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Effect of centralization and regionalization of pancreatic surgery on resection rates and survival

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Abstract

Background: Centralization of pancreatic surgery in the Netherlands has been ongoing since 2011. The aim of this study was to assess how centralization has affected the likelihood of resection and survival of patients with non-metastatic pancreatic head and perampullary cancer, diagnosed in hospitals with and without pancreatic surgery services.

Methods: An observational cohort study was performed on nationwide data from the Netherlands Cancer Registry (2009–2017), including patients diagnosed with non-metastatic pancreatic head or perampullary cancer. The period of diagnosis was divided into three time intervals: 2009–2011, 2012–2014 and 2015–2017. Hospital of diagnosis was classified as a pancreatic or non-pancreatic surgery centre. Analyses were performed using multivariable logistic and Cox regression models.

Results: In total, 10 079 patients were included, of whom 3114 (30.9 per cent) were diagnosed in pancreatic surgery centres. Between 2009–2011 and 2015–2017, the number of patients undergoing resection increased from 1267 of 3169 (40.0 per cent) to 1705 of 3566 (47.8 per cent) (P for trend < 0.001). In multivariable analysis, in 2015–2017, unlike the previous periods, patients diagnosed in pancreatic and non-pancreatic surgery centres had a similar likelihood of resection (odds ratio 1.08, 95 per cent c.i. 0.90 to 1.28; $P = 0.422$). In this period, however, overall survival was higher in patients diagnosed in pancreatic surgery than in those diagnosed in non-pancreatic surgery centres (hazard ratio 0.92, 95 per cent c.i. 0.85 to 0.99; $P = 0.047$).

Conclusion: After centralization of pancreatic surgery, the resection rate for patients with pancreatic head and perampullary cancer diagnosed in non-pancreatic surgery centres increased and became similar to that in pancreatic surgery centres. Overall survival remained higher in patients diagnosed in pancreatic surgery centres.

Introduction

The incidence of pancreatic ductal adenocarcinoma and perampullary cancer has increased over the past two decades, resulting in increasing numbers of patients amenable for cancer-directed treatment¹. Pancreatic surgery in combination with systemic chemotherapy provides the best outlook for long-term survival, but is associated with a relatively high risk of complications^{2–4}. Studies^{5–7} have demonstrated a clear relationship between hospital volume and postoperative mortality. To address this issue, centralization of pancreatic surgery occurred in many countries, resulting in increased resection rates and reduced in-hospital mortality^{8–10}. Based on these volume-outcome relations, centralization of pancreatic surgery was initiated in the Netherlands in 2011, with the advice to apply a threshold of at least 20 pancreatoduodenectomies (PDs) per year. This volume standard became officially mandatory in 2013.

However, patients diagnosed with non-metastatic pancreatic cancer (2005–2013) in a Dutch hospital without pancreatic surgery services had a lower likelihood of undergoing surgery compared with patients diagnosed in a centre performing pancreatic surgery¹¹. A frequently mentioned strategy to reduce this undesired practice variation is increased regionalization with regular interhospital multidisciplinary team meetings, online video meetings, and easily accessible consultation with pancreatic cancer experts for referral hospitals. In addition, the Dutch Pancreatic Cancer Group (DPCG) was established in 2011 to improve quality of care, and clinical and translational research¹². All centres performing pancreatic surgery in the Netherlands are incorporated within the DPCG and play an important role in their regional networks.

It is currently unknown whether the ongoing centralization and regionalization has equalized the surgical resection rate and consequently improved survival for patients with non-metastatic

pancreatic head and periampullary cancer across centres in the Netherlands. Therefore, the aim of this study was to assess whether the resection rate in patients with non-metastatic pancreatic head or periampullary carcinoma who were diagnosed in pancreatic surgery *versus* non-pancreatic surgery centres changed between 2009 and 2017, and whether this influenced survival patterns.

Methods

This observational nationwide cohort study used data from the Netherlands Cancer Registry (NCR), a prospective population-based database that covers all Dutch hospitals (a population of 17.3 million in 2019). All patients with newly diagnosed malignancy are identified from the national pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnoses, and included in the NCR. Trained administrators routinely collect data on patient, tumour and treatment characteristics from hospital records. This study was reported in accordance with the STROBE guidelines¹³.

Study population

ICD-O-3 was used to categorize patients with pancreatic head or periampullary carcinoma (codes C25.0, C24.1, C24.0-distal cholangiocarcinoma, C17.0, and morphology codes 'adenocarcinoma') (Appendix S1). All patients with non-metastatic disease or who had surgery with curative intent (together defined as patients with non-metastatic pancreatic head and periampullary cancer on imaging), and were diagnosed between 2009 and 2017, were included¹⁴. Surgery with curative intent included both patients undergoing 'exploration only' (surgery without resection because of locally advanced or disseminated disease) and those with 'resection of the primary tumour'. Patients with borderline resectable tumours and those with locally advanced pancreatic cancers were included, because information on the extent of vessel involvement was lacking and patients with locally advanced disease could not be excluded properly. Patients younger than 18 years at time of diagnosis, patients with neuroendocrine tumours and metastatic disease from other primary tumours, and patients diagnosed during autopsy were excluded. Patients were also excluded if they did not undergo surgery and died within 30 days of diagnosis (probably not surgical candidates).

Data definitions

The period of diagnosis was divided into three intervals: 2009–2011, 2012–2014 and 2015–2017, respectively corresponding to a 'baseline status' without nationwide centralization of pancreatic surgery (34 of 78 hospitals performing pancreatic surgery), the shift to the start of nationwide centralization with a mandatory volume standard introduced in 2011 (24 of 78 hospitals), and current ongoing centralization (18–19 of 78 hospitals).

Hospital of diagnosis was defined as the hospital of first visit or clinical diagnosis, and classified as 'pancreatic surgery' and 'non-pancreatic surgery' centres. Pancreatic surgery centres are hospitals performing pancreatic surgery and participating in the DPCG. This category label was based on the classification in 2017: 18 pancreatic surgery centres and 59 non-pancreatic surgery. Time trends were analysed with this hospital category fixed, using the category labels as assigned in 2017 even for the earlier time intervals, to avoid any 'category migration'.

Socioeconomic status was based on social deprivation scores per four-digit postal code (reference data from the Netherlands Institute of Social Research) and categorized into three groups: high status, first to third decile; intermediate status, fourth to seventh decile; and low status, 8th to 10th deciles.

In the NCR, staging was classified according to the TNM classification at the time of registration (6th edition of UICC TNM staging during 2009, 7th edition during 2010–2016, and 8th edition during 2017)^{15–17}. Both clinical and pathological stages was presented according to the seventh edition, because most patients were classified accordingly. For patients who underwent resection, the clinical TNM classification was used if the pathological TNM stage was missing or if patients received neo-adjuvant treatment. If T or N status was missing, extent of disease, a one-digit summary stage (local, regional, metastatic) was used for staging.

Surgery refers to surgery with curative intent, defined as described above. Use of chemotherapy was presented only for patients with pancreatic ductal adenocarcinoma, because in the study period no guideline recommendations on adjuvant chemotherapy were available in the Netherlands for patients with tumours of the ampulla of Vater, distal bile duct or duodenum.

Survival data were obtained by annual crosscheck with the Municipal Personal Records Database, which contains the vital status of all Dutch inhabitants. Survival was calculated as the time from date of diagnosis to date of death, or censored when alive at the last check of vital status (1 February 2020).

Study outcomes

The main study outcome was the resection rate in patients with non-metastatic pancreatic head or periampullary carcinoma diagnosed in pancreatic surgery *versus* non-pancreatic surgery centres in 2009–2001, 2012–2014 and 2016–2017. In addition, survival in patients diagnosed in these centres over these time intervals was analysed.

Statistical analysis

Baseline characteristics are presented using descriptive statistics. Normally distributed continuous data were compared using Student's *t* test, and are presented as mean(s.d.) values. Non-normally distributed continuous data were compared with the Mann-Whitney *U* test, and are presented as median (i.q.r.) values. Categorical data are presented as frequencies with percentages, and compared using the χ^2 test.

The association between diagnosis in a pancreatic surgery *versus* non-pancreatic surgery centre and the resection rate was analysed with multivariable logistic regression models stratified per period of diagnosis and adjusted for patient characteristics (age, sex and socioeconomic status), tumour location, and cT and cN status.

Overall survival was analysed by means of Kaplan-Meier curves and compared with the log rank test. To demonstrate whether the association between non-pancreatic surgery *versus* pancreatic surgery centre and survival after centralization changed over time, multivariable Cox regression models were performed and stratified by period of diagnosis. These models were adjusted for patient characteristics, tumour location and tumour stage.

As the completeness of the NCR probably improved over the years (including more patients without pathological confirmation and elderly patients), sensitivity analyses were performed for patients with pathologically verified tumours and for those aged

Table 1 Baseline characteristics of all patients with non-metastatic pancreatic head and periampullary cancer, and stratified for diagnosis in pancreatic surgery or non-pancreatic surgery centres

	All patients (n = 10 079)	Pancreatic surgery centre (n = 3114)	Non-pancreatic surgery centre (n = 6965)	P**
Age (years)*	71 (63–79)	70 (62–77)	72 (64–80)	< 0.001††
Sex ratio (F : M)	4827 : 5252	1448 : 1666	3379 : 3586	0.061
Social economic status				< 0.001
High	3115 (30.9)	886 (28.5)	2229 (32.0)	
Medium	4084 (40.5)	1241 (39.9)	2843 (40.8)	
Low	2855 (28.3)	969 (31.1)	1886 (27.1)	
Missing	25 (0.2)	18 (0.6)	7 (0.1)	
Primary tumour location				0.460
Head of pancreas	6853 (68.0)	2091 (67.1)	4762 (68.4)	
Ampulla of Vater	1271 (12.6)	405 (13.0)	866 (12.4)	
Distal bile duct	1268 (12.6)	411 (13.2)	857 (12.3)	
Duodenum	687 (6.8)	207 (6.6)	480 (6.9)	
cT status†				0.804
cT1	1076 (10.7)	340 (10.9)	736 (10.6)	
cT2	1561 (15.5)	472 (15.2)	1089 (15.6)	
cT3	1786 (17.7)	561 (18.0)	1225 (17.6)	
cT2–3	476 (4.7)	152 (4.9)	324 (4.7)	
cT4	1698 (16.8)	504 (16.2)	1194 (17.1)	
Unknown	3482 (34.5)	1085 (34.8)	2397 (34.4)	
cN status†				0.003
cN0	6090 (60.4)	1957 (62.8)	4133 (59.3)	
cN1	1885 (18.7)	539 (17.3)	1346 (19.3)	
Unknown	2104 (20.9)	618 (19.8)	1486 (21.3)	
Pathological tumour stage††	n = 4587	n = 1641	n = 2946	0.046
I	695 (15.2)	255 (15.5)	440 (14.9)	
II	3036 (66.2)	1099 (67.0)	1937 (65.8)	
II–III	227 (4.9)	70 (4.3)	157 (5.3)	
III	474 (10.3)	151 (9.2)	323 (11.0)	
IV	126 (2.7)	57 (3.5)	69 (2.3)	
Unknown	29 (0.6)	9 (0.5)	20 (0.7)	
Tumour stage§				< 0.001
I	1892 (18.8)	524 (16.8)	1368 (19.6)	
II	4147 (41.1)	1404 (45.1)	2743 (39.4)	
II–III	841 (8.3)	222 (7.1)	619 (8.9)	
III	1595 (15.8)	479 (15.4)	1116 (16.0)	
IV	784 (7.8)	254 (8.2)	530 (7.6)	
Unknown	820 (8.1)	231 (7.4)	589 (8.5)	
Surgery				< 0.001
Resection of primary tumour	4587 (45.5)	1641 (52.7)	2946 (42.3)	
Exploration only, no resection	1213 (12.0)	392 (12.6)	821 (11.8)	
No surgery	4279 (42.5)	1081 (34.7)	3198 (45.9)	
Resection¶	n = 2423	n = 907	n = 1516	0.143
Adjuvant chemotherapy	1274 (52.6)	463 (51.0)	811 (53.5)	
Neoadjuvant chemo(radio)therapy	59 (2.4)	18 (2.0)	41 (2.7)	
Neoadjuvant and adjuvant chemo(radio)therapy	83 (3.4)	26 (2.9)	57 (3.8)	
No (neo)adjuvant therapy	1007 (41.6)	400 (44.1)	607 (40.0)	
No resection#§	n = 2339	n = 711	n = 1628	0.427
Chemotherapy	821 (35.1)	258 (36.3)	563 (34.6)	
No chemotherapy	1518 (64.9)	453 (63.7)	1065 (65.4)	
Period of diagnosis				0.407
2009–2011	3169 (31.4)	993 (31.9)	2176 (31.2)	
2012–2014	3344 (33.2)	1049 (33.7)	2295 (33.0)	
2015–2017	3566 (35.4)	1072 (34.4)	2494 (35.8)	

Values in parentheses are percentages unless indicated otherwise; * Values are median (i.q.r.). † Tumour stage according to the TNM-7 classification. ‡ Only in patients who underwent resection (n = 4587). § Tumour stage based on clinical stage for patients who did not undergo resection and pathological stage for patients who had resection. ¶ Only in patients with pancreatic ductal adenocarcinoma who underwent resection of primary tumour (n = 2423). # Only in patients with pancreatic ductal adenocarcinoma who did not have resection, thus including those who only underwent exploration (n = 2339). ** χ^2 test, except. †† Mann-Whitney U test.

below 75 years to assess whether this affected the results, and also for patients with pancreatic ductal adenocarcinoma to exclude influences of other pathological tumours (such as ampulla of Vater and duodenal cancers). The resection rate in patients with non-metastatic pancreatic head or periampullary carcinoma in pancreatic surgery versus non-pancreatic surgery centres in 2009–2001, 2012–2014 and 2016–2017 was also

analysed after multiple imputation (with predictive mean matching and creation of 30 dummy sets) for cT and cN status, because of the relatively high proportion of unknowns in these groups (34.5 and 20.9 per cent). The results were reported as odds ratios (ORs) with corresponding 95 per cent c.i. in logistic regression, and as hazard ratios (HRs) with corresponding 95 per cent c.i. in Cox regression.

Fig. 1 Absolute numbers of patients diagnosed and resected in all centres, pancreatic surgery centres and non-pancreatic surgery centres per period
a All centres; b pancreatic surgery centres; c non-pancreatic surgery centres.

Fig. 2 Resection rate in all patients, and in patients diagnosed in pancreatic and non-pancreatic surgery centres per period

P for trend: < 0.001, 0.586 and < 0.001 for all centres, pancreatic surgery centres and non-pancreatic surgery centres respectively.

All P values were based on a two-sided test, and $P < 0.050$ was considered statistically significant. Data were analysed using IBM SPSS® Statistics for Windows® version 26 (IBM, Armonk, NY, USA).

Results

Between 2009 and 2017, 10 079 patients were diagnosed with non-metastatic pancreatic head and periampullary cancer. The number of patients increased over time (3169 (31.4 per cent) in 2009–2011, 3344 (33.2 per cent) in 2012–2014, and 3566 (35.4 per cent) in 2015–2017; P for trend = 0.158), whereas the number of hospitals performing pancreatoduodenectomies decreased (2009–2011: 34 hospitals with a median of 29 (i.q.r. 5–47) PDs in 3 years; 2012–2014: 24 hospitals with 59 (42–87) PDs; 2015–2017: 18–19 hospitals with 83 (70–108) PDs). The hospital categories of 2017 were fixed for labelling of pancreatic surgery centres, regardless of time period, and used in further analysis. Patients were diagnosed in up to 78 hospitals with a median of 12 (i.q.r. 8–20) diagnoses per hospital annually. In total, 4827 patients were women (47.9 per cent) and the median age was 71 years (Table 1). Of all patients, 5800 (57.5 per cent) underwent surgery with curative intent, of whom 4587 (79.1 per cent) had resection of the primary tumour; the remaining patients underwent exploration without resection.

In total, 3114 patients (30.9 per cent) were diagnosed in a pancreatic surgery centre and 6965 (69.1 per cent) in a non-pancreatic surgery centre. In pancreatic surgery centres,

resection was performed in 1641 patients (52.7 per cent), a higher proportion than in non-pancreatic surgery centres (2946 patients, 42.3 per cent) ($P < 0.001$), with similar proportions of patients undergoing exploration (12.0 and 12.6 per cent respectively). The proportion of patients with pancreatic ductal adenocarcinoma receiving chemotherapy was comparable between the centres, both for patients who underwent resection and for those who did not (Table 1).

Treatment over time

Fig. 1a shows that the absolute number of patients diagnosed with non-metastatic pancreatic head and periampullary cancer increased from 3169 in 2009–2011 to 3566 in 2015–2017. The increase in diagnosis did not significantly differ between non-pancreatic surgery (from 2176 to 2494 respectively, 14.6 per cent increase) and pancreatic surgery (from 993 to 1072 respectively, 8.0 per cent increase) centres (P for trend = 0.249) (Fig. 1b,c). Over the three periods of diagnosis, the proportion of patients undergoing surgery (resection or exploration only) did not change significantly (55.0 versus 60.3 versus 57.2 per cent; P for trend = 0.096), whereas the proportion undergoing resection increased from 40.0 to 47.8 per cent (P for trend < 0.001) (Fig. 2). In the 2423 patients with pancreatic ductal adenocarcinoma who underwent resection, the use of neoadjuvant chemotherapy increased over the periods (from 1.5 to 11.1 per cent; P for trend < 0.001), as did treatment with adjuvant chemotherapy (from 49.6 to 58.3 per cent; P for trend = 0.001). Chemotherapy was started in 821 of 2339 patients (35.1 per cent) with pancreatic ductal adenocarcinoma who did not undergo resection, increasing from 30.5 to 40.7 per cent (P for trend < 0.001).

Resection rate in pancreatic and non-pancreatic surgery centres

The resection rate in patients diagnosed in non-pancreatic surgery centres increased between 2009–2011 and 2015–2017 (from 35.5 to 46.4 per cent; P for trend < 0.001), reaching a level being more comparable with that in pancreatic surgery centres in the most recent period (Fig. 2). In multivariable analysis, the resection rate was higher in pancreatic surgery centres in 2009–2011 (OR 1.70, 95 per cent c.i. 1.39 to 2.08; $P < 0.001$) and 2012–2014 (OR 1.49, 1.24 to 1.78; $P < 0.001$) compared with that in non-pancreatic surgery centres, but this association disappeared in 2015–2017 (OR 1.08, 0.90 to 1.28; $P = 0.422$) (Table 2). As sensitivity analyses showed similar associations (Table S1), possible incompleteness of the NCR in early

Fig. 3 Kaplan–Meier survival curves of all patients with non-metastatic pancreatic head and periampullary cancer stratified per period of diagnosis in pancreatic and non-pancreatic surgery centres

a Pancreatic surgery centres (survival unknown in 18 patients); **b** non-pancreatic surgery centres (survival unknown in 7 patients). **a** $P = 0.654$, **b** $P = 0.001$ (log rank test).

years and missing data for cT and cN status did not affect the results.

Survival in pancreatic and non-pancreatic surgery centres

Median overall survival was higher in patients diagnosed in pancreatic surgery centres than in non-pancreatic surgery centres, regardless of the period of diagnosis (Table 3). Within the three periods, median survival did not improve significantly in pancreatic surgery centres and was 11.1 (i.q.r. 10.1–12.0) months in

2009–2011, 13.0 (11.9–14.1) months in 2012–2014, and 12.6 (11.5 to 13.6) months in 2015–2017 ($P = 0.654$) (Fig. 2a). Survival did improve in non-pancreatic surgery centres: from 9.9 (9.3–10.4) to 10.3 (9.8–10.9) to 10.7 (10.1–11.4) months respectively ($P = 0.001$) (Fig. 2b).

In multivariable analysis, survival was higher in pancreatic surgery than in non-pancreatic surgery centres in 2015–2017 (HR for mortality 0.92, 95 per cent c.i. 0.85 to 0.99; $P = 0.047$) (Table 3). Sensitivity analyses showed no significant association between pancreatic surgery centre versus non-pancreatic surgery centre

Table 2 Multivariable logistic regression analysis of the association between diagnosis in a pancreatic surgery centre and pancreatic resection

	No. of patients	Resection [*]	Univariable analysis [†]		Multivariable analysis ^{†‡}	
			Odds ratio	P	Odds ratio	P
2009–2011[§]						
All	3169	1267 (40.0)				
Non-pancreatic surgery centre	2176	772 (35.5)	1.00 (reference)		1.00 (reference)	
Pancreatic surgery centre	993	495 (49.8)	1.81 (1.55, 2.11)	< 0.001	1.70 (1.39, 2.08)	< 0.001
2012–2014						
All	3344	1615 (48.3)				
Non-pancreatic surgery centre	2295	1018 (44.4)	1.00 (reference)		1.00 (reference)	
Pancreatic surgery centre	1049	597 (56.9)	1.66 (1.43, 1.92)	< 0.001	1.49 (1.24, 1.78)	< 0.001
2015–2017[#]						
All	3566	1705 (47.8)				
Non-pancreatic surgery centre	2494	1156 (46.4)	1.00 (reference)		1.00 (reference)	
Pancreatic surgery centre	1072	549 (51.2)	1.22 (1.05, 1.40)	0.008	1.08 (0.90, 1.28)	0.422

^{*} Values in parentheses are percentages. [†] 95 per cent confidence intervals. [‡] Adjusted for patient characteristics (age, sex, socioeconomic status (SES)), tumour location (pancreas versus periampullary), and cT and cN status. [§] Multivariable analysis included 3162 patients (SES unknown in 7 patients). ^{||} Multivariable analysis included 3334 patients (SES unknown in 10 patients). [#] Multivariable analysis included 3558 patients (SES unknown in 8 patients).

Table 3 Multivariable Cox regression analyses of the association between diagnosis in a pancreatic surgery centre and mortality

	No. of patients	Overall survival [*]	Univariable analysis [†]		Multivariable analysis ^{†‡}	
			Hazard ratio	P	Hazard ratio	P
2009–2011[§]						
All	3162	10.2 (9.7–10.7)				
Non-pancreatic surgery centre	2174	9.9 (9.3–10.4)	1.00 (reference)		1.00 (reference)	
Pancreatic surgery centre	988	11.1 (10.1–12.0)	0.85 (0.78, 0.92)	< 0.001	0.94 (0.87, 1.02)	0.148
2012–2014						
All	3334	10.9 (10.3–11.4)				
Non-pancreatic surgery centre	2292	10.3 (9.8–10.9)	1.00 (reference)		1.00 (reference)	
Pancreatic surgery centre	1042	13.0 (11.9–14.1)	0.90 (0.84, 0.98)	0.010	0.93 (0.86, 1.00)	0.056
2015–2017[#]						
All	3558	11.2 (10.7–11.8)				
Non-pancreatic surgery centre	2492	10.7 (10.1–11.4)	1.00 (reference)		1.00 (reference)	
Pancreatic surgery centre	1066	12.6 (11.5–13.6)	0.90 (0.83, 0.97)	0.008	0.92 (0.85, 0.99)	0.047

^{*} Values are median (i.q.r.); [†] Values in parentheses are 95 per cent confidence intervals. [‡] Adjusted for patient characteristics (age, sex, socioeconomic status (SES)), tumour location (pancreas versus periampullary), and tumour stage. [§] Analysis of 3162 patients (survival status and SES unknown in 7 patients). ^{||} Analysis of 3334 patients (survival status and SES unknown in 10 patients). [#] Analysis of 3558 patients (survival status and SES unknown in 8 patients).

and survival in 2015–2017, in patients with pathologically verified tumours, patients under 75 years only, and patients with pancreatic ductal adenocarcinoma (Table S2).

Discussion

This population-based observational cohort study has shown that the resection rate for pancreatic head and periampullary cancer became similar for patients diagnosed in pancreatic and non-pancreatic surgery centres during centralization (2015–2017). Nevertheless, overall survival of all patients diagnosed in pancreatic surgery centres remained superior compared with that in patients diagnosed in non-pancreatic surgery centres in 2015–2017.

Over the study period, the rate of primary tumour resections in patients who underwent surgery increased, indicating an improved selection of patients being eligible for surgery and efficient referral patterns. This could be explained by centralization and regionalization¹⁸. The use of better diagnostic modalities with high-quality imaging and standardization of radiological image reporting within the DPCG could have contributed to increased identification of patients with metastatic pancreatic

head and periampullary cancer before surgery¹⁹. As the surgery rate was constant, it seems that more patients with (borderline) resectable and locally advanced tumours underwent resection due to more extended resections, venous resections, and improved surgical techniques. Consequently, the proportion of patients who had exploration only decreased over time. Unfortunately, the data were insufficient to identify patients with locally advanced tumours accurately. Although additional analyses could not be performed for this subgroup, it is well established that resection rates in these patients have increased since the introduction of neoadjuvant administration of FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin)^{20,21}.

Since the introduction of the minimum annual volume of 20 pancreatoduodenectomies per centre in 2011, centralization of pancreatic surgery has been ongoing in the Netherlands. The DPCG offered a nationwide framework to optimize centralization. As a result, in 2012–2014, a temporarily slightly higher rate of surgery was seen, as centres below the minimum volume stopped performing pancreatic surgery^{11,22}. Following the introduction of the volume standard, regionalization of pancreatic and periampullary cancer care in general occurred, which is important as most patients (69.1 per cent) are diagnosed in

non-pancreatic surgery centres. By 2017, 10 regional networks for hepatopancreatobiliary cancers were present in the Netherlands, each containing one or more pancreatic surgery centres and several non-pancreatic surgery centres, respectively named hubs and spokes, according to the so-called hub-and-spoke model^{23–25}. Regionalization consists of regional collaboration including improved referral patterns and interhospital multidisciplinary team meetings, and knowledge dissemination. Consequently, by 2015–2017 the resection rate in patients from non-pancreatic surgery centres increased and became similar to that in pancreatic surgery centres. This increase was caused mainly by an increased resection rate in patients considered to have unresectable disease during the earlier periods in non-pancreatic surgery centres (for instance, locally advanced pancreatic cancer). This may have been related to improved interhospital contact and subsequent increased referral of these patients to pancreatic surgery centres.

It was hypothesized that survival would be similar for non-pancreatic and pancreatic surgery centres, because of equalized odds for resection based on improved referral patterns. Survival, however, remained higher in pancreatic surgery centres in 2015–2017, even after adjustment for possible confounders. The absolute difference in survival was only 1.9 months, and the clinical relevance of this could be debated. The increased survival may be due to differences in other factors within pancreatic and periampullary cancer care: the implementation of more effective chemotherapies (such as (neo)adjuvant FOLFIRINOX), pancreatic enzyme supplementation, palliative care services, and endoscopic biliary drainage in pancreatic surgery centres²⁶. It is known that the rate of receiving adjuvant chemotherapy is highly variable between pancreatic surgery centres²⁷. In the Netherlands, patients are often referred back to their hospital of diagnosis to receive adjuvant chemotherapy or palliative care, taking into account the patient's preference and hospital characteristics. It was outside the scope of this study to analyse the effects of these referral patterns on survival, but this phenomenon could be an explanation for the observed differences. As the effect on survival was not shown in the sensitivity analysis for pancreatic ductal adenocarcinoma only, the above-mentioned factors were probably more affected in patients with periampullary carcinoma. Increased regionalization could further strengthen trial participation and equalize implementation of new or current treatment strategies, as these often arise from clinical trials²³. It could also be suggested that patients might receive better and faster diagnosis in a pancreatic surgery centre because of a well designed pancreatic and periampullary cancer infrastructure. This could lead to earlier initiation of treatment, resulting in improved patient outcomes. The differences in survival demonstrate that regionalization should be further improved. A step towards this improvement could be obtained via the nationwide PACAP-1 trial (NCT03513705) which aimed to enhance implementation of best practices in pancreatic cancer care²⁸. Results from this nationwide stepped-wedge cluster randomized trial are not yet available, but the trial operated within pancreatic cancer networks and implemented several best practices (regarding chemotherapy, exocrine pancreatic insufficiency, and biliary drainage) with the aim of equalizing and improving patient outcomes throughout the Netherlands.

This study had several limitations. First, exact reasons for referral or refraining from referral for individual patients were unknown. Future studies should obtain these data in order to improve referral patterns and current outcomes. Second, the completeness of the NCR may have been improved in more recent years because of improved notification methods, especially

for patients without pathological confirmation, elderly patients, and patients with a short survival²⁹. However, this effect is probably limited, because untreated patients who died within 30 days after diagnosis were excluded and sensitivity analyses showed similar associations between centre of diagnosis and the resection rate for patients with pathologically verified tumours and those aged under 75 years. Despite increasing completeness, a relatively large group of patients had an unknown cT and cN status, which also did not affect the outcome in a sensitivity analysis after imputation of these variables. Third, some important factors in decision-making for resection, such as multidisciplinary team meetings, WHO performance status, and reason for no treatment (for example, patient preference), were not registered during the majority of the study period. Fourth, identification of patients with locally advanced pancreatic cancer became possible from 2016, and should be investigated separately in future studies. In the present study, it was assumed that patients with locally advanced disease were diagnosed equally in pancreatic and non-pancreatic surgery centres.

In conclusion, after centralization and regionalization in the Netherlands, the resection rate of primary tumours improved in patients first diagnosed in non-pancreatic surgery centres and is now similar to that in patients diagnosed in centres performing pancreatic surgery. Survival remained superior in pancreatic surgery centres. These findings suggest that centralization and regionalization improved care for pancreatic head and periampullary cancer patients but that further improvement of existing regional networks is required as this could further improve patient outcomes.

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Supplementary material

Supplementary material is available at BJS online.

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