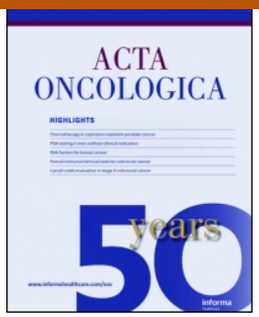

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ORIGINAL ARTICLE

Implementation of contemporary chemotherapy for patients with metastatic pancreatic ductal adenocarcinoma: a population-based analysis

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ABSTRACT

Background: Positive results of randomized trials led to the introduction of FOLFIRINOX in 2012 and gemcitabine with nab-paclitaxel in 2015 for patients with metastatic pancreatic ductal adenocarcinoma. It is unknown to which extent these new chemotherapeutic regimens have been implemented in clinical practice and what the impact has been on overall survival.

Material and methods: Patients diagnosed with metastatic pancreatic ductal adenocarcinoma between 2007–2016 were included from the population-based Netherlands Cancer Registry. Multilevel logistic regression and Cox regression analyses, adjusting for patient, tumor, and hospital characteristics, were used to analyze variation of chemotherapy use.

Results: In total, 8726 patients were included. The use of chemotherapy increased from 31% in 2007–2011 to 37% in 2012–2016 ($p < .001$). Variation in the use of any chemotherapy between centers decreased (adjusted range 2007–2011: 12–67%, 2012–2016: 20–54%) whereas overall survival increased from 5.6 months to 6.4 months ($p < .001$) for patients treated with chemotherapy. Use of FOLFIRINOX and gemcitabine with nab-paclitaxel varied widely in 2015–2016, but both showed a more favorable overall survival compared to gemcitabine monotherapy (median 8.0 vs. 7.0 vs. 3.8 months, respectively). In the period 2015–2016, FOLFIRINOX was used in 60%, gemcitabine with nab-paclitaxel in 9.7% and gemcitabine monotherapy in 25% of patients receiving chemotherapy.

Conclusion: Nationwide variation in the use of chemotherapy decreased after the implementation of FOLFIRINOX and gemcitabine with nab-paclitaxel. Still a considerable proportion of patients receives gemcitabine monotherapy. Overall survival did improve, but not clinically relevant. These results emphasize the need for a structured implementation of new chemotherapeutic regimens.

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Introduction

Most patients with pancreatic ductal adenocarcinoma (PDAC) are diagnosed with metastatic disease [1–3]. These patients are treated with palliative chemotherapy combined with supportive care or supportive care alone, depending on their performance status and preference. In 1997, gemcitabine was found to improve survival compared to 5-fluorouracil (5.7 vs. 4.4 months median overall survival) [4]. Over the years, several combination chemotherapy regimens have been investigated without any gain of survival [5,6]. More recently, FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) was associated with a survival benefit compared to gemcitabine (11.1 vs. 6.8 months median overall survival) in patients with a good performance status [7]. The phase III MPACT trial revealed a

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Supplemental data for this article can be accessed here.

superior survival with gemcitabine with nab-paclitaxel as compared to gemcitabine alone (8.7 vs. 6.6 months median overall survival) [8]. It is unclear how these findings of trials with often strict eligibility criteria translate to nationwide clinical practice.

Most population-based studies [1,9,10] on metastatic PDAC were performed in the gemcitabine era. A recent study in Canada [11] showed that use of FOLFIRINOX in patients with metastatic PDAC increased from 41% in 2012 to 56% in 2014 although treatment regimens varied considerably across geographic regions. In the Netherlands FOLFIRINOX and gemcitabine with nab-paclitaxel were introduced in 2012 and 2015 respectively [7,8,11,12]. The identification of nationwide trends over the years and variation across hospitals is relevant as different treatment strategies might influence patients' outcomes [7,8]. Patients could receive other chemotherapy regimens leading to a difference in survival. Nationwide variation between hospitals may exist over time, due to geographical or hospital volume differences, but also due to differences in patient characteristics and clinical practice in prescribing palliative chemotherapy [13–15]. For example, physicians with less experience with triplet chemotherapy in the treatment of PDAC, may have been reluctant to prescribe FOLFIRINOX treatment.

Therefore, the aim of this study is to assess whether the implementation of new more effective chemotherapy regimens (FOLFIRINOX and gemcitabine with nab-paclitaxel) for patients with metastatic PDAC has affected nationwide clinical practice and overall survival.

Methods

Data collection

For this nationwide study, data from the Netherlands Cancer Registry (NCR) were used, covering the total population of approximately 17 million inhabitants. Patients with a newly diagnosed malignancy were identified by automatic notifications of the national pathological archive (PALGA) and the National Hospital Discharge Register. Information on patient, tumor and treatment characteristics, and visited hospitals (for diagnosis and for treatment), were routinely collected from medical records by trained NCR administrators. This study was designed in accordance with the STROBE guidelines [16] and the study protocol was approved by the scientific committee of the Dutch Pancreatic Cancer Group.

Study population

Patients diagnosed in the period 2007–2016 with PDAC (International Classification of Disease – Oncology (ICD-O-3) morphology code 8000, 8010, 8012, 8020, 8140, 8141, 8260, 8310, 8440, 8453, 8480, 8481, 8490, 8500 and 8560) and distant metastasis at time of diagnosis were extracted from the NCR database. Patients younger than 18 years at diagnosis, patients who underwent pancreatic resection, patients who received neoadjuvant chemotherapy prior to surgical exploration or patients who died within 30 days after diagnosis were excluded.

For patients with metastatic PDAC, use of FOLFIRINOX was recommended in 2012 and gemcitabine with nab-paclitaxel in 2015, after positive judgement of a national commission (Commissie BOM). Therefore, the period of diagnosis was divided into a period before (2007–2011) and after (2012–2016) the implementation of the new regimens. Patients were assigned as receiving chemotherapy treatment if they started any chemotherapy regimen. Socioeconomic status (SES) was based on social deprivation scores per 4-digit postal code (reference data from The Netherlands Institute of Social Research) and categorized into three SES groups (high: 1st–3rd, intermediate 4th–7th, low: 8th–10th deciles). Primary tumor location was classified as pancreatic head (C25.0), body (C25.1), tail (C25.2), or other (C25.3, 7–9), according to the ICD-O-3. Metastatic organ site(s) was categorized as liver only, peritoneum only, lung only, extra-regional lymph nodes only, other site only, 2 sites (any combination), $\geq$3 sites (any combination) and unknown. Nationwide data on comorbid conditions, performance status (WHO; Karnofsky scores were converted to WHO according to the following values [17]: 90–100 to WHO 0, 80–90 to WHO 1, 60–70 to WHO 2, 40–50 to WHO 3, 20–30 to WHO 4) and type of first-line chemotherapy were available for diagnoses in 2015 and 2016 only. Survival data were obtained by annual linkage with the Municipal Personal Records Database, which contains vital status of all Dutch inhabitants. Survival time was defined as the time between the date of diagnosis and date of death or censoring (1 February 2018).

Hospital classifications

Patients were assigned to their hospital of diagnosis, which was defined as the hospital of first visit or clinical diagnosis of PDAC. In 2016, patients were diagnosed in 78 hospitals in the Netherlands, merged hospitals were counted as one for the entire study period. Classifications of hospitals were: (1) type of hospital, divided in university and non-university hospitals; (2) volume of diagnoses of metastatic PDAC per hospital per year, evenly divided into three groups (tertiles: 1–12, 13–19, 20–39); (3) volume of patients receiving chemotherapy per hospital per year (the number of patients with metastatic PDAC with chemotherapy per hospital per year was applied to all patients diagnosed with metastatic PDAC in that hospital) (tertiles: 0–3, 4–6, 7–31); or (4) diagnosed in a center for pancreatic surgery (no/yes, only available for 2012–2016). Nationwide variation for type of chemotherapy could only be assessed for 2015–2016, because type of chemotherapy was not registered before. In the analysis about type of chemotherapy per hospital in 2015–2016, type of chemotherapy was linked to the hospital of treatment.

Statistical analysis

Time trends in the use of chemotherapy and referral for chemotherapy (chemotherapy treatment in other hospital than hospital of diagnosis) were analyzed with the Chi-square for trend. Multilevel logistic regression models were built to analyze variation of chemotherapy treatment between hospitals, since patients were arranged in a natural hierarchy (clustered

within hospitals) [18]. For each hospital of diagnosis (separately for 2007–2011 and 2012–2016), a mean probability of receiving chemotherapy was calculated, adjusted for differences in patient and tumor characteristics. Change in hospital variation between both time periods was investigated using intraclass correlation coefficients (ICC) for the proportion of variance explained by hospital level. Sensitivity analyses were performed for patients (1) under 75 years only, (2) alive 60 days after diagnosis, (3) with pathologically verified PDAC, and (4) diagnosed in 2015–2016 additionally adjusted for number of comorbid conditions and WHO performance status. To investigate mechanisms underlying the variation of receiving chemotherapy between hospitals, the hospital classifications were added one by one to the multivariable multilevel models.

Overall survival was analyzed by means of Kaplan–Meier curves and compared with log-rank tests. Multivariable Cox regression analyses were performed to assess the effect of (1) the period of diagnosis (for all patients and for patients receiving chemotherapy), (2) probabilities of receiving chemotherapy per hospital grouped in tertiles (2007–2011 and 2012–2016 separately) and (3) the different chemotherapy regimens (patients with chemotherapy in 2015–2016) on survival. Results were presented as hazard ratios (HR) with a 95% confidence interval (CI). All multivariable regression analyses were adjusted for sex, age, SES, pathological confirmation, primary tumor location, and number and location of distant metastases. The third regression assessing the different chemotherapy regimens was also adjusted for performance status and number of comorbidities. All p-values were based on a 2-sided test and p-values of $<.05$ were considered statistically significant. Data was analyzed using IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armong, N.Y., USA) and Stata version 14.2 (StataCorp, TX, USA) for multilevel analyses of hospital variation, performed by LvdG to maintain anonymity of hospitals.

Results

Patient population

In total, 8726 patients diagnosed with metastatic PDAC were included. The median age was 68 years (range 21–99) and one-third of patients was treated with chemotherapy (34%). Table 1 provides an overview of the baseline characteristics. Use of palliative chemotherapy increased significantly from 31% in 2007–2011 to 37% in 2012–2016 ($p < .001$, Figure 1(A)). During 2012–2016, the use of chemotherapy stabilized (p-trend $= .20$). The percentage of patients that was referred to another hospital for chemotherapy treatment decreased from 22% to 10% from 2007–2011 (p-trend $= .001$) and fluctuated between 13% and 18% in 2012–2016 (p-trend $= .23$). Median age of patients receiving chemotherapy was 63 and 64 years in the consecutive time periods.

Nationwide variation in administration of chemotherapy

In the study period, an increasing number of hospitals provided chemotherapy to patients diagnosed with metastatic

Table 1. Baseline characteristics of 8726 patients with metastatic pancreatic ductal adenocarcinoma in the Netherlands diagnosed between 2007–2016.

	All patients 2007–2016, $N = 8726$ (%)	Period 1 (2007–2011) $N = 3941$ (%)	Proportion of chemotherapy (row %)	p-value	Period 2 (2012–2016) $N = 4785$ (%)	Proportion of chemotherapy (row %)	p-value
Gender							
Male	4496 (52%)	2033 (52)	33%	**.002**	2463 (51)	39%	**<.001**
Female	4230 (48)	1908 (48)	29%		2322 (49)	34%	
Age (years)				**<.001**			**<.001**
<50	413 (5%)	207 (5)	52%		206 (4)	67%	
50–59	1427 (16%)	683 (17)	46%		744 (16)	57%	
60–69	2857 (33%)	1294 (33)	41%		1563 (33)	47%	
70–79	2832 (32%)	1229 (31)	21%		1603 (36)	27%	
≥80	1197 (14%)	528 (13)	4%		669 (14)	4%	
Socioeconomic status				**.017**			**.016**
High	2619 (30)	1207 (31)	32%		1412 (30)	39%	
Medium	3490 (40)	1552 (39)	33%		1938 (41)	37%	
Low	2617 (30)	1182 (30)	28%		1435 (30)	34%	
Pathologically confirmed				**<.001**			**<.001**
Yes	6430 (74%)	2814 (71)	39%		3616 (76)	45%	
No	2296 (26)	1127 (29)	13%		1169 (24)	12%	
Primary tumor location				**<.001**			**<.001**
Head of pancreas	4121 (47%)	1971 (50)	28%		2150 (45)	33%	
Body of pancreas	1317 (15%)	552 (14)	36%		765 (16)	43%	
Tail of pancreas	1874 (21%)	784 (20)	38%		1090 (23)	40%	
Other	1414 (16%)	634 (16)	30%		780 (16)	37%	
Metastatic site				**<.001**			.114
Liver	4384 (50%)	2098 (53)	32%		2286 (48)	36%	
Lung	401 (5%)	187 (5)	21%		214 (5)	33%	
Peritoneum	746 (9%)	306 (8)	26%		440 (9)	39%	
Extra regional lymph nodes	317 (4%)	143 (4)	29%		174 (4)	41%	
Other	195 (2%)	88 (2)	18%		107 (20	26%	
2 Metastatic sites[a]	1920 (22%)	812 (21)	33%		1108 (23)	38%	
3 or more metastatic sites[a]	730 (8%)	275 (7)	37%		455 (10)	36%	
Unknown	33 (<1%)	32 (1)	22%		1 (<1)	–	

Bold numbers indicate statistical significance.
[a]Any combination of metastatic sites.

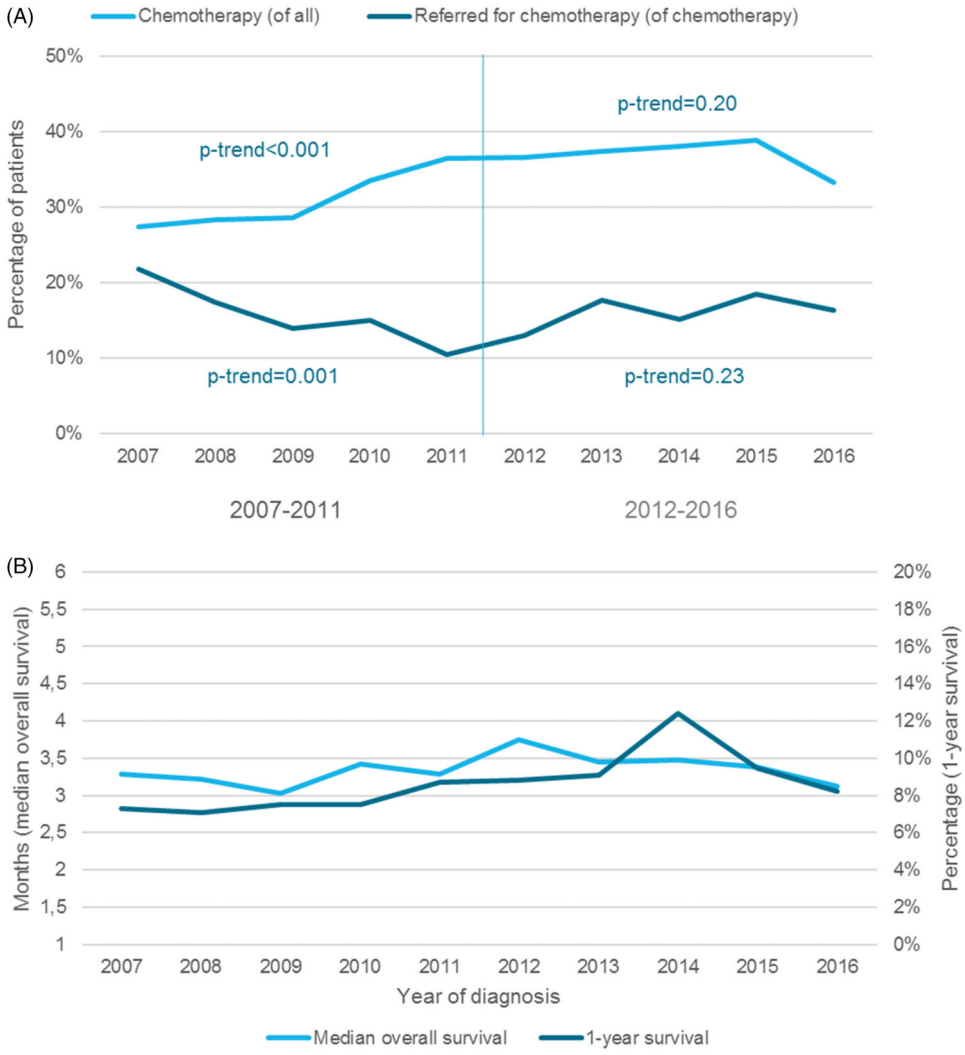

Figure 1. Use of chemotherapy in and survival of all patients with metastatic pancreatic ductal adenocarcinoma in 2007–2016. (A) Use of chemotherapy in patients with metastatic pancreatic ductal adenocarcinoma and the percentage of patients that were referred for chemotherapy treatment in 2007–2011 and 2012–2016 in the Netherlands. (B) Median overall survival and 1-year survival of all patients with metastatic pancreatic ductal adenocarcinoma in 2007–2016.

PDAC: 60 (IQR 58–67) hospitals per year in the period 2007–2011 and 71 (IQR 70–72) hospitals in the period 2012–2016 ($p = .009$). The median number of patients receiving chemotherapy per treating hospital was 13 and 21 patients per five-year period, respectively.

Between individual hospitals of diagnosis, a large variation in chemotherapy prescription for patients with metastatic pancreatic cancer was found (observed range in 2007–2011: 6.3–87%, 2012–2016: 14–62%). Multilevel analyses, adjusted for patient and tumor characteristics, showed that this variation decreased over time (adjusted probabilities ranges: 12–67% and 20–54%, and ICC: 14% and 6%, respectively, Supplementary Figure 1). Sensitivity analyses showed similar ranges between hospitals (Supplementary Table 1). In hospitals with high volumes of chemotherapy and in hospitals with high volumes of diagnoses, the likelihood of receiving chemotherapy was significantly higher (respectively, compared to medium and low volumes in both time periods and compared to low volumes in 2007–2011 only, Table 2). Being diagnosed in a university hospital or a center for pancreatic surgery was not associated with the likelihood of receiving chemotherapy.

Overall survival

Patients who received chemotherapy had a median overall survival of 6.0 months (95%CI 5.8–6.2) compared to 2.5 months (95%CI 2.4–2.6) in patients without chemotherapy use ($p < .001$). In all patients, median overall survival slightly improved between 2007–2011 and 2012–2016 (3.3 vs. 3.4 months, $p < .001$) with a 1-year survival of 7.6% vs. 9.6% respectively (Table 3, Figure 1(B)). After adjustment for patient and tumor characteristics, patients in 2012–2016 had a significantly higher overall survival compared with patients in 2007–2011 in multivariable Cox regression (adjusted HR 0.91, 95%CI 0.87–0.95, $p < .001$). Besides increased chemotherapy use, patients treated with chemotherapy in 2012–2016 also had slightly better median overall survival (6.4 months vs. 5.6 months, $p < .001$) and 1-year overall survival (20% vs. 15%) than in 2007–2011 (adjusted HR 0.82, 95%CI 0.76–0.89). Median overall survival did not increase sequentially per year (6.5–6.2–6.4–6.3–6.7 months in 2012–2013–2014–2015–2016).

In 2007–2011, patients diagnosed in hospitals with low and intermediate probabilities of receiving chemotherapy

Table 2. Proportion of patients receiving chemotherapy and multivariable multilevel logistic regression to investigate hospital-related predictors for chemotherapy use in patients diagnosed with metastatic pancreatic ductal adenocarcinoma in the Netherlands in 2007–2016, for 2 periods of diagnosis separately.

	Period 2007–2011				Period 2012–2016			
Hospital measures[a]	% of patients with chemotherapy	*p*-value	OR (95% CI)	*p*-value	% of patients with chemotherapy	*p*-value	OR (95% CI)	*p*-value
Classification 1								
Type of hospital		.858				.236		
University	31.5		1.00 (reference)		33.7		1.00 (reference)	
Non-university	31.1		1.66 (0.93–2.99)	.088	37.0		1.48 (0.98–2.24)	.065
Classification 2								
Hospital volume of diagnoses		.057				.467		
High	32.2		1.00 (reference)		37.0		1.00 (reference)	
Medium	33.0		0.86 (0.66–1.12)	.260	35.5		0.89 (0.72–1.12)	.322
Low	29.1		**0.66 (0.49–0.89)**	**.006**	37.6		0.96 (0.77–1.21)	.761
Classification 3								
Hospital volume of chemotherapy		<.001				<.001		
High	47.9		1.00 (reference)		44.5		1.00 (reference)	
Medium	38.0		**0.62 (0.47–0.80)**	**<.001**	38.0		**0.76 (0.64–0.91)**	**.003**
Low	19.9		**0.24 (0.19–0.31)**	**<.001**	25.3		**0.37 (0.30–0.46)**	**<.001**
Classification 4			Not applicable					
Pancreatic center (surgery)						.104		.052
No					37.5		1.00 (reference)	
Yes					34.9		0.77 (0.59–1.00)	

Bold numbers indicate statistical significance.
P: percentage of patients receiving chemotherapy; OR: odds ratio; CI: confidence interval.
[a]Individual hospital classifications were adjusted for sex, age, SES, pathological confirmation, location of primary tumor, number and location of distant metastases, and hospital of diagnosis by using multilevel regression analysis.

Table 3. Univariable and multivariable Cox regression analyses of overall survival for all patients with metastatic pancreatic ductal adenocarcinoma in the Netherlands in 2007–2016, overall and for 2 periods of diagnosis separately.

	N =	Crude 1-year OS (%)	Univariable HR (95% CI)	Multivariable[a] HR (95% CI)	*p*-value
All patients					
Period					
2007–2011	3941	7.6	1.00 (reference)	1.00 (reference)	
2012–2016	4785	9.6	**0.92 (0.88–0.96)**	**0.91 (0.87–0.95)**	**<.001**
Period 2007–2011					
Chemotherapy treatment probability[b]					
High (36%–67%)	1275	9.4	1.00 (reference)	1.00 (reference)	
Medium (25%–35%)	1344	7.9	**1.13 (1.04–1.22)**	**1.12 (1.03–1.20)**	**<.001**
Low (12%–25%)	1322	5.7	**1.22 (1.13–1.32)**	**1.21 (1.12–1.31)**	**.006**
Period 2012–2016					
Chemotherapy treatment probability[b]					
High (40%–54%)	1543	11.4	1.00 (reference)	1.00 (reference)	
Medium (35%–39%)	1571	9.4	**1.09 (1.01–1.17)**	1.05 (0.98–1.13)	**.202**
Low (20%–34%)	1671	8.2	**1.19 (1.11–1.28)**	**1.13 (1.05–1.21)**	**.001**

Bold numbers indicate statistical significance.
[a]Adjusted for sex, age, SES, pathological confirmation, location of primary tumor, number and location of distant metastases.
[b]Within periods of diagnosis patients were evenly divided into three groups according to the adjusted probabilities of receiving chemotherapy (per hospital per period) based on the hospital of diagnosis.

had a significant lower overall survival compared to patients in hospitals with high probabilities (adjusted HR 1.21, 95%CI 1.12–1.31 and 1.12, 95%CI 1.03–1.20, respectively, Table 3). In 2012–2016, a significant worse survival was only found in patients diagnosed in hospitals with a low probability of receiving chemotherapy treatment compared to a high probability (adjusted HR 1.13, 95%CI 1.05–1.21, Table 3).

Nationwide variation in type of chemotherapy

In 2015–2016, 36% of all patients (723 patients) received chemotherapy of whom most patients received the newly introduced regimens: 436 patients FOLFIRINOX (60%) and 70 patients gemcitabine plus nab-paclitaxel (9.7%, Supplementary Table 2). The remaining patients received gemcitabine only (182 patients, 25%), and other or unknown chemotherapy regimens (35 patients, 4.8%). FOLFIRINOX was given in nearly all hospitals (72/74 hospitals of treatment in 2015–2016), while less than one-third of hospitals administered gemcitabine plus nab-paclitaxel (22/74, Figure 2). Gemcitabine monotherapy was administered to a relatively low proportion of patients in university hospitals. In general, patients treated with FOLFIRINOX were younger (median 61 vs. 66–70 years) and had a better performance score compared to patients treated with other regimens (WHO 0–1 in 70% vs. 44–69%). Compared to patients treated with gemcitabine, patients receiving FOLFIRINOX and gemcitabine plus nab-paclitaxel had a significantly higher median OS (3.8 months vs. 8.0 months vs. 7.0 months respectively). In multivariable Cox regression the corresponding adjusted HR were 0.46 (95%CI 0.37–0.57, $p < .001$) and 0.46 (95%CI 0.34–0.63, $p < .001$), respectively, compared to gemcitabine only.

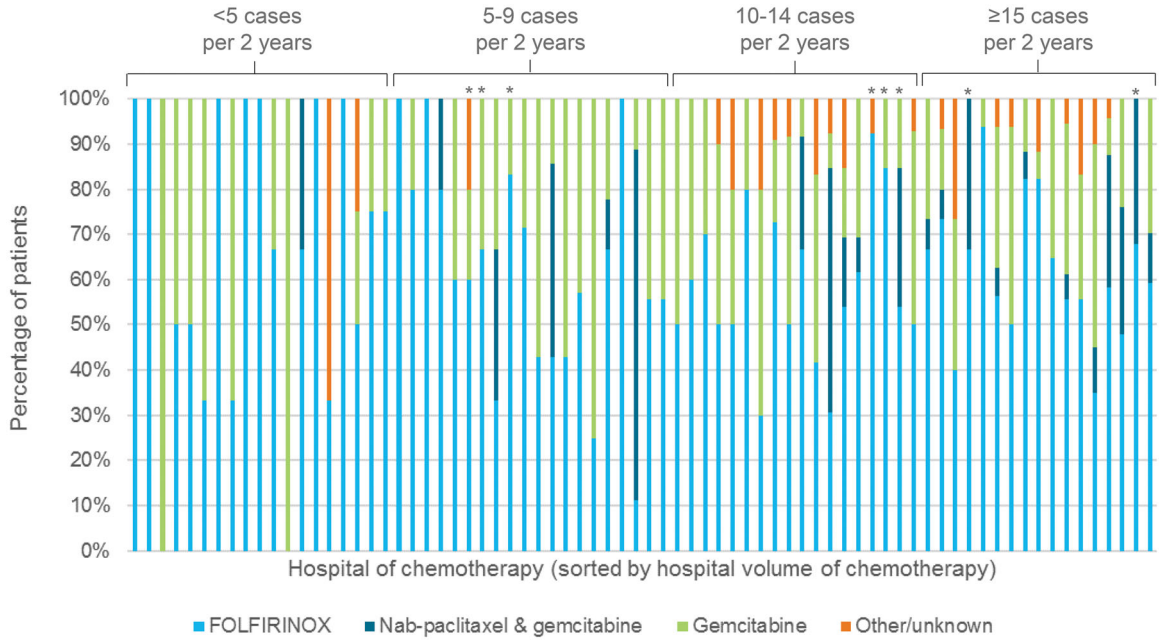

Figure 2. Proportions of type of chemotherapy per hospital of treatment for patients diagnosed with metastatic pancreatic ductal adenocarcinoma in 2015–2016, $N = 74/78$ hospitals prescribed chemotherapy. The number of patients receiving chemotherapy per 2 years was grouped and represented in the figure. The asterisk represents a university hospital.

Discussion

This population-based analysis of patients with metastatic PDAC showed that over the course of a decade the nationwide use of chemotherapy increased and the nationwide variation in the use of chemotherapy decreased. Since the introduction of FOLFIRINOX and gemcitabine with nab-paclitaxel the overall survival of all patients with metastatic disease increased slightly, yet significantly (from 0.1 to 0.8 months) although only one third of patients received chemotherapy. FOLFIRINOX was widely implemented in 2015–2016, but its use varied between hospitals. A considerable proportion of patients still received gemcitabine monotherapy. Nevertheless, differences in survival due to variation in use of chemotherapy between hospitals seem to have decreased over the study period.

During the last decade, on average 34% of patients with metastatic PDAC received chemotherapy in the Netherlands compared to 17–58% [9,10,15,19–22] reported from other countries. Between 2007–2011 and 2012–2016, an increase was observed in the use of chemotherapy. The volume of patients receiving chemotherapy per hospital increased, more hospitals prescribed chemotherapy and consequently the number of referrals to tertiary centers decreased. Moreover, variation between hospitals in the probability of receiving chemotherapy for metastatic PDAC per hospital decreased in 2012–2016. Hospitals with a higher volume of patients receiving chemotherapy had an increased likelihood of receiving chemotherapy in both 2007–2011 and 2012–2016. Hospital volume of diagnosis did affect the likelihood of receiving chemotherapy in 2007–2011, but this effect disappeared in 2012–2016. Type of hospital or pancreatic surgery centers did not affect the likelihood of receiving chemotherapy in both periods. There are several possible explanations for the increased use of chemotherapy (regardless of the type of chemotherapy) and the decrease in variation between hospitals: 1) the introduction of FOLFIRINOX and gemcitabine with nab-paclitaxel with reported higher survival benefits; 2) the rise of inter-hospital multidisciplinary meetings; and 3) the implementation of the national guideline on PDAC in 2011 [7,8,23].

On a population level, results of the new chemotherapy regimens on overall survival are somewhat disappointing. As expected, in patients receiving chemotherapy the survival increase was higher compared to patients who did not receive chemotherapy, but still only 0.8 months (24 days). The overall survival of patients treated with FOLFIRINOX was lower than in the randomized controlled trial (8.0 months in our study vs. 11.1 months in the trial of Conroy et al. [7]). This was also the case for gemcitabine with nab-paclitaxel (7.0 in our study vs. 8.7 months in the trial of Goldstein et al. [8]). The limited effect on survival on population level probably originates from differences in patient selection compared to clinical trials. Another study [24] including patients with advanced pancreatic cancer from a single institution showed that survival could achieve benefits as shown in randomized clinical trials, but that this differed between treatment regimens. Moreover, the study demonstrated protocol adherence to be one of the explanations for differences between real-world outcomes and results in randomized controlled trials. Both the effects of patient selection and protocol adherence emphasize the importance of population-based studies to show real-life effects of new treatments [25].

Remarkably, gemcitabine was still often prescribed (25%). The median overall survival of patients receiving this regimen was considerably low (3.8 months) compared to the new chemotherapy regimens (FOLFIRINOX and gemcitabine plus nab-paclitaxel 8.0 and 7.0 months, respectively) and to patients without chemotherapy use (2.5 months). This could

be related to worse performance status in these patients. A population-based study from the United States [13] found a rapid decline of the use of gemcitabine monotherapy after 2009. Gemcitabine can be considered currently in patients not eligible for FOLFIRINOX or gemcitabine with nab-paclitaxel. In daily practice these are patients with multiple comorbidities, a WHO performance status of $\geq$2, or patients older than 75 years, because those patients were not included in the previously mentioned trial [7]. In our cohort, gemcitabine was not only prescribed in this selected population, but it was also given to patients younger than 70 years old, with a WHO performance score of 0, and without comorbidities. Probably the relatively severe toxicity of these new regimens, and the inexperience with the chemotherapy combinations restrain the medical oncologist in prescribing these drugs [26].

Based on the results, speculations for future perspectives could be made. Better outcomes on population level and a decrease of variation might be achieved by further implementation of the new chemotherapy regimens. Enhanced implementation of new treatments should be performed on a national scale by a structured approach. It could be considered to centralize (palliative) care of PDAC, because in 2012–2016 there still was a difference in the probability of receiving chemotherapy between centers (however less pronounced compared to 2007–2011). Also, type of chemotherapy prescribed was highly variable between hospitals. In pancreatic surgery, centralization increased resection rates and reduced mortality [27,28]. In palliative care there is limited data on the benefit of centralization, or at least centralized assessment, but it has been demonstrated that volume matters regarding the use of chemotherapy [15].

This study has some limitations. First, the incidence of PDAC is underestimated in the NCR. The missing patient group consists especially of elderly patients without pathological confirmation of cancer, patients with no cancer treatment and patients with a very poor survival [29]. To reduce the influence of possible incompleteness, only patients alive at 30 days after diagnosis were included. Sensitivity analyses addressing these limitations (selecting younger patients, pathologically confirmed PDAC or patients alive at 60 days after diagnosis) showed similar patterns. Second, treatment allocation bias could have occurred. To reduce this bias, patients who died within 30 days after diagnosis were excluded. Third, important case-mix factors like comorbid conditions and performance status were not available in the total study period. However, a similar pattern was found in sensitivity analysis including these factors. Fourth, details about chemotherapy regimens were only available for the 2015–2016 period. Possible trends in the use of FOLFIRINOX and nab-paclitaxel with gemcitabine could not be confirmed.

In conclusion, nationwide variation in the use of chemotherapy in patients with metastatic PDAC decreased after the implementation of FOLFIRINOX and gemcitabine with nab-paclitaxel in 2012–2016. Nevertheless, a considerable proportion of patients still received gemcitabine with a disappointing survival benefit. This study clearly shows that the implementation of more effective chemotherapeutic regimens in patients with metastatic PDAC is difficult and does not translate directly to a clinically relevant improvement in overall survival. These results emphasize the need for a structured implementation of new and more effective chemotherapeutic regimens in order to increase the use of these regimens and further decrease prescription variations.

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