A nationwide evaluation of pancreatic cancer treatment

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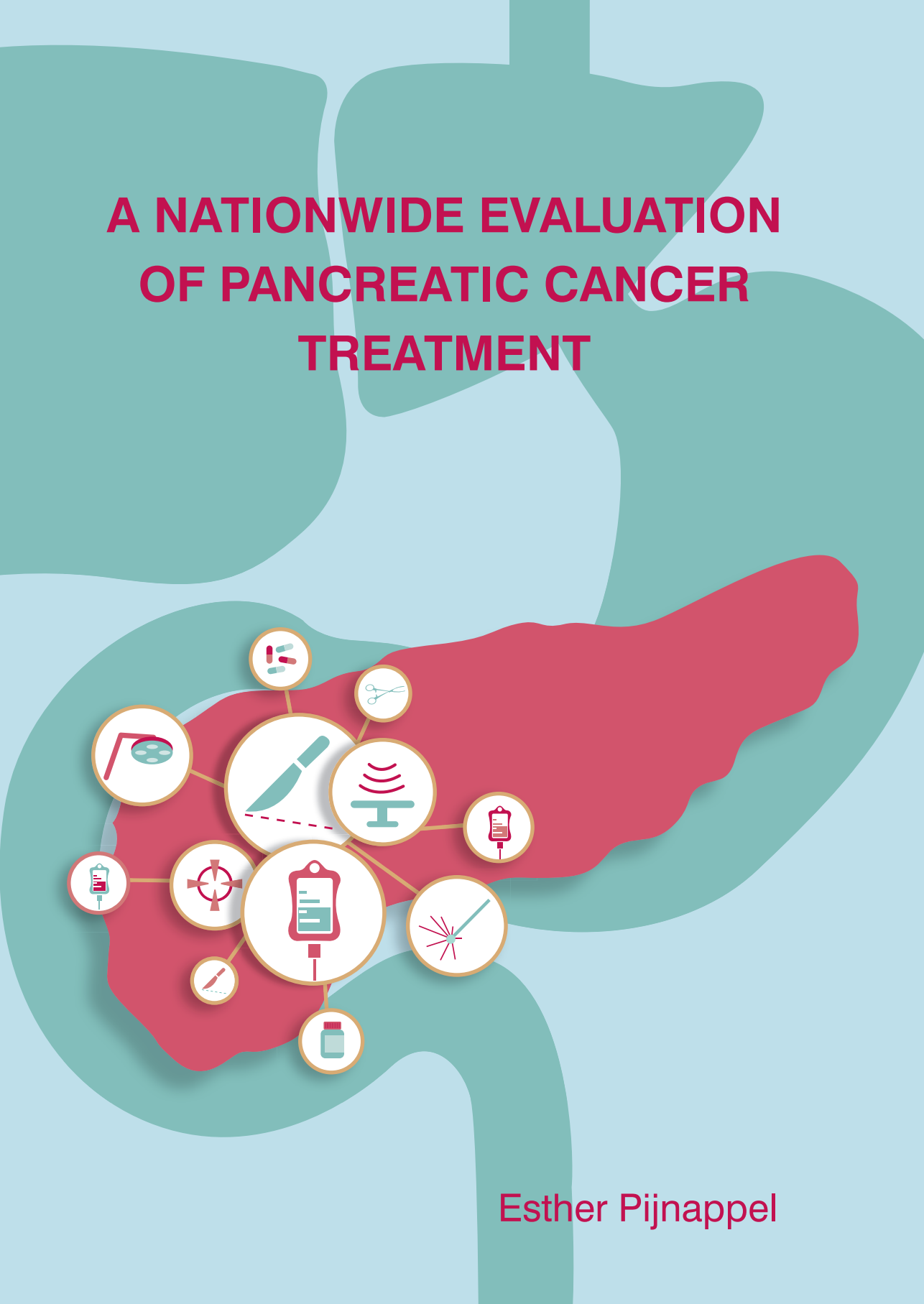

Esther Pijnappel

A NATIONWIDE EVALUATION OF PANCREATIC CANCER TREATMENT

Esther Pijnappel

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A NATIONWIDE EVALUATION OF PANCREATIC CANCER TREATMENT

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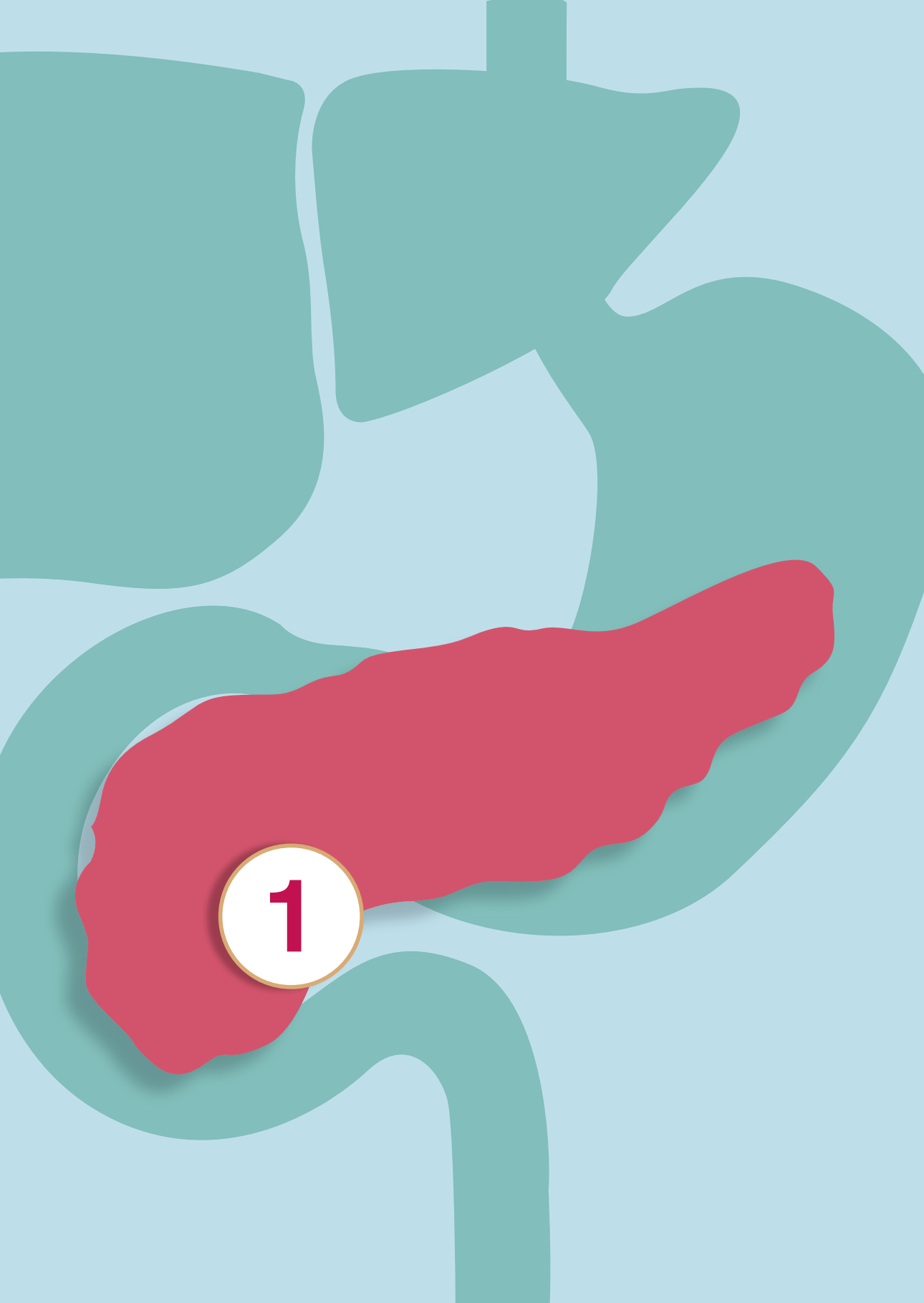
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CHAPTER1

Generalintroductionandoutlineofthisthesis

GENERAL INTRODUCTION

Function of the pancreas and development of pancreatic cancer

The pancreas is located in the upper abdomen behind the stomach in the retroperitoneal region, surrounded by the duodenum, gallbladder and spleen[1]. The pancreas is a gland anatomically subdivided into a head, body, and tail, with two main functions. The endocrine function regulates blood glucose levels by producing insulin and glucagon. The exocrine function plays an important role in the digestion of fats, carbohydrates and proteins with the production of pancreatic enzymes. These enzymes together with the bile that originates from the liver through the bile duct enter the duodenum via the ampulla of Vater and are essential in the digestion process[1].

Pancreatic cancer can develop from both exocrine and endocrine cells. The most common type of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC), derived from exocrine cells and is the main focus of this thesis (hereafter called pancreatic cancer)[2].

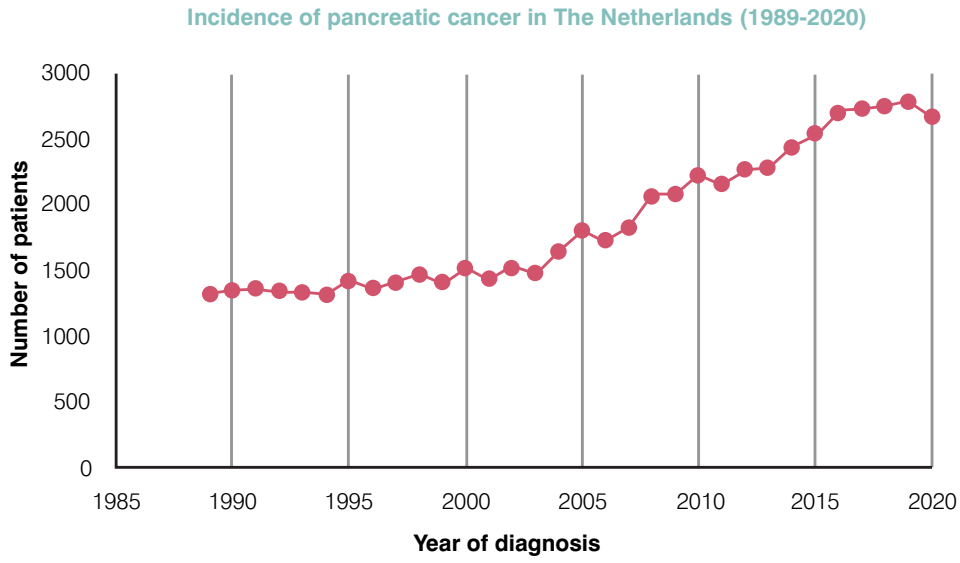

Figure 1. Incidence of pancreatic cancer in The Netherlands (1989-2020)

The numbers for 2019 and 2020 are based on estimations. Source: Netherlands Cancer Registry.

Epidemiology and symptoms of pancreatic cancer

In The Netherlands over 2,500 patients are diagnosed with pancreatic cancer on a yearly basis[3]. Patients with pancreatic cancer are predominantly male[3-5]. In 2019, the incidence rate for pancreatic cancer in men was 1,324 (52%) compared to 1,245 in women (48%)[3]. Due to its rising incidence and the lack of treatment improvements, pancreatic cancer is expected to be the second leading cause of cancer related death in 2030[6]. The median overall survival of pancreatic cancer patients is approximately four months[7]. This low survival can be explained by the fact that 80-85% of patients are diagnosed with locally advanced or metastatic disease and are no candidate for the only potentially curative treatment option, which is surgery in combination with systemic treatment[7, 8]. The majority of patients has an advanced disease stage at the time of diagnosis, probably because the symptoms associated with pancreatic cancer (e.g., fatigue, abdominal pain, weight loss and gastrointestinal problems) are not specific and can also be associated with more common and harmless causes[9].

Current treatment of pancreatic cancer

The treatment for patients with pancreatic cancer is dependent on the disease stage. There are three possible treatment modalities for pancreatic cancer patients; surgery, systemic treatment, and best supportive care. In the Netherlands, the standard of care for patients with (borderline) resectable disease includes resection, whether or not preceded by neoadjuvant treatment (e.g. chemotherapy), followed by adjuvant chemotherapy[10]. Patients with locally advanced pancreatic cancer receive chemotherapy after which a small subgroup (10-30%) can undergo resection or ablation in clinical studies[11]. For patients with metastatic disease standard care consists of palliative systemic treatment[12]. The percentage of patients undergoing resection is only 10-20%[7]. Even patients receiving this potential curative treatment have a poor median overall survival (OS) of 17-23 months[7, 13]. Since most patients have metastatic disease at diagnosis, the focus of this thesis lies on this disease stage. Unfortunately, there is still uncertainty about the optimal treatment for individual patients with metastatic pancreatic cancer.

First of all, there are limited therapeutic options after first-line systemic treatment. In the Netherlands, 28% of patients with metastatic pancreatic cancer receive systemic treatment with a median (OS) of six months[7]. For several decades, single-agent gemcitabine has been standard palliative care. It is well tolerated with few severe toxicities and associated with a significantly longer median OS of 5.7 months compared to 4.4 months with fluorouracil monotherapy[14]. After the introduction of gemcitabine, therapeutic improvements have been slow. Many cytotoxic agents in combination with gemcitabine did not show any improvement in OS or quality of life (QoL)[14]. Fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) was the first advance in treatment since the introduction of gemcitabine monotherapy. It showed an OS of 11.1 months, progression free survival (PFS) of 6.4 months and patients reported major improvements in the global QoL score[14-16]. Despite significant improvements in OS and QoL, FOLFIRINOX is also associated

with a higher incidence of grade 3/4 toxicities such as severe (febrile) neutropenia. Therefore, FOLFIRINOX may only be beneficial for patients with a good performance status (0-1), which include only 10-15% of the patients with advanced disease[14, 17, 18]. In addition to FOLFIRINOX, gemcitabine combined with nab-paclitaxel is one of the other currently used chemotherapy regimens. Gemcitabine and nab-paclitaxel showed a significantly longer OS of 8.7 vs 6.6 months for gemcitabine monotherapy. Since toxicity levels were not increased compared to gemcitabine monotherapy, gemcitabine and nab-paclitaxel is the recommended treatment for patients with a less optimal (>1) performance status[16, 19-21]. Most patients, approximately 70%, with metastatic disease receive, due to poor performance status or patient preference, best supportive care (BSC) only. BSC consists of for instance pain medication, palliative radiation therapy, biliary drainage and pancreatic enzymes supplementation. Both systemic treatment and BSC can prolong survival and increase QoL[22]. Nowadays FOLRIFINOX and gemcitabine with or without nab-paclitaxel are widely used first-line regimes[23]. However, there is scarce evidence for second-line systemic treatment for metastatic pancreatic cancer, especially after FOLFIRINOX[24, 25], and international consensus on the most optimal first and second-line palliative systemic treatment regimen is lacking. Since FOLFIRINOX is the recommended first-line treatment for patients with metastatic pancreatic cancer in The Netherlands, there is desperate need for a suitable second-line treatment after FOLFIRINOX failure.

Second, current practice for both patients with resectable and metastatic pancreatic cancer is primarily based on the results of randomized controlled trials (RCTs)[21, 26]. The reason why clinical practice is mainly based on the outcome of RCTs, is because the probability of introducing bias is limited due to the randomization. However, patients in RCTs have to meet strict eligibility criteria before entering and tend to have better performance status and less comorbidities than patients treated outside RCTs. Therefore, RCTs include a very selected patient group and may not sufficiently reflect the patient population as seen in daily clinical practice[27]. For instance, elderly and fragile patients are not included in most clinical trials. Studies that include patients with pancreatic cancer who are not eligible for RCTs are a valuable addition to trial results, because it deepens our understanding of the adherence to guidelines and outcome of therapies in the patients we encounter on a day-by-day basis. In addition, there is a great variety in selection of patients and reported baseline and prognostic factors among RCTs in this patient group. To compare outcomes of RCTs, a complete definition of the study population is crucial. Therefore, improvement of the reporting of these baseline and prognostic factors in RCTs could lead to better comparison of outcomes across studies in the future.

Moreover, because of the small differences in OS between the specific treatment options, more attention should be raised for the QoL of patients with pancreatic cancer. Treatment allocation not only affects a patient's survival, but also the QoL[22]. The Dutch Pancreatic Cancer Project (PACAP) is a nationwide project that was founded in 2013 by the Dutch Pancreatic Cancer Group

(DPCG). PACAP is a registry that comprises data on clinical information and patient reported outcome measures (PROMs) including, among others, information on health-related QoL[28, 29]. These registries facilitate the identification of therapy trends and guideline compliance and can be used to describe and ultimately improve the patient outcome such as patients' satisfaction and QoL in combination with survival outcome data[30]. Since patients with pancreatic cancer report a high symptom burden and have a poor prognosis, QoL and its relation to other outcome measures is of particular interest[31].

Lastly, treatment effects might be different in specific subgroups. Many studies have reported that pancreatic cancer has a higher incidence in men than in women[3-5, 32, 33]. Moreover, worse survival has been described for men with pancreatic cancer compared to women[3-5, 32, 33]. It is currently unknown whether there are gender differences in treatment allocation and overall survival in patients with pancreatic cancer in The Netherlands. Investigation of variation in treatment allocation and clinical characteristics of both men and women with pancreatic cancer is essential in order to explain potential differences in outcome and optimize the personalization of treatment strategies for subgroups (e.g. gender-based).

The above-mentioned issues regarding the optimal therapy for patients with pancreatic cancer are investigated in this thesis.

OUTLINE OF THIS THESIS

The objective of the studies in this thesis is to improve the outcome of patients with pancreatic cancer and describe the use and OS of first and second-line systemic treatment for patients with advanced disease. In addition, factors that should be reported in future RCTs for patients with resectable disease are identified, facilitating better comparison between studies. Furthermore, quality of life and patient characteristics that may influence treatment allocation and outcome are evaluated.

Chapter 2 describes first and second-line systemic treatment in patients with metastatic pancreatic cancer in Dutch clinical practice and analyses the association between first and second-line treatment regimen on overall survival.

Since FOLFIRINOX is the recommended first-line treatment for patients with metastatic pancreatic cancer in The Netherlands, there is a desperate need for a suitable second-line treatment after FOLFIRINOX failure. In **Chapter 3**, the efficacy and safety of LDE225 in combination with gemcitabine and nab-paclitaxel after prior treatment with FOLFIRINOX in first-line for patients with metastatic disease is evaluated.

Nowadays, there is a great variety in selection of patients and reported baseline and prognostic factors among RCTs in patients with resectable and borderline resectable pancreatic cancer. Therefore, improvement of the reporting of these baseline and prognostic factors could lead to better comparison of outcomes across studies. In **Chapter 4 and 5** mandatory reporting measurements in trials for potentially resectable pancreatic cancer were identified.

The fear of cancer recurrence and progression in patients with pancreatic cancer is assessed in **Chapter 6**. Due to late detection and its unfavorable prognosis, the risk of progression or recurrence of pancreatic cancer is considerable. It is plausible that patients with pancreatic cancer experience fear of tumor recurrence or progression. The aim was to compare the fear of cancer recurrence or progression in patients with pancreatic cancer treated with surgical resection, palliative systemic treatment or best supportive care (BSC).

Biological sex, gender, and age have an impact on the incidence and outcome in patients with metastatic pancreatic cancer. Whether biological sex, gender and age are associated with the treatment allocation and overall survival (OS) of patients with metastatic pancreatic cancer is investigated in **Chapter 7**.

Summary of the research questions in this thesis

Chapter	Research question
2	*What is the nationwide use of first and second-line systemic treatment in patients with metastatic pancreatic cancer in The Netherlands and what is their effectiveness in terms of overall survival?*
3	*What is the safety and efficacy of second-line treatment with the hedgehog inhibitor LDE225 in combination with gemcitabine and nab-paclitaxel in FOLFIRINOX pretreated patients with metastatic pancreatic cancer?*
4 & 5	*Which baseline and prognostic factors should be regarded mandatory in randomized controlled trials for patients with resectable pancreatic cancer?*
6	*To what extent is the fear of progression or recurrence of the disease present in patients with pancreatic cancer and what is the association between quality of life and overall survival and the fear of progression or recurrence of the disease?*
7	*Are biological sex and gender of patients with metastatic pancreatic cancer associated with treatment allocation and overall survival?*

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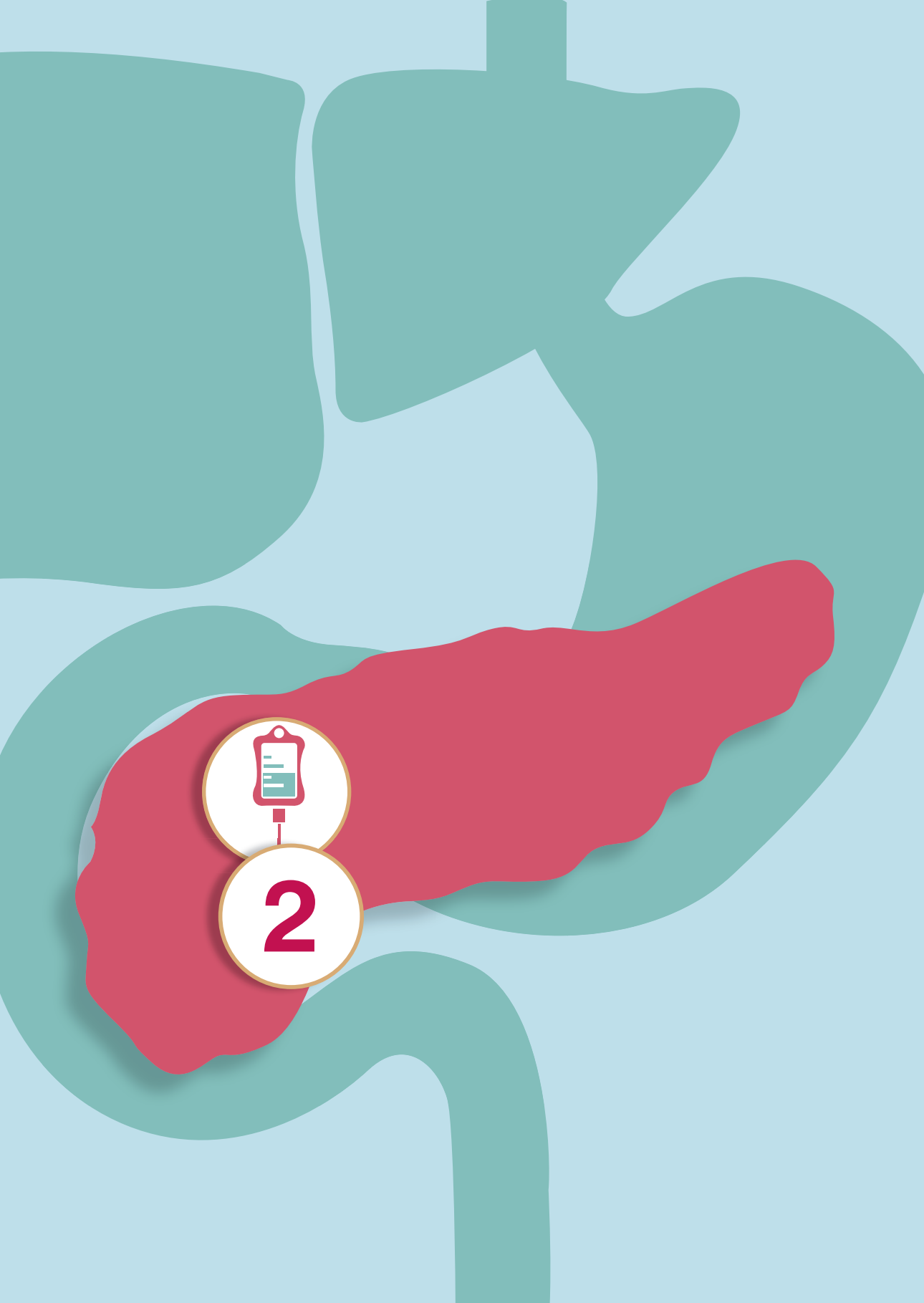
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CHAPTER 2

First and second-line palliative systemic treatment outcomes in a real-world metastatic pancreatic cancer cohort

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ABSTRACT

Background

Metastatic pancreatic ductal adenocarcinoma (PDAC) is characterized by a very poor survival rate, which can be improved by systemic treatment. Consensus on the most optimal first and second-line palliative systemic treatment is lacking. The aim of the study was to describe the use of first and second-line systemic treatment, overall survival (OS) and time to failure (TTF) of first and second-line treatment in metastatic PDAC in a real world setting.

Methods

Patients with synchronous metastatic PDAC diagnosed between 2015 and 2018 who received systemic treatment were selected from the nationwide Netherlands Cancer Registry. OS and TTF were evaluated using Kaplan Meier curves with log-rank test and multivariable Cox proportional hazard analyses.

Results

The majority of 1,586 included patients received FOLFIRINOX (65%), followed by gemcitabine (18%) and gemcitabine+nab-paclitaxel (13%) in first-line. Median OS for first-line FOLFIRINOX, gemcitabine+nab-paclitaxel and gemcitabine monotherapy was 6.6, 4.7 and 2.9 months, respectively. Compared to FOLFIRINOX, gemcitabine+nab-paclitaxel showed significantly inferior OS after adjustment for confounders (hazard ratio [HR] 1.20, 95% CI 1.02-1.40), and gemcitabine monotherapy was independently associated with a shorter OS and TTF (HR 1.98, 95% CI 1.70-2.30 and HR 2.31, 95% CI 1.88-2.83, respectively). Of the 121 patients who received second-line systemic treatment, 33% received gemcitabine+nab-paclitaxel, followed by gemcitabine (31%) and FOLFIRINOX (10%).

Conclusion

Based on population-based data in patients with metastatic PDAC, treatment predominantly consists of FOLFIRINOX in the first and gemcitabine with or without nab-paclitaxel in the second-line. FOLFIRINOX in first-line shows superior OS compared with gemcitabine with or without nab-paclitaxel.

INTRODUCTION

Despite recent therapeutic advances, the prognosis of patients with metastatic pancreatic ductal adenocarcinoma (PDAC) remains poor[1,2]. Because more than 80% of patients with pancreatic cancer are diagnosed at an advanced stage, chemotherapy is the cornerstone of treatment[3-5]. However, international consensus on the most optimal first and second-line palliative systemic treatment regimen is lacking.

Since 1997, single-agent gemcitabine has been the standard first-line palliative treatment,[3-7] and progress in the development of new agents has been slow. Many cytotoxic agents in combination with gemcitabine did not show improvement in overall survival (OS) or quality of life (QoL)[3-5,8-12]. In 2011 irinotecan, oxaliplatin and fluorouracil (5-FU) (FOLFIRINOX) was the first treatment regimen that showed a significant advancement (OS of 11.1 months) over gemcitabine but its use is generally restricted to patients with a good performance status[13]. Another chemotherapy combination that demonstrated a survival improvement compared with gemcitabine monotherapy was gemcitabine in combination with nab-paclitaxel with a median OS of 6.7 and 8.5 months respectively[5,14]. Nowadays FOLRIFINOX and gemcitabine with or without nab-paclitaxel are widely used first-line regimes[15], but there is limited evidence for second-line treatment for metastatic PDAC, especially after FOLFIRINOX[16,17]. In 2016 the NAPOLI-1 trial showed that nanoliposomal irinotecan in combination with 5-FU and folinic acid prolonged survival for patients previously treated with gemcitabine-based therapy in first-line with a median OS of 6.1 months[18].

Current practice is based on the results of randomized controlled trials (RCTs)[9,14]. However, these trials do not sufficiently reflect the patient population as seen in daily clinical practice[19]. For instance, elderly and fragile patients are not included in most clinical trials. Therefore, the aim of this real-world data study was to describe first and second-line systemic treatment in patients with metastatic PDAC, and analyze the association between first and second-line treatment regimens on OS and time to failure (TTF) of first and second-line treatment.

MATERIALS AND METHODS

Data collection

All patients diagnosed with synchronous metastatic PDAC in The Netherlands between 2015 and 2018 were identified in the Netherlands Cancer Registry (NCR) (see supplementary table 1). The NCR is a population-based registry that covers the total Dutch population of more than 17 million people and is directly linked to the pathological archive that comprises all histologically confirmed cancer diagnoses and is in combination with the National Hospital Discharge Register

a suitable representation of the metastatic PDAC patient population nationwide (microscopically verified and non-verified PDAC).

Information about the patient (sex, age, performance status, previous cancer diagnosis, comorbidities), tumor (TNM-stage, tumor histology, location of metastases), treatment (systemic treatment, radiotherapy, other palliative interventions such as stents/bypasses) and follow-up were recorded from the hospital's electronically health record system or medical records by trained registrars of the NCR.

Patients who received first-line systemic treatment outside the Netherlands were excluded (n=4). This study was designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[20].

Systemic therapy

First-line systemic treatment was defined as the first chemotherapeutic agent(s) given until discontinuation. A combination regimen was defined as all systemic agents starting within three days after the start of the first systemic agent. If the same therapy was restarted after a treatment break, this was still regarded first-line treatment. If one agent of a combination therapy discontinued but the other agents continued, this was considered as continuation of first-line therapy (e.g. irinotecan and 5-FU combination after FOLFIRINOX). Treatment was considered as next line if an agent of a new drug group was started that was not applied in the previous systemic treatment regimen.

Systemic therapy strategies, first and second-line, were classified into the following regimens: FOLFIRINOX, gemcitabine monotherapy, gemcitabine+nab-paclitaxel and other. FOLFIRINOX was assumed if only oxaliplatin and irinotecan were registered (n=6). Targeted therapy in addition to FOLFIRINOX or in combination with gemcitabine+nab-paclitaxel was ignored (n=5). If the start date of first-line palliative systemic therapy was missing (n=6), we used the date of diagnosis to calculate the survival rates. If the start date of second-line palliative systemic therapy was missing (n=3), we used the stop date of first-line treatment as start date of second-line treatment to calculate the survival rates.
Second-line systemic treatment was described in patients in whom follow-up was completed, i.e. diagnosed in 2015-2016. The follow-up of sequential treatment lines of patients diagnosed in 2017 and 2018 was not entirely completed by the NCR, therefore these years were not included.

Overall survival (OS) and time to failure (TTF) of first-line treatment

OS was defined as time interval from start of first or second-line treatment until the end of follow-up or death, and updated on 1 February 2020. If the start date of first systemic treatment was missing, and in patients who received best supportive care only, OS was calculated since the day

of diagnosis. Since progression in the NCR is not registered according to formal RECIST criteria, we calculated TTF from start of treatment to end of follow-up or first termination of treatment, as representation of the progression-free survival. Data on TTF was only available for patients with complete follow-up (diagnosis in 2015-2016).

Statistical analysis

Data in this study were analyzed using SAS software (version 9.4, SAS institute, Cary, NC, USA). Baseline characteristics were described using means with standard deviations (SDs) or medians with interquartile ranges (IQRs) for continuous variables, and absolute numbers with percentages for categorical variables. Chi-square tests were used to analyze differences between groups (with and without systemic treatment) in combination with Fisher's exact tests where appropriate. A Kaplan Meier analysis described the median OS between the different treatment groups including log-rank test. To identify independently associated systemic treatment strategies for OS, multivariable Cox proportional hazard regression analyses were used with adjustments for sex, age, number of comorbidities, performance status, year of diagnosis and number of metastatic organ sites. The probability of a type-I error was set at 0.05.

RESULTS

Patient characteristics

A total of 5,892 patients with metastatic PDAC were included in this study (figure 1). Patients were predominantly male (52%) with a median age of 71 years (IQR 63-78; table 1). Most patients had pancreatic head tumors (42%), no comorbidities (40%) and one metastatic location at diagnosis (61%). Performance status was 0 to 1 in 36% of patients and was unknown in 46%.

Of all patients, 1,586 (27%) were treated with palliative systemic treatment. Patients treated with systemic therapy were significantly younger, had fewer comorbidities, and had a better performance status than those who did not receive systemic treatment (table 1).

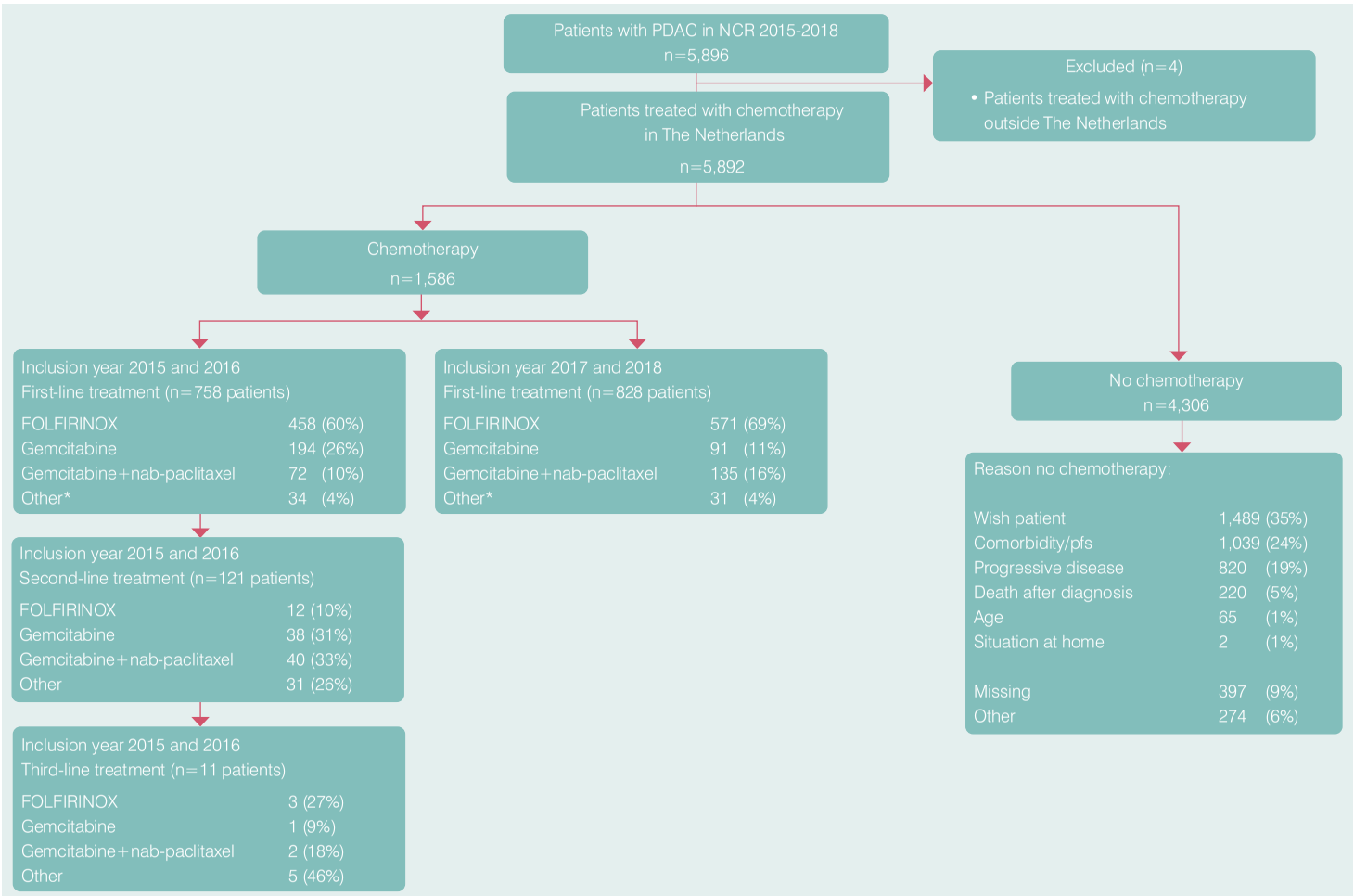

Figure 1. Study flow diagram

Abbreviations: PDAC, pancreatic ductal adenocarcinoma; NCR, Netherlands Cancer Registry; n, number; FOLFIRINOX, irinotecan/oxaliplatin/5-FU; PFS, performance status.

*Other consists of 14 different first-line regimen

Table 1. Baseline characteristics

Variable	Total (n=5,892)	Patients with chemotherapy (n=1,586)	Patients without chemotherapy (n=4,306)	P-value
Sex				
Male	3,049 (52%)	852 (54%)	2,197 (51%)	
Female	2,843 (48%)	734 (46%)	2,109 (49%)	0.0660
Age, median (years)	71 (IQR 63-78)	65 (IQR 58-70)	73 (IQR 66-80)	
<55	449 (8%)	264 (17%)	185 (4%)	
55-64	1,200 (20%)	512 (32%)	688 (16%)	
65-74	2,168 (37%)	639 (40%)	1,529 (36%)	
≥75	2,075 (35%)	171 (11%)	1,904 (44%)	<0.0001
Tumor location				
Head	2,465 (42%)	616 (39%)	1,849 (43%)	
Body	993 (17%)	318 (20%)	675 (16%)	
Tail	1,436 (24%)	400 (25%)	1,036 (24%)	
Overlapping sites	610 (10%)	166 (11%)	444 (10%)	
Pancreas NOS	388 (7%)	86 (5%)	302 (7%)	0.0001
Number of comorbidities				
0				
1	2,384 (40%)	827 (52%)	1,557 (36%)	
2	1,988 (34%)	502 (32%)	1,486 (34%)	
Missing	1,064 (18%)	169 (11%)	895 (21%)	
	456 (8%)	88 (5%)	368 (9%)	<0.0001
Performance status				
WHO 0-1	2,077 (36%)	996 (63%)	1,081 (25%)	
WHO 2	607 (10%)	166 (10%)	441 (10%)	
WHO 3-4	476 (8%)	25 (2%)	451 (11%)	
Unknown	2,732 (46%)	399 (25%)	2,333 (54%)	<0.0001
Year of diagnosis				
2015	1,378 (24%)	385 (24%)	993 (23%)	
2016	1,531 (26%)	373 (24%)	1,158 (27%)	
2017	1,481 (25%)	442 (28%)	1,039 (24%)	
2018	1,502 (25%)	386 (24%)	1,116 (26%)	0.0039
Number of metastatic sites				
1	3,569 (61%)	975 (61%)	2,594 (60%)	
≥2	2,323 (39%)	611 (39%)	1,712 (40%)	0.3900

Abbreviations: IQR, interquartile range; NOS, not otherwise specified; PS, performance status.

First and second-line systemic treatment regimens and strategies

We found seventeen different first-line regimens of which FOLFIRINOX (65%) was administered most often, followed by gemcitabine (18%), gemcitabine+nab-paclitaxel (13%), and other regimens (4%). The percentage of patients receiving treatment with FOLFIRINOX was comparable in the inclusion years 2015-2016 and 2017-2018. Compared with inclusion year 2015-2016, treatment with gemcitabine+nab-paclitaxel was given more often and fewer patients received gemcitabine monotherapy in 2017-2018.

In general, of the 1,586 patients who received first-line systemic therapy, 419 patients died and 339 patients did not die within 90 days after stopping treatment. Of the patients who died within 90 days, only 4% received second-line chemotherapy, and of the patients who did not die within 90 days, 31% received second-line chemotherapy (supplementary figure 1).

Of the 758 patients treated with first-line systemic therapy in 2015-2016, 121 (8%) patients received second-line treatment, consisting of gemcitabine+nab-paclitaxel (33%), gemcitabine (31%), FOLFIRINOX (10%), and other regimens (26%) [figure 2]. The proportion of patients who received second-line treatment after first-line treatment with gemcitabine was significantly lower compared with first-line treatment with FOLFIRINOX and gemcitabine+nab-paclitaxel (P=.0003). Patients who received second-line treatment were predominantly male (54%), had a median age of 62 years (IQR, 56–69years), had a performance status of 0–1 in most cases (59%), and largely had no comorbidities (75%). Cancer was diagnosed in the head (44%), body (20%), tail (20%), overlapping sites (12%), or a location not otherwise specified (4%) (data not shown).

Survival

Median OS (n=1,586) and median TTF (in patients diagnosed in 2015-2016, n=758) were 5.4 months (IQR 2.5-10.4 months) and 3.4 months (IQR 1.6-7.5 months) respectively, for patients who received first-line palliative systemic treatment (figure 3 and 4). For patients receiving FOLFIRINOX, median OS and TTF were 6.6 and 4.8 months, respectively, and the median OS for those with a performance status of 0–1 and 2 was 7.4 and 5.1 months, respectively (P=.043). For patients receiving gemcitabine+nab-paclitaxel, median OS and TTF were 4.7 and 4.1 months, respectively, and the median OS for those with a performance status of 0–1 and 2 was 4.3 and 5.2 months, respectively (P=.575). For gemcitabine monotherapy, the median OS and TTF were 2.9 and 1.9 months, respectively, and the median OS for those with a performance status of 0–1 and 2 was 3.9 and 2.4 months, respectively (P=.116) [figure 3 and 4]. When we restricted our analyses to patients with performance status 0-1, those treated with gemcitabine+nab-paclitaxel and gemcitabine monotherapy had an OS of 4.3 and 3.9 months respectively. Compared with FOLFIRINOX, gemcitabine+nab-paclitaxel showed significantly inferior OS after adjustment for confounders (adjusted hazard ratio [HR] 1.20, 95% confidence interval [CI] 1.02-1.40) but no significant inferior TTF (HR 1.22, 95% CI 0.92-1.62; table 2), whereas gemcitabine monotherapy

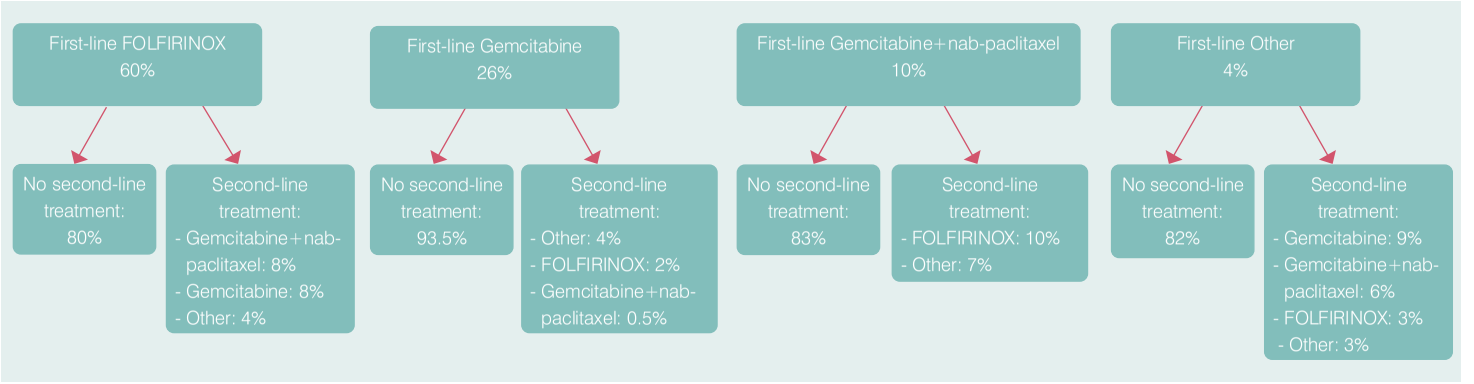

Figure 2. First- and second-line treatment administration in patients with metastatic PDAC diagnosed in 2015 and 2016

Abbreviation: FOLFIRINOX, irinotecan/oxaliplatin/5-FU

was independently associated with a shorter OS and TTF (HR 1.98, 95% CI 1.70-2.30 and HR 2.31, 95% CI 1.88-2.83 respectively; table 2 and 3).

In patients diagnosed in 2015-2016 who received second-line systemic treatment (n=121), the median OS since start of second-line treatment was 4.6 (IQR 2.5-8.3) months. Numbers were too small to analyze various treatment sequences.

Median OS for patients who received first-line treatment followed by best supportive care (BSC) was 4.1 months (n=637) and 11.2 months for patients who received first-and second-line treatment (n=121; figure 5). Median OS since day of diagnosis in patients who received BSC only (n=4,306) was 1.5 (IQR 0.8-3.0) months.

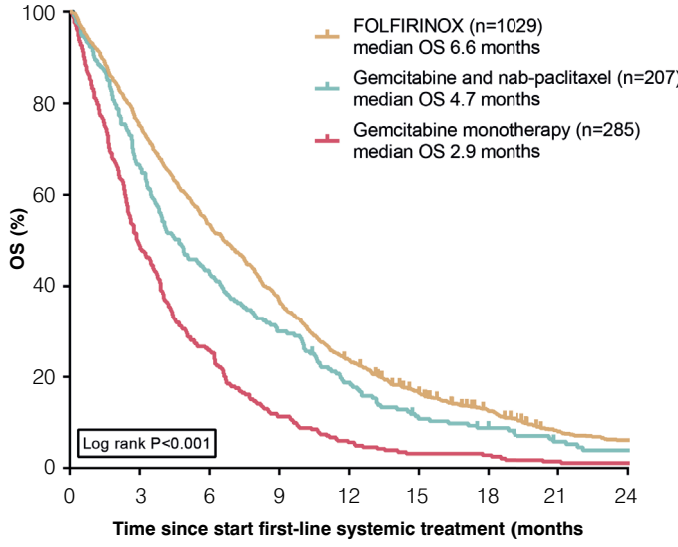

Figure 3. Kaplan Meier curves displaying overall survival in patients who received first-line systemic therapy

Overall survival is displayed for the treatment regimens that were administered in at least 100 patients. Patients who received "other" treatment (n=65) are not depicted. Abbreviations: FOLFIRINOX, irinotecan/oxaliplatin/5-FU; OS, overall survival.

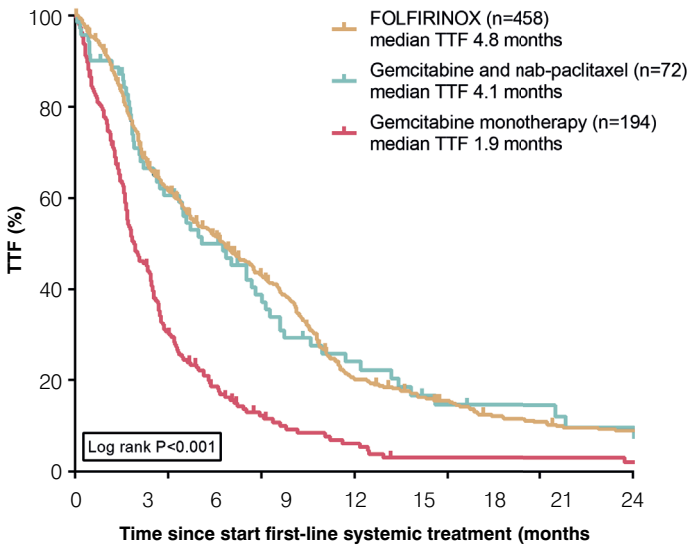

Figure 4. Kaplan-Meier curves displaying time to failure in patients diagnosed in 2015-2016 who received first-line systemic therapy

Patients who received "other" treatment (n=34) are not depicted. Abbreviations: FOLFIRINOX, irinotecan/oxaliplatin/5-FU; TTF, time to failure.

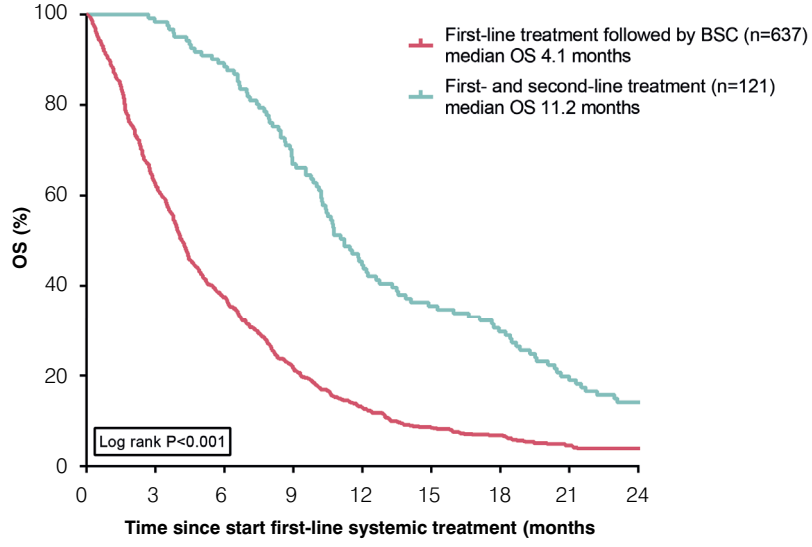

Figure 5. Kaplan-Meier curve displaying OS in patients who received first-line treatment followed by BSC andfirst- and second-line treatment

Abbreviations: BSC, best supportive care; OS, overall survival.

Table 2. Multivariable Cox-regression first-line systemic therapy

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
FOLFIRINOX (n=1,029)	ref			
Gemcitabine (n=285)	1.983	1.707	2.304	<.0001
Gemcitabine+nab-paclitaxel (n=207)	1.200	1.024	1.407	0.0244
Other (n=65)	1.042	0.800	1.357	0.7594

Adjusted for: sex, age, number of comorbidities, performance status, year of diagnosis and number of metastases locations
Reference group: FOLFIRINOX
Abbreviations: FOLFIRINOX, irinotecan/oxaliplatin/5-FU.

Table 3. Multivariable Cox-regression time to failure first-line systemic therapy

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
FOLFIRINOX (n=458)	ref			
Gemcitabine (n=194)	2.307	1.882	2.828	<.0001
Gemcitabine+nab-paclitaxel (n=72)	1.224	0.922	1.624	0.1627
Other (n=34)	1.318	0.855	2.032	0.2117

Adjusted for: sex, age, number of comorbidities, performance status, year of diagnosis and number of metastases locations
Reference group: FOLFIRINOX
Abbreviations: FOLFIRINOX, irinotecan/oxaliplatin/5-FU.

DISCUSSION

This nationwide study included 5,892 patients with synchronous metastatic PDAC diagnosed between 2015 and 2018, of whom 1,586 (27%) received palliative systemic treatment. FOLFIRINOX was the most frequently applied first-line treatment, with a superior OS compared with gemcitabine+nab-paclitaxel and gemcitabine monotherapy in multivariable analyses. A minority of patients received second-line treatment (8% of patients treated in first line), with a favorable survival compared with patients who received BSC (OS 11.2 versus 4.1 months $P<0.001$).

For both first and second-line systemic treatment the OS on a population based level is disappointing compared with the OS results of RCTs. The OS of patients who received first-line treatment with FOLFIRINOX in our study was 6.6 months compared with 11.1 months in the landmark RCT[13]. The same applies for gemcitabine+nab-paclitaxel and gemcitabine monotherapy (OS 4.7 and 2.9 months respectively in our study compared with 8.5 and 6.7

months respectively in the RCT[14]). This difference in OS might be explained by the different inclusion criteria in RCTs compared with population-based studies. Patients in RCTs have to meet strict inclusion and exclusion criteria before entering a clinical trial and tend to have, for example, better performance status and fewer comorbidities than patients treated outside a clinical trial. Performance status is one of the strongest predictors of OS in this setting[19,21], however even when we restricted our analyses to patients with performance status 0-1, the OS was still unsatisfactory compared with RCTs, it should be mentioned that performance status was not found in 25% of patients. Therefore, real-world data are a valuable addition to trial results because it deepens our understanding of the outcome of therapies in the patients we encounter on a day-by-day basis.

Overall survival of patients receiving (first-line) systemic treatment in our study was also lower compared with other real-world studies. OS of patients receiving FOLFIRINOX, gemcitabine+nab-paclitaxel and gemcitabine monotherapy in first-line treatment was 6.6, 4.7 and 2.9 months respectively in our study. Other real-world studies found OS of 14.1 and 9.0 months for FOLFIRINOX, 10.5 and 6.6 months for gemcitabine+nab-paclitaxel and 4.2 months for gemcitabine monotherapy[22-25]. This survival difference might be (partly) explained by differences in definition of OS. In our study, OS was defined as time from start of systemic treatment to death or the date of last follow-up, while OS in most other studies is defined as time from diagnosis to death[22,24,25]. The median time between diagnosis and start treatment in our study was 27 days (supplementary table 2). This could be specifically important to patients with pancreatic head tumors since patients with nonhead tumors tend to start chemotherapy sooner after diagnosis[26]. Another explanation might be that in our study the median age at diagnosis was higher compared with other population-based studies and that these studies included patients with locally advanced disease, which are known to have a better prognosis[22-25].

As first-line treatment, most patients received FOLFIRINOX, which was also the dominant regimen in nearly all Dutch hospitals[15]. Compared with other real-world studies, our study shows a higher rate of first-line treatment with FOLFIRINOX[22-24]. Although OS has significantly improved compared with gemcitabine monotherapy, in current practice FOLFIRINOX is often reserved for patients with a performance status of 0 or 1, because of the FOLFIRINOX associated incidence of grade 3/4 toxicities (e.g. neutropenia, thrombocytopenia, fatigue, vomiting)[13,27,28]. Because the OS of patients receiving FOLFIRINOX in our study was higher among both those with performance status 0–1 and those with performance status 2 compared with those receiving gemcitabine+nab-paclitaxel (7.4 and 5.1 months vs 4.7 months, respectively; P=.043), one could question whether FOLFIRINOX should be administered only to patients with the most favorable performance status, when our study showed that patients with less optimal performance status also benefited from FOLFIRINOX treatment in terms of OS. However, this finding should be balanced with data on toxicity/adverse events and quality of life (QoL), which are not yet available.

Although we observed inferior OS of first-line systemic gemcitabine+nab-paclitaxel compared with FOLFIRINOX, preferably OS of both regimens would be compared directly, also taking into account QoL, toxicity and exposure to second-line therapy, to identify the most preferable first-line treatment regimen. Alternative first and second-line sequences may be, for example, gemcitabine+nab-paclitaxel followed by FOLFIRINOX or the NAPOLI regimen[29].

In our study, gemcitabine monotherapy had a significantly lower OS and TTF (2.9 and 1.9 months respectively) compared with the other regimens. Patients receiving BSC in our study (n=4,306) had a median OS of 1.5 months. Therefore, one could argue that the marginal survival benefit of treatment with monotherapy gemcitabine does not outweigh the possible side-effects of gemcitabine and instead these patients should receive BSC only[30,31].

Only 8% of patients in our study who started first-line treatment received second-line treatment, of which gemcitabine with or without nab-paclitaxel were the most frequently administered regimens. This is a reasonable choice of regimens since the majority of patients received first-line treatment with FOLFIRINOX. However, the number of patients treated with second-line chemotherapy in our study is lower compared with other real world studies[22,23]. This might be explained by the fact that in other real-world studies patients were predominantly treated with gemcitabine with or without nab-paclitaxel in first-line, which provides more opportunities for treatment in second-line compared with our study in which FOLFIRINOX is the predominant regime in first-line treatment (e.g. FOLFOX)[22,23,32]. It may be hypothesized that clinicians find FOLFIRINOX after a gemcitabine containing regime in first-line therapy less optimal given the superiority of FOLFIRINOX over gemcitabine with or without nab-paclitaxel. Moreover, there is little randomized evidence for second-line therapy in metastatic PDAC patients, and the fact that treatment administration in the last months before death is generally considered undesirable[16,17,33,34].

Although this is the largest population based study describing the use of first and second-line systemic treatment in metastatic PDAC, our study has several limitations. First, there is likely an underestimation of pancreatic cancer in the NCR due to insufficient notification sources for older patients without pathological confirmation of PDAC and no hospital admission related to PDAC[35]. With the inclusion of these patients, median OS for patients treated with BSC could even be shorter than described here. Second, the performance status was unknown in nearly half of the patients before the start of first-line systemic treatment, resulting in less optimal adjustment for performance status in multivariable analyses. In addition, toxicity was missing in the majority of patients and could not be reported in our study. Third, we did not have data on follow-up and beyond first-line treatment in patients who were diagnosed in 2017-2018, which resulted in a limited number of patients. Therefore, future research should include complete follow-up data after implementation nanoliposomal irinotecan and 5-FU to be able to make statements about the best sequence strategy for first and second-line treatment in metastatic PDAC patients.

In conclusion, this nationwide study including real-world data on systemic treatment in patients with synchronous metastatic PDAC in the Netherlands shows that in an era before implementation of nanoliposomal irinotecan and 5-FU in second-line therapy, treatment predominantly consists of FOLFIRINOX in the first-line and gemcitabine with or without nab-paclitaxel in second-line therapy.

ACKNOWLEDGEMENT SECTION

Author contributions

Esther N. Pijnappel (Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Resources; Visualization; Writing – original draft; Writing – review & editing)
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Lydia van der Geest (Conceptualization; Data curation; Writing – original draft; Writing – review & editing)
Judith de Vos-Geelen (Conceptualization; Writing – review & editing)
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Hanneke W.M. van Laarhoven (Conceptualization; Investigation; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)
Hanneke W. Wilmink, MD PhD (Conceptualization; Investigation; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)

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SUPPLEMENTARY MATERIAL

Supplementary table 1. Morphology codes according to ICD-10[1]

The following list of morphology codes were included in our analyses:
8000, 8001, 8010, 8011, 8012, 8020, 8021, 8022, 8031, 8032, 8033, 8035, 8046, 8070, 8071, 8072, 8140, 8141, 8143, 8144, 8145, 8154, 8163, 8201, 8211, 8255, 8260, 8263, 8310, 8440, 8480, 8481, 8490, 8500, 8510, 8521, 8523, 8560, 8570, 8572, 8575, 8576

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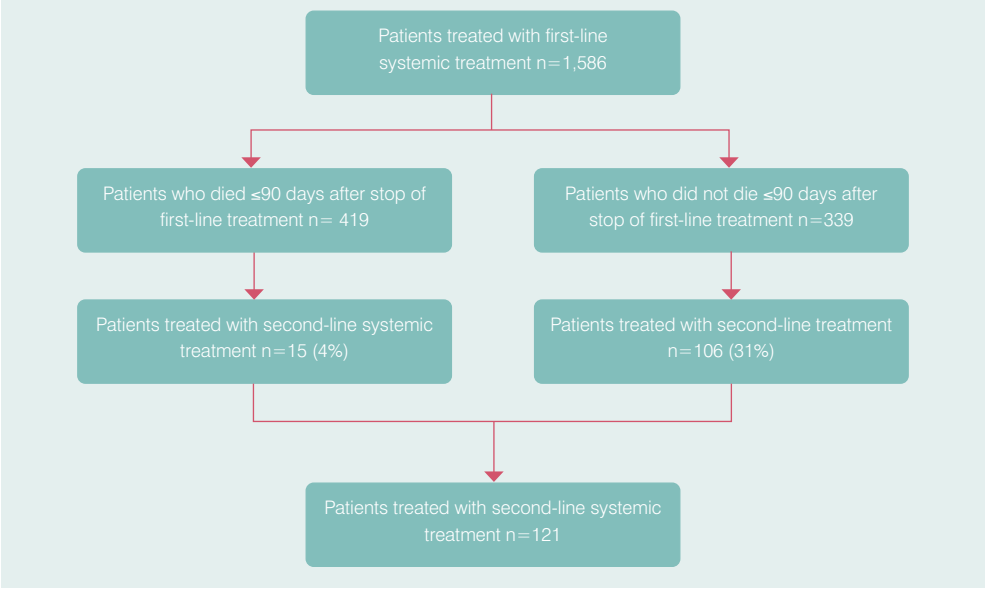

Supplementary figure 1. Flow diagram first and second-line systemic treatment

Supplementary Table 2. Baseline characteristics in patients who received first-line treatment

Variable	FOLFIRINOX (n=1,029)	Gemcitabine/ nab-paclitaxel (n=207)	Gemcitabine (n=285)	Other (n=65)
Sex				
Male	556 (54%)	104 (50%)	152 (53%)	40 (61%)
Female	473 (46%)	103 (50%)	133 (47%)	25 (39%)
Age, years median (IQR)	62 (56, 68)	69 (62, 74)	70 (65, 74)	66 (57, 72)
<55	225 (22%)	14 (7%)	14 (5%)	11 (18%)
55-64	391 (38%)	47 (23%)	57 (20%)	17 (27%)
65-74	371 (36%)	98 (47%)	144 (51%)	26 (39%)
≥75	42 (4%)	48 (23%)	70 (25%)	11 (15%)
Tumor location				
Head	393 (38%)	80 (39%)	115 (40%)	28 (42%)
Body	212 (21%)	46 (22%)	51 (18%)	9 (15%)
Tail	270 (26%)	49 (24%)	66 (23%)	15 (24%)
Overlapping sites	100 (10%)	24 (12%)	39 (14%)	3 (4%)
Pancreas NOS	54 (5%)	8 (4%)	14 (5%)	10 (14%)
Number of comorbidities				
0	597 (58%)	83 (40%)	113 (40%)	34 (52%)
1	299 (29%)	75 (36%)	107 (38%)	21 (34%)
2	73 (7%)	34 (16%)	57 (20%)	5 (7%)
Missing	60 (6%)	15 (7%)	8 (3%)	5 (7%)
Performance status				
WHO 0-1	711 (69%)	134 (65%)	120 (42%)	31 (48%)
WHO 2	69 (7%)	32 (15%)	57 (20%)	8 (11%)
WHO 3-4	11 (1%)	0 (0%)	12 (4%)	2 (3%)
Unknown	238 (23%)	41 (20%)	96 (34%)	24 (38%)
Year of diagnosis				
2015	217 (21%)	33 (16%)	119 (42%)	16 (24%)
2016	243 (24%)	39 (19%)	75 (26%)	16 (24%)
2017	294 (29%)	74 (36%)	61 (21%)	13 (21%)
2018	275 (27%)	61 (29%)	30 (11%)	20 (31%)
Number of metastatic sites				
1	639 (62%)	128 (62%)	172 (60%)	36 (55%)
≥2	390 (38%)	79 (38%)	113 (40%)	29 (45%)
Median time between date of diagnosis and start of first-line treatment (days, IQR)	26 (17, 38)	24 (15, 36)	34 (20, 56)	28 (17, 55)

Abbreviations: FOLFIRINOX, irinotecan/oxaliplatin/5-FU; IQR, interquartile range; NOS, not otherwise specified; WHO, World Health Organization

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3

CHAPTER 3

Phase I/II study of LDE225 in combination with gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer

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SIMPLE SUMMARY

One of the reasons for treatment resistance of PDAC, is the desmoplastic reaction initiating the production of large amounts of tumor stroma. LDE225 is a pharmacological Hedgehog signaling pathway inhibitor and is thought to specifically target tumor stroma. LDE225 in combination with gemcitabine and nab-paclitaxel was well-tolerated in patients with metastatic PDAC and has promising efficacy after prior treatment with FOLFIRINOX. Quantitative MRI suggested that LDE225 causes increased tumor diffusion and works particularly well in patients with poor baseline tumor perfusion. This suggests a clinical benefit of gemcitabine and nab-paclitaxel in combination with LDE225 in patients who received prior FOLFIRINOX, future phase III clinical trials should confirm these results.

ABSTRACT

Background

Desmoplasia is a central feature of the tumor microenvironment in pancreatic ductal adenocarcinoma (PDAC). LDE225 is a pharmacological Hedgehog signaling pathway inhibitor and is thought to specifically target tumor stroma. We investigated the combined use of LDE225 and chemotherapy to treat PDAC patients.

Methods

This was a multi-center, phase I/II study for patients with metastatic PDAC establishing the maximum tolerated dose of LDE225 co-administered with gemcitabine and nab-paclitaxel (phase I) and evaluating efficacy and safety of the treatment combination after prior FOLFIRINOX treatment (phase II). Tumor microenvironment assessment was performed with quantitative MRI using intra-voxel incoherent motion diffusion weighted MRI (IVIM-DWI) and dynamic contrast enhanced (DCE) MRI.

Results

The MTD of LDE225 was 200 mg once daily co-administered with gemcitabine 1000 mg/m2 and nab-paclitaxel 125 mg/m2. In phase II, six therapy related grade 4 adverse events (AE) and three grade 5 were observed. In 24 patients target lesion response was evaluable. Three patients had partial response (13%), 14 patients showed stable disease (58%) and 7 patients had progressive disease (29%). Median overall survival (OS) was 6 months (IQR 3.9-8.1). Blood plasma fraction (DCE) and diffusion coefficient (IVIM-DWI) significantly increased during treatment. Baseline perfusion fraction could predict OS (>222 days) with 80% sensitivity and 85% specificity.

Conclusion

LDE225 in combination with gemcitabine and nab-paclitaxel was well-tolerated in patients with metastatic PDAC and has promising efficacy after prior treatment with FOLFIRINOX. Quantitative MRI suggested that LDE225 causes increased tumor diffusion and works particularly well in patients with poor baseline tumor perfusion.

Trial registration

NCT02358161

Key words

Pancreatic neoplasms, metastatic pancreatic ductal adenocarcinoma, hedgehog signaling pathway inhibitor, LDE225, quantitative MRI

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is often a lethal condition and is ranked as the seventh highest cause of cancer related mortality in the world[1]. Of the newly diagnosed patients, 80-85% have locally advanced or metastatic disease[2]. Metastatic disease is characterized by a poor prognosis with 5-year survival of less than 5%[2] and palliative chemotherapy is the only treatment option for this patient category[2].

The combination of 5-fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) was the first major step forward in palliative systemic treatment since the introduction of gemcitabine monotherapy. Overall survival (OS) and quality of life (QOL) were significantly improved compared to gemcitabine monotherapy (11.5 vs 6.8 months and QOL improvement of 10 points)[2-5]. Gemcitabine combined with nab-paclitaxel is one of the other currently used chemotherapy regimens. Survival was significantly improved with this combination compared to gemcitabine monotherapy (8.5 versus 6.7 months), while grade 3-4 toxicity was not increased[2, 6, 7]. Nowadays FOLFIRINOX and gemcitabine with or without nab-paclitaxel are widely used first-line regimes, but there is limited evidence for second-line treatment for metastatic PDAC, especially after FOLFIRINOX[8, 9].

One of the reasons for treatment resistance of PDAC, is the desmoplastic reaction initiating the production of large amounts of tumor stroma[10-13]. Stroma limits the vascularization of tumor cells, which restricts the effective delivery of anti-cancer agents to the tumor[14]. The hedgehog signaling pathway is known to be involved in tumor stroma formation in PDAC[14, 15]. PDAC cells produce an increased amount of the Sonic Hedgehog ligand (SHh)[14-18]. By stimulating the patched 1 receptor, the ligand initiates the desmoplastic reaction resulting in activation of the Hedgehog signaling pathway transcription factors Gli1,2,3 by Smoothened (SMO). Elevated production of the SHh ligand results in large amounts of tumor stroma and restricts vascularization[15-18]. A study in gemcitabine resistant mouse models showed that by targeting the hedgehog pathway, tumor vascularization increased, initiating higher efficacy of the chemotherapeutic treatment. Indeed, when combining gemcitabine with hedgehog inhibition, tumor vasculature and subsequently gemcitabine delivery in the tumors were enhanced[13, 19-21]. LDE225 is a pharmacological Hedgehog signaling pathway inhibitor and is thought to reduce the amount of tumor stroma.

Over the years, trials on hedgehog inhibition (e.g. IPI-926, vismodegib) in combination with gemcitabine monotherapy, gemcitabine+nab-paclitaxel or FOLFIRINOX showed no statistically difference in drug delivery or treatment efficacy[22, 23]. However, there has not yet been a trial evaluating the effect of LDE225 in combination with gemcitabine+nab-paclitaxel.

In order to establish early signs of efficacy, we incorporate two tumor microenvironment imaging techniques in our study: Intravoxel-incoherent motion modelled diffusion weighted magnetic resonance imaging (IVIM-DWI MRI) and dynamic contrast enhanced (DCE) MRI. IVIM-DWI can non-invasively assess tumor diffusion and perfusion *in vivo*[24, 25]. Low diffusion is typically associated with dense cell structures as in solid tumor and stroma whereas an increased diffusion is associated with necrosis[26]. DCE MRI further probes the tumor's micro vascularity and vascular permeability[27]. Our hypothesis is that a reduction in stroma caused by LDE225 leads to an increased diffusion[28, 29] and to revascularization of the tumor showing an increased perfusion[30, 31] and can be evaluated using these quantitative imaging techniques. Additionally, necrosis of the tumor as an overall result of the treatment is expected to show an increase in diffusion[28]. In previous work, we already optimized IVIM-DWI and DCE MRI specifically for PDAC patients[32, 33]. Using optimized pipelines, we correlated both IVIM-DWI and DCE MRI to pancreatic cancer pathology and treatment response in PDAC patients receiving surgery and illustrated response in IVIM-DWI in patients receiving chemo-radiotherapy[26, 34]. This highlights the potential of these techniques for evaluating treatment in PDAC patients.

Our current study is the first to explore the modification of the desmoplastic reaction seen in pancreatic cancer using two approaches, targeting tumor stroma by nab-paclitaxel and the hedgehog inhibitor LDE225 and targeting the tumor cells with gemcitabine and nab-paclitaxel as a second-line treatment for patients with metastatic PDAC after first-line FOLFIRINOX.

PATIENTS AND METHODS

Patient population

Patients registered in this study were 18 years of age or older with histologically or cytologically confirmed diagnosis of metastatic PDAC and provided written informed consent. All patients had measurable disease on a pre-treatment CT scan according to response evaluation criteria in solid tumors (RECIST) 1.1, a World Health Organization (WHO, Geneva, Switzerland) performance status <2 and adequate bone marrow and organ function. Patients were excluded if they had a history of hypersensitivity to LDE225, or to drugs of similar chemical classes. Additionally, patients who underwent previous treatment with smoothened inhibitors or with known central nervous system (CNS) metastases were excluded.

Study design and treatment

This was a multi-center, open-label, interventional, noncontrolled, nonrandomized dose finding, phase I/II study, conducted in the Amsterdam University Medical Centers, location AMC in Amsterdam and in the Medical Spectrum Twente hospital in Enschede, both in the Netherlands. The study was approved by the ethical committee and registered at ClinicalTrials.gov with

identifying number NCT02358161. This study was conducted in agreement with the latest revision of the declaration of Helsinki and with the guidelines of good clinical practice issued by the European Union.

The objective of the phase I part of the study was to assess the safety, maximum tolerated dose (MTD), and dose limiting toxicities (DLTs) of LDE225 when co-administered with fixed doses of gemcitabine and nab-paclitaxel. The objective of the phase II part was to evaluate efficacy and safety of the treatment combination after prior FOLFIRINOX treatment with response rates according to RECIST 1.1, median overall survival (OS) and progression free survival (PFS), changes in vascularity with DCE MRI and changes I tumor stroma with DWI MRI.

At the start of our study, the largest study published on second-line treatment with gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer was the study by Portal et al[35]. In this study, an objective response rate of 17% was seen. For the sample size calculation of the phase II part of the trial, we hypothesized that if the combination could lead to a response rate of 20%, developing a randomized trial is reasonable. With a power of 80% to detect such an increase and a significance level (alpha) of 0.10, the minimum sample size needed was 27 evaluable patients. Anticipating on 10% of patients not available for analysis, we planned to include a total amount of 30 patients.

The starting dose of LDE225 was 400mg daily dosed orally[36]. The doses for nab-paclitaxel and gemcitabine were 125 mg/m2 and 1000 mg/m2 respectively, administered weekly for three weeks every 4 weeks[6].

A DLT was defined as any dose limiting toxicity that was considered related to LDE225 alone or in combination with nab-paclitaxel and gemcitabine and unrelated to disease progression, inter-current illness or concomitant medications (see table 1). A minimum of three patients were entered on each dose level and followed for six weeks. Subsequent enrolment of new cohorts was based on the toxicity assessment in the first cycle and the documentation of any DLTs (see table 2). If 0 out of 3 patients experienced a DLT at a given dose level, 3 patients were entered at the next dose level (+200mg LDE225). When 1 out of 3 patients experienced a DLT, 3 patients were entered at the same dose level. Dose escalation was stopped when more than 2 patients experienced a DLT at a certain dose level. This dose level was declared the MTD.

Table 1. Criteria for defining dose-limiting toxicities (DLTs)

Toxicity	DLT criteria
Toxicity leading to skipped/ delayed dose	An AE (except for alopecia) of any grade, considered to be related to the study drug, leading to a dose interruption of more than 7 consecutive days, despite supportive treatment, will be considered to be a DLT.
Re-occurred toxicity	If the 2nd occurrence of an initially non-dose limiting toxicity (e.g., grade 1 neutropenia that resolved within 7 days at 1st occurrence) leads to a dose reduction within 42 days of the first dose of LDE225 ,this will be considered a DLT
Hematologic[a]	CTCAE grade 4 neutropenia for > 5 consecutive days
	CTCAE grade 4 thrombocytopenia CTCAE grade 3 with CTCAE grade > 2 bleeding
	CTCAE grade > 3 neutropenia with fever > 38.5oC (non axillary)
Renal	≥ CTCAE grade 3 serum creatinine
Hepatic	Total bilirubin ≥ 2.0 x ULN to ≤ 3.0 x ULN for > 7 consecutive days. AST or ALT CTCAE grade ≥ 3 in conjunction with blood bilirubin CTCAE grade ≥ 2 of any duration. If not related to biliary obstruction / biliary stent dysfunction.
	≥ CTCAE grade 3 total bilirubin. If not related to biliary obstruction / biliary stent dysfunction.
	CTCAE grade 3 AST or ALT for > 7 consecutive days
	CTCAE grade 4 AST or ALT
Metabolic/Laboratory	CTCAE grade 3 asymptomatic amylase and/or lipase > 7 consecutive days
	CTCAE grade 4 asymptomatic amylase and/or lipase
Pancreatitis	≥ CTCAE grade 2, if not related to biliary obstruction / stent dysfunction
Cardiac	Cardiac toxicity ≥ CTCAE grade 3 or cardiac event that is symptomatic or requires medical intervention
	QTcF > 500 msec confirmed by at least one ECG
	Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or Troponin ≥ CTCAE grade 3
Neurotoxicity	≥ 1 CTCAE grade level increase
Dematologic	≥ CTCAE Grade 2 photosensitivity
	CTCAE Grade 3 rash for > 7 consecutive days despite skin toxicity treatment
	CTCAE Grade 4 rash
Fatigue	≥ CTCAE grade 3 for > 7 consecutive days
	CTCAE grade 4
Other adverse events	≥ CTCAE grade 3 adverse events (excluding ≥ CTCAE grade 3 lymphopenia or ≥ CTCAE grade 3 elevations in alkaline phosphatase
	≥ CTCAE grade 3 vomiting/nausea ≥ 48 hrs, despite the use of anti-emetic therapy
	≥ CTCAE grade 3 diarrhea ≥ 48 hrs, despite the use of anti-diarrheal therapy
CK elevation	≥ CTCAE grade 3
Exception to DLT criteria	CTCAE grade 3 or 4 hypersensitivity or signs of allergic reaction

Whenever a DLT occurs:

Study drug MUST be completely discontinued immediately

A single patient is assumed not to tolerate the dose if he/she experiences at least one DLT

[a] ≥ CTCAE grade 3 anemia will not be considered DLT unless judged to be a hemolytic process secondary to study drug

≥ CTCAE grade 3 lymphopenia will not be considered DLT unless clinically significant

Table 2. dose escalation scheme phase 1

Dose level	LDE225	Gemcitabine	Nab-Paclitaxel	Minimum number of patients
-1	200 mg	1000 mg/m2	125 mg/m2	--
1 (starting)	400 mg	1000 mg/m2	125 mg/m2	3
2	600 mg	1000 mg/m2	125 mg/m2	3
3	800 mg	1000 mg/m2	125 mg/m2	3

Toxicity assessment

Toxicity was graded using the common terminology criteria for adverse events (CTCAE) version 4.0. Before every treatment with gemcitabine and nab-paclitaxel, adverse events (AEs) were scored and reported in the case report file (CRF).

Tumor response evaluation

At baseline and subsequently every 8 weeks, tumor assessment and evaluation according to RECIST 1.1 was performed using CT-scan. (non)Target lesions were measured per organ side and documented in the CRF.

Overall response as well as response to (non)target lesions were described as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). If there were any new lesions compared to earlier screening this was also documented in the case report file and regarded as PD.

IVIM-DWI and DCE MRI were performed at baseline (prior to treatment) and 8 weeks after the start of chemotherapy on a 3T MRI scanner (Ingenia, Philips, Best, The Netherlands). For IVIM-DWI MRI, a diffusion—weighted multi-slice echo-planar imaging sequence was used with TR/TE 2200/45 ms**,** respiratory triggering, and 12 b-values from 0 to 600[33, 34]. To minimize bowel movement, 20 mg hyoscine bromide (Buscopan, Boehringer, Ingelheim, Germany) was administered intravenously before the acquisition. Detailed relevant MRI sequence parameters for all scans are given in table 1 in the supplementary materials. The IVIM model was fitted to the signal decay of the DWI MRI as a function of the b-values using a bi-exponential fit to obtain the diffusion (D), pseudodiffusion (D*) and perfusion fraction (f) maps.

DCE MRI was performed identical to our previous work[32]: we acquired a dynamic series of 3D spoiled gradient echo images with temporal resolution of 1.75 seconds, TR/TE 3.2/2.0 ms and FA 20°. Scans were repeated for 280 seconds and after 10 dynamics, 0.1 mmol/kg of 1.0 mmol/mL gadobutrol (Gadovist, Bayer Healthcare, Leverkusen, Germany) was injected intravenously at 5 mL/s followed by a 15 mL saline flush. Prior to the DCE acquisition, a Look-Locker ultrafast gradient echo was performed to assess the baseline T1 values, which were used to determine

contrast concentration. A population-based arterial input fraction was derived from another dataset of pancreatic cancer patients using the same scan settings and contrast administration protocol[32, 37]. The Tofts model was fitted voxel-wise to acquire the extracellular extravascular space (EES) volume fraction (v_e), the fractional plasma volume (v_p), the transfer rate of contrast from plasma to EES (K^{trans}) and the reflux rate of contrast from EES to plasma (k_{ep})[38].

The primary tumor was manually delineated on the baseline and post-treatment MRI scans using 3D Slicer (available online: http://www.slicer.org, accessed on 7 September 2021) under guidance of a contrast-enhance MRI from the same scan session and a contrast-enhanced CT scan[39]. Cancerous pancreatic tissue was included into the region of interest (ROI) and biliary stents were excluded from the ROI. The mean parameter values of DCE and IVIM-DWI MRI from within the ROI were used for further analysis.

MRI data of patients from the phase I and phase II part of the trial were all combined to analyze the influence of LDE225 combined with gemcitabine and nab-paclitaxel on the characteristics of the tumor. A total of 36 patients underwent a baseline MRI scan of which 23 patients also underwent a post-treatment MRI scan (see supplementary table 1).

Statistical analysis

Data in this study were analyzed using IBM SPSS software version 22. Baseline characteristics were described using mean (standard deviation) or median (interquartile range) for continuous variables and absolute number (percentage) for categorical variables. Evaluation of adverse events, safety and efficacy of LDE225 combined with gemcitabine and nab-paclitaxel was performed with descriptive statistics. A Kaplan Meier analysis described the median OS between the different dose levels and treatment groups. Data analysis was anonymous. The probability of a type-I error was set at 0.05.

All statistical tests in the response evaluation using DCE and IVIM-DWI MRI were two-tailed and a significance level of $\alpha=0.05$ was used. The overall effect of the chemotherapy on the tumor was assessed by a Wilcoxon signed-rank test between MRI scans at baseline and post-treatment for all DCE and IVIM-DWI parameters. Subsequently, a receiver operating characteristics (ROC) analysis was performed to determine the specificity and sensitivity (using the Youden's index) of baseline MRI parameters and the relative change in parameter value during treatment to predicting OS of PDAC patients receiving chemotherapy. The mean OS of 222 days was taken as cut-off value to divide the patient group in long and short OS for the purpose of the ROC analysis.

The baseline and post-treatment CA 19.9 levels in combination with the relative change in MRI parameter values during treatment were also used to evaluate the treatment response. This was assessed with the spearman's rank correlation coefficient.

RESULTS

Phase I

Characterization of the study cohort

In total, 39 patients were screened for eligibility between September 2014 and October 2016. In total, 13 patients were excluded, one patient because of gastrointestinal dysfunction, one patient because of the use of coumarin derivatives and CYP3A4/5 inhibitors, the remaining 11 did not meet the inclusion criteria. A total of 26 patients were enrolled in the phase I part of this trial. For LDE225 there were eight dose reductions among six patients at various dose levels, all of them were due to adverse events. Furthermore there were 12 temporary stops of LDE225 in six patients due to adverse events. Of the 26 patients, six patients had to discontinue the study due to adverse events, and twenty patients had to discontinue due to disease progression. Twenty-three patients were eligible for tumor response evaluation.

MTD and DLT

Of the 26 patients that enrolled in the phase I part of study, one patient experienced a DLT at dose level 1. The DLT concerned diarrhea CTCAE grade 3 for more than 48 hours, for which the patient had to discontinue study participation. This patient had received prior chemotherapy for metastatic disease. Moreover, the additional patients at this dose level that received prior chemotherapy for metastatic disease (i.e. FOLFIRINOX), the study treatment was less well tolerated with more grade 2/3 toxicities (11 grade 2/3 toxicities in the first month of treatment in three patients, compared with 7 grade 2/3 toxicities in the first month of treatment in three patients that had received no prior chemotherapy for metastatic disease). Therefore we made the decision, with the approval of the local ethics committee, to split the study in two separate cohorts with individual dose-escalation schedules, based on whether or not patients had received prior chemotherapy for metastatic pancreatic cancer. We continued the dose-escalation schedule for the patients with no prior chemotherapy at dose level 1 and we de-escalated the dose level schedule for the previously treated patients to dose level -1.

The recommended phase II dose was 200 mg LDE225 in combination with gemcitabine 1000 mg/m2 and nab-paclitaxel 125 mg/m2 for patients treated with prior chemotherapy for metastatic disease (i.e. FOLFIRINOX) and 600 mg LDE225 in combination with gemcitabine 1000 mg/m2 and nab-paclitaxel 125 mg/m2 for patients that received no prior chemotherapy.

In phase II, we included the outcomes of the five patients of phase I that received 200mg LDE225 and had prior treatment with FOLFIRINOX (n=30 patients in total).

Phase II

Characterization of study cohort

We started the trial as a phase I study for patients with metastatic pancreatic cancer, in which patients could be included that were both chemotherapy naïve, but also patients that had received prior FOLFIRINOX. Based on the results of the phase I part, we decided to continue in phase II with the patients that received prior FOLFIRINOX for metastatic disease. The reason for this decision was that in this patient cohort, despite the lower dose of LDE225, we saw responses, which was unprecedented at that time. Since FOLFIRINOX is the recommended first-line treatment for patients with metastatic PDAC in The Netherlands, there is desperate need for a suitable second-line treatment after FOLFIRINOX failure. Therefore, we decided to continue with this patient cohort. Unfortunately, we do not have phase II data of the chemo naïve group since we only included patients after first-line FOLFIRINOX failure in phase II.

In total, 33 patients were screened for eligibility between April 2017 and May 2018. Eight patients were excluded; 7 did not meet the inclusion criteria and in one case it was the decision of the patient. A total of 25 patients were enrolled in the phase II part of this trial. The baseline characteristics of the 25 patients, combined with the patients from phase I that received prior treatment with FOLFIRINOX and the LDE225 dosage of 200mg (n=5), are depicted in table 3.

Table 3. Patient characteristics phase I and II combined for the patients of phase I that received prior treatment with FOLFIRINOX and treatment with LDE225 200mg

Variable	n=30
Gender	
Male	17 (57%)
Female	13 (43%)
Age at start of study	62.1 (6.7)
WHO performance status at start study	
0	12 (40%)
1	16 (53%)
2	2 (7%)
Prior chemotherapy	30 (100%)
Prior surgery	11 (37%)
Median number of cycles	2 (2-6)
Median survival	6.0 months (3.9-8.1)

WHO; World Health Organization, Mean has standard deviation (SD) between brackets, median has interquartile range (IQR) between brackets and number has percentages between brackets

Patients were treated with a median number of two cycles (IQR 2-6). For LDE225, there was one dose reduction due to pneumonia and five temporary stops in four patients due to possible interaction with co-medication (1), hospitalization and LDE225 not present (1), and adverse events (3).
Patients discontinued treatment because of progressive disease (22), bacterial infection (1), sepsis (1) and diminished quality of life (1).

Safety

Six therapy-related grade 4 adverse events (AEs) were observed: sepsis (2), neutropenia (2), elevated gamma GT (1) and thromboembolic event (1), and three therapy-related grade 5 AEs (sepsis [2] and pneumonia). Most common grade 3 therapy-related AEs were neutropenia (37%) and diarrhea (14.8%). The most frequently observed therapy-related AEs of any grade were fatigue 43 (14%), thrombocytopenia 34 (11%) , diarrhea 28 (9%), fever 26 (8%) and vomiting 25 (8%) (see table 4).

Tumor response

In 24 patients target lesion response was evaluable on CT scan. These 24 patients received a median of 3 (IQR 2.0-6.0) cycles and a median of 232 days (IQR 136.25-350.75) of study treatment. Tumor responses, defined as the percentage of change in target lesion volume of the best radiological response, are shown in figure 1 as a waterfall plot. Three patients had partial response (13%), stable disease was seen in 14 patients (58%) and 7 patients had progressive disease (29%). Evaluation of progression and responses in days are shown in figure 2 as a swimmers plot. The median overall survival was 6.0 months (IQR 3.9-8.1). Median PFS was 4.0 months (IQR 1.2-6.7).

Table 4. Adverse events phase I and II combined (all the patients that received prior treatment with FOLFIRINOX and treatment with LDE225 200mg); possible, probable or definitely treatment related

Adverse event	N (%)
Alopecia	17 (6)
Anemia	7 (2)
Anorexia	12 (4)
Bacterial infection	2 (1)
Chills	7 (3)
Constipation	1 (0.3)
Diarrhea	28 (8)
Dysgeusia	3 (1)
Edema limb	6 (2)
Epistaxis	2 (1)
Erythema multiform	1 (0.3)
Eye disorder other: decreased vision	1 (0.3)
Fatigue	43 (14)
Febrile neutropenia	2 (1)
Fever	26 (8)
Flu-like symptoms	4 (1)
Hematoma hands	1 (0.3)
Infection	1 (0.3)
Infusion related infection	6 (2)
Leukocytopenia	1 (0.3)
Malaise	3 (1)
Mucositis oral	11 (4)
Myalgia	3 (1)
Nail loss	1 (0.3)
Nausea	23 (7)
Neuropathy	11 (4)
Neutropenic fever	1 (0.3)
Neutropenia	15 (5)
Papulopustular rash	1 (0.3)
Rash	3 (1)
Rash acneiform	1 (0.3)
Rash, maculo popular	1 (0.3)
Sepsis	2 (1)
Stomatitis	1 (0.3)
Thrombocytopenia	35 (11)
Vomiting	25 (8)

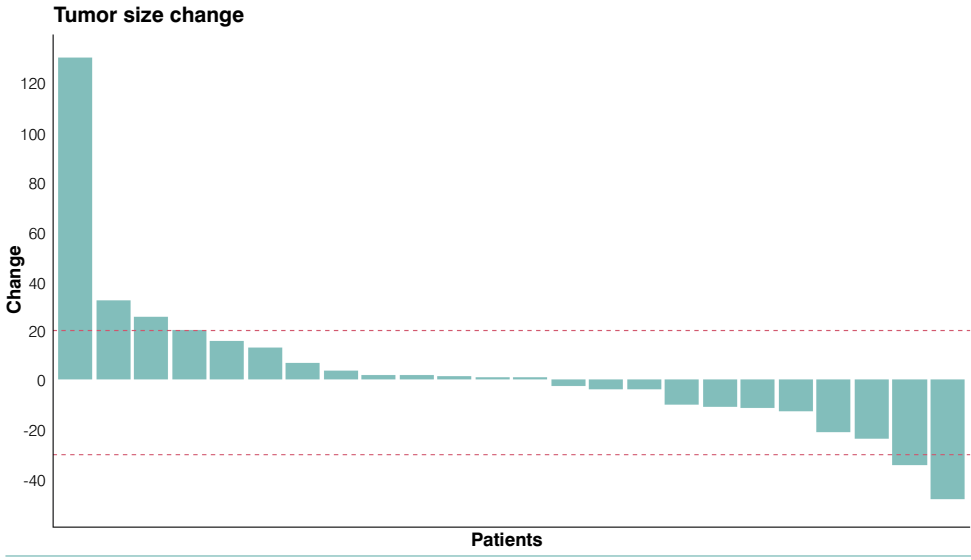

Figure 1. Waterfall plot of tumor response depicted as percentage tumor volume change phase I and II combined for the patients of phase I that received prior treatment with FOLFIRINOX and treatment with LDE225 200mg

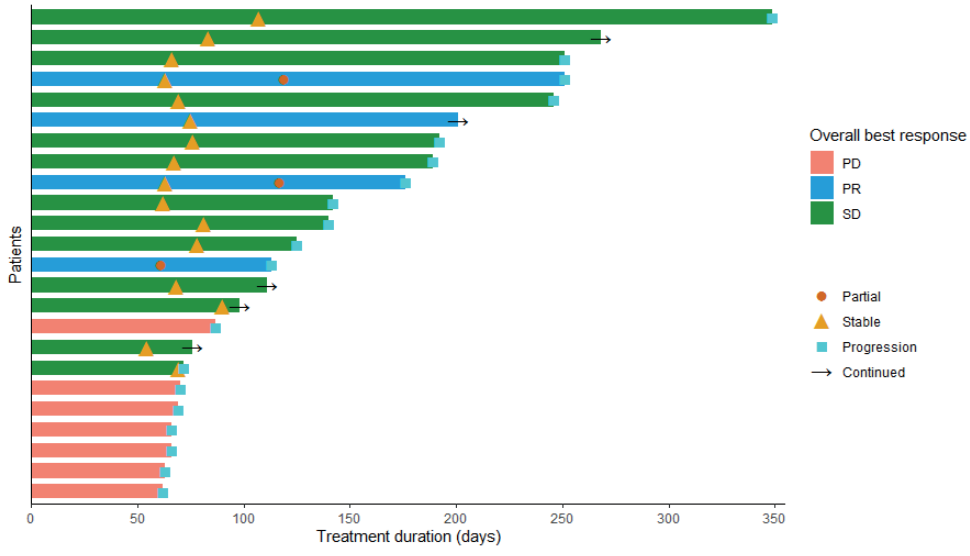

Figure 2. Swimmers plot for evaluation of progression and responses in days, responses as indicated phase I and II combined for the patients of phase I that received prior treatment with FOLFIRINOX and treatment with LDE225 200mg

PD= progressive disease, PR=partial response, SD=stable disease

MRI analysis

All patients who received a MRI scan were included in the analysis (phase I and II part)., This means that also patients who were treated with other doses than 200mg LDE225 were included. In 36 patients, baseline MRI data were available for analysis of whom 23 patients also underwent a post-treatment MRI scan, however we had to exclude one patient from the analysis because of major outliers in D (baseline D = 3.41 x 10^{-3} mm^2/s) as a result of a necrotic tumor core at baseline. Therefore we had 35 baseline and 22 post-treatment MRI scans in our analysis. However, one patient had no data on perfusion, diffusion and pseudo diffusion and had to be excluded from these analyses too. The total number of patients with post-treatment IVIM-DWI MRI scans that were analyzable was 21. An example of the parameter maps can be seen in figure 3. A significant increase of v_p and D was seen post-treatment compared to baseline values (see table 5 and figure 4).

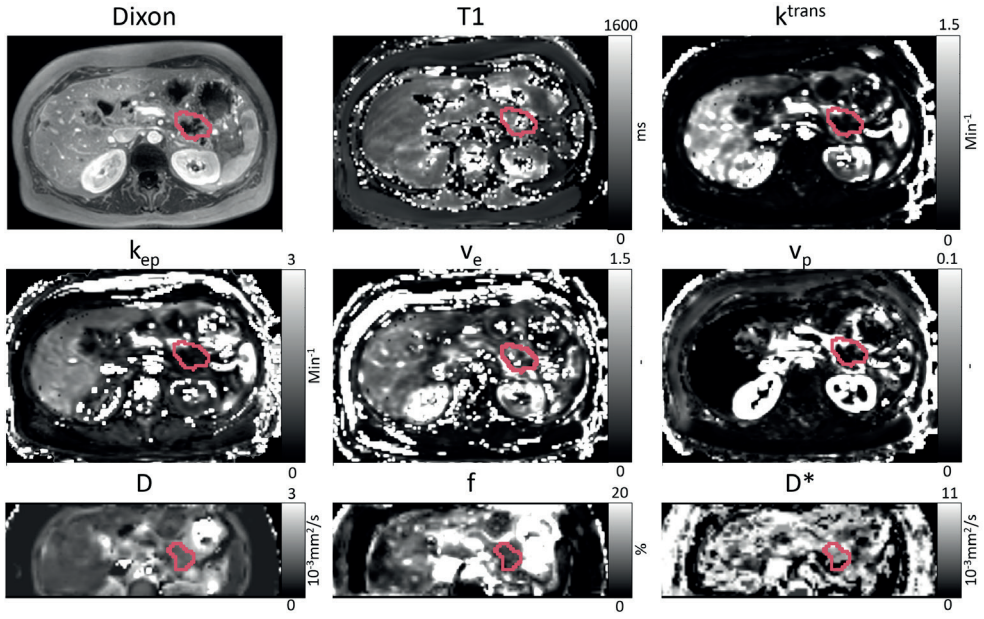

Figure 3. Example of an anatomical image (Dixon), T1 map, parameter maps of DCE MRI (ktrans, kep, ve and vp) and parameter maps of IVIM-DWI MRI (D, f and D*) for one patient at baseline. The primary tumor is manually delineated in red. The delineation is performed separately for IVIM-DWI and DCE MRI scans.

There was no statistical difference in OS between different dose levels. The area under the curve (AUC), the sensitivity, specificity and cut off value are shown in table 6. At baseline, the IVIM-DWI parameter f was most promising for predicting OS, with highest AUC of 0.85, with a sensitivity of 80% and a specificity of 85% (see figure 5). Patients with low baseline perfusion (f<5%) had highest chance of having above-median OS. When assessing change in parameter

value over treatment, Δf gave the highest AUC value (0.786), with a sensitivity and specificity of 80% and 86% respectively. Patients with an increase in perfusion during treatmet (Δ>16%) had the highest chance of above-median OS. Ten out of 21 patients had an increase in perfusion during treatment higher than 16% (Δ>16%). The median OS of this subgroup was 291 days. CA 19.9 levels at baseline and at evaluation can be found in supplementary table 2.We found a significant correlation between CA 19.9 levels and perfusion at evaluation r=-0.618 (P=0.019) and a significant correlation between CA 19.9 and OS r=-0.487 (P=0.026).

Table 5. Median and IQR values for DCE and IVIM parameters at baseline and post-chemotherapy. The p-value of the Wilcoxon signed-rank test is also presented. v_p and D show a significant increase between baseline and post-treatment values.

		Median (IQR25%-75%)	*Wilcoxon p-value*
K^{trans} (min^{-1})	Baseline	0.172 (0.113 - 0.295)	0.101
	Post	0.179 (0.113 - 0.301)	
k_{ep} (min^{-1})	Baseline	0.375 (0.287 - 0.469)	0.527
	Post	0.343 (0.261 - 0.427)	
v_e (-)	Baseline	0.581 (0.435 - 0.768)	0.961
	Post	0.623 (0.403 - 0.797)	
v_p (-)	Baseline	0.0159 (0.0075 - 0.0304)	0.005
	Post	0.0190 (0.0125 - 0.0317)	
T1	Baseline	674 (554 - 877)	0.987
	Post	695 (590 - 871)	
D (10^{-3} mm^2/s)	Baseline	1.35 (1.22 - 1.50)	<0.001
	Post	1.52 (1.39 - 1.69)	
f (%)	Baseline	5.1 (3.0 - 7.1)	0.279
	Post	5.1 (3.8 - 6.5)	
D* ($10^{-3}mm^2/s$)	Baseline	24.0 (10.6 - 71.5)	0.165
	Post	45.4 (24.1 - 108.3)	

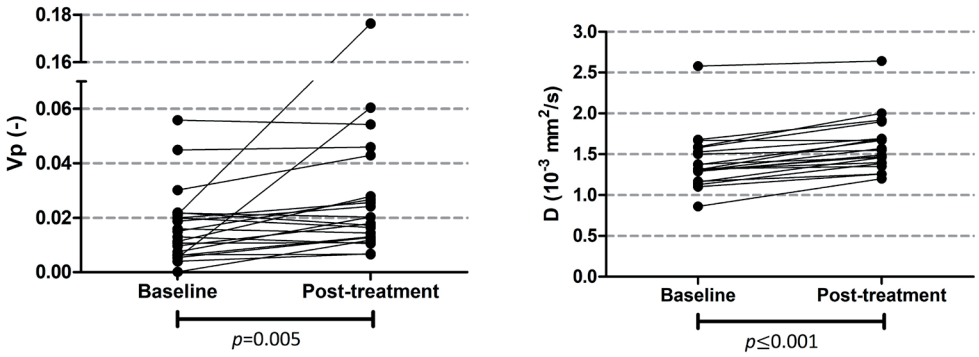

Figure 4. Plot of v_p and D at baseline and post-treatment. Both parameters significantly increased after treatment.

Table 6. Results of ROC analysis for all MRI parameters at baseline. The AUC, sensitivity, specificity and the cut off value determined with the Youden's Index is given. If the baseline parameter meets the statement of the cut-off value, the OS is expected to be higher.

Parameter	Cut off value	Sensitivity	Specificity	AUC
		Baseline		
K^{trans} (min^{-1})	≥0.181	62%	60%	0.600
k_{ep} (min^{-1})	≤0.345	67%	46%	0.508
v_e (-)	≥0.544	54%	60%	0.569
v_p (-)	≥0.0155	69%	60%	0.600
T1	≤834	47%	85%	0.528
D (10^{-3} mm^2/s)	≥1.32	69%	47%	0.574
f (%)	≤5.1	80%	85%	0.846
D* ($10^{-3}mm^2/s$)	≤22.9	73%	77%	0.779
		Parameter change		
ΔK^{trans} (%)	≤14	71%	70%	0.614
Δk_{ep} (%)	≤-8	71%	70%	0.714
Δv_e (%)	≥4	60%	71%	0.571
Δv_p (%)	≤60	86%	80%	0.743
ΔT1 (%)	≥-18	80%	43%	0.614
ΔD (%)	≤9	86%	50%	0.586
Δf (%)	≥16	80%	86%	0.786
ΔD* (%)	≥35	80%	57%	0.586

Δ indicates that we are looking at percent changes between baseline and post treatment.

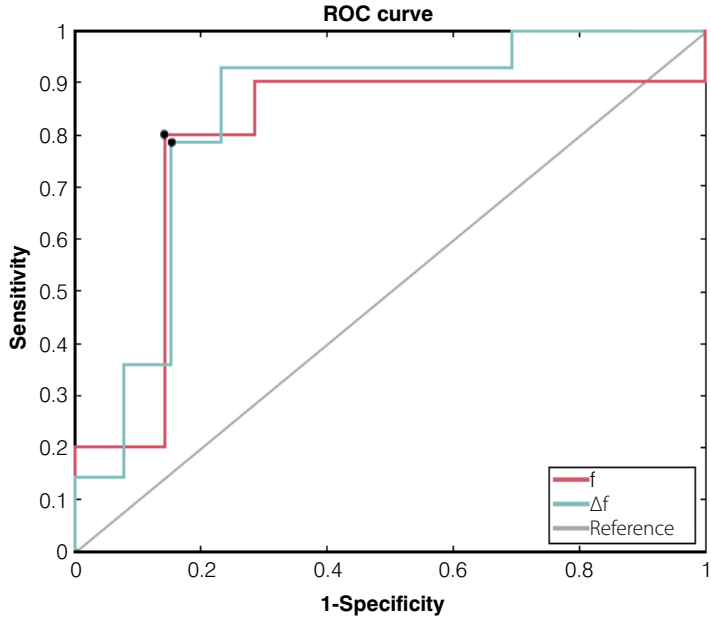

Figure 5. ROC curve of baseline f and Δf values for the prediction of OS >222 days. The black dots indicate the cut-off values on which the sensitivity and specificity are determined. The AUC of f and Δf are 0.846 and 0.786 respectively.

DISCUSSION

In this phase I/II trial, which mainly focused on FOLFIRINOX pretreated patients with metastatic pancreatic cancer, LDE225 in combination with gemcitabine and nab-paclitaxel demonstrated a manageable safety profile and promising efficacy. The overall response rate (ORR) and durability of response compares favorably with outcomes provided with currently available therapy for this population.

The reason for this focus was that in the patient cohort that was previously treated with FOLFIRINOX in the phase I part of the trial, despite the lower dose of LDE225, we saw responses, which was unprecedented at that time. Therefore, we decided to focus on the post-FOLRIRINOX group in the phase II part of the trial. Indeed, the evidence for second-line treatment after failure on FOLFIRINOX is scarce. Since FOLFIRINOX is the recommended first-line treatment for patients with metastatic PDAC in The Netherlands, there is desperate need for a suitable second-line treatment after FOLFIRINOX.

There are a few randomized clinical trials in advanced pancreatic cancer, but they all have been conducted after first-line gemcitabine-based chemotherapy. The most promising combination in

this setting is liposomal irinotecan in combination with 5-FU/LV, demonstrating a median survival of 6.1 months versus 4.2 months for the 5-FU/LV single agent[40]. After failure on FOLFIRINOX, data on second-line treatment are sparse. Although a gemcitabine-based regimen combined with nab-paclitaxel might be an option, randomized trials to confirm this suggestion are lacking. In the ACCORD/ PRODIGE 4 trial, about 50% of patients underwent second-line treatment with gemcitabine, with a median OS of 4.4 months, which is less favourable compared to an OS of 6 months in our clinical trial[4]. Other studies describing treatment with gemcitabine and nab-paclitaxel after FOLFIRINOX failure found lower median OS compared to our study[41-43]. Currently, there is no randomized evidence available on second-line treatment with gemcitabine and nab-paclitaxel after FOLFIRINOX failure. Observational cohort studies on second-line treatment with gemcitabine and nab-paclitaxel after FOLFIRINOX treatment in first-line showed ORR of 13% and 17%[35, 44, 45]. These might be comparable to our ORR of 13%, but as opposed to other phase II/III studies on metastatic PDAC patients, median PFS and ORR in our study were higher[40, 46-48]. The combination treatment of LDE225 with gemcitabine and nab-paclitaxel showed an improved biologic activity and was safely tolerated. However, the non-controlled design does not permit any conclusions, future phase III clinical trials should confirm these results.

In The Netherlands, FOLFIRINOX is currently the recommended first-line treatment for patients with metastatic PDAC[8, 49]. For patients who are not eligible for FOLFIRINOX in first-line, it would be interesting to preselect patients for LDE225 in combination with gemcitabine and nab-paclitaxel by using MRI (lower baseline perfusion fraction results in higher OS) in future studies.

The adverse events observed in our study were different from phase I studies with LDE225 monotherapy in patients with advanced solid tumors of any kind, including medulloblastoma and basal cell carcinoma. These studies most commonly found fatigue (2.3%), anorexia (2.3%), and elevated creatine phosphokinase (CPK) levels (4.7%)[36, 50, 51]. The difference in adverse events might be attributable to the addition of gemcitabine and/or nab-paclitaxel. However, although the incidence of adverse events is higher compared to previous studies, the toxicity was manageable enough for patients to continue treatment.

We were able to detect treatment effects from combined LDE225, gemcitabine and nab-paclitaxel using quantitative MRI. We showed that the fractional plasma volume and diffusion of the tumor increased during treatment. Two mechanisms might contribute to this increase, apoptosis as a result of the chemotherapy reaching the tumor and the decrease of stroma due to LDE225. The lower cellularity due to these two processes causes a higher diffusion[28, 52]. Various studies also described an increase of diffusion in tumors due to chemotherapy[53, 54]. We excluded one patient from the analysis because of necrosis at baseline resulting in outliers in baseline D values. In this specific case, the response of the tumor to chemotherapy is expected to be different, the necrotic cells will be cleared and less tumor cells will become necrotic.

Furthermore, we found that the baseline perfusion fraction can be used to predict OS. In patients with lower baseline perfusion fraction the OS was higher. Additionally, an increase in perfusion fraction during treatment resulted in a better prognosis. These results can be explained by the treatment with LDE225, which specifically targets the tumor stroma. Patients with tumors that have a higher level of stroma at baseline will show a lower baseline perfusion fraction. The relative reduction of stroma by LDE225 will be higher in these patients than in patients with a lower amount of stroma at baseline. Our findings highlight the importance of assessing tumor microenvironment with DCE and particularly IVIM-DWI during treatment. Furthermore, we have showed that these techniques may allow for precision medicine by selecting patients most likely to benefit from LDE225.

A limitation of this study is that all patients who received MRI scans, also patients with LDE225 doses other than 200mg, were included in the MRI analyses. Since all other analyses (e.g. on OS and PFS) were only performed on patients receiving 200mg LDE225, there could be some discprepancy between these results. In addition, the studied patients is a very selected group, because metastatic PDAC with a WHO performance status of 0 or 1 after pre-treatment with FOLFIRINOX is remarkable.

CONCLUSION

In conclusion, this study shows that LDE225 in combination with gemcitabine and nab-paclitaxel as second-line treatment is well-tolerated in patients with metastatic pancreatic cancer and has promising efficacy. The underlying mechanism of targeting stroma was validated in vivo. IVIM-DWI imaging may allow for selecting patients that could most benefit from LDE225 in the future.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of AmsterdamUMC location AMC (protocol code 2013_215, date of approval December 3 2013).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflicts of Interest

JWW has served as a consultant for Shire, Servier and Celgene and reports grants from Servier, Halozyne, Novartis, Celgene, Astra Zeneca, Pfizer, Roche, Amgen and Merck. HWMvL reports a consult/advisory role for BMS, Celgene, Lilly, Merck, and Nordic, and Servier and has received unrestricted research funding from Bayer, BMS, Celgene, Lilly, Merck Serono, MSD, Nordic, Philips, Roche and Servier. The other authors declare that they have no conflicts of interest.

SUPPLEMENTARY MATERIALS

Supplementary tables

Supplementary table 1. Summary of the relevant MRI parameters for IVIM-DWI, DCE MRI and T1 mapping

	IVIM-DWI	DCE	T1 look-locker
FOV (RL x AP) (mm²)	432 x 108	400 x 400	400 x 350
Acquisition matrix	144 x 34	160 x 160	132 x 116
Slices	18	30	13
Slice thickness/gap (mm)	3.7/0.3	2.5 (5.0 non-interpolated)	5.7 (11.4 non-interpolated)
TR/TE (ms)	>2200/45	3.19/2.0	3.5/1.6
FA (°)	90	20	8
Parallel imaging	1.3 (AP)	3.6/1.5 (RL/AP)	3/1.3 (RL/AP)
Respiratory compensation	Respiratory trigger (navigator)	Postprocessing	1 breath-hold
Fat saturation	Gradient reversal during slice selection + SPIR	-	-
b-values (s/mm²) and directions/averages	0 (15), 10 (9), 20 (9), 30 (9), 40 (9), 50 (9), 75 (4), 100 (12), 150 (4), 250 (4), 400 (4), 600 (16)	-	-
Diffusion times δ/Δ (ms)	10.1/22.6	-	-

FOV: field of view, RL: right left, AP: anterior posterior, TR: repetition time, TE: echo time, FA: flip angle, SPIR: spectral presaturation with inversion recovery.

Supplementary table 2. CA 19.9 levels at baseline and at evaluation of the 36 patients who received a baseline MRI scan

Patient	Baseline CA 19-9 in kU/L	Evaluation (8 weeks) CA 19-9 in kU/L
	9	14
	1,667	454
	1,453	1,256
	352	293
	171,394	217
	N.D.	N.D.
	N.D.	N.D.
	171,088	57,801
	11,260	5,800
	57,300	52,246
	3,380	13,371
	745	786
	4,744	719
	N.D.	N.D.
	N.D.	N.D.
	419,660	N.D.
	N.D.	N.D.
	N.D.	N.D.
	6,203	1,681
	N.D.	N.D.
	25,697	N.D.
	N.D.	1,814
	591	262
	2,252	1,125
	9,250	5,977
	N.D.	N.D.
	1,107	2,321
	904	1,076
	30	N.D.
	4,088	182
	13,522	208
	180	194
	8,583	8,876
	3	6
	4,077	864
	101,833	68,696

N.D.: not defined

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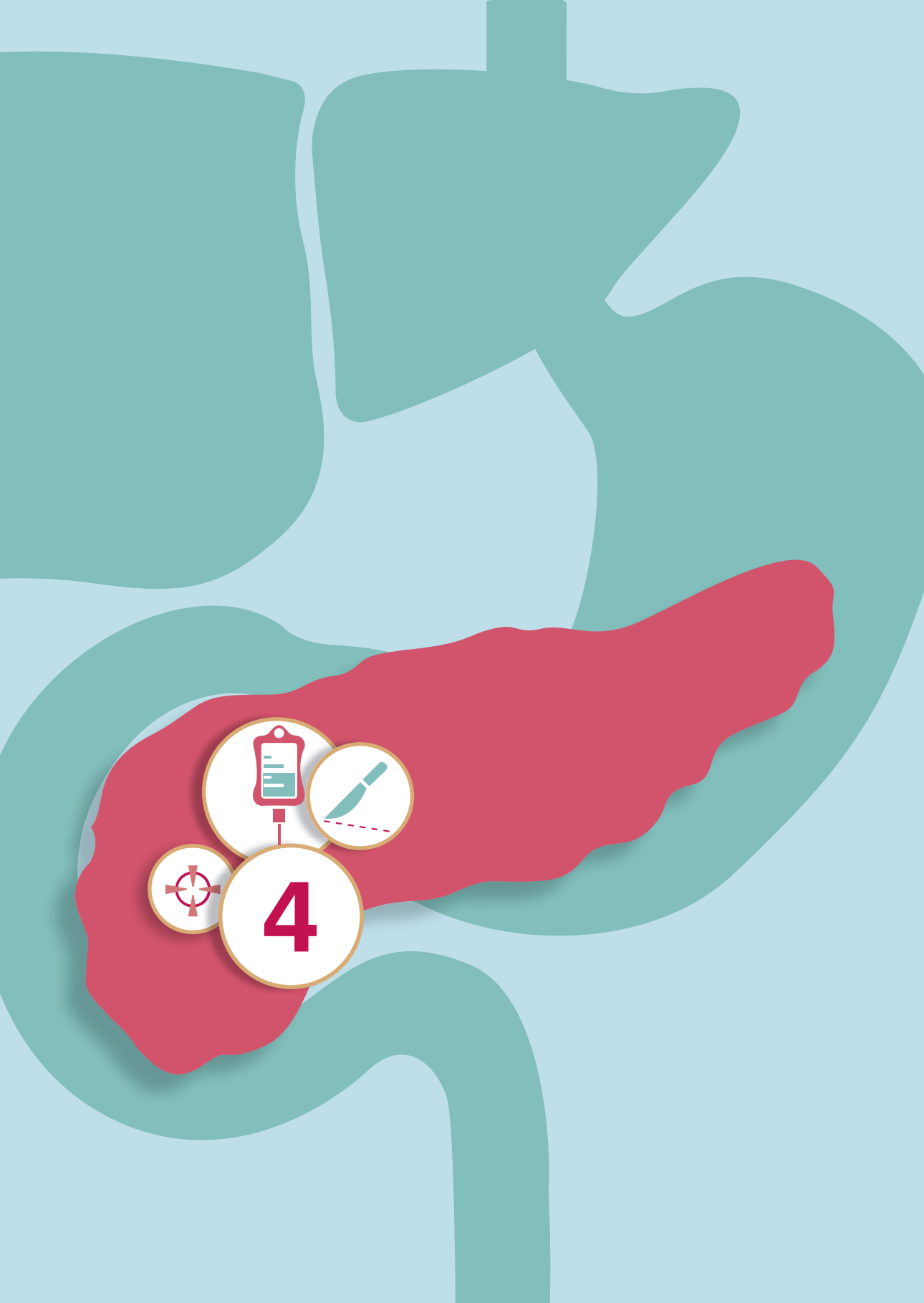
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CHAPTER 4

Mandatory reporting measurements in trials for potentially resectable pancreatic cancer

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ABSTRACT

Well-defined outcome measures enable comparisons between clinical trials. However, the reporting of baseline and prognostic characteristics largely vary in studies investigating potentially resectable pancreatic cancer patients. This makes accurate comparisons between studies challenging. By standardization of the reporting of mandatory baseline and prognostic characteristics, possible confounders can be identified which will allow for a better comparison of outcomes across studies. We created a structured overview describing the reporting frequencies of baseline characteristics and the clinical relevance of these factors. This chapter is the first to describe a set of mandatory baseline and prognostic variables for patients with potentially resectable pancreatic cancer.

Keywords

systematic review, potentially resectable pancreatic neoplasms, mandatory measurements, overall survival

Take home message

- 14 baseline and 7 prognostic characteristics for potentially resectable pancreatic cancer trials are mandatory to be included in future clinical trials
- Mandatory reporting of factors should allow for better outcome comparisons of future studies and facilitates new studies in the field of potentially resectable pancreatic cancer

INTRODUCTION

Treatment decisions for patients with potentially resectable pancreatic cancer have become increasingly complex. (Neo)adjuvant therapy has been proposed in addition to surgery alone, but, unfortunately, around 50% of patients fail to receive adjuvant therapy due to post-operative complications, patient preference or disease progression[1]. Therefore, the benefits of different treatment trajectories, including high risk surgery with major impact on quality of life, high morbidity and mortality and poor survival outcomes, have to be properly considered with the patient in a process of shared decision making[2]. Adequate information on outcomes is crucial in this process and prognostic and predictive measures may help in decision making for individual patients[1].

"Prognostic" and "predictive" are terms that describe the clinical relationship between a specific factor, for example performance status, and a certain outcome, for example survival. Unfortunately these terms are rarely well-used and often seen as identical terminologies in many publications[3]. In this chapter, we use the definitions as suggested by Clark et al 2006. A *prognostic* factor is a measurement related to the clinical outcome without the use of therapy or with standard therapy only. The control group in a randomized controlled trial can be used to determine the prognostic value of a biomarker[4]. A *predictive* factor is a measurement related to response or absence of response to a therapy. It describes the relationship between predictive factor and the treatment benefit and makes it possible to select the therapy with the highest likelihood of efficacy to the individual patient (e.g. KRAS mutational status is a predictive factor for anti-EGFR (cetuximab) treatment, as downstream mutation in KRAS would predict failure of EGFR pathway inhibition in colorectal cancer) (see Box 1)[4, 5]. The response can be measured with any of the commonly used outcomes in clinical trials[3, 4].

In the hierarchy of evidence, systematic reviews with meta-analysis could provide the most robust and reliable evidence[6, 7]. To allow for comparisons between clinical trials and perform meta-analyses, a uniform description of the study population (i.e. the reporting of baseline characteristics) is necessary. With baseline characteristics the study population is defined at the start of the trial, these characteristics do not necessarily have a relation with the outcome of the trial (e.g. survival). In contrast, prognostic factors do have a relationship with the outcome of a trial (e.g. survival). By standardization of reporting of these baseline and prognostic characteristics, possible confounders can be identified and allow for a better comparison of outcomes across studies. For patients with unresectable disease, a consensus statement from a group of experts in the field of pancreatic cancer is available on mandatory and recommended measurements of baseline and prognostic characteristics to be included in trials for this patient population[8]. This includes a list of 23 mandatory baseline characteristics (e.g., age, sex, tumor differentiation) and

12 mandatory prognostic characteristics (e.g. CA 19-9, liver metastasis , performance status) to be included in future randomized controlled trials[8].

Despite the fact that the interest in predictive and prognostic factors in pancreatic cancer is growing, the availability of prognostic research and methodologies is limited in the surgical literature for pancreatic cancer[9, 10]. In this chapter we aim to describe baseline and prognostic characteristics, which are regarded mandatory in trials for patients with potentially resectable pancreatic ductal adenocarcinoma (PDAC) based on the currently available literature.

Box 1 Definition of prognostic and predictive factors

A *prognostic factor* is a measurement related to the clinical outcome without the use of therapy or with standard therapy only. The control group in a randomized controlled trial can be used to determine the prognostic value of a biomarker4

A *predictive factor* is a measurement related to response or absence of response to a therapy. It describes the relationship between predictive factor and the treatment benefit and makes it possible to select the therapy with the highest likelihood of efficacy to the individual patient4.5

Baseline characteristics in trials of patients with potentially resectable pancreatic cancer

Given the current knowledge gap on relevant baseline and prognostic variables for patients with potentially resectable pancreatic cancer, we performed a systematic review following the PRISMA guidelines and searched the electronic databases PubMed, Embase and the Cochraine Register Controlled Trials (CENTRAL) for randomized controlled trials investigating surgery as a treatment for potentially resectable pancreatic cancer patients with or without (neo)adjuvant therapy. Eligibility criteria for inclusion were English language, published after January 2000, randomized controlled trial, patients aged 18 years or older, histopathologically proven PDAC in at least 70% of the study population, potentially resectable pancreatic cancer with or without (neo)adjuvant therapy, and overall survival as an endpoint. A total of 2883 titles were retrieved from our database search. After title and abstract screening 79 studies remained for full text assessment, resulting in 39 studies that were eligible and contained information on 8993 patients (see figure 1)[11-40].

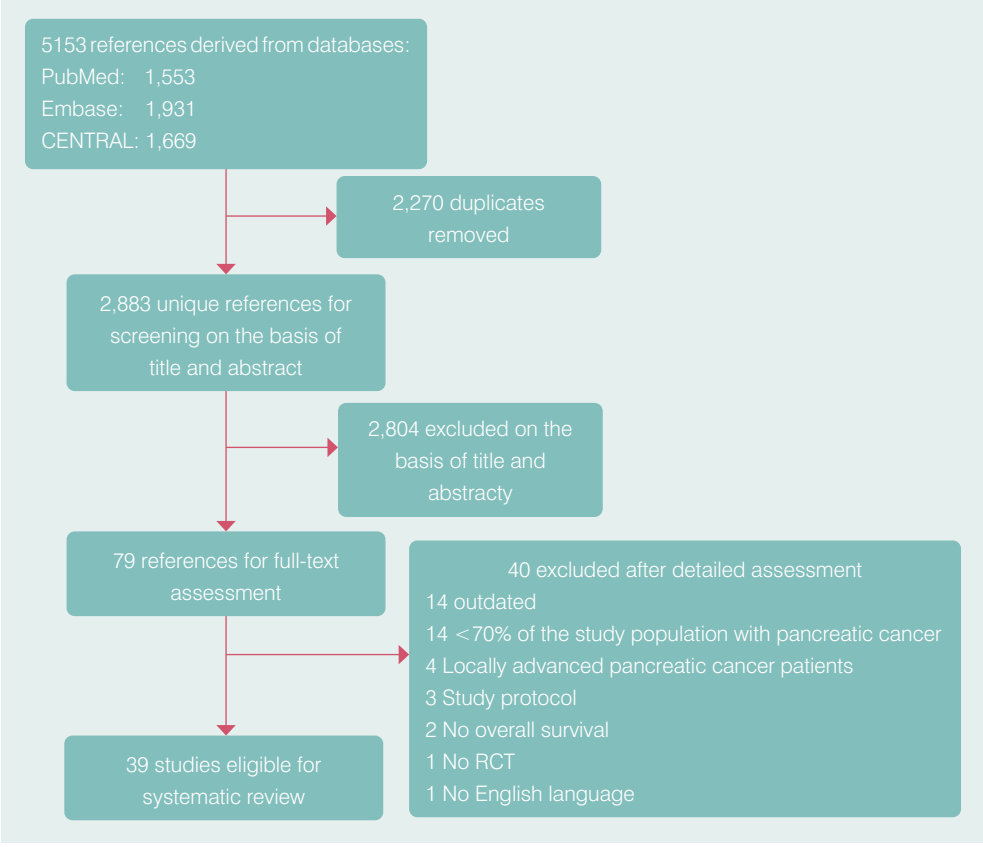

Figure 1. Literature search
Flowchart of our literature search used in the identification of baseline and prognostic factors for potential pancreatic cancer patients. CENTRAL; Cochrane Central Register of Controlled Trials, RCT; randomized controlled trial

Baseline characteristics were extracted from the 39 included studies in order to create a structured overview of all reported baseline characteristics. Mandatory baseline characteristics were selected based upon the most frequently reported characteristics. A characteristic was defined as such when the number of studies describing that characteristics were more than 45% of the total number of studies. For example, when the characteristic 'age' was studied in 30 of the 40 studies, 'age' would be defined as a frequently reported factor because it was included in 75% of the total number of RCTs.

We identified a total of 61 baseline characteristics and the most frequently reported were: age (n=38 studies), sex (n=37), surgical resection margins (n=25), pT stage (n=20), tumor size (n=19), pN stage (n=18) and performance status (n=18) (see figure 2). Also, for trials on

patients with unresectable PDAC age, sex and performance status were identified as frequently reported baseline characteristics[8]. To allow for cross trial comparisons between studies on patients with potential resectable and unresectable PDAC, we advocate that at least age, sex and performance status are reported as mandatory baseline characteristics.

Prognostic factors in trials of patients with potentially resectable pancreatic cancer

To identify potential prognostic factors for overall survival we adopted the criteria as previously described by Ter Veer et al to determine the clinical relevance of the prognostic factors: to reach clinical relevance a prognostic factor should be statistically significant in a multivariate regression analysis ($p \leq 0.05$) in at least one RCT, the combined sample size of all RCTs in which that specific factor was statistically significant should be >50% of the total sample size of all RCTs reporting that factor[41]. For example, if three RCTs report the factor 'sex' (total 1000 patients) and in two (300 patients) of the three studies the factor is statistically significant, this factor is not clinically relevant since 300 of 1000 is 30%, which does not exceed the required limit of 50%.

Prognostic factors were regarded mandatory when the factor was studied in at least 3 trials and were found to be clinically relevant based upon the criteria mentioned above.

Seventeen studies (44%) reported a multivariate regression analysis with overall survival as an endpoint. In total, 20 unique prognostic factors were identified from which 11 were found to be clinically relevant: patient characteristics; performance status, smoking status, age, tumor characteristics; nodal status, tumor size, post-operative CA 19-9, tumor grade, tumor stage, endovascular tumor emboli, treatment characteristics; adjuvant therapy, portal vein resection. The most frequently studied prognostic factors were adjuvant therapy (n=10), nodal status (n=9), tumor grade (n=8), tumor size (n=8) and surgical margin status (n=7), the latter one not being statistically significant in the majority of studies (see figure 3, Box 2 and 3). These frequently reported prognostic factors showed no overlap with the factors found to be the five most frequently reported in trials for unresectable pancreatic cancer patients. Indeed, in patients with potentially resectable pancreatic cancer other prognostic factors (e.g. surgical margins, tumor size) are important compared to unresectable patients (disease status; locally advanced pancreatic cancer vs metastatic pancreatic cancer).

In future clinical trials, the clinically relevant factors that we identified can be pre-specified, used as stratification factor and accounted for as possible predictors in regression analyses. Future research should validate the clinically relevant prognostic factors found in this study using large cohort studies to allow for the establishment of a comprehensive prognostic index[41].

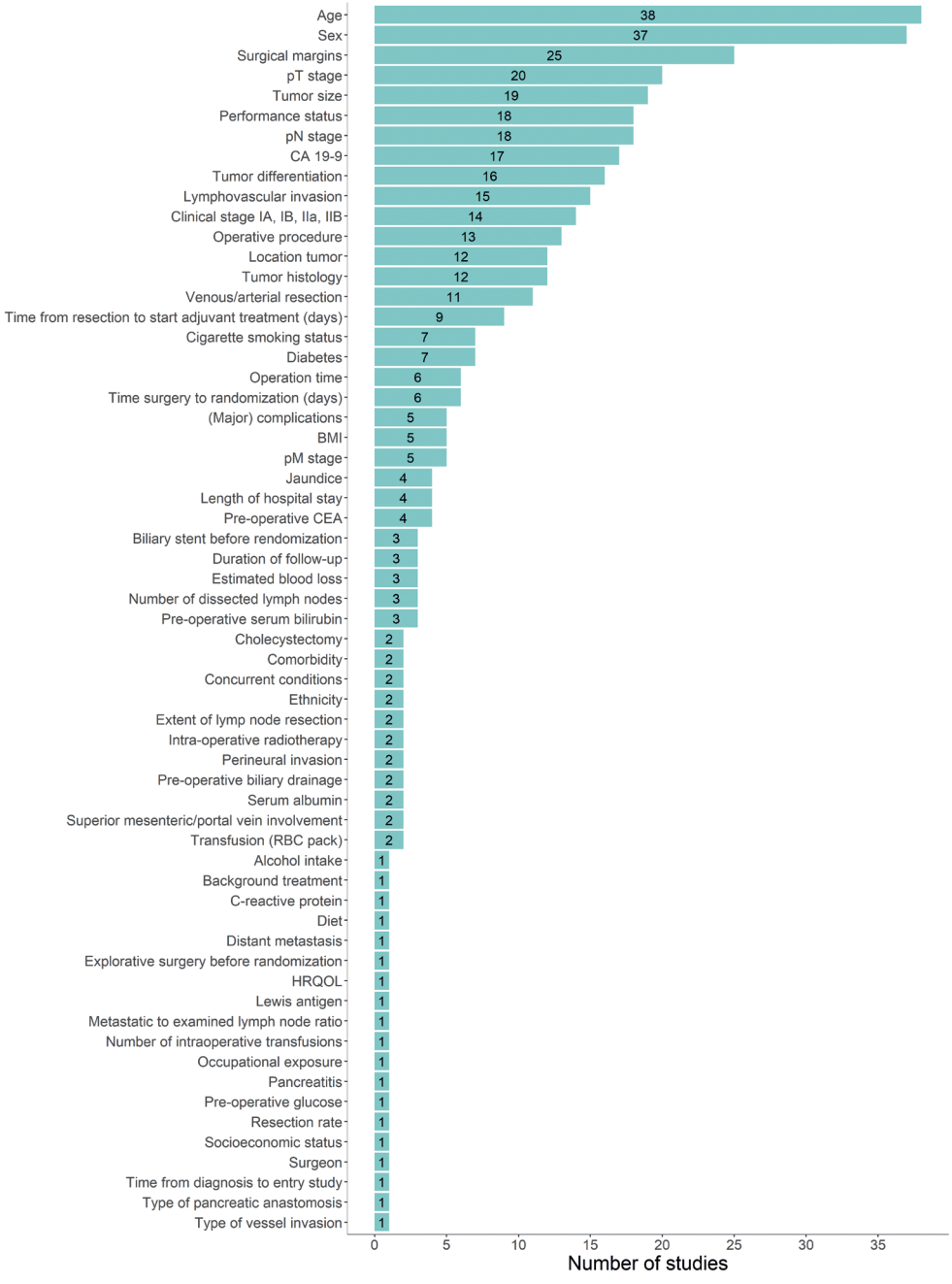

Figure 2. Baseline characteristics

The y-axis shows the identified baseline characteristics and the x-axis shows the number of randomized controlled trials in which the characteristic was reported. CA 19-9; cancer antigen (CA) 19–9, BMI; body mass index, CEA; carcinoembryonic antigen, RBC pack; red blood cell pack, HRQOL; health related quality of life.

Interestingly, based on the currently available randomized trials only one biomarker –thymidylate synthase mRNA – was included as a prognostic marker. A biomarkers is defined as a characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention[42]. Lately, molecular and genetic characteristics have been identified as important factors determining survival of pancreatic cancer[43, 44]. RNA expression analysis has been performed in several studies defining different epithelial and stromal PDAC subtypes. Bailey et al (2016) described 4 epithelial subtypes: squamous (TP53 and KDM6A mutations), pancreatic progenitor (FOXA2/3, PDX1 and MNX1), immunogenic (pathways involved in acquired immune suppression) and aberrantly differentiated endocrine exocrine (ADEX, KRAS activation NR5A2, RBPJL, NEUROD1 and NKX2-2) that correlate with histopathological characteristics[43]. In the classification by Collison et al (2019) 3 epithelial subtypes were identified; squamous, immunogenic progenitor and ADEX[44]. Although the Bailey and Collison subtypes do show overlap, they are not identical. In yet another study only two epithelial subtypes were defined: classical/progenitor vs. basal-like/squamous[45]. The exocrine subtypes might be confounded by contaminated acinar tissue and are therefore not mentioned in this study[45]. The COMPASS trial confirmed the RNA-signature of these two subtypes and was able to show prospectively that patients with the basal subtype typically do not respond to standard chemotherapy[46]. Stromal subtypes have also been distinguished and are not directly associated with epithelial subtypes, these include Normal stroma and Activated stroma[44]. In addition to RNA expression analyses, mutational analysis has shown that BRCA mutations are frequently associated with an inferior prognosis of pancreatic cancer[47-49]. However, BRCA mutated pancreatic cancer is reported to better respond to platinum containing chemotherapeutic regimens compared to sporadic pancreatic cancer, making it both a prognostic and predictive marker[50-52]. Remarkably, none of the RCT's included in our search investigated other biomarkers than thymidylate synthase mRNA as a prognostic factor and were therefore not included in our analysis. Consensus on the most promising biomarkers is urgently needed in order to include these in future randomized controlled trials.

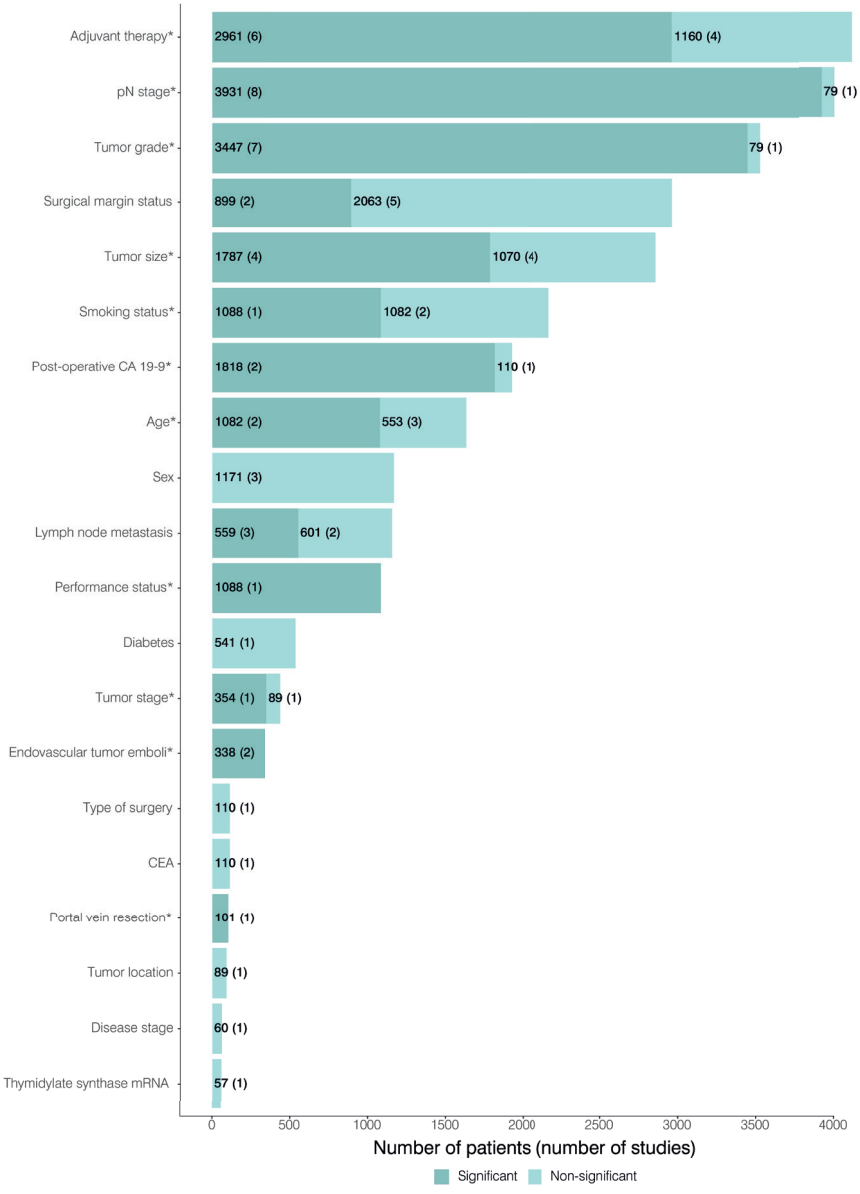

Figure 3. Prognostic factors for overall survival. All factors have been included in a multivariate regression analysis in at least one RCT

*The factors that met the criteria for clinical relevance. CA 19-9; cancer antigen (CA) 19–9, CEA; carcinoembryonic antigen, mRNA; messenger ribonucleic acid

Box 2. Mandatory baseline characteristics in randomized controlled trials for potentially resectable pancreatic cancer

- Age
- Sex
- Surgical margins
- T stage
- Tumor size
- N stage
- Performance status
- CA 19-9
- Tumor differentiation
- Lymphovascular invasion
- Clinical stage
- Operative procedure
- Location tumor
- Tumor histology

Box 3. Mandatory prognostic factors in randomized controlled trials for potentially resectable pancreatic cancer

- Adjuvant therapy
- Nodal status
- Tumor grade
- Tumor size
- Smoking status
- Post-operative CA 19-9
- Age

CONCLUSION

Meta-analyses of outcomes of clinical trials are essential for standardization of care for pancreatic cancer patients. They allow for better outcome comparisons of future studies and may provide the most appropriate control arm for new studies in the field of potentially resectable pancreatic cancer[8]. We defined mandatory baseline characteristics as the most frequently reported characteristic, when the number of studies describing that characteristics included more than 45% of the complete study sample. Prognostic factors were regarded mandatory if they were studied in at least 3 trials and were found to be clinically relevant. Based on these criteria and the currently available randomized controlled trials in potentially resectable pancreatic cancer, we advise 14 baseline and 7 prognostic characteristics as mandatory covariates for future clinical trials (see Box 2 and 3). To further advance the field, we also recommend to include novel molecular markers in future trials on resectable pancreatic cancer.

Pearls

- Definition of prognostic factors is of major importance to generate conclusions and standardization of care in potentially resectable pancreatic cancer patients
- The baseline and prognostic factors identified in this study are uniformly presented in the different studies based on a large number of randomized patients
- Clinical relevance of prognostic factors is assessed per criteria of Ter Veer et al (41)

Pitfalls

- Nowadays, mainly imprecisely defined prognostic factors are described in clinical trials, be critical on the definition
- Newly identified e.g. molecular-based prognostic factors have not (yet) been analyzed in RCTs and are therefore not included in this chapter
- Failure of reporting of factors in previous research might have led to an erroneous exclusion of some factors due to lack of reporting

Future perspectives

- Validation of the prognostic factors that were found to be clinically relevant in large cohort studies

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Author contributions

Study concepts: ENP, MGB, JWW, HWMvL. Study design: ENP, JAS, BGK, MGB, JWW, HWMvL. Data acquisition: ENP, JAS. Quality control of data and algorithms: ENP, JAS. Data analysis and interpretation: ENP, JAS, BGK, MGB, JWW, HWMvL. Statistical analysis: ENP. Manuscript preparation: ENP. Manuscript editing: ENP, JAS, MGB, JWW, HWMvL. Manuscript review: all authors.

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5

CHAPTER5

Consensusstatementonmandatorymeasurements inpancreaticcancertrialsforresectablediseasethat focuson(neo)adjuvantsystemictreatmentandsurvival outcomes(COMM-PACT-RB)-Asystematicreview

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KEY POINTS

Question

Which baseline and prognostic factors should be reported among randomized controlled trials (RCTs) in patients with resectable and borderline resectable pancreatic cancer?

Findings

We produced a systematic summary describing all baseline and prognostic factors in RCTs. We used a Delphi panel including 13 experts to find consensus about mandatory baseline and prognostic factors. We found 50 mandatory baseline and 20 mandatory prognostic factors for future trials.

Meaning

The results could have substantial impact on future clinical trials, leading to better comparison of outcomes across studies and eventually have an effect on daily clinical practice.

ABSTRACT

Importance

Reporting of baseline and prognostic factors differ between clinical trials investigating survival in patients with resectable pancreatic cancer. Therefore, comparisons of outcome measures between these studies are hampered.

Objective

The aim was to develop a consensus on baseline and prognostic factors in clinical trials for patients with resectable and borderline resectable pancreatic cancer.

Evidence Review

We performed a systematic literature search including a Delphi consensus statement of two rounds and explored the electronic databases Cochrane Register Controlled Trials (CENTRAL), PubMed and Embase for randomized controlled trials (RCTs) on (borderline) resectable pancreatic cancer with overall survival as outcome. We produced a systematic summary describing all baseline and prognostic factors in RCTs. We used a Delphi panel including 13 experts to find consensus about mandatory baseline and prognostic factors.

Findings

Overall, 42 RCTs were identified, reporting 60 baseline and 19 prognostic factors. After two Delphi rounds, agreement was reached on 50 mandatory baseline and 20 mandatory prognostic factors for future RCTs, with a distinction between studies including neoadjuvant treatment and adjuvant treatment.

Conclusion and Relevance

The Consensus statement on Mandatory Measurements in Pancreatic Cancer Trials for Resectable/Borderline resectable disease (COMM-PACT-RB) describes the international consensus on a set of mandatory baseline and prognostic factors for patients with resectable and borderline resectable pancreatic cancer to enable better comparisons across RCTs. The most important strength of this review was the large number of included RCTs from which the baseline and prognostic factors were derived. In combination with the Delphi consensus this provides complete and robust results.

Keywords

systematic review, resectable and borderline resectable pancreatic neoplasms, pancreatic cancer, mandatory measurements, overall survival, consensus statement

INTRODUCTION

Pancreatic cancer is ranked as the 3rd most common cause of cancer death and the 14th most common cancer type[1,2]. At diagnosis, the 5-year survival of pancreatic cancer is less than 8%[1]. Therapeutic choices for patients with resectable and borderline resectable pancreatic cancer have progressed in recent years and now mostly include surgery in combination with (neo) adjuvant therapy. Unfortunately, around 50% of patients do not receive adjuvant treatment due to disease progression, patient choice, or post-operative complications[3]. Consequently, shared decision making is key in the process of determining the advantages versus the negative aspects of a treatment trajectory such as high-risk surgery, potentially causing high morbidity and mortality, poor survival and a considerable effect on quality of life[4]. Appropriate advice about the outcomes of the different treatment options are essential and prognostic and predictive factors might be of beneficial assistance in the decision making for individual patients[3].

In this review, we use the definitions for prognostic and predictive factors as suggested by Clark et al. A *prognostic* factor is associated with clinical outcome without treatment or with standard care only[5]. A *predictive* factor is connected with response or absence of response to treatment. It defines the association between a predictive measurement and treatment advantage and facilitates the selection of treatment with the highest probability of efficacy to the individual patient (e.g. impact of KRAS mutation on the effect of anti-EGFR (cetuximab/panitumumab) therapy in colorectal cancer)[5,6].

To compare outcomes of randomized controlled trials (RCTs, e.g. in meta-analyses), a complete definition of the study population is crucial. Baseline factors describe the patient population at the start of a study and are not necessarily associated with the outcome of interest. On the contrary, prognostic factors are related to outcome variables[5]. Clearly, it can be argued that to allow for good comparison between trials, relevant prognostic factors should also be included in the description of a patient population.

Nowadays, there is a great variety in selection of patients and reported baseline and prognostic factors among RCTs in patients with resectable and borderline resectable pancreatic cancer[7,8]. Therefore, improvement of the reporting of these baseline and prognostic factors could lead to better comparison of outcomes across studies. Previously, a group of experts published the COMM-PACT consensus statement for patients with unresectable pancreatic cancer and described the mandatory baseline and prognostic factors that should be incorporated in trials[9].

The aim of this systematic review, including a Delphi consensus statement, was to develop a consensus on baseline and prognostic factors in RCTs investigating survival in patients with resectable and borderline resectable pancreatic cancer. We conducted a Delphi procedure to

systematically obtain expert opinions in this field. We aimed to combine the factors found in our literature search together with the expert opinions from the Delphi to describe baseline and prognostic factors, which should be regarded mandatory in trials for patients with resectable pancreatic cancer.

METHODS

Search strategy and selection criteria

We executed a systematic review adopting the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and explored the electronic databases Cochrane Register Controlled Trials (CENTRAL), PubMed and Embase for RCTs on survival on patients with (borderline) resectable pancreatic cancer, considering surgery with or without (neo)adjuvant therapy as therapeutic option. We updated our search described in the book chapter for the European Society of Surgical Oncology[10] (see supplementary material 1 for the used search terms).

Eligibility criteria

Eligibility criteria for inclusion were RCT, English language, published between January 2000 and March 2020, patients aged 18 years or older, histopathological proof of pancreatic cancer in at least 70% of the study population, resectable and borderline resectable pancreatic cancer according to the National Comprehensive Cancer Network (NCCN) criteria with or without (neo) adjuvant therapy, and overall survival as primary outcome[11]. Authors ENP and JAS independently screened title and abstracts and full texts of the search results to find studies that met the eligibility criteria. Differences were discussed between the reviewers until consensus was reached.

Since the definitions of the baseline and prognostic factors found in the RCTs are not always unequivocal, we produced a list with definitions of all the baseline and prognostic factors described in this review (supplementary material 4). These definitions facilitate the use of these factors in conducting trials for patients with resectable pancreatic cancer.

Outcome measures

Baseline factors were obtained from Table 1 of the included RCTs and from these we extracted all potentially prognostic factors that were analyzed in a multivariable regression analyses. To determine the relevance of a prognostic factor for overall survival we followed the previously published criteria by Ter Veer et al (2018): for a prognostic factor to be regarded clinically relevant in the systematic review, this factor needed to be statistically significant ($p \leq 0.05$) in a multivariable regression analysis in at least one RCT. The pooled sample size of RCTs in which this factor was statistically significant should be >50% of the total sample size of RCTs in which

that factor was investigated[12]. For instance, if 'age' is described in four RCTs (1000 patients total) and in two of the four RCTs the factor is statistically significant (600 patients total), this factor is clinically relevant because it passes the mandatory minimum of 50% (600 of 1000 is 60%). When a prognostic factor was investigated in at least 3 RCTs and considered clinically relevant (according to the criteria discussed above), the factor was defined potentially mandatory based on the literature.

We also conducted a risk of bias analysis using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2; supplementary material 5).

Consensus procedure

All corresponding authors (n=31) of the included trials were invited to participate as experts in the Delphi consensus process in an online survey consisting of two rounds. Thirteen (41%) authors completed the first and second consensus round and became part of the here presented COnsensus statement on Mandatory Measurements in PAncreatic Cancer Trials for patients with Resectable/Borderline resectable disease (COMM-PACT-RB) (see supplementary material 2).

In the first round an overview of all baseline and prognostic factors found in the literature search were presented. Experts could vote on as many factors as they wanted. In addition, the experts were asked whether there were, to their opinion, any factors missing. After the first round, only factors with >50% of the votes were included in the mandatory set.

In the second round only the baseline factors that had 20-50% of the votes or <20% of the votes but were mentioned in more than 4 studies were presented again. The prognostic factors with 20-50% of the votes or <20% of the votes but determined clinically relevant with the adopted criteria previously described by Ter Veer et al were presented as well[9]. A structured overview of the outcome of the first round was also presented in the second round. Suggestions of the experts on additional factors were put up for voting too. Excluded for further analysis were: baseline and prognostic factors with <20% of the votes and mentioned in less than 4 RCTs (baseline), or prognostic factors that did not meet the criteria of clinical relevance. After the second consensus round all remaining baseline and prognostic factors that received >50% of the votes were included into the mandatory set. The factors that received 20-50% of the votes were included into the recommended set. Factors that received <20% of votes were excluded.

Prognostic factors that were mandatory or recommended based on the outcome of the Delphi consensus round were also added to the corresponding baseline set if not already included. Furthermore, we discriminated between the baseline and prognostic factors that can only be part of adjuvant trials (e.g. consists post-operative information at baseline) and indicated these in Boxes 1-12 (supplementary material 6).

RESULTS

Literature review

In total, 3025 studies were identified from which 85 studies continued full-text screening after title and abstract assessment, ultimately leading to 42 eligible studies containing data on 10291 patients (Figure 1)[13-54]. Overall, 32 studies included patients with resectable pancreatic cancer and 10 included patients with borderline resectable pancreatic cancer (supplementary material 7).

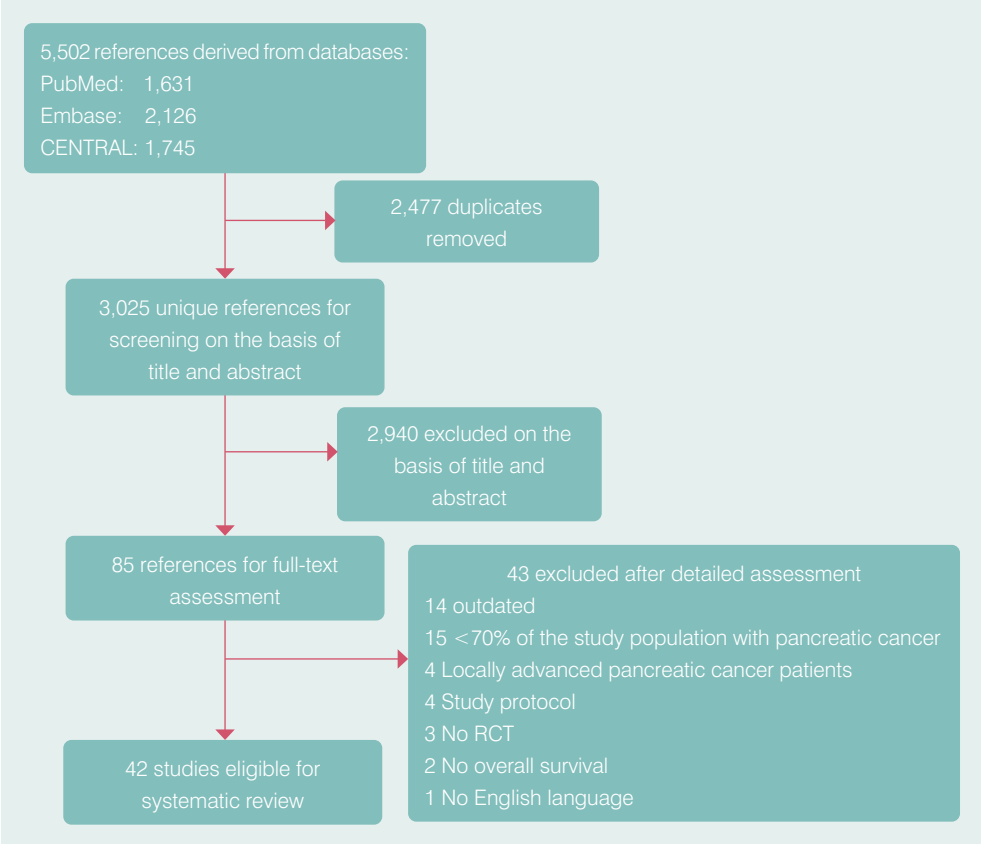

Figure 1. Literature search

Flowchart of the literature search. CENTRAL; Cochrane Central Register of Controlled Trials, RCT; randomized controlled trial

In total, we determined 60 baseline factors. The most frequently reported were: age (n=41 studies), sex (n=40), surgical margin status (n=27), T stage (n=22), tumor size (n=22), performance status (n=21) and pN stage (n=20) (see Figure 2). Of note, in the included adjuvant trials RCTs, surgery/post-operative factors could be part of the baseline tables and were therefore reported as baseline factors.

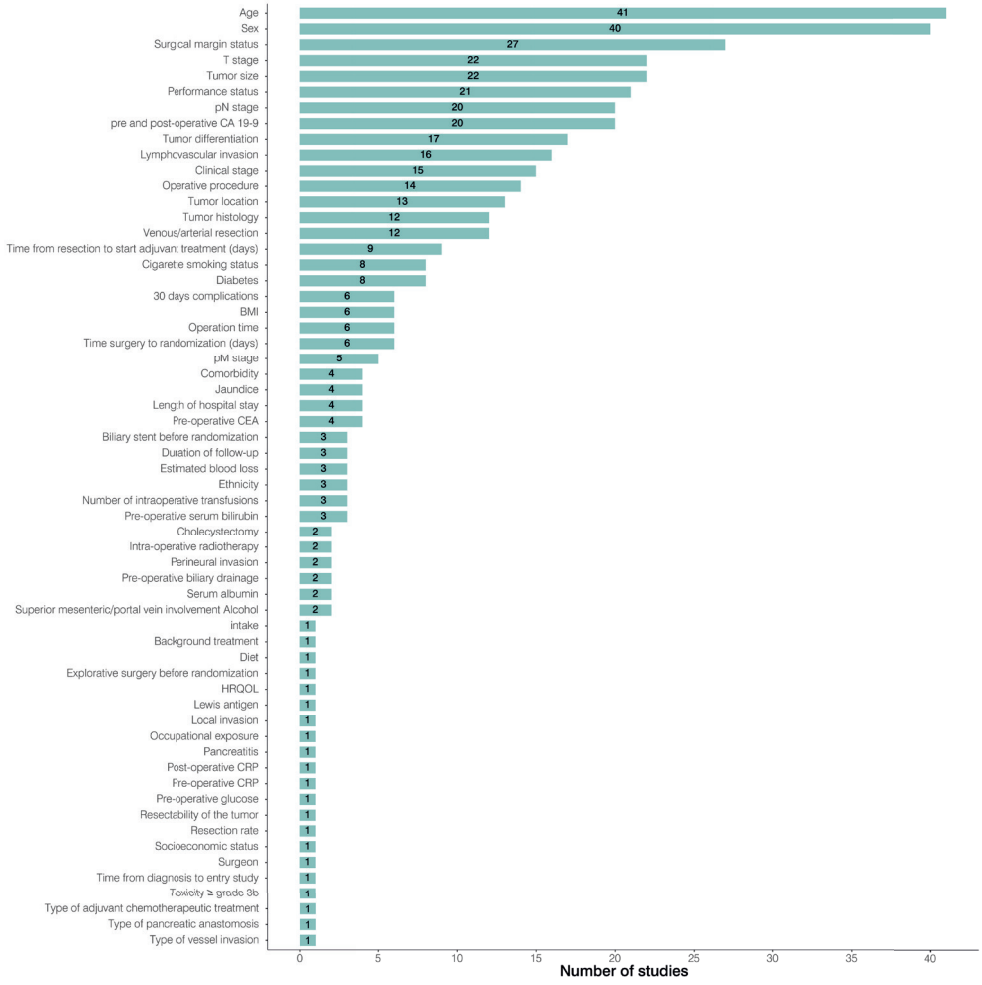

Figure 2. Baseline factors

The y-axis shows the baseline factors and the x-axis shows the number of randomized controlled trials in which the factor was described. CA 19-9; cancer antigen (CA) 19–9, BMI; body mass index, CEA; carcinoembryonic antigen, RBC pack; red blood cell pack, HRQOL; health related quality of life, CRP; C-reactive protein

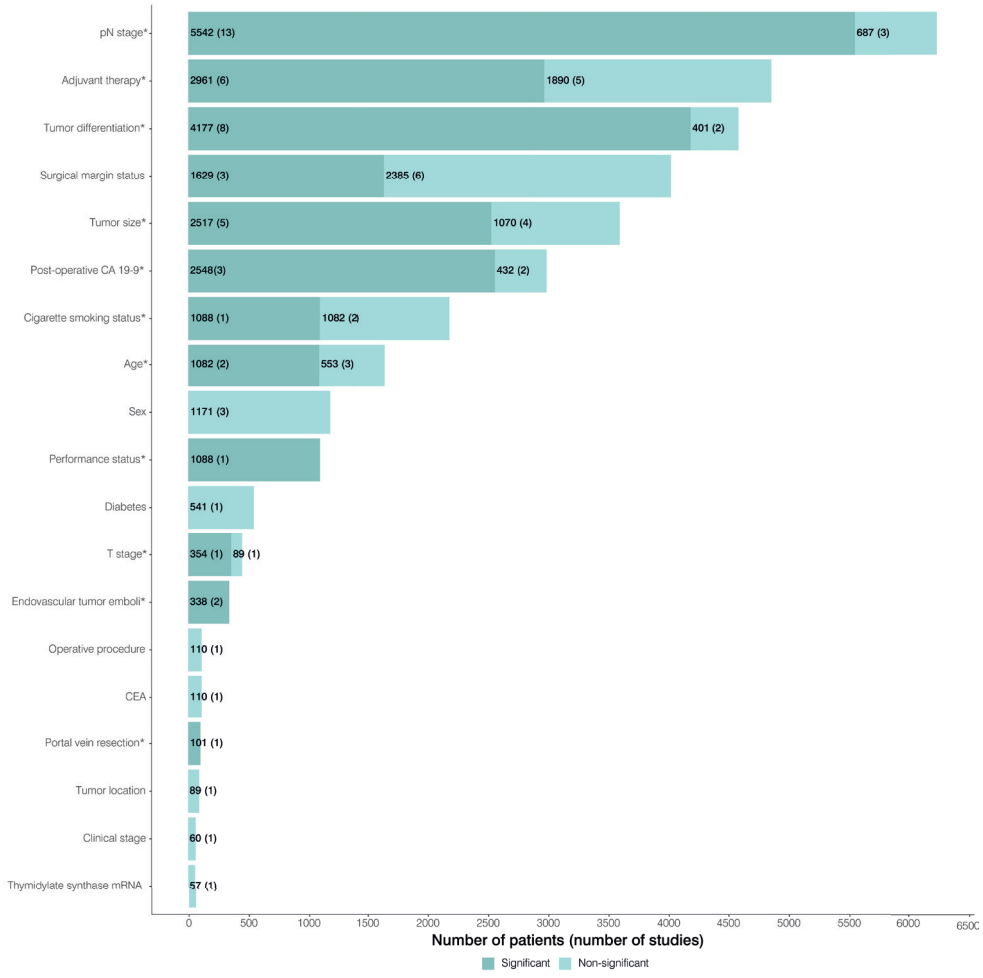

Figure 3. Prognostic factors for overall survival

All prognostic factors were studied in a multivariable regression analysis in at least one randomized controlled trial. *The factors that met the criteria for clinical relevance. CA 19-9; cancer antigen (CA) 19–9, CEA; carcinoembryonic antigen, mRNA; messenger ribonucleic acid

A total of 19 different prognostic factors were described in 19 studies (45%) that reported a multivariable regression analysis. The most commonly reported prognostic factors included pN stage (n=16), adjuvant therapy (n=11), tumor differentiation (n=10), tumor size (n=9) and surgical margin status (n=9) (see Figure 3). The following factors reached the criteria for potential clinical relevance: 1) patient characteristics; performance status, cigarette smoking status, age, 2) tumor characteristics; pN stage, tumor size, post-operative CA 19-9, tumor differentiation, T stage, endovascular tumor emboli, 3) treatment characteristics; adjuvant therapy and portal vein

resection. Again, prognostic factors could include surgery/post-operative factors if these were derived from adjuvant trials.

Consensus rounds

The consensus procedure is described in Figure 4. A total of 60 baseline and 19 prognostic factors were identified from literature search. In the first round 31 baseline and 14 prognostic factors were voted for by more than 50% of the panel and were classified as mandatory. Six baseline factors and one prognostic factor were excluded because they had <20% of votes and were reported in fewer than 4 studies (baseline) or did not fulfill the preset criteria for clinical relevance (prognostic). Twenty-three baseline and four prognostic factors entered round 2 because they received 20-50% of votes or <20% of votes but were mentioned in more than four studies or were clinically relevant in round 1. Seventeen additional baseline and 10 additional prognostic factors were recommended by experts in round 1 and also included in the second round. In round 2, sixteen baseline and six prognostic factors obtained >50% of the expert votes and were determined mandatory. Three baseline and zero prognostic factors were excluded after the second round, because they received less than 20% of votes and were reported in <4 studies or were not clinically relevant. Twenty-one baseline and 8 prognostic factors obtained 20-50% of votes or <20% of votes but were mentioned in more than 4 studies or clinically relevant and were included in the recommended set.

After the expert's voting in the two consensus rounds, a total of 47 baseline factors were included in the mandatory set of factors that should be reported in clinical trials for (borderline) resectable pancreatic cancer patients investigating survival outcome (Figure 4 and supplementary material 3). In addition, the mandatory set consists of 20 prognostic factors that should be reported in (borderline) resectable pancreatic cancer trials investigating survival outcome to enable the identification of possible confounders, which will allow for a better comparison of outcomes across studies. Moreover, after the second round 21 baseline and 8 prognostic factors were recommended to be reported in trials for resectable pancreatic cancer patients investigating survival outcome (Figure 4 and supplementary material 3).

To provide a complete overview of a patient population, we suggested that the three mandatory prognostic factors found after the consensus rounds that were not yet part of the baseline sets were also added to the mandatory baseline set, which makes a total of 50 mandatory baseline factors in which we discriminated between the neoadjuvant and adjuvant factors in separate boxes (Boxes 1, 3 and 4). Similarly, to the recommended baseline set four extra factors from the recommended prognostic set were added, resulting in 25 recommended baseline factors (Boxes 2, 5 and 6). Here, we also discriminated between the neoadjuvant and adjuvant factors in separate boxes (Boxes 5 and 6).

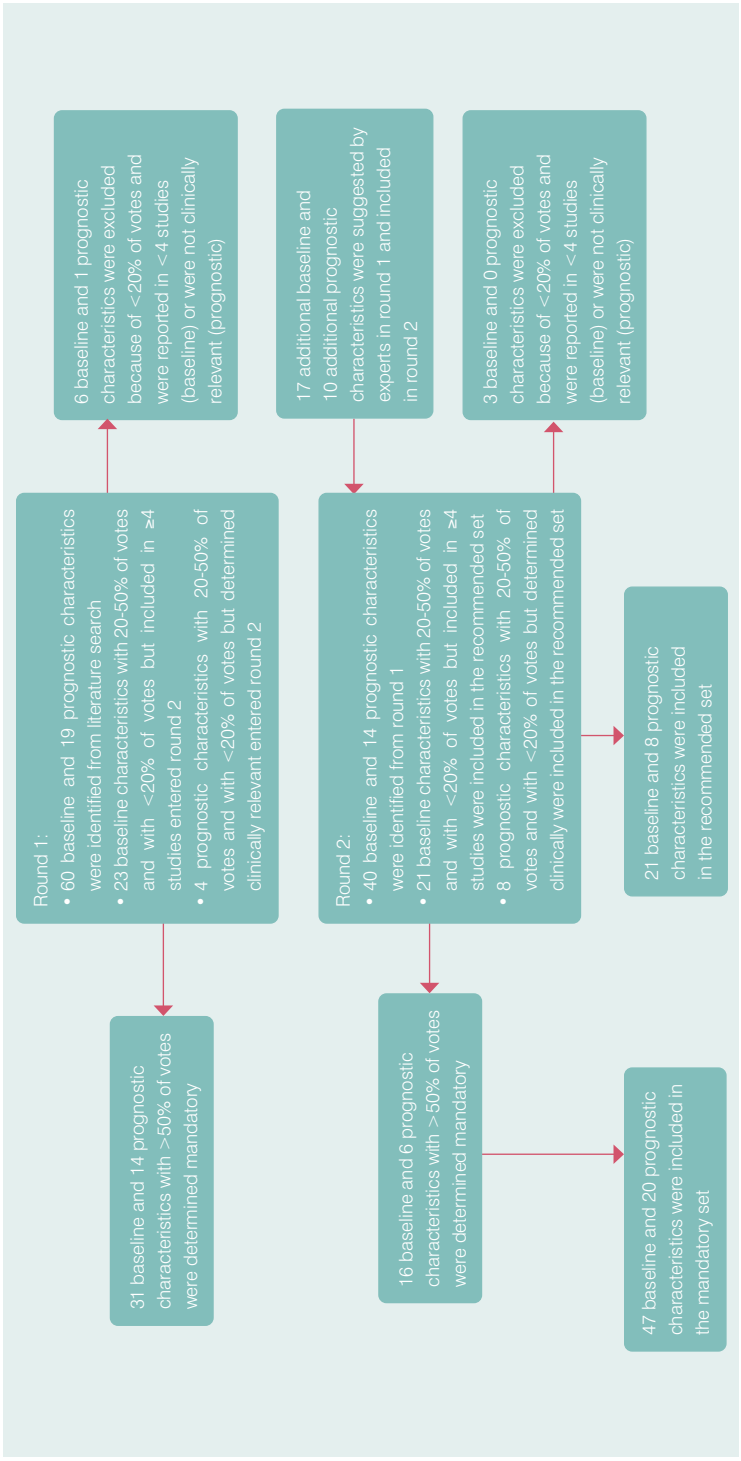

Figure 4. Flow chart of the consensus procedure

DISCUSSION

This first systematic review including a Delphi consensus statement on RCTs in patients with resectable and borderline resectable pancreatic cancer identified 50 mandatory baseline and 20 mandatory prognostic factors. The recommended set of factors includes 25 baseline and 8 prognostic factors (supplementary material 6).

The presentation of mandatory baseline factors assures that the cohorts analyzed are comparable and a respectable illustration of the general population of patients with (borderline) resectable pancreatic cancer. The identified clinically relevant prognostic factors may be used to pre-specify the factors to be included in the statistical analyses to adjust for possible confounding or used as stratification factor in future clinical trials. Future studies need to validate the clinically relevant prognostic factors of our study using sizable cohort studies to be able to build a complete prognostic index[12].

Most of the mandatory baseline and prognostic factors found in the literature search, corresponded with the outcome after the two consensus rounds with votes of the experts. After the first consensus round, 17 baseline factors and 10 prognostic factors were suggested by the experts. These novel factors mainly concerned the type of neo-adjuvant treatment and findings at PET, CT and MRI scan. The association between survival and most of the mandatory prognostic factors was already described in other studies[55-57]. However, for some factors that were deemed mandatory, limited evidence was available about the associations with survival. These were reported in only two RCTs (endovascular tumor emboli, T stage) or one RCT (performance status, portal vein resection)[23,24,27-29,46], or were not clinically relevant according to our adopted criteria (surgical margin status, sex, diabetes, operative procedure, CEA, tumor location, clinical stage, thymidylate synthase mRNA)[17,21,23,26,28,32,33,36,37,46-49,52,53]. However, since these factors received enough votes of the experts during the consensus rounds, these were included in the mandatory set of prognostic factors. In contrast, cigarette smoking status was mandatory based on the literature, but received not enough votes in both consensus rounds and was therefore added to the recommended set of factors only.

The consensus statement for patients with unresectable pancreatic cancer (COMM-PACT) also included age, sex, and performance status as most commonly reported baseline factors[9]. To be able to assess and compare different trials including patients with resectable and unresectable pancreatic cancer, we encourage that age, sex, and performance status are described as mandatory baseline factors. The most frequently described prognostic factors in our review (adjuvant therapy, pN stage, tumor differentiation, tumor size and surgical margin status) differ from the five most commonly reported prognostic factors found in RCTs for patients

with unresectable pancreatic cancer, which were performance status, disease status (locally advanced pancreatic cancer vs metastatic pancreatic), sex, age and baseline CA 19-9.

In this review we focused on patients with (borderline) resectable pancreatic cancer and therefore included RCTs on (borderline) resectable patients with or without (neo)adjuvant treatment. We are aware that some of the baseline and prognostic factors we used were only available after surgery (resected patients) or after (neo)adjuvant therapy. This means that for instance the mandatory baseline factors set includes a variable such as 'resection rate', which clearly cannot be included as a baseline variable in a neoadjuvant trial. Therefore, we indicated the adjuvant and neoadjuvant factors in the separate Boxes. Although the impact of neoadjuvant treatment for (borderline) resectable pancreatic cancer on survival is debatable[22,54], we recommend to report neoadjuvant treatment as a prognostic factor in future RCTs to improve comparisons of outcome measures between studies. In addition, the baseline factor "experience of the surgeon" is a factor that was not unequivocally defined in the different RCTs. However, it is a relevant factor and received enough votes in the Delphi rounds, we therefore defined it as years of experience in pancreatic surgery in our definition list (see supplementary material 4).

From our literature review only three biomarkers, CA 19-9, CEA and thymidylate synthase mRNA, were identified as a prognostic factor. In the consensus rounds, the experts voting did not add any biomarkers. Both CA 19-9 and CEA received enough votes to become part of the mandatory or recommended prognostic set. However, thymidylate synthase mRNA did not receive enough votes in the consensus rounds to be part of any of the prognostic sets. This is remarkable, because recent studies have shown that the impact of molecular and genetic factors on survival of pancreatic cancer patients may be substantial[58-61]. Various studies have completed RNA expression analysis to allow for the characterization of several epithelial and stromal pancreatic cancer subtypes[58,59,62]. Besides RNA expression analyses, DNA mutation analysis in pancreatic cancer patients demonstrated a relationship between BRCA mutations and an inferior prognosis[63-65]. In addition, circulating tumor DNA (ctDNA) has found to be associated with a poor prognosis in patients with pancreatic cancer[66]. The absence of these biomarkers in our consensus statement can be explained by the fact that these biomarkers are still too complicated for implementation in routine diagnostics, including large RCTs. However, it may be expected that this will change in the course of time and thus this consensus will need updating.

This review has several limitations. First, because established criteria to determine whether a prognostic factor is clinically relevant were lacking, we used the criteria described earlier by Ter Veer et al[12]. Since we used the cut-off P-value of ≤0.05 we could have missed factors in trials with smaller sample sizes. In addition, because studies tend to primarily report the statistically significant (P≤0.05) factors, pooling of these results might induce bias. Second, new prognostic factors, including novel biomarkers, may not yet have been studied in published RCTs. However,

in the Delphi consensus rounds the experts were asked whether there were, to their opinion, any missing factors. Unfortunately, the Delphi consensus rounds were only online surveys, so experts did not get the chance to discuss the clinical value of the different factors in person. Third, because of the nature of the eligibility criteria we have mostly included trials on systemic treatment. Therefore, additional factors may be relevant in trials on other treatment modalities (e.g. surgery, endoscopy, radiotherapy) in resectable pancreatic cancer. In addition, some baseline and prognostic factors were not well defined in the different RCTs, therefore we provided a file with definitions for every baseline and prognostic factor (see supplementary material 4) to meet this inconsistency.

The most important strength of this review is the inclusion of a large number of RCTs from which the baseline and prognostic factors were derived. During the voting process, experts could vote individually without being influenced by opinions of other experts. Therefore, the results of the consensus process were based upon the clinical knowledge of the experts in combination with our literature overview derived from our search, making the results as comprehensive and robust as possible.

CONCLUSION

Based on the outcome of our Delphi consensus rounds and our pre-specified criteria to evaluate the RCTs from our literature search, we recommend 50 mandatory baseline and 20 mandatory prognostic factors for future trials. Outcomes of RCTs should be meta-analyzed in order to inform the research on pancreatic cancer patients. These meta-analyses enables improved outcome comparisons on resectable and borderline resectable pancreatic cancer patients[9].

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Contributors

ENP: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Resources; Visualization; Writing – original draft; Writing – review & editing. JAS: Conceptualization; Data curation; Writing – review & editing. BGK: Conceptualization; Writing – original draft; Writing – review & editing. JTS: Conceptualization; Writing – original draft; Writing – review & editing. RS: Conceptualization; Writing – original draft; Writing – review & editing. PG: Conceptualization; Writing – original draft; Writing – review & editing. CHJvE: Conceptualization; Writing – original draft; Writing – review & editing. FSvEJ: Conceptualization; Data curation. RA: Expert in the Delphi consensus rounds; Writing – review & editing. BB: Expert in the Delphi consensus rounds; Writing – review & editing. MWB: Expert in the Delphi consensus rounds; Writing – review & editing. RC: Expert in the Delphi consensus rounds; Writing – review & editing. JLvL: Expert in the Delphi consensus rounds; Writing – review & editing. JB: Expert in the Delphi consensus rounds; Writing – review & editing. NB: Expert in the Delphi consensus rounds; Writing – review & editing. TC: Expert in the Delphi consensus rounds; Writing – review & editing. HG: Expert in the Delphi consensus rounds; Writing – review & editing. MS: Expert in the Delphi consensus rounds; Writing – review & editing. JPN: Expert in the Delphi consensus rounds; Writing – review & editing. GJvT: Expert in the Delphi consensus rounds; Writing – review & editing. MGB: Conceptualization; Supervision; Methodology; Visualization; Writing – original draft; Writing – review & editing. JWW: Conceptualization; Supervision; Methodology; Visualization; Writing – original draft; Writing – review & editing. HWMvL: Conceptualization; Supervision; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Declaration of interest

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Access to data and data analysis

HWMvL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

SUPPLEMENTRARY MATERIAL

Online supplemental files

1. Searches
2. List of experts included in the consensus
3. Consensus procedure outcomes
4. Definitions of the mandatory and recommended baseline and prognostic factors
5. Risk of bias assessment table
6. Boxes 1-12 with mandatory and recommended ((neo)adjuvant) baseline and prognostic factors for resectable pancreatic cancer patients
7. Overview of the 42 included randomized controlled trials

Supplementary material 1. Searches

Mandatory measurements in pancreatic cancer trials

Search strategies

PubMed:

((“Pancreatic Neoplasms”[Mesh] OR pancreatic neoplas*[tiab] OR pancreatic cancer*[tiab] OR pancreatic tumo*[tiab] OR pancreatic head cancer*[tiab] OR pancreatic carcinoma*[tiab] OR pancreatic adenocarcinoma*[tiab] OR pancreas tumo*[tiab] OR pancreas cancer*[tiab] OR pancreas neoplasm*[tiab] OR pancreas carcinom*[tiab] OR pancreas adenocarcinom*[tiab] OR cancer of the pancreas[tiab]) AND (“surgery” [Subheading] OR “Surgical Procedures, Operative”[Mesh:NoExp] OR “Pancreaticoduodenectomy”[Mesh] OR “Pancreatectomy”[Mesh] OR “Pancreaticojejunostomy”[Mesh] OR “Antineoplastic Combined Chemotherapy Protocols”[Mesh] OR “Neoadjuvant Therapy”[Mesh] OR “Chemotherapy, Adjuvant”[Mesh] OR “Chemoradiotherapy, Adjuvant”[Mesh] OR “Capecitabine”[Mesh] OR “Albumin-Bound Paclitaxel”[Mesh] OR “Leucovorin”[Mesh] OR “Oxaliplatin”[Mesh] OR “Fluorouracil”[Mesh] OR “Irinotecan”[Mesh] OR “Erlotinib Hydrochloride”[Mesh] OR resect*[tiab] OR surg*[tiab] OR operat*[tiab] OR pancreatico*[tiab] OR pancreatect*[tiab] OR pancreato duoden*[tiab] OR pancreatoduoden*[tiab] OR whipple[tiab] OR pylorus preserving pancreaticoduodenectom*[tiab] OR abraxane[tiab] OR capecitabine[tiab] OR systemic treatment*[tiab] OR systemic therap*[tiab] OR leucovorin[tiab] OR folinic acid[tiab] OR oxaliplatin[tiab] OR 5- fluorouracil[tiab] OR irinotecan[tiab] OR erlotinib[tiab] OR gemcitabine[tiab] OR S1[tiab] OR chemotherap*[tiab] OR neoadjuvant radiotherap*[tiab] OR neoadjuvant treat*[tiab] OR adjuvant treat*[tiab] OR adjuvant systemic treat*[tiab] OR adjuvant chemotherap*[tiab] OR adjuvant radiat*[tiab] OR neoadjuvant systemic treat*[tiab] OR neoadjuvant chemotherap*[tiab] OR neoadjuvant radiat*[tiab] OR radio-chemotherap*[tiab] OR chemoradiotherap*[tiab] OR chemo-radiotherap*[tiab]) AND (“Survival”[Mesh] OR “Survival Analysis”[Mesh] OR “Survival Rate”[Mesh] OR “Quality of Life”[Mesh] OR “complications” [Subheading] OR “Postoperative Complications”[Mesh] OR quality of life[tiab] OR “toxicity”[Subheading] OR toxicit*[tiab] OR surviv*[tiab] OR complication*[tiab]) AND (“Randomized Controlled Trial” [Publication Type] OR random*[tiab] OR trial*[ti])) NOT (“Animals”[Mesh] NOT “Humans”[Mesh]) NOT (“Review” [Publication Type] OR “Case Reports” [Publication Type] OR “Letter” [Publication Type] OR “Congress” [Publication Type] OR “Consensus Development Conference” [Publication Type] OR “Comment” [Publication Type] OR letter[ti] OR comment[ti] OR case report[ti])

EMBASE (Ovid):

Database(s): Embase Classic+Embase 1947 to 2019 July 29

Search Strategy:

#	Searches
1	exp pancreatic neoplasms/ or (pancreatic neoplas* or pancreatic cancer* or pancreatic tumo* or pancreatic head cancer* or pancreatic carcinoma* or pancreatic adenocarcinoma* or pancreas tumo* or pancreas cancer* or pancreas neoplasm* or pancreas carcinom* or pancreas adenocarcinom*).ti,ab,kw. or (cancer adj3 pancrea*).ti,ab,kw.
2	exp abdominal surgery/ or exp pancreas surgery/ or surgery.fs. or systemic therapy/ or paclitaxel/ or folinic acid/ or oxaliplatin/ or fluorouracil/ or irinotecan/ or erlotinib/ or gemcitabine/ or exp chemoradiotherapy/ or adjuvant chemoradiotherapy/ or neoadjuvant chemotherapy/ or (resect* or surg* or operat* or pancreatico* or pancreatect* or pancreato duoden* or pancreatoduoden* or whipple or pylorus preserving pancreaticoduodenectom* or abraxane or capecitabine or systemic treatment* or systemic therap* or leucovorin or folinic acid or oxaliplatin or 5- fluorouracil or irinotecan or erlotinib or gemcitabine or S1 or chemotherap* or neoadjuvant radiotherap* or neoadjuvant treat* or adjuvant treat* or adjuvant systemic treat* or adjuvant chemotherap* or adjuvant radiat* or neoadjuvant systemic treat* or neoadjuvant chemotherap* or neoadjuvant radiat* or radio-chemotherap* or chemoradiotherap* or chemo-radiotherap*).ti,ab,kw.
3	exp survival/ or exp "quality of life"/ or exp postoperative complication/ or (complication or drug toxicity).fs. or exp toxicity/ or (quality of life or toxicit* or surviv* or complication*).ti,ab,kw.
4	randomized controlled trial/ or random*.ti,ab,kw. or trial*.ti.
5	"review"/ or case report/ or letter/ or editorial/ or note/ or exp conference paper/ or consensus development/ or (letter or comment or case report).ti.
6	animal/ not human/
7	1 and 2 and 3 and 4
8	7 not 5
9	8 not 6
10	limit 9 to conference abstract status
11	9 not 10

Cochrane Central Register of Controlled Trials (CENTRAL):

ID	Search	Hits
#1	(pancreatic neoplas* OR pancreatic cancer* OR pancreatic tumo* OR pancreatic head cancer* OR pancreatic carcinoma* OR pancreatic adenocarcinoma* OR pancreas tumo* OR pancreas cancer* OR pancreas neoplasm* OR pancreas carcinom* OR pancreas adenocarcinom* OR cancer of the pancreas):ti,ab,kw	
#2	(resect* or surg* or operat* or pancreatico* or pancreatect* or pancreato duoden* or pancreatoduoden* or whipple or pylorus preserving pancreaticoduodenectom* or abraxane or capecitabine or systemic treatment* or systemic therap* or leucovorin or folinic acid or oxaliplatin or irinotecan or erlotinib or gemcitabine or fluorouracil or chemotherap* or neoadjuvant radiotherap* or neoadjuvant treat* or adjuvant treat* or adjuvant systemic treat* or adjuvant chemotherap* or adjuvant radiat* or neoadjuvant systemic treat* or neoadjuvant chemotherap* or neoadjuvant radiat* or chemoradiotherap* or radio chemotherap* or chemo radiotherap*):ti,ab,kw	
#3	(surviv* or quality of life or toxicit* or complication*):ti,ab,kw	
#4	#1 and #2 and #3	
#5	(clinicaltrials or trialsearch):so	
#6	#4 not #5 in Trials	
#7	(conference abstract):pt	
#8	#6 not #7	

Supplementary material 2. List of experts included in the consensus

Dr. R. Abrams, MD PhD
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Dipartimento di Scienze Mediche e Chirurgiche (DIMEC), Bologna, Italy

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Dr. M. Reni, MD PhD
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Dr. H. Golcher, MD
Department of Surgery, University Hospital Erlangen, Germany

Dr. M. Sinn, MD
Charite–Universitatsmedizin Berlin, CONKO-study group, Berlin, Germany
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Dr. G.J. van Tienhoven, MD PhD
Department of Radiation Oncology, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Supplementary material 3. Consensus procedure outcomes

Baseline factors

Round 1	Round 2
Age	Age
Sex	Sex
Surgical margin status	Surgical margin status
Tumor size	Tumor size
T stage	T stage
Performance status	Performance status
pN stage	N stage
CA 19-9	CA 19-9
Tumor differentiation	Tumor differentiation
Lymphovascular invasion	Lymphovascular invasion
Clinical stage	Clinical stage
Operative procedure	Operative procedure
Tumor location	Tumor location
Tumor histology	Tumor histology
Venous/arterial resection	Venous/arterial resection
Time from resection to start adjuvant treatment (days)	Time from resection to start adjuvant treatment (days)
Diabetes	Diabetes
Cigarette smoking status	Cigarette smoking status
BMI	BMI
30 days complications	(Major) complications
Time surgery to randomization (days)	Time surgery to randomization (days)
pM stage	pM stage
Jaundice	Jaundice
Duration of follow-up	Duration of follow-up
Superior mesenteric/portal vein involvement	Superior mesenteric/portal vein involvement
Perineural invasion	Perineural invasion
Comorbidity	Comorbidity
Type of vessel invasion	Type of vessel invasion
Resection rate	Resection rate
Type of adjuvant chemotherapeutic treatment	Type of adjuvant chemotherapeutic treatment
Resectability of the tumor	Resectability of the tumor
Operation time	Explorative surgery before randomization
Length of hospital stay	Local invasion
Pre-operative CEA	Neoadjuvant chemotherapy
Pre-operative serum bilirubin	Neoadjuvant chemoradiotherapy
Biliary stent before randomization	Other neoadjuvant therapy
Estimated blood loss	Response to therapy (CT, PET, CA 19-9)
Serum albumin	History of IPMN
Pre-operative biliary drainage	Weight change in the last 3 months

Supplementary material 3. Continued

Intra-operative radiotherapy	Staging with CT or MRT before therapy
Explorative surgery before randomization	Pre-operative CA 19-9
Experience of the surgeon	Post-operative CA 19-9
Type of pancreatic anastomosis	TNM classification according to AJCC 8th edition
Number of intraoperative transfusions	Number of cycles and total dose chemotherapy
Socioeconomic status	Vascular involvement arterial pre-operative
Pancreatitis	Radiotherapy yes/no
Alcohol intake	Dose radiotherapy
Background treatment	Operation time
Time from diagnosis to entry study	Length of hospital stay
Pre-operative glucose	Pre-operative CEA
Local invasion	Pre-operative serum bilirubin
Toxicity ≥ grade 3b	Biliary stent before randomization
Pre-operative CRP	Estimated blood loss
Post-operative CRP	Serum albumin
Neoadjuvant chemotherapy	Pre-operative biliary drainage
Neoadjuvant chemoradiotherapy	Intra-operative radiotherapy
Other neoadjuvant therapy	Experience of the surgeon
Positive LN at PET CT if any	Number of intraoperative transfusions
Positive findings at PETCT	Socioeconomic status
Preoperative therapt chemo +/-RT	Pancreatitis
Response to therapy (CT, PET, CA 19-9)	Background treatment
History of IPMN	Time from diagnosis to entry study
Weight change in the last 3 months	Toxicity ≥ grade 3b
Staging with CT or MRT before therapy	Pre-operative CRP
Pre-operative CA 19-9	Post-operative CRP
Post-operative CA 19-9	Positive LN at PET CT if any
TNM classification according to AJCC 8th edition	Positive findings at PETCT
Number of cycles and total dose chemotherapy	Preoperative therapt chemo +/-RT
Vascular involvement arterial pre-operative	Pre-operative glucose
Radiotherapy yes/no	Type of pancreatic anastomosis
Dose radiotherapy	Alcohol intake
Ethnicity	
Cholecystectomy	
Lewis antigen	
HRQOL	
Diet	
Occupational exposure	

Supplementary material 3. Continued

Prognostic factors

Round 1	Round 2
pN stage*	pN stage*
Adjuvant therapy*	Adjuvant therapy*
Tumor differentiation*	Tumor differentiation*
Surgical margin status	Surgical margin status
Tumor size*	Tumor size*
Post-operative CA 19-9*	Post-operative CA 19-9*
Age*	Age*
Sex	Sex
Performance status	Performance status
T stage	T stage
Operative procedure	Operative procedure
Portal vein resection	Portal vein resection
Tumor location	Tumor location
Clinical stage	Clinical stage
Cigarette smoking status	Neoadjuvant therapy
Diabetes	Reponse to preoperative therapy
Endovascular tumor emboli	Pathological response to neoadjuvant therapy
CEA	30 days complications
Neoadjuvant therapy	Arterial resection
Reponse to preoperative therapy	Pre-operative CA-19-9
Pathological response to neoadjuvant therapy	Cigarette smoking status*
30 days complications	Diabetes
Arterial resection	Endovascular tumor emboli
Pre-operative CA-19-9	CEA
Staging interval	Staging interval
Pre and post-operative CRP	Pre and post-operative CRP
Surgery to adjuvant therapy interval	Surgery to adjuvant therapy interval
Neoadjuvant to surgery interval	Neoadjuvant to surgery interval
Thymidylate synthase mRNA	

Green color indicates more than 50% of votes and was directly included in the mandatory set.
Blue color indicates 20-50% of votes or reported in more than four studies (baseline) or clinically relevant (prognostic) and included in the second round or included the recommended set.
Red color indicates less than 20% of votes and was directly excluded from further analysis.
Orange color indicates additional baseline and prognostic characteristics suggested by experts in round 1 and included in round 2.
*=clinically relevant prognostic factors

Supplementary material 4. Definitions of the mandatory and recommended baseline and prognostic factors

Mandatory baseline factors (n=50)

1. **Age**: someone's age at start study. Report: median, minimum and maximum age in years
2. **Sex:** biological gender at start study. Report: Male or Female
3. **BMI**: body mass index is a person's weight in kilograms divided by the square of height in meters
4. **Performance status:** Eastern Cooperative Oncology Group (ECOG)/World health organization (WHO)/ Zubrod performance status
5. **Diabetes:** whether a patients has diabetes. Report: No, Non-insulin-dependent, Insulin-dependent or Unknown
6. **Cigarette smoking status:** whether someone smokes cigarettes. Report: Never, Past, Present Unknown
7. **Comorbidity**: the co-occurrence of a medical condition next to pancreatic cancer. Report: Yes, No, Unknown
8. **Jaundice**: yellow pigmentation of the skin and/or sclera. Report: Yes or No
9. **History of IPMN**: whether someone has a history of IPMN or not
10. **Weight change in the last 3 months**: whether or not someone changed weight. Report Yes or No, if yes how much in kilograms
11. **Tumor size**: maximum size of the tumor in millimeters based on imaging. Report: Number of patients with measurements and Median
12. **Tumor histology**: histological type. Report: Ductal adenocarcinoma, nonductal adenocarcinoma
13. **T stage**: tumor stage according to AJCC 8th edition. Report: T1 Maximum, tumor diameter ≤2, T2 Maximum tumor diameter >2cm but ≤4cm, T3 Maximum tumor diameter >4cm, T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
14. **pN stage**: pathological N stage. Report: Lymph nodes stage according to AJCC. Report: N0 No regional lymph node metastasis, N1 Metastasis in 1-3 regional lymph nodes, N2 Metastasis in ≥4 regional lymph nodes
15. **pM stage**: pathological metastatic stage according to AJCC 8th edition. Report: M0 No distant metastasis, M1 Distant metastasis
16. **TNM classification according to AJCC 8th edition**: tumor stage according to AJCC 8th edition. Report: T1 Maximum, tumor diameter ≤2, T2 Maximum tumor diameter >2cm but ≤4cm, T3 Maximum tumor diameter >4cm, T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor). Lymph nodes stage according to AJCC 8th edition. Report: N0 No regional lymph node metastasis, N1 Metastasis in 1-3 regional lymph nodes, N2 Metastasis in ≥4 regional lymph nodes. metastatic stage according to AJCC 8th edition. Report: M0 No distant metastasis, M1 Distant metastasis
17. **Clinical stage**: According to AJCC 8th edition. Report: Stage IA: T1, N0, M0; Stage IB: T2, N0, M0; Stage IIA: T3, N0, MO; Stage IIB: T1, T2, T3, N1, M0; Stage III: T1, T2, T3, N2, M0; Stage IV: Any T, Any N, M1
18. **Tumor differentiation**: Report: Well differentiated, Moderately differentiated, Poorly differentiated, Undifferentiated, Unknown
19. **Tumor location**: Report: Head, Body, Tail
20. **Lymphovascular invasion**: whether there is lymphovascular invasion based on imaging. Report: yes/ no, if yes report the number of degrees

21. **Superior mesenteric/portal vein involvement**: whether there is superior mesenteric/portal vein involvement based on imaging. Report: yes/no, if yes report the number of degrees
22. **Perineural invasion**: whether there is perineural invasion based on imaging. Report: yes/no, if yes report the number of degrees
23. **Type of vessel invasion**: Report type of vessel invasion
24. **Local invasion**: whether the tumor has local invasion or not. Report: Yes, No, Unknown
25. **Vascular involvement arterial pre-operative**: whether there is vascular, arterial involvement based on imaging. Report: Yes, No, if yes report the number of degrees
26. **Staging with CT or MRT before surgery**: tumor staging with CT of MRT before surgery according to AJCC 8th edition. Report: T1 Maximum, tumor diameter ≤2, T2 Maximum tumor diameter >2cm but ≤4cm, T3 Maximum tumor diameter >4cm, T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor). Lymph nodes stage according to AJCC 8th edition. Report: N0 No regional lymph node metastasis, N1 Metastasis in 1-3 regional lymph nodes, N2 Metastasis in ≥4 regional lymph nodes. metastatic stage according to AJCC 8th edition. Report: M0 No distant metastasis, M1 Distant metastasis
27. **Pre-operative CA 19-9:** pre-operative cancer antigen 19-9 in KU/L. Report: Number of patients with measurements and Median and interquartile range (IQR)
28. **Post-operative CA 19-9**: post-operative cancer antigen 19-9 in KU/L. Report: Number of patients with measurements and Median and interquartile range (IQR)
29. **Resectability of the tumor**: report: resectable, borderline resectable, non resectable
30. **Operative procedure**: Type of surgical procedure. Report: Whipple resection, Total pancreatectomy, Pylorus-preserving resection, Distal pancreatectomy
31. **Surgical margin status**: resection margin status. Report: number of patients with negative status and/or number of patients with positive status
32. **Venous/arterial resection**: whether venous/arterial resection has been performed. Report Yes, No, Unknown
33. **30 days complications**: Complications within 30 days after surgery. Report: Yes, No, Unknown
34. **Portal vein resection**: whether portal vein resection was performed. Report: Yes, No, Unknown
35. **Resection rate**: Report: R0 and R1 and numbers and percentages
36. **Explorative surgery before randomization**: whether there was explorative surgery before randomization. Report: Yes or No and, if yes report number and whether it was a Laparoscopy or Laparotomy
37. **Response to therapy (CT, PET, CA 19-9)**: Report the response to therapy. For CT and PET report results according to RECIST. For CA 19-9 report the number of patients with measurements and median
38. **Number of cycles and total dose chemotherapy**: Report: Type of chemotherapy Gemcitabine, Gemcitabine+nab-paclitaxel, FOLFIRINOX or Other and Dose and number of completed cycles
39. **Radiotherapy yes/no**: whether radiotherapy was administered. Report Yes or No, if yes report the amount fractions and Gray per fraction
40. **Dose radiotherapy:** Report the amount fractions and Gray per fraction
41. **Duration of follow-up**: Report the number of patients with follow-up data and median follow-up time in days
42. **Neoadjuvant chemotherapy**: whether neoadjuvant chemotherapy was administered. Report: Yes or No, if yes report gemcitabine, gemcitabine+nab-paclitaxel, FOLFIRINOX, other and Dose and number of completed cycles

43. **Neoadjuvant chemoradiotherapy**: whether neoadjuvant chemoradiotherapy was administered. Report chemotherapy Yes or No, if yes: gemcitabine, gemcitabine+nab-paclitaxel, FOLFIRINOX, other and Dose and number of completed cycles. Report radiotherapy Yes or No, if yes report the amount fractions and Gray per fraction
44. **Other neoadjuvant therapy**: whether there was any other neoadjuvant therapy, Report: Yes or No, if yes specify (e.g. chemotherapy, radiotherapy etc.)
45. **Adjuvant therapy**: whether there was any adjuvant therapy administered, Report: Yes or No, if yes specify (e.g. chemotherapy, radiotherapy etc.)
46. **Time from resection to start adjuvant treatment (days)**: time in days between resection and start of adjuvant treatment. Report: Median
47. **Time surgery to randomization (days)**: time in days between surgery and randomization to an adjuvant trial. Report: Median
48. **Type of adjuvant chemotherapeutic treatment**: Report: gemcitabine, gemcitabine+nab-paclitaxel, FOLFIRINOX, other
49. **Response to preoperative therapy**: Report the response to therapy according to RECIST. Report: Complete response, Partial response, Stable disease, Progressive disease
50. **Pathological response to neoadjuvant therapy**: based on the College of American Pathologists grading system. Report: Complete pathologic response, Marked pathologic response, Moderate pathologic response, Minimal pathologic respons

Recommended baseline factors (n=25):

1. **Pancreatitis**: report percentage of patients who has pancreatitis during the trial
2. **Socioeconomic status**: report socioeconomic status High, Middle or Low based on level of education (The lower education level includes primary education plus the first three years of senior general secondary education and pre-university secondary education. The medium education level includes upper secondary education and middle management and specialist education. Higher education refers to associate degree programmes, Bachelor programmes; 4-year education at universities of applied sciences; Master degree programmes at universities of applied sciences and at research universities and doctoral degree programmes at research universities)
3. **Positive LN at PET CT if any**: report: Number of patients with measurements and Median number of positive lymph nodes
4. **Positive findings at PETCT**: report: Number of patients with measurements and Median
5. **Endovascular tumor emboli**: whether there were endovascular tumor emboli in resected patients. Report: Yes, No, Unknown, if yes report number of patients and percentage
6. **Staging interval**: average time that a T1-stage pancreatic cancer patients progresses to T4 stage. Report: Median time in days
7. **Estimated blood loss**: estimated perioperative blood loss. Report: mean in milliliters
8. **Pre-operative CEA**: Pre-operative carcinoembryonic antigen in Ug/L. Report: Number of patients with measurements and Median and interquartile range (IQR)
9. **Pre-operative serum bilirubin**: pre-operative serum bilirubin in Umol/L. Report: Number of patients with measurements and Median and interquartile range (IQR)
10. **Pre-operative CRP**: pre-operative C-reactive protein in mg/L. Report: Number of patients with measurements and Median and interquartile range (IQR)

11. **Post-operative CRP**: post-operative C-reactive protein in mg/L. Report: Number of patients with measurements and Median and interquartile range (IQR)
12. **Serum albumin**: serum albumin in g/L. Report: Number of patients with measurements and Median and interquartile range (IQR)
13. **Operation time**: Report: Median operation time of all operated patients in minutes
14. **Length of hospital stay**: Report: Median length of hospital stay of all patients in days
15. **Biliary stent before randomization**: whether patients have a biliary stent before randomization. Report Yes, No, Unknown
16. **Pre-operative biliary drainage**: whether pre-operative biliary drainage has taken place. Report: Yes (number, percentage), No (number, percentage), Unknown (number, percentage)
17. **Intra-operative radiotherapy**: whether radiotherapy was intra-operative administered. Report Yes or No, if yes report the amount fractions and Gray per fraction
18. **Experience of the surgeon**: indicate which surgeon performed the operative procedure. Report: which surgeon and the years of surgical experience
19. **Number of intraoperative transfusions**: report: the number of transfusions and the median amount of the transfusions in milliliters
20. **Background treatment**: whether there is treatment with other medicines that could conflict the current therapy. Report: Yes, No, Unknown, if yes report which medication
21. **Time from diagnosis to entry study**: time in days between diagnosis and date of signing informed consent. Report: Median
22. **Toxicity ≥ grade 3b**: whether there has been any toxicity ≥ grade 3b due to chemotherapy. Report: Yes, No, Unknown, if yes report which chemotherapeutic agent caused the toxicity, Number and Percentage
23. **Preoperative therapy chemo +/-RT**: whether neoadjuvant chemotherapy with or without radiotherapy was administered. Report chemotherapy Yes or No, if yes: gemcitabine, gemcitabine+nab-paclitaxel, FOLFIRINOX, Other and Dose and number of completed cycles. Report radiotherapy Yes or No, if yes report the amount fractions and Gray per fraction
24. **Neoadjuvant to surgery interval**: time in days between start neoadjuvant treatment and resection. Report: Median
25. **Surgery to adjuvant therapy interval**: time in days between resection and start of adjuvant treatment. Report: Median

Mandatory prognostic factors (n=20):

1. **Age**: someone's age at start study. Report: median, minimum and maximum age in years
2. **Sex**: biological gender at start study. Report: Male or Female
3. **Performance status**: Eastern Cooperative Oncology Group (ECOG)/World health organization (WHO)/ Zubrod performance status
4. **pN stage**: pathological N stage. Report: Lymph nodes stage according to AJCC. Report: N0 No regional lymph node metastasis, N1 Metastasis in 1-3 regional lymph nodes, N2 Metastasis in ≥4 regional lymph nodes
5. **Tumor differentiation**: Well differentiated, Moderately differentiated, Poorly differentiated, Undifferentiated, Unknown
6. **Tumor size**: maximum size of the tumor in millimeters based on imaging. Report: Number of patients with measurements and Median
7. **T stage**: tumor stage according to AJCC. Report: T1 Maximum, tumor diameter ≤2, T2 Maximum tumor diameter >2cm but ≤4cm, T3 Maximum tumor diameter >4cm, T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

8. **Clinical stage**: According to AJCC 8th edition. Report: Stage IA: T1, N0, M0; Stage IB: T2, N0, M0; Stage IIA: T3, N0, MO; Stage IIB: T1, T2, T3, N1, M0; Stage III: T1, T2, T3, N2, M0; Stage IV: Any T, Any N, M1
9. **Tumor location**: Report: Head, Body, Tail
10. **Pre-operative CA-19-9**: pre-operative cancer antigen 19-9 in KU/L. Report: Number of patients with measurements and Median and interquartile range (IQR)
11. **Post-operative CA 19-9**: post-operative cancer antigen 19-9 in KU/L. Report: Number of patients with measurements and Median and interquartile range (IQR)
12. **Surgical margin status**: resection margin status. Report: number of patients with negative status and/or number of patients with positive status
13. **Operative procedure**: Whipple resection, Total pancreatectomy, Pylorus-preserving resection, Distal pancreatectomy
14. **Portal vein resection**: whether portal vein resection was performed. Report: Yes, No, Unknown
15. **30 days complications**: Complications within 30 days after surgery. Report: Yes, No, Unknown
16. **Arterial resection**: whether arterial resection has been performed. Report Yes, No, Unknown
17. **Neoadjuvant chemotherapy**: whether neoadjuvant chemotherapy was administered. Report: Yes or No, if yes report gemcitabine, gemcitabine+nab-paclitaxel, FOLFIRINOX, other and Dose and number of completed cycles
18. **Response to preoperative therapy**: Report the response to therapy according to RECIST. Report: Complete response, Partial response, Stable disease, Progressive disease
19. **Pathological response to neoadjuvant therapy**: based on the College of American Pathologists grading system. Report: Complete pathologic response, Marked pathologic response, Moderate pathologic response, Minimal pathologic response
20. **Adjuvant therapy**: whether there was any adjuvant therapy administered, Report: Yes or No, if yes specify (e.g. chemotherapy, radiotherapy etc.)

Recommended prognostic factors (n=8):

1. **Cigarette smoking status**: whether someone smokes cigarettes. Report: Never, Past, Present Unknown
2. **Diabetes**: whether a patients had diabetes. Report: No, Non-insulin-dependent, Insulin-dependent or Unknown
3. **Endovascular tumor emboli**: whether there were endovascular tumor emboli in resected patients. Report: Yes, No, Unknown, if yes report number of patients and percentage
4. **CEA**: carcinoembryonic antigen in Ug/L. Report: Number of patients with measurements and Median and interquartile range (IQR)
5. **Pre and post-operative CRP**: pre and post-operative C-reactive protein in mg/L. Report: Number of patients with measurements and Median and interquartile range (IQR)
6. **Staging interval**: average time that a T1-stage pancreatic cancer patients progresses to T4 stage. Report: Median time in days
7. **Neoadjuvant to surgery interval**: time in days between start neoadjuvant treatment and resection. Report: Median
8. **Surgery to adjuvant therapy interval**: time in days between resection and start of adjuvant treatment. Report: Median

Supplementary material 5. Risk of bias assessment table

	Domain I: Risk of bias arising from the randomization process	Domain II: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Domain II: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Domain III: Missing outcome data	Domain IV: Risk of bias in measure-ment of the outcome	Domain V: Risk of bias in selection of the reported result	Overall risk of bias
1. Abrams 2012	Some concerns	Some concerns	Low	Low	Low	Low	Some concerns
2. Abrams 2020	Some concerns	Low	Low	Low	Low	Low	Low
3. Berlin 2018	Some concerns	Low	Low	Low	Low	Low	Low
4. Brasiuniene 2007	Some concerns	Some concerns	High	Some concerns	Low	Low	High
5. Caproti 2008	Some concerns	Some concerns	Low	Low	Low	Low	Some concerns
6. Casadei 2015	Low	Low	Low	Low	Low	Low	Low
7. Conroy 2018	Low	Low	Low	Low	Low	Low	Low
8. Farnell 2005	Some concerns	Some concerns	Low	Low	Low	Low	Some concerns
9. Gall 2014	Some concerns	Some concerns	Low	Low	Low	Low	Some concerns
10. Golcher 2015	Some concerns	Low	Low	Low	Low	Low	Low
11. Hagiwara 2018	Low	Some concerns	Low	Low	Low	Low	Low
12. Ignjatovic 2017	Some concerns	Some concerns	Low	Low	Low	Low	Some concerns
13. Imamura 2004	Some concerns	Some concerns	Low	Low	Low	Low	Some concerns
14. Jang 2014	Low	Low	Low	Low	Low	Low	Low
15. Jang 2017	Low	Some concerns	Low	Low	Low	Low	Low
16. Jang 2018	Low	Low	Low	Low	Low	Low	Low
17. Jin 2009	Low	Some concerns	Some concerns	Low	High	Low	High
18. Jones 2019	Some concerns	Low	Low	Low	Low	Low	Low
19. Kosuge 2006	Some concerns	Some concerns	Low	Low	Low	Low	Some concerns
20. Lygidakis 2002	Some concerns	Some concerns	Low	Low	Low	Low	Some concerns
21. Neoptolemos 2001 (Ann Surg)	Some concerns	Low	Low	Low	Low	Low	Low
22. Neoptolemos 2001 (Lancet)	Some concerns	Low	Low	Low	Low	Low	Low

23. Neoptolemos 2004	Some concerns	Low	Low	Low	Low	Low	Low
24. Neoptolemos 2010	Low	Low	Low	Low	Low	Low	Low
25. Neoptolemos 2017	Low	Low	Low	Low	Low	Low	Low
26. Nimura 2012	Low	Low	Low	Low	Low	Low	Low
27. Oettle 2007	Low	Low	Low	Low	Low	Low	Low
28. Oettle 2013	Low	Low	Low	Low	Low	Low	Low
29. Palmer 2007	Some concerns	Low	Low	Low	Low	Low	Low
30. Regine 2008	Some concerns	Low	Low	Low	Low	Low	Low
31. Regine 2011	Some concerns	Low	Low	Low	Low	Low	Low
32. Reni 2012	Low	Low	Low	Low	Low	Low	Low
33. Reni 2018	Low	Low	Low	Low	Low	Low	Low
34. Schmidt 2012	Some concerns	Low	Low	Low	Low	Low	Low
35. Shimoda 2015	Low	Low	Low	Low	Low	Low	Low
36. Sinn 2017	Low	Low	Low	Low	Low	Low	Low
37. Ueno 2009	Low	Low	Low	Low	Low	Low	Low
38. Uesaka 2016	Low	Low	Low	Low	Low	Low	Low
39. Van Laethem 2010	Some concerns	Low	Low	Low	Low	Low	Low
40. Versteijne 2020	Some concerns	Low	Low	Low	Low	Low	Low
41. Yeo 2012	Low	Low	Some concerns	Low	Low	Low	Low
42. Yoshitomi 2008	Low	Low	Low	Low	Low	Low	Low

Supplementary material 6. Boxes 1-12 with mandatory and recommended ((neo)adjuvant) baseline and prognostic factors for resectable pancreatic cancer patients

Box 1. Mandatory baseline factors in clinical trials for resectable pancreatic cancer patients (n=50)*

Mandatory baseline factors (n=30)*:

Patient characteristics:
- Age
- Sex
- BMI
- Performance status
- Diabetes
- Cigarette smoking status
- Comorbidity
- Jaundice
- History of IPMN
- Weight change in the last 3 months

Tumor characteristics:
- Tumor size
- Tumor histology
- T stage[b]
- pN stage
- pM stage
- TNM classification according to AJCC 8th edition
- Clinical stage
- Tumor differentiation
- Tumor location
- Lymphovascular invasion
- Superior mesenteric/portal vein involvement
- Perineural invasion
- Type of vessel invasion
- Local invasion
- Vascular involvement arterial pre-operative
- Staging with CT or MRT before therapy

Laboratory/biomarker characteristics:
- Pre-operative CA 19-9

Treatment characteristics:
- Resectability of the tumor
- Explorative surgery before randomization
- Response to therapy (CT, PET, CA 19-9)

Box 2. Recommended baseline factors in clinical trials for resectable pancreatic cancer patients (n=25) ^

Recommended baseline factors (n=16) ^:

Patient characteristics:
- Pancreatitis
- Socioeconomic status

Tumor characteristics:
- Positive LN at PET CT if any
- Positive findings at PETCT
- Endovascular tumor emboli[a]
- Staging interval[a]

Intermediate characteristic:
- Time from diagnosis to entry study

Laboratory/biomarker characteristics:
- Pre-operative CEA
- Pre-operative serum bilirubin
- Pre-operative CRP
- Serum albumin[c]

Treatment characteristics:
- Biliary stent before randomization
- Pre-operative biliary drainage
- Experience of the surgeon
- Background treatment
- Toxicity ≥ grade 3b

[a]= prognostic factors from the mandatory and recommended prognostic sets added to the mandatory and recommended baseline sets

[b]= not always indicated whether it was clinical or pathological staging

[c]= not always indicated whether it was measured pre or post-operatively

Box 3. Mandatory baseline factors in clinical trials on neoadjuvant treatment

Mandatory neoadjuvant baseline factors (n=9)*:

Treatment characteristics:

- Number of cycles and total dose chemotherapy
- Radiotherapy
- Dose radiotherapy
- Duration of follow-up
- Neoadjuvant chemotherapy
- Neoadjuvant chemoradiotherapy
- Other neoadjuvant therapy
- Response to preoperative therapy[a]
- Pathological response to neoadjuvant therapy[a]

Box 4. Mandatory baseline factors in clinical trials on adjuvant treatment

Mandatory adjuvant baseline factors (n=11)*:

Laboratory/biomarker characteristics:

- Post-operative CA 19-9

Treatment characteristics:

- Operative procedure
- Surgical margin status
- Venous/arterial resection
- 30 days complications
- Portal vein resection
- Resection rate
- Adjuvant therapy[a]
- Time from resection to start adjuvant treatment (days)
- Time surgery to randomization (days)
- Type of adjuvant chemotherapeutic treatment

*= The total number of mandatory baseline factors (n=50) also includes the neoadjuvant and adjuvant factors (Boxes 1, 3 and 4 added together)

[a]= prognostic factors from the mandatory and recommended prognostic sets added to the mandatory and recommended baseline sets

[b]= not always indicated whether it was clinical or pathological staging

[c]= not always indicated whether it was measured pre or post-operatively

Box 5. Recommended baseline factors in clinical trials on neoadjuvant treatment

Recommended neoadjuvant baseline factors (n=2) ^ :

Intermediate characteristic:
- Neoadjuvant to surgery interval[a]

Treatment characteristics:
- Preoperative therapy chemotherapy +/- radiotherapy

Box 6. Recommended baseline factors in clinical trials on adjuvant treatment

Recommended adjuvant baseline factors (n=7) ^ :

Intermediate characteristic:
- Estimated blood loss
- Surgery to adjuvant therapy interval[a]

Laboratory characteristics:
- Post-operative CRP

Treatment characteristics:
- Operation time
- Length of hospital stay
- Intra-operative radiotherapy
- Number of intraoperative transfusions

^ = The total number of recommended baseline factors (n=25) also includes the neoadjuvant and adjuvant factors (Boxes 2, 5 and 6 added together)

[a] = prognostic factors from the mandatory and recommended prognostic sets added to the mandatory and recommended baseline sets

[b] = not always indicated whether it was clinical or pathological staging

[c] = not always indicated whether it was measured pre or post-operatively

Box 7. Mandatory prognostic factors in clinical trials for resectable pancreatic cancer patients (n=20)α

Mandatory prognostic factors (n=10)α:

Patient characteristics:
- Age
- Sex
- Performance status

Tumor characteristics:
- pN stage
- Tumor differentiation
- Tumor size
- T stage[b]
- Clinical stage
- Tumor location

Laboratory/biomarker characteristics:
- Pre-operative CA-19-9

Box 8. Recommended prognostic factors in clinical trials for resectable pancreatic cancer patients (n=8)β

Recommended prognostic factors (n=6)β:

Patient characteristics:
- Cigarette smoking status
- Diabetes

Tumor characteristics:
- Endovascular tumor emboli

Laboratory/biomarker characteristics:
- CEA[c]
- Pre and post-operative CRP

Treatment characteristics:
- Staging interval

[a]= prognostic factors from the mandatory and recommended prognostic sets added to the mandatory and recommended baseline sets
[b]= not always indicated whether it was clinical or pathological staging
[c]= not always indicated whether it was measured pre or post-operative

Box 9. Mandatory prognostic factors in clinical trials on neoadjuvant treatment

Mandatory neoadjuvant prognostic factors (n=3)α:

Treatment characteristics:
- Neoadjuvant therapy
- Response to preoperative therapy
- Pathological response to neoadjuvant therapy

Box 10. Mandatory prognostic factors in clinical trials on adjuvant treatment

Mandatory adjuvant prognostic factors (n=7)α:

Laboratory/biomarker characteristics:
- Post-operative CA 19-9

Treatment characteristics:
- Surgical margin status
- Operative procedure
- Portal vein resection
- 30 days complications
- Arterial resection
- Adjuvant therapy

[α]= The total number of mandatory prognostic factors (n=20) also includes the neoadjuvant and adjuvant factors (Boxes 7, 9 and 10 added together)

Box 11. Recommended prognostic factors in clinical trials on neoadjuvant treatment

Recommended neoadjuvant prognostic factors (n=1)β:

Treatment characteristics:

- Neoadjuvant to surgery interval

Box 12. Recommended prognostic factors in clinical trials on adjuvant treatment

Recommended adjuvant prognostic factors (n=1)β:

Intermediate characteristics:

- Surgery to adjuvant therapy interval

β= The total number of recommended prognostic factors (n=8) also includes the neoadjuvant and adjuvant factors (Boxes 8, 11 and 12 added together)

Supplementary material 7. Overview of the 42 included randomized controlled trials

Study		Resectable/borderline resectable pancreatic cancer
1.	Abrams 2012[13]	Resectable pancreatic cancer
2.	Abrams 2020[52]	Resectable pancreatic cancer
3.	Brasiuniene 2007[43]	Resectable pancreatic cancer
4.	Caprotti 2008[14]	Resectable pancreatic cancer
5.	Casadei 2015[15]	Resectable pancreatic cancer
6.	Conroy 2018[16]	Resectable pancreatic cancer
7.	Farnell 2005[17]	Resectable pancreatic cancer
8.	Gall 2014[18]	Borderline resectable pancreatic cancer
9.	Golcher 2015[19]	Borderline resectable pancreatic cancer
10.	Hagiwara 2018[20]	Resectable pancreatic cancer
11.	Ignjatovic 2017[21]	Borderline resectable pancreatic cancer
12.	Imamura 2004[44]	Borderline resectable pancreatic cancer
13.	Jang 2014[24]	Borderline resectable pancreatic cancer
14.	Jang 2017[23]	Borderline resectable pancreatic cancer
15.	Jang 2018[22]	Borderline resectable pancreatic cancer
16.	Jin 2009[45]	Resectable pancreatic cancer
17.	Jones 2019[53]	Resectable pancreatic cancer
18.	Kosuge 2006[46]	Resectable pancreatic cancer
19.	Lygidakis[25]	Resectable pancreatic cancer
20.	Neoptolemos 2001[47]	Resectable pancreatic cancer
21.	Neoptolemos 2001[48]	Resectable pancreatic cancer
22.	Neoptolemos 2004[49]	Resectable pancreatic cancer
23.	Neoptolemos 2010[27]	Resectable pancreatic cancer
24.	Neoptolemos 2017[26]	Resectable pancreatic cancer
25.	Nimura 2012[28]	Borderline resectable pancreatic cancer
26.	Oettle 2007[30]	Resectable pancreatic cancer
27.	Oettle 2013[29]	Resectable pancreatic cancer
28.	Pal 2018[31]	Resectable pancreatic cancer
29.	Palmer 2007[50]	Borderline resectable pancreatic cancer
30.	Regine 2008[33]	Resectable pancreatic cancer
31.	Regine 2011[32]	Resectable pancreatic cancer
32.	Reni 2012[34]	Resectable pancreatic cancer
33.	Reni 2018[35]	Resectable pancreatic cancer
34.	Schmidt 2012[36]	Resectable pancreatic cancer
35.	Shimoda 2015[37]	Resectable pancreatic cancer
36.	Sinn 2017[38]	Resectable pancreatic cancer

37.	Ueno 2009[39]	Resectable pancreatic cancer
38.	Uesaka 2016[40]	Resectable pancreatic cancer
39.	Van Laethem 2010[41]	Resectable pancreatic cancer
40.	Versteijne 2020[54]	Borderline resectable pancreatic cancer
41.	Yeo 2012[51]	Resectable pancreatic cancer
42.	Yoshitomi 2008[42]	Resectable pancreatic cancer

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6

CHAPTER 6

The fear of cancer recurrence and progression in patients with pancreatic cancer

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ABSTRACT

Purpose

It is plausible that patients with pancreatic cancer experience fear of tumor recurrence or progression (FOP). The aim of this study was to compare FOP in patients with pancreatic cancer treated with surgical resection, palliative systemic treatment, or best supportive care (BSC) and analyze the association between quality of life (QoL) and FOP and the effect of FOP on overall survival (OS).

Methods

This study included patients diagnosed with pancreatic cancer between 2015 and 2018, who participated in the Dutch Pancreatic Cancer Project (PACAP). The association between QoL and WOPS was assessed with logistic regression analyses. OS was evaluated using Kaplan–Meier curves with the log-rank tests and multivariable Cox proportional hazard analyses adjusted for clinical covariates and QoL.

Results

Of 315 included patients, 111 patients underwent surgical resection, 138 received palliative systemic treatment, and 66 received BSC. Patients who underwent surgical resection had significantly lower WOPS scores (i.e., less FOP) at initial diagnosis compared to patients who received palliative systemic treatment or BSC only ($P<0.001$). Better QoL was independently associated with the probability of having a low FOP in the BSC (OR 0.95, 95% CI 0.91–0.98) but not in the surgical resection (OR 0.97, 95% CI 0.94–1.01) and palliative systemic treatment groups (OR 0.97, 95% CI 0.94–1.00). The baseline WOPS score was not independently associated with OS in any of the subgroups.

Conclusion

Given the distress that FOP evokes, FOP should be explicitly addressed by health care providers when guiding pancreatic cancer patients through their treatment trajectory, especially those receiving palliative treatment or BSC.

Keywords

Pancreatic neoplasms; Pancreatic ductal adenocarcinoma; Fear of cancer recurrence; Fear of cancer progression

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a lethal condition with 80-85% of the newly diagnosed patients suffering from locally advanced or metastatic disease. Despite advances in treatment, PDAC is still characterized by a very poor prognosis with a 5-year survival of 3.5%[1]. Due to late detection and its unfavorable prognosis, even when treatment is started, the risk of progression or recurrence, eventually leading to death, is high.

Fear of progression (FOP) is defined as "patients' fear that the illness will progress or that it will recur" and is one of the most frequent distress symptoms of patients with cancer[2, 3]. There is a growing tendency to approach FOP as a multidimensional concept; a combination of cognitive, behavioral, and emotional concerns of cancer patients[4, 5]. Research has shown that about 50% of cancer patients experience a moderate to a high degree of FOP of the disease[2, 6, 7]. High FOP prevalence was reported in 56% of patients with first-ever cancer diagnosis[2, 8]. In cancer survivors, FOP is also high; 24-70% in breast cancer, 35% in head and neck cancer, and 31% in testicular cancer survivors[9-13]. The prevalence of FOP in pancreatic cancer patients is unknown.

Recent studies identified potential factors that were found to correlate with and predict FOP. Increasing age, a higher disease stage, a higher number of somatic symptoms, and impaired quality of life (QoL) were found to be correlated with higher FOP[14, 15]. All of these variables are also predictive of a higher chance of imminent death. We assume that the treatment intent (curative versus palliative) in pancreatic cancer patients may affect FOP. Therefore patients are categorized based on their therapy (surgical resection, palliative systemic treatment, and best supportive care [BSC]). We also hypothesize that FOP might decrease over time in the individual patients undergoing curative treatment and may increase in patients receiving palliative treatment; therefore, it is important to examine FOP over time.

To the best of our knowledge, no data are available on the relationship between these correlating variables and FOP in pancreatic cancer patients. In the context of pancreatic cancer, such a relationship is of particular interest, given its poor prognosis, high symptom burden, and relatively poor QoL[16]. Specifically, the question arises whether disease stage, symptom burden, and QoL are also discriminative for different levels of FOP[17]. Hence, in this study, we will examine the association between overall QoL (measured with a summary score including in particular symptoms) and FOP.

Previously, an association has been reported between an increased level of FOP and inferior overall survival (OS) in lymphoma patients[18]. It might be hypothesized that this relationship is indirect, where patients with elevated levels of FOP experience a higher number of symptoms

related to a higher tumor load and therefore have lower chances of survival[19, 20]. We will investigate the hypothesis that FOP is associated with OS.

Therefore, the aims of this study are to compare the prevalence of FOP, analyze changes of FOP over time, and examine the association between QoL and FOP and the association between FOP and OS.

MATERIALS AND METHODS

Data collection

All patients diagnosed with pancreatic ductal adenocarcinoma, excluding patients with neuroendocrine tumors, between 2015 and 2018 who participated in the Pancreatic Cancer Project (PACAP) were selected from the Netherlands Cancer Registry (NCR). The NCR is a population-based registry and is linked to the pathological reports of all histologically proved cancer diagnoses in the Netherlands. The NCR comprises data of more than 17 million (also deceased) individuals of the Dutch population and contains a fair representation of all the pancreatic cancer patients nationally. PACAP is a nationwide Dutch project that was founded in 2013 by the Dutch Pancreatic Cancer Group (DPCG) and comprises data on clinical information and patient-reported outcome measures (PROMs)[21, 22]. Information on patients (gender, age, world health organization (WHO) performance status, number of comorbidities), tumor (location, stage), treatment (surgical resection, systemic treatment, BSC), and day to the last follow-up were identified from the NCR and were matched with the PROMS data for analyses.

Patients were categorized based on their initial treatment: surgical resection, palliative systemic treatment, or BSC. This study was designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[23].

Patient Reported Outcome Measures

FOP was assessed with the Worry of Progression Scale (WOPS), which is part of the PACAP survey. The WOPS questionnaire is a modified Dutch seven-item version of the six-item English Cancer Worry Scale (CWS), enquiring about the fear of cancer progression and the impact of fear on daily functioning[24, 25]. In the WOPS questionnaire, we used the six questions of the CWS and adapted these to also include fear of progression, instead of fear of recurrence only.[25, 26]. We added one question about the fear of having no medical treatment options left (see supplementary information). A four-point Likert scale was used to rate the seven items ranging from 1 (“never” or “not at all”) to 4 (“almost always” or “very much”). The sum score ranged from 7 to 28, with higher scores indicating more fear. A WOPS score below the median (i.e., <15) was defined as low.

Cancer-specific health-related quality of life (HRQL) was assessed with the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30)[27,28]. Its 30 questions are combined to form five multi-item functioning scales on physical, role, social, emotional and cognitive functioning; three multi-item symptom scales on fatigue, nausea and vomiting, and pain; six single-item symptoms scores on dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact; and a two-item global quality of life scale[28]. QLQ-C30 was rated on a four-point Likert scale ranging from "not at all" to "very much", except for the two questions on global QoL that employed a seven-point Likert scale, ranging from "not at all" to "very much". The original score was linearly transformed into scores ranging between zero and 100. As a measure of overall QoL we used the summary score, which is defined as the mean of the combined QLQ-C30 scores excluding global QoL and financial impact questions[29, 30]. A higher summary score indicates a better overall QoL.

These PROMs were administered at baseline and 3, 6, 9, 12, 18, 24 and 36 months after baseline and yearly until death or study withdrawal. The WOPS and QLQ-C30 data obtained at baseline and 3 and 9 months after baseline were used for the current analyses. For the WOPS to be defined as a baseline measure, it had to be completed at any point in time after diagnosis (best supportive care), filled out before surgical resection (between diagnosis and surgical resection), or before the start of palliative systemic treatment or within 7 days after the start of palliative systemic treatment (since it is not likely that one cycle of chemotherapy will affect WOPS scores). Only patients with a baseline questionnaire were included in the analyses.

Statistical analysis

Data were analyzed with SAS software (version 9.4, SAS institute, Cary, NC, USA). Baseline characteristics were presented with means and standard deviations (SD) for continuous variables or medians and interquartile ranges (IQRs) for categorical variables. The latter variables were described with absolute numbers and percentages. Differences in patient and tumor characteristics among the treatment groups (surgical resection, palliative systemic treatment, and BSC) were tested with chi-square tests combined with Fisher's exact tests where suitable. The difference in mean WOPS score between the three treatment groups was tested with ANOVA. The proportion of high versus low WOPS scores between the three treatment groups was tested with chi-square tests. The association between QoL and WOPS scores was assessed with logistic regression analysis adjusted for gender, age, comorbidity, performance status and year of diagnosis in all subgroups, and a number of metastatic locations in the palliative systemic treatment and BSC groups. OS was defined as the time interval from diagnosis until the end of follow-up or death, updated on February 1, 2020. We calculated OS from the day of diagnosis and not from the day of completion of the questionnaires because all other patient and tumor characteristics were defined on the day of diagnosis as well. Kaplan-Meier analyses with log-rank test were used to examine median OS for each treatment group (surgical resection,

palliative systemic treatment, BSC) and each group according to their WOPS score (high vs low). With multivariable Cox proportional hazard regression analyses, the independent association between WOPS scores at baseline and OS was identified, adjusted for age, gender, the number of comorbidities, performance status, year of diagnosis and QoL (in all subgroups), and the number of metastatic organ sites (in the systemic treatment and BSC groups). The probability of a type-I error was set at 0.05 without correction for multiple testing since we only compared three treatment groups.

RESULTS

Patient characteristics

A total of 593 patients with PDAC participated in the PACAP cohort between 2015 and 2018, 278 of whom were excluded as they lacked a baseline WOPS questionnaire (figure 1). The majority of the remaining 315 patients was male (55%) with a median age of 66 years (IQR 60-72; table 1). Most patients had pancreatic head tumors (60%). No comorbidities (42%) and a performance status of 0 or 1 was observed in the majority of patients (70%). Of all 315 included patients, 111 (35%) underwent surgical resection, 138 (44%) received palliative systemic treatment, and 66 (21%) received BSC (table 1). After 3 months, 193 patients and after 9 months 95 patients completed the WOPS questionnaires (supplementary table 1).

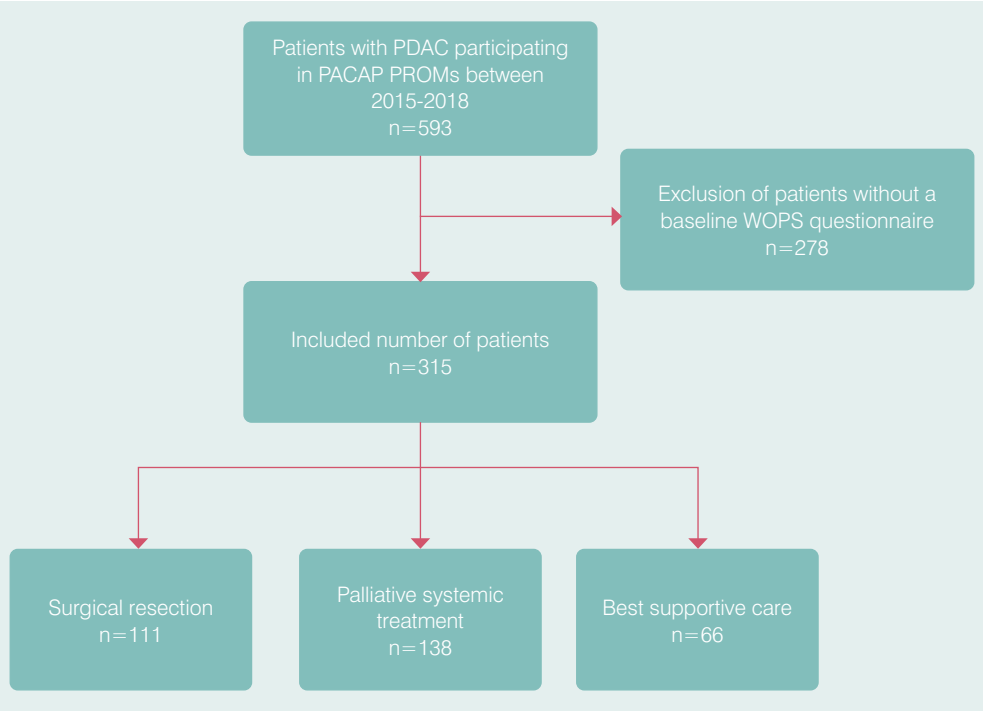

Figure 1. Flow diagram of patient inclusion

Abbreviation: PDAC=pancreatic ductal adenocarcinoma, PACAP= Pancreatic Cancer Project, PROMs= patient reported outcome measures, WOPS=Worry of Progression Scale, n=number

Table 1. Baseline characteristics

Variable	Total (n=315)	Surgical resection (n=111)	Palliative systemic treatment (n=138)	Best supportive care (n=66)
Gender, n (%)				
Male	174 (55%)	68 (61%)	72 (52%)	34 (52%)
Female	141 (45%)	43 (39%)	66 (48%)	32 (48%)
Age years, median (IQR)	66 (60-72)	66 (61-72)	65 (57-70)	71 (65-76)
<55	41 (14%)	15 (13%)	23 (17%)	3 (5%)
55-64	86 (27%)	33 (30%)	41 (30%)	12 (18%)
65-74	140 (44%)	50 (45%)	62 (45%)	28 (42%)
≥75	48 (15%)	13 (12%)	12 (8%)	23 (35%)
Tumor location, n (%)				
Head	191 (60%)	90 (80%)	65 (47%)	36 (55%)
Body	50 (16%)	3 (3%)	35 (25%)	12 (18%)
Tail	43 (14%)	14 (13%)	20 (15%)	9 (14%)
Overlapping sites	21 (7%)	1 (1%)	14 (10%)	6 (9%)
Pancreas NOS	10 (3%)	3 (3%)	4 (3%)	3 (4%)
Number of comorbidities, n (%)				
0	131 (42%)	39 (35%)	61 (44%)	31 (47%)
1	93 (29%)	37 (33%)	37 (27%)	19 (29%)
2	48 (15%)	15 (14%)	22 (16%)	11 (17%)
Missing	43 (14%)	20 (18%)	18 (13%)	5 (7%)
Performance status, n (%)				
WHO 0-1	221 (70%)	77 (69%)	112 (81%)	32 (48%)
WHO 2	25 (8%)	4 (4%)	10 (7%)	11 (17%)
WHO 3-4	10 (3%)	2 (2%)	1 (1%)	7 (11%)
Unknown	59 (19%)	28 (25%)	15 (11%)	16 (24%)
Year of diagnosis, n (%)				
2015	36 (11%)	13 (12%)	14 (10%)	9 (14%)
2016	33 (10%)	14 (13%)	17 (12%)	2 (3%)
2017	121 (38%)	39 (35%)	54 (39%)	28 (42%)
2018	125 (41%)	45 (40%)	53 (39%)	27 (41%)
Number of metastatic sites, n (%)				
0	203 (64%)	111 (100%)	65 (47%)	29 (44%)
1	75 (24%)	0 (0%)	47 (34%)	26 (39%)
≥2	37 (12%)	0 (0%)	26 (19%)	11 (17%)

Abbreviations: n=number, IQR=interquartile range, NOS=not other specified, WHO=World Health Organization.

Prevalence of WOPS scores over time

At baseline, the mean WOPS score for all patients was 16 (SD 5), with 58% of the patients scoring above the median of 15 (i.e., high WOPS scores). The mean WOPS scores were 15 (SD 5), 17 (SD 5), and 17 (SD 6) for the surgical resection (n=111), the palliative systemic treatment (n=138) and BSC group (n=66), respectively (table 1). Patients who underwent surgical resection had significantly lower (mean) WOPS scores compared to patients in the palliative systemic treatment and BSC groups at baseline (p=0.001 and p=0.004; supplementary table 1, figure 2). WOPS scores at 3 months and 9 months did not differ across the subgroups (supplementary table 1).

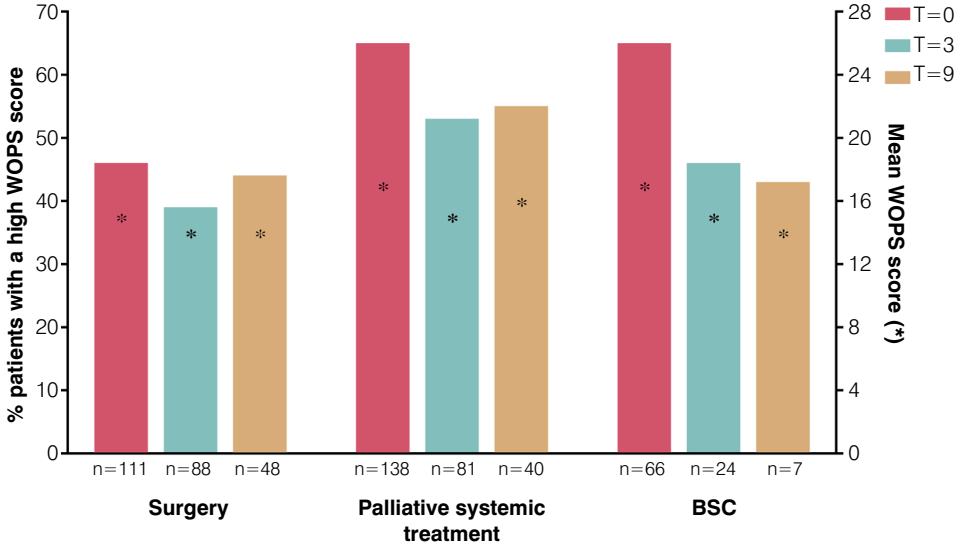

Figure 2. Percentage of patients with high WOPS scores over time for the different treatment groups (surgical resection, palliative systemic treatment and BSC)

Abbreviation: BSC=best supportive care, WOPS= Worry of Progression Scale, T=0 baseline; T=3 after 3 months, T=9 after 9 months, n=number

Relationship of QoL with WOPS

Only for the BSC group a better QoL score was independently associated with the probability of having a low FOP (OR 0.94; 95% CI 0.91-0.98) (supplementary table 2). For the surgical resection and palliative systemic treatment groups, higher QoL was not statistically significantly associated with lower FOP (OR 0.97; 95% CI 0.94-1.01 and OR 0.97; 95% CI 0.94-1.00).

Survival and FOP

Median OS was 31.2 months for patients in the surgical resection group, 14.1 months for patients undergoing palliative systemic treatment and 5.6 months for patients who received BSC (Supplementary figure 1). Median OS did not statistically significantly differ between patients with a high or low WOPS score for all treatment subgroups (Figure 3, 4, 5).

WOPS scores were not independently associated with OS in all treatment subgroups after adjustment for patient and tumor characteristics (supplementary table 3).

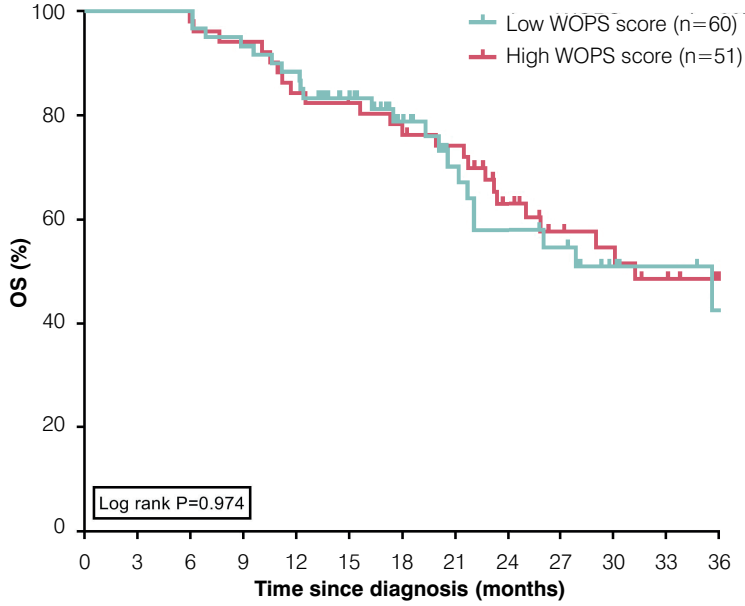

Figure 3. Kaplan Meier curves displaying overall survival in patients with high and low WOPS scores treated with surgical resection

Abbreviation: WOPS= Worry of Progression Scale, OS=overall survival

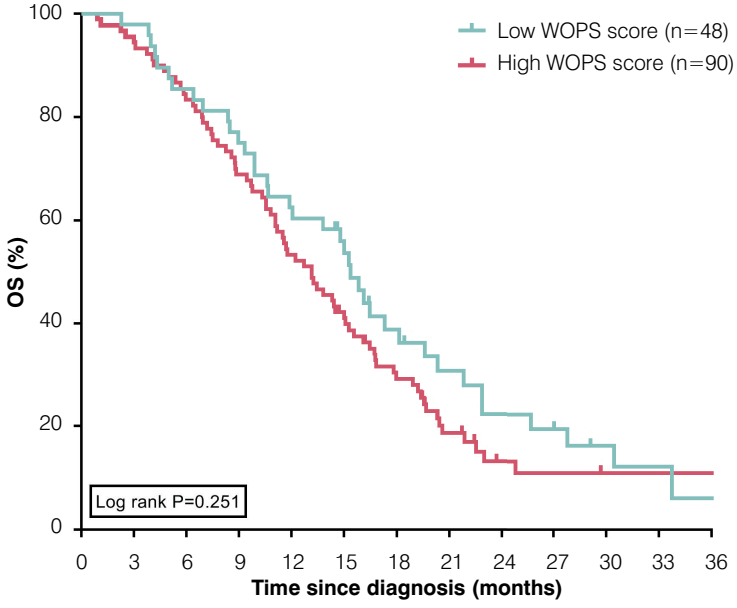

Figure 4. Kaplan Meier curves displaying overall survival in patients with high and low WOPS scores treated with palliative systemic treatment

Abbreviation: WOPS= Worry of Progression Scale, OS=overall survival

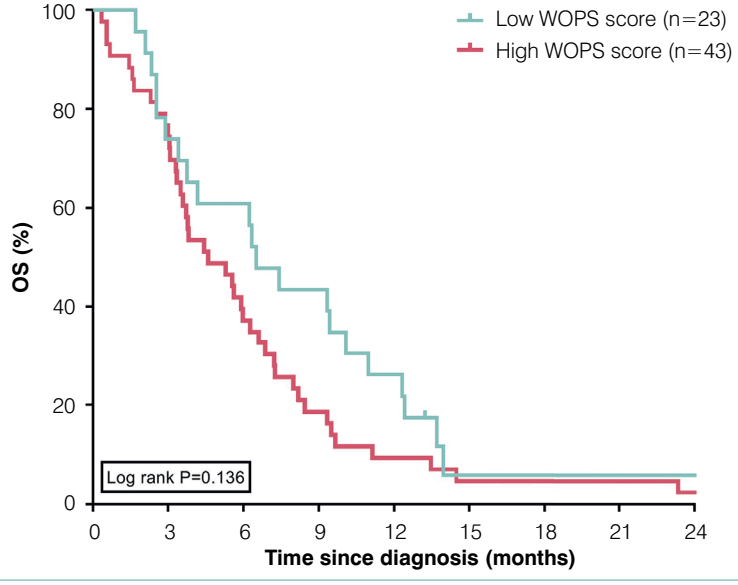

Figure 5. Kaplan Meier curves displaying overall survival in patients with high and low WOPS scores treated with BSC

Abbreviation: WOPS= Worry of Progression Scale, OS=overall survival

DISCUSSION

To the best of our knowledge, this is the first study assessing FOP in patients with pancreatic cancer. As expected, patients who underwent surgical resection had significantly lower baseline WOPS scores compared to patients in the palliative systemic treatment and BSC group. Better QoL was only independently associated with the probability of having a low FOP in the BSC group. A high WOPS score at baseline was not independently associated with OS after adjustment for patient and tumor characteristics for any of the treatment subgroups.

Although previous studies, describing other cancer types than pancreatic cancer, suggested that disease- and treatment-related factors may be less relevant to FOP[2, 15], in our study, patients who received palliative systemic treatment or BSC presented more often with high WOPS scores at baseline, reflecting more fear compared to patients who underwent surgical resection. This trend was only observed at baseline, not at the other time points as we expected. This result may be explained by the poor overall survival of PDAC patients, especially in the advanced disease setting. The median overall survival of patients with PDAC treated with palliative chemotherapy or best supportive care is 6 months and 1.5 months, respectively[1, 31]. Indeed, surgery is the treatment of choice for patients with a limited disease without metastases and provides the best chance for long-term survival without disease recurrence[1]. Unfortunately, surgery is not an option for patients with advanced, metastatic disease. This could explain why patients who are planning to undergo curative surgery have less FOP compared to patients receiving palliative treatment. Other prognostic studies also reported elevated levels of FOP because of worsening of the prognosis due to an advanced disease stage[8, 32, 33]. In addition, studies have shown that patients' expectations are often too high for cancer surgery in general[34-36].

WOPS scores in our study remained stable and did not increase over time in all subgroups. This is in line with the outcomes of other studies that showed a slight reduction in FOP in the first months after baseline score and stabilization afterwards or that showed a steady and significant decline after diagnosis[8, 37]. Higher scores at baseline might be explained by the fact that FOP is related to the elevated overall psychological distress at diagnosis[37]. The statistical phenomenon "regression to the mean" may also explain, in part, the decrease of FOP following baseline[8].

This study showed that better QoL was statistically significantly associated with the probability of having a low FOP in patients who received BSC (OR 0.94). The same trend was found in patients who were treated with surgical resection or palliative systemic treatment (both with an OR of 0.97), although these ORs were not statistically significant. These results are in line with other studies showing increasing or maintaining QoL may reduce fear[38-40]. Acceptance and recognition of a patients' FOP should be an important treatment goal in patients with PDAC. The fact that cancer brings a risk to psychological wellbeing should be a subject of discussion

in the consultation room to determine the needs of a patient in order to find the most suitable psychological support[41]. A medical provider has a signaling function and should refer patients to a mental health professional if necessary. However, research on supportive care or psychological support, specifically for patients with PDAC, is limited. Studies among patients with other cancer types suggest that study nurses who coach the patients during their entire treatment process, optimize information provision, and provide supportive care, were found to have a beneficial effect on psychosocial functioning and acceptance of the disease. These studies also identified a role of peer support groups showing a favorable outcome on QoL[42-44]. Other studies have shown that psychological interventions performed by a mental health professional help to reduce feelings of distress for patients with other cancer types than PDAC and are a necessary element of comprehensive cancer care[45, 46]. Further research on this topic is essential in order to identify the supportive care and psychological assistance for this patient population.

Currently, there is only one study in cancer that found that severe FOP in lymphoma patients was associated with an increased mortality risk[18]. In our study, we did not observe a significant association between FOP and survival. However, despite being not significant, the numerically higher median OS observed in patients with low WOPS scores compared to high WOPS scores in the palliative systemic treatment and BSC groups tend towards an association, indicating that WOPS scores are related to survival. Possibly, the subgroups were too small to reach statistically significant associations. More data are needed to draw conclusions on the prognostic effect of FOP on OS.

A limitation of this study is that 53% of the patients had to be excluded from the analysis because the baseline WOPS was not completed, and that a considerable part of the included patients did not complete questionnaires at 3 or 9 months, which limited the group sizes. Second, there might be a selection bias in the data collection of the PACAP PROMs. In our study, 35% of the patients received surgical resection, and 44% was treated with palliative systemic therapy. These percentages are higher compared to the average in The Netherlands, with a resection rate of around 15% and 25% of the patients receiving palliative chemotherapy[47]. In addition, patients in both treatment groups show better OS compared to other real-world studies[47-49], suggesting that patients with a better condition more often completed these PROMs. Fourth, if patients filled out their baseline questionnaires before a decision about a specific treatment was made, this may have led to uncertainty and could also be an explanation for the high FOP levels at diagnosis. As a result, the FOP levels decrease after 3 months because this second time point would fall after the start of treatment.

In conclusion, this real-world study is the first to provide information about the FOP in patients with PDAC. We observed that patients with PDAC report FOP at diagnosis, which stabilized over time. Patients who received palliative treatment or BSC had a higher FOP compared to surgically

treated patients at baseline. Better QoL was associated with the probability of having a low FOP in patients receiving BCS. Given the distress that FOP evokes, FOP should be explicitly addressed by health care providers when guiding pancreatic cancer patients through their treatment trajectory.

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Author contributions

Study concepts: ENP, JWW, HWMvL. Study design: ENP, WPMD, MAGS, JWW, HWMvL. Data acquisition: ENP, SA. Quality control of data and algorithms: ENP, WPMD. Data analysis and interpretation: ENP, WPMD, MAGS, MGB, JWW, HWMvL. Statistical analysis: ENP, WPMD. Manuscript preparation: ENP. Manuscript editing: ENP, WPMD, MAGS, MGB, JWW, HWMvL. Manuscript review: all authors.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics approval

According to the Central Committee on Research involving Human Subjects, this type of study does not require approval from an ethics committee in the Netherlands.

Code availability

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

SUPPLEMENTARY MATERIAL

Supplementary material Methods

CWS 6-items (original English version)

1. How often have you thought about your chances of getting cancer (again)?
2. Have these thoughts affected your mood?
3. Have these thoughts interfered with your ability to do daily activities?
4. How concerned are you about the possibility of getting cancer (again) one day?
5. How often do you worry about developing cancer (again)?
6. How much of a problem is this worry?

CWS 8-items including the two added questions (validated)

1. How often have you thought about your chances of getting cancer (again)?
2. Have these thoughts affected your mood?
3. Have these thoughts interfered with your ability to do daily activities?
4. How concerned are you about the possibility of getting cancer (again) one day?
5. How often do you worry about developing cancer (again)?
6. How much of a problem is this worry?
7. **How often do you worry about the chance of family members developing cancer?**
8. **How concerned are you about the possibility that you will ever need surgery (again)?**

WOPS questionnaire including fear of recurrence and progression and one extra question in addition to the CWS 6-items, as used in the PACAP questionnaire

1. How often have you thought about your chances of getting cancer again or cancer progression?
2. How often have these thoughts affected your mood?
3. How often have these thoughts about recurrence of progression interfered with your ability to do daily activities?
4. How concerned are you about the possibility of getting cancer again or cancer progression one day?
5. How often do you worry about developing cancer again or cancer progression?
6. How much of a problem is this worry?
7. **How concerned are you about the possibility that you will have no more medical treatment options?**

Supplementary table 1. WOPS scores over time for the different treatment groups

WOPS score	Surgical resection	Palliative systemic treatment	Best supportive care	p-value
baseline	N=111	N=138	N=66	
Mean score (SD)	15 (5)	17 (5)	17 (6)	0.001 [a]
Score high*	51 (46%)	90 (65%)	43 (65%)	
Score low	60 (54%)	48 (35%)	23 (35%)	0.004[b]
3 months	N=88	N=81	N=24	
Mean score(SD)	14 (5)	15 (4)	15 (6)	0.253 [a]
High*	34 (31%)	43 (31%)	11 (16%)	
Low	54 (49%)	38 (28%)	13 (20%)	0.169[b]
9 months	N=48	N=40	N=7	
Mean score (SD)	14 (5)	16 (5)	14 (5)	0.226 [a]
High*	21 (19%)	22 (16%)	3 (5%)	
Low	27 (24%)	18 (13%)	4 (6%)	0.549[b]

Abbreviation: WOPS= Worry of Progression Scale, SD=standard deviation, [a] = ANOVA tests for the comparison of the continues variable WOPS score between the surgical resection, palliative treatment and best supportive care groups; [b] = Chi squared tests of the comparison of high and low scores across the surgical resection, palliative systemic treatment and best supportive care groups.

* A high WOPS score is defined as a WOPS score >15 (i.e. above median)

Supplementary table 2. Multivariable logistic regression Quality of life and WOPS score (high/low) Adjusted for: gender, age, number of comorbidities, performance status, year of diagnosis in all subgroups, and number of metastases locations in the palliative systemic treatment and BSC groups.

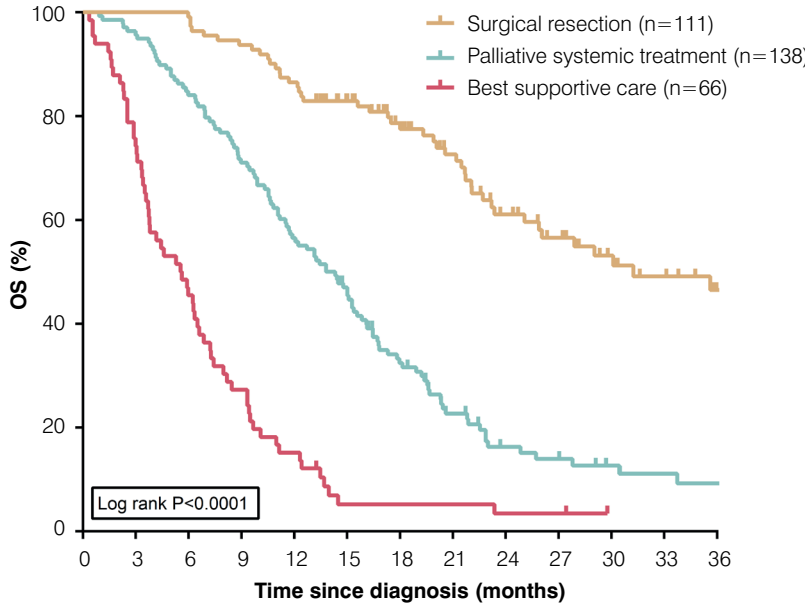
	Surgical resection			Palliative systemic treatment			Best supportive care		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**OR**	**95% C**	**P value**
Quality of life	0.97	0.94-1.01	0.0979	0.97	0.94-1.00	0.069	0.94	0.91-0.98	*0.00320
Gender									
Male	Ref		Ref	Ref			Ref		
Female	1.34	0.51-3.56	0.556	3.08	1.33-7.14	*0.0087	0.67	0.19-2.37	0.535
Age years									
<55	Ref		Ref	Ref			Ref		
55-64	0.95	0.21-4.25	0.945	0.62	0.19-2.01	0.427	1.67	0.069-40.21	0.752
65-74	0.73	0.16-3.31	0.683	1.22	0.40-3.70	0.726	0.79	0.037-16.97	0.882
≥75	1.00	0.14-7.08	0.999	1.75	0.28-10.96	0.549	1.77	0.073-42.91	0.726
Performance status									
WHO 0-1	Ref			Ref			Ref		
WHO 2-4	0.38	0.036-3.94	0.839	2.48	0.55-11.16	0.235	1.09	0.23-5.16	0.910
Unknown	0.13	0.024-0.63	*0.0186	2.39	0.66-8.73	0.186	0.90	0.18-4.49	0.895
Number of comorbidities									
0	Ref			Ref			Ref		
1	1.26	0.36-4.49	0.719	2.60	0.91-7.43	0.0739	0.70	0.14-3.50	0.667
≥2	4.72	0.87-25.51	0.072	0.81	0.26-2.54	0.713	0.22	0.031-1.61	0.137
Unknown	2.17	0.54-8.74	0.275	1.61	0.44-5.83	0.471	0.42	0.029-6.11	0.524
Number of metastatic sites									
0	NA		NA	Ref			Ref		
1				2.74	1.11-6.77	*0.0295	6.90	1.28-37.28	*0.0249
2 or more				1.24	0.42-3.71	0.701	4.90	0.61-39.64	0.137
Year of diagnosis									
2015-2016	Ref			Ref			Ref		
2017-2018	0.55	0.20-1.55	0.258	1.04	0.41-2.65	0.939	0.21	0.034-1.37	0.103

Abbreviations: WHO=World Health Organization, NA=not applicable, OR=odds ratio, 95% CI=95% confidence interval, Ref=reference group,

* statistically significant.

Supplementary table 3. Multivariable Cox-regression WOPS score and overall survival
Multivariable Cox-regression analysis was stratified for the three treatment groups (surgical resection, palliative systemic treatment and BSC)
Adjusted for: gender, age, number of comorbidities, performance status, year of diagnosis and QoL in all treatment groups and only in the palliative systemic and BSC group adjusted for number of metastatic locations
Reference group: Low WOPS score

Parameter	Hazard ratio	95% Hazard Ratio		P-value
		Confidence	Limits	
Surgical resection (n=111)				
Low WOPS score	Ref			
High WOPS score	0.841	0.417	1.697	0.628
Palliative systemic treatment (n=138)				
Low WOPS score	Ref			
High WOPS score	1.162	0.727	1.857	0.530
Best supportive care (n=66)				
Low WOPS score	Ref			
High WOPS score	1.437	0.721	2.865	0.303



Supplementary figure 1. Kaplan Meier curves displaying overall survival in patients who received surgical resection, palliative systemic treatment and BSC

Abbreviation: OS=overall survival, BSC=Best supportive care

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7

CHAPTER 7

Sex, gender and age differences in treatment allocation and survival of patients with metastatic pancreatic cancer: a nationwide study

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ABSTRACT

Background

Biological sex, gender and age have an impact on the incidence and outcome in patients with metastatic pancreatic cancer. The aim of this study is to investigate whether biological sex, gender and age are associated with treatment allocation and overall survival (OS) of patients with metastatic pancreatic cancer in a nationwide cohort.

Methods

Patients with synchronous metastatic pancreatic cancer diagnosed between 2015 and 2019 were selected from the Netherlands Cancer Registry (NCR). The association between biological sex and the probability of receiving systemic treatment were examined with multivariable logistic regression analyses. Kaplan Meier analyses with log-rank test were used to describe OS.

Results

A total of 7,470 patients with metastatic pancreatic cancer were included in this study. Forty-eight percent of patients were women. Women received less often systemic treatment (26% vs. 28%, P=0.03), as compared to men. Multivariable logistic regression analyses with adjustment for confounders showed that women ≤55 years of age, received more often systemic treatment (odds ratio [OR] 1.82, 95% CI 1.24-2.68) compared to men of the same age group. In contrast, women at >55 years of age had a comparable probability to receive systemic treatment compared to men of the same age groups. After adjustment for confounders, women had longer OS compared to men (hazard ratio [HR] 0.89, 95% CI 0.84-0.93).

Conclusion

This study found that women in general had a lower probability of receiving systemic treatment compared to men, but this can mainly be explained by age differences. Women had better OS compared to men after adjustment for confounders.

INTRODUCTION

Pancreatic cancer has a higher incidence in men than in women. In The Netherlands in 2019, the incidence of pancreatic cancer in absolute numbers for men was 1,324 (52%) compared to 1,245 for women (48%)[1-3]. Many studies have reported on the predominance of pancreatic cancer diagnosis in men[1-5]. Also, worse survival has been described for men suffering from pancreatic cancer[1-5].

Differences in incidence rates and outcome among women and men might be explained by biological (sex) and gender based-causes. These biological factors include sex differences in molecular and genetic subtypes (e.g. BRCA mutations). Gender-related factors are, for example, individual exposure to risk factors as tobacco and obesity[6-10]. Also, gender may impact patient and physicians' attitudes[11] and accessibility to health care.

Sex differences in cancer risk and survival have been described for multiple cancer types[12]. Theoretically, sex differences in cancer survival may be attributed to differences in disease stage and/or (sub)-type at diagnosis, differences in biology of a given type of cancer of similar stage, differences in treatment allocation or differences in treatment effects.

Differences in treatment effects are classified in differences in pharmacokinetics and differences in pharmacodynamics[13, 14]. However, little is known about the association between gender and the probability of receiving systemic treatment in metastatic pancreatic cancer. Examination of differences in treatment allocation and clinical characteristics of both men and women with metastatic pancreatic cancer might help to explain potential differences in outcome.

The aim of this study is to investigate patient characteristics, systemic treatment allocation and overall survival (OS) of women and men with metastatic pancreatic cancer in a nationwide cohort in general and also stratified for age ≤55 years, 56-64 years, 65-74 years and ≥75 years.

MATERIALS AND METHODS

Data collection

All patients diagnosed with synchronous metastatic pancreatic adenocarcinoma in The Netherlands between 2015 and 2019 were selected from the Netherlands Cancer Registry (NCR). In order to keep the patient population as homogenous as possible, we only included patients with metastatic disease. The NCR is a population-based registry containing data on all cancers in the Dutch population of over 17 million individuals. The database is directly linked with the nationwide network and registry of histology and cytopathology (PALGA), comprising

all histologically confirmed cancer diagnoses. This registry, in combination with the National Registration of Hospital Care is a suitable representation of the metastatic pancreatic cancer patient population nationwide. Information about the patient (sex, age, performance status, previous cancer diagnosis, comorbidities), tumor (TNM-stage, tumor histology, location of primary tumor and metastases) and systemic treatment were identified from the hospital's electronically health record system by trained registrars of the NCR. The main reason for deciding no cancer-directed treatment was also routinely registered in the NCR and categorized into comorbidity, social context, patient's whish, short life expectancy, old age, extensive disease and other. Multiple metastases in one organ were defined as one metastatic site. Day to last follow-up was obtained by the annual linkage with data from the Municipal Personal Records Database, containing information on vital status and date of death from all Dutch inhabitants. These data were complete up to 1 February 2020. This study proposal was approved by the scientific committee of the Dutch Pancreatic Cancer Group [15]. According to the Central Committee on Research involving Human Subjects, this type of study does not require approval from an ethics committee in the Netherlands. This study was designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[16].

Statistical analysis

Data in this study were analyzed using SAS software (version 9.4, SAS institute, Cary, NC, USA). Patient and tumor characteristics were presented with means and standard deviations (SD) for continuous variables. Categorical variables were described with absolute numbers and percentages. Differences regarding patient and tumor characteristics between women and men were tested with chi-squared tests, or with Fisher's exact tests when appropriate. The association between sex and the probability of receiving systemic treatment was examined with multivariable logistic regression analyses with adjustment for age, comorbidity, performance status, year of diagnosis and number of metastatic locations. OS was defined as the time interval from diagnosis until the end of follow-up or death. Kaplan Meier analyses with log-rank test were used to describe median OS and sex also stratified for age ≤55 years, 56-64 years, 65-74 years and ≥75 years because differences in outcome between patients of different sex in these age categories were expected based on the descriptives. The probability of a type-I error was set at 0.05.

RESULTS

Patient characteristics

A total of 7,470 patients with metastatic pancreatic cancer were included in this study. Just under half of all patients were women (48%; [Table 1]). Median age was 71 years (IQR 63-78 years) and was slightly higher in women compared to men (72 vs. 70 years, $P<0.001$). Women had less

comorbidities than men (P<0.001). Of all patients, 27% received systemic treatment and 73% best supportive care (BSC).

Table 1. Baseline characteristics of 7,470 patients with metastatic pancreatic cancer stratified by sex

Variable	All (n=7,470)	Men (n=3,884)	Women (n=3,586)	P value
Age years, median (IQR)	71 (63-78)	70 (63-77)	72 (64-79)	<0.001[a]
≤55	574 (8%)	326 (8%)	248 (7%)	
56-64	1,512 (20%)	831 (21%)	681 (19%)	
65-74	2,726 (36%)	1,460 (38%)	1,266 (35%)	
≥75	2,658 (36%)	1,267 (33%)	1,391 (39%)	<0.001[b]
Tumor location, n (%)				
Head of pancreas	3,089 (41%)	1,598 (41%)	1,491 (42%)	
Body of pancreas	1,274 (17%)	620 (16%)	654 (18%)	
Tail of pancreas	1,870 (25%)	1,027 (26%)	843 (24%)	
Overlapping sites	755 (10%)	381 (10%)	374 (10%)	
Pancreas NOS	482 (6%)	258 (7%)	224 (6%)	0.0098[b]
Number of comorbidities, n (%)				
0	3,047 (41%)	1,441 (37%)	1,606 (45%)	
1	2,503 (34%)	1,352 (35%)	1,151 (32%)	
≥2	1,376 (18%)	825 (21%)	551 (15%)	
Missing	544 (7%)	266 (7%)	278 (8%)	<0.0001[b]
Performance status, n (%)				
WHO 0-1	2,630 (35%)	1,411 (36%)	1,219 (34%)	
WHO 2	796 (11%)	444 (11%)	352 (10%)	
WHO 3-4	685 (9%)	362 (9%)	323 (9%)	
Unknown	3,359 (45%)	1667 (43%)	1,692 (47%)	0.0017[b]
Year of diagnosis				
2015	1,380 (18%)	746 (19%)	634 (18%)	
2016	1,533 (21%)	791 (20%)	742 (21%)	
2017	1,485 (20%)	767 (20%)	718 (20%)	
2018	1,522 (20%)	758 (20%)	764 (21%)	
2019	1,550 (21%)	822 (21%)	728 (20%)	0.1904[b]
Number of metastatic sites, n (%)				
1	4,493 (60%)	2,340 (60%)	2,153 (60%)	
≥2	2,977 (40%)	1,544 (40%)	1,433 (40%)	0.854[b]

Abbreviations: n:number; IQR: interquartile range; NOS: not other specified; a: Kruskal-Wallis test; b: Chi-Square test

Treatment

Among all patients, women received less often systemic treatment as compared to men (26% vs. 28%, P=0.03). Differences were mainly seen in the younger age groups. Figure 1 shows the treatment allocation (systemic treatment and BSC) of men and women by age category. Women aged ≤55 years received more often systemic treatment than men (p=0.03), whereas in the older age categories the allocation of systemic therapy did not differ. Furthermore, at younger age (≤55 years and 56-64 years) reasons for no administration of systemic treatment did not differ between women and men (P= 0.9952 and P=0.6195 [Table 2]). At higher age (65-74 years and ≥75 years) a significant difference in the reasons for not administering systemic treatment between women and men (P=0.0287 and P=0.0017) has been observed, with women choosing more often BSC.

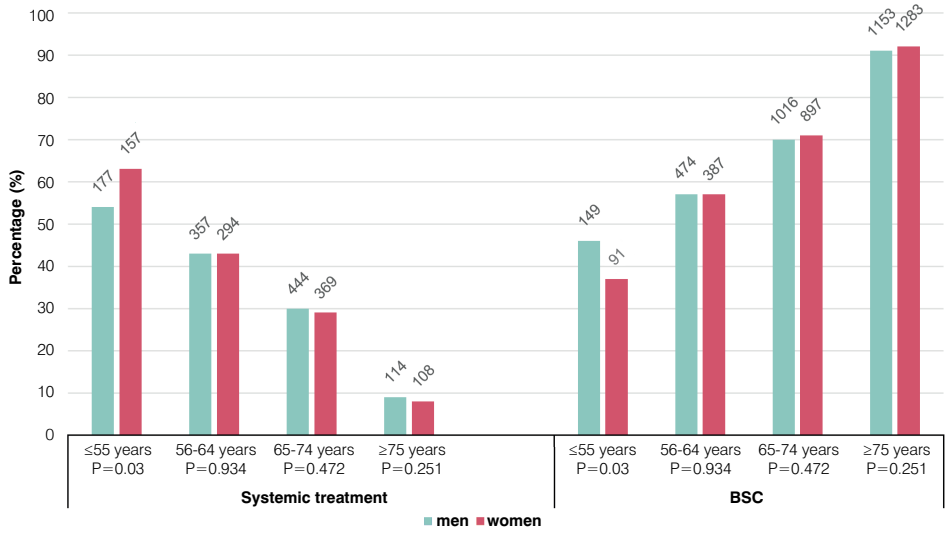

Figure 1. Treatment characteristics of women and men with metastatic pancreatic cancer
Abbreviations: BSC: best supportive care; P: Chi square p-value

Association of biological sex and the probability of receiving systemic treatment

Logistic regression showed that among all patients, women had a lower probability of receiving systemic treatment compared to men (adjusted odds ratio [OR] 0.89, 95% confidence interval [CI] 0.81-0.99). When we restricted our analyses to patients with a good performance status (0-1), the patients generally most suitable for systemic therapy, we did not find a statistically significant difference in the probability of receiving systemic treatment between women and men (OR 0.92, 95% CI 0.79-1.07). However, in patients with performance status 2 or higher we did find a statistically significant difference to the disadvantage of women (OR 0.89, 95% CI 0.81-0.98).

The statistically significant difference between women and men observed in the total group of patients is therefore driven by performance status.

Table 2. Reasons for no administration of systemic treatment in women and men with metastatic pancreatic cancer per age group

Age groups	**All patients**		**≤55 years**		**56-64 years**		**65-74 years**		**≥75 years**	
Sex	Men	Women	Men	women	Men	Women	Men	Women	Men	Women
Patients not receiving systemic treatment (n)	2,792	2,658	149	91	474	387	1,016	897	1,153	1,283
Main reason for not receiving systemic treatment:										
Wish patient (%)	33	38	30	27	38	40	36	43	30	35
Comorbidity/Performance status (%)	27	23	23	27	26	26	27	23	28	22
Progressive disease (%)	19	19	21	23	17	13	16	15	21	22
Death after diagnosis (%)	5	5	5	5	5	6	6	5	5	4
Age (%)	1	2							3	4
Situation at home (%)	0	0							0	
Other (%)	6	6	3	3	6	6	6	4	6	7
Missing (%)	8	15	17	13	9	9	8	32	7	6
Chi square p-value		0.0002		0.9952		0.6195		0.0287		0.0017

Multivariable logistic regression analyses, stratified by age category, showed that at ≤55 years of age, women were more likely to receive systemic treatment (OR 1.82, 95% CI 1.24-2.68 [Table 3]) as compared to men of the same age group. In the older age categories the probability to receive systemic treatment did not significantly differ between women and men (56-64 years OR women vs men) 0.99, 95% CI 0.80-1.24; and 65-74 years OR 0.93, 95% CI 0.76-1.10; and ≥75 years OR 0.85, 95% CI 0.63-1.13). When we restricted our analyses to patients with a good performance status (0-1), we found comparable results. At younger age ≤55 years, women had a higher probability of receiving systemic treatment compared to men (OR 1.83, 95% CI 1.02-3.29). Older women and men had no significantly different probability to receive systemic treatment (55-64 years OR (women vs men) 0.89, 95% CI 0.65-1.21; and 65-74 years OR 0.94, 95% CI 0.74-1.21; and ≥75 years OR 0.96. 95% CI 0.65-1.42).

Table 3. Multivariable logistic regression analyses for the probability of receiving systemic treatment in patients with metastatic pancreatic cancer stratified by age

	≤55 years (n=574)			56-64 years (n=1,512)			65-74 years (n=2,726)			≥75 years (n=2,658)		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Sex												
Men	Reference			Reference			Reference			Reference		
Women	1.82	1.24-2.68	0.0025	0.99	0.80-1.24	0.942	0.93	0.76-1.10	0.385	0.85	0.63-1.13	0.260
Performance status												
WHO 0-1	Reference			Reference			Reference			Reference		
WHO 2	0.22	0.12-0.41	<0.001	0.48	0.33-0.69	<0.001	0.51	0.39-0.67	<0.0001	0.53	0.35-0.79	<0.0001
WHO 3-4	0.04	0.01-0.10	<0.001	0.07	0.04-0.14	<0.001	0.07	0.04-0.12	<0.0001	0.03	0.01-0.13	0.0021
Unknown	0.21	0.14-0.32	<0.001	0.29	0.23-0.37	<0.001	0.25	0.21-0.31	<0.0001	0.15	0.10-0.20	<0.0001
Number of comorbidities												
0	Reference			Reference			Reference			Reference		
1	1.03	0.65-1.63	0.905	0.80	0.63-1.03	0.0842	0.90	0.74-1.10	0.311	0.95	0.69-1.31	0.749
≥2	0.85	0.31-2.32	0.757	0.53	0.37-0.76	0.0007	0.72	0.56-0.93	0.0117	0.48	0.30-0.75	0.0015
Unknown	0.46	0.24-0.88	0.0187	0.79	0.51-1.24	0.305	0.67	0.46-0.97	0.0319	0.85	0.46-1.57	0.594
Number of metastatic sites												
1	Reference			Reference			Reference			Reference		
2 or more	0.76	0.52-1.10	0.147	1.04	0.83-1.29	0.761	1.06	0.89-1.27	0.497	0.77	0.56-1.04	0.0905
Year of diagnosis												
2015	Reference			Reference			Reference			Reference		
2016-2019	1.06	0.93-1.21	0.334	0.99	0.92-1.07	0.867	1.03	0.97-1.10	0.356	1.04	0.94-1.16	0.470

Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval; WHO: World Health Organization

Survival

Median OS of women with metastatic pancreatic cancer was 2.3 months and 2.1 months for men with metastatic pancreatic cancer (P=0.137 [Figure 2]).

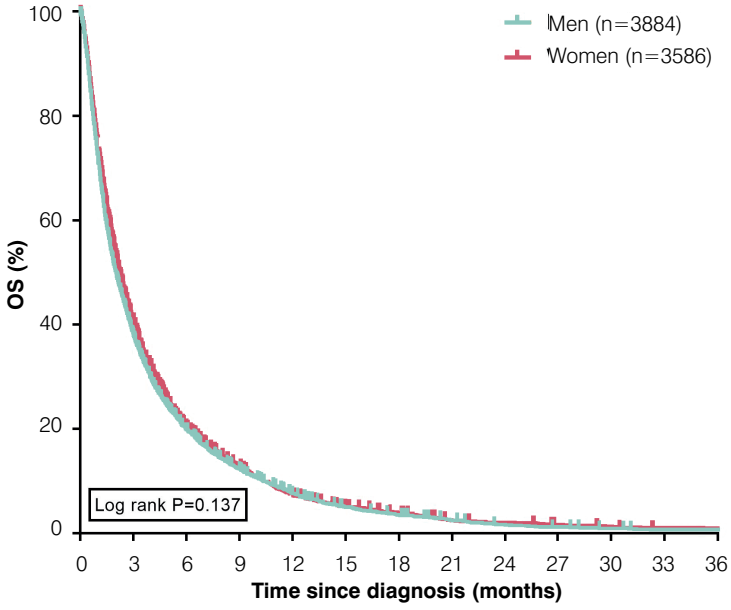

Figure 2. Kaplan Meier curves displaying overall survival in patients with metastatic pancreatic cancer stratified for sex
Abbreviations: OS: overall survival

In most age groups, women had (slightly) better median OS compared to men (Figure 3), except for the oldest age group (≥75 years of age) and in patients ≤55 years of age receiving systemic treatment.

In patients treated with BSC-only the median OS was only different between women and men in the age groups 56-64 and 65-74 years. Median OS in the age group ≤55 years was 1.8 months for women and 1.7 months for men (P=0.08). Women aged 56-64 years had a median OS of 1.8 months versus 1.5 months for older men (P=0.007). In the age group 65-74 years, women had a median OS of 1.7 months compared to 1.4 months for men (P=0.0007). In the age group ≥75 years, women had a median OS of 1.4 months versus 1.3 months for men (P=0.207).

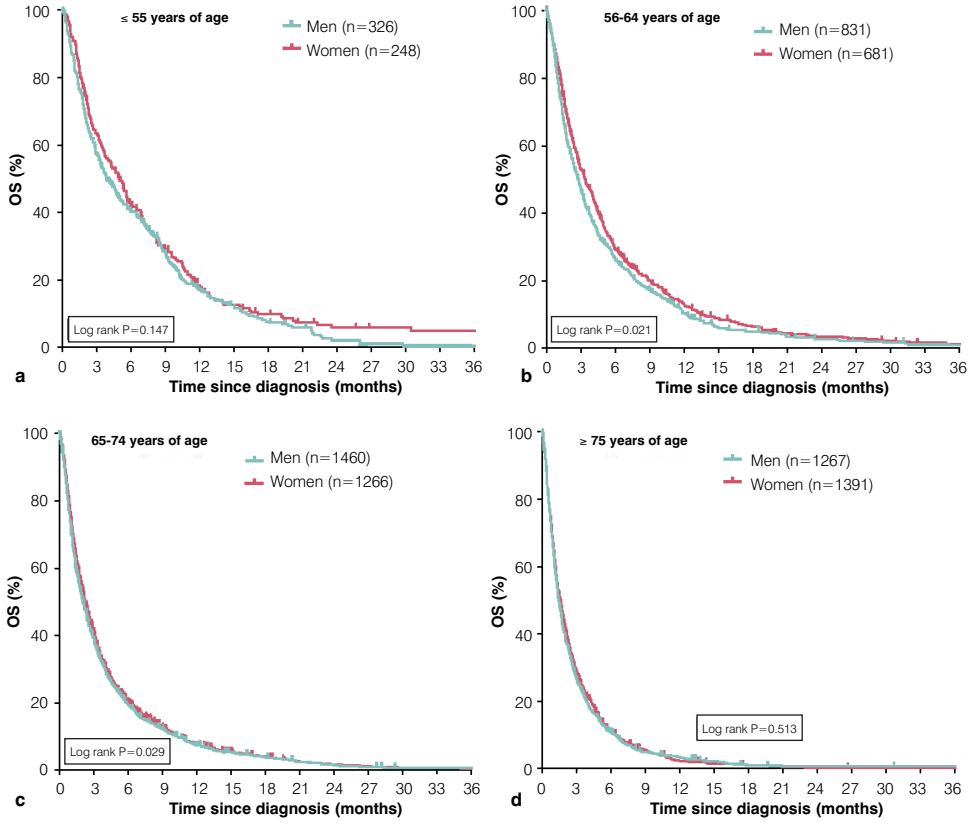
≤ 55 years of age
Men (n=326)
Women (n=248)
Log rank P=0.147
a
56-64 years of age
Men (n=831)
Women (n=681)
Log rank P=0.021
b
65-74 years of age
Men (n=1460)
Women (n=1266)
Log rank P=0.029
c
≥ 75 years of age
Men (n=1267)
Women (n=1391)
Log rank P=0.513
d
OS (%)
Time since diagnosis (months)

Figure 3. >>

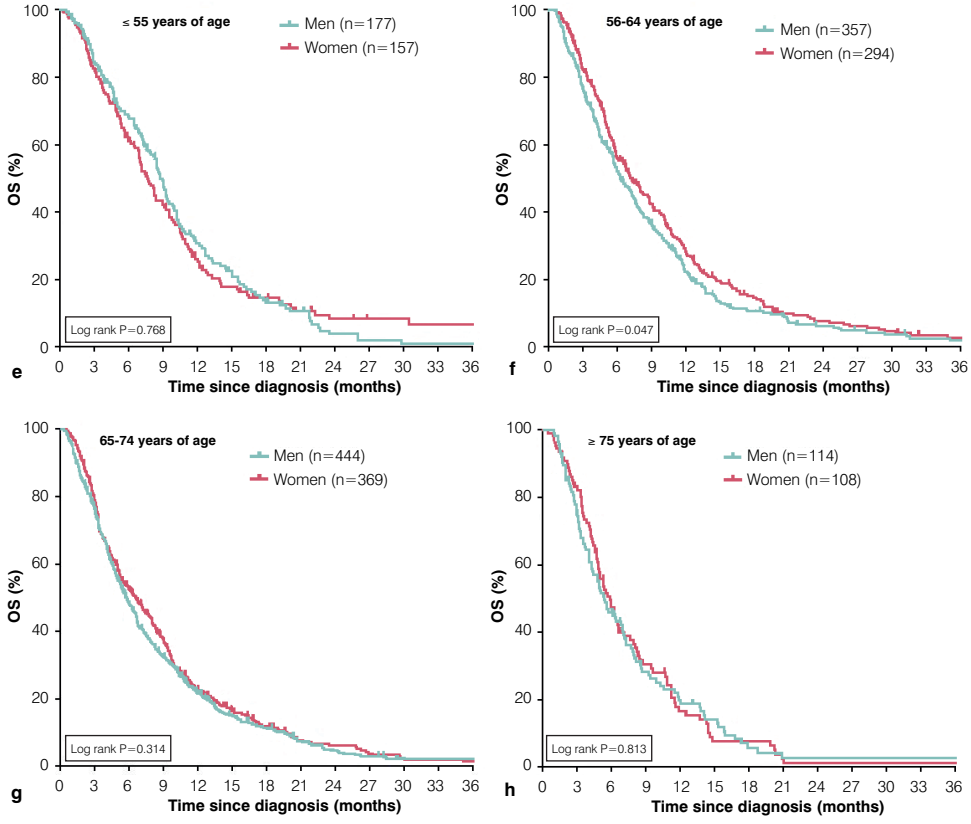

Figure 3. Kaplan Meier curves displaying overall survival in patients with metastatic pancreatic cancer stratified for sex

Graphs a-d depict all patients with pancreatic cancer stratified for sex, graphs e-h depict patients with pancreatic cancer who received systemic treatment stratified for sex

Abbreviations: OS: overall survival

Multivariable Cox proportional hazard analyses including all patients showed that women had a longer OS compared to men after adjustment for confounders (adjusted hazard ratio [HR] 0.89, 95% CI 0.84-0.93 [Table 4]). Increasing age and performance status, and metastatic sites all resulted in an increased risk of dying. Compared to tumors located in the head of the pancreas, patients with tumors in the body and tail had an increased risk of dying. Multivariable Cox proportional hazard analyses stratified for the different age groups (≤55, 56-64, 65-74 and ≥75 years of age) showed similar results. Women had a longer OS compared to men in all age groups. Increasing performance status and number of metastatic sites resulted both in an increased risk of dying in all age groups (Table 4).

Table 4. Multivariable Cox proportional hazard regression analyses for overall survival

	All patients (n=7,470)		≤55 years (n=574)		56-64 years (n=1,512)		65-74 years (n=2,726)		≥75 years (n=2,658)	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Sex										
Men	Reference		Reference		Reference		Reference		Reference	
Women	0.89 (0.84-0.93)	<.0001	0.79 (0.66-0.95)	0.0137	0.88 (0.79-0.98)	0.0171	0.85 (0.79-0.92)	<.0001	0.93 (0.86-0.99)	0.0387
Age			-		-		-		-	
≤55 years	Reference									
56-64 years	1.11 (1.00-1.23)	0.0450								
64-74 years	1.15 (1.04-1.27)	0.0054								
≥75 years	1.18 (1.07-1.31)	0.0012								
Performance status										
WHO 0-1	Reference		Reference		Reference		Reference		Reference	
WHO 2	1.37 (1.26-1.49)	<.0001	1.63 (1.19-2.23)	0.0026	1.42 (1.18-1.72)	0.0002	1.31 (1.15-1.50)	<.0001	1.41 (1.22-1.63)	<.0001
WHO 3-4	2.07 (1.89-2.27)	<.0001	2.49 (1.69-3.67)	<.0001	1.89 (1.54-2.31)	<.0001	2.20 (1.90-2.55)	<.0001	2.16 (1.85-2.52)	<.0001
Unknown	1.63 (1.54-1.72)	<.0001	1.30 (1.05-1.62)	0.0159	1.58 (1.40-1.79)	<.0001	1.52 (1.39-1.67)	<.0001	1.87 (1.69-2.08)	<.0001
Number of comorbidities										
0	Reference		Reference		Reference		Reference		Reference	
1	1.01 (0.96-1.07)	0.6980	0.90 (0.72-1.13)	0.3530	1.01 (0.89-1.14)	0.8955	1.04 (0.94-1.14)	0.4590	1.00 (0.90-1.09)	0.8667
≥2	1.02 (0.95-1.09)	0.5901	1.06 (0.65-1.72)	0.8269	0.90 (0.76-1.08)	0.2574	1.00 (0.90-1.12)	0.9610	1.07 (0.96-1.19)	0.2243
Unknown	0.85 (0.77-0.93)	0.0005	1.13 (0.83-1.55)	0.4420	0.66 (0.54-0.82)	0.0002	0.93 (0.79-1.09)	0.3507	0.85 (0.72-1.00)	0.0546
Number of metastatic sites										
1	Reference		Reference		Reference		Reference		Reference	
2 or more	1.30 (1.24-1.37)	<.0001	1.34 (1.12-1.61)	0.0015	1.43 (1.28-1.60)	<.0001	1.40 (1.29-1.51)	<.0001	1.15 (1.06-1.25)	0.0011
Year of diagnosis										
2015	Reference		Reference		Reference		Reference		Reference	
2016-2019	1.01 (0.99-1.03)	0.4017	0.95 (0.89-1.02)	0.1343	1.03 (0.99-1.07)	0.1202	0.99 (0.96-1.02)	0.5670	1.02 (0.99-1.06)	0.1193
Systemic treatment										
No	Reference		Reference		Reference		Reference		Reference	
Yes	0.31 (0.29-0.33)	<.0001	0.23 (0.19-0.29)	<.0001	0.25 (0.22-0.28)	<.0001	0.31 (0.28-0.34)	<.0001	0.40 (0.34-0.47)	<.0001
Tumor location										
Head of pancreas	Reference		Reference		Reference		Reference		Reference	
Body of pancreas	1.14 (1.07-1.22)	0.0002	1.06 (0.82-1.38)	0.6561	1.11 (0.96-1.30)	0.1650	1.16 (1.04-1.30)	0.0076	1.34 (1.01-1.28)	0.0309
Tail of pancreas	1.21 (1.14-1.29)	<.0001	1.21 (0.96-1.52)	0.1045	1.17 (1.03-1.34)	0.0206	1.24 (1.12-1.37	<.0001	1.23 (1.11-1.36)	<.0001
Overlapping sites	1.27 (1.17-1.38)	<.0001	1.36 (1.01-1.82)	0.0421	1.33 (1.10-1.59)	0.0025	1.16 (1.01-1.34)	0.0411	1.35 (1.18-1.54)	<.0001
Pancreas NOS	1.28 (1.16-1.42)	<.0001	1.08 (0.72-1.62)	0.7240	1.26 (1.00-1.58)	0.0502	1.37 (1.17-1.60)	<.0001	1.25 (1.05-1.47)	0.0100

Abbreviations: HR: hazard ratio; 95% CI: 95% confidence interval; WHO: World Health Organization; NOS: not other specified

DISCUSSION

In this population-based study on sex and gender differences in patients with metastatic pancreatic adenocarcinoma, treatment use and survival differed between women and men. In general, women were slightly less often treated with systemic therapy compared to men. At a younger age (≤55 years), women more often received systemic treatment than men, but this difference disappeared at older age. Overall, after adjustment for confounding factors, women had a more favorable overall survival, however it should be mentioned that this statistically significant difference in survival between women has limited clinical relevance since the difference described is 0.3 months only. These results confirm the hypothesis that gender may influence treatment allocation and survival in patients with metastatic pancreatic cancer.

Treatment allocation not only affects a patient's survival, but also the quality of life[17]. Consequently, it is important to create awareness of the potential impact of gender stereotypes of caregivers on treatment decisions for each individual patient as they may compromise a patients' access to care. To be able to understand these differences, it is important to make a distinction between gender based (behavioral and/or social) and sex based (tumor biology) aspects.

Gender based aspects that may contribute to the treatment allocation process include the preferences of the patient, social support and (unconscious) discrimination of the health care giver[18]. Overall, only 27% of the patients in our study received systemic treatment with a median overall survival of 2.1-2.3 months. These outcomes are in line with other real-world studies on systemic treatment for patients with metastatic pancreatic cancer in The Netherlands[19-21]. Gender has been proposed to be the most prominent predictor of a patients' preference and may have an impact on treatment choices[22]. Women tend to prefer BSC only more often compared to men[18, 23] – an observation, which is confirmed in our study. However, this does not explain our finding that younger women have a higher probability to receive systemic treatment. Also, the lack of differences in the older age groups are not explained, nor the fact that at younger age there was no difference in reasons for not starting systemic treatment. Overall, women had less comorbidities compared to men, which might be related to the higher probability for younger women to receive systemic treatment in our study. The family support of patients, e.g. marital status, plays a role in the treatment decision of cancer patients too[24]. Married patients seem to choose active treatment more often and this trend has also been described for patients with pancreatic cancer[25, 26]. Unfortunately, we did not have information on the marital status of the patients in our study. Since it is known that older women more often have a single status compared to younger women, this might explain why younger women were more likely to receive systemic treatment in our study compared to women of older age[25, 26]. Another gender based factor that may affect treatment allocation is the possible bias of health care givers. Physicians are known to be susceptible to stereotypes and preconceptions[27, 28]. For instance, single patients are

offered treatment less often because of the assumption that there would not be enough support throughout the treatment trajectory[29]. It is difficult to relate this possible bias of health care givers to our patient population. While patients preferences, marital status and unconscious bias of health care givers are factors with potential impact, it is currently not completely understood why younger women receive more often systemic treatment compared to men of the same age group.

A sex based effect that plays a role in the development of pancreatic cancer is the female sex hormone. Women are less likely to develop pancreatic cancer, and this is not fully explained by the exposure to the main risk factors cigarette smoking, high body mass index and diabetes mellitus (all gender based aspects), which are all more common in men[30-33]. Studies showed that the female sex hormone estrogen decreases pancreatic cancer growth, which might explain why women have a lower risk to develop pancreatic cancer compared to men at younger ages but not at older ages[34-37]. In our study, which focused on metastatic disease, we found a higher age at diagnosis in women. Maybe the drop in estrogen levels after menopause could be an additional explanation besides the fact that women live longer than men and therefore can be diagnosed with pancreatic cancer at an older age than men[38].

Moreover female sex hormone might have an impact on survival by a protective effect[39]. The outcome of our study, with women having a better survival compared to men, cannot completely be explained by the difference in hormone levels, because we assume that the majority of women in our study was post-menopausal. However, post-menopausal women still have a different endocrine system compared to men. Another explanation might be the suggestion that the efficacy of systemic treatment may be different in women and men[13]. Studies with various chemotherapeutic agents in different cancer types have shown treatment responses and survival rates in the advantage of women[40-43]. However, in randomized studies on patients with pancreatic cancer the hazard ratios show the same treatment effect in women and men[44, 45] and our study did not show important differences in the population with all patients, therefore a difference in treatment effect in our population is unlikely. Our study showed that older women (>55 years) had the same probability to be treated with systemic therapy compared to men. This suggests differences in disease biology in men and women that might be responsible for the longer survival of women and warrants further investigation.

A limitation of this study is that the performance status was unknown in 45% of the patients, consequently less optimal adjustment for performance status in multivariable logistic regression analyses was possible. Second, data on toxicity were not available in our study, therefore it was not possible to describe potential differences between men and women in toxicity of systemic treatment. Third, since literature is unequivocal about the effect of social and family support on the treatment decision of oncological patients, it is unfortunate that we did not have any

information about marital status or social support of the patients in our study. These factors and their impact on treatment decisions need further investigation. Although the findings in our study on the percentage of patients being treated with systemic treatment and pancreatic cancer diagnosis being more common in men than in women are in line with other European and American studies[46, 47], it might be difficult to generalize our findings to the rest of the (Western) world because ethnic differences may have an impact. Information on ethnicity is not captured in our study because this was not registered in the NCR. Fifth, age subgroups in the stratified analyses were small and might not have enough power to become statistically significant due to the group sizes. Since the aim of this study was to provide insight in the systemic treatment allocation and survival between women and men, describing the specific systemic treatment regimen was beyond the scope of this study. However, it would be interesting to describe therapy schedules and dose density in future studies to give a more comprehensive overview of OS in relation to treatment. In addition, in order to interpret treatment allocation and OS in a more complete group of patients with pancreatic cancer, it would be important to add information of patients of all stages of the disease with a need for systemic treatment (e.g. locally advanced disease) in future studies.

In conclusion, the current study showed a statistically significant sex difference in survival in multivariable analyses, with women having a slightly better outcome. Since this difference in survival is 0.3 months only the clinical impact is limited. This study suggested that differences in survival might not always be fully explained by patient and treatment characteristics, disease biology might also play a role in the survival of patients with pancreatic cancer. To further personalize the treatment of these patients, it is important to understand the biological basis for sex differences while tailoring medical decisions to the patients' wish and be aware of and avoiding gender stereotypes. Besides, it would be of interest to further investigate the difference seen between the age categories. We were not able to explain why the more frequent application of systemic therapy among females, disappeared at older ages.

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Author contributions

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Disclaimers

Not applicable.

Prior presentations

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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8

CHAPTER8

Generaldiscussion

GENERAL DISCUSSION

The purpose of this thesis was to evaluate the use and effect of systemic treatment for patients with advanced pancreatic cancer. It also identified factors that should be reported in future randomized controlled trials (RCTs) to improve comparison between RCTs on patients with resectable disease. In addition, patient characteristics that may influence treatment allocation and outcome and quality of life (QoL) of patients with pancreatic cancer were analyzed. This concluding chapter discusses the outcome of the previous chapters and its clinical implication. It also describes future perspectives for scientific research and personalized treatment in patients with pancreatic cancer.

Real-world data and randomized trials in the treatment of patients with pancreatic cancer

The guidelines for treating patients with pancreatic cancer are primarily based on the outcomes of RCTs. Survival rates in RCTs on patients with metastatic pancreatic cancer were better compared to the OS results of our population based study (**Chapter 2**). The OS of patients who received first-line treatment with FOLFIRINOX in our study was 6.6 months compared to 11.1 months in the landmark RCT[1]. This difference in OS might be explained by the different inclusion procedure in RCTs compared to population-based studies. Patients in RCTs have to meet strict in and exclusion criteria and therefore may not reflect the patient population we encounter in daily clinical practice[2, 3].

Real-world data are a valuable addition to trial results because it deepens our understanding of the outcome of therapies in the patients we encounter on a day-by-day basis. It is particularly helpful in describing therapy trends, treatment sequencing, adverse event management and indicating to what extent guidelines are followed[4-8]. Real-world data can also be used to evaluate the effectiveness of a proven effective treatment in different patient groups (e.g. older patients or patients with a higher number of comorbidities)[6]. Adding patient reported outcome measures (PROMs) data to registries on patient and tumor characteristics, gives the opportunity to analyze patients' QoL. In The Netherlands, this is currently performed in the Dutch Pancreatic Cancer Project (PACAP)[9, 10]. PROMs data can be used for multiple purposes e.g. in shared decision making or as stratification factor in analyses.

Real-world data should not be regarded as an alternative to RCTs. To evaluate the effect of a new treatment, RCTs are still the reference standard to describe causal relationships between interventions and outcome[11, 12]. The main reason why real-world data are not appropriate to analyze treatment effectivity, is the lack of randomization inducing several biases, e.g. selection bias and confounding[3, 13]. In the statistical analyses of real-world data, it is not possible to adjust for all possible confounders. In the studies we conducted with real-world data on patients with

pancreatic cancer, we tried to minimize bias by using data from the Netherlands Cancer Registry (NCR), which is a population-based registry that covers the total Dutch population of more than 17 million people and is an appropriate representation of the pancreatic cancer patient population nationwide. In addition, we tried to limit selection bias and confounding by adjusting for patient characteristics such as comorbidities and performance status in multivariable analyses (**Chapter 2, 6 & 7**).

Although well designed and conducted RCTs are the reference standard of health care intervention research[11, 12], RCTs are complex and expensive to perform and in more than 66% of the RCTs, the recruitment targets are not met[12]. In addition, adequate reporting in RCTs frequently fails because authors do not provide a complete description of the study population [14]. The Consolidated Standards of Reporting Trials (CONSORT) statement is an evidence based minimum set of recommendations for reporting randomized trials improving the transparency and completeness of RCTs[14, 15]. It was first developed in 1996 and updated in 2010 to improve the quality of reporting of RCTs[16]. The CONSORT statement provides authors with a checklist on a minimal set of factors that should be reported in all trials, which simplifies the critical appraisal and reading of RCTs[11]. The statement has been recommended by several medical journals and editorial groups[16]. Although this CONSORT statement guides authors on a methodical level on the mandatory factors to be reported, there is still a great variety in the selection of patients and the reporting of baseline and prognostic factors, which restricts the comparison of the outcome measures between RCTs in specific patient groups. This is also the case in RCTs on patients with pancreatic cancer. By developing consensus about the mandatory baseline and prognostic factors that should be reported in clinical trials for patients with pancreatic cancer, research is uniformed, leading to better comparison of outcomes across studies and eventually have an effect on daily clinical practice (**Chapter 4 & 5**).

Lately, RCTs using cohort or routinely collected data are raising attention[11, 12]. Data in these RCTs derived from electronic health records, administrative databases such as education or government databases and registries[17, 18]. In a cohort, persons are included with the intention to accomplish scientific research, when in fact routinely collected data are accumulated for purposes other than research or without pre-established research questions at the start of collection[11, 19]. Routinely collected databases comprise several important outcome measures for doctors, researchers and patients e.g. mortality, hospital admission, but information on biological processes e.g. biomarkers are commonly lacking[20]. RCTs may utilize cohort or routinely collected data for different intentions such as revealing eligible candidates for inclusion and carrying out an intervention or a combination of such. The use of cohorts and routinely collected data may simplify the establishment of RCTs because it reduces costs and time[21]. It also assists the development of RCTs that are more closely related to real-world data comprising a better reflection of the patients treated in daily clinical practice because it avoids artificial research

settings[11, 12, 20]. In addition, RCTs using routinely collected data possibly better reflect real-world treatment effects because patients are only monitored during the regular appointments without research driven follow-up visits[20]. Therefore, biases attributed to outcome ascertainments are less likely to occur compared to conventional RCTs[20]. The quality of routinely collected data may differ for the different outcome measures. For instance, mortality can be collected accurately because database linkage to death registries are easy to obtain, but the quality of for instance specific adverse events might not always be adequate because this information should be manually entered based on data in the electronic patient file, which often is far from complete[20]. Another advantage of RCTs using cohort or routinely collected data is that, when described in the methodology, researchers may have the opportunity to access information on patients not included in the trial. In this way, enrolled trial participants can be compared with participants who were not included in the trial in order to assess the representativeness of the participants in the trial and the generalizability of the results[12].

Since this RCT design with cohorts and routinely collected data has only been established rather recently, a standardized methodology has not yet been recognized. RCTs carried out with cohort or routinely collected data show some overlap with the traditional RCT, however there are some distinctions. Therefore, the CONSORT Extension for Trials Conducted Using Cohorts and Routinely Collected Data (CONSORT-ROUTINE) statement was established to guide authors conducting such trials[12]. This statement recommends a core set of information these trials should include to make these easier interpretable and comparable.

Although there is a desperate need for randomized evidence on treatment for patients with pancreatic cancer after first-line FOLFIRINOX therapy, carrying out such a trial is difficult due to the progressive nature of the disease and the complexity of such trials. RCTs using cohort or routinely collected data might be a good alternative to traditional RCT designs to find new treatment options and developing guidelines for this patient group.

Towards national and international collaboration

Pancreatic cancer has a rare nature with a poor prognosis, even with the most favorable tumor stage survival rates are far from optimal[22, 23]. Pancreatic cancer is a worldwide problem in which different countries have to challenge this same disease[23]. In The Netherlands, experts on pancreatic cancer are united in the Dutch Pancreatic Cancer group (DPCG). The DPCG is a multidisciplinary collaboration of doctors, researchers and patients focusing on improvement of treatment and outcome of patients with pancreatic cancer, which is crucial for nationwide registries. The PACAP project, initiated by the DPCG in 2013, is the cornerstone of pancreatic cancer research in The Netherlands. PACAP includes several registries e.g. the NCR and PROMs. These registries facilitate the identification of, amongst others, guideline compliance and patient's QoL[9, 10]. These registries were also used in **Chapter 2, 6 & 7** of this thesis. In addition

to the DPCG, The Delta Plan on Pancreatic Cancer 'Deltaplan Alvleesklierkanker' was initiated in 2019. Within this nationwide collaboration the DPCG, patient organization Living with Hope and the 'Maag Lever Darm Stichting' (Stomach Liver Bowel Foundation) are working together in facilitating the improvement of future research, treatment and QoL of patients with pancreatic cancer. 'Deltaplan Alvleesklierkanker' aims to enable the establishment of a nationwide database including all patients diagnosed with pancreatic cancer in The Netherlands. This database currently includes information of over 2400 patients from 48 different Dutch hospitals. The centralization of pancreatic cancer care in The Netherlands demonstrated advanced treatment outcomes[24-27].

Due to the fact that there might be variation in disease knowledge on pancreatic cancer worldwide, it is important to also establish international collaborations to overcome these knowledge gaps[28]. In these collaborations one can learn from each other's experiences, which may help in the development of new research to deepen the understanding of pancreatic cancer even more[28]. In this way, research quality and standardized treatment definitions can be improved. Currently, the DPCG and 'Deltaplan Alvleesklierkanker' provide opportunities for international collaborations for pancreatic cancer care (e.g. International Hepato-Pancreato-Biliary Association [IHPBA], European consortium on Minimally Invasive Pancreatic Surgery registry [E-MIPS]). However, these collaborations are mainly focused on the outcome of surgical interventions for these patients and not so much on linkage of international data registries. If we could unify registries worldwide, we would have a treasure chest of information for future research and optimization of standard care for patients with pancreatic cancer. For the establishment of worldwide linked registries, not only international health care specialist on pancreatic cancer care (e.g. surgeons, medical oncologists, radiation oncologists, pathologists, radiologists and gastroenterologist) but also patients and researchers should be united. These international experts should think beyond the walls of their hospitals and land borders. By using for instance Delphi panels combining the knowledge of these experts and available scientific evidence to reach consensus about a core parameter set (like we did in **Chapter 4 & 5** of this thesis) these registries should include, registries can be internationally uniformed. After harmonization of these registries, international practice variation can be identified and improved. These registries might even be used in future RCTs using routinely collected data.

Towards personalized treatment and future research

Personalization of treatment for patients with pancreatic cancer can be improved. It is known that the desmoplastic reaction resulting in high levels of tumor stroma, limits effective systemic treatment delivery in some patients with pancreatic cancer[29-31]. Quantitative magnetic resonance imaging (MRI) showed that treatment targeting tumor stroma with the Hedgehog inhibitor LDE225 in combination with chemotherapy, was most favorable in patients with poor baseline perfusion (**Chapter 3**). In an attempt to personalize treatment in the future, patients that can

benefit most from specific anti-cancer treatment should be selected using imaging techniques and be the objective of future studies. **Chapter 7** suggested that survival differences are not fully explained by patient and treatment characteristics. Disease biology might be responsible for these differences too. Lately, molecular and genetic characteristics have been identified as important factors determining survival and clinical outcome of patients with pancreatic cancer[32, 33]. Different subtypes of pancreatic cancer show contrasting responses to the same treatment [34-36]. Understanding the biological basis for these differences, evaluating treatment benefits for subgroups, and tailoring medical decisions to the patients wish, is considered an important step towards precision oncology. Artificial intelligence (AI) may also be a tool to improve personalized treatment for patients with pancreatic cancer. Pancreatic cancer is currently diagnosed at an advanced disease stage in the majority of patients. Therefore, recent studies on AI mainly focused on the diagnosis of pancreatic cancer using machine and deep learning[37]. Due to difficulties in acquiring large numbers of patient samples, the applicability of these techniques is still limited[37, 38]. The nationwide databases of PACAP and 'Deltaplan Alvleesklierkanker' and possible future internationally linked registries, might be the starting point for the establishment of AI systems enabling earlier cancer detection and prediction of cancer prognosis. AI has the future potential to facilitate prediction models optimizing personalized treatment and survival outcomes for patients with pancreatic cancer by taking individual patient characteristics into account[39].

Personalization of care for patients with pancreatic cancer goes beyond medical treatment strategies, it also includes psychological guidance. **Chapter 6** showed that patients with pancreatic cancer report fear of progression or recurrence of the disease. Cancer diagnoses entail not only physical but also psychological stress[40]. It is of great importance to manage the mental wellbeing of patients with pancreatic cancer too. Studies on cancer patients in general suggested psychological interventions such as cognitive behavioral therapy to be part of the cancer treatment to make the care as comprehensive as possible[41, 42]. Currently, there are no studies on the most suitable psychological support for patients with pancreatic cancer, therefore there should be more attention for this in future studies in order to personalize treatment strategies even more.

Conclusion

The studies in this thesis underline that real-world data are helpful to describe treatment allocation, patient characteristics and QoL, however they are not suitable to determine new treatment effectivity. In the current randomized evidence, trials on second-line systemic treatment for patients with metastatic pancreatic cancer are lacking. In addition to the NAPAN trial, a RCT on second-line treatment with liposomal irinotecan in combination with S-1 after first-line gemcitabine failure that is currently conducted in our center, RCTs using cohorts or routinely

collected data might be a suitable option for future research on second-line treatment for patients with pancreatic cancer. Future international research collaborations should link registries in order to improve therapy guidelines and further personalize the treatment for patients with pancreatic cancer.

Summary of the research questions and main findings in this thesis

Chapter	Research question
2	*What is the nationwide use of first and second-line systemic treatment in patients with metastatic pancreatic cancer in The Netherlands and what is their effectiveness in terms of overall survival?* FOLFIRINOX was the most frequently applied first-line regimen, with a superior overall survival compared to gemcitabine+nab-paclitaxel and gemcitabine monotherapy in multivariable analyses. Only a minority of patients received second-line systemic treatment (8% of patients treated in first-line), these patients showed better overall survival compared to those who received first-line systemic treatment followed by best supportive care only.
3	*What is the safety and efficacy of second-line treatment with the hedgehog inhibitor LDE225 in combination with gemcitabine and nab-paclitaxel in FOLFIRINOX pretreated patients with metastatic pancreatic cancer?* A manageable safety profile and favorable efficacy of LDE225 in combination with gemcitabine and nab-paclitaxel as second-line treatment in patients with metastatic pancreatic cancer was observed. Quantitative magnetic resonance imaging (MRI) showed that in patients with lower baseline perfusion, the overall survival was higher. Quantitative MRI imaging may facilitate appointing patients that could most profit from LDE225 treatment in the future.
4 & 5	*Which baseline and prognostic factors should be regarded mandatory in randomized controlled trials for patients with resectable pancreatic cancer?* After the literature search and two rounds with the Delphi panel consisting of 13 experts on pancreatic cancer, agreement was reached on 50 mandatory baseline and 20 mandatory prognostic factors. These factors, including a distinction between neoadjuvant and adjuvant treatment, should be reported in future randomized controlled trials for these patients.
6	*To what extent is the fear of progression or recurrence of the disease present in patients with pancreatic cancer and what is the association between quality of life and overall survival and the fear of progression or recurrence of the disease?* Patients who received surgical resection showed significantly less fear of progression or recurrence of the disease at initial diagnosis compared to patients who received palliative systemic treatment or best supportive care only. Only in patients who received best supportive care only, higher quality of life scores were independently associated with the probability of lower fear of progression or recurrence of the disease. Fear of progression or recurrence of the disease was not associated with survival in any of the treatment subgroups.
7	*Are biological sex and gender of patients with metastatic pancreatic cancer associated with treatment allocation and overall survival?* In general, women received less often systemic treatment compared to men. In multivariable logistic regression analyses, women at younger age (≤55 years), received more often systemic treatment as compared to men of the same age, but this disparity was absent at older age. After adjustment for clinical covariates, women had longer overall survival compared to men in all age groups.

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9

CHAPTER9

Summary

This thesis strives to give an overview of systemic treatment use and effectivity in patients with metastatic pancreatic cancer in The Netherlands. It focusses on overall survival (OS) and quality of life (QoL) as main outcome measures, adjusted for patient and tumor characteristics. In addition, it identified mandatory factors that should be included in future randomized controlled trials (RCTs) on patients with resectable pancreatic cancer.

In **Chapter 2** data from The Netherlands Cancer Registry (NCR) were used to study the use and effectiveness of first and second-line systemic treatment in patients with metastatic pancreatic cancer in The Netherlands. Irinotecan, oxaliplatin and fluorouracil (FOLFIRINOX) was the most frequently applied first-line regimen, with a superior OS compared to gemcitabine+nab-paclitaxel and gemcitabine monotherapy in multivariable analyses. Only a minority of patients received second-line systemic treatment (8% of patients treated in first-line), these patients showed better OS compared to those who received first-line systemic treatment followed by best supportive care (BSC) only. Since FOLFIRINOX is associated with the occurrence of grade 3/4 toxicities, FOLFIRINOX is often restricted to patients with a good performance status (0-1). We showed that patients with less optimal performance scores also benefited from FOLFIRINOX treatment in terms of OS. Patients treated with gemcitabine monotherapy or BSC only as first-line treatment, showed comparable median OS rates. Therefore, one could argue whether the negligible survival advantage of gemcitabine monotherapy overcomes the possible adverse effects of this treatment. These outcomes suggest to treat these patients with BSC only.

The desmoplastic reaction, resulting in elevated levels of tumor stoma, is one of the main reasons for therapy resistance in patients with pancreatic cancer. **Chapter 3** aimed to explore the modification of the desmoplastic reaction in patients with pancreatic cancer by targeting tumor stroma with the hedgehog inhibitor LDE225 and tumor cells with gemcitabine and nab-paclitaxel as second-line treatment after first-line FOLFIRINOX therapy. The Dutch guideline recommends FOLFIRINOX as first-line systemic treatment, there is a need for a suitable second-line treatment after first-line FOLFIRINOX failure. We observed good tolerability and favorable efficacy of LDE225 in combination with gemcitabine and nab-paclitaxel as second-line treatment in patients with metastatic pancreatic cancer. Quantitative magnetic resonance imaging (MRI) showed that in patients with lower baseline perfusion, the OS was higher. Quantitative MRI may facilitate appointing patients that could most profit from LDE225 treatment in the future.

Randomized controlled trials (RCTs) are the reference standard determining the effectivity of new treatment options. However, the selection of patients and reported baseline and prognostic characteristics differ greatly among these trials, hampering the comparison of outcome measures between studies. This is also the case in RCTs on patients with pancreatic cancer. Therefore, a systematic review including a Delphi consensus statement on mandatory baseline and prognostic factors to be reported in future RCTs on patients with resectable pancreatic cancer entitled

COnsensus statement on Mandatory Measurements in PAncreatic Cancer Trials for patients with Resectable/Borderline resectable disease (COMM-PACT-RB) was described in **Chapter 4 and 5**. The literature search identified 42 RCTs from which the baseline and prognostic factors were up for voting in the consensus procedure. After two rounds with the Delphi panel consisting of 13 experts on pancreatic cancer, agreement was reached on 50 mandatory baseline and 20 mandatory prognostic factors. These factors, including a distinction between neoadjuvant and adjuvant treatment, should be reported in future RCTs for these patients.

The risk of progression or recurrence of the disease in patients with pancreatic cancer is substantial. Pancreatic cancer has a poor prognosis, even when treatment is started. And in the majority of patients, the disease is detected at a late stage. Therefore, it is reasonable that patients with pancreatic cancer experience a certain amount of fear of progression or recurrence of the disease (FOP). **Chapter 6** includes results on patients with pancreatic cancer who participated in the Dutch Pancreatic Cancer Project (PACAP) and compares FOP in patients treated with surgical resection, palliative systemic treatment and BSC. Patients with pancreatic cancer report FOP at diagnosis, which stabilized over time. Patients who received surgical resection showed significantly less FOP at initial diagnosis compared to patients who received palliative systemic treatment or BSC only. Only in patients who received BSC only, higher QoL scores were independently associated with the probability of lower FOP. FOP was not associated with survival in any of the treatment subgroups. To make the treatment for patients with pancreatic cancer as comprehensive as possible, FOP should be discussed by the healthcare professional to be able to provide patients with the most suitable psychological support.

Biological sex and gender are known to have an impact on the incidence rates in patients with pancreatic cancer. However, it is unclear whether biological sex and gender are associated with treatment allocation and OS of patients with metastatic pancreatic cancer. Therefore, in **Chapter 7,** this was investigated. Patients with metastatic disease diagnosed between 2015 and 2019 were selected from the NCR. In general, women received less often systemic treatment compared to men. In multivariable logistic regression analyses, women at younger age (≤55 years), received more often systemic treatment as compared to men of the same age, but this disparity was absent at older age. After adjustment for clinical covariates, women had longer OS compared to men in all age groups. These results suggest that patient and treatment characteristics do not completely describe differences in survival, disease biology and sociocultural reasons might also contribute to the survival of patients with metastatic pancreatic cancer. It is important to understand the biological and sociocultural basis for sex differences in order to better personalize the treatment for these patients in the future.


10

CHAPTER10

NederlandseSamenvatting

Dit proefschrift geeft een overzicht van het gebruik en de effectiviteit van systemische therapie bij patiënten met gemetastaseerd pancreascarcinoom in Nederland. Daarnaast identificeerde dit proefschrift factoren die gerapporteerd moeten worden in toekomstige gerandomiseerde studies voor patiënten met resectabel pancreascarcinoom. Ook werden patiëntkarakteristieken die van invloed kunnen zijn op het toewijzen van behandeling en de kwaliteit van leven van patiënten met pancreascarcinoom geanalyseerd.

In **Hoofdstuk 2** werd aan de hand van data van de Nederlandse kankerregistratie het gebruik en de effectiviteit van eerste en tweedelijns systemische therapie bij patiënten met gemetastaseerd pancreascarcinoom in Nederland bestudeerd. De combinatie therapie irinotecan, oxaliplatine en 5-fluoro-uracil (FOLFIRINOX), werd het meest gegeven als eerstelijnstherapie en gaf een betere overleving dan behandeling met gemcitabine gecombineerd met nab-paclitaxel of gemcitabine monotherapie. Een klein deel van de patiënten, slechts 8% van de patiënten die met eerstelijnstherapie behandeld werden, kreeg tweedelijns behandeling. Deze patiënten hadden een betere overleving ten opzichte van patiënten behandeld met eerstelijnstherapie gevolgd door optimale ondersteunende behandeling (best supportive care [BSC]). Omdat FOLFIRINOX geassocieerd is met het optreden van bijwerkingen zoals hooggradige toxiciteit, is deze behandeling vaak alleen voorbehouden aan patiënten met een goede conditie. In deze studie werd aangetoond dat ook patiënten met een slechtere conditie baat hebben van behandeling met FOLFIRINOX. Patiënten die eerstelijnsbehandeling met gemcitabine monotherapie of BSC kregen, hadden vergelijkbare overlevingscijfers. Dit zou kunnen betekenen dat het verwaarloosbare overlevingsvoordeel van gemcitabine niet opweegt tegen de mogelijke bijwerkingen van deze behandeling. Deze uitkomst suggereert dat deze patiënten enkel behandeld zouden moeten worden met BSC.

Een van de belangrijkste redenen voor therapie resistentie bij patiënten met pancreascarcinoom is het optreden van de desmoplastische reactie waarbij tumor stroma vrijkomt. Tumor stroma zorgt voor verminderde vascularisatie van de tumor waardoor effectieve afgifte van chemotherapie aan tumorcellen wordt bemoeilijkt. In **Hoofdstuk 3** werd de modificatie van de desmoplastische reactie bij patiënten met gemetastaseerd pancreascarcinoom die als eerstelijnstherapie FOLFIRINOX hadden gekregen onderzocht. De tumorcellen werden behandeld met gemcitabine en nab-paclitaxel en tumor stroma met de hedgehog inhibitor LDE225. De Nederlandse richtlijn voor pancreascarcinoom adviseert FOLFIRINOX als eerstelijnsbehandeling, voor tweedelijnsbehandeling, in het bijzonder na eerstelijnsbehandeling met FOLFIRINOX, is weinig wetenschappelijk bewijs. Het identificeren van een gepaste tweedelijnsbehandeling voor deze patiëntengroep is daarom noodzakelijk. Er werd een goede tolerantie en gunstige effectiviteit van LDE225 in combinatie met gemcitabine+nab-paclitaxel als tweedelijnsbehandeling in deze patiëntengroep geobserveerd. Kwantitatieve beeldvorming middels magnetic resonance imaging (MRI) toonde aan dat patiënten met een lage perfusie op baseline een langere overleving

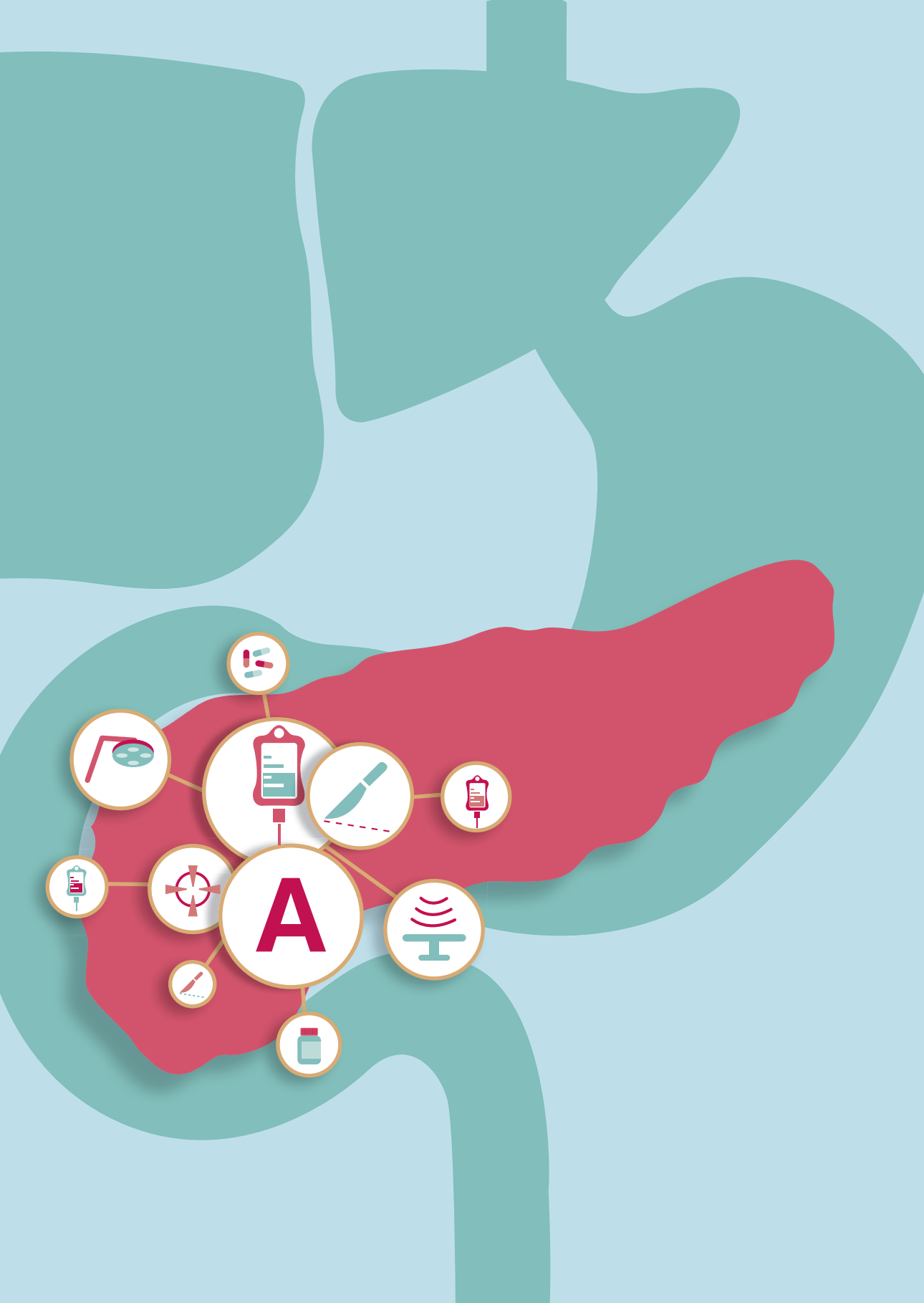
hadden. Met behulp van kwantitatieve beeldvorming zou de selectie van patiënten die het meest baat hebben van behandeling met LDE225 in de toekomst bevorderd kunnen worden.

Gerandomiseerde studies zijn de gouden standaard voor het aantonen van de effectiviteit van nieuwe behandelmogelijkheden. Echter is de selectie van patiënten en het rapporteren van baseline en prognostische factoren in deze studies niet gestandaardiseerd. Hierdoor wordt de vergelijking van uitkomsten van studies onderling bemoeilijkt. Dit geldt ook voor gerandomiseerde studies over patiënten met pancreascarcinoom. Daarom werd in **Hoofdstuk 4 en 5** de eerste internationale consensus beschreven over de noodzakelijke baseline en prognostische factoren die altijd vermeld moeten worden in gerandomiseerd onderzoek voor patiënten met resectabel pancreascarcinoom genaamd: COnsensus statement on Mandatory Measurements in PAncreatic Cancer Trials for patients with Resectable/Borderline resectable disease (COMM-PACT-RB). In de systematische literatuurstudie zijn 42 gerandomiseerde studies gevonden. Uit deze studies werden de baseline en prognostische factoren gedestilleerd. In de twee Delphi rondes konden 13 experts op het gebied van pancreascarcinoom aangeven welke factoren noodzakelijk vermeld moeten worden in toekomstige studies. Uiteindelijk werden er 50 baseline en 20 prognostische factoren geïdentificeerd waarbij neoadjuvante en adjuvante behandeling werd onderscheiden. Deze factoren zullen altijd gerapporteerd moeten worden in studies over patiënten met resectable pancreascarcinoom om zo de vergelijkbaarheid van studies onderling te vergroten.

Pancreascarcinoom wordt vaak pas laat gediagnosticeerd en heeft een slechte prognose, daarom is het aannemelijk dat patiënten met pancreascarcinoom een zekere mate van angst voor terugkeer en/of progressie van ziekte ervaren. In **Hoofdstuk 6** werd de angst voor terugkeer en/of progressie van ziekte bestudeerd in patiënten die tussen 2015 en 2018 werden gediagnosticeerd met pancreascarcinoom en deelnamen aan het Dutch Pancreatic Cancer Project (PACAP). Het doel was het beschrijven van de angst voor terugkeer en/of progressie van ziekte in patiënten met pancreascarcinoom binnen de verschillende behandelgroepen, chirurgische resectie, palliatieve systeemtherapie en best supportive care (BSC); het analyseren van de associatie tussen kwaliteit van leven en angst voor terugkeer en/of progressie van ziekte en het beschrijven van het effect van deze angst op de overleving. Op baseline hadden patiënten die chirurgische resectie ondergingen significant minder angst voor terugkeer en/of progressie van ziekte ten opzichte van de patiënten die palliatieve systeemtherapie of BSC kregen. Betere kwaliteit van leven was alleen onafhankelijk geassocieerd met de kans op een lagere angstscore voor terugkeer en/of progressie van ziekte in de BSC behandelgroep en niet in de chirurgische resectie of palliatieve systeemtherapie groepen. Baseline angstscore voor terugkeer en/of progressie van ziekte was in alle behandelgroepen niet onafhankelijk geassocieerd met overleving. Gezien het leed dat de angst voor terugkeer en/of progressie van ziekte bij patiënten

met pancreascarcinoom veroorzaakt, is het noodzaak dat deze angst expliciet benoemd en ondersteund wordt door zorgverleners gedurende het gehele zorgtraject.

De incidentie van pancreascarcinoom verschilt tussen mannen en vrouwen, echter is onbekend of er ook verschillen zijn in behandeling en overleving. In **Hoofdstuk 7** werden de verschillen tussen mannen en vrouwen in het krijgen van systemische therapie en de overleving van patiënten met gemetastaseerd pancreascarcinoom onderzocht. Patiënten die tussen 2015 en 2019 de diagnose gemetastaseerd pancreascarcinoom kregen, werden geselecteerd uit de Nederlandse kankerregistratie. In de gehele patiëntengroep ondergingen vrouwen minder vaak behandeling met systemische therapie ten opzichte van mannen. Regressieanalyses toonden aan dat jonge vrouwen (≤55 jaar) vaker behandeld werden met systemische therapie in vergelijking met mannen van dezelfde leeftijd, dit verschil verdween op latere leeftijd. Ook werd aangetoond dat vrouwen een betere overleving hadden ten opzichte van mannen in alle leeftijdsgroepen na correctie voor klinische covariaten. Deze bevindingen impliceren dat patiënt en behandel karakteristieken het verschil in overleving tussen mannen en vrouwen niet geheel verklaren. Mogelijk hebben ziektebiologie en socioculturele oorzaken een aandeel in de overleving van patiënten met gemetastaseerd pancreascarcinoom. Het is noodzakelijk de biologische en socioculturele basis voor sekseverschillen te begrijpen om de behandeling van patiënten met gemetastaseerd pancreascarcinoom in de toekomst verder te personaliseren.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APPENDICES

Authors&publications

Listofcontributingauthorsandpublications

Personalinformation

PhDportfolio

Curriculumvitae

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List of publications included in this thesis

Pijnappel EN, Dijksterhuis WPM, van der Geest LG, de Vos-Geelen J, de Groot JWB, Homs MYV, Creemers GJ, Mohammad NH, Besselink MG, van Laarhoven HWM, Wilmink JW; Dutch Pancreatic Cancer Group. First- and Second-Line Palliative Systemic Treatment Outcomes in a Real-World Metastatic Pancreatic Cancer Cohort. J Natl Compr Canc Netw. 2021 Aug 27:1-8. doi: 10.6004/jnccn.2021.7028. Epub ahead of print. PMID: 34450595.

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Pijnappel EN, Suurmeijer JA, Groot Koerkamp B, Kos M, Siveke JT, Salvia R, Ghaneh P, van Eijck CHJ, van Etten-Jamaludin FS, Abrams R, Brasiūnienė B, Büchler MW, Casadei R, van Laethem JL, Berlin J, Boku N, Conroy T, Golcher H, Sinn M, Neoptolemos JP, van Tienhoven GJ, Besselink MG, Wilmink JW, van Laarhoven HWM. Consensus statement on mandatory measurements in pancreatic cancer trials for resectable disease that focus on (neo)adjuvant systemic treatment and survival outcomes (COMM-PACT-RB)-A systematic review. JAMA Oncology, 2022.

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Kos M, **Pijnappel EN**, Buffart LM, Balvers BR, Kampshoff CS, Wilmink JW, van Laarhoven HWM, van Oijen MGH. The association between wearable activity monitor metrics and performance status in oncology: a systematic review. Support Care Cancer. 2021 Nov;29(11):7085-7099. doi: 10.1007/s00520-021-06234-5. Epub 2021 Jun 12. PMID: 34117567; PMCID: PMC8464563.

PHD PORTFOLIO

Name PhD student:	Esther N. Pijnappel
PhD period:	October 2018-February 2022
Name PhD supervisors:	Prof. Dr. J.W. Wilmink, Prof. dr. H.W.M. van Laarhoven Prof. dr. M.G.H. Besselink

PhD training	**Year**	**Workload (ECTS)**
Academic education		
Master Evidence Based Practice in Health Care AMC-UvA	2019-2021	97
Courses		
- Practical Biostatistics	2019	1.1
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2019	1.0
- Scientific Writing in English for Publication	2019	1.5
- Medical Literature: EndNote	2019	0.1
- Clinical epidemiology: Evaluation of Medical Tests	2019	0.9
Seminars, workshops and master classes		
- Dutch Pancreatic Cancer Group seminars	2018-2021	1.0
- Academic Medical Center department of oncology seminars	2019-2020	2.0
- Journal club (2/month; 24 in total)	2020	2.0
- Supportive and palliative care research group seminars	2020-2022	2.0
- Research meeting medical oncology	2021-2022	1.0
Presentations		
- Phase I/II study of LDE225 in combination with gemcitabine and nab-paclitaxel in patients with locally advanced or metastasized pancreatic cancer. Poster presentation at the European Society of Medical Oncology (ESMO) annual meeting	2019	1.0
- A randomized phase II study of second line treatment with liposomal irinotecan and S-1 versus liposomal irinotecan and 5-fluorouracil in gemcitabine-refractory metastatic pancreatic cancer patients (NAPAN Trial). Poster presentation at the Virtual American Society of Clinical Oncology (ASCO) annual meeting	2020	1.0
- Outcome of first and second-line treatment strategies in a real world patient cohort of metastatic pancreatic cancer. Poster presentation at the Virtual European Society of Medical Oncology (ESMO) annual meeting	2020 2021	1.0 1.0
- The fear of cancer recurrence and progression in patients with pancreatic cancer. Poster presentation at the Virtual American Society of Clinical Oncology (ASCO) annual meeting		
- Gender differences in treatment allocation and survival of patients with metastatic pancreatic cancer: a nationwide real-world study. Poster presentation at the Virtual European Society of Medical Oncology (ESMO) annual meeting	2021	1.0

Attended conferences			
-	Cancer Center Amsterdam retreat	2019-2020	1.0
-	European Society of Medical Oncology annual meeting	2019	1.5
-	American Society of Clinical Oncology virtual annual meeting	2020	1.0
-	European Society of Medical Oncology virtual annual meeting	2020	1.0
-	Pancreasdagen	2020-2021	0.5
-	American Society of Clinical Oncology virtual annual meeting	2021	1.0
-	European Society of Medical Oncology virtual annual meeting	2021	1.0
-	HPBeter symposium	2021	1.0
Committees			
-	Organizing committee HPBeter symposium	2021	1.0
Other contributions			
-	Mandatory reporting measurements in trials for potentially resectable pancreatic cancer. Chapter in Textbook of the European society of Surgical Oncology (publication springer textbook)	2019-2020	2.0
-	Trial coordinator of the NAPAN trial, An international randomized phase II study of second line treatment with liposomal irinotecan and S-1 versus liposomal irinotecan and 5-fluorouracil in gemcitabine-refractory metastatic pancreatic cancer patients	2018-2022	2.0
-	NAPAN initiation visits to Maastricht University Medical Center (MUMC+); Vall d'Hebron Barcelona, Spain; University Hospital of Verona, Italy; and Medical University of Vienna, Austria	2019-2022	2.0
-	Kos M, *Pijnappel EN*, Buffart LM, Balvers BR, Kamsoff CS, Wilmink JW, Laarhoven HWM, van Oijen MGH. The association between wearable activity monitor metrics and performance status in oncology: a systematic review. Support care Cancer 2021	2019-2022	1.0
-	Contact person researchers medical oncology during lateralization between AMC and VUmc	2020-2022	1.5

CURRICULUM VITAE

Esther Pijnappel was born on September 3th, 1991 in Amsterdam. She grew up in Amsterdam and in Haren (Groningen). She has always been interested in studying medicine. After she graduated from Maartenscollege Haren, she got rejected to go to medical school by numerus fixus. Therefore, she studied the Pre-Medical track at University College Roosevelt (University of Utrecht) and finished her bachelor's degree cum laude. Afterwards, she studied the Master Physician-Clinical Investigator at Maastricht University and obtained her medical and clinical research degree. During her bachelor's degree, her interest in research was aroused and she performed an independent research project at University Medical Center Utrecht (UMCU) on breast cancer. This was the first time she came in touch with cancer research and resulted in her first publication as a first-author. Afterwards, she performed many other research projects during her study, all in the field of oncology. In October 2018, she started her PhD project on pancreatic cancer under supervision of Hanneke Wilmink, Hanneke van Laarhoven and Marc Besselink at Amsterdam UMC. During her PhD, she obtained a master's degree in epidemiology at the University of Amsterdam (UvA). Currently, she is working as a surgical resident at Erasmus Medical Center in Rotterdam.

DANKWOORD

Velen hebben bijgedragen aan de totstandkoming van dit proefschrift, hiervoor wil ik graag een aantal mensen in het bijzonder bedanken.

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Speciale dank gaat uit naar mijn promotieteam, professor Wilmink, professor van Laarhoven en professor Besselink.
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