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The yield of staging laparoscopy for resectable and borderline resectable pancreatic cancer in the PREOPANC randomized controlled trial☆

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ABSTRACT

Background: The necessity of the staging laparoscopy in patients with pancreatic cancer is still debated. The objective of this study was to assess the yield of staging laparoscopy for detecting occult metastases in patients with resectable or borderline resectable pancreatic cancer.
Method: This was a post-hoc analysis of the randomized controlled PREOPANC trial in which patients with resectable or borderline resectable pancreatic cancer were randomized between preoperative chemoradiotherapy or immediate surgery. Patients assigned to preoperative treatment underwent a staging laparoscopy prior to preoperative treatment according to protocol, to avoid unnecessary chemoradiotherapy in patients with occult metastatic disease.
Results: Of the 246 included patients, 7 did not undergo surgery. A staging laparoscopy was performed in 133 patients (55.6%) and explorative laparotomy in 106 patients (44.4%). At staging laparoscopy, occult metastases were detected in 13 patients (9.8%); 12 liver metastases and 1 peritoneal metastasis. At direct explorative laparotomy, occult metastases were found in 9 patients (8.5%); 6 with liver metastases, 1 with peritoneal metastases, and 2 with metastases at multiple sites. One patient had peritoneal metastases at exploration after a negative staging laparoscopy. Patients with occult metastases were more likely to receive palliative chemotherapy if found with staging laparoscopy compared to laparotomy (76.9% vs. 30.0%, $p = 0.040$).
Conclusions: Staging laparoscopy detected occult metastases in about 10% of patients with resectable or borderline resectable pancreatic cancer. These patients were more likely to receive palliative systemic

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chemotherapy compared to patients in whom occult metastases were detected with laparotomy. A staging laparoscopy is recommended before planned resection.

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1. Introduction

Pancreatic cancer is currently the fourth cancer-related cause of death, with projections to be the second leading cause in 2030 [1]. Pancreatic cancer can be categorized into four stages: resectable, borderline resectable, locally advanced, or metastatic disease [2]. The diagnostic work-up for staging patients with the suspicion of pancreatic cancer consists of computed tomography (CT) scan of the chest and abdomen [3]. Staging laparoscopy, however, is not routinely incorporated in the work-up of patients with resectable or borderline resectable pancreatic cancer in most centers. The potential benefit of staging laparoscopy is the possible avoidance of an unnecessary laparotomy [4,5]. This might reduce perioperative morbidity and mortality, hospital stay, healthcare costs, and improve quality of life [6,7]. Moreover, patients may be more likely to undergo palliative chemotherapy if occult metastases are detected with staging laparoscopy rather than explorative laparotomy, due to more morbidity after laparotomy. Currently, only retrospective studies investigated the yield of staging laparoscopy in resectable or borderline resectable pancreatic cancer [8,9].

Recently, the phase III PREOPANC trial was published, comparing preoperative chemoradiotherapy with upfront surgery in patients with resectable or borderline resectable pancreatic cancer [10]. According to the trial protocol, prior to preoperative chemoradiotherapy, staging laparoscopy was to be performed, while in the immediate surgery group it was left to the discretion of the treating physician whether or not to perform a staging laparoscopy prior to laparotomy. The aim of this study is to assess the yield of the staging laparoscopy for detecting occult metastasis within this phase III trial. The second aim was to determine whether patients were more likely to receive palliative chemotherapy if occult metastases were detected by staging laparoscopy compared to explorative laparotomy.

2. Methods

2.1. Patients and study design

The current study is a post-hoc analysis of the PREOPANC randomized controlled trial, which was conducted in 16 pancreatic surgery centers from the Dutch Pancreatic Cancer Group (DPCG) in the Netherlands [10]. The inclusion period was from April 2013 until July 2017. Patients with the suspicion of resectable or borderline resectable pancreatic cancer underwent a multiphase CT scan four weeks before inclusion. All patients were discussed in a local multidisciplinary meeting. Pathological confirmation of pancreatic adenocarcinoma was obtained before inclusion. Resectability definitions were according to the DPCG definitions [11]. Patients with a cT1 tumor, history of other malignancy within five years prior to the pancreatic cancer, or a history of radio- or chemotherapy precluding the trials chemoradiation were excluded.

After written informed consent, patients were randomly assigned 1:1 for preoperative chemoradiotherapy or immediate surgery. Patients assigned for preoperative chemoradiotherapy underwent staging laparoscopy within four weeks after randomization, prior to the start of chemoradiotherapy. The reason for the staging laparoscopy was to avoid unnecessary chemoradiotherapy and surgery in patients with occult metastatic disease and to allow early switch to palliative chemotherapy. Staging laparoscopy consisted routinely inspection of the liver, diaphragm, bowel, and peritoneum to exclude occult metastases. No exploration of the local tumor extension and lymph nodes was performed during laparoscopy. If no occult metastatic disease was found, patients were scheduled for three cycles of gemcitabine, the second combined with radiotherapy, followed by resection and four cycles of adjuvant gemcitabine. Patients in the immediate surgery group were scheduled for surgery starting with or without a preceding staging laparoscopy within four weeks from randomization, followed by six cycles of adjuvant gemcitabine if a resection was performed. At explorative laparotomy visual inspection of the viscera was performed to detect metastases. No blinding was performed.

2.2. Endpoints

The primary endpoint of this study is occult metastatic disease at staging laparoscopy or explorative laparotomy in treatment naïve patients. Occult metastases were defined as metastases in intra-abdominal organs (e.g. liver) or in the abdominal cavity (e.g. peritoneal or diaphragm). Lymph node metastases at explorative laparotomy were not considered in this study, because lymph node sampling was not routinely performed during staging laparoscopy. Secondary endpoint was the start of palliative chemotherapy in patients with occult metastatic disease at staging laparoscopy or explorative laparotomy.

2.3. Data collection

All data were collected in a prospectively maintained database and included age, sex, length, weight, comorbidities, tumor size, tumor location, CA 19.9, vascular involvement, and information on preoperative and adjuvant treatment, and survival data. In addition, additional data was collected which included number of lesion sites, location of lesion sites, number of biopsies, staging laparoscopy in the immediate surgery group, and start of palliative treatment.

2.4. Statistical analysis

Continuous variables were expressed as mean with standard deviation or as median with interquartile range, as appropriate. For univariable analysis, continuous variables were compared using a T-test (parametric) or Mann-Whitney *U* test (non-parametric). Categorical variables were compared using a Fisher's exact test. Overall survival was calculated from time of randomization until death from any cause. Kaplan-Meier curves with log-rank tests were constructed to compare overall survival distributions between groups. Univariable Cox proportional hazard models were used to determine hazard ratios. P-values <0.05 were considered statistically significant. R statistical software was used for all statistical analyses (version 4.0.3.; www.r-project.org).

3. Results

A total of 248 patients were randomized in the PREOPANC trial. One-hundred-twenty patients were allocated to receive preoperative

chemoradiotherapy and 128 patients to the immediate surgery group (Fig. 1). Two patients withdrew consent and were excluded from all analyses. Baseline patient characteristics are presented in Supplemental Table 1.

A total of 133 patients (55.6%) underwent a staging laparoscopy; 115 in the preoperative therapy group and 18 patients in the immediate surgery group. One hundred and six patients (44.4%) underwent explorative laparotomy without staging laparoscopy. Seven patients never underwent surgery; five patients had progressive disease before surgery, one patient died from unknown cause, and one patient decided not to undergo surgery. In patients who underwent a laparotomy, patients were more often WHO performance status 1 and tumors were more often localized in the pancreatic head. Otherwise, characteristics of both groups were comparable (Table 1).

In 13 patients (9.8%) occult metastases were found at laparoscopy; liver metastases in 12 patients and peritoneal metastasis in one patient. In 53 patients a biopsy was performed during laparoscopy (40%). A total of 77 biopsies were performed of suspicious lesions; 32 patients (60.4%) underwent one biopsy, 17 patients (32.1%) underwent two biopsies, and four patients (7.5%) underwent more than two biopsies. The most common site of biopsy was the liver (60.1%), followed by the peritoneum (18.1%). Of all 77 biopsies, 20.8% was positive for cancer.

In the patients who underwent explorative laparotomy without laparoscopy, nine patients (8.5%) had occult metastases. The most common sites of occult metastases were liver (n = 6), peritoneal (n = 1), or metastases at multiple sites (n = 2). The yield of staging laparoscopy and explorative laparotomy in discovering occult metastatic disease was similar (p = 0.733). In addition, one patient had a peritoneal metastasis at explorative laparotomy after a negative staging laparoscopy in the same session. In univariable analysis, only lower BMI appeared to be associated with occult metastases at staging laparoscopy or explorative laparotomy (Table 2).

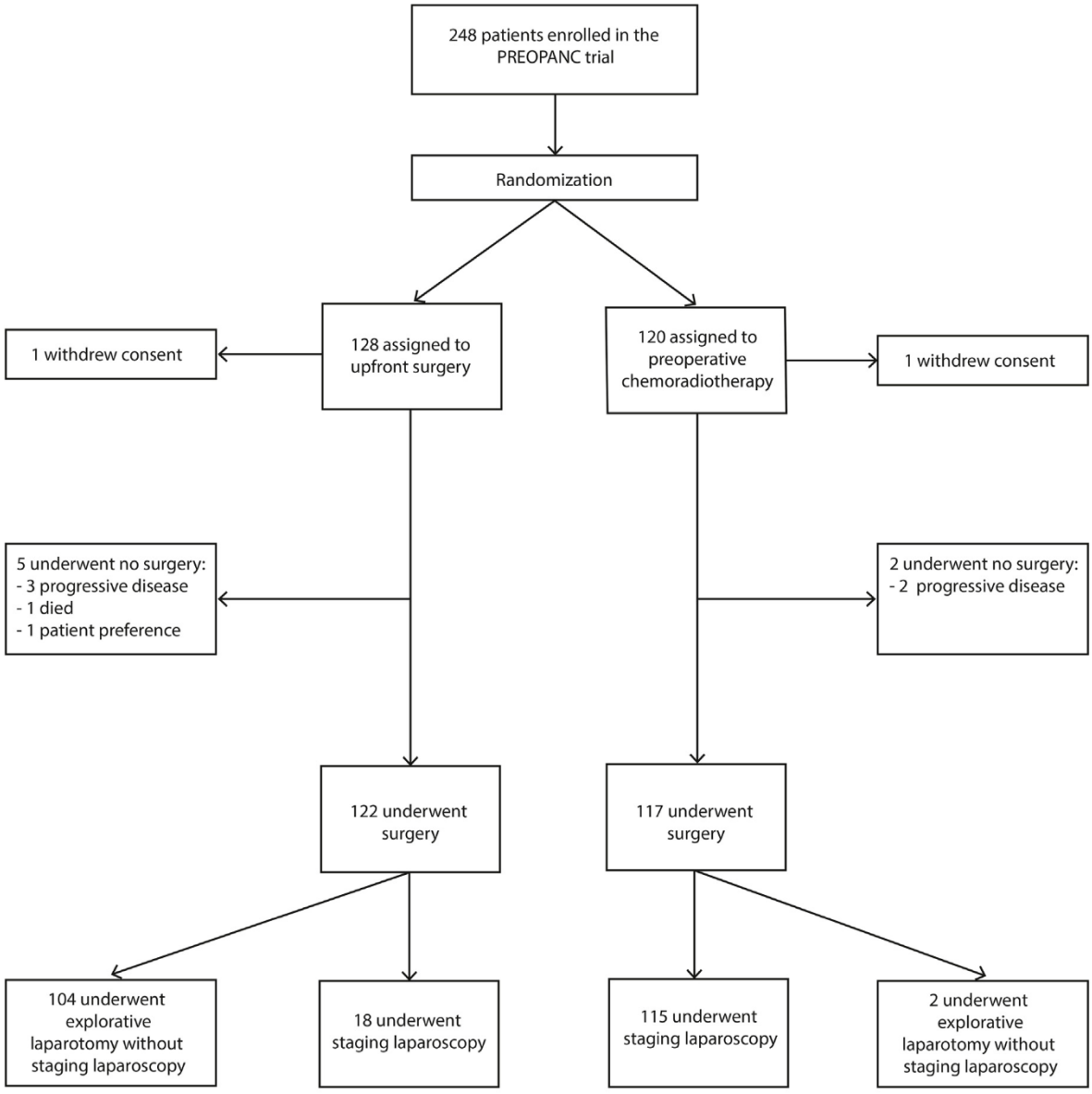

Fig. 1. Flowchart of patients included in the PREOPANC trial.

Table 1
Patient characteristics of 239 patients that underwent surgery in the randomized PREOPANC trial.

Characteristic	Overall N = 239	Staging laparoscopy N = 133	Immediate explorative laparotomy N = 106	p–value
Age at randomization, median (IQR)	66.5 (59.0–72.1)	66.0 (59.0–71.9)	67.5 (58.6–73.1)	0.403
Female sex, no. (%)	110 (46%)	60 (45%)	50 (48%)	0.700
Diabetes mellitus, no. (%)	77 (32%)	41 (31%)	36 (34%)	0.571
Body mass index, kg/m^2, median (IQR)	24.9 (22.2–27.4)	25.0 (21.9–27.7)	24.8 (23.1–27.1)	0.864
WHO performance status, no. (%)				0.022
0	117 (52%)	74 (58%)	43 (43%)	
1	110 (48%)	53 (42%)	57 (57%)	
Pancreatic head tumors, no. (%)	201 (85%)	105 (80%)	96 (91%)	0.015
Borderline resectable, no. (IQR)	108 (45%)	60 (45%)	48 (45%)	0.979
Tumor size, in mm, median (IQR)	30.0 (25.0–37.0)	30.0 (25.0–37.0)	30.0 (25.0–36.0)	0.880
Regional suspicious lymph nodes, no. (%)	69 (29%)	33 (25%)	36 (35%)	0.099
Baseline CA 19–9, kU/L, median (IQR)	192 (43–671)	152 (37–634)	216 (56–680)	0.497
Days between CT–scan and surgery, median (IQR)	66.5 (59.0–72.1)	66.0 (59.0–71.9)	67.5 (58.6–73.1)	0.403

The median time between the abdominal CT-scan and staging laparoscopy was 35 days (IQR 25–48 days) and 43 days (IQR 33–54) in case of explorative laparotomy. The median time was 37 days for patients with occult metastatic disease compared to 40 days without occult metastatic disease (p = 0.956).

Ten of the 13 patients (76.9%) with metastases at laparoscopy received palliative chemotherapy, compared to three of the 10 patients (30.0%) with metastases at explorative laparotomy (p = 0.040). In patients with occult metastases at staging laparoscopy, eight patients received FOLFIRINOX, one patient received gemcitabine with nab-paclitaxel, and one patient received gemcitabine monotherapy. Patients with metastases after explorative laparotomy received FOLFIRINOX (n = 2) or gemcitabine with nab-paclitaxel (n = 1). Patients started with chemotherapy after a median of 48 days (range: 10–59) after staging laparoscopy and 54.5 days (range: 31–78) after explorative laparotomy.

Patients with metastatic disease found at staging laparoscopy had a median survival of 8.0 months compared to 4.5 months in patients with occult metastasis found at explorative laparotomy (Fig. 2, p = 0.140).

Patients who underwent staging laparoscopy prior to immediate surgery more often had regional suspicious lymph nodes on preoperative imaging compared to patients that underwent this procedure prior to preoperative chemoradiotherapy (50% vs. 21%, p = 0.016), other characteristics were comparable between groups (Supplemental Table 2). A sensitivity analysis was performed only including patients assigned to preoperative chemoradiotherapy who underwent staging laparoscopy (n = 115) and patients assigned to immediate resection who underwent explorative laparotomy without staging laparoscopy (n = 104). This showed a comparable percentage occult metastases between groups (10.4% vs. 8.6%, p = 0.654). In this subgroup, patients with occult metastases at laparoscopy received palliative chemotherapy more often than patients with occult metastases at explorative laparotomy (75.0% vs. 22.2%, p = 0.030).

Of the 75 patients who underwent explorative laparotomy after preoperative chemoradiotherapy, 6 patients had metastatic disease (8%). Three patients had liver metastases, one patient had peritoneal metastases and two patients had metastases at liver and peritoneum.

4. Discussion

In the PREOPANC trial, the yield of staging laparoscopy in resectable or borderline resectable pancreatic cancer was 10%. Occult metastases, which were not detected by multiphase CT scan of the abdomen, were found in liver and peritoneum. In patients who underwent explorative laparotomy without staging laparoscopy, 9% had occult metastases. The similar yield suggests that occult metastasis can be successfully detected by staging laparoscopy. Patients who were diagnosed with occult metastatic disease at staging laparoscopy were more likely to receive palliative chemotherapy than patients who underwent exploratory laparotomy (77% vs. 30%, p = 0.040).

A Cochrane review and meta-analysis on the diagnostic accuracy of staging laparoscopy in patients with pancreatic or periampullary cancer was published in 2017 [9]. The analysis included 16 studies comprising 1146 patients with non-metastatic pancreatic or periampullary cancer published between 1986 and 2014. Staging laparoscopy decreased the chance of unresectable disease at laparotomy in patients with pancreatic cancer from 40% to 18%. A meta-analysis by Ta et al. was published in 2018, comprising 12 studies published between 1996 and 2009 with a total of 1756 patients with resectable or borderline resectable pancreatic cancer,

Table 2
Univariable analysis of predictive factors of occult metastatic disease at staging laparoscopy or explorative laparotomy.

Characteristic	No occult metastasis N = 216	Occult metastasis N = 23	p-value
Age at randomization, median (IQR)	66.6 (59.0–72.3)	66.0 (59.5–70.5)	0.674
Female sex, no. (%)	99 (46%)	11 (48%)	0.871
Diabetes mellitus, no. (%)	69 (32%)	8 (35%)	0.793
Body mass index, kg/m^2, median (IQR)	25.1 (22.6–27.6)	23.5 (21.3–25.2)	0.038
WHO performance status, no. (%)			0.936
0	106 (51%)	11 (52%)	
1	100 (49%)	10 (48%)	
Pancreatic head tumors, no. (%)	182 (85%)	19 (86%)	>0.999
Borderline resectable, no. (IQR)	100 (46%)	8 (35%)	0.292
Tumor size, in mm, median (IQR)	30.0 (24.8–37.0)	28.0 (25.0–36.0)	0.761
Regional suspicious lymph nodes, no. (%)	64 (30%)	5 (23%)	0.489
Baseline CA 19–9, kU/L, median (IQR)	198.0 (45.0–671.0)	167.0 (33.0–630.5)	0.688
Days between CT–scan and surgery, median (IQR)	40.0 (28.0–51.0)	37.0 (33.0–46.0)	0.934

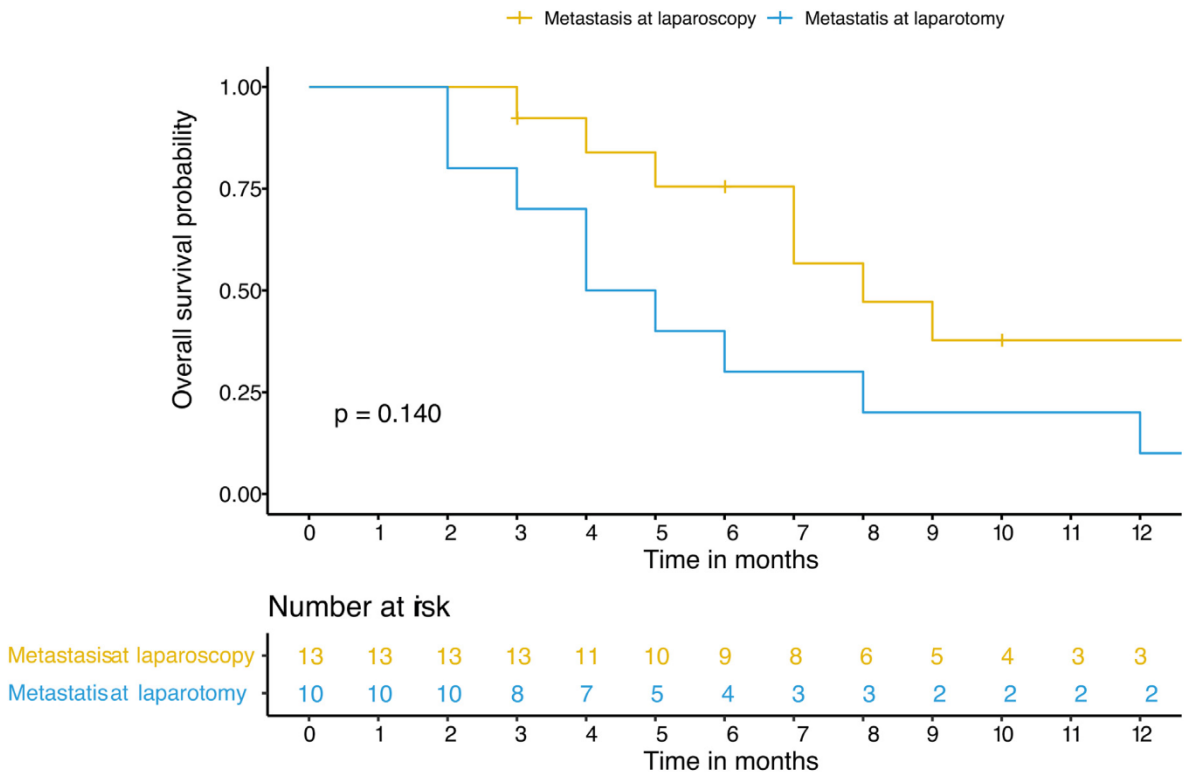

Fig. 2. Overall survival of patients with metastatic disease at laparoscopy and explorative laparotomy.

and found a yield of staging laparoscopy of 20% [8]. These studies report a higher yield of the staging laparoscopy than our findings, which could be explained by the improvement of imaging modalities over the years as these meta-analyses include many old studies. Moreover, inclusion of patients in the PREOPANC trial required a recent high quality multiphase CT scan and multidisciplinary review. This may have led to an improved preoperative staging and lower yield of the staging laparoscopy. Finally, some of these studies included patients with locally advanced pancreatic cancer who are more likely to have occult metastatic disease. In a recent study on locally advanced pancreatic cancer the yield of staging laparoscopy was 19% [12].

The NCCN guidelines indicate that staging laparoscopy for resectable or borderline pancreatic cancer could be considered in high-risk patients. These high-risk features include imaging findings, strongly elevated serum CA 19–9, large tumor size, enlarged regional lymph nodes, excessive weight loss or extreme pain [3]. The rationale for identifying predictive factors is to improve patient selection and thereby increase the yield of staging laparoscopy. In this respect, De Rosa et al. identified 24 studies for their review published in 2016 on the indications for staging laparoscopy in patients with a resectable or borderline resectable tumor on imaging [13]. Findings suggested that CA 19–9 or tumor size might be suitable to identify patients who might benefit from staging laparoscopy. However, this review was limited by small, retrospective studies. Thus, the clinical value of CA 19.9 and tumor size remains questionable. We found that only lower BMI appeared associated with metastatic disease at staging laparoscopy or explorative laparotomy. This could related to more excessive weight loss in patients with occult metastatic disease, or a type I error. Other predictors might not be identified because of a type II error due to the limited number of occult metastases.

In our study, majority of intraoperative biopsies were of lesions with a benign origin. Additional modalities could be considered to increase the yield of biopsies. Intraoperative ultrasound proved useful in addition to tactile and visual detection in liver metastases in colorectal cancer [14], however it has been scarcely studied in PDAC [15]. In addition, fluorescence guided laparoscopy may enhance the detection of liver metastases in the future [16]. The role of the PET/CT-scan for improving preoperative staging remains controversial. In Dutch clinical practice a PET/CT-scan is not recommended since it might hold several disadvantages. The detection of small lesions detectable only by PET-scan that are too small to perform a biopsy on may lead to unnecessary delay of treatment. In addition, false positive findings cause by non-malignant inflammatory disease can cause delay. PET/CT-scan is not recommended by most European and American guidelines [17–20].

In the present study, patients were more likely to receive palliative chemotherapy if metastases were found during staging laparoscopy rather than explorative laparotomy. Patients appeared to receive palliative FOLFIRINOX more often in the staging laparoscopy group. This could be caused by increased morbidity and a lower performance status after explorative laparotomy. A previous retrospective study of 151 patients with occult metastatic disease (89 after laparoscopy and 62 after laparotomy) demonstrated that patients after staging laparoscopy had fewer complications, were more likely to receive palliative chemotherapy, and had a shorter time to initiation of the chemotherapy compared to explorative laparotomy [21]. The overall survival after staging laparoscopy was significantly better than after laparotomy in that study. This is in line with our findings, although this was not statistically significant.

A staging laparoscopy prior to preoperative chemoradiotherapy was mandatory in the PREOPANC trial, to avoid chemoradiotherapy in patients who have occult metastasis, since patients who appear to have occult metastatic disease are more likely to benefit from FOLFIRINOX than from chemoradiotherapy. Therefore, staging laparoscopy may play a critical role in patient selection and may alter treatment recommendations for patients with a resectable

tumor on imaging [22]. It would require approximately 10 staging laparoscopies to prevent one unnecessary laparotomy or radiotherapy in resectable or borderline resectable patients. Based on this study no recommendations can be made on the timing of the staging laparoscopy prior to surgery. The staging laparoscopy could be planned immediately before planned resection within the same session. From patient perspective this might be preferred as the surgical procedures require only one hospital admission and general anesthesia. Nonetheless, this would cost one full day of the operating room and two days of hospital admission in case of metastatic disease at laparoscopy. This decision should be based on local hospital logistics, waiting list and patient and surgeon's preference. In the move towards centralization, surgeons in peripheral hospitals could offer staging laparoscopy for their patients before referral for resection to a specialized hospital. Furthermore, when considering neoadjuvant therapy, it may be important for patients to be optimally informed about the actual spread of the disease. This prevents major disappointment when a resection after intensive pre-treatment is not possible because of the presence of metastases.

The number of patients with metastases at surgery in this study differs slightly from previously published results in the PREOPANC trial [10]. This is because all data were checked for the purpose of this study, and minor inconsistencies in data were corrected. Furthermore, lymph nodes metastases were not considered in this study as previously explained.

This is the first study comparing staging laparoscopy and explorative laparotomy directly using data from a recent RCT. The main limitation of our study is the small sample size of patients with metastasis on staging laparoscopy or explorative laparotomy. Yet, no oncological trial will be powered to compare the yield between laparoscopy and laparotomy. Another limitation of our study is that the time between CT-scan and surgery in both groups was long, and preoperative staging might improve by more recent imaging. The time presented does reflect clinical practice, but this is a point of potential improvement. Further research, including tumor- and biomarkers is needed to increase the yield of this minimal invasive procedure to reduce the additional costs.

In conclusion, staging laparoscopy could avoid an unnecessary laparotomy in 10% of the patients with a resectable or borderline resectable PDAC based on multiphase CT scan imaging. Patients who were upstaged to metastatic disease during staging laparoscopy were more likely to receive palliative chemotherapy than patients upstaged during laparotomy. Although the detection rate of occult metastatic disease was only 10%, we recommend a staging laparoscopy in all patients with resectable or borderline resectable pancreatic cancer prior to planned resection or neoadjuvant therapy especially when it includes (chemo)radiotherapy.

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Registration

The PREOPANC trial was registered in the EU Clinical Trials Register (2012-003181-40). The PREOPANC study was preregistered including an analysis plan.

Protocol

The protocol was centrally approved by the Erasmus MC ethics committee (MEC-2012-249; December 11, 2012) and has been previously published [11].

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Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Jelle C. van Dongen: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **Eva Versteijne:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Bert A. Bonsing:** Conceptualization, Methodology, Investigation, Writing – review & editing. **J. Sven D. Mieog:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Ignace H.J.T. de Hingh:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Sebastiaan Festen:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Gijs A. Patijn:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Ronald van Dam:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Erwin van der Harst:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Jan H. Wijsman:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Koop Bosscha:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Marion van der Kolk:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Vincent E. de Meijer:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Mike S.L. Liem:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Olivier R. Busch:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Marc G.H. Besselink:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Geertjan van Tienhoven:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Bas Groot Koerkamp:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing, Supervision. **Casper H.J. van Eijck:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing, Supervision. **Mustafa Suker:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing, Supervision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.12.011.

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