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ORIGINAL ARTICLE

The risk of not receiving adjuvant chemotherapy after resection of pancreatic ductal adenocarcinoma: a nationwide analysis

Tara M. Mackay[1], F. Jasmijn Smits[2], Daphne Roos[3], Bert A. Bonsing[4], Koop Bosscha[5], Olivier R. Busch[1], Geert-Jan Creemers[6], Ronald M. van Dam[7], Casper H.J. van Eijck[8], Michael F. Gerhards[9], Jan Willem B. de Groot[10], Bas Groot Koerkamp[8], Nadia Haj Mohammad[11], Erwin van der Harst[12], Ignace H.J.T. de Hingh[13], Marjolein Y.V. Homs[14], Geert Kazemier[15], Mike S.L. Liem[16], Vincent E. de Meijer[17], I. Quintus Molenaar[11], Vincent B. Nieuwenhuijs[18], Hjalmar C. van Santvoort[11], George P. van der Schelling[19], Martijn W.J. Stommel[20], Albert Jan ten Tije[21], Judith de Vos-Geelen[22], Fennie Wit[23], Johanna W. Wilmink[24], Hanneke W.M. van Laarhoven[24,*], Marc G. Besselink[1*] on behalf of the Dutch Pancreatic Cancer Group

[1]Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, [2]Department of Surgery, University Medical Center Utrecht, Utrecht, [3]Department of Surgery, Reinier de Graaf Group, Delft, [4]Department of Surgery, Leiden University Medical Center, Leiden, [5]Department of Surgery, Jeroen Bosch Hospital, Den Bosch, [6]Department of Medical Oncology, Catharina Hospital, Eindhoven, [7]Department of Surgery, Maastricht UMC+, Maastricht, [8]Department of Surgery, Erasmus Medical Center, Rotterdam, [9]Department of Surgery, OLVG, Amsterdam, [10]Oncology Center Isala, Zwolle, [11]Department of Medical Oncology, Regional Academic Cancer Center Utrecht, University Medical Center Utrecht Cancer Center & St. Antonius Hospital Nieuwegein, [12]Department of Surgery, Maasstad Hospital, Rotterdam, [13]Department of Surgery, Catharina Hospital, Eindhoven, [14]Department of Medical Oncology, Erasmus Medical Center, Rotterdam, [15]Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, VU Medical Center, Amsterdam, [16]Department of Surgery, Medisch Spectrum Twente, Enschede, [17]Department of Surgery, University Medical Center Groningen, Groningen, [18]Department of Surgery, Isala, Zwolle, [19]Department of Surgery, Amphia Hospital, Breda, [20]Department of Surgery, Radboud UMC, Nijmegen, [21]Department of Medical Oncology, Amphia Hospital, Breda, [22]Department of Internal Medicine, Division of Medical Oncology, GROW - School for Oncology and Developmental Biology, Maastricht UMC+, Maastricht, [23]Department of Surgery, Tjongerschans, Heerenveen, and [24]Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, the Netherlands

Abstract

Background: The relation between type of postoperative complication and not receiving chemotherapy after resection of pancreatic ductal adenocarcinoma (PDAC) is unclear. The aim was to investigate which patient factors and postoperative complications were associated with not receiving adjuvant chemotherapy.

Methods: Patients who underwent resection (2014–2017) for PDAC were identified from the nationwide mandatory Dutch Pancreatic Cancer Audit. The association between patient-, tumor-, center-, treatment characteristics, and the risk of not receiving adjuvant chemotherapy was analyzed with multivariable logistic regression.

Results: Overall, of 1306 patients, 24% (n = 312) developed postoperative Clavien Dindo $\geq$3 complications. In-hospital mortality was 3.5% (n = 46). Some 433 patients (33%) did not receive adjuvant chemotherapy. Independent predictors (all $p < 0.050$) for not receiving adjuvant chemotherapy were older age (odds ratio (OR) 0.96), higher ECOG performance status (OR 0.57), postoperative complications (OR 0.32), especially grade B/C pancreatic fistula (OR 0.51) and post-pancreatectomy hemorrhage (OR 0.36), poor tumor differentiation grade (OR 0.62), and annual center volume of <40 pancreatoduodenectomies (OR 0.51).

Conclusions: This study demonstrated that a third of patients do not receive chemotherapy after resection of PDAC. Next to higher age, worse performance status and lower annual surgical volume, this is mostly related to surgical complications, especially postoperative pancreatic fistula and post-pancreatectomy hemorrhage.

This paper is not based on a previous communication to a society or meeting.

[*] Shared senior authorship.

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Correspondence
Marc G. Besselink, Dept. of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, G4-146-1, 1105 AZ Amsterdam, the Netherlands. E-mail: m.g.besselink@amc.nl

Introduction

Adjuvant chemotherapy substantially improves survival and quality of life in patients undergoing resection of pancreatic ductal adenocarcinoma (PDAC) and is therefore the current standard of care for patients with a good performance status after resection.[1,2] Several studies have shown that a substantial number of patients do not receive adjuvant treatment after pancreatic resection (range 24%–54%).[3–6] These data are rather worrisome, especially since the recent French-Canadian PRODIGE-24 trial demonstrated an impressive 54 months overall survival with adjuvant modified FOLFIRINOX as compared to 35 months with adjuvant gemcitabine.[1]

Whether adjuvant chemotherapy is given depends on patient, doctor, and hospital factors. With respect to patient factors, postoperative complications are important. Several small retrospective studies have suggested an association between complications after pancreatic resection and delay or omission of adjuvant chemotherapy.[4,6–10] Larger studies either investigated only one specific complication (e.g., pancreatic fistula), or are relatively outdated, especially since the quality and efficiency of both perioperative care and adjuvant therapy has improved.[4,11,12] Large, observational studies on the impact of patient factors, hospital factors and postoperative complications on the risk of not receiving adjuvant chemotherapy are lacking.

The aim of this study, which used data from a nationwide mandatory prospective surgical audit, was to investigate which patient factors, hospital factors and postoperative complications are associated with not receiving adjuvant chemotherapy after resection of PDAC.

Methods

Study design

This was a nationwide analysis of prospectively collected data within the Dutch Pancreatic Cancer Audit (DPCA).[13,14] All Dutch patients with PDAC who underwent resection in the period 2014–2017 in 19 centers were included. One center stopped pancreatic surgery after 2015 and two centers merged, leaving 17 centers at the end of the study period. Patients were divided into subgroups of (A) no or minor complications (Clavien Dindo <3) and (B) major complications (Clavien Dindo ≥3).[15] Patients with more than one complication were categorized according to their most severe complication. Patients were excluded if data on postoperative complications or on adjuvant chemotherapy were missing. This study was designed in accordance with the STROBE guidelines.

Data collection

Data were retrieved from the DPCA database, including patient characteristics (i.e. age at resection, sex, preoperative ECOG performance status, ASA score, and comorbidities), tumor characteristics (i.e. resection margins, T-stage, N-stage, and tumor differentiation grade), treatment characteristics (i.e. neoadjuvant chemotherapy, surgical procedure, and minimally invasive surgery), length of hospital stay, postoperative complications (i.e. general and pancreatic surgery specific complications), in-hospital mortality, the use of adjuvant chemotherapy, and interval between resection and start of adjuvant chemotherapy. General complications were pneumonia (diagnosed with X-ray), wound infection (requiring at least opening, flushing and covering of the wound with gauze), organ failure (dialysis, inotropes, and/or artificial respiration required), and death. Pancreatic surgery specific complications (only grade B and C) included postoperative pancreatic fistula, delayed gastric emptying, bile leakage, post pancreatectomy hemorrhage, and chyle leakage, all of which defined according to the International Study Group on Pancreatic Surgery (ISGPS).[16–21] Data on pancreatic fistula and chyle leakage according to ISGPS 2016 definitions were only available for 2017. Tumor stage was defined in accordance with the 7th TNM classification edition. Margin status was classified as microscopically radical resection (>1 mm; R0) and microscopically irradical resection (≤1 mm; R1). Time to adjuvant chemotherapy was defined as time between pancreatic resection and start date of chemotherapy. To assess the accuracy of data on adjuvant chemotherapy in the DPCA, validation was performed through the Netherlands Cancer Registration, an independent population-based registry collecting data on all patients with cancer in the Netherlands. The percentage of resected PDAC patients receiving adjuvant chemotherapy was compared between both registries. A 96% concordance was found for the years 2013–2015.

Centers participating in the DPCA were classified into 2 groups based on the mean annual pancreatoduodenectomy (PD) volume (regardless of the indication for resection) according to predefined groups[22]: medium (<40 PDs) and high (≥40 PDs) volume centers.

Table 1 Characteristics of 1306 Dutch patients with resected PDAC (2014–2017)

Age at resection (± SD)	67 (±9.5)
BMI (± SD)	24.9 (±4.1)
Sex (male)	719 (55.1%)
ECOG performance status	
0	588 (45.0%)
I	542 (41.5%)
II	121 (9.3%)
III	20 (1.5%)
IV	34 (2.6%)
ASA score	
I	165 (12.6%)
II	837 (64.1%)
III	299 (22.9%)
IV	5 (0.4%)
Comorbidity	
Cardiovascular	608 (46.6%)
Pulmonary	165 (12.6%)
Renal	127 (9.7%)
Hepatic	16 (1.2%)
Neoadjuvant chemotherapy (received)	111 (8.5%)
Surgical procedure	
Pancreatoduodenectomy[a]	1067 (81.7%)
Distal pancreatectomy	188 (14.4%)
Central pancreatectomy	1 (0.1%)
Total pancreatectomy	44 (3.4%)
Other	6 (0.5%)
Minimally invasive surgery[b]	211 (16.2%)
Pancreatoduodenectomy volume	
Medium (<40)	716 (54.8%)
High (≥40)	590 (45.2%)
Microscopic resection margins	
R0	783 (60.0%)
R1	523 (40.0%)
T stage	
T1	67 (5.1%)
T2	151 (11.6%)
T3	1033 (79.1%)
T4	55 (4.2%)
N stage	
N0	403 (30.9%)
N1	903 (69.1%)
Tumor differentiation grade	
Well	161 (12.3%)
Moderate	729 (55.8%)
Poor	356 (27.3%)
Undifferentiated	60 (4.6%)
Adjuvant chemotherapy (not received)	433 (33.2%)
Median time to adjuvant chemotherapy in days (IQR)[c]	48 (37–62) (n = 380)

[a] Whipple, pylorus preserving and pylorus resecting pancreatoduodenectomy.
[b] Including procedures with conversion to open surgery (n = 214, 25.7%).
[c] Patients excluded that died during initial hospital admission (n = 46, 3.5%).

Statistical analysis

Baseline characteristics and outcomes were assessed using descriptive statistics. Categorical variables were reported as proportions. Parametric continuous variables were reported as mean with standard deviation (SD) and non-parametric continuous variables as median with interquartile range (IQR). Missing data (range 0.6–13.2%) were imputed by multiple imputation techniques in which 10 dummy sets were created.

Patient and tumor characteristics, as well as treatment and surgical outcome parameters were assessed with univariable analysis as potential predictors for not receiving adjuvant chemotherapy. Variables with $p < 0.10$ were subsequently selected for multivariable logistic regression analysis with backward stepwise selection and reported as odds ratio (OR) with corresponding 95% confidence interval (CI). A subgroup analysis was performed in which the effect of individual complications on not receiving chemotherapy was evaluated, when adjusted for other previously identified confounders. Sensitivity analyses were performed excluding (i) patients who received neoadjuvant chemotherapy (n = 111) and (ii) patients with in-hospital mortality (n = 46). All p-values were based on a 2-sided test. A p-value of below 0.05 was considered statistically significant. Statistical analyses were performed in SPSS Statistics version 24 and R version 3.4.4.

Results

Study population

In total, 1457 patients underwent a resection for PDAC between 2014 and 2017. After exclusion of patients with missing data on postoperative complications (n = 29, 2.0%) or on adjuvant chemotherapy (n = 122, 8.4%), the final cohort consisted of 1306 patients. Patient, tumor and treatment characteristics are given in Table 1.

Adjuvant chemotherapy and postoperative complications

The in-hospital mortality was 3.5% (n = 46/1306). Overall, 427 patients (32.7%) suffered from minor complications and 312

(23.9%) from major complications. A total of 873 patients (66.8% of the total cohort and 69.3% after exclusion of patients with in-hospital mortality) received adjuvant chemotherapy, of whom 848 (97.1%) received only chemotherapy and 25 (2.9%) received a combination of chemotherapy and radiotherapy.

The proportion of patients who did not receive adjuvant chemotherapy differed significantly between centers during the study period (range 11.9%–68.3%, $p < 0.001$, Fig. 1) and varied from 39.9% in medium volume to 25.1% in high volume centers respectively ($p < 0.001$).

Patients with major complications less frequently received adjuvant chemotherapy, as compared with patients with minor or no complications (51.6% vs. 27.4%, $p < 0.001$). Overall, median time to commence adjuvant chemotherapy was 48 days (IQR 37–62) after resection, and was significantly longer for patients with major versus minor or no complications (56 vs. 47 days, $p < 0.001$).

The univariable and multivariable analyses of factors that predict not receiving adjuvant chemotherapy are shown in Table 2.

Table 3 summarizes the sub-analysis of the association of specific complications with not receiving adjuvant chemotherapy. After sensitivity analyses, excluding 111 patients who received neoadjuvant chemotherapy, results remained similar (Supplementary Tables S1 and S2). After sensitivity analyses, excluding 46 patients with in-hospital mortality, results remained similar (Supplementary Tables S3 and S4).

Of the 305 patients with ECOG 0 or 1 performance status and age <70 years who underwent surgery in high volume centers, 57 (18.8%) did not receive adjuvant chemotherapy; 45 (14.7%) developed minor or no complications versus 95 (31.1%) who developed major complications ($p = 0.003$). The risk of not receiving adjuvant chemotherapy in this 'best-case-scenario' was still high for patients with major complications (OR 0.38, 95% CI 0.21–0.70, $p = 0.002$).

Discussion

This nationwide multicenter study demonstrated that a third of patients did not receive adjuvant chemotherapy after resection of PDAC, with considerable variation among centers. Postoperative surgical complications, especially pancreatic fistula and post-pancreatectomy hemorrhage, were the strongest predictor for not receiving adjuvant chemotherapy, followed by increased age and a lower annual center volume.

Reported rates of not receiving adjuvant chemotherapy range from 26% to 54% in previous population-based studies,[3,4,6] and was 33% in this study. In this cohort, 24% of patients suffered from major postoperative complications. Previous studies report similar complication rates.[4,6,9,10,12,23] The odds of receiving adjuvant chemotherapy decreased significantly in these patients (OR 0.32, 95% CI 0.24–0.42). Patients suffering from postoperative complications, specifically pancreatic fistula and post-pancreatectomy hemorrhage, may have a performance status which is too poor to start adjuvant chemotherapy within the advocated three months after surgery.[24,25] Similar results have been found for adjuvant treatment after surgery for colon and gastric cancer.[26–28] In addition, a recent Dutch study showed that pancreatic centers differed little in the incidence of postoperative complications, but that centers of excellence had much better 'failure to rescue rates' from these complications.[29] This emphasizes the importance of prevention but also early detection and adequate management of postoperative complications, especially pancreatic fistula.[30,31] To improve

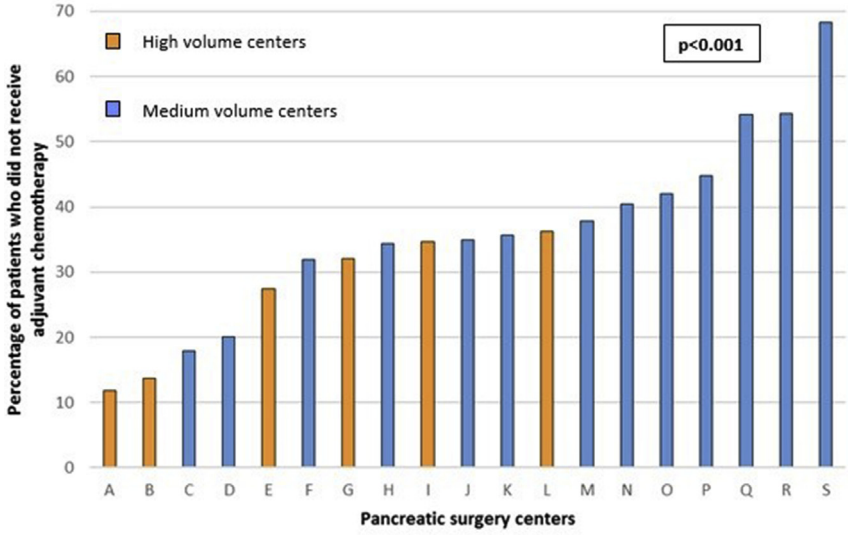

Figure 1 Proportion of patients after surgical resection of PDAC who did not receive adjuvant chemotherapy per Dutch center between 2014 and 2017

Table 2 Uni- and multivariable logistic regression for the risk not receiving adjuvant chemotherapy after surgical resection for PDAC in a nationwide cohort

	Univariable		Multivariable	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age at resection	**0.95 (0.94–0.97)**	**<0.001**	**0.96 (0.94–0.97)**	**<0.001**
ECOG performance status				
0-I	Ref		Ref	
II-IV	**0.53 (0.38–0.74)**	**<0.001**	**0.57 (0.39–0.83)**	**0.003**
ASA score				
I	Ref			
II	0.76 (0.52–1.12)	0.172		
III-IV	**0.40 (0.26–0.61)**	**<0.001**		
Comorbidity				
Cardiovascular	**0.67 (0.53–0.85)**	**0.001**		
Pulmonary	**0.71 (0.51–1.00)**	**0.056**		
Renal	**0.60 (0.41–0.88)**	**0.081**		
Hepatic	0.72 (0.24–2.14)	0.558		
Neoadjuvant chemotherapy	**1.49 (0.93–2.40)**	**0.090**		
Surgical procedure				
Pancreatoduodenectomy[a]	Ref			
Distal pancreatectomy	0.83 (0.60–1.14)	0.254		
Central pancreatectomy[b]	–	–		
Total pancreatectomy	0.62 (0.39–1.00)	0.133		
Other	0.47 (0.21–1.07)	0.369		
Annual volume of pancreatoduodenectomy				
Medium (<40)	**0.51 (0.40–0.65)**	**<0.001**	**0.51 (0.39–0.66)**	**<0.001**
High (≥40)	Ref		Ref	
Microscopic resection margins				
R0	Ref			
R1	0.99 (0.78–1.27)	0.971		
T stage				
T1	Ref			
T2	1.10 (0.59–2.05)	0.783		
T3	1.23 (0.72–2.11)	0.452		
T4	0.63 (0.30–1.34)	0.224		
N stage				
N0	Ref			
N1	1.21 (0.95–1.55)	0.130		
Tumor differentiation grade				
Well	Ref		Ref	
Moderate	0.90 (0.61–1.32)	0.584	0.90 (0.59–1.40)	0.612
Poor	**0.68 (0.43–0.99)**	**0.040**	**0.62 (0.39–0.98)**	**0.041**
Undifferentiated	0.88 (0.33–2.36)	0.797	0.96 (0.32–2.88)	0.944
Postoperative complications				
None or minor	Ref		Ref	
Major	**0.35 (0.27–0.46)**	**<0.001**	**0.32 (0.24–0.42)**	**<0.001**

Bold in univariable analysis indicates variables ($p < 0.10$) that were entered in multivariable analysis. Bold in multivariable analysis indicates statistical significance ($p < 0.05$).
[a] Whipple, pylorus preserving and pylorus resecting pancreatoduodenectomy.
[b] Not enough events for statistical analysis.

Table 3 Uni- and multivariable analysis for the association between the various individual complications with adjuvant chemotherapy after surgical resection for PDAC

	Univariable		Multivariable	
	OR (95% CI)	**p-value**	**OR (95% CI)[a]**	**p-value**
Pancreatic fistula (ISGPS 2005)				
None or grade A	Ref		Ref	
Grade B/C	**0.46 (0.31–0.68)**	**<0.001**	**0.51 (0.33–0.79)**	**0.003**
Pancreatic fistula (ISGPS 2016)				
None or biochemical leak	Ref			
Grade B/C	**0.48 (0.23–0.99)**	**0.050**		
Delayed gastric emptying				
None or grade A	Ref			
Grade B/C	0.79 (0.57–1.11)	0.173		
Bile leakage				
None or grade A	Ref			
Grade B/C	**0.45 (0.22–0.92)**	**0.038**		
Post-pancreatectomy hemorrhage				
None or grade A	Ref		Ref	
Grade B/C	**0.35 (0.22–0.55)**	**<0.001**	**0.36 (0.22–0.59)**	**<0.001**
Chyle leakage				
None or grade A	Ref			
Grade B/C	0.68 (0.31–1.51)	0.344		
Pneumonia				
No	Ref			
Yes	**0.39 (0.20–0.75)**	**0.013**		
Surgical site infection				
No	Ref			
Yess	0.81 (0.48–1.39)	0.455		
Atrial fibrillation				
No	Ref			
Yes	**0.42 (0.18–1.01)**	**0.057**		

Bold in univariable analysis indicates variables ($p < 0.10$) that were entered in multivariable analysis. Bold in multivariable analysis indicates statistical significance ($p < 0.05$).
[a] Analysis adjusted for age at resection, ECOG performance status, pancreatoduodenectomy volume and tumor differentiation grade.

postoperative complication management and subsequent oncological care in pancreatic cancer, two nationwide randomized stepped-wedge trials, PORSCH (NCT03400280) and PACAP-1 (NCT03513705) were recently launched in the Netherlands.

Increased age at the time of resection, poor ECOG performance status and poor tumor differentiation grade were independent predictors for not receiving adjuvant chemotherapy and may influence the decision of clinicians and patients to pursue upfront surgery followed by adjuvant treatment. Increased age is a known risk factor for not receiving adjuvant chemotherapy in PDAC[7,8,10,24,32] and other types of cancer.[26–28] Previous studies on adjuvant treatment have not investigated the influence of ECOG performance status in PDAC, but this relationship was previously described in colorectal cancer.[33]

Although tumor differentiation grade should not influence the administration of adjuvant treatment after PDAC resection, poor differentiation grade was an independent risk factor for not receiving adjuvant chemotherapy. This finding is different from previous studies that suggest higher willingness of clinicians to administer adjuvant chemotherapy to patients with worse prognosis PDAC (e.g. higher T-stage).[24,32] However, specifically for cancers with a poor prognosis, such as PDAC, oncologists may be pessimistic about the added value of adjuvant treatment, especially when predictors for worse outcomes such as poor differentiation grade are present. With the introduction of newer and more effective chemotherapy regimens such as

FOLFIRINOX with a clear survival benefit compared to gemcitabine (median overall survival 54 vs. 35 months),[1] it may be speculated that in the future more patients with PDAC will be treated with adjuvant chemotherapy, even if negative outcome predictors are present. Nevertheless, it should be noted that implementation of improvements in daily medical care are inherently slow, underlining the relevance of bringing to attention the thus far limited uptake of adjuvant chemotherapy after pancreatic resection.

Adjuvant chemotherapy was administered more often in patients who underwent pancreatic resection in a high volume as compared to a medium volume center (40% vs. 25%). Volume-outcome relationships have clearly been established for surgical outcome after PD for cancer.[22,29,34] A previous study showed that center volume is also relevant for palliative chemotherapy for metastatic PDAC.[35] The current study results suggest that institutional volume may also be relevant for adjuvant chemotherapy. Oncologists from high volume centers may be more willing to administer systemic treatment to a broader selection of patients. It may also be possible that more motivated patients who are willing to undergo chemotherapy are more likely to visit high volume centers for treatment.

Neoadjuvant chemotherapy for patients with PDAC is currently gaining popularity and several studies have shown a survival benefit compared to adjuvant therapy.[36–38] Some have argued that neoadjuvant treatment may improve the use of systemic treatment, as this treatment strategy avoids the issue of postoperative complications, as treatment is given prior to surgery. Neoadjuvant treatment may also improve R0-resection rates compared to upfront surgery for (borderline) resectable PDAC.[36–38] To assess the effect of neoadjuvant FOLFIRINOX in patients with (borderline) resectable PDAC, the PREOPANC-2 trial (NTR7292) was recently launched in the Netherlands. Neoadjuvant treatment in the Netherlands is only given in trial settings, as the current standard of care is adjuvant chemotherapy.

This study has several limitations. First, the nationwide DPCA does not collect data on type of chemotherapy, side effects, dose reductions, completion of treatment, or long-term survival. Second, the DPCA may not collect data from patients referred to another hospital for adjuvant chemotherapy correctly. Cross-validation with the Netherlands Cancer Registry data, however, showed a 96% concordance. Therefore, the impact of this bias is probably small. The strength of the current study is that the participation in the DPCA is mandatory and contains data on all pancreatic resections in the Netherlands.

In conclusion, increased age at resection, worse ECOG performance status, poor tumor differentiation, annual center volume of <40 PDs, but mostly major postoperative complications are independently associated with not receiving adjuvant chemotherapy after resection of PDAC. Pancreatic fistula and post-pancreatectomy hemorrhage were the strongest predictors for not receiving adjuvant chemotherapy. These findings may further fuel the current debate of the value of neoadjuvant versus adjuvant treatment strategies in PDAC.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2019.06.019.