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ORIGINAL ARTICLE

Does long-term survival exist in pancreatic adenocarcinoma?

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ABSTRACT

Background: We conducted a population-based study to investigate long-term survival in patients diagnosed with a (suspected) pancreatic adenocarcinoma.

Methods: All patients diagnosed with a pancreatic adenocarcinoma or with a pathologically unverified tumour of the pancreas between 1993 and 2008 in the South of the Netherlands were selected from the Netherlands Cancer Registry (NCR). Medical charts of patients who were alive five years or longer since diagnosis were reviewed.

Results: A total of 2 564 patients were included, of whom 1 365 had a pancreatic adenocarcinoma and 1 199 had a pathologically unverified pancreatic tumour. Five-year survival of patients with pathologically verified adenocarcinomas was 1.7% (24 of 1 365 patients). Twenty-one-one of these 24 long-term survivors were among the 207 cases that underwent surgical resection as initial treatment; five-year survival after resection thus being 10.1%. Half of the long-term survivors who underwent surgical resection still eventually died of recurrent disease. Five-year survival among patients with clinically suspected but microscopically unverified pancreatic tumours was 1.3% (16 of 1 199 patients). In 15 of these 16 long-term survivors the initial clinical diagnosis was revised: 14 had benign disease and one a premalignant tumour.

Conclusions: Long-term survival among patients with pancreatic adenocarcinoma is extremely rare. As long-term survival in clinically suspected but pathologically unverified cancer is very unlikely, repeated fine needle aspiration or, preferably, histological biopsy is recommended in order to establish an alternative diagnosis in patients who survive longer than expected (more than 6–12 months).

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Survival after a diagnosis of pancreatic cancer is often short, with a five-year survival rate reported as low as 7% in Europe [1]. The only potential option for cure is radical surgery, which is, together with adjuvant chemotherapy, associated with moderate improvement in survival for patients with resectable pancreatic adenocarcinoma [2]. Nevertheless, the majority of patients are diagnosed with inoperable locally advanced or metastatic disease and therapeutic options in these stages are limited.

In Europe, the overall microscopic verification rate for pancreatic tumours is 63% [3]. The major histological type of pancreatic tumours is ductal adenocarcinoma, which represents about 85% of all pancreatic neoplasms and is associated with poor survival rates. Other types of pancreatic cancer, such as neuroendocrine tumours, may exhibit a less aggressive behaviour. A recent population-based Dutch study showed a poor prognosis in patients with pancreatic tumours both with and without pathological verification, suggesting that virtually all patients, including those without verification, suffered from true pancreatic adenocarcinoma [4]. Only a small proportion of the patients had an overall survival exceeding two years. Considering these results, one might question whether long-term survival in pancreatic cancer exists at all.

We conducted a population-based study in order to investigate long-term survival in all patients diagnosed with pancreatic cancer in the South of the Netherlands in the years 1993–2008. Long-term survival was defined as an overall survival exceeding five years.

Methods

Data collection

We used data from the Netherlands Cancer Registry (NCR), maintained by the Comprehensive Cancer Centre Netherlands. The registry collects data on all patients with newly diagnosed cancer in the Netherlands. We limited our study to the area of the previous Eindhoven Cancer Registry (ECR), in order to be able to perform a medical chart review. This area hosts 2.4

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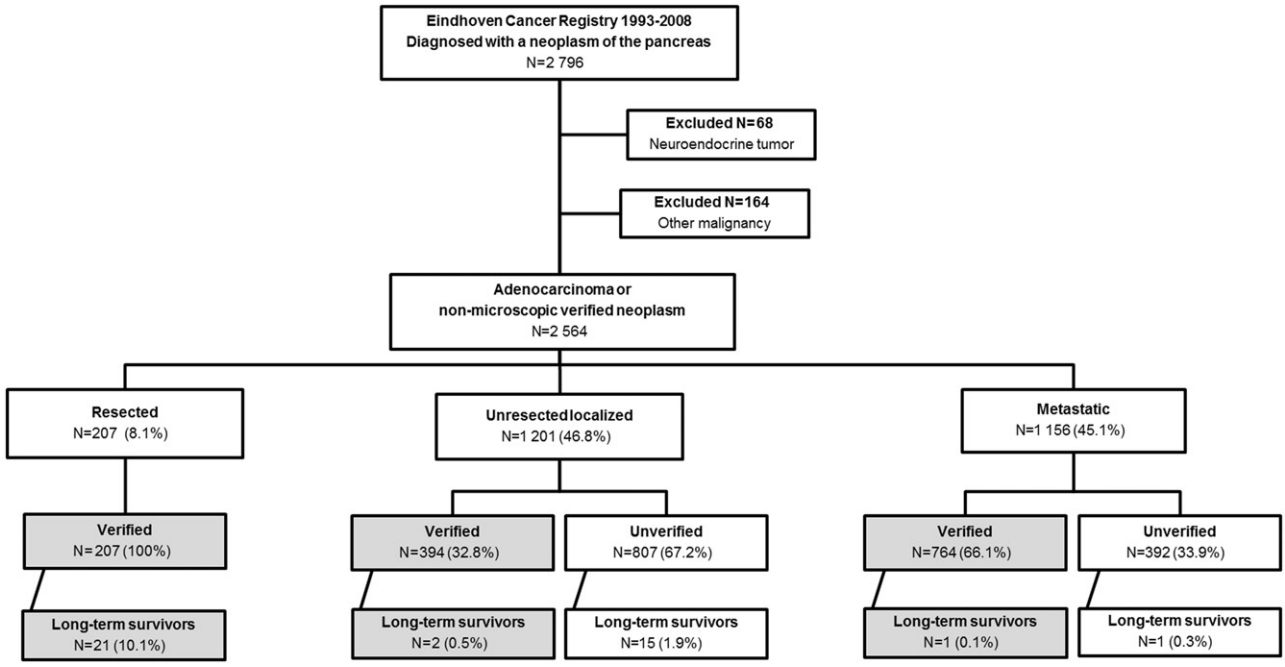

Figure 1. Study flow chart.

million inhabitants (~15% of the Dutch population) and is served by 10 general hospitals, two large radiotherapy institutes and six pathology laboratories. The pathology laboratories all participate in the nationwide automated pathology archive (PALGA) which notifies the cancer registry. Additional sources responsible for notification are the national registry of hospital discharge (LMR), multidisciplinary team reports and diagnosis-therapy combinations (specific codes used for reimbursement purposes). The completeness of the registry exceeds 95%.

After notification, information on patient characteristics, tumour characteristics and initial treatment is routinely extracted from medical records by trained administrators within 6–9 months after diagnosis. For the present study we selected patients with a malignancy of the pancreas diagnosed between 1 January 1993 and 31 December 2008. We decided to restrict our inclusion to adenocarcinomas (ICD-O morphology codes 8140, 8141, 8260, 8440, 8453, 8470, 8471, 8480, 8481, 8490, 8500) and pancreatic neoplasms without pathological verification (ICD-O morphology code 8 000). Vital status of patients was assessed at 1 January 2014 through linkage with civil municipal registries and the central bureau for genealogy. The latter is an institution that collects data on all deceased Dutch citizens. The survival was calculated based on all-cause mortality. We defined patients with an overall survival of more than five years as long-term survivors. Additional data were retrospectively extracted from the medical records of long-term survivors by two experienced researchers with the approval and under supervision of the treating physicians. The additional data concerned letters and pathology reports to investigate if the initial clinical or pathological diagnosis had been re-evaluated.

Statistical analyses

We performed all statistical analyses using SAS statistical software (version 9.3, SAS institute, Cary, NC, USA).

Table I. General characteristics of 2 564 patients diagnosed with a neoplasm of the pancreas, between 1993 and 2008 in the Southern Netherlands.

	N	%
Sex		
Male	1 327	51.8
Female	1 237	48.2
Age (years)		
<50	140	5.5
50–59	353	13.8
60–69	751	29.3
70–79	904	35.3
≥80	416	16.2
Socioeconomic status (SES)		
Low	737	28.7
Intermediate	964	37.6
High	667	26.0
Institutionalised	156	6.1
Unknown	40	1.6
Number of comorbid conditions		
0	1 210	47.2
1	767	29.9
≥2	301	11.7
Unknown	286	11.2
Histologic subtype		
Adenocarcinoma	1 365	53.2
Unknown	1 199	46.8
Extent of disease		
Resected	207	8.1
Unresected localised	1 201	46.8
Metastatic	1 156	45.1
Period of diagnosis		
1993–1996	522	20.4
1997–2000	653	25.5
2001–2004	601	23.4
2005–2008	788	30.7
Chemotherapy		
Adjuvant	23	0.9
Palliative	245	9.6
No	2 296	89.5

Survival time was defined as the time from diagnosis to death or 1 January 2014, for patients who were still alive. The crude survival was calculated with the life test, a log rank test was carried out to compare survival curves between different subgroups.

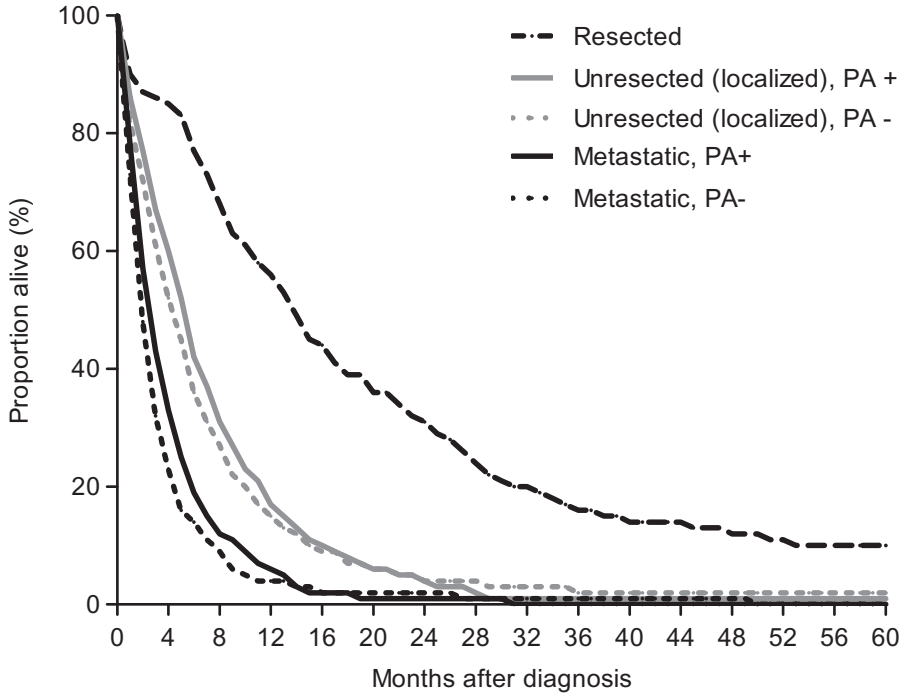

Figure 2. Overall survival of patients diagnosed with pancreatic cancer between 1993 and 2008 in the Southern Netherlands according to extent of disease ($N = 2564$). PA+, pathologically verified pancreatic adenocarcinoma; PA−, clinically suspected but microscopically unverified pancreatic cancer.

Results

Between 1 January 1993 and 31 December 2008 a total of 2 796 patients were diagnosed with a neoplasm of the pancreas of whom 1 365 (48.8%) patients had an adenocarcinoma, and 1 199 (42.9%) patients had a pathologically unverified tumour of the pancreas. Two hundred thirty-two patients were excluded from further analyses: 68 (2.4%) patients with a neuroendocrine tumour and 164 (5.9%) patients with other types of pancreatic malignancies (Figure 1).

General characteristics of the remaining 2 564 patients are depicted in Table I. Fifty-two percent of our study population was male and the median age at time of diagnosis was 70 years (range 32–100) and 45.1% had metastases at time of diagnosis. The proportion of patients presenting with metastatic disease increased from 34.7% in 1993–1996 to 52.8% in 2005–2008 ($p < 0.0001$).

Eight percent (N=207) of the total study population was eligible for surgery with a curative intent. The resection rate did not change over time ($p = 0.08$). However, an increasing proportion ($p < 0.0001$) of the surgically treated patients received adjuvant chemotherapy. In 2008, 50.0% of the surgically treated patients received adjuvant chemotherapy.

Forty-seven percent of the patients ($N = 1\,201$) had non-metastatic unresected pancreatic cancer, of whom 32.8% had their diagnosis pathologically confirmed. Eight percent (N=100) of these patients received treatment within six months after diagnosis. The treatment rate was higher in patients with a microscopically verified pancreatic adenocarcinoma compared to patients with a non-microscopically verified pancreatic tumour (16.5% vs. 4.3%, $p < 0.0001$). Fifty-nine patients (59.0%) received palliative chemotherapy and 24 patients (24.0%) were treated with chemoradiotherapy.

The remaining 45.1% of the patients ($N = 1\,156$) had metastases at time of diagnosis, the verification rate in these patients was 66.1%. Sixteen percent of the patients with metastatic pancreatic cancer received chemotherapy, the prescription of chemotherapy increased significantly over time (8.8% in 1993–1996 to 20.4% in 2005–2008, $p < 0.0001$) and was significantly higher in patients with microscopically verified disease (20.9% vs. 6.1%, $p < 0.0001$).

The median overall survival of surgically treated patients was 13.7 months (95% CI 11.3–16.1) with a one-year survival rate of 55.8% (Figure 2). The outcome of these patients significantly improved over time from a median survival of 7.1 months (95% CI 4.7–13.8) in 1993–1996 to 17.4 months (95% CI 13.6–25.0) in 2005–2008 (log rank for these periods $p = 0.004$). The outcome of patients with unresected and metastatic pancreatic cancer remained unchanged over time. The median survival for patients with unresected localised pancreatic cancer was 4.6 months (95% CI 4.2–5.0) with a one-year survival rate of 15.4%. Patients with metastatic pancreatic cancer carried the poorest prognosis of only 2.2 months (95% CI 2.1–2.4) with a one-year survival rate of 5.2%. There were small but significant differences in survival between patients with metastatic microscopically verified pancreatic cancer and patients with non-verified metastatic disease (Figure 2).

Only 40 patients (1.6%) of our total study population had an overall survival exceeding five years (Figure 1). Of the long-term survivors, 21 patients underwent surgical resection as initial treatment which represented 10.1% of the total of 207 surgically resected patients. The general characteristics of this group of patients are depicted in Table II. Additional data collection of this group of 21 long-term survivors showed that despite surgery, three patients developed locoregional

recurrence or metastases within five years, and seven patients more than five years after initial diagnosis. Nine of these 10 patients with recurrent disease died between five and 10 years after initial diagnosis.

Seventeen long-term survivors had non-metastatic unresected cancer, of whom 15 patients had non-microscopically verified disease at time of diagnosis. In 14 of these 15 patients the diagnosis was revised by the treating physician. The majority of these patients had a pancreatitis (focal or auto-immune), one patient had an intraductal papillary mucinous neoplasm (IPMN), one patient had a cystic adenoma, and one patient sclerosing cholangitis. The patient without revision of the diagnosis died 5.1 years after the initial diagnosis.

Two long-term survivors with unresected disease had a histologically verified adenocarcinoma at time of diagnosis. One of these patients only received a palliative bypass, the other patient was treated with palliative chemotherapy. Both tumours showed a remarkable indolent disease course.

Table II. General characteristics of 21 long-term survivors with surgically resected pancreatic cancer.

	N
Sex	
Male	12
Female	9
Age (years)	
<50	2
50–59	3
60–69	11
70–79	5
≥80	0
Socioeconomic status (SES)	
Low	6
Intermediate	6
High	7
Institutionalised	1
Unknown	1
Number of comorbid conditions	
0	13
1	4
≥2	2
Unknown	2
Tumour grade	
Good/moderate	14
Poor/undifferentiated	2
Unknown	5
T stage	
1	7
2	5
3	6
4	1
X	2
N stage	
0	8
1	7
X	6
TNM stage	
1	9
2	6
3	4
X	2
Period of diagnosis	
1993–1996	1
1997–2000	7
2001–2004	4
2005–2008	9
Adjuvant chemotherapy	
Yes	6
No	15

Another extraordinary disease course was observed in the long-term survivor with a pathologically proven metastatic adenocarcinoma of the pancreas. This patient was treated with palliative chemotherapy as well. In the long-term survivor diagnosed with metastatic disease without microscopic verification, however, the diagnosis was revised. Additional biopsies revealed a Wegener's granulomatosis/ANCA associated vasculitis and after correct immunosuppressive treatment the imaging studies normalised within a couple of months.

Discussion

In this population-based study including all patients with pathologically verified (adenocarcinoma) pancreatic cancer or clinically suspected pancreatic cancer in the period 1993 until 2008 we found that only 40 of 2 564 patients (1.6%) survived for more than five years.

The recently published Eurocare-5 data, reported a remarkably high five-year survival rate of 7% for patients diagnosed between 2000 and 2007 throughout Europe with any type of pancreatic tumour [1]. The authors suggest that difficulties with ascertainment of vital status in some countries might have biased their long-term survival estimates.

More in line with our results are the five-year survival rates reported in population-based studies in Norway (1965–2007), Finland (1990–1996) and Australia (2002–2003) of <3%, 1.8% and 2.6%, respectively, in patients with pancreatic cancer. The Norwegian cohort included all registered pancreatic cancer patients, both pathologically verified and unverified. At five years of diagnosis, relative survival was 5.3% in men and 2.6% in women. Five-year survival rate in patients with pancreatic cancer diagnosed in 1990–2006 was less than 3% [5]. In the Finnish study, all types of pancreatic cancer were included. Re-evaluation of histological specimens of the long-term survivors initially recorded as having histologically proven pancreatic adenocarcinoma, confirmed pancreatic adenocarcinoma in only 10 of 26 patients, representing 11.2% of all long-term survivors (10 of 89 patients) [6]. In the Australian study, neuroendocrine and ampullary tumours were excluded and, similar to our results, half of the long-term survivors had undergone surgical resection. As the other half of the long-term survivors had no pathologically confirmed diagnosis, true pancreatic cancer in these patients may be doubted because long-term survival in patients with pancreatic cancer, especially if the primary tumour has not been resected, is extremely rare and a more indolent or benign disease seems a more likely cause [7].

In our study the five-year survival among patients with clinically suspected but microscopically unverified pancreatic cancer was 1.3% (16 of 1 199 patients). However, in 15 of the 16 long-term survivors without initial pathological verification, the diagnosis was revised: 14 patients had a benign disease and one a premalignant tumour. As data collection by the registry occurred within 6–9 months after initial diagnosis, revision of the primary diagnosis had taken place after this period of time.

None of the long-term survivors with pathologically unverified metastatic or unresected pancreatic cancer were diagnosed with pancreatic malignancies that exhibit a more

indolent clinical course, such as neuroendocrine tumours. Several explanations could be proposed for this finding. First of all, pancreatic neuroendocrine tumours are rare, representing only 1–3% of all pancreatic tumours [8,9]. Second, computed tomography technology, the imaging modality that is most commonly used to investigate known or suspected pancreatic tumours, has improved. As a result, it has become increasingly common to identify pancreatic neuroendocrine tumours, with a detection rate exceeding 80% [10]. Finally, although overall survival for patients with pancreatic neuroendocrine tumours is more favourable than for patients with pancreatic adenocarcinomas, the median overall survival in metastatic disease does not exceed 2–5.8 years [11,12].

The five-year survival of patients with pathologically verified pancreatic cancer in our study was 1.7% (24 of 1 365 patients). The majority of these long-term survivors with a verified adenocarcinoma had undergone surgical resection (21 of 24 patients), comprising 10.1% of all surgically treated patients ($N = 207$). The five-year survival rate of surgically treated patients in our study is comparable with the five-year survival rate of 12.2%, found in a recently published large cohort study, including 11 081 patients with surgically resected invasive pancreatic adenocarcinoma [13]. By contrast, our results seem inferior to the results found in the phase III CONKO-001 trial, in which patients who underwent surgical resection had a five-year survival of 15.0% [14]. However, this trial was performed in a selected group of patients. In addition, another explanation for the lower five-year survival of surgically treated patients in our study might be that adjuvant chemotherapy was not part of standard care during the first period of this study. Significant survival differences were found in the CONKO-001 trial between patients treated with surgery alone and those who received adjuvant chemotherapy, five-year survival rates were, respectively, 9.1% and 20.7%.

In our study, we tried to identify prognostic factors predicting long-term survival, however, the small number of five-year survivors among the surgically treated patients was not suitable for testing in a multivariate model. In a recently published large cohort study, Paniccia et al. identified pathologic T stage, lymph node ratio and administration of adjuvant chemotherapy as variables associated with long-term survival in surgically treated pancreatic adenocarcinomas [14]. In our study, the surgically treated long-term survivors had very different tumour characteristics. It is noteworthy that approximately half of surgically treated long-term survivors (9 of 21 patients) eventually died from metastatic or locoregional recurrence, further emphasising the largely palliative nature of surgery in pancreatic cancer.

Several studies have shown that surgical resection is performed in 8–15% of all pancreatic carcinomas [7,15,16]. In the present study, 8.1% of the patients underwent surgical resection. While the resection rate did not change over time, some important surgery-related improvements were made, including the implementation of centralisation of pancreatic cancer surgery from 2005 onwards and the standard use of adjuvant chemotherapy, improving disease-free and overall survival through the administration of adjuvant gemcitabine during six months [17–19]. Our population-based data showed an increase in median overall survival of surgically treated patients from seven months in the early period to 17 months in the period 2005–2008, which is consistent with median survival rates demonstrated in several other population-based studies [16,20,21].

In contrast to the surgically treated patients, the median overall survival of patients with unresected and metastatic pancreatic cancer remained unchanged over time. While the proportion of patients presenting with metastatic disease increased due to improved and more accurate diagnostic imaging techniques, no beneficial effect on survival as a result of stage migration could be observed. Unfortunately, in this population-based study we have no information as to why surgical resection could not be performed in patients referred to as having irresectable non-metastatic pancreatic cancer. Among unresected patients (locally advanced unresected + metastatic disease), 10.3% received chemotherapy. During the course of the study, no substantial progress has been made in chemotherapeutic treatment of advanced pancreatic cancer. However, the prescription of chemotherapy in metastatic disease had more than doubled, from 8.8% in 1993–1996 to 20.4% in 2005–2008, possibly because physicians gained more experience with the use of chemotherapy in the adjuvant setting. Since 2011, new treatment options for metastatic pancreatic cancer have emerged, demonstrating an overall survival benefit by using combination chemotherapy [22,23]. The FOLFIRINOX regimen is currently the most effective treatment in metastatic disease, but due to toxicity, its use is restricted to a select group of patients.

In conclusion, long-term survival in patients suffering from pancreatic cancer is extremely rare. We found that only 1.6% of all patients survived for more than five years. Of the patients who were eligible for surgical resection, 10.1% survived for at least five years. Perhaps the number of long-term survivors may further increase in the future, by optimising centralisation, more extensive surgery, and increased use of possibly better (neo) adjuvant strategies, though unresectable and metastatic disease at presentation remains the key problem, stressing the need for better understanding of the disease and better systemic treatment options. Survival in patients with pathologically verified (adenocarcinoma) pancreatic cancer and clinically suspected but microscopically unverified pancreatic cancer was very similar, demonstrating the reliability of the clinical and radiological judgement. However, if a patient with pathologically unverified pancreatic cancer survives longer than expected (more than 6–12 months depending on the extent of the disease at the time of primary diagnosis), we recommend to perform fine needle aspiration or, preferably, histological biopsy in order to obtain pathological confirmation of the diagnosis.

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References

1. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999–2007 by country and age: Results of EUROCARE-5 – a population-based study. Lancet Oncol 2014;15:23–34.
2. Seufferlein T, Bachet JB, Van Cutsem E, Rougier P. Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(Suppl 7):vii33–40.
3. De Angelis R, Francisci S, Baili P, Marchesi F, Roazzi P, Belot A, et al. The EUROCARE-4 database on cancer survival in Europe: Data standardisation, quality control and methods of statistical analysis. Eur J Cancer 2009;45:909–30.
4. Bernards N, Creemers GJ, Huysentruyt CJ, de Hingh IH, van der Schelling GP, de Bruine AP, et al. The relevance of pathological verification in suspected pancreatic cancer. Cancer Epidemiol 2015;39:250–5.
5. Soreide K, Aagnes B, Moller B, Westgaard A, Bray F. Epidemiology of pancreatic cancer in Norway: Trends in incidence, basis of diagnosis and survival 1965–2007. Scand J Gastroenterol 2010;45:82–92.
6. Carpelan-Holmstrom M, Nordling S, Pukkala E, Sankila R, Luttges J, Kloppel G, et al. Does anyone survive pancreatic ductal adenocarcinoma? A nationwide study re-evaluating the data of the Finnish Cancer Registry. Gut 2005;54:385–7.
7. Speer AG, Thursfield VJ, Torn-Broers Y, Jefford M. Pancreatic cancer: Surgical management and outcomes after 6 years of follow-up. Med J Aust 2012;196:511–15.
8. Fesinmeyer MD, Austin MA, Li CI, De Roos AJ, Bowen DJ. Differences in survival by histologic type of pancreatic cancer. Cancer Epidemiol Biomark Prevent 2005;14:1766–73.
9. Dixon E, Pasieka JL. Functioning and nonfunctioning neuroendocrine tumors of the pancreas. Curr Opin Oncol 2007;19:30–5.
10. Khashab MA, Yong E, Lennon AM, Shin EJ, Amateau S, Hruban RH, et al. EUS is still superior to multidetector computerized tomography for detection of pancreatic neuroendocrine tumors. Gastrointest Endosc 2011;73:691–6.
11. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after ''carcinoid'': Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–72.
12. Strosberg J, Gardner N, Kvols L. Survival and prognostic factor analysis of 146 metastatic neuroendocrine tumors of the mid-gut. Neuroendocrinology 2009;89:471–6.
13. Paniccia A, Hosokawa P, Henderson W, Schulick RD, Edil BH, McCarter MD, et al. Characteristics of 10-year survivors of pancreatic ductal adenocarcinoma. JAMA Surg 2015;150:701–10.
14. Sinn M, Striefler JK, Sinn BV, Sallmon D, Bischoff S, Stieler JM, et al. Does long-term survival in patients with pancreatic cancer really exist? Results from the CONKO-001 study. J Surg Oncol 2013;108:398–402.
15. Nienhuijs SW, van den Akker SA, de Vries E, de Hingh IH, Visser O, Lemmens VE. Nationwide improvement of only short-term survival after resection for pancreatic cancer in the Netherlands. Pancreas 2012;41:1063–6.
16. Cress RD, Yin D, Clarke L, Bold R, Holly EA. Survival among patients with adenocarcinoma of the pancreas: A population-based study (United States). Cancer Causes Control 2006;17:403–9.
17. Lemmens VE, Bosscha K, van der Schelling G, Brenninkmeijer S, Coebergh JW, de Hingh IH. Improving outcome for patients with pancreatic cancer through centralization. Br J Surg 2011;98:1455–62.
18. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: A randomized controlled trial. JAMA 2007;297:267–77.
19. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: The CONKO-001 randomized trial. JAMA 2013;310:1473–81.
20. Baxter NN, Whitson BA, Tuttle TM. Trends in the treatment and outcome of pancreatic cancer in the United States. Ann Surg Oncol 2007;14:1320–6.
21. Sharp L, Carsin AE, Cronin-Fenton DP, O'Driscoll D, Comber H. Is there under-treatment of pancreatic cancer? Evidence from a population-based study in Ireland. Eur J Cancer 2009;45:1450–9.
22. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. New Engl J Med 2011;364:1817–25.
23. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. New Engl J Med 2013;369:1691–703.