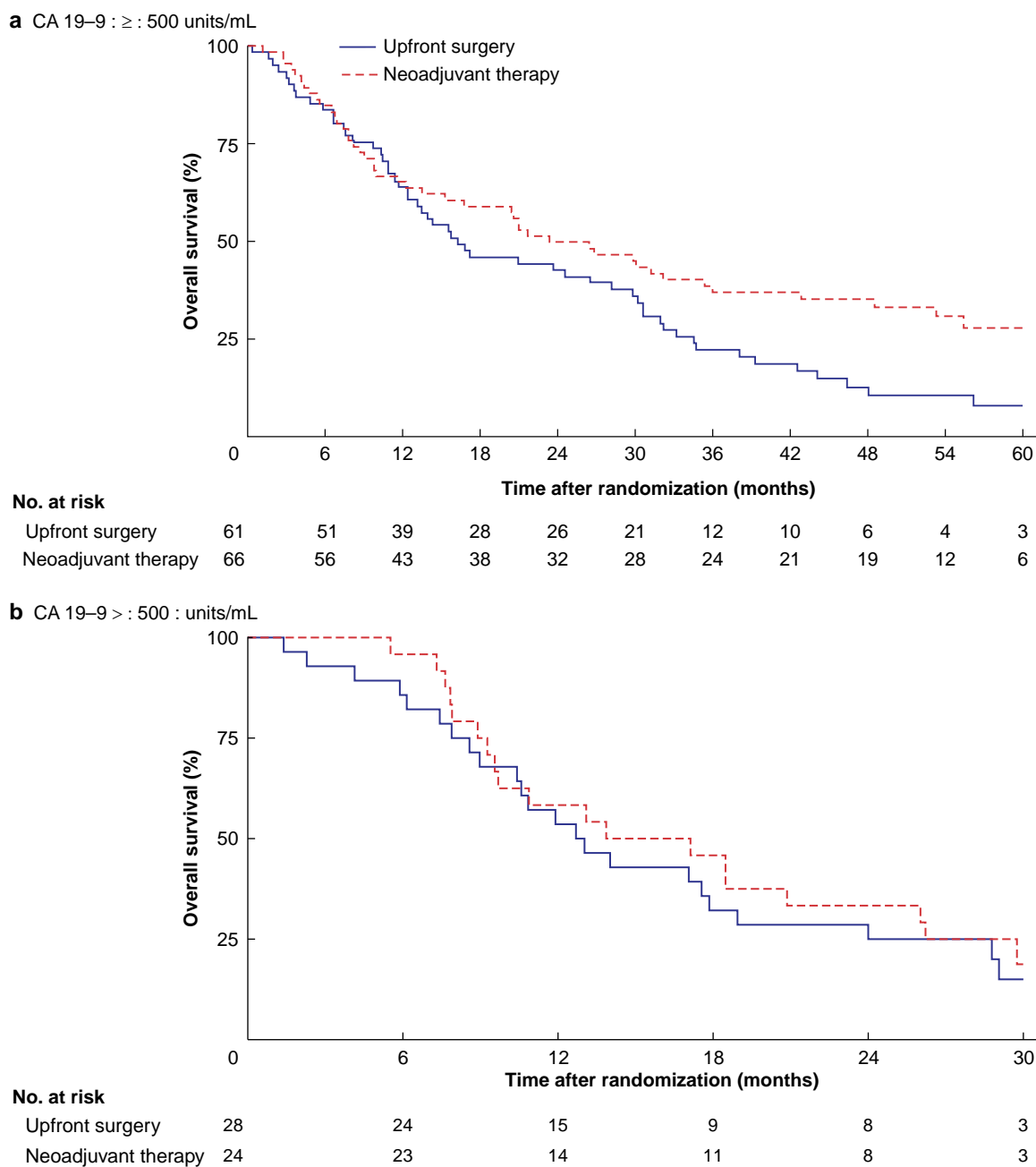


Fig. 3 Overall survival by treatment group according to carbohydrate antigen 19-9 level **a** 500 units/ml or less and **b** over 500 units/ml. CA19-9, carbohydrate antigen 19-9.

a $P = 0.020$, **b** $P = 0.509$ (log rank test).

the upfront surgery group. In the neoadjuvant therapy group, 24 patients (27 per cent) had a CA19-9 level over 500 units/ml compared with 28 (31 per cent) in the upfront surgery group.

Survival

After a median follow-up of 55 months, patients in the neoadjuvant CRT group had a median OS of 20.9 months compared with 15.6 months in the upfront surgery group (HR 0.67, 95 per cent c.i. 0.48 to 0.94; $P = 0.019$). In patients with a low CA19-9 level (500 units/ml or less), median OS was 23.5 months with neoadjuvant CRT compared with 16.3 months with upfront surgery (HR 0.63, 0.42 to 0.93) (Fig. 3a). In patients with a high CA19-9 level (over 500 units/ml), median OS was 15.5 months with neoadjuvant CRT compared with 12.9 months with

upfront surgery (HR 0.82, 0.45 to 1.49) (Fig. 3b). The interaction test did not detect an impact of CA19-9 on treatment effect of neoadjuvant CRT ($P = 0.501$). Using cut-off values for CA19-9 of 180 and 1000 units/ml also did not show a difference in treatment effect ($P = 0.210$ and $P = 0.511$ respectively) (Figs S1 and S2). In a subgroup analysis excluding 17 patients with a CA19-9 level below 5 units/ml (non-producers), no impact of CA19-9 on treatment effect was detected by an interaction test ($P = 0.616$) (Fig. S3).

Surgical resection

Among patients with a low CA19-9 level (500 units/ml or less), 44 of 66 patients (67 per cent) in the neoadjuvant CRT group underwent resection compared with 44 of 61 (72 per cent) in the

Table 3 Impact of carbohydrate antigen 19-9 on treatment outcomes

	Neoadjuvant CRT (n = 90)	Upfront surgery (n = 89)	P [¶]	P for interaction [#]
Resection				0.072
CA19-9 ≤ 500 units/ml	44 of 66 (67)*	44 of 61 (72)‡	0.635	
CA19-9 > 500 units/ml	13 of 24 (54)†	24 of 28 (86)§	0.084	
R0 resection				0.019
CA19-9 ≤ 500 units/ml	29 of 66 (44)	21 of 61 (34)	0.360	
CA19-9 > 500 units/ml	12 of 24 (50)	8 of 28 (29)	0.194	
NO resection				0.983
CA19-9 ≤ 500 units/ml	33 of 66 (50)	12 of 61 (20)	< 0.001	
CA19-9 > 500 units/ml	7 of 24 (29)	3 of 28 (11)	0.183	

Values are n (%). Reasons for not undergoing resection: *progression before chemoradiotherapy (CRT) (7), progression during CRT (6), locally unresectable during surgery (1), metastatic disease found during surgery (7), medical decision (1); †progression before CRT (1), progression during CRT (4), locally unresectable during surgery (1), metastatic disease found during surgery (4), patient's decision (1); ‡progression before surgery (1), locally unresectable during surgery (4), metastatic disease found during surgery (12). §patient's decision (1), metastatic disease found during surgery (3). CA19-9, carbohydrate antigen 19-9. ¶ χ^2 test; #interaction test.

upfront surgery group ($P = 0.635$) (Table 3). In patients with a high CA19-9 level (over 500 units/ml), 13 of 24 patients (54 per cent) in the neoadjuvant CRT group underwent resection compared with 24 of 28 (86 per cent) in the upfront surgery group ($P = 0.084$) (Table 3).

R0 resection

Pathological outcomes are shown in Table 3. In patients with a low CA19-9 level (500 units/ml or less), an R0 resection was reported in 29 of 66 patients (44 per cent) who had neoadjuvant CRT and 21 of 61 (34 per cent) in the upfront surgery group ($P = 0.360$). In patients with a high CA19-9 level (over 500 units/ml), an R0 resection was reported in 12 of 24 patients (50 per cent) and 8 of 28 (29 per cent) respectively ($P = 0.194$). The interaction test revealed a treatment effect of neoadjuvant CRT on R0 resection between high and low CA19-9 groups ($P = 0.019$).

NO resection

Among patients with a low CA19-9 level (500 units/ml or less), 33 of 66 patients (50 per cent) with neoadjuvant CRT had an NO resection compared with 12 of 61 (20 per cent) in the upfront surgery group ($P < 0.001$). In patients with a high CA19-9 level (over 500 units/ml), an NO resection was obtained in 7 of 24 patients (29 per cent) in the neoadjuvant CRT group and in 3 of 28 (11 per cent) in the upfront surgery group ($P = 0.183$). The interaction test found no difference in treatment effect on NO resection between high and low CA19-9 groups ($P = 0.983$).

Discussion

This patient-level *post hoc* analysis of two RCTs found no impact of baseline serum CA19-9 (cut-off 500 units/ml) on the treatment effect of neoadjuvant CRT in patients with resectable and borderline resectable pancreatic cancers. Overall, OS was better after neoadjuvant CRT compared with upfront resection (HR 0.67, 95 per cent c.i. 0.48 to 0.94)^{7,9}. If anything, neoadjuvant CRT seemed to improve OS, especially in patients with a low CA19-9 level (less than 500 units/ml), but the interaction test was negative.

This is the first study to assess the impact of CA19-9 on neoadjuvant CRT in data from RCTs. Currently, CA19-9 is used for diagnosis, treatment evaluation, and prognostication in patients with pancreatic cancer. Several authors^{13,14}, including the MD Anderson group, have long advocated for staging to go beyond tumour anatomy. In addition to anatomy, staging should consider biology (CA19-9 value) and patient condition (performance status). Several studies have found that a CA19-9 level above 500 units/ml in patients with resectable pancreatic cancer is associated with

similar or worse OS than in patients with borderline resectable pancreatic cancer¹¹. The NCCN⁶ and ASCO⁵ guidelines recommend considering neoadjuvant treatment in patients with resectable pancreatic cancer and 'markedly elevated' CA19-9 levels. The present study confirmed the strong association between a raised CA19-9 concentration and worse OS. However, a difference in treatment effect of neoadjuvant CRT associated with high or low baseline CA19-9 levels could not be demonstrated (Fig. 3). Although baseline serum CA19-9 level is a strong prognostic factor, in the present study it was not a predictive factor for the treatment effect of neoadjuvant treatment on OS.

The evidence for systemic therapy in patients with resectable and borderline resectable pancreatic cancers is shifting from purely adjuvant to perioperative/neoadjuvant administration. One of the problems of upfront surgery followed by adjuvant therapy is that about 40 per cent of patients do not receive chemotherapy after surgical resection^{15,16}. A recent meta-analysis¹⁷ of seven RCTs found better OS with neoadjuvant therapy compared with upfront surgery followed by adjuvant therapy (pooled HR 0.66, 95 per cent c.i. 0.52 to 0.85). A limitation of this meta-analysis was that it did not identify studies that used adjuvant FOLFIRINOX (a combination of fluorouracil with leucovorin, oxaliplatin, and irinotecan). Several ongoing RCTs are comparing neoadjuvant with adjuvant FOLFIRINOX in patients with resectable pancreatic cancer: the Scandinavian NorPACT-1 (NCT02919787), the United States Alliance A021806 (NCT04340141), and the Dutch PREOPANC-3 (NCT04927780) trials. While the results of these trials are awaited, the NCCN guidelines⁶ recommend participation in clinical trials or upfront surgery followed by adjuvant FOLFIRINOX for patients with resectable pancreatic cancer. To allow proper subgroup analysis, future RCTs should stratify by baseline CA19-9 level.

Among patients with CA19-9 levels above 500 units/ml, the resection rate was lower in the neoadjuvant CRT group whereas OS was better. Neoadjuvant CRT avoided a (futile) resection in one in three patients, and was still associated with better OS. A treatment effect of baseline serum CA19-9 level was demonstrated only for R0 resection. The higher R0 rate after neoadjuvant CRT was most profound in patients with a high CA19-9 level. This treatment effect, however, did not translate into a treatment effect for OS. No such treatment effect of baseline CA19-9 concentration could be demonstrated for the association between neoadjuvant CRT and nodal status.

Some limitations should be taken into account when assessing the present findings. First, baseline CA19-9 values were missing for some patients in the PREOPANC trial. Consequently, the relatively small sample size for investigation of interactions in

the present study may have resulted in a lack of statistical power to detect a small treatment effect. Second, baseline CA19-9 levels may have been influenced by residual cholestasis after excluding only patients with a bilirubin level of more than 5.85 mg/dl (100 µmol/l). Third, approximately 10 per cent of the population are Lewis antigen-negative and are unable to synthesize CA19-9¹⁸. This is a well known problem that should be addressed in future prospective studies, for instance by taking other tumour markers such as carcinoembryonic antigen into account. Fourth, one might hypothesize that higher levels of CA19-9 represent a higher systemic tumour load and the presence of micrometastatic disease. Neoadjuvant gemcitabine-based CRT may be inadequate for these patients. The ESPAC-4¹⁹ and PRODIGE-24/CCTG PA.6²⁰ RCTs have demonstrated superior OS with multiagent regimens compared with gemcitabine monotherapy in the adjuvant setting. Future studies will have to assess whether the observations in the present analysis hold true in trials with FOLFIRINOX and other multiagent regimens.

Funding

The authors have no funding to declare.

Acknowledgements

D.D. and J.L.v.D. are joint first authors, and G.v.T., J.Y.J., M.G.B., and B.G.K., are joint senior authors, of this article.

Author contributions

Conceptualization DD;JD;MB;BG; Methodology DD;JD; Software n.a., Validation n.a., Formal analysis JD;DD;SR, Investigation DD; JD;YH;BB;OB;SF;IH;MH;WK;ML;DL;VM;IM;JN;GP;SR;GS;MS;EV;JV; JW;CE;GT;JY;MB;BG, Resources DD;JD;YH;BB;OB;SF;IH;MH;WK; ML;DL;VM;IM;JN;GP;SR;GS;MS;EV;JV;JW;CE;GT;JY;MB;BG, Data curation DD;JD;YH, Writing-Original draft DD;JD, Writing - Review&Editing DD;JD;YH;BB;OB;SF;IH;MH;WK;ML;DL;VM;IM;JN; GP;SR;GS;MS;EV;JV;JW;CE;GT;JY;MB;BG, Visualization DD;JD, Supervision MB;JY;BG, Project Administration DD, Funding Acquisition n.a.

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at BJS online.

Data availability

The data that support the findings of this study are available on reasonable request from the corresponding author.

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