

ORIGINAL ARTICLE

Impact of centralization of pancreatoduodenectomy on reported radical resections rates in a nationwide pathology database

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Abstract

Background: Centralization of a pancreatoduodenectomy (PD) leads to a lower post-operative mortality, but is unclear whether it also leads to improved radical (R0) or overall resection rates.

Methods: Between 2004 and 2009, pathology reports of 1736 PDs for pancreatic and peri-ampullary neoplasms from a nationwide pathology database were analysed. Pre-malignant lesions were excluded. High-volume hospitals were defined as performing ≥ 20 PDs annually. The relationship between R0 resections, PD-volume trends, quality of pathology reports and hospital volume was analysed.

Results: During the study period, the number of hospitals performing PDs decreased from 39 to 23. High-volume hospitals reported more R0 resections in the pancreatic head and distal bile duct tumours than low-volume hospitals (60% versus 54%, $P = 0.035$) although they operated on more advanced (T3/T4) tumours (72% versus 58%, $P < 0.001$). The number of PDs increased from 258 in 2004 to 394 in 2009 which was partly explained by increased overall resection rates of pancreatic head and distal bile duct tumours (11.2% in 2004 versus 17.5% in 2009, $P < 0.001$). The overall reported R0 resection rate of pancreatic head and distal bile duct tumours increased (6% in 2004 versus 11% in 2009, $P < 0.001$). Pathology reports of low-volume hospitals lacked more data including tumour stage (25% versus 15%, $P < 0.001$).

Conclusions: Centralization of PD was associated with both higher resection rates and more reported R0 resections. The impact of this finding on overall survival should be further assessed.

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Introduction

Pancreatic adenocarcinoma is the fourth cause of cancer mortality worldwide with nearly 37 000 deaths annually in the

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United States and 78 000 deaths in the European Union.¹ As a result of the late occurrence of symptoms and the aggressive tumour biology, less than 20% of patients are suitable candidates for curative surgery.¹ The median survival after an R0 resection in these patients is 22 months whereas the survival for non-resectable patients is only 14 months.²

A number of studies have outlined the relationship between hospital volume, post-operative mortality, and survival for patients undergoing surgery for pancreatic and peri-ampullary neoplasms.^{3–12} It has been postulated that both short- and long-term improvements in the outcome of a pancreatic resection are mainly as a result of improvements in the quality of

surgery and peri-operative care.⁷ In patients with pancreatic ductal adenocarcinoma (PDAC), the ratio of nodal involvement and, to a somewhat lesser extent, the negative resection margin (R0) are the most important prognostic factors for long-term survival. It has been suggested that high-volume hospitals achieve more R0 resections but data are lacking.^{13–15} Some have suggested that supporting specialities, such as pathology, may also be of better quality in high-volume hospitals¹⁶ but evidence is lacking.

In the Netherlands, a recent nationwide guideline led to the implementation of a minimum volume of 20 annual procedures for high-risk surgery such as a pancreatoduodenectomy (PD). A recent analysis demonstrated that in the period 2005 to 2009 centralization occurred in the Netherlands, which resulted in a decreased post-operative mortality from 9.8% to 5.1%.⁵ Two additional studies showed that both in the south and the west of the Netherlands, centralization was associated with an increased 2-year survival.^{7,8} It is unknown which factors have contributed to the increased survival after the centralization of PD. Does detection bias play a role, or is the surgical technique somehow improved, leading to an increase in radical (R0) resections?

The aim of the present work was to analyse the impact of centralization of PD in the period 2004–2009 in the Netherlands on resection rates and reported R0 resections of pancreatic and peri-ampullary neoplasms and the quality of pathology reports.

Methods

The summaries of the pathology reports of all the PDs carried out in the Netherlands between 2004 and 2009 (6 years) were obtained from the Dutch nationwide pathology database (PALGA).¹⁷ After 2009, these data were no longer collected for all hospitals by PALGA. Only patients who underwent a PD for pancreatic head or a peri-ampullary neoplasm [including pancreatic, cholangio, ampullary and duodenum adenocarcinoma, neuroendocrine tumours, malignant intraductal papillary mucinous neoplasm (IPMN) and mucinous cystadenocarcinoma] were included. PDs carried out for benign or pre-malignant disease, metastases to the pancreas and peri-ampullary region (such as renal cell carcinoma) or (auto-immune) pancreatitis, total pancreatectomies and left-sided pancreatectomies, or reports which did not mention the tumour type nor the type of surgery were excluded. Finally, data on the number of pancreas, ampulla, duodenum and distal bile duct tumours in the Netherlands for the period 2004–2009 were collected from the Netherlands Cancer Registry managed by the Comprehensive Cancer Centre Netherlands (CCCNL).¹⁸

Variables

The following variables were recorded for each entry: age, gender, year of surgery, hospital volume, radicality of the

resection, tumour size, histological type, pTN status, tumour differentiation, ingrowth in surrounding organs and the number of resected lymph nodes. If the pTN status was not stated in the report, it was classified according to the AJCC criteria, 7th edition¹⁹ but only if enough information, such as ingrowth in surrounding organs and/or tumour size was available.

If a report presented two different malignant tumours, the one described as a chance finding was excluded. If a malignant and a benign tumour were reported on the same specimen, the malignant tumour was recorded.

The quality of the pathology reports was assessed by measuring the percentage of missing data, such as the pTN status, tumour diameter, differentiation and radicality of the resection in the summaries of the pathology reports.

During this study period, neoadjuvant treatment (chemotherapy or chemoradiotherapy) was used in less than 1% of patients.

Definitions

The PD volume of each hospital was assessed per year; centres with ≥ 20 PDs per year were defined as high-volume hospitals.⁵ The old definition of resection margins were used as that was the definition during the study period. According to the old definition an R0 resection is the absence of cancer cells in the pancreatic or circumferential resection margin, and an R1 is the presence of microscopic tumour invasion at the resection margin. If there was any doubt as to the radicality of the excision or if this was not stated in the report an unknown resection margin was recorded. Reports using the new definition were removed.

Tumours were divided according to histological type. Carcinomas *in situ*, and adenomas or neoplasms with high-grade dysplasia (which were defined as carcinoma *in situ*), IPMNs (without invasive growth) and low-grade or moderate dysplasia, pseudo-papillary tumours, and mucinous cystadenomas were considered to be premalignant. All neuroendocrine tumours, indifferent of grade were (arbitrarily) included in the malignant tumour group. If the histological type was not named, but the description was that of a malignant tumour, this was marked as unknown. Specimens with unknown histological type were only included in the calculations of the trends.

For data analysis, the various histology types of malignant tumours were pooled according to the anatomic origin of the tumour: pancreatic head, peri-ampullary and distal bile duct tumours. Pancreatic head tumours included pancreatic adenocarcinoma, invasive IPMN's and neuroendocrine tumours of the pancreatic head. Peri-ampullary tumours included all papilla and duodenum tumours, such as adenocarcinomas, neuro-endocrine tumours and any remaining histological types such as sarcomas and lymphomas. Distal bile duct tumours included adenocarcinomas and neuro-endocrine tumours of the distal bile ducts. Pancreatic head tumours were analysed

together with distal bile duct tumours. This was based on the assumption that when distal bile duct tumours invade the pancreas it is often difficult to assess the origin of the primary tumour (i.e. the pancreas or in the distal bile duct) and as a result of this patients will often undergo similar surgical procedures.

The pT stage was pooled for all further analysis into four categories: high stage, low stage, unknown stage (Tx) and NA (not applicable). The high stage included all T3/T4 tumours, the low stage included all T1/T2s tumours and NA included several tumours for which no pTNM staging system was available, such as lymphomas and gastro-intestinal stroma cell tumours (GIST).

The differentiation of malignant tumours was graded as poor, moderate, well and unknown. If more than one differentiation degree was stated in the report (i.e. a well to moderately differentiated tumour), the worst differentiation degree was registered.

Statistical analysis

Continuous non-normally distributed variables were compared using the Mann–Whitney *U*-test while normally distributed variables were compared using the *t*-test. Categorical variables were compared with the Chi-squared test. Resectability rates were calculated by dividing the total number of PDs (R0, R1/R2 and unknown resection margins) by the total number of tumours per anatomic localization per year as provided by the Comprehensive Cancer Centre The Netherlands (CCCNL). R0 resectability rates were calculated by dividing the number of R0 resection margins by the total number of tumours per anatomic localization per year. In order to analyse any changes throughout the study period, the difference between the total and R0 resection rates in 2004 and 2009 were calculated. This was achieved by applying the *Z*-test for the difference between two percentage means. A two-tailed *P*-value of < 0.05 was considered statistically significant. All calculations were carried out in IBM SPSS Statistics (version 16.0, SPSS Inc, Chicago, IL, USA).

Results

A total of 2180 pathology reports were obtained, out of which 444 (20%) reports were excluded for the following reasons: 81 premalignant tumours (4%), 174 pancreatitis (8%), 65 benign tumours (3%), 26 reports in which no histological abnormalities were observed (0.01%), 19 metastases (0.9%), 13 pancreatic tail tumours (0.6%), 2 gallbladder carcinomas (0.09%), 4 reports that did not mention the tumour type or type of surgery (0.2%), 60 reports (3%) that stated the resection margin only according to the new definition, thus leaving a total of 1736 pathology reports for analysis.

Centralization and trends

During the study period, centralization of pancreatic surgery occurred: the number of hospitals performing PDs decreased from 39 to 23 (out of a total of 95 hospitals in the Netherlands; 16.7 million inhabitants), whereas the number of high-volume hospitals increased from 3 to 9. The total volume of PDs for malignant tumours increased from [250 in 2004 to 389 in 2009 (56% relative increase)]. According to data from CCCNL, this increase is partly explained by increased overall resection rates of pancreatic head and distal bile duct tumours (11.2% in 2004 versus 17.5% in 2009, $P < 0.001$). During this period, the overall reported R0 resection rate also increased from 6.3% in 2004 to 10.5% in 2009, $P < 0.001$ (Fig. 1).

Comparison of patient and tumour characteristics by hospital volume are shown in Tables 1 and 2.

High-volume hospitals reported to resect more lymph nodes per procedure [median (IQR, interquartile range): 10 (6.00–14.00) versus 7 (4.00–11.00), $P < 0.001$]. High-volume hospitals operated on significantly more N1 cancers than low-volume hospitals (Table 1). This was due to more N1 pancreatic head and distal bile duct tumours (61.2% versus 52.2%, $P = 0.002$), but not in peri-ampullary tumours.

The resection margin status by hospital type and tumour subtype are shown in Table 3.

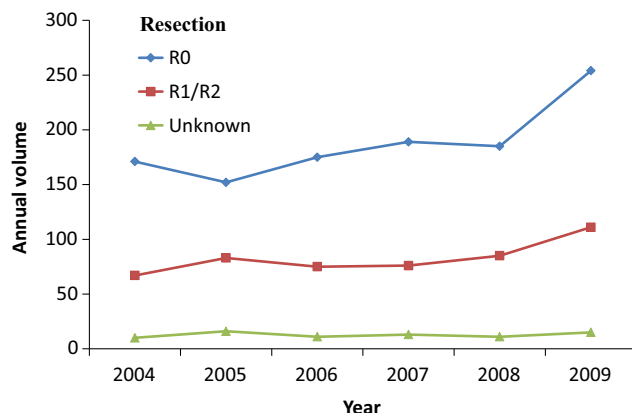


Figure 1 Annual trends in volume of pancreatoduodenectomy in all malignant tumors per resection margin in the Netherlands (2004–2009)

Table 1 Characteristics of pancreatoduodenectomies (2004–2009) for malignant tumours

	High-volume (N = 747)	Low-volume (N = 989)	P-value
Age, mean (SD)	64.3 (10.39)	64.4 (9.6)	0.831
Gender, male (%)	435 (58.1)	596 (60.1)	0.386
Pancreatic and distal bile duct tumours, number (%)	500 (66.9)	653 (66.0)	0.653
Peri-ampullary tumours, number (%)	229 (30.7)	317 (32.1)	0.535
Unknown tumour type, number (%)	18 (2.4)	19 (1.90)	0.485
T1/T2, number (%)	144 (19.3)	203 (20.5)	0.519
T3/T4, number (%)	491 (65.7)	538 (54.4)	<0.001
Unknown pT Stage, number (%)	111 (14.9)	245 (24.8)	<0.001
Not applicable, number (%)	1 (0.1)	3 (0.3)	0.466
N0, number (%)	302 (40.4)	450 (45.5)	0.038
N1, number (%)	424 (56.8)	471 (47.6)	<0.001
Unknown pN Stage, number (%)	21 (2.8)	68 (6.9)	<0.001
R0, number (%)	512 (68.5)	641 (64.8)	0.103
R1/R2, number (%)	208 (27.8)	297 (30.0)	0.343
Unknown resection margin, number (%)	27 (3.6)	51 (5.2)	0.125
Poorly differentiated, number (%)	235 (31.5)	243 (24.6)	0.001
Moderately differentiated, number (%)	307 (41.1)	470 (47.5)	0.008
Well differentiated, number (%)	73 (9.8)	114 (11.5)	0.243
Unknown, number (%)	132 (17.7)	162 (16.4)	0.478

The frequency of missing data from pathology reports by hospital type is shown in Table 4.

Discussion

This study has shown that during a period where centralization of pancreatic surgery took place both the overall and reported R0 resection rates of pancreatic head and distal bile duct tumours increased. High-volume hospitals more frequently reported R0 resections in tumours of the pancreatic head and distal bile duct, even although they operated on more advanced (T3/T4) tumours. Additionally, high-volume hospitals reported more resected lymph nodes and the pathology reports were less often incomplete.

These findings are probably best explained by the additional surgical expertise in high-volume hospitals, despite operating on more advanced cancers. With additional experience, sur-

Table 2 Tumour stage and differentiation in subtypes of malignant tumours

Tumour stage in subtypes of malignant tumours			
Pancreatic head and distal bile duct tumours	High-volume (N = 500)	Low-volume (N = 653)	P-value
High stage, number (%)	360 (72.0)	380 (58.2)	<0.001
Low stage, number (%)	49 (9.8)	82 (12.6)	0.
Unknown pT Stage, number (%)	90 (18.0)	190 (29.1)	<0.001
NA, number (%)	1 (0.2)	1 (0.2)	0.850
Peri-ampullary tumours			
High-volume (N = 229)	Low-volume (N = 317)	P-value	
High stage, number (%)	123 (53.7)	153 (48.3)	0.209
Low stage, number (%)	95 (41.5)	118 (37.2)	0.144
Unknown pT stage, number (%)	11 (4.8)	44 (13.9)	0.001
NA, number (%)	0 (0)	2 (0.6)	0.229
Tumour differentiation in all subtypes of malignant tumours			
Pancreatic head and distal bile duct tumours	High-volume (N = 500)	Low-volume (N = 653)	P-value
Poorly differentiated, number (%)	173 (34.6)	163 (25.0)	<0.001
Moderately differentiated, number (%)	186 (37.2)	308 (47.2)	0.001
Well differentiated, number (%)	46 (9.2)	85 (13.0)	0.043
Unknown differentiation, number (%)	95 (19.0)	97 (14.9)	0.061
Peri-ampullary tumours			
High-volume (N = 229)	Low-volume (N = 317)	P-value	
Poorly differentiated, number (%)	56 (24.5)	76 (24.0)	0.897
Moderately differentiated, number (%)	112 (48.9)	152 (47.2)	0.825
Well differentiated, number (%)	25 (10.9)	29 (9.1)	0.494
Unknown differentiation, number (%)	36 (15.7)	60 (18.9)	0.331

NA, not applicable.

geons can resect more tumours and possibly also achieve higher R0 resection rates. It has previously been shown that high-volume hospitals are more likely to resect tumours in pancreatic cancer.^{20–22} Additionally, Michalski *et al.*¹⁶ showed that 42% of the patients who were given an initial diagnosis of unresectability as a result of venous involvement in lower volume hospitals were resected at a large tertiary referral centre with a 55% R0 resection rate. This phenomenon probably also occurred in the Netherlands. Because the pathology reports in the current study provided too little information no trends in portomesenteric vein resections could be performed.

Table 3 Resection margins for subtypes of malignant tumours

Pancreatic head and distal bile duct tumours	High-volume (N = 500)	Low-volume (N = 653)	P-value
R0, number (%)	299 (59.8)	350 (53.6)	0.035
R1/R2, number (%)	183 (36.6)	268 (41.0)	0.126
Unknown R margin, number (%)	18 (3.6)	35 (5.4)	0.157
Peri-ampullary	High-volume (N = 229)	Low-volume (N = 317)	P-value
R0, number (%)	200 (87.3)	277 (87.4)	0.987
R1/R2, number (%)	20 (8.7)	26 (8.2)	0.825
Unknown R margin, number (%)	9 (3.9)	14 (4.4)	0.780

In the present study, high-volume hospitals did not report more R0 resections in peri-ampullary tumours. Peri-ampullary tumours usually present at an earlier stage and are less bulky than pancreatic head tumours. It might, therefore, be easier to remove radically them than it is to remove pancreatic head tumours. This is reflected in the higher percentage of R0 resections in papilla and duodenum, as compared with pancreatic head and distal bile duct tumours, respectively, 82–100%,^{23–27} 46–90%,^{25,27} 41–88%^{24,25,27,28} and 22–80%.^{24,25,27,29} It should be taken in to account that the reported R0 resection rate in the present study is clearly influenced by the (old) definition used, not requiring a 1-mm-free margin.

Lastly, in this study most of the distal bile duct tumours were either a T3/T4 or an unknown stage, therefore, pancreatic head and distal bile duct tumours were analysed as one group. This was based on the assumption that when distal bile duct tumours invade the pancreas it is often difficult to assess the origin of the primary tumour (i.e. the pancreas or in the distal bile duct) and therefore patients will often undergo similar surgical procedures.

The effect of centralization on the reported R0 resection rates has been scarcely analysed: a recent systematic review¹⁰ has shown that institutions with a minimum of 12 PDs per year achieve higher R0 rates in pancreatic adenocarcinoma

than in centres with lower volumes. This study did, however, not assess overall resection rates. The achievement of an R0 resection margin is one of the most important prognostic factors in the treatment of pancreatic head tumours,^{13–15} thus the current results suggest that patients treated in high-volume hospitals may have a better long-term survival in patients with pancreatic head tumours than those treated in low-volume hospitals. This is confirmed by two recent studies^{8,11} that showed that centralization improves the 2- and 3-year survival after surgery for pancreatic head tumours.

This study does not show any improvement in the resection rates of peri-ampullary tumours. To the author's knowledge, no other study has analysed the effect of PD volume on the achievement of R0 resections of peri-ampullary tumours. One study, however, has shown that centralization improves the 2-year survival after surgery in peri-ampullary tumours.⁹ Besides a negative resection margin,^{26,27,30} other quoted prognostic factors include: lymph node invasion,^{23,24,27,30} the use of adjuvant chemotherapy,²⁸ tumour recurrence²⁴ and histopathological factors, such as invasion in the pancreas,²³ poor differentiation²⁸ and perineural invasion.¹⁵ Birkmeyer *et al.*¹² showed that patients undergoing pancreatic surgery at high-volume hospitals were more likely to have pre-operative stress tests, invasive peri-operative monitoring and consultation with medical or radiation oncologists compared with patients in low-volume hospitals. Previous studies also showed that high-volume hospitals were more likely to apply multi-modality therapy in pancreatic adenocarcinoma.^{21–23} It is, therefore, possible that the better supportive care and the use of adjuvant chemotherapy may play a role in the improvement of the long-term prognosis of peri-ampullary as pancreatic head tumours in high-volume institutions.

The present study also shows that pathologist in high-volume hospitals report more lymph nodes during a PD than low-volume institutions do and that pathology reports in low-volume institutions lack essential data, such as the pT-, pN stage and tumour diameter. The optimal histopathological staging of regional lymph nodes for pancreatic and ampullary cancer should include at least 10 lymph nodes, for distal bile duct tumours this number is 3.¹⁴ Previous literature has suggested that the analysis of more lymph nodes is an independent prognostic factor in the long-term survival.^{31–34} Two randomized controlled trials^{29,35} have shown that extended retroperitoneal lymphadenectomy does not prolong survival but

Table 4 Missing data in pathology reports for all malignant tumours

	High-volume (N = 747)	Low-volume (N = 989)	Total (N = 1736)	P-value
Unknown R margin, number (%)	19 (2.5)	29 (2.9)	48 (2.8)	0.625
Unknown pT stage, number (%)	111 (14.9)	245 (24.8)	356 (20.5)	<0.001
Unknown diameter, number (%)	128 (17.1)	254 (25.7)	382 (22.0)	<0.001
Unknown differentiation, number (%)	132 (17.2)	163 (16.2)	295 (16.6)	0.596
Unknown pN stage, number (%)	21 (2.8)	68 (6.9)	89 (5.1)	<0.001

increases morbidity. It is unclear whether the higher mean number of lymph nodes detected per PD in high-volume hospitals reflects better surgical or better pathology techniques in these hospitals (or both): surgeons potentially remove more lymph nodes per procedure and pathologists potentially identify more lymph nodes in resection specimens.

This does also reflect the importance of 'high-volume pancreatic pathologists'. It is unlikely that pathologists will gain sufficient experience when they only occasionally assess a pancreatoduodenectomy specimen. One suggested solution to this is central reviewing of pathology samples from several hospitals as in this way experience can be bundled and expertise obtained.

The results of this study should be interpreted in light of some limitations, which are mainly the high percentage of missing data in the pathology reports, such as tumour stage (20%) and size (23%). The distribution of the data was also skewed: there are more missing data for tumour stage and size in low- than in high-volume hospitals (25% versus 15%, $P < 0.001$ and 26% versus 17%, $P < 0.001$, respectively). Importantly, a recent study³⁶ has shown that owing to an improved, standardized pathological staging system the R1 resection rate increased from 14% to 76%, suggesting that an improvement in experience leads to the detection of more positive resection margins. Additionally, the Leeds protocol³⁷ that includes multi-colour margin staining, axial slicing and extensive tissue sampling also improves the reporting of R1 resection margins. It is, therefore, possible that some of the observed differences in the resection rates of high and low-volume hospitals may be in fact be underestimated. This study underlines the importance of centralization of pancreatic surgery: it improves not only surgical expertise but also that of supporting specializations.

Another limitation of this study is the lack of correlation with post-operative mortality and survival data. However, multiple previous Dutch studies have already shown that throughout the same period (2005–2009) post-operative mortality decreased (from 9.8% to 5.1%) whereas the 2-year survival increased.^{7,8}

In conclusion, in a period where centralization of pancreatic surgery occurred, the annual volume of PDs carried out for malignant tumours in the Netherlands increased by 56%. This is largely explained by higher resection rates. Although high-volume hospitals operated on more advanced and poorly differentiated pancreatic tumours, they reported more R0 resections in tumours of the pancreatic head. The exact impact of this finding on overall survival should be assessed in future studies. Finally, pathology reports of low-volume hospitals more often lacked essential data. Thus pathology reports should be standardized in order to minimize missing data.

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Conflicts of interest

None declared.

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