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Published in:
Annals of Surgery

DOI:
10.1097/SLA.0000000000004364

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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External Validity of the Multicenter Randomized PREOPANC Trial on Neoadjuvant Chemoradiotherapy in Pancreatic Cancer

Outcome of Eligible but Nonrandomized Patients

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Objectives: To investigate the accrual proportion and patients’ reasons for not participating in the PREOPANC trial on neoadjuvant chemoradiotherapy versus immediate surgery in resectable and borderline resectable pancreatic cancer, and to compare these patients’ outcomes with those of patients who had been randomized in the trial.

Summary of Background Data: The external validity of multicenter randomized trials in cancer treatment has been criticized for suboptimal nonrepresentative inclusion. In trials, it is unclear how outcomes compare between randomized and nonrandomized patients.

Methods: At 8 of 16 participant centers, this multicenter observational study identified validation patients, who had been eligible but not randomized during recruitment for the PREOPANC trial. We assessed the accrual proportion, investigated their most common reasons for not participating in the trial, and compared resection rates, radical (R0) resection rates, and overall survival between the validation patients and PREOPANC patients, who had been randomized in the trial to immediate surgery.

Results: In total, 455 patients had been eligible during the recruitment period, 151 of whom (33%) had been randomized. Fifty-five percent of the 304 validation patients had refused to participate. Median overall survival in the validation group was 15.2 months, against 15.5 months in the PREOPANC group (P = 1.00). The respective resection rates (76% vs 73%) and R0 resection rates (51% vs 46%) did not differ between the groups.

Conclusions: The PREOPANC trial included a reasonable percentage of eligible patients. In terms of the outcomes survival, resection rate, and R0 resection rate, this appeared to be a representative group.

Keywords: eligible nonrandomized patients, external validity, PREOPANC trial

By 2030, pancreatic ductal adenocarcinoma (PDAC) is predicted to become the second greatest cause of cancer-related death in the United States. As neoadjuvant treatment may improve survival in patients with resectable or borderline resectable PDAC, it is increasingly being investigated in randomized controlled trials (RCTs). But whereas RCTs are essential for testing safety and efficacy while minimizing the risk of bias, accrual is often slow, particularly in RCTs for pancreatic cancer. For this reason, 2 earlier RCTs that investigated the role of neoadjuvant chemoradiotherapy in pancreatic cancer were terminated prematurely. In general, RCTs tend to accrue under 5% of eligible patients. This leads in about 20% of trials to close prematurely.

The low percentage of eligible patients may also cause a sample to be nonrepresentative, and thus external validity to be poor. To take 1 example, accrual in a recent trial on adjuvant FOLFIRINOX in pancreatic cancer was 493 patients at 58 centers over 54 months—an average of almost 2 patients per center per year. The trial reported median survival in the standard arm with gemcitabine to be much better than the survival previously reported for surgery followed by gemcitabine.

Low accrual rates in clinical trials may result partly from the views of physicians and patients. Physicians, for example, may have various reasons—such as their strong belief in the standard or interventional treatment—for omitting to inform patients about a trial. Similarly, if they suspect that the interventional treatment will be too burdensome, they may omit to inform older patients or those with greater comorbidity. Patients may also have various reasons for withholding informed consent, especially a preference for one of the treatments within the trial.

Eligibility criteria notwithstanding, there is thus a risk that patients will be selected for participation in a clinical trial. The smaller the percentage of eligible patients randomized into a trial, the
higher the risk that the population selected will not be representative. In turn, this may lead the outcomes of patients participating in clinical trials to be better but nonrepresentative.10

By comparing findings in the trial patients with those in eligible patients who were not randomized, one could actually assess whether patients in that trial resemble the “real-world” population. Recently, we published the results of the Dutch Pancreatic Cancer Group (DPCG) multicenter randomized PREOPANC trial, for which recruitment ran from April 2013 to July 2017, and in which a total of 246 patients with resectable and borderline resectable PDAC were randomized between (1) neoadjuvant chemoradiotherapy followed by surgery and the remaining chemotherapy, and (2) immediate surgery followed by adjuvant chemotherapy.11 Although the primary endpoint—improved overall survival with neoadjuvant chemoradiotherapy—was not met, the neoadjuvant approach demonstrated significant benefits in secondary outcomes, such as radical (R0) resection rate, disease-free survival, and loco-regional recurrence-free interval.

As the accrual of patients to the trial had been slower than expected, inclusion being completed only after 51 months rather than the 36 months envisaged,11 we decided to describe the accrual proportion, determine why some of the eligible patients had not been randomized, and compare the outcome of these eligible but nonrandomized patients in the PREOPANC trial (the validation group) to that of the patients randomized to the standard arm (the PREOPANC group). From a sample of 8 of the 16 original participating centers, the present multicenter observational study therefore collected data retrospectively, covering the period from January 2014 to July 2017. By comparing outcomes in this validation group with those of patients in the PREOPANC group, it was intended to test the external validity of the trial results.

METHODS

Design
This multicenter, observational study was initiated and approved within the DPCG network. As the ethics committee at Amsterdam University Medical Center determined on 4 April 2017 that the study was not subject to the Dutch law on Medical Research Involving Human Subjects, official approval from the accredited ethics committee was not required.

Data Collection
At 8 of the 16 centers that had participated in the PREOPANC trial, we searched for patients who had been diagnosed with resectable or borderline resectable PDAC between January 2014 and July 2017. To ensure a representative sample, we selected the 4 centers that had randomized the highest number of patients during the accrual period, and the 4 that had randomized the fewest. Patient data were obtained from the Dutch Pancreatic Cancer Audit (DPCA), which collects complete data on all patients who have undergone explorative laparotomy since 1 January 2014. Per center, we identified all eligible patients who had not participated in the trial between January 2014 (or later if a center had started participating in the study after January 2014) and the end of the accrual period. This was the validation group. For the PREOPANC group, we collected the data of the patients who, in the trial, had been randomized to immediate surgery at the same 8 centers in the same period (the PREOPANC group). We excluded the 20 patients (9%) who had been recruited to the PREOPANC trial between its start in April 2013 and January 2014.

According to standard practice in the Netherlands, all patients with resectable or borderline resectable pancreatic cancer are discussed preoperatively by a multidisciplinary tumor board, which recommends explorative laparotomy followed, if possible, by surgical resection. The inclusion criteria for our current study were the same as those in the PREOPANC trial: patients had to have a World Health Organization (WHO) performance status of <1 and adequate hematologic, renal, and hepatic function. The DPCG criteria12 were used to classify tumors as resectable or borderline resectable pancreatic cancer. The following patients were excluded: those with cT3 tumors (<2 cm on imaging without vascular involvement); those with a history of malignancy in the 5 years before study participation; and those for whom previous radiotherapy or chemotherapy were not suitable. Because pathologic confirmation was not required in this cohort, we selected only patients with (1) suspicious pancreatic tumors with vascular involvement, or (2) tumors without vascular involvement larger than 2 cm. In this analysis we did not include patients who had been scheduled for exploratory laparotomy but whose progressive disease or deterioration had precluded surgery, as such patients are not registered in the DPCA. In the PREOPANC study, this had been the case with 4% of the patients randomized for the immediate surgery arm. Due to this low percentage, these patients had not been excluded from our analyses. The data on all validation group (eligible but nonrandomized) patients were collected by 3 researchers: EV, MS, and JV.

Treatment
All patients had been operated on a DPCG center, each of which performed at least 20 pancreatectomies per year. The surgical procedure and adjuvant treatment had been similar for all the patients included in the validation group and the PREOPANC group. Staging laparoscopy during the explorative laparotomy had been performed at the discretion of the surgeon. In the absence of metastases or unexpected locally advanced disease, resection of the tumor had been performed according to the consensus statement of the International Study Group on Pancreatic Surgery.13 Standard resection was a pylorus-preserving pancreatectoduodenectomy, classic Whipple resection, or pancreatic tail resection with or without corpus resection. If histopathology confirmed PDAC, and if performance was sufficient within 12 weeks of surgery, patients received standard adjuvant gemcitabine consisting of 6 cycles at 1000 mg/m² on days 1, 8, and 15.

Follow-up
Standard follow-up consisted of medical history and, according to the practice of each multidisciplinary team, physical examination at regular intervals. Under the Dutch national guidelines, additional diagnostic investigations were performed only in the event of clinical signs of progression or suspicion of complications. Patients in the PREOPANC study underwent follow-up—including computer tomography—at 6, 12, 18, and 24 months offollow-up, and yearly thereafter.

Endpoints
This observational study analyses the percentage of eligible patients randomized to the PREOPANC trial (ie, the accrual proportion) and the reasons the validation patients had not been randomized. These reasons were categorized in 3 major groups: (1) patients whose medical chart did not indicate they had been informed about the trial, (2) patients who had been informed about the trial but had not provided informed consent, and (3) patients for whom no pathologic confirmation of malignancy could be obtained.

Overall survival (OS), resection rates, and R0 resection rates were compared between the validation group and the PREOPANC group. The primary endpoint was defined as OS. For the PREOPANC group, OS was defined as the time from randomization until death from any cause. Because no randomization had been performed in...
In the validation group, the OS in these patients was defined as the time between the preoperative multidisciplinary tumor board meeting and death from any cause. If the date of death was missing, patients were censored at the last date they were known to have been alive. In addition, for OS, subgroup analyses were performed for patients with resectable and borderline resectable PDAC. Secondary endpoints were resection rate and R0 resection rate. R0 resection was defined as a resection with a margin of >1 mm without vital tumor cells.14

STATISTICAL ANALYSES
Baseline characteristics were compared between the validation and PREOPANC group. Fisher exact test was used to compare categorical variables, and the Mann Whitney test was used for continuous variables. The Kaplan-Meier curve for OS in the validation group was compared with that for the PREOPANC group using the log-rank test (stratified for resectability, including the hazard ratio and 95% confidence interval [CI]). To determine the reasons for nonenrollment, we calculated the percentages of the patients per group and presented the results in a pie chart without statistical analysis. The accrual proportion was calculated by dividing the randomized patients by all eligible patients, overall and per institution. The resection rates and R0 resection rates (R0 resection rate perprotocol, only of patients who actually underwent resection of the tumor) were quantified by proportions and the associated 95% CI; the Fisher 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 26 of SPSS.

RESULTS
Patients
During the recruitment period, 455 patients had been eligible at the 8 centers, 304 of whom (67%) had not been randomized in the PREOPANC trial (validation group (Fig. 1). Forty-eight percent of these 304 patients were female. Their mean age was 68 years, and 82% had a pancreatic-head tumor (Table 1). We compared these patients with the 78 patients at the same 8 centers who had been randomized between January 1, 2014 and July 25, 2017 for immediate surgery in the PREOPANC trial (PREOPANC group). The 2 groups were comparable in terms of sex, age, location of the tumor, initial maximum tumor diameter on the computer tomography at diagnosis, and resectability status (Table 1).

Trial Participation
Between January 1, 2014 and July 25, 2017, 226 patients had been randomized at the 16 centers participating in the PREOPANC

![FIGURE 1. CONSORT flow diagram.](image)

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics of the Validation and PREOPANC Group</th>
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<tr>
<td>Validation patients (n = 304)</td>
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<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Mean age at diagnosis*</td>
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<tr>
<td>Initial WHO performance score</td>
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<tr>
<td>Pancreatic head tumors</td>
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<tr>
<td>Initial maximal tumor diameter (mean, mm)</td>
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<td>Resectable pancreatic cancer</td>
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<tr>
<td>Borderline resectable pancreatic cancer</td>
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*Mean age of control patients at discussion in the multidisciplinary tumor board. The mean age of the PREOPANC patients is reported at time of randomization.
trial: 119 patients to immediate surgery (control arm) and 107 to preoperative chemoradiotherapy (intervention arm). At the 8 selected centers, 151 of this total of 226 patients (67%) had been randomized. At the center with the highest accrual rate for the PREOPANC study, between 1 and 2 patients had been randomized per month; at the center with the lowest inclusion rate, 1 patient had been randomized in a total period of 10 months. The actual accrual proportion had been 33% (151/455). Per institution, accrual had ranged between 6% and 75% (Fig. 2). The 4 institutions that included the highest number of patients in the PREOPANC trial (range 54–15) had also had the highest accrual (range 19%–75%).

The most common reason for nonenrollment was not having obtained informed consent (from 168 patients; 55%), despite the fact the patient had been specifically informed about the trial. Sixty-six of these patients (39%) had been informed about the trial, but were reported in the medical chart to have chosen immediate surgery. For 33 patients (20%), the electronic medical chart reported no reason for withholding informed consent. In 42 patients (25%), the medical chart mentioned that informed consent had been withheld without further specification of the reason. For the minority, other reasons were reported, such as fear that their condition would deteriorate due to the preoperative chemoradiotherapy (15 patients), participation in another trial (5 patients), travel distance (2 patients), and mixed reasons (5 patients) (Fig. 3).

In total, 124 patients (41%) had not been informed about the trial, or had no report in their medical file about on being informed (noted in this study as “not informed”). In the 4 centers that had included the greatest numbers of patients, this applied to 13% to 52% of the validation group patients, and to 53% to 90% in the 4 institutions that had included the smallest numbers of patients. Despite various attempts on our part to do so, we could not obtain the pathological confirmation required for almost 4% of patients.

**Overall Survival**

After a median follow-up of 39 months in the validation group, we found that 251 of the 304 validation patients (83%) had died. After a median follow-up of 25 months in the PREOPANC group, 60 of the 78 patients (77%) had died. After adjustment for resectability, we found that median OS in the 304 validation patients was 15.2 months (95% CI, 13.5–17.0), against 15.5 months (95% CI, 11.1–19.9) in the PREOPANC patients (hazard ratio 1.00, 95% CI 0.75–1.33, \( P = 1.00 \)). The survival curves of the 2 groups contained no obvious differences (Fig. 4). In both groups, the subgroup analyses of patients with suspected resectable pancreatic cancer showed a nonsignificant difference: median OS 16.0 months (95% CI, 13.9–18.1) in the validation group, versus 18.9 months (95% CI, 11.7–26.2) in the PREOPANC group, \( P = 0.34 \). Neither did OS differ significantly between the groups for patients with...
borderline resectable pancreatic cancer: median OS 14.2 months (95% CI, 11.7–16.6) in the control group versus 13.3 months (95% CI, 11.6–15.0) in the PREOPANC group, \( P = 0.27 \) (Supplemental Digital Content, http://links.lww.com/SLA/C489).

**Resection Rate and Radicality**

In the validation patients, the resection rate was 76%, against 73% in the PREOPANC patients (\( P = 0.65 \); Table 2). In the validation group, the R0 resection rate was 51%, against 46% in the PREOPANC group (\( P = 0.55 \); Table 2).

**DISCUSSION**

This observational, multicenter study found that 33% of eligible patients had been included in the multicenter randomized PREOPANC trial at 8 of the 16 participating centers. The main reason for nonenrollment was that 55% of patients had not given informed consent; 39% of whom had preferred immediate surgery. We also found that OS in the validation patients was similar to that in the PREOPANC patients (\( P = 1.00 \)). The resection rate and R0 resection rate did not differ significantly between these groups.

It is often suggested that outcome is better in patients who participate in clinical trials than in those in the same patient groups who do not participate. Since this challenges the external validity of clinical trials, an important question is whether the outcomes of randomized patients are actually representative.\(^{15}\) Previously, 2 comprehensive reviews were unable to confirm the common perception that the outcomes of patients who participate in trials are better.\(^{16,17}\) In our study, the accrual was 33%, and the baseline characteristics and outcomes of the PREOPANC and validation patients were comparable, suggesting that our trial population did indeed consist of a representative sample of patients with resectable or borderline resectable PDAC in the Netherlands.

It is known that approximately 20% to 33% of phase III trials are stopped prematurely due to poor accrual.\(^{7,8,18}\) Earlier studies reported that enrollment in trials investigating the treatment of localized pancreatic were approximately 15% in 2011,\(^{19}\) and even as low as 10% in 2014.\(^{4}\) Compared to these data, the accrual of 33% within the PREOPANC study is reasonably high. Although this may have been attributable partly to the organization, centralization, and multidisciplinary management of pancreatic surgery in the Netherlands,\(^{20}\) the trial was completed 15 months later than anticipated, and accrual differed widely between the various centers. The accrual proportion was also higher in the centers with the highest number of randomized patients (19%–75%) than in the centers with the lowest number (6%–18%). At the latter, enrollment also opened later; the slower accrual of patients is also explained by the longer time from trial opening to first enrollment.\(^{21}\) Conceivably, 1 factor that contributed to the low accrual proportion in these centers was the possibility that the new preoperative treatment regimen in the PREOPANC trial had presented greater challenges to lower-volume centers. The PREOPANC trial was also the first clinical trial in the Netherlands to study neoadjuvant treatment in pancreatic cancer. Yet another factor is that, during the PREOPANC accrual period, new regimens such as FOLFIRINOX were introduced, which may have caused competition between studies. The last factor is the possible influence of the variability of socioeconomic status (SES) between various regions in the Netherlands, as patients with a lower SES tend to undergo surgery less often and may therefore lead to slower accrual.\(^{22}\)

Our results showed either that 41% of the control patients had not been informed about the PREOPANC trial, or that their medical charts failed to report that they had been informed. It is known from 1 study\(^{23}\) that large numbers of patients may never have been informed about ongoing clinical trials; another study\(^{24}\) reported that patients had a poor understanding of the key concepts of clinical trials. Other studies have also reported that a large majority of patients (89%) indicated that the physician had often recommended a specific type of treatment, and that patients had been likely to follow it.\(^{19,23}\) Similarly, in 2 other studies, the physicians’ preference was the primary reason for not discussing a trial with eligible patients.\(^{25,26}\)

Before the PREOPANC trial opened, and also early in the accrual period, a number of pancreatic surgeons in the Netherlands were somewhat skeptical about the concept of neoadjuvant treatment. This may have affected the proportion of patients who did not give informed consent but instead opted for immediate surgery, and also the proportion of patients who had not been informed. A small majority of validation patients (55%) decided not to give informed consent for the trial, 39% of them because they preferred to opt for immediate surgery. In view of the poor survival of patients with pancreatic cancer, it is not surprising that those who receive no additional information may wish to have the tumor removed as quickly as possible. It is also possible that physicians in the PREOPANC trial decided that they would not always discuss the trial at a preliminary visit, due for instance to their age, frailty, or low SES—or perhaps even their own belief in the standard treatment.

Trials that accrue slowly tend to close early, thereby failing to serve their purpose. It is therefore important to reduce the barriers to participating in them. If accrual increases, new therapies are also likely to be introduced more quickly.\(^{25}\) The use of clinical trial alerts in patients’ electronic medical charts may increase physicians’ awareness of new trials, and thus patients’ enrollment in them.\(^{27}\) In our view, adequate information and time to think over should be present in obtaining informed consent, first by discussing eligibility in the multidisciplinary tumor board meeting, and then, as soon as possible thereafter, by discussing it with every eligible patient. Currently, the DPCG is implementing this strategy in the PREOPANC-2 study randomizing between 2 neoadjuvant regimes. Indeed, the current accrual rate of the PREOPANC-2 study in the same 16 DPCG centers is higher: > 10 patients per month versus 5 patients per month in the first PREOPANC study. Another reason for this higher accrual may be that, thanks to the first PREOPANC trial, overall confidence in the value of neoadjuvant treatment among the members of the DPCG has increased tremendously.

Slow accrual of clinical trials tends to bring the risk that these trials will close early, as happened with 2 previous trials on neoadjuvant treatment in pancreatic cancer.\(^{5,6}\) Another important risk of slow accrual is that, as the trial drags on, new developments in the

<table>
<thead>
<tr>
<th>Resection Rate and R0 Resection Rates</th>
<th>Validation patients (n = 304)</th>
<th>PREOPANC patients (n = 78)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection rate</td>
<td>232/304 (76%)</td>
<td>55/75 (73%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Resection classification</td>
<td></td>
<td></td>
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<tr>
<td>R0</td>
<td>118/232 (51%)</td>
<td>25/55 (46%)</td>
<td>0.55</td>
</tr>
<tr>
<td>R1/R2</td>
<td>114/232 (49%)</td>
<td>22/55 (40%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>4/55 (14%)</td>
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field change the standard of care, ultimately rendering the trial results less relevant. For all the reasons stated above, higher accrual rates are necessary.

One interesting method of speeding up accrual in randomized trials is the Trials within Cohorts design, also known as cohort multiple RCT design (cmRCT). This design embeds 1 or more randomized clinical trials within a large prospective single-center or multicenter cohort of patients. At baseline, patients provide initial informed consent for potential participation in 1 or more randomized trial. When a trial opens for accrual, eligible patients are identified within the cohort and then randomized. Patients randomized to the intervention arm are then offered the intervention, for which they can then decide to provide additional informed consent. Patients randomized in the control group are not informed about the trial. This trial design can lead to accrual rates as high as 67% to 100%.

As well as improving recruitment, the Trials within Cohorts design has advantages such as higher generalizability, and lower probabilities of disappointing patients and of contaminating the control arm. It thus makes it possible to compare the intervention in question with real-life practice.

Some possible limitations of this study must be addressed. The first is our inclusion of 8 of the 16 centers that had participated in the PREOPANC trial, which, between them, had accrued 67% of the trial patients. As we selected the 4 institutions with the highest accrual to the PREOPANC trial and the 4 with the lowest, we consider this sample to be representative. The second possible limitation is the fact that we did not include all validation patients, who, due to progression or deterioration between the multidisciplinary tumor board discussion and surgery, had not undergone surgery and thus an uncertain histopathological diagnosis of PDAC. In the PREOPANC group, this category included only 4% of the patients in the immediate surgery group, and our findings were not influenced by excluding them. Third, because we did not repeat the analysis of the PREOPANC trial, there was a 14-month difference between the 2 groups in living patients’ median follow-up time. However, because most patients died within 24 months of diagnosis, and because the numbers at risk were low at longer follow-up, this is unlikely to have influenced survival results. Fourth, since this observational study is retrospective, eligible patients may have been missed. And as the baseline characteristics were similar between the 2 groups, it is also possible that other factors that differed between the groups were not measured. For example, more older patients with multicormorbidity who nonetheless fulfilled all the inclusion criteria may have been included in the control group because they preferred not to participate or were not informed by their physician. Despite the dissimilar survival times calculated for the 2 groups in the PREOPANC trial, the median time between date of diagnosis (which we estimated to be similar to the date of discussions by the multidisciplinary board) and randomization was 7 days. For this reason, we do not believe survival would have been influenced by starting calculations 1 or 2 weeks earlier or later.

In conclusion, this multicenter, observational study showed that the accrual proportion in the PREOPANC trial on neoadjuvant chemoradiotherapy in pancreatic cancer was 33%. On the basis of the similar outcomes between validation patients and PREOPANC patients (randomized for immediate surgery), we believe that the trial population is representative of the Dutch population of patients with resectable and borderline resectable pancreatic cancer.

ACKNOWLEDGMENTS

We would like to thank Jasmin Smits, Loes van den Nieuwenhof-Biesheuvel, Stijn van Roessel, Tinke Bodeliers-Broeders, and Bobby Pranger for their contributions to collecting the DPCA data for the analyses. We would also like to thank Koos Zwinderman for his thoughtful contribution to the statistical methods.

REFERENCES

19. van Roest MH, van der Aa MA, van der Geest LG, et al. The impact of socioeconomic status, surgical resection and type of hospital on survival in...


