original reports

Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial

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abstract

PURPOSE Preoperative chemoradiotherapy may improve the radical resection rate for resectable or borderline resectable pancreatic cancer, but the overall benefit is unproven.

PATIENTS AND METHODS In this randomized phase III trial in 16 centers, patients with resectable or borderline resectable pancreatic cancer were randomly assigned to receive preoperative chemoradiotherapy, which consisted of 3 courses of gemcitabine, the second combined with 15 × 2.4 Gy radiotherapy, followed by surgery and 4 courses of adjuvant gemcitabine or to immediate surgery and 6 courses of adjuvant gemcitabine. The primary end point was overall survival by intention to treat.

RESULTS Between April 2013 and July 2017, 246 eligible patients were randomly assigned; 119 were assigned to preoperative chemoradiotherapy and 127 to immediate surgery. Median overall survival by intention to treat was 16.0 months with preoperative chemoradiotherapy and 14.3 months with immediate surgery (hazard ratio, 0.78; 95% CI, 0.58 to 1.05; $P = .096$). The resection rate was 61% and 72% ($P = .058$). The R0 resection rate was 71% (51 of 72) in patients who received preoperative chemoradiotherapy and 40% (37 of 92) in patients assigned to immediate surgery ($P < .001$). Preoperative chemoradiotherapy was associated with significantly better disease-free survival and locoregional failure-free interval as well as with significantly lower rates of pathologic lymph nodes, perineural invasion, and venous invasion. Survival analysis of patients who underwent tumor resection and started adjuvant chemotherapy showed improved survival with preoperative chemoradiotherapy (35.2 *v* 19.8 months; $P = .029$). The proportion of patients who suffered serious adverse events was 52% versus 41% ($P = .096$).

CONCLUSION Preoperative chemoradiotherapy for resectable or borderline resectable pancreatic cancer did not show a significant overall survival benefit. Although the outcomes of the secondary end points and predefined subgroup analyses suggest an advantage of the neoadjuvant approach, additional evidence is required.

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ASSOCIATED CONTENT

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Data Supplement

Protocol

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

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Written on behalf of the Dutch Pancreatic Cancer Group.

INTRODUCTION

Approximately 20% of patients with pancreatic ductal adenocarcinoma (PDAC) have resectable or borderline resectable disease. Standard treatment is resection followed by adjuvant chemotherapy.[1,2] Only approximately half of the patients who undergo tumor resection actually receive adjuvant chemotherapy.[3-5] Furthermore, approximately half of the resections are microscopically incomplete (R1)[6,7]; one quarter of patients will develop disease recurrence within 6 months.[8]

Preoperative (neoadjuvant) chemoradiotherapy in patients with resectable or borderline resectable PDAC has not yet been proven superior, although it is standard of care for many other cancers.[9,10] Preoperative chemoradiotherapy, by inducing downstaging of the tumor, might increase the R0 resection rate. R0 resection rate is an important prognostic factor, diminishing local and distant recurrence rates, hence improving survival. In addition, compliance with preoperative chemoradiotherapy is better compared with postoperative chemotherapy. Potential

disadvantages of preoperative chemoradiotherapy are more complicated surgery by radiation toxicity and fewer resections because of early tumor progression. Whether the latter is a disadvantage in the long run is not completely certain.

Most of the studies that advocate preoperative chemoradiotherapy are nonrandomized studies with selection bias by reporting survival after resection rather than by intention to treat (ITT). Interpretation and comparison of these studies are difficult, if not impossible. Surgical radicality after preoperative chemoradiotherapy has never been studied in a multicenter randomized trial. A recent meta-analysis of the effect of preoperative chemo(radio)therapy in resectable or borderline resectable PDAC showed a prolonged overall survival (OS) when compared with immediate surgery (18.8 *v* 14.8 months).[7] This evidence, however, is weak because most studies were observational. Apart from ours, 11 trials are reported, 4 of which are phase III trials. Three trials were completed, of which 2 reported results (1 in abstract only)[11,12]; 1 was prematurely closed because of positive results at interim analysis,[13] and 2 were prematurely closed because of poor accrual.[14,15] Four are active or recruiting, and 1 is of unknown status[16-20] (Data Supplement, online only). The Dutch Pancreatic Cancer Group (DPCG) initiated the PREOPANC trial with the aim to investigate whether preoperative chemoradiotherapy provides better OS than immediate surgery in patients with resectable or borderline resectable PDAC.

PATIENTS AND METHODS

Patients and Study Design

This randomized phase III study was performed in 16 high-volume pancreatic surgery centers from the DPCG. The protocol was centrally approved by the Erasmus MC ethics committee (MEC-2012-249; December 11, 2012).

Eligible patients had pathologically confirmed resectable or borderline resectable PDAC, without distant metastases (M0), according to the Union for International Cancer Control classification (TNM 7th edition).[21] A multiphase computed tomography (CT) scan of the abdomen, including noncontrast enhanced, arterial, venous, and portal contrast phase axial scans, were required within 4 weeks before randomization. Tumor size, location, and relation to the celiac axis, superior mesenteric artery (SMA) and superior mesenteric vein (SMV), common hepatic artery, and portal vein were reported. A tumor without arterial involvement and with venous involvement $< 90°$ was considered resectable; a tumor with arterial involvement $< 90°$ and/or venous involvement between 90° and 270° without occlusion was considered borderline resectable. Other inclusion criteria were a WHO performance status of ≤ 1 and adequate hematologic, renal, and hepatic function. Exclusion criteria were cT1 tumor (< 2 cm, without vascular involvement), history of malignancy within 5 years, and previous radiotherapy or chemotherapy that precluded treatment.[22] Eligible patients provided written informed consent and were randomly assigned before biliary drainage, which carried a risk of dropout but optimally reflects clinical practice, wherein immediate surgery is preferably performed before biliary drainage.[23]

Treatment

Patients were randomly assigned 1:1 to preoperative chemoradiotherapy or immediate surgery. Patients assigned to preoperative chemoradiotherapy underwent a staging laparoscopy to rule out occult metastases. Chemoradiotherapy was to start within 4 weeks after random assignment. Patients with jaundice underwent biliary drainage, preferably with a self-expandable metal stent; bilirubin level had to be < 1.5 times the normal limit before chemotherapy was started. Radiotherapy consisted of 15 fractions of 2.4 Gy in 3 weeks to the pancreatic tumor and suspicious lymph nodes, combined with 1,000 mg/m^2 gemcitabine on days 1, 8, and 15 of 4 weeks, preceded and followed by a modified course of gemcitabine (1,000 mg/m^2 gemcitabine on days 1 and 8 of 3 weeks).[24-26] Within 4 weeks thereafter, CT evaluation was performed. Explorative laparotomy, with subsequent resection, if possible, was conducted between 14 and 18 weeks after random assignment. After resection and confirmation of PDAC, the remaining gemcitabine was administered at 1,000 mg/m^2 on days 1, 8, and 15 in 4 courses of 4 weeks.

For patients randomly assigned to immediate surgery, preoperative biliary drainage was recommended for bilirubin levels > 250 μmol/L. Surgery was to be performed within 4 weeks after random assignment; staging laparoscopy was at the surgeon's discretion. After resection and confirmation of PDAC, patients received 6 courses of adjuvant gemcitabine at 1,000 mg/m^2 on days 1, 8, and 15 of 4 weeks.

In both groups, resection was performed according to the consensus statement of the International Study Group on Pancreatic Surgery (ISGPS).[27] A classic or a pylorus-preserving pancreatoduodenectomy with locoregional lymph node dissection was performed for pancreatic head tumors. For tumors that involved the pancreatic body or tail, pancreas body and tail resection with splenectomy was performed. Reconstruction after pancreatoduodenectomy was left to the surgeon's preference. A standardized pathology procedure, on the basis of the Leeds Pathology Protocol, was applied,[28] including description of the tumor origin, extension, lymph node metastases, vascular and/or perineural invasion, and resection margins. Margins were considered microscopically positive (R1) if vital tumor was present at ≤ 1 mm from the transection margins (pancreas, bile duct, stomach, and/or duodenum) or the circumferential dissection (the anterior and posterior sides of the pancreas, the SMA, and the SMV).[29]

All patients underwent follow-up assessment with CT scans and serum cancer antigen 19-9 (CA19.9) at 6, 12, 18, and

24 months after random assignment and yearly thereafter. WHO performance status, weight, disease status (locoregional and distant), death, and cause of death were assessed at follow-up.

End Points

The primary end point was OS, defined as time from random assignment to death as a result of any cause. Secondary end points were disease-free survival (DFS), locoregional failure–free interval (LFFI), distant metastasis–free interval (DMFI), resection rate, R0 resection rate (per protocol), and toxicity of both surgery and pre- and postoperative treatment. In case of missing follow-up data, patients were censored when last known to be alive and disease free. Subgroup analyses were prespecified for resectable and borderline resectable PDAC separately and for patients who underwent resection and started adjuvant chemotherapy. Post hoc, a per-protocol analysis was added, including data of patients who appeared to have no distant metastases and started the intended treatment. In addition, a per-protocol analysis was added that investigated the prognostic value of R0 resection on OS. Postoperative mortality was defined as mortality as a result of any cause within 30 days after resection or during the index hospitalization if > 30 days. Postoperative complications were registered and graded according to ISGPS guidelines. Toxicity was scored according to Common Terminology Criteria for Adverse Events (version 4.0).[30]

Statistical Analysis

The trial was designed to have 80% power to detect a 6-month difference in median OS by ITT between both treatment groups (17 months with preoperative chemoradiotherapy and 11 months with immediate surgery). At least 176 events were required to detect this (2-sided test; α-level, 0.05; β-level, 0.20). Assuming a 10% dropout rate, 122 patients in each treatment arm were required. Primary analyses were performed by ITT, irrespective of any protocol deviations or violations. The Kaplan-Meier curves for OS, DFS, LFFI, and DMFI (including the hazard ratio [HR] and 95% CI) were compared between the 2 groups with the log-rank test (stratified for resectability [resectable *v* borderline resectable]). We tested differences between the resectable and borderline resectable groups with the interaction test of hazard rates. Moreover, for the per-protocol analyses and the predefined subgroup analyses, the outcomes were presented as Kaplan-Meier curves and compared with the log-rank test (stratified for resectability). The resection rate, R0 resection rate, and toxicity were quantified by proportions and odds ratios and associated 95% CIs; Fisher's exact test was used to test for differences. All tests were 2-sided and performed at the 5% significance level. All statistical analyses were performed using version 3.5.2 of the R statistical package (R Foundation for Statistical Computing, Vienna, Austria). This trial was registered with EudraCT (2012-003181-40) and the Netherlands Trial Register (3709).

RESULTS

From April 2013 to July 2017, 248 patients from 16 centers were randomly assigned: 120 were assigned to preoperative chemoradiotherapy and 128 to immediate surgery. Two patients were excluded from the analysis for withdrawal of informed consent, which left 119 and 127 patients, respectively, for the ITT analysis (Fig 1). Baseline characteristics were well balanced between both groups (Table 1). Seven patients in the preoperative chemoradiotherapy group did not receive preoperative treatment, 3 of whom had an urgent indication for surgery (Data Supplement).

In the preoperative chemoradiotherapy group, 5 patients (4%) had no staging laparoscopy; in 13 patients (11%), metastatic disease was found at laparoscopy (Fig 1). After laparoscopy, 91 patients (91 of 119; 76% by ITT) started preoperative chemoradiotherapy, which in 10 patients was postponed because of persistent high bilirubin levels. Eighty-one patients (89%) completed chemoradiotherapy. Reasons for not completing chemoradiotherapy were disease progression (3 patients) and toxicity (5 patients). Two patients died as a result of a myocardial infarction during preoperative treatment. CT evaluation revealed disease progression in 10 patients (Fig 1). Explorative laparotomy was performed in 82 patients (including 7 patients who underwent immediate surgery for several reasons), of whom 72 underwent a resection (72 of 119; 61% by ITT). The R0 resection rate was 71% (51 of 72 patients). Of these 72 patients, 24 (33%) had pathologic lymph nodes, 28 (39%) perineural invasion, and 14 (19%) venous invasion (Data Supplement).

In the immediate surgery group, 6 patients (5%) did not undergo surgery (Fig 1). Staging laparoscopy or laparotomy revealed metastatic disease in 14 patients (12%) and unexpected locally advanced disease in 15 patients (12%). Resection was performed in 92 patients (92 of 127; 72% by ITT). The R0 resection rate was 40% (37 of 92 patients). Of these 92 patients, 72 (78%) had pathologic lymph nodes, 67 (73%) perineural invasion, and 33 (36%) venous invasion (Data Supplement).

The resection rate was not significantly different between the preoperative chemoradiotherapy and the immediate surgery groups (61% *v* 72%; $P = .058$). However, the R0 resection rate was higher in patients treated with preoperative chemoradiotherapy (72% *v* 40%; $P < .001$), and fewer patients had pathologic lymph nodes (33% *v* 78%; $P < .001$), perineural invasion (39% *v* 73%; $P < .001$), or venous invasion (19% *v* 36%; $P = .024$). Overall, patients with an R0 resection had a better OS than patients with non-R0 resection (HR, 0.47; 95% CI, 0.31 to 0.72; $P < .001$; Data Supplement).

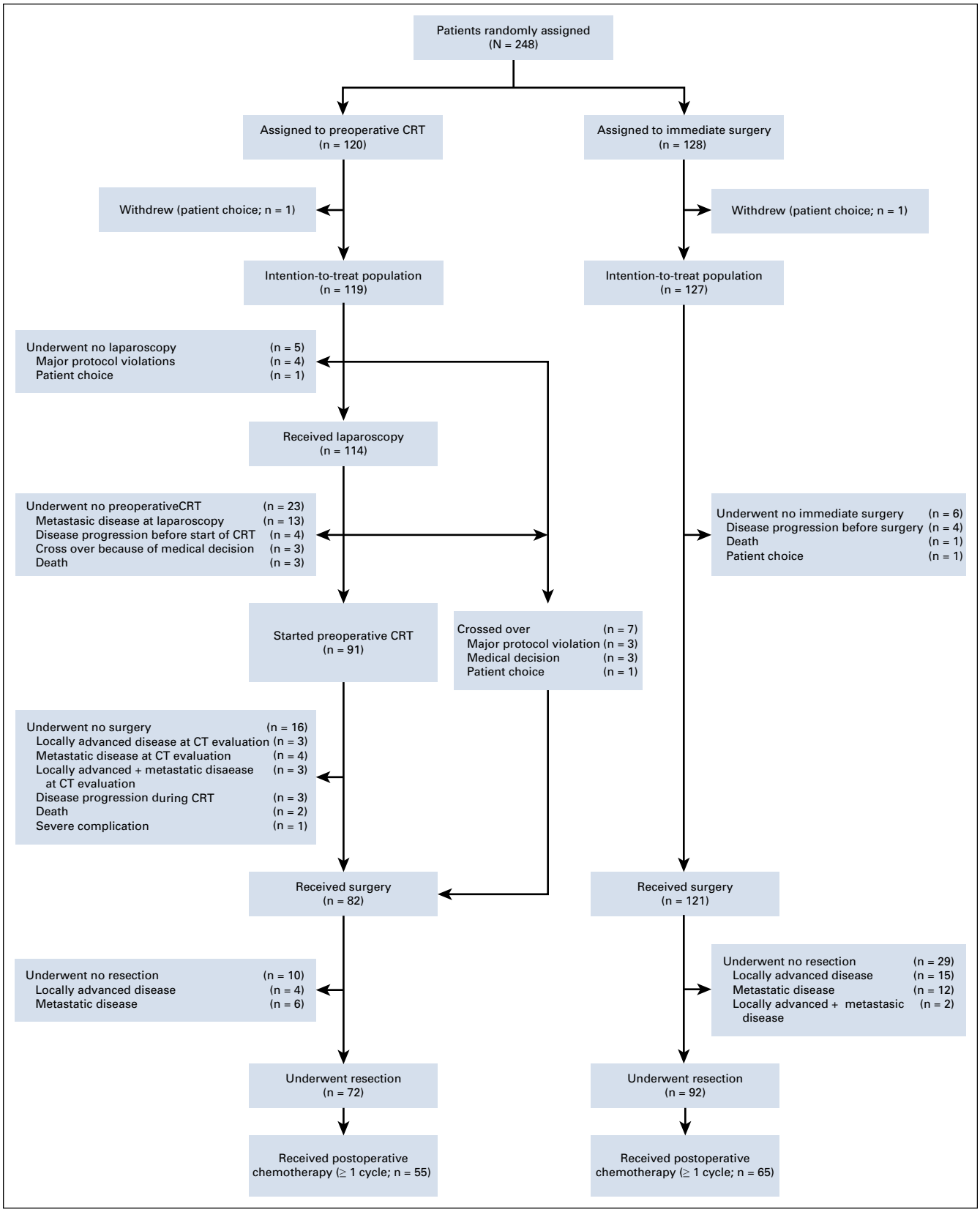

FIG 1. CONSORT diagram. CRT, chemoradiotherapy; CT, computed tomography.

TABLE 1. Baseline Patient and Tumor Characteristics by Treatment Regimen

Characteristic	Preoperative CRT, No. (%)	Immediate Surgery, No. (%)
No. of patients	119	127
Female sex	55 (46)	53 (42)
Median age at random assignment, years (IQR)	66 (59-71)	67 (60-73)
Median BMI, kg/m^2 (IQR)	25 (22-28)	25 (23-28)
Initial WHO performance status[a]		
0	69 (58)	49 (39)
1	49 (41)	78 (61)
2	1 (1)	0 (0)
Pancreatic head tumors	97 (82)	117 (92)
Resectable pancreatic cancer[b]	65 (55)	68 (53)
Borderline resectable pancreatic cancer	54 (45)	59 (47)
Median initial maximum tumor diameter, mm (IQR)	30 (25-38)	30 (23-35)
Regional suspicious lymph nodes	27 (23)	44 (35)
Median CA 19-9,[c] kU/L (IQR)	111 (26-603)	257 (83-727)

NOTE. Lower WHO numbers indicate better performance status: 0 able to carry out all normal activity; 1 able to carry out light work.

Abbreviations: BMI, body mass index; CA, cancer antigen; CRT, chemoradiotherapy; IQR, interquartile range.

[a]The WHO performance score of 13 patients was 0/1 (7 in the preoperative CRT group and 6 in the immediate surgery group). For the purpose of this table, those patients are classified as WHO performance score 1.

[b]Resectability was based on Dutch Pancreatic Cancer Group criteria as assessed by computed tomography scan.

[c]In 40 patients, CA 19-9 was missing (13 in the preoperative CRT group and 27 in the immediate surgery group). Difference in CA 19-9 was not significant (P = .98, 2-tailed independent t test).

In 14 patients (14 of 164; 9%), histopathology revealed a different diagnosis than PDAC, not statistically different between both groups (6% *v* 11%; P = .127; Data Supplement). In the preoperative chemoradiotherapy group, 68 of the 72 patients had PDAC. Fifty-five of those patients (55 of 68; 81%) started adjuvant chemotherapy, of whom 34 (62%) completed their treatment. By ITT, 46% (55 of 119 patients) started adjuvant chemotherapy. In the immediate surgery group, 82 of 92 patients had PDAC, of whom 65 (79%) started adjuvant chemotherapy and 35 completed it (53%). By ITT, 51% (65 of 127 patients) started adjuvant chemotherapy.

After a median follow-up of 27 months, 180 patients (73%) died: 81 (68%) in the preoperative chemoradiotherapy group and 99 (78%) in the immediate surgery group. The median OS in the preoperative chemoradiotherapy group was 16.0 months (95% CI, 13.0 to 20.9 months) and 14.3 months (95% CI, 12.7 to 17.9 months) in the

TABLE 2. Intention-to-Treat Analyses of Primary and Secondary End Points for Both Treatment Groups

Outcome	Preoperative CRT (n = 119)	Immediate Surgery (n = 127)	HR (95% CI)	*P*
Primary				
Median OS, months	16.0	14.3	0.78 (0.58 to 1.05)	.0960
Secondary				
Median DFS, months	8.1	7.7	0.73 (0.55 to 0.96)	.0320
Median LFFI, months	NR	13.4	0.56 (0.38 to 0.83)	.0034
Median DMFI, months	17.4	12.5	0.82 (0.58 to 1.14)	.2400
	No. (%)	**No. (%)**	**OR (95% CI)**	
Resection rate	72 of 119 (61)	92 of 127 (72)	0.58 (0.34 to 1.00)	.0580
R0 rate	51 of 72 (71)	37 of 92 (40)	3.61 (1.87 to 6.97)	< .0010
Safety				
Patients with SAEs (all grades)	62 of 119 (52)	52 of 127 (41)	1.57 (0.95 to 2.60)	.0960

Abbreviations: CRT, chemoradiotherapy; DFS, disease-free survival; DMFI, distant metastasis–free interval; HR, hazard ratio; LFFI, locoregional failure–free interval; NR, not reached; OR, odds ratio; OS, overall survival; SAE, serious adverse event.

immediate surgery group (HR, 0.78; 95% CI, 0.58 to 1.05; $P = .096$). The DFS (HR, 0.73; 95% CI, 0.55 to 0.96; $P = .032$) and LFFI (HR, 0.56; 95% CI, 0.38 to 0.83; $P = .0034$) were significantly better in the preoperative chemoradiotherapy group. The DMFI was comparable (HR, 0.82; 95% CI, 0.58 to 1.14; $P = .24$; Table 2; Fig 2). The per-protocol analysis of 91 patients who started preoperative chemoradiotherapy compared with the 104 patients in the immediate surgery group who underwent exploration and had no distant metastasis showed a median OS of 20.2 *v* 16.8 months (HR, 0.73; 95% CI, 0.51 to 1.03; $P = .073$; Data Supplement).

The predefined subgroup of patients with suspected resectable PDAC showed no significant difference in OS, DFS, LFFI, and DMFI (Table 3). The predefined subgroup of patients with suspected borderline resectable PDAC showed a significantly improved OS, DFS, and LFFI for preoperative chemoradiotherapy (Table 3). The interaction test of hazard rates showed no significant difference between these subgroups ($P = .14$). The predefined subgroup of patients with tumor resection who started adjuvant treatment showed a significantly improved median OS of 35.2 months (95% CI, 26.2 months to not available) in the preoperative chemoradiotherapy group and 19.8 months (95% CI, 16.8 to 32.2 months) in the immediate surgery group (HR, 0.58; 95% CI, 0.35 to 0.95; $P = .029$) as well as significant differences in DFS, LFFI, and DMFI (Fig 3).

With regard to toxicity, 62 patients (52%) in the preoperative chemoradiotherapy group and 52 (41%) in the immediate surgery group experienced at least 1 serious adverse event ($P = .096$). Grade 5 serious adverse events were observed in 16 patients (7%), 8 in each group. This includes 3 postoperative mortalities in each group (Data

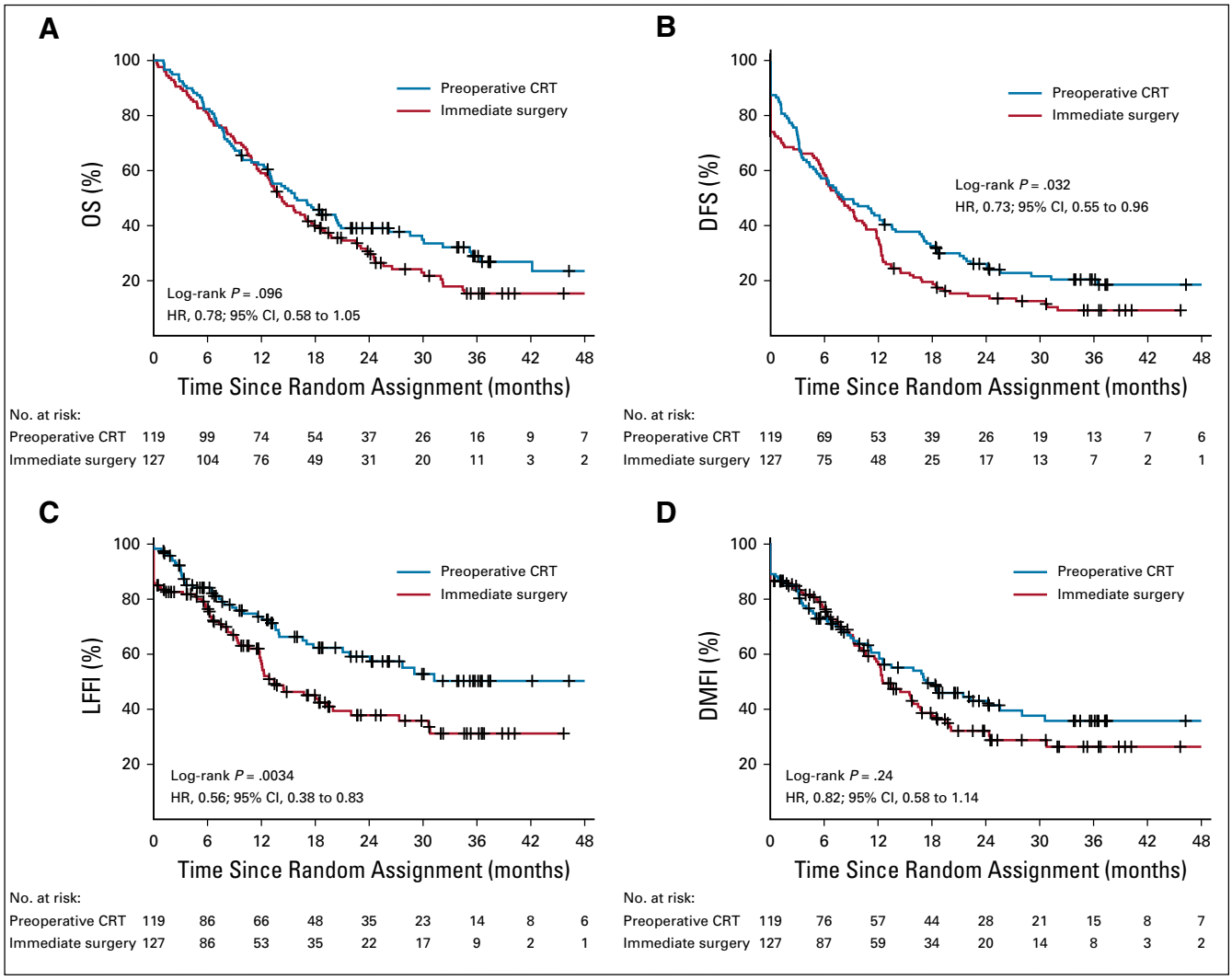

FIG 2. (A) Overall survival (OS), (B) disease-free survival (DFI), (C) locoregional failure–free interval (LFFI), and (D) distant metastasis–free interval (DMFI) in 246 patients randomly assigned to preoperative chemoradiotherapy (CRT; 119 patients) or immediate surgery (127 patients) according to intention-to-treat analysis. Tick marks indicate censored observations. HR, hazard ratio.

TABLE 3. Intention-to-Treat Analyses of Primary and Secondary End Points for Both Subgroups of Patients With Resectable and Borderline Resectable Pancreatic Cancer

	Resectable Pancreatic Cancer (n = 133)				Borderline Resectable Pancreatic Cancer (n = 113)			
Outcome	Preoperative CRT (n = 65)	Immediate Surgery (n = 68)	HR (95% CI)	*P*	Preoperative CRT (n = 54)	Immediate Surgery (n = 59)	HR (95% CI)	*P*
Primary								
Median OS, months	14.6	15.6	0.96 (0.64 to 1.44)	.830	17.6	13.2	0.62 (0.40 to 0.95)	.029
Secondary								
Median DFS, months	9.2	9.3	0.88 (0.60 to 1.28)	.520	6.3	6.2	0.59 (0.39 to 0.89)	.013
Median LFFI, months	NR	20.0	0.59 (0.33 to 1.04)	.067	27.7	11.8	0.54 (0.32 to 0.91)	.022
Median DMFI, months	17.0	13.5	0.93 (0.59 to 1.47)	.770	21.5	12.2	0.69 (0.42 to 1.15)	.150
	No. (%)	No. (%)	OR (95% CI)		No. (%)	No. (%)	OR (95% CI)	
Resection rate	44 of 65 (68)	54 of 68 (79)	0.54 (0.25 to 1.19)	.170	28 of 54 (52)	38 of 59 (64)	0.60 (0.28 to 1.27)	.190
R0 rate	29 of 44 (66)	32 of 54 (59)	1.33 (0.58 to 3.04)	.540	22 of 28 (79)	5 of 38 (13)	24.20 (6.57 to 89.12)	< .001
Safety								
Patients with SAEs (all grades)	35 of 65 (54)	31 of 68 (46)	1.39 (0.70 to 2.76)	.390	27 of 54 (50)	21 of 59 (36)	1.81 (0.85 to 3.85)	.130

Abbreviations: CRT, chemoradiotherapy; DFS, disease-free survival; DMFI, distant metastasis–free interval; HR, hazard ratio; LFFI, locoregional failure–free interval; NR, not reached; OR, odds ratio; OS, overall survival; SAE, serious adverse event.

Supplement). Two serious adverse events were considered as suspected unexpected serious adverse reactions (Data Supplement). At least 1 postoperative complication occurred in 49 (68%) of 72 patients in the preoperative chemoradiotherapy group and 46 (50%) of 92 patients in the immediate surgery group ($P = .026$). By ITT, these figures were 41% *v* 36% ($P = .44$).

DISCUSSION

To our knowledge, this is the first completed multicenter, randomized trial on preoperative chemoradiotherapy versus immediate surgery in patients with resectable or borderline resectable PDAC, and did not demonstrate an OS benefit in the ITT population (median, 16.0 *v* 14.3 months; HR, 0.78; $P = .096$). Nevertheless, the secondary end points DFS, LFFI, R0 resection rate, and pathologic parameters were superior with preoperative chemoradiotherapy. Together with the predefined subgroup analysis of patients undergoing a resection and starting adjuvant chemotherapy, this suggests a clinically relevant benefit of preoperative chemoradiotherapy in patients with resectable or borderline resectable PDAC. We consider this in line with the evidence from nonrandomized and early-terminated randomized trials.[6,7,11-15,31]

Compliance of intended preoperative chemoradiotherapy (ITT, 76%) was better than that of intended postoperative chemotherapy in the immediate surgery group (ITT, 51%). Preoperative chemoradiotherapy was completed by 81 (89%) of 91 patients; postoperative treatment was completed by 69 of 120 patients (58% in both study arms). In view of the high dropout rate (24%) in the preoperative chemoradiotherapy group, the per-protocol analysis showed a nonsignificant trend in OS in the preoperative chemoradiotherapy group, in line with the results of the primary and secondary end points.

Laparoscopy or laparotomy revealed metastases in 11% in the preoperative chemoradiotherapy group and 12% in the immediate surgery group. Unexpected locally advanced disease was found in 5% in the preoperative chemoradiotherapy group and 12% in the immediate surgery group. A previous study reported unsuccessful laparotomy in up to 25% of patients despite contemporary imaging techniques,[32] which corresponds to the 24% in our immediate surgery group. Thirteen patients (14%) showed disease progression during preoperative chemoradiotherapy who might have had tumor progression shortly after surgery if randomly assigned for immediate surgery.

A comparison of our results with those of published trials of adjuvant gemcitabine and capecitabine (ESPAC-4; median OS, 28 months)[1] or modified fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX; PRODIGE 24/CCTG PA.6; median OS, 54.4 months)[2] is difficult. Adjuvant trials

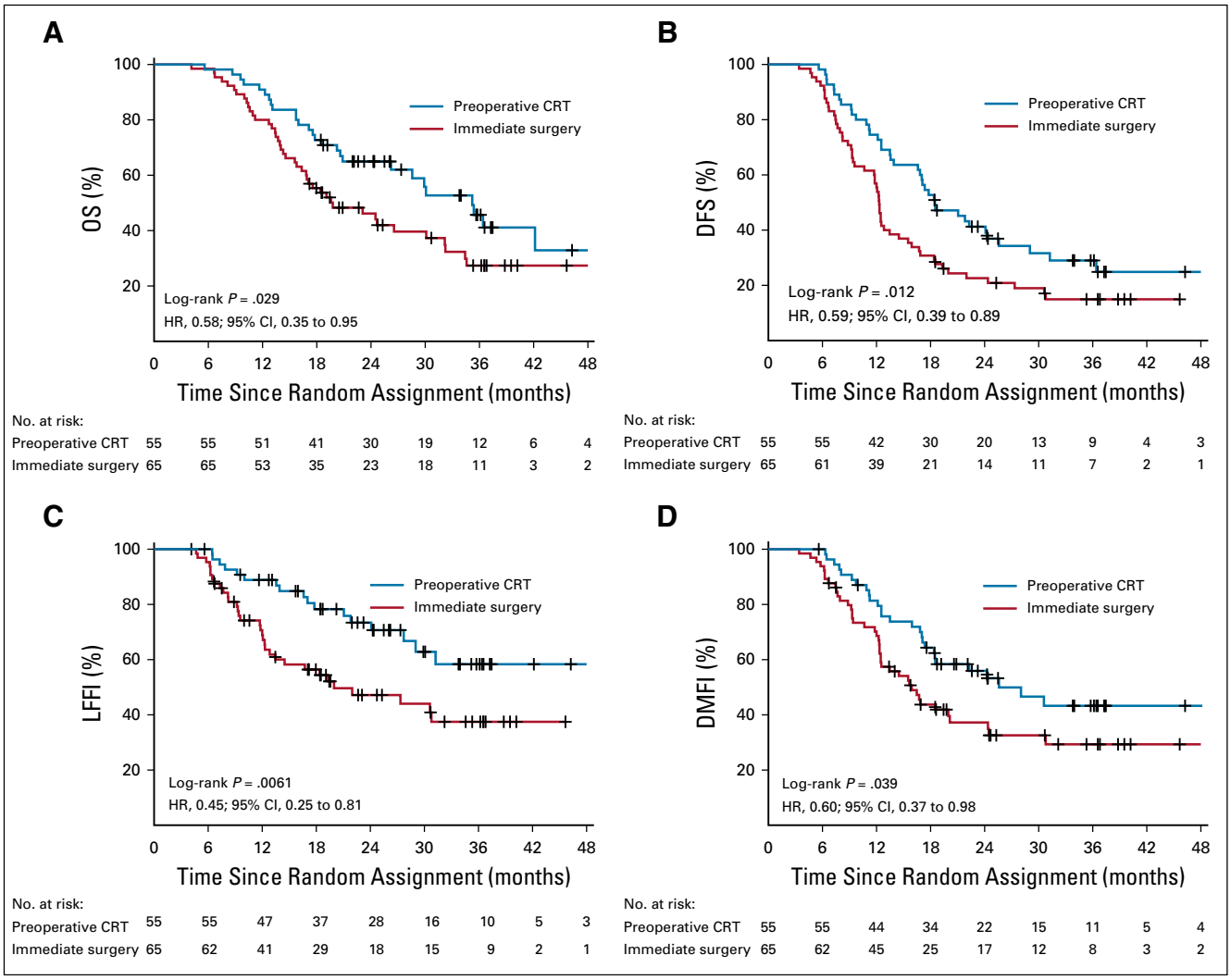

FIG 3. (A) Overall survival (OS), (B) disease-free survival (DFI), (C) locoregional failure–free interval (LFFI), and (D) distant metastasis–free interval (DMFI) in the 120 patients who had a resection of the tumor and started the postoperative chemotherapy and randomly assigned to preoperative chemoradiotherapy (CRT; 55 patients) or immediate surgery (65 patients). Tick marks indicate censored observations. HR, hazard ratio.

exclude patients with disease progression before surgery, occult metastases, or locally advanced disease detected at exploration as well as patients poorly recovering from surgery. To enable observational comparison with these trials, we analyzed data of the 120 patients who underwent resection and started adjuvant chemotherapy. This subgroup analysis showed a clinically and statistically relevant OS benefit of preoperative chemoradiotherapy over immediate surgery (35.2 *v* 19.8 months; $P = .029$).

Preoperative FOLFIRINOX might further improve the outcome and is currently being investigated in the PREOPANC-2 trial (Netherlands Trial Register identifier: NTR7292, 2018-06-19), the NorPACT-1 trial (ClinicalTrials.com identifier: NCT02919787),[19] and the PANACHE01-PRODIGE48 trial (ClinicalTrials.com identifier: NCT02959879).[20] The addition of radiotherapy to preoperative FOLFIRINOX could be a next step, as preoperative chemoradiotherapy gives higher R0 rates, less lymph node positivity, and local recurrences compared with preoperative chemotherapy only,[33] in line with our results. FOLFIRINOX followed by (chemo)radiotherapy for borderline resectable or locally advanced PDAC is feasible, with high R0 resection rates and prolonged median progression-free survival and OS.[34-36]

A predefined subgroup analysis showed superior OS after preoperative chemoradiotherapy for borderline resectable PDAC and no significant difference for resectable PDAC. This suggests a benefit in borderline resectable disease and a lack of benefit in resectable disease. Indeed, theoretically, the effect of creating R0 resection and other pathologic advantages by preoperative treatment might be greater in borderline resectable disease. However, these differences

must be interpreted with caution because the interaction test of hazard rates between both groups was not significant. The benefit of preoperative treatment in borderline resectable PDAC was also observed in an interim analysis after inclusion of 58 patients in a published phase II/III trial.[12] On the other hand, the recently presented phase II/III Prep-02/JSAP-05 trial showed a significant benefit of preoperative chemotherapy (gemcitabine and S-1) over immediate surgery for resectable PDAC, with a median OS of 36.7 *v* 26.6 months.[13] Ongoing studies, both in resectable and borderline resectable disease, will clarify whether preoperative treatment works predominantly in borderline resectable disease or in both groups[16-20] (Data Supplement). Probably the biologic behavior is more important than the local extent of the tumor's susceptibility to neoadjuvant therapy.

Some of our findings need further clarification. First, the median OS in the immediate surgery group was better than expected (14 instead of 11 months), which probably resulted in an underpowered study. This might be explained by effective lines of salvage therapies in patients with locoregional or distant failure. Second, 10 patients had persistent jaundice after biliary drainage, which caused a delay of preoperative treatment. These aspects should be taken into account when considering neoadjuvant therapy in patients with suspected PDAC. In addition, 14 patients (6%) had other pathology than PDAC; 9 (4%) had a cholangiocarcinoma, which implies a more favorable prognosis than PDAC.

In conclusion, this national, multicenter, randomized, phase III trial of preoperative chemoradiotherapy versus immediate surgery in resectable or borderline resectable PDAC did not show a significant OS benefit of preoperative chemoradiotherapy. The consistent benefits for most secondary end points and the better compliance with preoperative chemoradiotherapy compared with postoperative adjuvant chemotherapy suggest superiority of the neoadjuvant approach.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial

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