Neoadjuvant chemoradiotherapy versus upfront Surgery for resectable and borderline resectable pancreatic cancer: long-term results of the Dutch randomized PREOPANC trial

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Neoadjuvant Chemoradiotherapy Versus Upfront Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Long-Term Results of the Dutch Randomized PREOPANC Trial

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abstract

PURPOSE The benefit of neoadjuvant chemoradiotherapy in resectable and borderline resectable pancreatic cancer remains controversial. Initial results of the PREOPANC trial failed to demonstrate a statistically significant overall survival (OS) benefit. The long-term results are reported.

METHODS In this multicenter, phase III trial, patients with resectable and borderline resectable pancreatic cancer were randomly assigned (1:1) to neoadjuvant chemoradiotherapy or upfront surgery in 16 Dutch centers. Neoadjuvant chemoradiotherapy consisted of three cycles of gemcitabine combined with 36 Gy radiotherapy in 15 fractions during the second cycle. After restaging, patients underwent surgery followed by four cycles of adjuvant gemcitabine. Patients in the upfront surgery group underwent surgery followed by six cycles of adjuvant gemcitabine. The primary outcome was OS by intention-to-treat. No safety data were collected beyond the initial report of the trial.

RESULTS Between April 24, 2013, and July 25, 2017, 246 eligible patients were randomly assigned to neoadjuvant chemoradiotherapy (n = 119) and upfront surgery (n = 127). At a median follow-up of 59 months, the OS was better in the neoadjuvant chemoradiotherapy group than in the upfront surgery group (hazard ratio, 0.73; 95% CI, 0.56 to 0.96; P = .025). Although the difference in median survival was only 1.4 months (15.7 months *v* 14.3 months), the 5-year OS rate was 20.5% (95% CI, 14.2 to 29.8) with neoadjuvant chemoradiotherapy and 6.5% (95% CI, 3.1 to 13.7) with upfront surgery. The effect of neoadjuvant chemoradiotherapy was consistent across the prespecified subgroups, including resectable and borderline resectable pancreatic cancer.

CONCLUSION Neoadjuvant gemcitabine-based chemoradiotherapy followed by surgery and adjuvant gemcitabine improves OS compared with upfront surgery and adjuvant gemcitabine in resectable and borderline resectable pancreatic cancer.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Pancreatic cancer is the third leading cause of cancer-related death in the United States and the fourth in Europe.[1,2] Although some improvement in survival has recently been reported, pancreatic cancer is expected to become the second cause of cancer-related death by 2030.[3]

Approximately 15% of patients present with resectable or borderline resectable pancreatic cancer, with surgery followed by chemotherapy as the mainstay of treatment until recently. Adjuvant chemotherapy improves overall survival (OS) in patients with resected pancreatic cancer.[4-6] However, about 50% of patients do not receive adjuvant chemotherapy because of early recurrence, surgical complications, or clinical deterioration.[7-9] Neoadjuvant therapy may increase the proportion of patients that actually receive chemotherapy and thereby improve survival. Furthermore, neoadjuvant therapy may increase the microscopically margin-negative (R0) resection rate

CONTEXT

Key Objective

The benefit of neoadjuvant chemoradiotherapy in resectable and borderline resectable cancer over upfront surgery remains controversial, although many centers recommend neoadjuvant treatment on the basis of phase II trials and retrospective studies. Initially, the PREOPANC trial failed to demonstrate a survival benefit of neoadjuvant chemoradiotherapy. Here, we report the long-term results of this trial.

Knowledge Generated

With a median follow-up of 59 months, long-term overall survival improved for patients with resectable and borderline resectable pancreatic cancer treated with neoadjuvant gemcitabine-based chemoradiotherapy (hazard ratio 0.73; $P = .025$). In addition, the secondary outcomes disease-free survival, locoregional failure-free interval, and pathologic outcomes were significantly better after neoadjuvant treatment.

Relevance

Currently, there is a shifting paradigm worldwide from upfront surgery to neoadjuvant treatment. In the PREOPANC trial, neoadjuvant chemoradiotherapy resulted in a significant improvement in long-term overall survival compared with upfront surgery. The optimal neoadjuvant regimen warrants further investigation.

and may identify patients with rapidly progressive disease who can be spared futile surgery.

Nowadays, many centers recommend neoadjuvant therapy for patients with borderline resectable pancreatic cancer on the basis of meta-analyses that include retrospective studies and small phase II trials. No large randomized controlled trials have been published yet to support this approach.[10-12]

We previously reported the initial results of the multicenter phase III PREOPANC trial.[13] This trial aimed to determine whether neoadjuvant gemcitabine-based chemoradiotherapy improves OS compared with upfront surgery, both followed by adjuvant gemcitabine in patients with resectable and borderline resectable pancreatic cancer. At a median follow-up of 27 months, no statistically significant difference in OS was observed. Here, we report the long-term results of the PREOPANC trial.

METHODS

Study Design and Patients

The PREOPANC trial was an investigator-initiated, nationwide, multicenter, randomized controlled trial conducted in 16 centers in the Netherlands and initiated by the Dutch Pancreatic Cancer Group (DPCG). The Protocol (online only) was centrally approved by the Erasmus MC ethics committee (MEC 2012-249; December 11, 2012). The study protocol and the initial trial results were published previously.[13,14]

Eligible patients had pathologically confirmed resectable or borderline resectable pancreatic cancer without evidence of distant metastases. Resectability was determined on multiphase computed tomography (CT) imaging according to the DPCG criteria; pancreatic cancer was considered resectable if tumor contact with the superior mesenteric vein or portal vein was $\leq 90°$ without any arterial contact. It was considered borderline resectable in case of tumor contact with the superior mesenteric vein or portal vein of $\leq 270°$ without occlusion, or tumor contact with the celiac axis, hepatic artery, or superior mesenteric artery of $\leq 90°$.[14] Patients with tumors smaller than 2 cm (T1) without vascular contact were excluded. Other eligibility criteria included a WHO performance status of 0 or 1 and adequate hematologic, hepatic, and renal function. There were no restrictions on the level of serum carbohydrate antigen 19-9 (CA 19-9). A full list of the inclusion and exclusion criteria is available in the protocol.[14] All patients provided written informed consent.

Random Assignment

Patients were randomly assigned (1:1) to neoadjuvant gemcitabine-based chemoradiotherapy followed by surgery or to upfront surgery, both followed by adjuvant gemcitabine. Random assignment was performed online using computer-generated permuted blocks with stratification according to center and resectability (resectable *v* borderline resectable). The study was open-label, and no masking was used.

Procedures

For patients randomly assigned to neoadjuvant chemoradiotherapy, endoscopic biliary drainage was performed when serum bilirubin was above 1.5 mg/dL (25 μmol/L), preferably with a self-expanding metal stent. For patients randomly assigned to upfront surgery, preoperative biliary drainage was only recommended for those with bilirubin levels above 14.6 mg/dL (250 μmol/L).

Patients in the neoadjuvant chemoradiotherapy group underwent a staging laparoscopy before chemoradiotherapy. Neoadjuvant chemoradiotherapy was to be started within 4 weeks after random assignment. Chemoradiotherapy consisted of three cycles of gemcitabine and radiotherapy.

The first and third cycles had a duration of 3 weeks with gemcitabine once weekly in the first 2 weeks at a dose of 1,000 mg/m^2. The second cycle had a duration of 4 weeks with gemcitabine once weekly in the first 3 weeks at a dose of 1,000 mg/m^2, combined with hypofractionated radiotherapy of the pancreatic tumor and radiologically suspected lymph nodes at a dose of 36 Gy in 15 fractions (five fractions per week). A quality assurance procedure to evaluate compliance with the radiotherapy protocol was performed in the beginning of the trial.[15] Patients were restaged within 4 weeks after the last dose of chemotherapy. When the CT scan showed no metastases or locally unresectable disease, patients were scheduled for surgical exploration within 4-6 weeks after the last chemotherapy. Patients in the upfront surgery group were scheduled for surgical exploration no later than 4 weeks after random assignment.

Resection was performed according to the consensus statement of the International Study Group on Pancreatic Surgery.[16] A pancreatoduodenectomy with locoregional lymph node dissection was performed for pancreatic head tumors. For tumors involving the pancreatic body or tail, pancreas body and tail resection with splenectomy was performed.

Adjuvant gemcitabine was administered in cycles of 4 weeks with gemcitabine once weekly in the first 3 weeks at a dose of 1,000 mg/m^2 and was to be started no later than 12 weeks after surgery. Patients in the neoadjuvant chemoradiotherapy group were scheduled for the remaining four cycles, and patients in the upfront surgery group for six cycles.

Patients underwent follow-up using CT scans and serum CA 19-9 examinations every 6 months during the first 2 years after random assignment and yearly thereafter, or when recurrence was suspected. Data were collected until December 2020, guaranteeing a minimum follow-up of 35 months for all patients.

End Points

The primary end point was OS by intention-to-treat (ITT), defined as the time between random assignment and death from any cause. Patients alive at last follow-up were censored. Secondary end points included disease-free survival, locoregional failure-free interval, distant metastases-free interval, resection rate, margin-negative (R0) resection rate, serious adverse events, and postoperative complications. Pathologic staging was performed using the seventh edition of the TNM staging system by the Union for International Cancer Control (UICC).[17] A resection was considered microscopically complete (R0) if no tumor cells were identified within 1 mm of the resection margin, according to the definition of the Royal College of Pathologists.[18] Serious adverse events were graded according to the Common Terminology Criteria for Adverse Events (version 4.0).

Statistical Analysis

The trial was designed to detect a 6-month difference in median OS (11 *v* 17 months). On the basis of 80% power and a 5% two-sided significance level, at least 176 events were required. Assuming a dropout rate of 10%, at least 244 patients were needed. The primary outcome was analyzed by ITT. Survival was estimated using the Kaplan-Meier method. Treatment effect was estimated using a Cox proportional-hazards model with stratification by resectability. Subgroup analyses for the effect of neoadjuvant chemoradiotherapy on survival for baseline characteristics were investigated using interaction tests. Categorical variables were compared using the Fisher's exact test, and continuous variables were compared using the Mann-Whitney U test. All tests were performed two-sided. A P value of $< .05$ indicated statistical significance. Analyses were performed using R software, version 4.0.2. The trial was registered with EudraCT (2012-003181-40) and the Netherlands Trial Register (3709).

RESULTS

From April 24, 2013, to July 25, 2017, a total of 248 patients were enrolled in the study: 120 were assigned to neoadjuvant chemoradiotherapy and 128 to upfront surgery. Two patients (one in each group) withdrew consent, thus ineligible, leaving 119 patients in the neoadjuvant chemoradiotherapy group and 127 in the upfront surgery group for the ITT analyses (Fig 1). Baseline characteristics per treatment group are reported in Table 1.

In the chemoradiotherapy group, five patients underwent no staging laparoscopy (Fig 1). After laparoscopy, 91 of 119 patients (76%) started neoadjuvant chemoradiotherapy (Fig 1). Seven patients crossed over to surgery without neoadjuvant treatment. Three had an indication for early surgery (bleeding, liver abscess, and cholangitis), two had a change in diagnosis to benign disease and cholangiocarcinoma, respectively, in one patient no pathologic diagnosis was obtained, and one patient decided for upfront surgery. CT evaluation after completion of chemoradiotherapy showed locally unresectable or metastatic disease in 10 patients (Fig 1).

Including the seven crossovers that did not undergo chemoradiotherapy, 82 of the 119 patients in the chemoradiotherapy group underwent surgical exploration, and of these, 72 had a resection (resection rate 72 of 119; 61%). In the upfront surgery group, 121 of the 127 patients underwent exploration, and of these, 92 underwent a resection (resection rate 92 of 127; 72%). The R0 resection rate by ITT was 41% (49 of 119) in the neoadjuvant group and 28% (35 of 127) in the upfront surgery group ($P = .025$).

Final histopathology showed pancreatic cancer in 150 of 164 patients (91%) who underwent a resection: 68 patients in the neoadjuvant chemoradiotherapy group and 82 in the upfront surgery group (Table 2). For patients with histologically confirmed pancreatic cancer, R0 resection was achieved in 49 of 68 patients (72%) in the neoadjuvant chemoradiotherapy group compared with 35 of 82 patients

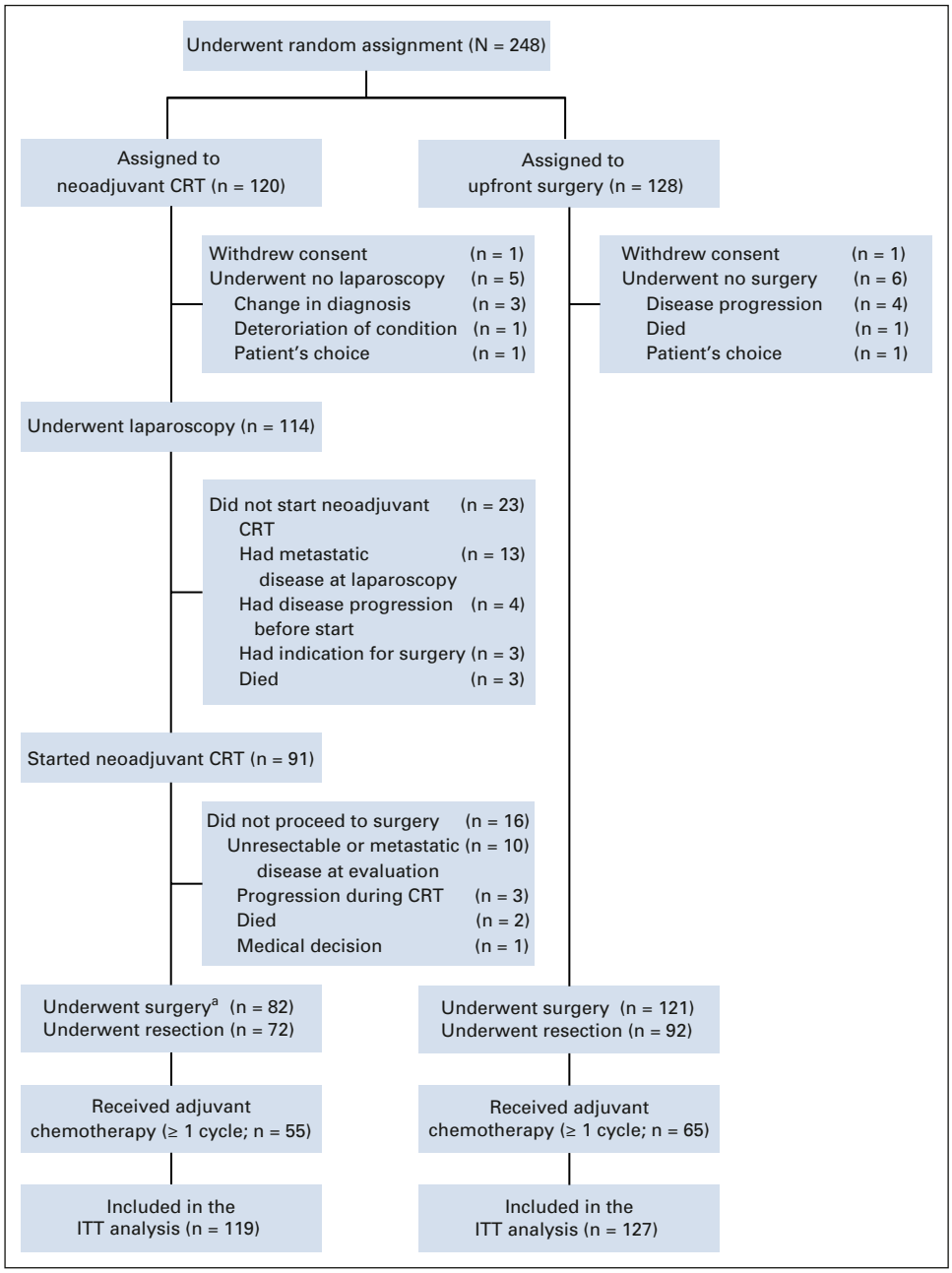

FIG 1. CONSORT diagram. [a]Seven patients proceeded to surgery without neoadjuvant chemoradiotherapy. CRT, chemoradiotherapy; ITT, intention-to-treat.

(43%) in the upfront surgery group ($P < .001$). Tumor size was smaller with neoadjuvant chemoradiotherapy (25 mm *v* 33 mm; $P < .001$). Pathologic lymph nodes (35 *v* 82%; $P < .001$), perineural invasion (45 *v* 85%; $P < .001$), and vascular invasion (36 *v* 65%; $P < .001$) were all less frequent in the neoadjuvant chemoradiotherapy group (Table 2).

In the neoadjuvant chemoradiotherapy group, 55 of the 68 patients with pancreatic cancer (81%) started adjuvant chemotherapy, of whom 34 completed all cycles (62%). In the upfront surgery group, 65 of the 82 patients with pancreatic cancer (79%) started adjuvant chemotherapy, of whom 35 completed all cycles (54%). By ITT, 46% of the 119 patients in the neoadjuvant chemoradiotherapy group started adjuvant chemotherapy, versus 51% of the 127 patients in the upfront surgery group.

When combining neoadjuvant and adjuvant therapy, 92 patients (77%) in the neoadjuvant chemoradiotherapy group and 65 patients (51%) in the upfront surgery group received at least one cycle of chemotherapy ($P < .001$; Data Supplement, online only). The total cumulative dose of chemotherapy was significantly higher in the neoadjuvant

TABLE 1. Baseline Characteristics of the Intention-to-Treat Population

Characteristic	Neoadjuvant Chemoradiotherapy (n = 119)	Upfront Surgery (n = 127)
Age, years		
Median (IQR)	66 (59-71)	67 (60-73)
< 65, No. (%)	55 (46)	50 (39)
≥ 65, No. (%)	64 (54)	77 (61)
Sex, No. (%)		
Male	64 (54)	74 (58)
Female	55 (46)	53 (42)
WHO performance status,[a] No. (%)		
0	69 (58)	49 (39)
1	49 (41)	78 (61)
2	1 (1)	0
Resectability status, No. (%)		
Resectable	65 (55)	68 (54)
Borderline resectable	54 (45)	59 (47)
Tumor location, No. (%)		
Head	99 (83)	119 (92)
Other	20 (17)	10 (8)
Tumor size at baseline		
< 30 mm, No./n (%)	51/117 (44)	56/124 (45)
≥ 30 mm, No./n (%)	66/117 (56)	68/124 (55)
Missing, No.	2	3
CA 19-9 at baseline		
< 500 U/mL, No./n (%)	76/107 (71)	65/100 (65)
≥ 500 U/mL, No./n (%)	31/107 (29)	35/100 (35)
Missing, No.	12	27

Abbreviations: CA 19-9, carbohydrate antigen 19-9; IQR, interquartile range.
[a]WHO performance status was either 0 or 1 for 13 patients who were classified as WHO 1.

chemoradiotherapy group (Appendix Table A1, online only).

After a median follow-up of 59 months, 210 patients had died: 93 (78%) in the neoadjuvant chemoradiotherapy group and 117 (92%) in the upfront surgery group. The median OS by ITT was 15.7 months (95% CI, 12.9 to 20.6) in the neoadjuvant chemoradiotherapy group and 14.3 months (95% CI, 12.7 to 17.9) in the upfront surgery group (hazard ratio [HR] 0.73; 95% CI, 0.56 to 0.96; $P = .025$; Fig 2A). Survival estimates at 3 and 5 years were 27.7% (95% CI, 20.7 to 37.1) and 20.5% (95% CI, 14.2 to 29.8), respectively, for the neoadjuvant chemoradiotherapy group and 16.5% (95% CI, 11.1 to 24.4) and 6.5% (95% CI, 3.1 to 13.7), respectively, for the upfront surgery group.

The effect of neoadjuvant chemoradiotherapy on OS was consistent across subgroups of baseline age, sex, WHO performance, resectability, tumor size, and CA 19-9 level (cutoff 500 U/ml), without any statistically significant interaction identified (Fig 3). Survival curves by resectability are shown in Figure 2B. For patients with resectable pancreatic cancer, the HR was 0.79, and for borderline resectable pancreatic cancer, the HR was 0.67, both in favor of the patients treated with neoadjuvant chemoradiotherapy.

The secondary time-to-event outcomes disease-free survival (HR, 0.69; 95% CI, 0.53 to 0.91; $P = .009$), locoregional failure-free interval (HR, 0.57; 95% CI, 0.39 to 0.83; $P = .004$), and distant metastases-free interval (HR, 0.74; 95% CI, 0.54 to 1.03; $P = .070$) were also in favor of the neoadjuvant chemoradiotherapy group (Appendix Table A2, online only). Palliative chemotherapy for progression or recurrence was initiated in 35 of 84 patients (40%) in the neoadjuvant chemoradiotherapy group and in 36 of 108 patients (33%) in the upfront surgery group ($P = .37$; Appendix Table A3, online only).

Serious adverse events occurred in 62 patients (52%) in the neoadjuvant chemoradiotherapy group and in 52 patients (41%) in the upfront surgery group ($P = .096$). Major

TABLE 2. Surgical and Pathologic Outcomes

Outcome	Neoadjuvant Chemoradiotherapy (n = 119), No. of Events/Total No. (%)	Upfront Surgery (n = 127), No. of Events/Total No. (%)	*P*
Underwent surgical exploration	82/119 (69)	121/127 (95)	< .001
Underwent resection	72/119 (61)	92/127 (72)	.058
Type of surgery			< .001
Pancreatoduodenectomy	59/119 (50)	80/127 (63)	
Pancreas body and tail resection	12/119 (10)	8/127 (6)	
Total pancreatectomy	1/119 (1)	4/127 (3)	
Exploration without resection	10/119 (8)	29/127 (23)	
No exploration	37/119 (31)	6/127 (5)	
Diagnosis at pathology			.42
Pancreatic adenocarcinoma	68/72 (94)	82/92 (89)	
Distal cholangiocarcinoma	2/72 (3)	7/92 (8)	
Other	2/72 (3)	3/92 (3)	
Tumor differentiation			.91
Well	8/55 (15)	9/75 (12)	
Moderate	30/55 (55)	44/75 (59)	
Poor	17/55 (31)	21/75 (28)	
Undifferentiated	0	1/75 (1)	
Missing, No.	13	7	
Tumor size, mm (IQR)[a]	25 (20-35)	33 (27-40)	< .001
Tumor stage[b]			< .001
T1	10/68 (15)	0	
T2	7/68 (10)	2/82 (2)	
T3	51/68 (75)	78/82 (95)	
T4	0	2/82 (2)	
Nodal status[b]			< .001
N0	44/68 (65)	15/82 (18)	
N1	24/68 (35)	67/82 (82)	
Margin status			< .001
R0	49/68 (72)	35/82 (43)	
R1	19/68 (28)	47/82 (57)	
Perineural invasion			< .001
Yes	28/62 (45)	67/79 (85)	
No	34/62 (55)	12/79 (15)	
Missing, No.	6	3	
Vascular invasion			< .001
Yes	23/64 (36)	51/78 (65)	
No	41/64 (64)	29/78 (35)	
Missing, No.	4	4	

[a]Tumor size was missing for 12 patients.

[b]Tumor stage and nodal status according to the seventh edition of the TNM staging system by the Union for International Cancer Control (UICC).[17]

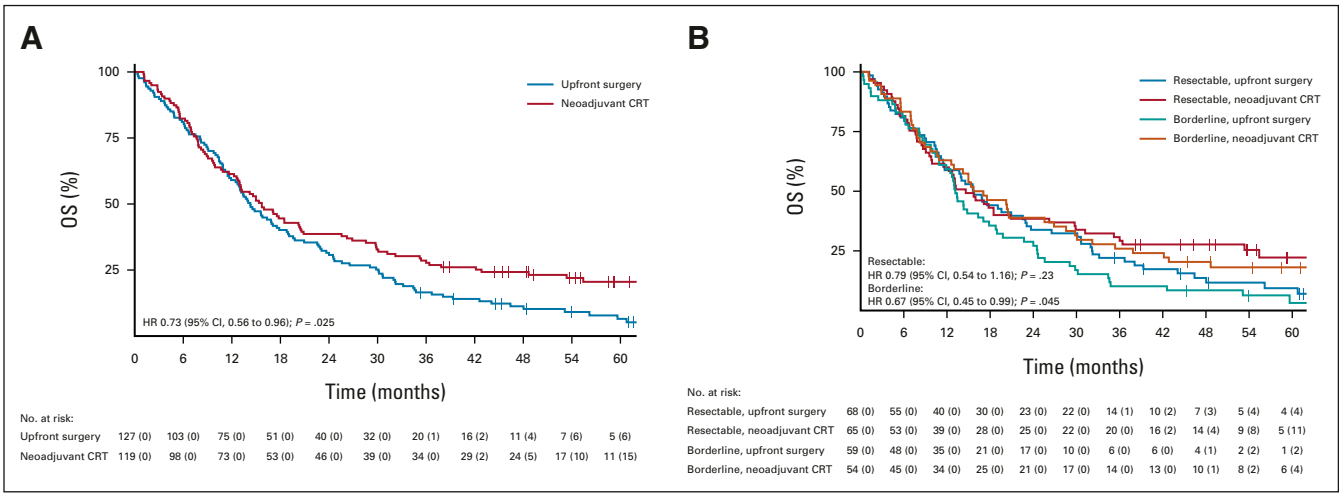

FIG 2. Kaplan-Meier estimates of OS by (A) treatment group and (B) by resectability and treatment group. CRT, chemoradiotherapy; HR, hazard ratio; OS, overall survival.

surgical complications and postoperative mortality were not different between both groups.[19]

DISCUSSION

This phase III, randomized trial demonstrates a long-term survival benefit with neoadjuvant treatment compared with upfront surgery in patients with resectable and borderline resectable pancreatic cancer (HR, 0.73; $P = .025$). The 5-year OS rate showed a clinically relevant improvement of 14%. The effect of neoadjuvant chemoradiotherapy was consistent across subgroups, including resectable and borderline resectable disease.

The initial results of the PREOPANC trial found a HR of 0.78 (95% CI, 0.58 to 1.05; $P = .096$) after a median follow-up of 27 months with 180 deaths (73%).[13] At the time of the present analysis, the median follow-up was 59 months and 210 patients (85%) had died. Other randomized trials comparing perioperative treatments in pancreatic cancer have shown that long-term follow-up is required to detect a clinically relevant survival difference. For example, the CONKO-001 trial, comparing adjuvant gemcitabine with observation after surgery, initially found no survival difference,[20] but at longer follow-up, HR was 0.76 (95% CI, 0.61 to 0.95; $P = .01$).[4] Pancreatic cancer is characterized by a high progression rate shortly after diagnosis. Our trial population consisted of representative patients at the time of initial diagnosis.[21] This high progression rate in the first year is seen in both groups. Apparently, our neoadjuvant schedule was not able to prevent many of these early progressions, and more effective schedules are warranted. However, a futile surgical intervention was spared in a subset of these patients with early progression in the neoadjuvant group. The steep initial slope of the survival curves starts to bend and divide clearly after a year from diagnosis, close to the median survival time, explaining the small difference in median survival (1.4 months) between the groups, whereas the 3-year and 5-year survival show a 7.2% and 14% difference, respectively. This suggests that in neoadjuvant trials, median survival is a suboptimal end point, and long-term follow-up is required to demonstrate clinically relevant survival differences. Further research should investigate predictive factors for early disease progression.

The PREOPANC trial found survival outcomes that are lower than those reported in adjuvant trials.[4-6] This is explained by differences in patient population of neoadjuvant and adjuvant trials. Neoadjuvant trials randomly assign patients at initial diagnosis with resectable or borderline resectable pancreatic cancer on imaging, whereas adjuvant trials randomly assign patients who recovered well from resection without evidence of early recurrence, who are fit enough for chemotherapy. This latter subgroup has a more favorable prognosis. Only about 80% of patients with initially resectable or borderline resectable pancreatic cancer do actually undergo a resection because a proportion deteriorates before surgery or metastases are found during exploration.[22] After resection, many patients do not recover enough and consequently, only about 50% of patients with resected pancreatic cancer receive adjuvant chemotherapy.[7-9] Furthermore, most adjuvant trials require a postoperative CT scan without evidence of early recurrence or metastases and some have upper limits on postoperative CA 19-9.[4,6] Because of this selection, survival estimates in most adjuvant trials are superior to those of neoadjuvant trials.

Four other randomized trials comparing neoadjuvant therapy with upfront surgery for resectable and borderline resectable pancreatic cancer have been published.[23-26] The results of these trials are in line with ours. Two additional trials, only available as published abstracts, also found superior survival outcomes with neoadjuvant therapy.[27,28] A recent meta-analysis of six of these trials showed

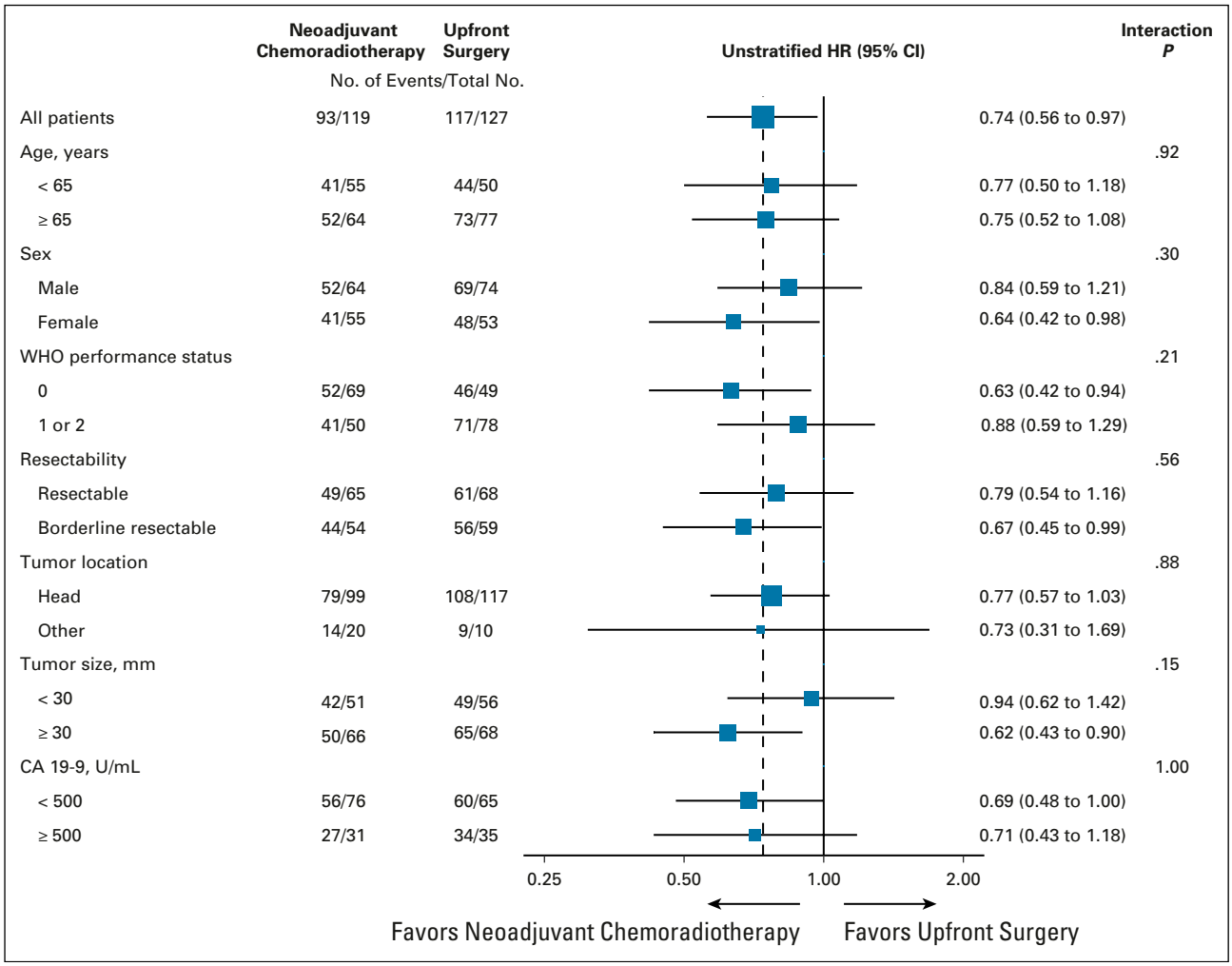

FIG 3. Forest plot of treatment effect on overall survival according to baseline characteristics of patients. The position of each square represents the point estimate of the treatment effect in the subgroup, and error bars represent 95% CIs. The sizes of the squares are proportional to the number of patients. The dashed line represents the unstratified HR for all patients. Tumor size was missing for five patients. CA 19-9 was missing for 39 patients. CA 19-9, carbohydrate antigen 19-9; HR, hazard ratio.

a survival benefit for resectable and borderline resectable disease.[29]

In the neoadjuvant chemoradiotherapy group, 61% of patients underwent a resection, versus 72% in the upfront surgery group. The lower resection rate in the neoadjuvant chemoradiotherapy group is explained by patients who had progressive disease during neoadjuvant therapy. We hypothesize that these patients would not have benefited from upfront resection because early progression reflects aggressive tumor biology rather than a missed opportunity for resection. This is reflected by the superior survival in the neoadjuvant chemoradiotherapy group, despite the lower resection rate. In the neoadjuvant chemoradiotherapy group, more patients received chemotherapy compared with the upfront surgery group (77% *v* 51%; $P < .001$). In addition, the cumulative dose was higher in the neoadjuvant group, suggesting better tolerability with neoadjuvant administration. The neoadjuvant chemoradiotherapy consisted of both chemotherapy and radiotherapy. It is unclear to what extent the improved outcomes in the neoadjuvant chemoradiotherapy group can be attributed to the addition of radiotherapy or to the timing of treatment as such.

The main limitation of the study is the use of adjuvant gemcitabine monotherapy, a regimen that is nowadays considered out of date. Gemcitabine was the standard of care in the Netherlands at the time the trial was designed and patients were enrolled. New evidence has become available since closure of the trial. In 2017, the ESPAC-4 trial demonstrated that adjuvant gemcitabine with capecitabine is superior to gemcitabine monotherapy.[5] In 2018, the PRODIGE-24/CCTG PA.6 trial showed that adjuvant fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) is superior to adjuvant gemcitabine.[6] In the neoadjuvant setting, however, no randomized trial has been published comparing gemcitabine-based chemoradiotherapy with multiagent neoadjuvant regimens with or

without radiation. In addition, the resectability criteria used within this trial are slightly different from the National Comprehensive Cancer Network (NCCN) criteria, with the result that a subgroup of patients with borderline resectable pancreatic cancer according to the NCCN criteria are not included in this study.

At final histopathology, 14 patients (9%) had other pathology than pancreatic adenocarcinoma, and most of these patients had cholangiocarcinoma. This reflects the diagnostic difficulties, particularly concerning cytologic diagnosis at the time of initial diagnosis. This percentage compares favorably with an earlier multicenter observational study.[30]

Another important aspect of the PREOPANC trial is that it has shown that large RCTs studying neoadjuvant treatment in pancreatic cancer are feasible in terms of accrual. It has paved the way for the PREOPANC-2 trial, comparing neoadjuvant gemcitabine-based chemoradiotherapy with neoadjuvant FOLFIRINOX that recently completed accrual of 375 patients in < 3 years with results expected in 2022.[31] Neoadjuvant FOLFIRINOX is currently investigated in four randomized trials for resectable pancreatic cancer (NorPACT-1,[32] PANACHE01-PRODIGE48,[33] ALLIANCE A021806 [NCT04340141], and PREOPANC-3 [NCT04927780]).

In conclusion, the PREOPANC trial demonstrates that neoadjuvant therapy is superior to upfront surgery in pancreatic cancer. The PREOPANC trial found that neoadjuvant gemcitabine-based chemoradiotherapy followed by surgery and adjuvant gemcitabine improves OS compared with upfront surgery and adjuvant gemcitabine in patients with resectable and borderline resectable pancreatic cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Neoadjuvant Chemoradiotherapy Versus Upfront Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Long-Term Results of the Dutch Randomized PREOPANC Trial

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TABLE A1. Treatment Exposure by Treatment Group

Treatment	Neoadjuvant Chemoradiotherapy (n = 119)	Upfront Surgery (n = 127)	*P*
By ITT			
Planned No. of cycles	7	6	
Actual No. of cycles[a]			
≥ 1 cycle of chemotherapy, No. (%)	92 (77)	65 (51)	< .001
Median (IQR)	3 (1-7)	1 (0-6)	< .001
Planned drug administrations, No.	19	18	
Actual drug administrations			
Median (IQR)	7 (2-17)	2 (0-16)	.003
Total cumulative dose, mg/m^2			.003
Average	8,554	6,349[b]	
Median (IQR)	7,000 (2,000-15,643)	1,511 (0-13,841)	
Per protocol			
Patients who started neoadjuvant chemotherapy			
≥ 1	91 (100)	—	
≥ 2	87 (96)	—	
3	81 (89)	—	
Patients who started neoadjuvant radiotherapy	87 (96)		
Total cumulative dose (Gray)			
Median (IQR)	36.0 (2.4-36.0)		
Patients who started adjuvant chemotherapy			
≥ 1	55 (100)	65 (100)	
≥ 2	48 (87)	61 (94)	
≥ 3	42 (76)	58 (89)	
≥ 4	34 (62)	50 (77)	
≥ 5	—	42 (65)	
6	—	36 (55)	

NOTE. Data are No. (%) unless otherwise indicated.
Abbreviations: IQR, interquartile range; ITT, intention-to-treat.
[a]At least one administration of gemcitabine per cycle.
[b]Dose was missing for one patient.

TABLE A2. Secondary Time-to-Event Outcomes

Outcome	Median Time to Event, months (95% CI)		HR (95% CI)	*P*
	Neoadjuvant Chemoradiotherapy	Upfront Surgery		
DFS	8.1 (5.4 to 12.5)	7.7 (6.2 to 10.4)	0.69 (0.53 to 0.91)	.009
Locoregional failure-free interval	31.2 (21.1 to NR)	13.4 (11.9 to 22.0)	0.57 (0.39 to 0.83)	.004
Distant metastasis-free interval	17.4 (12.1 to 28.0)	12.5 (10.6 to 16.7)	0.74 (0.54 to 1.03)	.070

Abbreviations: DFS, disease-free survival; HR, hazard ratio; NR, not reached.

TABLE A3. Treatment of Progression or Recurrence

Treatment	Neoadjuvant Chemoradiotherapy (n = 87)	Upfront Surgery (n = 108)
Chemotherapy[a]	35 (40)	36 (33)
FOLFIRINOX	26 (30)	23 (21)
Gemcitabine/nab-paclitaxel	1 (1)	6 (6)
Gemcitabine	3 (3)	3 (3)
Gemcitabine/cisplatin	0	1 (1)
Capecitabine	2 (2)	0
Irinotecan	1 (1)	0
Unspecified	2 (2)	3 (3)
Radiotherapy	5 (6)	5 (5)
Other	1 (1)	3 (3)
No treatment	43 (49)	60 (56)
Missing	3 (3)	4 (4)

NOTE. Only the first treatment for progression or recurrence is indicated. Data are No. (%).
Abbreviation: FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin.
[a]$P = .37$.