Original article

Hospital of diagnosis and likelihood of surgical treatment for pancreatic cancer

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Background: **Surgical resection for pancreatic cancer offers the only chance of cure. Assessment of the resectability of a pancreatic tumour is therefore of great importance. The aim of the study was to investigate whether centre of diagnosis influences the likelihood of surgery and whether this affects long-term survival.**

Methods: **Patients diagnosed with non-metastasized pancreatic cancer (M0) between 2005 and 2013 in the Netherlands were selected from the Netherlands Cancer Registry. Hospitals were classified as a pancreatic centre (at least 20 resections/year) or a non-pancreatic centre (fewer than 20 resections/year). The relationship between centre of diagnosis and likelihood of surgery was analysed by multivariable logistic regression. Influence of centre on overall survival was assessed by means of multivariable Cox regression analysis.**

Results: **Some 8141 patients were diagnosed with non-metastasized pancreatic cancer, of whom 3123 (38·4 per cent) underwent surgery. Of the 2712 patients diagnosed in one of 19 pancreatic centres, 52·4 per cent had exploratory laparotomy compared with 31·4 per cent of 5429 patients diagnosed in one of 74 non-pancreatic centres ($P < 0·001$). A pancreatectomy was performed in 42·8 and 24·6 per cent of the patients respectively ($P < 0·001$). Multivariable analysis revealed that patients diagnosed in a pancreatic centre had a higher chance of undergoing surgery (odds ratio 2·21, 95 per cent c.i. 1·98 to 2·47). Centre of diagnosis was not associated with improved long-term survival (hazard ratio 0·95, 95 per cent c.i. 0·91 to 1·00).**

Conclusion: **Patients with non-metastasized pancreatic cancer had a greater likelihood of having surgical treatment when the diagnosis was established in a pancreatic centre.**

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Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in Europe and the USA, and is known for its poor long-term survival[1]. Some 40 per cent of patients present with metastatic disease at the time of diagnosis[2,3]. Surgery offers the only chance of cure in patients presenting without distant metastases. Usually this involves a pancreatoduodenectomy, a procedure associated with a high morbidity rate[1].

Centralization of pancreatoduodenectomy in high-volume centres (at least 20 resections/year) has significantly reduced postoperative mortality and morbidity[4,5]. However, the diagnostic and staging processes in patients with a pancreatic tumour have not yet been centralized.

According to the Dutch guidelines for pancreatic cancer[6], all newly diagnosed patients with pancreatic cancer should be discussed in a multidisciplinary tumour board meeting in the hospital of diagnosis. Given that surgical and non-surgical treatments are becoming increasingly complex and limited mainly to specialized centres, the treatment being offered might reflect the experience of the multidisciplinary tumour board with pancreatic cancer surgery. This could especially be true in the current era of portal vein resections and neoadjuvant treatment strategies[7]. This study assessed whether the likelihood of surgical treatment is influenced by the presence of pancreatic cancer surgery in the centre of diagnosis and whether this affects long-term survival.

Methods

Patients with a clinical or histological diagnosis of pancreatic cancer (C25)[8], between 1 January 2005 and 31 December 2013 in the Netherlands were selected from the Netherlands Cancer Registry (NCR). The NCR collects data for all newly diagnosed patients with cancer in 93 hospitals in the Netherlands, comprising approximately 16·7 million inhabitants in 2013. Specially trained registry administrators routinely extract diagnostic and treatment variables from the medical records (hospital of initial diagnosis, date of diagnosis, age, sex, histology, TNM stage, treatment, hospital of treatment and survival). Data essential for the present analysis were collected after 1 January 2005. Data on centre of diagnosis and treatments were complete.

Tumour stage and histology

The TNM sixth (2005–2009)[9] and seventh (2010–2013)[10] editions or Clinical Extent of Disease (CEoD) were used for tumour staging. CEoD was established by combining clinical and radiological findings (abdominal ultrasonography or CT)[11]. Only patients without distant metastases were included in the study. Patients were grouped by TNM stage as TNM I, II, III, II/III or TN unknown. If T or N status was missing, CEoD was used for staging. CEoD classification 2 was categorized as TNM I, and CEoD 4 as TNM III. CEoD stages 3 and 5 represent tumours growing outside the pancreas but, as information on vascular involvement is missing in CEoD, these tumours were categorized as TNM II/III. Tumours with missing T or N status and missing CEoD were categorized as TN unknown.

Tumours were analysed in two groups based on tumour histology: neuroendocrine tumours (NETs) and all other pancreatic cancers (carcinoma group).

Treatments

Patients were classified into three groups according to treatment: surgery with curative intent, including pancreatoduodenectomy, pancreatic body resection or distal pancreatectomy; palliative chemotherapy; and no surgery or chemotherapy.

Centres

Centre of initial diagnosis was defined as the hospital in which the clinical diagnosis of pancreatic cancer was first made, even in the absence of pathological confirmation. Based on the number of pancreatic resections for cancer dictated by the Dutch inspectorate for healthcare, hospitals were classified as either a pancreatic centre (20 or more resections/year) or a non-pancreatic centre (fewer than 20 resections/year).

Statistical analysis

Patient and tumour characteristics were compared between pancreatic and non-pancreatic centres using χ^2 tests. The relationship between centre of diagnosis and the likelihood of surgery was investigated by multivariable logistic regression analysis. Other variables included in this analysis were: sex, age at diagnosis, interval of diagnosis, morphology and tumour stage. The results are reported as odds ratios (ORs) with 95 per cent c.i.

The influence of hospital of diagnosis on overall survival was assessed using Kaplan–Meier analysis and multivariable Cox regression. In the regression analysis, adjustments were made for sex, age at diagnosis, interval of diagnosis, tumour stage and treatment. Overall survival was calculated using data retrieved from the Municipal Personal Records Database. This database records all deaths or emigrations in the Netherlands. Survival time was defined as the interval between diagnosis and death, or until 1 January 2015 for patients who were still alive. Patients lost to follow-up or still alive on 1 January 2015 were censored. The results are reported as hazard ratios (HRs) with 95 per cent c.i. NETs were excluded from the survival analysis because of their favourable survival compared with pancreatic carcinoma.

All analyses were performed using SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA). $P < 0{\cdot}050$ was considered statistically significant.

Results

Between 2005 and 2013, 18 733 patients were diagnosed with pancreatic cancer, including 9958 patients with

Table 1 Characteristics of 8141 patients with M0 pancreatic cancer diagnosed between 2005 and 2013 in the Netherlands according to hospital of diagnosis

	All patients ($n = 8141$)	Pancreatic centre ($n = 2712$)	Non-pancreatic centre ($n = 5429$)	P*
Age (years)				< 0·001
< 60	1517 (18·6)	663 (24·5)	854 (15·7)	
60–69	2149 (26·4)	801 (29·5)	1348 (24·8)	
70–79	2624 (32·2)	820 (30·2)	1804 (33·2)	
≥ 80	1851 (22·7)	428 (15·8)	1423 (26·2)	
Sex ratio (M : F)	3938 : 4203	1367 : 1345	2571 : 2858	0·010
Interval of diagnosis				0·046
2005–2007	2387 (29·3)	840 (31·0)	1547 (28·5)	
2008–2010	2791 (34·3)	892 (32·9)	1899 (35·0)	
2011–2013	2963 (36·4)	980 (36·1)	1983 (36·5)	
Histology				< 0·001
Carcinoma	7739 (95·1)	2500 (92·2)	5239 (96·5)	
Neuroendocrine tumour	402 (4·9)	212 (7·8)	190 (3·5)	
Tumour stage (TNM)				< 0·001
I	2961 (36·4)	1019 (37·6)	1942 (35·8)	
II	2335 (28·7)	806 (29·7)	1529 (28·2)	
III	1596 (19·6)	602 (22·2)	994 (18·3)	
II/III	1047 (12·9)	236 (8·7)	811 (14·9)	
TN unknown	202 (2·5)	49 (1·8)	153 (2·8)	
Treatment				< 0·001
No surgery or chemotherapy	4782 (58·7)	1287 (47·5)	3495 (64·4)	
Palliative chemotherapy	862 (10·6)	265 (9·8)	597 (11·0)	
Surgery with curative intent	2497 (30·7)	1160 (42·8)	1337 (24·6)	

Values in parentheses are percentages. *χ^2 test.

metastatic disease and 634 patients for whom it was uncertain whether metastatic disease was present at the time of diagnosis. In total, 8141 patients (43·5 per cent) had no signs of metastasis, and these were included in the present study. Pancreatic cancer was diagnosed in 89 (96 per cent) of 93 hospitals in the Netherlands. Some 19 hospitals (21 per cent) were classified as pancreatic centres and 70 (79 per cent) as non-pancreatic centres. Patient characteristics differed between the centres (*Table 1*). Patients diagnosed in a pancreatic centre were younger than those diagnosed in a non-pancreatic centre: median (i.q.r.) 68 (60–76) *versus* 73 (64–80) years respectively ($P < 0·001$).

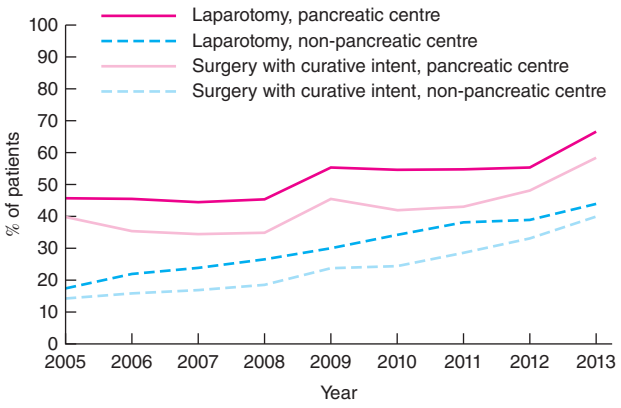


Fig. 1 Treatment of M0 pancreatic cancer by centre of diagnosis in the Netherlands, 2005–2013

Surgery

An exploratory laparotomy was performed in 3123 patients (38·4 per cent). Resection with curative intent was undertaken in 2497 (80·0 per cent) of these patients (*Table 1*). This represented 30·7 per cent of patients diagnosed with non-metastasized pancreatic cancer and 13·3 per cent of all patients diagnosed with pancreatic cancer in the study interval.

Rates of surgery differed significantly between patients diagnosed in a pancreatic centre *versus* a non-pancreatic centre. Exploratory laparotomy was performed in 1421 (52·4 per cent) and 1702 (31·4 per cent) patients respectively ($P < 0·001$), and surgery with curative intent in 1160 (42·8 per cent) *versus* 1337 (24·6 per cent) ($P < 0·001$) (*Table 1*). The resection rate increased with time for both

Table 2 Multivariable regression analyses of factors influencing the likelihood of undergoing exploratory laparotomy for pancreatic cancer between 2005 and 2013 in the Netherlands

	Exploratory laparotomy ($n = 3123$)*	Odds ratio†
Age (years)		
< 60	859 (56·6)	1·00 (reference)
60–69	1124 (52·3)	0·89 (0·77, 1·03)
70–79	1008 (38·4)	0·48 (0·42, 0·56)
≥ 80	132 (7·1)	0·05 (0·04, 0·06)
Sex		
M	1653 (42·0)	1·00 (reference)
F	1470 (35·0)	0·88 (0·79, 0·98)
Hospital of diagnosis		
Pancreatic centre	1421 (52·4)	2·21 (1·98, 2·47)
Non-pancreatic centre	1702 (31·4)	1·00 (reference)
Interval of diagnosis		
2005–2007	704 (29·5)	1·00 (reference)
2008–2010	1043 (37·4)	1·62 (1·41, 1·85)
2011–2013	1376 (46·4)	2·28 (2·00, 2·61)
Histology		
Carcinoma	2819 (36·4)	1·00 (reference)
Neuroendocrine tumour	304 (75·6)	2·44 (1·87, 3·18)
Tumour stage (TNM)		
I	1358 (45·9)	1·00 (reference)
II	1205 (51·6)	0·98 (0·86, 1·11)
III	421 (26·4)	0·24 (0·21, 0·28)
II/III	119 (11·4)	0·16 (0·13, 0·20)

Values in parentheses are *percentages and †95 per cent c.i.

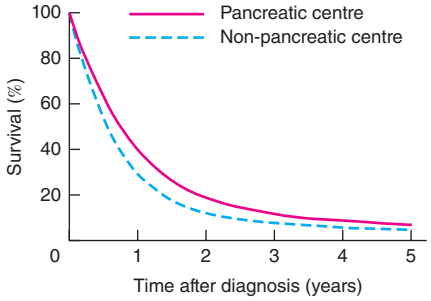
types of centre, but differences in resection rates remained throughout the study (*Fig. 1*).

Likelihood of undergoing surgery

Results of multivariable logistic regression to determine factors influencing the likelihood of surgery are shown in *Table 2*. Patients initially diagnosed in a pancreatic centre had a significantly higher likelihood of surgical treatment (OR 2·21, 95 per cent c.i. 1·98 to 2·47). Patients aged 70 years or more were less likely to have surgical treatment than patients aged less than 60 years (age 70–79 years: OR 0·48, 0·42 to 0·56; 80 years or older: OR 0·05, 0·04 to 0·06). Patients diagnosed in 2008 or later had a significantly higher likelihood of undergoing surgery than patients diagnosed before 2008.

Survival

There was a significant difference in 5-year survival between patients diagnosed in pancreatic centres *versus* non-pancreatic centres: 8·7 *versus* 5·7 per cent respectively ($P < 0·001$) (*Fig. 2*). In multivariable Cox regression analyses, diagnosis in a pancreatic centre was associated with reduced long-term mortality compared with diagnosis



No. at risk

Non-pancreatic centre	5429	1524	561	293	173	111
Pancreatic centre	2712	1000	402	211	134	87

Fig. 2 Survival of patients with M0 pancreatic cancer by centre of diagnosis. $P < 0·001$ (log rank test)

Table 3 Cox regression analyses of predictors of long-term mortality in patients with pancreatic cancer diagnosed between 2005 and 2013

	Hazard ratio
Age (years)	
< 60	1·00 (reference)
60–69	1·16 (1·08, 1·25)
70–79	1·30 (1·20, 1·39)
≥ 80	1·48 (1·36, 1·61)
Sex	
M	1·00 (reference)
F	0·99 (0·94, 1·04)
Centre of diagnosis	
Pancreatic centre	0·95 (0·91, 1·00)
Non-pancreatic centre	1·00 (reference)
Interval of diagnosis	
2005–2007	1·00 (reference)
2008–2010	0·93 (0·87, 0·98)
2011–2013	0·97 (0·92, 1·03)
Tumour stage (TNM)	
I	1·00 (reference)
II	1·36 (1·28, 1·45)
III	1·32 (1·23, 1·42)
II/III	1·31 (1·21, 1·42)
TN unknown	1·15 (0·99, 1·34)
Treatment	
No surgery or chemotherapy	1·00 (reference)
Palliative chemotherapy	0·57 (0·53, 0·62)
Surgery with curative intent	0·33 (0·31, 0·35)

Values in parentheses are 95 per cent c.i. Patients with neuroendocrine tumours were excluded from the survival analysis.

in a non-pancreatic centre, but this was not statistically significant (HR 0·95, 95 per cent c.i. 0·91 to 1·00) (*Table 3*).

Discussion

The centralization of pancreatic cancer surgery in the Netherlands has resulted in a reduction in postoperative

mortality, improved survival and increased resection rates[4,12,13]. However, the diagnostic evaluation and staging of patients with pancreatic cancer is still performed in most Dutch hospitals. In 74 of 93 hospitals, patients with pancreatic cancer were discussed in a multidisciplinary tumour board meeting without involvement of a specialized pancreatic surgeon. Hence, the grounds for the decision to refer a patient to a pancreatic cancer centre for surgical treatment could be questioned. This population-based study has shown that the likelihood of undergoing surgical treatment for pancreatic cancer is higher in centres with a high-volume pancreatic surgery service. Recognition as a pancreatic cancer centre in the Netherlands is currently based solely on the annual volume of pancreatectomies. In 2007, a minimum of ten pancreatoduodenectomies per year was specified and this increased to 20 procedures in 2010. As a result, the number of hospitals performing pancreatic surgery decreased from 40 in 2005 to 19 in 2013. As all 19 centres performed pancreatic surgery during the entire study interval, these hospitals were defined as pancreatic cancer centres in the present study.

A previous nationwide study[14] in the USA demonstrated that patients with clinical stage I pancreatic adenocarcinoma treated in low-volume centres between 1995 and 2004 were less likely to undergo surgery than patients treated in high-volume centres (OR 0·36, 95 per cent c.i. 0·30 to 0·45). The same study reported a nationwide undertreatment of patients with pancreatic cancer because only 29 per cent of those with stage I disease underwent surgery. This percentage was unexpectedly low as stage I pancreatic cancer is potentially resectable. Reasons for no surgical treatment were old age, presence of co-morbidities or patient refusal. There was no identifiable reason for not opting for surgery in 52 per cent of the patients. An Irish nationwide study[15] also reported undertreatment of patients with pancreatic cancer between 1994 and 2003. Some 42 per cent of the patients did not receive any therapy and only a minority underwent resection. These studies suggest underutilization of potentially curative surgery in patients without clear contraindications, especially in low-volume hospitals.

In the present study, tumour resection was carried out in 13·3 per cent of all patients with pancreatic cancer and in 30·7 per cent of those with stage I disease. This is in line with previous studies showing that only 10–20 per cent of patients with pancreatic cancer undergo surgery with curative intent[1,12,15,16]. Reasons for no surgery were older age and advanced tumour stage with vascular involvement of the tumour. Patients' preference and co-morbidity may also have influenced choice of treatment, but these data were not available from the NCR.

The classification of pancreatic cancer as resectable, borderline resectable, locally advanced or metastatic can be complex, and requires an experienced multidisciplinary team with up-to-date knowledge of all treatment strategies[16]. Previous studies have shown that exposure to a higher volume of surgery improves more than surgical skill. Dedicated CT performed at high-volume centres resulted in improved preoperative staging compared with CT at low-volume centres[17]. The present authors speculate that the experience of the entire multidisciplinary tumour board might be of great importance and explain the difference in resection rates between centres. Furthermore, a more nihilistic approach to surgery for pancreatic cancer might still exist in non-pancreatic centres[18]. This may be especially true for elderly patients, given the findings that such patients had a lower likelihood of surgery. Patients aged more than 70 years, or even 80 years, have a higher risk of postoperative morbidity and mortality after pancreatoduodenectomy, but they still have a better chance of survival than patients who are not treated surgically[19–22]. Hence, elderly patients should be selected carefully and informed about all treatment options; they should not be denied surgery just because of their age[21,22]. Assessment by an experienced multidisciplinary team may be particularly of benefit for this vulnerable patient group.

Diagnosis in a pancreatic centre was associated with reduced long-term mortality compared with diagnosis in a non-pancreatic centre, but this was not statistically significant. Similar findings were published in a contemporary study[23] of oesophageal cancer that showed an important influence of the centre of diagnosis on survival and the likelihood of undergoing surgical treatment. Although the NCR used for this study is a reliable and complete database, co-morbidity was not registered and could not be used for correction of case mix. This may have influenced the results[3,24]. In the Netherlands, patients can choose a hospital of their own preference, but it is likely that they will follow the advice of their general practitioner. Age may have biased referral patterns, as patients diagnosed in pancreatic centres were younger than those diagnosed in non-pancreatic centres. However, the greater likelihood of surgical treatment in pancreatic centres remained present after multivariable analyses correcting for age. This once more suggests that the experience of the multidisciplinary tumour board results in a more adequate assessment and selection for surgery with curative intent. Concentration of care in pancreatic centres may further improve outcomes in patients with pancreatic cancer.

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