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Original Research

Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma

Anouk E.J. Latenstein [a], Lydia G.M. van der Geest [b], Bert A. Bonsing [c], Bas Groot Koerkamp [d], Nadia Haj Mohammad [e], Ignace H.J.T. de Hingh [f], Vincent E. de Meijer [g], Izaak Q. Molenaar [h], Hjalmar C. van Santvoort [h], Geertjan van Tienhoven [i], Joanne Verheij [j], Pauline A.J. Vissers [b], Judith de Vos-Geelen [k], Olivier R. Busch [a], Casper H.J. van Eijck [d], Hanneke W.M. van Laarhoven [l], Marc G. Besselink [a], Johanna W. Wilmink [l,*], for the Dutch Pancreatic Cancer Group

[a] *Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands*
[b] *Department of Research, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, the Netherlands*
[c] *Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands*
[d] *Department of Surgery, Erasmus MC, Rotterdam, the Netherlands*
[e] *Department of Medical Oncology, Regional Academic Cancer Center Utrecht, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands*
[f] *Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands*
[g] *Department of Hepatobiliary Surgery and Liver Transplantation, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands*
[h] *Department of Surgery, Regional Academic Cancer Center Utrecht, St Antonius Hospital Nieuwegein and University Medical Center Utrecht Cancer Center, Utrecht, the Netherlands*
[i] *Department of Radiation Oncology, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands*
[j] *Department of Pathology, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands*
[k] *Department of Internal Medicine, Division of Medical Oncology, GROW - School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands*
[l] *Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands*

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* *Corresponding author*: Department of Medical Oncology, G4-212, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. Fax: +31 20 691 9743.
E-mail addresses: a.e.latenstein@amsterdamumc.nl (A.E.J. Latenstein), j.w.wilmink@amsterdamumc.nl (J.W. Wilmink).

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Abstract ***Background:*** In recent years, new treatment options have become available for pancreatic ductal adenocarcinoma (PDAC) including 5-fluorouracil, leucovorin, irinotecan and oxaliplatin. The impact hereof has not been assessed in nationwide cohort studies. This population-based study aimed to investigate nationwide trends in incidence, treatment and survival of PDAC.

Materials and methods: Patients with PDAC (1997–2016) were included from the Netherlands Cancer Registry. Results were categorised by treatment and by period of diagnosis (1997–2000, 2001–2004, 2005–2008, 2009–2012 and 2013–2016). Kaplan–Meier survival analysis was used to calculate overall survival.

Results: In a national cohort of 36,453 patients with PDAC, the incidence increased from 12.1 (1997–2000) to 15.3 (2013–2016) per 100,000 ($p < 0.001$), whereas median overall survival increased from 3.1 to 3.8 months ($p < 0.001$). Over time, the resection rate doubled (8.3%–16.6%, p-trend<0.001), more patients received adjuvant chemotherapy (3.0%–56.2%, p-trend<0.001) and 3-year overall survival following resection increased (16.9%–25.4%, $p < 0.001$). Over time, the proportion of patients with metastatic disease who received palliative chemotherapy increased from 5.3% to 16.1% (p-trend<0.001), whereas 1-year survival improved from 13.3% to 21.2% ($p < 0.001$). The proportion of patients who only received supportive care decreased from 84% to 61% (p-trend<0.001).

Conclusion: The incidence of PDAC increased in the past two decades. Resection rates and use of adjuvant or palliative chemotherapy increased with improved survival in these patients. In all patients with PDAC, however, the survival benefit of 3 weeks is negligible because the majority of patients only received supportive care.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease with a poor survival. Reported 5-year relative survival rates range around 8.5%, and in 2018 alone, 430,000 patients died from PDAC worldwide [1]. In the last two decades, studies showed an improved survival in patients with PDAC based on new oncological treatments. In 2007, a randomised controlled trial demonstrated that the use of adjuvant gemcitabine-improved survival in patients after resection [2]. Randomised trials also demonstrated that the use of FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin), and gemcitabine plus nab-paclitaxel improved survival in patients with metastatic PDAC, as compared with gemcitabine alone [3–5]. In addition, prospective cohort studies and a systematic review described that FOLFIRINOX improved survival in patients with locally advanced PDAC, though randomised studies are not yet available [6–9].

It is currently unclear what the impact of these improvements in the treatment of PDAC has been on a nationwide scale [10]. It is known that the strict eligibility criteria in randomised trials hamper extrapolation to the general population. Global trends of PDAC have recently been reviewed, but the most recent nationwide evaluation from Europe dates over a decade ago (i.e. 2008) [11–13].

In 2012, the Dutch Pancreatic Cancer Group was formed with the aim to improve survival of PDAC. Since then, the centralisation and standardisation of PDAC care in the Netherlands has continued, and the implementation of new chemotherapy regimens has been supported. We were interested whether these developments have changed the survival of patients with PDAC on a population-based scale in the Netherlands. The objective of this study, therefore, is to evaluate trends in incidence, treatment and survival for patients with all stages of PDAC in the Netherlands between 1997 and 2016.

2. Materials and methods

2.1. Study design

All patients with primary PDAC diagnosed from 1997 to 2016 were included from the Netherlands Cancer Registry (NCR), a population-based database that covers all Dutch hospitals (i.e. a population of 17.3 million). Patients with a newly diagnosed malignancy are identified by two-step signalling consisting of (1) automatic notifications of the national pathological archive and the National Registry of Hospital Discharge Diagnoses and (2) verification of notifications in medical files in hospitals. Patient, tumour and treatment characteristics are routinely collected from medical records by trained NCR administrators. This study was

designed in accordance with the STROBE guidelines [14]. The scientific committee of the Dutch Pancreatic Cancer Group approved the study protocol.

2.2. Study population

Patients with primary PDAC were included. This diagnosis was based on the International Classification of Disease-Oncology (ICD-O-3) morphology codes according to the WHO classification (Supplementary Material) [15]. Patients aged younger than 18 years at diagnosis or patients diagnosed during autopsy were excluded.

2.3. Data collection

Socioeconomic status (SES) was based on social deprivation scores per 4-digit postal code (reference data from The Netherlands Institute of Social Research) and categorised into three SES groups (high: 1st-3rd, intermediate 4th-7th, low: 8th-10th deciles). The time of diagnosis was divided into five periods: 1997–2000, 2001–2004, 2005–2008, 2009–2012 and 2013–2016 to facilitate analyses. Primary tumour location was classified as pancreatic head, body, tail or other/non-specified (C25.3, C25.5–9), according to the ICD-O-3 codes. Tumour stage was based on the pathological tumour-node-metastasis (TNM) classification at the time of registration (revised 4th edition of IUCC TNM staging during 1997–1998, 5th edition during 1999–2002, 6th edition during 2003–2009, 7th edition during 2010–2016), supplemented with the clinical TNM classification in case of non-resected tumours or neo-adjuvant therapy [16–19]. A one-digit summary stage (Extent of Disease) was recorded in patients without pathological confirmation of cancer [20]. Based on the tumour stage at primary diagnosis and the primary subsequent treatment, patients with PDAC were divided into four groups: (1) patients with localised disease who underwent resection with or without (neo)adjuvant chemo (radio)therapy; (2) patients with localised disease who received chemo (radio)therapy without resection (patients with locally advanced pancreatic cancer and patients unfit for surgery); (3) patients with metastatic disease at diagnosis who received chemotherapy; (4) patients who received supportive care only (and did not receive any tumour directed therapy). Patients treated with chemotherapy but without the possibility to distinguish metastatic or localised diseased (n = 43) were excluded. Time to treatment analyses could not be performed because the diagnosis is based on pathology which was often the date of surgery. Furthermore, date of resection was only available since 2015 and start of chemotherapy since 2011. Survival was defined as the time between date of diagnosis and date of death or censored at last follow-up date and was obtained by linkage of the NCR with the Municipal Personal Records Database (updated in February 2019).

2.4. Statistical analysis

The incidence of PDAC was described in new cases per 100.000 persons per year stratified by sex, together with the estimated annual percent of change (EAPC). To compare results with old and new literature, the incidence rates were age-standardised to both the European standard population from 1976 (ESP) and the revised ESP from 2013 (RESP) [21,22]. The age-standardised incidence is the incidence that would be observed if the study population had the age structure of the standard population and is essential to compare rates over time or between geographical regions. Imputation was not performed, and missing data were described in the baseline characteristics. Trends over time in treatment were analysed with the Chi-square test for trend. Median overall survival, 3-month survival and 1-, 3- and 5-year survival were calculated using the Kaplan–Meier method and compared using the log rank test. Analyses were based on type of treatment and stratified by period. To demonstrate whether changes in resection and chemotherapy rate were associated with differences in overall survival over time, multivariable Cox regression models, adjusted for potential confounders, were performed without and with these treatment variables. Potential confounders were sex, age, SES, primary tumour location and tumour stage. Results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). All p-values were based on a 2-sided test, and p-values of <0.05 were considered statistically significant. Data were analysed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armong, NY, USA), SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.4.3 (cran.r-project.org).

3. Results

From 1997 to 2016, 36,453 patients were diagnosed with PDAC. The incidence increased from 12.1 to 15.3 per 100,000 persons from 1997 to 2016 (RESP-based, EAPC 1.5%, $p < 0.001$, Fig. 1A). The incidence was higher in males and increased significantly for both sexes from 1997 to 2016 (RESP-based, EAPC 1.5%, $p < 0.001$ and EAPC 1.6%, $p < 0.001$, respectively). The ESP-based incidence increased similarly with an EAPC of 1.5% for the overall group (Fig. 1B). Median age at diagnosis was 71 years (Table 1). The incidence was highest in patients aged 60–74 year compared with patients aged <60 year or ≥ 75 year, but increased significantly in all age categories (RESP based, EAPC 1.95 $p < 0.001$, EAPC 0.87 $p = 0.01$ and EAPC $p < 0.001$, respectively, Fig. 2A).

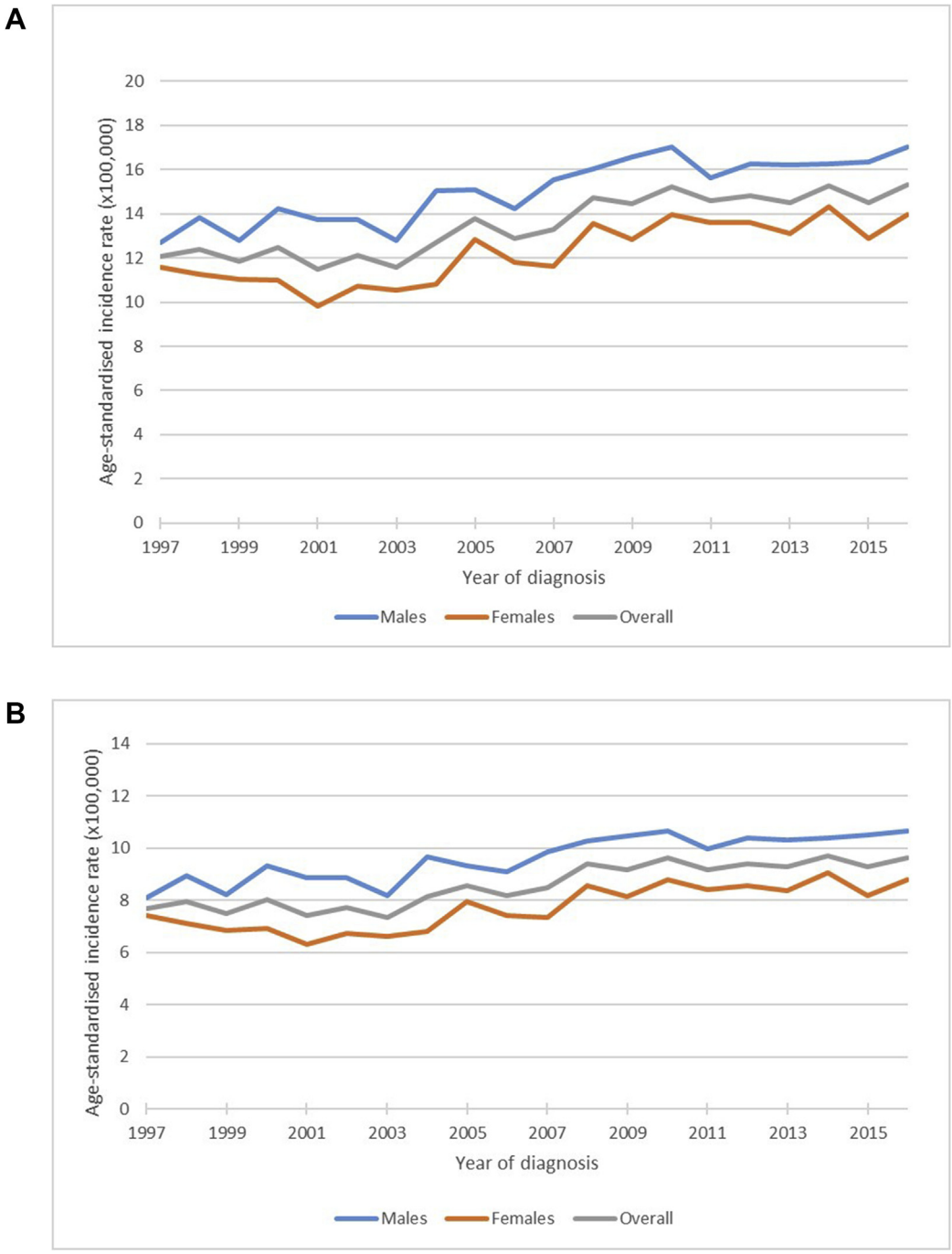


Fig. 1. **Age-standardised incidence rates of patient with pancreatic ductal adenocarcinoma in the Netherlands stratified by sex (1997–2016)**. Fig. 1A. Age-standardised incidence rates based on the Revised European Standard Population; Fig. 1B. Age-standardised incidence rates based on the European Standard Population.

3.1. All stages pancreatic cancer

Pathological confirmation increased over the years from 58.4% in 1997–2000 to 71.9% in 2013–2016 (p-trend<0.001). Metastatic disease at diagnosis was present in 19,119 patients (52.4%) and increased from 45.2% in 1997–2000 to 57.0% in 2013–2016 (p-trend<0.001). More patients were treated with (neo) adjuvant or palliative chemotherapy (Table 2). Median overall survival was 3.5 months (95%CI 3.5–3.6) for the entire cohort and increased from 3.1 months in 1997–2000 to 3.8 months in 2013–2016 ($p < 0.001$, Table 1). Survival at 3 months after diagnosis increased from 50.9% (95%CI 49.6–52.2) to 56.5% (95%CI 55.5–57.5) ($p < 0.001$, Fig. 3D) and 1-year survival from 13.4% (95%CI 12.5–14.3) to 21.0% (95%CI 20.1–21.8, $p < 0.001$). The association between time period of diagnosis and overall survival was significant

Table 1
Patient, tumour and treatment characteristics of 36,453 patients diagnosed with pancreatic ductal adenocarcinoma between 1997 and 2016 in the Netherlands.

Characteristics	All patients (n = 36,453)	Patients with localised disease who underwent resection (n = 4387)	Patients with localised disease who received chemo (radio) therapy (n = 1604)	Patients with distant metastases who received chemotherapy (n = 4074)	Patients who only received supportive care (n = 26,388)
Male	18,161 (59.8%)	2348 (53.5%)	873 (54,4%)	2288 (56,2%)	12,652 (47.9%)
Age, median (IQR)	71.0 (62.0–78.0)	66.0 (59.0–72.0)	64.0 (56.0–70.0)	63.0 (56.0–69.0)	74.0 (65.0–80.0)
<60 years	6658 (18.3%)	1184 (27.0%)	556 (34.7%)	1491 (36.6%)	3427 (13.0%)
60–74 years	16,300 (44.7%)	2488 (56.7%)	877 (54.7%)	2267 (55.6%)	10,668 (40.4%)
≥75 years	13,495 (37.0%)	715 (16.3%)	171 (10.7%)	316 (7.8%)	12,293 (46.6%)
SES					
Low	10,862 (29.8%)	1389 (31.7%)	511 (31.9%)	1323 (32.5%)	7639 (28.9%)
Medium	14,610 (40.1%)	1775 (405%)	626 (39.0%)	1649 (40.5%)	10,560 (40.0%)
High	10,981 (30.1%)	1223 (27.9%)	467 (29.1%)	1102 (27.0%)	8189 (31.0%)
Primary tumour location					
Head of pancreas	23,129 (63.4%)	3559 (81.1%)	1097 (6.,4%)	1810 (44.4%)	16,663 (63.1%)
Body of pancreas	3589 (9.8%)	166 (3.8%)	258 (16.1%)	666 (16.3%)	2499 (9.5%)
Tail of pancreas	4682 (12.8%)	319 (7.3%)	68 (4.2%)	956 (23.5%)	3339 (12.7%)
Other/non-specified (C25.3, C25.5–9)	5053 (13.9%)	343 (7.8%)	181 (11.3%)	642 (15.8%)	3887 (14.7%)
Tumour stage[a]					
Local disease/within pancreas	3915 (10.7%)	594 (13.5%)	125 (7.8%)	–	3196 (12.1%)
Extended disease/growth outside pancreas	10,776 (29.6%)	3579 (81.6%)	1451 (90.5%)	–	5746 (21.8%)
Metastatic disease	19,119 (52.4%)	185 (4.2%)	–	4074 (100%)	14,860 (56.3%)
Unknown	2643 (7.3%)	29 (0.7%)	28 (1.7%)	–	2586 (9.8%)
Overall survival in months, median (95% CI)	3.5 (3.5–3.6)	16.9 (16.4–17.4)	10.5 (10.1–11.0)	5.8 (5.7–6.0)	2.3 (2.3–2.3)
Patient treated with chemo (radio)therapy		21.9 (20.8–23.1)			
Patients not treated with chemo (radio)therapy		13.4 (12.8–14.1)			

IQR, interquartile range; SES, socioeconomic status; CI, confidence interval; TNM, tumour-node-metastasis.
[a] Tumour stage was based on the pathological TNM classification at the time of registration, supplemented with the clinical TNM or a summary stage (no microscopic verification) in case of non-resected tumours or neoadjuvant therapy.

in multivariable Cox regression, but after including resection and chemotherapy treatment to the Cox model, this association disappeared for all periods except for 2001–2004 (Table 3).

3.2. Patients with localised disease who underwent resection

Resection was performed in 4387 patients (12.0%), and this percentage doubled from 8.3% in 1997–2000 to 16.6% in 2013–2016 (p-trend<0.001). This increase applied to all age groups (<60 years from 15.2% to 23.8%, 60–74 years from 10.7% to 19.4% and ≥75 years from 2.0% to 9.6%). The use of adjuvant chemotherapy increased from 3.0% in 1997–2000 to 21.1% in 2005–2008 and 56.2% in 2013–2016 ($p < 0.001$, Table 2). In 2013–2016, 8.5% of patients who underwent resection received neoadjuvant chemotherapy. The use of (mainly adjuvant) radiotherapy remained negligible over the years (3.5% of patients).

In all patients who underwent resection, median overall survival was 16.9 months (95% CI 16.4–17.4, Table 1 and Fig. 3A). Median overall survival was better with (neo)adjuvant chemotherapy (21.9 months, 95% CI 20.8–23.1) than without (13.4 months, 95% CI 12.8–14.1, $p < 0.001$, Supplemental Fig. 1A and B). In all patients after resection, 1-year survival increased significantly from 56.1% (95%CI 51.8–60.8) in 1997–2000 to 68.7% (95%CI 66.5–71.1) in 2013–2016 and 5-year survival from 9.1% (95%CI 6.8–12.2) to 16.5% (95%CI 14.3–18.9), respectively.

3.3. Patients with localised disease who received chemo(radio)therapy without resection

Of all patients with PDAC, 1604 patients (4.4%) had localised disease and received chemo (radio)therapy without resection (Table 2). This proportion of patients increased from 2.1% in 1997–2000 to 5.8% in 2013–2016 (p-trend < 0.001). Pathological confirmation was present in 1363 of these patients (85.0%). The use of radiotherapy decreased from 39.5% to 17.7% (p-trend < 0.001). Median overall survival was 11 months (95% CI 10–11, Table 1). Three-month and 1-year and 3-year survival were relatively constant over time (Fig. 3B).

3.4. Patient with metastatic disease who received chemotherapy

In total, 4074 patients (11.2% of patients with all stages of PDAC, 21.3% of patients with metastatic disease) received chemotherapy for distant metastases (Table 2).

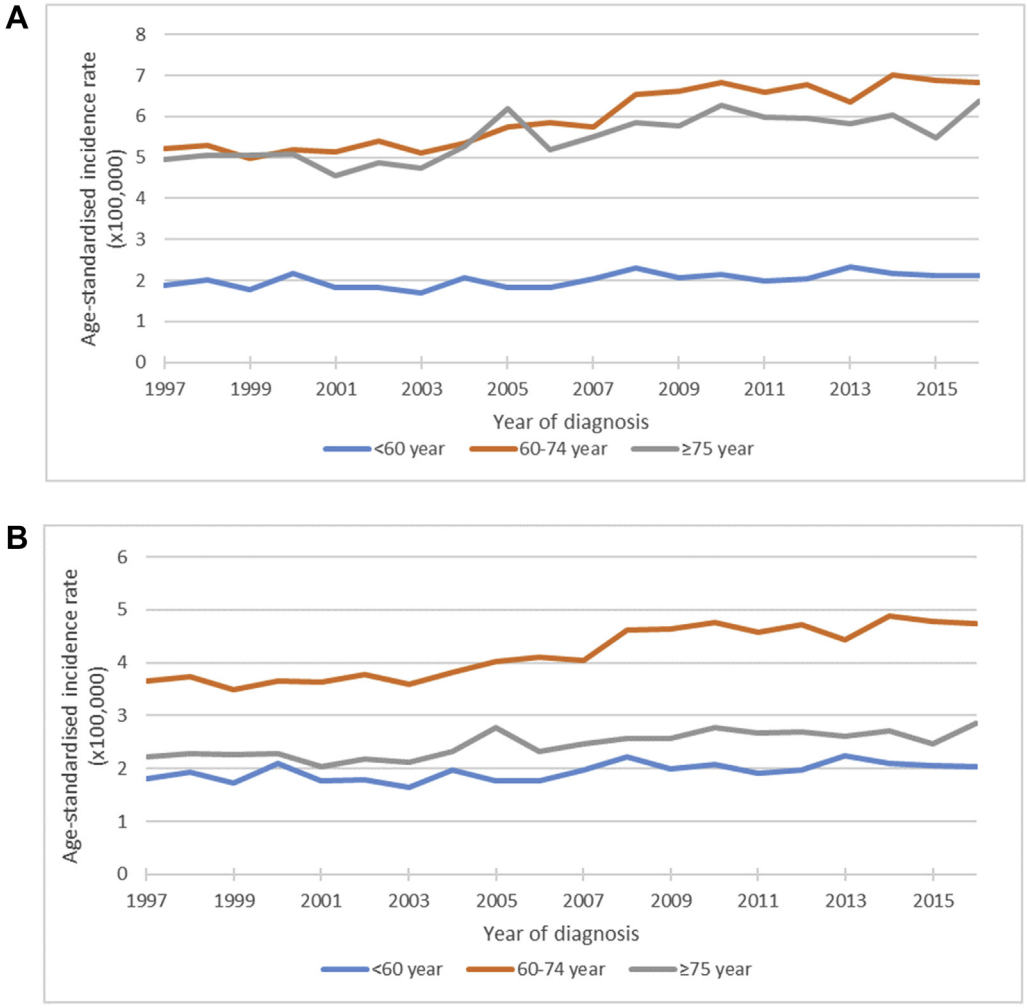
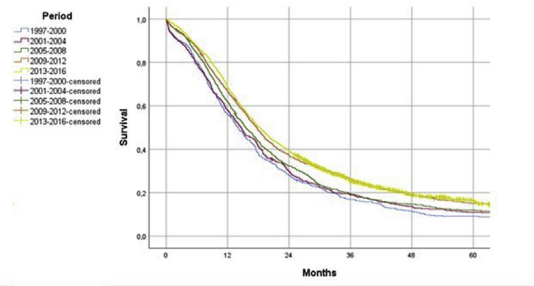


Fig. 2. **Age-standardised incidence rates of patient with pancreatic ductal adenocarcinoma in the Netherlands stratified by age (1997–2016)**. Fig. 2A Age-standardised incidence rates based on the Revised European Standard Population. Fig. 2B. Age-standardised incidence rates based on the European Standard Population.

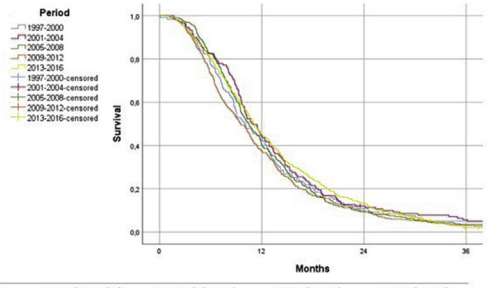
Table 2
Trends in treatment.

Patients	1997–2016 n = 36,453	1997–2000 n = 5572	2001–2004 n = 5858	2005–2008 n = 7179	2009–2012 n = 8470	2013–2016 n = 9374	p-value (trend over periods)
Patients with localised disease who underwent resection	4387 (12.0%)	465 (8.3%)	485 (8.3%)	730 (10.2%)	1153 (13.6%)	1554 (16.6%)	<0.001
Neoadjuvant chemotherapy	168 (3.8%)	1 (0.2%)	4 (0.8%)	7 (1.0%)	24 (2.1%)	132 (8.5%)	<0.001
Adjuvant chemotherapy	1646 (37.5%)	14 (3.0%)	33 (6.8%)	154 (21.1%)	571 (49.5%)	874 (56.2%)	<0.001
Patients with localised disease who received chemo(radio)therapy	1604 (4.4%)	119 (2.1%)	149 (2.5%)	321 (4.5%)	463 (5.5%)	552 (5.8%)	<0.001
Patients with metastatic disease who received chemotherapy	4074 (11.2%)	294 (5.3%)	420 (7.2%)	660 (9.2%)	1188 (14.0%)	1512 (16.1%)	<0.001
Patients who only received supportive care	26,388 (72.4%)	4694 (84.2%)	4804 (82.0%)	5468 (76.2%)	5666 (66.9%)	5756 (61.4%)	<0.001

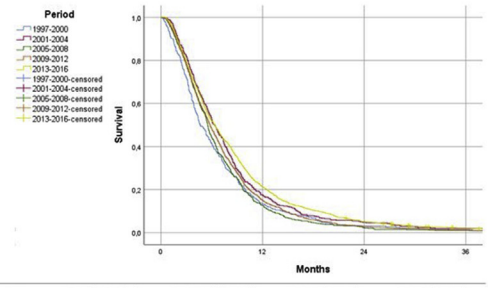
In 3724 treated patients (91.4%), the tumour was pathologically confirmed. The proportion of patients who received chemotherapy for distant metastases increased from 5.3% in 1997–2000 to 16.1% of all patients with PDAC in 2013–2016 (p-trend < 0.001) and from 11.7% to 28.3% of patients with metastatic disease (p-trend < 0.001), respectively. The use of radiotherapy decreased from 7.8% to 1.1%, p-trend < 0.001. Median overall survival was 5.9 months (95% CI 5.7–6.0, Table 1 and Fig. 3C) and the 1-year survival increased from 13.3%



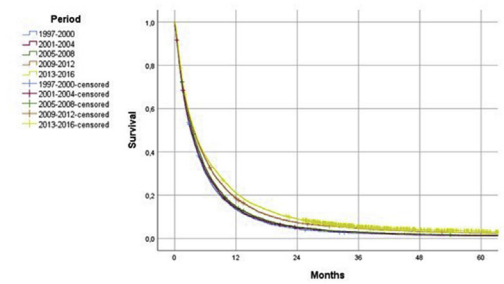
A	mOS (months)	3 month (95%CI)	1 year (95%CI)	3 year (95%CI)	5 year (95%CI)
1997-2000	14.0 (12.5-15.4)	89.5% (86.7-92.3%)	56.1% (51.8-60.8%)	16.9% (13.8-20.7%)	9.1% (6.8-12.2%)
2001-2004	14.6 (12.9-16.3)	88.9% (86.1-91.7%)	57.9% (53.7-62.5%)	19.1% (15.9-22.9%)	11.0% (8.5-14.2%)
2005-2008	15.5 (14.2-16.9)	93.6% (91.8-95.4%)	61.9% (58.5-65.5%)	19.5% (16.8-22.6%)	12.0% (9.8-14.6%)
2009-2012	17.6 (16.7-18.6)	93.1% (91.7-94.6%)	66.7% (64.0-69.5%)	26.3% (23.8-28.9%)	15.1% (13.2-17.3%)
2013-2016	18.1 (17.1-19.1)	95.0% (94.0-96.1%)	68.7% (66.5-71.1%)	25.4% (23.3-27.8%)	16.5% (14.3-18.9%)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001



B	mOS (months)	3 month (95%CI)	1 year (95%CI)	3 year (95%CI)
1997-2000	10.1 (8.1-12.1)	95.8% (92.3-99.5%)	42.8% (34.8-52.7%)	5.0% (2.3-1.1%)
2001-2004	11.0 (9.6-12.4)	96.6% (93.8-99.6%)	44.3% (37.0-53.0%)	5.7% (2.9-11.0%)
2005-2008	10.5 (9.5-11.5)	97.2% (95.4-99.0%)	40.5% (35.5-46.2%)	3.4% (1.9-6.1%)
2009-2012	9.5 (8.7-10.4)	94.4% (92.3-96.5%)	37.4% (33.2-42.0%)	3.0% (1.8-5.1%)
2013-2016	11.0 (10.3-11.7)	94.6% (92.7-96.5%)	45.1% (41.1-49.4%)	2.1% (1.1-4.1%)
p-value	0.106	0.315	0.040	0.072



C	mOS (months)	3 month (95%CI)	1 year (95%CI)	3 year (95%CI)
1997-2000	4.6 (4.0-5.3)	72.1% (67.6-77.4%)	13.3% (9.9-17.7%)	1.4% (0.5-3.6%)
2001-2004	6.3 (5.7-7.0)	81.9% (78.3-85.7%)	17.6% (14.3-21.7%)	1.9% (1.0-3.8%)
2005-2008	5.5 (5.2-5.8)	77.9% (74.8-81.1%)	12.7% (10.4-11.5%)	1.1% (0.5-2.2%)
2009-2012	5.8 (5.5-6.1)	78.1% (75.8-80.5%)	15.1% (13.2-17.2%)	1.0% (0.6-1.8%)
2013-2016	6.3 (5.9-6.7)	79.5% (77.5-81.6%)	21.2% (19.2-23.3%)	2.2% (1.5-3.1%)
p-value	<0.001	0.013	<0.001	<0.001



D	mOS (months)	3 month (95%CI)	1 year (95%CI)	3 year (95%CI)	5 year (95%CI)
1997-2000	3.1 (2.9-3.2)	50.9% (49.6-52.2%)	13.4% (12.5-14.3%)	2.4% (2.0-2.8%)	1.3% (1.1-1.7%)
2001-2004	3.2 (3.1-3.4)	52.1% (50.8-53.4%)	14.1% (13.2-15.0%)	2.8% (2.4-3.2%)	1.2% (0.98-1.6%)
2005-2008	3.5 (3.3-3.6)	54.3% (53.2-55.5%)	14.7% (13.9-15.6%)	3.0% (2.6-3.4%)	1.6% (1.3-1.9%)
2009-2012	3.7 (3.6-3.9)	55.7% (54.6-56.8%)	18.5% (17.7-19.4%)	4.6% (4.2-5.1%)	2.5% (2.2-2.8%)
2013-2016	3.8 (3.7-4.0)	56.5% (55.5-57.5%)	21.0% (20.1-21.8%)	5.4% (4.9-5.9%)	3.4% (3.0-3.9%)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001

Fig. 3. **Kaplan–Meier curve and survival at 3 months, 1, 3, 5 years among patients with pancreatic ductal adenocarcinoma per period of diagnosis (1997–2016)**. Fig. 3A. Survival of patients with localised disease who underwent tumour resection; Fig. 3B. Survival of patients with localised disease who received chemo (radio)therapy without resection; Fig. 3C. Survival of patients with synchronous distant metastases who received chemotherapy; Fig. 3D. Survival of all patient. CI, confidence interval.

(95%CI 9.9–17.7) in 1997–2000 to 21.2% (95%CI 19.2–23.3) in 2013–2016 ($p < 0.001$).

3.5. Patients who received supportive care only

The majority of patients with PDAC (72.4%) received supportive care only. This percentage decreased significantly (84% in 1997–2000 to 61% in 2013–2016, Table 2, p-trend<0.001). Median overall survival was 2.3 months (70 days, 95%CI 2.3–2.3 months, Table 1) and was less for patients with metastatic disease compared with local or extended disease (1.6 months, 95%CI 1.6–1.7; 4.6 months, 95%CI 4.4–4.8; 4.1 months, 95% CI 4.0–4.3, respectively). In all patients with supportive care only, the 3-month survival decreased significantly from 44.6% (95%CI 43.2–46.1) in 1997–2000 to 36.4% (95%CI 35.2–37.7) in 2013–2016 (Supplemental Fig. 1C).

4. Discussion

This Dutch population-based study found an increasing incidence of PDAC in the period 1997–2016 and 23% more patients being treated with resection and/or systemic treatment. The resection rate doubled (8.3%–16.6%), more patients received adjuvant chemotherapy (3.0%–56.2%), and 3-year overall survival following resection increased (16.9%–25.4%). The proportion of patients with metastatic disease who received palliative chemotherapy increased (5.3%–16.1%), whereas 1-year survival improved (13.3%–21.2%). Most strikingly, however, throughout the entire study period, the majority of patients received supportive care only. This could explain the negligible improvement in overall survival of only 3 weeks (0.7 months) to 3.8 months for the entire population.

It appears that improvements in oncological treatments of any kind are the most likely explanations for the increased overall survival. However, the overall survival advantage for all patients is disappointing compared with for example colorectal cancer [23]. It is clear that improvements are needed, for instance through early detection of PDAC and better or individualised treatments [24]. Survival increased in patients with localised disease who underwent resection in the most recent years (2009–2016). Resection rates doubled,

Table 3
Univariate and multivariable Cox regressions to assess the effect of resection and chemotherapy on the association between time of diagnosis and mortality in patients with pancreatic ductal adenocarcinoma (1997–2016).

Cox regression	Median overall survival, months	Multivariable analysis without treatment variables HR (95 %CI)	Multivariable analysis including treatment variables HR (95% CI)
Time of diagnosis			
1997–2000	3.1	1.00 (reference)	1.00 (reference)
2001–2004	3.2	**0.94 (0.91–0.98)**	**0.96 (0.93–1.00)**
2005–2008	3.5	**0.92 (0.89–0.96)**	1.00 (0.96–1.03)
2009–2012	3.7	**0.82 (0.79–0.85)**	0.99 (0.95–1.02)
2013–2016	3.8	**0.75 (0.72–0.77)**	0.98 (0.95–1.02)
Sex			
Male	3.5	1.00 (reference)	1.00 (reference)
Female	3.6	**0.98 (0.96–1.00)**	**0.96 (0.94–0.98)**
Age			
<60 years	5.2	1.00 (reference)	1.00 (reference)
60–74 years	3.9	**1.24 (1.21–1.28)**	**1.11 (1.08–1.14)**
≥75 years	2.5	**1.91 (1.86–1.97)**	**1.32 (1.27–1.36)**
SES			
Low	3.8	1.00 (reference)	1.00 (reference)
Medium	3.5	**1.03 (1.01–1.06)**	**1.01 (0.99–1.04)**
High	3.3	**1.08 (1.06–1.11)**	**1.05 (1.02–1.08)**
Primary tumour location			
Head of pancreas	4.3	1.00 (reference)	1.00 (reference)
Body of pancreas	3.2	**1.08 (1.04–1.12)**	**1.06 (1.02–1.10)**
Tail of pancreas	2.1	**1.19 (1.15–1.23)**	**1.24 (1.20–1.28)**
Other	2.4	**1.23 (1.19–1.27)**	**1.21 (1.17–1.25)**
Tumour stage[a]			
Local disease/within pancreas	5.7	1.00 (reference)	1.00 (reference)
Extended disease/growth outside pancreas	7.6	**1.09 (1.05–1.13)**	**1.35 (1.30–1.40)**
Metastases	2.2	**2.69 (2.59–2.79)**	**2.53 (2.44–2.63)**
Unknown	2.7	**1.59 (1.51–1.67)**	**1.40 (1.33–1.47)**
Resection		Not included	
Yes	16.9		1.00 (reference)
No	2.9		**2.54 (2.45–2.64)**
Any chemotherapy treatment		Not included	
Yes	9.1		1.00 (reference)
No	2.6		**2.21 (2.14–2.27)**

HR, hazard ratio; SES, socioeconomic status; CI, confidence interval; TNM, tumour-node-metastasis.
Bold numbers indicate statistical significance.
[a] Tumour stage was based on the pathological TNM classification at the time of registration, supplemented with the clinical TNM in case of non-resected tumours or neoadjuvant therapy

and this is likely explained by centralisation with improved referral patterns, improved surgical techniques and—in recent years—extending indications for surgery (e.g. locally advanced disease with response to chemotherapy) [25]. Moreover, postoperative complications and mortality after pancreatic resection decreased, which increased the number of patients eligible for adjuvant treatment [26–28]. This increase was probably also strongly related to several adjuvant chemotherapy studies, such as the ESPAC-1 trial in 2004 and the CONKO-001 trial in 2007 [2,29]. The use of neoadjuvant chemo (radio)therapy mainly increased since 2013 with the start of the Dutch PREOPANC-1 trial on neoadjuvant chemoradiotherapy in patients with (borderline) resectable pancreatic cancer (NL3525, EudraCT number 2012-003181-40) [30]. Survival in patients with localised disease who undergo a resection may further improve because of new (neo)adjuvant chemotherapy regimens, as recently was proven for adjuvant therapy with modified FOLFIRINOX [31]. In patients who underwent a resection, the use of radiotherapy was negligible during the study period. The role of radiotherapy remains under debate, and literature is inconclusive [32].

In patients with metastatic disease who received chemotherapy, survival rates increased, especially from 2005 to 2008 to 2009–2012 (1-year survival 12.7% and 21.2%, respectively), probably explained by the uptake of new combinations of chemotherapeutic agents FOLFIRINOX and gemcitabine plus nab-paclitaxel [3–5]. The percentage of patients who only received supportive care decreased, as did their survival. More patients were treated with chemotherapy and relatively more elderly underwent surgery and thus especially

patients with a relatively poor prognosis received supportive care only and subsequently overall survival decreased [33].

Locally advanced pancreatic cancer was initially not registered in the NCR, and in this study, these patients were categorised as patients with localised disease without metastases. Depending on their treatment, they were included in the group of patients who underwent resection or patients with localised disease who received chemo (radio)therapy without resection. This last group was small but increased over the years, probably related to more attention for patients with locally advanced disease after the introduction of FOLFIRINOX [34]. In addition, after FOLFIRINOX treatment emerged, resection rates in patients with locally advanced disease increased [7,8].

Survival differed between tumour locations. Patients with tumours of the pancreatic body or tail had worse survival compared with patients with pancreatic head tumours. This was also seen in other series [35,36]. Diagnostic delay of patients with body and tail tumours, because of lack of early symptoms such as jaundice, may play some role, but it seems that body and tail tumours mostly have a more aggressive tumour biology [37–39].

In general, the incidence of PDAC varies across countries [11,12,40]. The incidence is highest in North America and Western Europe and continues to increase [11,12,41,42]. This increase could be related to the increased exposure to risk factors, such as obesity, alcohol or diabetes and because of increased availability of high-quality cross-sectional imaging [11,12,40]. Better diagnostic modalities could explain the increased proportion of patients with metastatic disease at diagnosis (i.e. stage migration). Older age was given a greater weighting in the RESP, and therefore, the incidence was higher if calculated with the RESP than with the ESP, which represents the age shift that is occurring in Europe. An analysis of incidence of PDAC across Europe described an age-standardised incidence, based on the ESP, between 12 (UK/Ireland and southern Europe) to 15 (northern and eastern Europe) per 100.000 persons per year between 2000 and 2007 [43]. The incidence in our population was lower in this period with 8–9 per 100.000 person annually.

The findings of this study should be seen in light of several limitations. First, the division of the patients into four subgroups based on clinical findings of metastases and treatment. A classification in the commonly seen subgroups of resectable, locally advanced, and metastatic disease was not possible. Second, the actual incidence of PDAC might have been higher than reported in the NCR [44]. However, this probably did not influence the trend over the years because the notification sources of the NCR remained stable, and similar patterns of mortality rates in Statistics Netherlands were found [45]. Third, information on tumour stage was lacking in several patients diagnosed in earlier time periods. Stage migration because of improved imaging equipment may have influenced grouping of patients but not patterns in the entire population. The main strength of this study is the analysis of population-based nationwide data with a very high national coverage. The results are therefore more representative than studies with selective cohorts, for example randomised controlled trials or from single, high volume centres.

In conclusion, the incidence of PDAC increased over the last two decades, while overall survival only improved marginally despite an increase of patients receiving treatment (16%–39%). Survival increased in the subgroup of patients who underwent pancreatic resection (3-year survival: 16.9%–25.4%) and in patients with metastatic disease who received chemotherapy (1-year survival: 13.3%–21.2%). However, because the survival of pancreatic cancer only improved with 3 weeks for the entire population and still the majority of patients only received supportive care, there is a clear and urgent need for further improvement in diagnostics and treatment of PDAC.

Conflict of interest statement

The authors have no competing interest to declare.

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Appendix A. Supplementary data

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