A multidisciplinary approach to improve treatment strategies for patients with hepatic or pancreatic cancer

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CHAPTER 8

An international comparison of treatment and short-term survival for elderly patients with pancreatic cancer

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ABSTRACT

Background

A significant proportion of pancreatic cancer patients is over the age of 70 years. International comparisons could provide evidence for the optimal treatment strategy. The aim of this study was to compare treatment and survival for pancreatic cancer patients ≥70 years treated throughout the Netherlands or at Moffitt Cancer Center, a US-NIH designed comprehensive cancer and research center in Tampa, Florida.

Methods

All age-eligible patients with pancreatic adenocarcinoma (2008 – 2012) were identified. Results were stratified by stage. Treatment (neo-adjuvant, surgery, adjuvant and palliative treatment) and short-term survival at 1 and 3 years were compared, and where appropriate adjusted (sex, age, grade, year) or stratified according to age or type of hospital (Netherlands–academic, teaching, non-teaching).

Results

In total, 2728 patients were included. After stratification for stage, there were no marked differences in age, sex or grade. Neo-adjuvant chemoradiation was more often administered at Moffitt (non-metastatic stages), as was adjuvant chemoradiation and chemotherapy ($p<0.001$). However, the proportion surgery was not significantly different. In patients with advanced disease, more patients at Moffitt underwent palliative chemotherapy (64.5% versus 17.4%; $p<0.001$). Short-term 1-year survival rate was statistically significantly better among Moffitt patients (HR 0.30 (95%CI 0.11-0.82), HR 0.56 (0.41-0.72), HR 0.43 (0.36-0.52) for early, locally advanced and advanced, respectively). In subgroup analyses, differences were less pronounced comparing Dutch academic hospitals to Moffitt.

Conclusions

In the present comparison, a treatment regimen as delivered at Moffitt was associated with prolonged short-term survival. Further detailed analyses of selection criteria for systemic treatment could lead to tailored treatment and improved outcomes in older patients with pancreatic cancer.

INTRODUCTION

Due to the aging of Western populations, the number of older patients with cancer is expected to increase at an accelerating rate in coming years. For pancreatic cancer, more than half of patients is over the age of 70 years at diagnosis. Despite developments in treatment modalities, overall and cancer specific survival are however still poor for most pancreatic cancer patients. [1] A multidisciplinary approach including radical surgical resection and systemic therapy is the only potentially curative option for selected patients. [2] This is however associated with a high risk of perioperative morbidity and mortality, especially in older patients. [3, 4] Moreover, most patients present at an advanced stage, where surgery is not an option, thereby largely precluding long-term survival. [5]

Studies concerning the outcome of complex major surgery in older patients are most crucial, as the proportion of older cancer patients increases, and concerns are expressed as to whether these surgical endeavors are justified. [6] Surgical treatment of pancreatic cancer presents distinctive challenges due to a high perioperative morbidity in patients with a dismal prognosis. [6] Previous studies have shown conflicting results with respect to pancreatoduodenectomy in older patients. Some studies show a comparable complication rate and survival as compared to younger patients; [7]others have shown that older patients present more often with postoperative cardiac events, stay longer in the intensive care unit, experience more nutritional and functional difficulties, and are more often readmitted than younger patients. [8, 9] [10] Therefore, as mentioned by Turrini et al [11], two questions are pertinent in the selection of older patients for surgery: is the older patient able to overcome the complex pancreatic surgery and secondly, will the older patient benefit from surgery considering the reduced life expectancy? Van der Geest et al [12] showed that over time resection rates increased in older patients, and that despite higher short-term mortality, octogenarians who underwent pancreatic resection showed long-term survival similar to younger patients.

Beyond surgery, the appropriate use of adjuvant chemoradiation in older patients is controversial [13]; a prospective randomized study conducted by the Gastrointestinal Tumor Study Group (GITSG) showed a significant longer median survival in patients who received radiation and chemotherapy. [14] However, two RCTs from the European Study Group for Pancreatic Cancer (ESPAC) showed no survival benefit. (Neoptolemos *et al.*, 2001;Neoptolemos *et al.*, 2004) On the other hand, studies have clearly shown the benefit of adjuvant chemotherapy and adjuvant Gemcitabine has become the standard of care in many centres . [15] [16] [17] [18]. Nonetheless, population-based studies show that a lower proportion of older patients receive chemotherapy

and due to the inclusion criteria in the RCTs, leaving older patients out, its efficacy in (frail) older patients is still unclear.

A large proportion of the pancreatic cancer patients will present with metastatic (unresectable) disease; Gemcitabine is widely used in the treatment of unresectable pancreatic cancer. [19] [20] More recently, trials have shown an improvement in efficacy with combination chemotherapies such as FOLFIRINOX or combinations of gemcitabine over gemcitabine alone. [21] However, there are only a few studies evaluating the efficacy and safety of these treatments for older patients. [19]

Beyond RCTs, observational studies offer an important alternative source of evidence; in particular, comparisons of treatment and survival using the instrumental variable assumptions could provide clues to optimize the treatment strategy for older patients. Country may be a suitable instrumental variable as place of residence determines a patient allocation to one of the cohorts, assuming that there are differences in treatment between the countries to study and that patient and tumor characteristics are equally distributed and that, in general, health systems are similar in both countries. The aim of the present study was to compare treatment and survival for pancreatic cancer patients aged 70 years and older in the Netherlands or treated at Moffitt Cancer Center, Tampa (Florida, US) which offers specialized care tailored to geriatric cancer patients.

METHODS

All age-eligible patients with histologically confirmed pancreatic adenocarcinoma (ICD-O morphology codes 8140 and 8500, where known) diagnosed between 2008 and 2012 were identified. At Moffitt Cancer Center, patients were identified through the Moffitt Cancer Registry and the Total Cancer Care™ program and details were retrieved from medical records. Only patients who had their first treatment at Moffitt (and not in another hospital) were included in the cohort. For the Netherlands, treatment and survival data was retrieved from the Netherlands Cancer Registry for all hospitals in the Netherlands; this population-based registry contains data from all cancer patients in the Netherlands.

For the present comparison, the instrumental variable methodology was followed, and the 'three assumptions' to use country as a valid instrument were assessed. In short, the three assumptions are that (1) "country" (cohort from a specific country) should be related to the chance of receiving a specific treatment strategy, (2) that the instrument should not be related to the prognosis of the patients and (3) that

country should not have an effect on the outcome other than through the chance of receiving a certain treatment strategy. Baseline patient and tumor characteristics were compared between the two cohorts; as stage was differentially distributed between the cohorts (p<0.001) and associated with survival, analyses were stratified for stage (early stage T1-2, N0,M0 (UICC stage IA and IB); locally advanced T3, N0, M0 or T1-3, N1, M0 (UICC stage IIA and IIB) or advanced disease (T4, N0-1, M0 or metastatic disease M1). Baseline patient and tumor characteristics were compared between the two cohorts. Neo-adjuvant treatment (none, chemo-radiation, chemotherapy), surgery (yes or no), adjuvant treatment (none, chemo-radiation, chemotherapy) and non-surgical treatment (no treatment, chemo-radiation, chemotherapy) were compared. For advanced stage, palliative treatment by type (no treatment, chemo-radiation, chemotherapy or radiotherapy) was compared.

Overall Survival (OS) and 95% Confidence Intervals (95%CI) at 1 and 3 years after diagnosis were calculated with death due to any cause as event with time from diagnosis to death, stratified by stage. Cause of death was not recorded for the Netherlands cohort, we used Overall Survival; this seems justified as cause of death was known for the Moffitt cohort and 92.8% died as a result of pancreatic cancer. Besides, a Dutch study showed that 94.7% of the deaths was attributable to pancreatic cancer. [22] Cox proportional hazards models were used to compare the short-term survival with the Netherlands cohort as reference. Two adjusted models were constructed; one with adjustment for age, sex, grade and year of incidence and one model with an additional adjustment for treatment. Kaplan-Meier survival curves for both cohorts were generated according to stage at diagnosis. Finally, stratified survival analyses (adjusted for sex, grade, year and age (where appropriate), with the Netherlands as reference cohort) were performed according to age (70-74, 75-79 and 80 years and older) and type of hospital in the Netherlands (academic, teaching or non-teaching) as pancreatic (surgical) cancer care is mostly centralized in specialized hospitals.

RESULTS

Overall, 2837 patients of 70 years and older were included: 2523 from the Netherlands (early stage 179; locally advanced 603; advanced 1639 and unknown stage 102 patients) and 314 from Moffitt Cancer Center (early stage 15, locally advanced 124, advanced 168 and unknown stage 7 patients). Table 1 shows the characteristics of the patients, according to stage at diagnosis. Age, sex and grade were not differentially distributed between the cohorts, with the exception of age in patients with locally advanced disease (median age Netherlands 75.0 and Moffitt 77.0 years; p=0.02).

TABLE 1 **Characteristics of patients, according to stage at diagnosis**

		Netherlands	Moffitt	p-value
Early stage T1-2, N0, M0 (UICC stage IA & IB)		**N=179**	**N=15**	
Age	Median (range)	77.0 (70.0-93.0)	78.0 (71.0-85.0)	0.8
Sex	Male Female	83 (46.4) 96 (53.6)	11 (73.3) 4 (26.7)	0.1
Differentiation grade	I II III Unknown	22 (12.3) 34 (19.0) 17 (9.5) 106 (59.2)	1 (6.7) 5 (33.3) 0 (0.0) 9 (60.0)	0.4
Locally advanced T3, N0, M0 or T1-3, N1, M0 (UICC stage IIA & IIB)		**N=603**	**N=124**	
Age	Median (range)	75.0 (70.0-98.0)	77.0 (70.0-90.0)	0.02
Sex	Male Female	285 (47.3) 318 (52.7)	71 (57.3) 53 (42.7)	0.1
Differentiation grade	I II III Unknown	32 (5.3) 188 (31.2) 136 (22.6) 247 (40.9)	3 (2.4) 45 (36.3) 23 (18.6) 53 (42.7)	0.3
T4, N0-1, M0 or metastatic (UICC stage III & IV)		**N=1639**	**N=168**	
Age	Median (range)	75.0 (70.0-99.0)	74.0 (70.0-90.0)	0.2
Sex	Male Female	802 (48.9) 837 (51.1)	79 (47.0) 89 (53.0)	0.6
Differentiation grade	I II III Unknown	31 (1.9) 105 (6.4) 176 (10.7) 1327 (81.0)	5 (3.0) 10 (6.0) 15 (8.9) 138 (82.1)	0.7

Treatment

Table 2 shows the treatment strategy in both cohorts according to stage. Most early stage pancreatic cancer patients received no neo-adjuvant treatment, both in the Netherlands (97.2%) and at Moffitt (88.9%). Surgical resection was more often performed at Moffitt though the difference was not significant (60.0% versus 39.7%; p=0.1). Adjuvant treatment was initiated more frequently at Moffitt (66.7% versus 18.3%; p<0.001). For early stage patients who had no surgery, chemo-radiation (33.3% versus 0%) or chemotherapy (16.7% versus 3.7%) was more often part of the treatment strategy at Moffitt than in the Netherlands (p<0.001).

In patients with locally advanced disease, neo-adjuvant chemo-radiation was more often part of the treatment strategy at Moffitt (16.7% versus 0.3%; p<0.001). The proportion of patients who received surgery was higher in the Netherlands (63.3%

TABLE 2: **Treatment strategies in both cohorts, according to stage**

Treatment		Netherlands	Moffitt	p-value
Early stage T1-2, N0, M0				
Neo-adjuvant treatment#	None	69 (97.2)	8 (88.9)	0.3
	Chemo-radiation	1 (1.4)	1 (11.1)	
	Chemotherapy	1 (1.4)	0 (0.0)	
Surgery	No	108 (60.3)	6 (40.0)	0.1
	Yes	71 (39.7)	9 (60.0)	
Adjuvant treatment#	None	58 (81.7)	3 (33.3)	<0.001
	Chemo-radiation	0 (0.0)	1 (11.1)	
	Chemotherapy	13 (18.3)	5 (55.6)	
Non-surgical treatment	No treatment	104 (96.3)	3 (50.0)	<0.001
	Chemo-radiation	0 (0.0)	2 (33.3)	
	Chemotherapy	4 (3.7)	1 (16.7)	
Locally advanced T3, N0, M0 or T1-3, N1, M0				
Neo-adjuvant treatment#	None	380 (99.5)	54 (81.8)	<0.001
	Chemo-radiation	1 (0.3)	11 (16.7)	
	Chemotherapy	1 (0.3)	1 (1.5)	
Surgery	No	221 (36.7)	58 (46.8)	0.04
	Yes	382 (63.3)	66 (53.2)	
Adjuvant treatment#	None	266 (69.6)	17 (25.8)	<0.001
	Chemo-radiation	0 (0.0)	21 (31.8)	
	Chemotherapy	116 (30.4)	28 (42.4)	
Non-surgical treatment	No treatment	192 (86.9)	14 (24.1)	<0.001
	Chemo-radiation**	6 (2.7)	28 (48.3)	
	Chemotherapy	21 (9.5)	16 (27.6)	
	Radiotherapy	2 (0.9)	0 (0.0)	
T4, N0-1, M0 or metastatic				
Palliative treatment$	No treatment	1284 (79.5)	25 (15.1)	<0.001
	Chemo-radiation	23 (1.4)	34 (20.5)	
	Chemotherapy	281 (17.4)	107 (64.5)	
	Radiotherapy	27 (1.7)	0 (0.0)	

#Proportion calculated for the operated patients. $Selection of patients who received no surgery, **Typically initiated as neo-adjuvant treatment, however detection of liver metastases resulted in cancellation of the surgery.

versus 53.2%; p=0.04). In patients that underwent surgery, adjuvant therapy was more often administrated at Moffitt (74.2% versus 30.4%; p<0.001). In patients who received no surgery, treatment strategies were different with a higher proportion of no treatment in the Netherlands and a higher proportion of systemic treatment at Moffitt (p<0.001).

With respect to palliative treatment for patients with advanced pancreatic cancer, treatment strategies were also different (p<0.001); in particular, the proportion of

TABLE 3. **Short-term survival for older pancreatic cancer patients, according to stage**

	OS NL (%)	OS Moffitt (%)	Comparison	HR (95%CI)*	p-value
1-year Overall Survival					
T1-2,N0,M0	40.7 (33.2-48.0)	72.0 (41.2-88.6)	Comparison cohort Adjusted* Adjusted model 2**	0.35 (0.13-0.95) 0.30 (0.11-0.82) 0.61 (0.07-5.19)	0.04 0.02 0.65
T3, N0, M0 or T1-3, N1, M0	43.0 (38.7-47.3)	57.4 (48.1-65.6)	Comparison cohort Adjusted* Adjusted model 2**	0.63 (0.47-0.84) 0.56 (0.41-0.75) 0.68 (0.34-1.33)	0.002 <0.001 0.26
T4, N0-1, M0 or metastatic	8.2 (6.9-9.8)	27.7 (21.1-34.6)	Comparison cohort Adjusted* Adjusted model 2**	0.45 (0.37-0.54) 0.43 (0.36-0.52) 0.84 (0.68-1.03)	<0.001 <0.001 0.10
3-years Overall Survival					
T1-2,N0,M0	21.5 (14.9-28.9)	32.0 (8.2-59.5)	Comparison cohort Adjusted* Adjusted model 2**	0.52 (0.25-1.06) 0.39 (0.19-0.81) 0.33 (0.04-2.50)	0.07 0.01 0.28
T3, N0, M0 or T1-3, N1, M0	11.4 (8.0-15.3)	12.9 (6.9-20.9)	Comparison cohort Adjusted* Adjusted model 2**	0.74 (0.59-0.92) 0.66 (0.52-0.83) 0.64 (0.40-1.04)	0.007 <0.001 0.07
T4, N0-1, M0 or metastatic	0.9 (0.4-1.7)	1.0 (0.1-4.7)	Comparison cohort Adjusted* Adjusted model 2**	0.51 (0.43-0.60) 0.49 (0.42-0.58) 0.90 (0.74-1.09)	<0.001 <0.001 0.27

Netherlands as reference cohort, *adjusted for age, sex, grade and year, **additionally adjusted for treatment.

patients receiving chemotherapy was higher at Moffitt (17.4% in the Netherlands versus 64.5% at Moffitt).

Survival

Table 3 shows the 1-year and 3-years OS rate; overall, survival was higher for patients from Moffitt. The adjusted (age, sex, grade and year) Hazard Ratio (HR) for early stage patients was 0.30 (95%CI 0.11-0.82; p=0.02) at 1 year and 0.39 (95%CI 0.19-0.81; p=0.01) at 3 years, respectively. Further adjustment for treatment partly explained the association; the HR was attenuated and no longer significant with treatment included in the regression (HR 0.61 (95%CI 0.07-5.19; p=0.65) at 1 year and HR 0.33 (95%CI 0.04-2.50; p=0.28) at 3 years.

For patients with locally advanced disease, survival rate was higher for patients at Moffitt (HR 0.56 (95%CI 0.41-0.75; p<0.001) at 1 year and HR 0.66 (95%CI 0.52-0.83; p<0.001) at 3 years. Further adjustment for treatment explained part of the association, although the survival rate seems to be higher at Moffitt at 3 years (HR 0.64 (95%CI 0.40-1.04; p=0.07)).

Pancreatic cancer patients with advanced disease showed a higher survival rate in the Moffitt cohort, adjusted HR at 1 year was 0.43 (95%CI 0.36-0.52; p<0.001), and at 3 years (HR 0.49 (95%CI 0.42-0.58; p<0.001). Further adjustment for treatment again explained part of the association, especially at three years OS (HR 0.90 (95%CI 0.74-1.09; p=0.27). Figure 1 shows the corresponding survival curves according to stage.

Table 4 shows the differences in survival stratified by age and stratified by type of hospital in the Netherlands. A significantly improved survival rate at Moffitt was more pronounced for patients over the age of 75 years with early stage or locally advanced disease; for patients with advanced disease the survival rate was better at Moffitt in all age groups. Comparing survival between academic hospitals in the Netherlands and Moffitt showed no statistically significant difference in survival for patients with early stage (adjusted HR 0.42 (95%CI 0.16-1.07; p=0.07)) and locally advanced stage (adjusted HR 0.81 (95%CI 0.61-1.08; p=0.15)).

TABLE 4 **Adjusted HR (with Netherlands as reference category), stratified for stage, age and type of hospital in the Netherlands**

Stage	3-years survival	Adjusted HR (95%CI)	p-value
Stratified according to age			
T1-2,N0,M0	70-74	1.26 (0.26-6.07)	0.77
	75-79	0.22 (0.05-1.00)	0.05
	80+	0.32 (0.11-0.98)	0.05
T3, N0, M0 or T1-3, N1, M0	70-74	0.82 (0.56-1.19)	0.30
	75-79	0.60 (0.39-0.92)	0.02
	80+	0.57 (0.37-0.86)	0.009
T4, N0-1, M0 or metastatic	70-74	0.54 (0.43-0.68)	<0.001
	75-79	0.51 (0.36-0.73)	<0.001
	80+	0.39 (0.28-0.53)	<0.001
Stratified according to type of hospital			
T1-2,N0,M0	Academic	0.42 (0.16-1.07)	0.07
	Teaching	0.40 (0.19-0.84)	0.02
	Non-teaching / other	0.30 (0.09-0.99)	0.05
T3, N0, M0 or T1-3, N1, M0	Academic	0.81 (0.61-1.08)	0.15
	Teaching	0.60 (0.47-0.77)	<0.001
	Non-teaching / other	0.43 (0.29-0.64)	<0.001
T4, N0-1, M0 or metastatic	Academic	0.66 (0.54-0.81)	<0.001
	Teaching	0.46 (0.38-0.54)	<0.001
	Non-teaching / other	0.41 (0.33-0.50)	<0.001

Adjusted for sex, grade, year and age

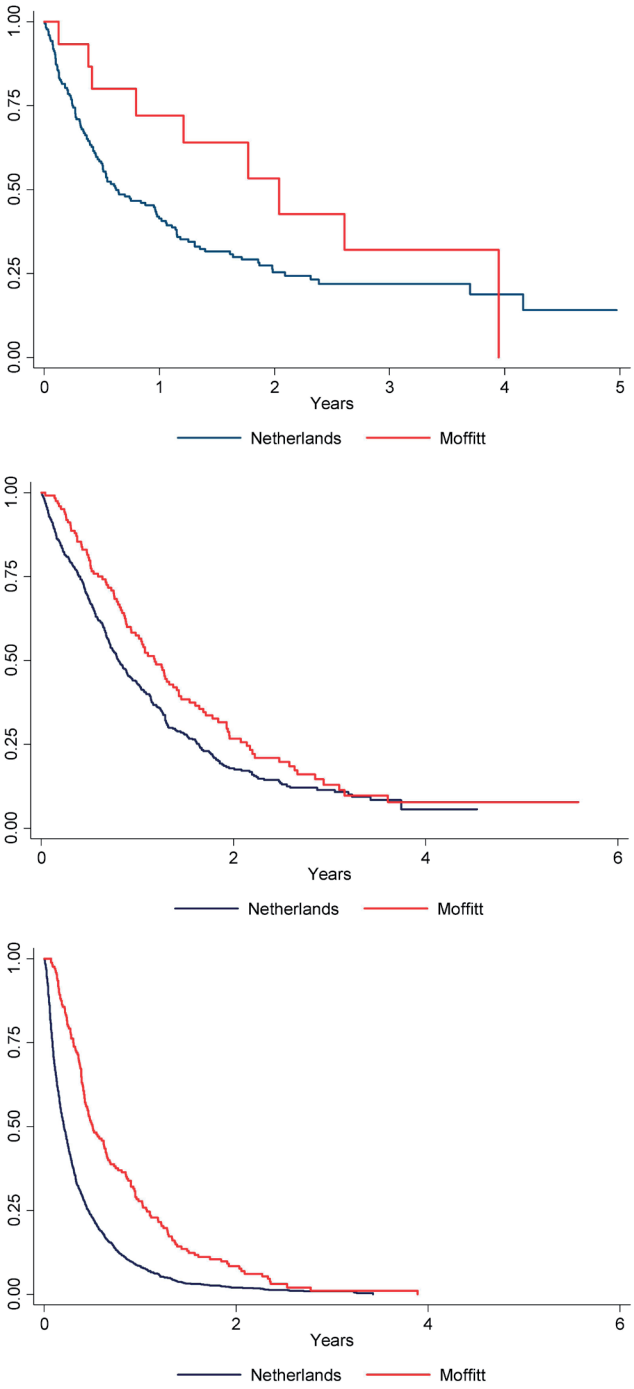

FIGURE 1. **Survival curves according to stage at diagnosis, (A) T1-2,N0,M0; (B) T3, N0, M0 or T1-3, N1, M0; (C) T4, N0-1, M0 or metastatic**

DISCUSSION

This international comparison of older pancreatic cancer patients treated at Moffitt Cancer Center and the Netherlands shows differences in treatment strategies, especially in systemic treatment administration with a higher proportion at Moffitt. Overall Survival rates were higher for patients treated at Moffitt, and were in a large part explained by the differences in treatment. The survival difference was less pronounced when compared with patients with locally advanced disease treated at an academic hospital in the Netherlands.

For locally advanced disease, earlier data from the US (Duke University Medical Center) showed that the proportion of older patients receiving neoadjuvant therapy was similar to younger patients, but a smaller proportion of older patients received adjuvant therapy. [23] In the present study, the proportion of patients who received neoadjuvant chemoradiation was higher for patients at Moffitt (16.7% versus 0.3% for patients with locally advanced disease). One possible explanation is a difference in the approach to borderline resectable disease, where a neoadjuvant chemotherapy with or without radiation is often used in the US to attempt to improve resectability, and is described as an option in the NCCN guidelines but not yet in the Dutch guidelines (2011). Currently the benefit of neoadjuvant chemoradiation is being investigated in a multicenter clinical trial in the Netherlands. Furthermore, a geriatric oncologist is included in the multidisciplinary tumor board at Moffitt and might provide a more accurate evaluation and management plan for older patients. In addition, a more favorable health status of elderly patients at Moffitt compared with the nationwide Dutch cohort cannot be ruled out.

Differences in the administration of adjuvant chemoradiation and chemotherapy were also observed in the present study, with a larger proportion of patients receiving adjuvant therapy for Moffitt in both early stage and locally advanced patients. Decision-making in choosing adjuvant chemotherapy or chemoradiation is complex; some RCTs show an improved overall survival with the use of adjuvant chemoradiation followed by adjuvant chemotherapy [14] or adjuvant chemoradiation versus surgical resection alone [24]; while others did not confirm a survival benefit with chemoradiation [25] or even found a detrimental effect of chemoradiation compared with chemotherapy or surgery alone . The survival benefit of adjuvant chemotherapy after surgical resection was however clearly demonstrated in two RCTs. [26] [15] [18] . Whereas few older patients were included in RCTs, a recent retrospective series demonstrated a longer survival in patients 75 and older from adjuvant chemoradiation. [27] However others have also shown that older patients less often receive adjuvant chemotherapy. Many factors contribute to this difference, some

are patient driven and some physician driven; factors that are mentioned in studies are the observation that older patients are more often discharged to a rehabilitation facility, and have a longer recovery period after surgery and consequently are less likely to pursue further therapy. [23] Besides, older patients who undergo surgical resection with the intention of receiving adjuvant therapy might never receive it because of complications. Studies in older patients are however scarce and more evidence is needed regarding the efficacy and safety of chemotherapy for older patients and for appropriate patient selection. [19]

The difference in receipt of systemic treatment is particularly striking for advanced disease: 85% of Moffitt patients received chemotherapy and /or radiation therapy, versus only 20% of the Dutch patients. A significant difference in 1 year overall survival was observed for these patients: 27.7% (21.1-34.6) for patients at Moffitt versus 8.2% (6.9-9.8). This might be due to various factors; one hypothesis might be the differences in cultural perception of the benefit of giving palliative chemotherapy to pancreatic cancer patients. Transcultural perceptions were explored in detail between French and American patients. [28] Interestingly enough, whereas older non-cancer patients were less interested in moderate chemotherapy on the European side, nearly all older cancer patients were interested in the option on either side of the Atlantic Ocean. Given the associated survival benefit, this indicates that there might be a need for a reconsideration of the general avoidance of chemotherapy observed in our cohort of Dutch patients. Although one might hypothesize some referral bias at Moffitt, it should be noted that even in Dutch academic centers, only 54% of patients with advanced disease did receive systemic treatment. Therefore in our opinion, this would only explain a small proportion of the inter-country variance. The Moffitt practice appears representative of the practice at other American Comprehensive Cancer Centers with geriatric oncologists. A recent series in pancreatic cancer patients with metastatic disease showed that 65% of patients above age 65 did receive chemotherapy, compared with 75% of younger ones. [29] In that series, receipt of chemotherapy, preferably with two agents, was also associated with a survival benefit at all ages.

Whereas survival is improved with palliative systemic treatment, this benefit might be counterbalanced by quality of life concerns. The commonly used regimens for advanced pancreatic cancer are: FOLFIRINOX, gemcitabine doublets (nab-paclitaxel, erlotinib, or capecitabine) or, when tolerance is a concern, gemcitabine single agent. FOLFIRINOX was studied in patients below the age of 76 with ECOG 0-1(median 61) and has significant side effects. However, a recent series showed that with a reduced-dose of FOLFIRINOX in patients aged 70 and older a median overall survival of 11 months could be achieved, comparable to that obtained in younger patients.

However this comes at the cost of a greater impact on quality of life [30], and most older patients are treated with gemcitabine or a gemcitabine doublet. Studies for older patients are also scarce in this area. One retrospective study compared older and younger patients who received gemcitabine and patients under best supportive care. The response rate, disease stabilization, improvement of tumor makers and median survival time were similar in young and older patients, although bone marrow suppression and hematological toxicity of grade 3 or more was seen more frequently in older patients and older patients tended to need dose reduction of gemcitabine in the first cycle .[19]. The benefits of chemotherapy are clearly linked to baseline performance status, and there is no evidence of a benefit for patients with poor ECOG performance status. On the other hand, with proper supportive care such as e.g. provided with a geriatric oncology program, older patients maintain quite well their functional status despite side effects of chemotherapy. [31] Yamagishi et al mentioned several reasons for the tendency to avoid chemotherapy in older pancreatic cancer patients with advanced disease: the fact that unresectable pancreatic cancer is not curable by chemotherapy alone (possibly resulting in patient distress), the higher susceptibility of older patients for severe toxicity and the presence of comorbidities which may lead to contraindications for chemotherapy.

An accurate estimation of the expected perioperative morbidity and mortality is based on thorough preoperative (geriatric) patient assessment and is central to surgical decision-making with respect to the risks and benefits for an individual patient. [23] As a Whipple resection is a major surgery, treating physicians may hesitate to refer elderly patients for surgery, concerned with the risk of poor post-operative quality of life. [32] There is however a lack of evidence with respect to quality of life studies for older patients with pancreatic cancer, although it is known from the literature that older patients have a higher complication rate and a significant proportion will be admitted to a chronic care facility after surgery. Studies from Khan et al [6] and Hardacre et al [33] showed that one out of five patients (21%) over the age of 80 years in the first study and 59% in the second were discharged to an outside health care facility and that 51% of the patients developed complications. Comorbidities and functional reserve might have a key role in the postoperative morbidity (and mortality); the presence of comorbidities such as hyperlipidemia, diabetes and coronary artery disease were shown to be possible risk factors for major complications. [34] [4] Despite this, one of the few quality of life studies in older patients who underwent pancreatoduodenectomy in a high-volume referral center showed that within 3 months after surgery, quality of life scores were lower yet comparable to their matched controls undergoing laparoscopic cholecystectomy. A gradual rather than a rapid recovery process was observed for the older patients, and fatigue was common, lasting for 3 to 6 months after surgery. [32] Other studies

have shown a higher prevalence of postoperative depression in the older population , which was confirmed in this study; a longer emotional recovery in older patients.

A large number of studies compared younger and older patients who received surgery, however the results with respect to survival are difficult to interpret due to selection bias. Nonetheless these studies show that pancreatoduodenectomy can be safely performed in selected older patients, [11] [35] although some series show that age is one of the determinants for postoperative mortality. [8] Recently there have been unquestioned advancements in patient selection, techniques, perioperative care and management of complications, which resulted in better outcomes for patients who underwent pancreatic resection. [36] In the present study, the proportion of patients who underwent surgery in each country was not significantly different between the two cohorts for early stage patients, although this might be due to a low number of patients in this group. For patients with locally advanced disease, there was a 10% difference in surgery rate with a higher proportion in the Netherlands. This higher proportion of surgery was especially marked for academic hospitals in the Netherlands (80.9% versus 53.2%, p<0.001), and less pronounced in the teaching (54.2% versus 53.2%; p=0.8) and non-teaching/other hospitals (50.0% versus 53.2%; p=0.7). This can be explained by centralization of pancreatic cancer care in academic hospitals in the Netherlands. Chronological age is a poor predictor for functional status (physically, mentally and medical) and selecting appropriate therapy for older patients remains challenging because of concerns with respect to the patients comorbidities, their functional and nutritional status, cognitive function, social support and their expected survival. [6] [37]

The present study showed a higher survival rate for patients treated at Moffitt; these differences seem to be largely explained by differences in treatment strategy between the Netherlands and Moffitt. The assumptions for the instrumental variable methodology were assessed: country was indeed related to the chance of a certain treatment strategy and there were large differences between both countries; second, there were no differences in known patient and tumor characteristics between the countries that are associated with the outcome, apart from age for locally advanced stage. Stratification for age showed that the survival difference was more pronounced for the patients above the age of 75 years. The third assumption, that country should not influence outcome other than through the chance to receive a certain treatment strategy, is difficult to assess with the data. Although differences in health care systems do exist between the Netherlands and Moffitt, patients included in this cohort were of Medicare age. Besides, a previous study comparing both countries, showed that there are no marked differences between patients who resided inside or outside the catchment area of Moffitt Cancer Center.

(38) As pancreatic surgical care is centralized in the larger hospitals in the Netherlands, we performed a sensitivity analysis to compare the survival stratified by type of hospital. This showed smaller survival differences for patients treated at an academic hospital in the Netherlands compared to Moffitt, especially for patients with locally advanced disease. Another drawback in the present comparison is related to the administration of neo-adjuvant treatment, which is not part of the Dutch guidelines. Some patients treated at Moffitt with locally advanced disease progressed during neo-adjuvant chemoradiation and thus became not surgical candidates. Last/ Finally, for older patients with pancreatic cancer, it is essential to balance quality of life and expected survival. Unfortunately, we had no quality of life information for the patients in these cohorts. In summary, patients treated at Moffitt were more often treated with systemic treatment and had a higher survival rate. Differences in survival were largely explained by differences in treatment and less pronounced in comparison with academic hospitals in the Netherlands. Further detailed analyses of selection criteria for systemic treatment and assessment of quality of life could lead to tailored treatment and improved outcomes in older patients with pancreatic cancer.

REFERENCES

1. Sehgal R, Alsharedi M, Larck C, Edwards P, Gress T. Pancreatic cancer survival in elderly patients treated with chemotherapy. Pancreas. 2014;43(2):306-10.
2. Brachet D, Lermite E, Vychnevskaia-Bressollette K, Mucci S, Hamy A, Arnaud JP. Should pancreaticoduodenectomy be performed in the elderly? Hepatogastroenterology. 2012;59(113):266-71.
3. Scurtu R, Bachellier P, Oussoultzoglou E, Rosso E, Maroni R, Jaeck D. Outcome after pancreaticoduodenectomy for cancer in elderly patients. J Gastrointest Surg. 2006;10(6):813-22.
4. Ballarin R, Spaggiari M, Di Benedetto F, Montalti R, Masetti M, De Ruvo N, et al. Do not deny pancreatic resection to elderly patients. J Gastrointest Surg. 2009;13(2):341-8.
5. Morganti AG, Falconi M, van Stiphout RG, Mattiucci GC, Alfieri S, Calvo FA, et al. Multi-institutional pooled analysis on adjuvant chemoradiation in pancreatic cancer. Int J Radiat Oncol Biol Phys. 2014;90(4):911-7.
6. Khan S, Sclabas G, Lombardo KR, Sarr MG, Nagorney D, Kendrick ML, et al. Pancreatoduodenectomy for ductal adenocarcinoma in the very elderly; is it safe and justified? J Gastrointest Surg. 2010;14(11):1826-31.
7. Stauffer JA, Grewal MS, Martin JK, Nguyen JH, Asbun HJ. Pancreas surgery is safe for octogenarians. J Am Geriatr Soc. 2011;59(1):184-6; Lee MK, Dinorcia J, Reavey PL, Holden MM, Genkinger JM, Lee JA, et al. Pancreaticoduodenectomy can be performed safely in patients aged 80 years and older. J Gastrointest Surg. 2010;14(11):1838-46; Oliverius M, Kala Z, Varga M, Gurlich R, Lanska V, Kubesova H. Radical surgery for pancreatic malignancy in the elderly. Pancreatology. 2010;10(4):499-502.
8. de la Fuente SG, Bennett KM, Pappas TN, Scarborough JE. Pre- and intraoperative variables affecting early outcomes in elderly patients undergoing pancreaticoduodenectomy. HPB (Oxford). 2011;13(12):887-92.
9. Lightner AM, Glasgow RE, Jordan TH, Krassner AD, Way LW, Mulvihill SJ, et al. Pancreatic resection in the elderly. J Am Coll Surg. 2004;198(5):697-706.
10. Yermilov I, Bentrem D, Sekeris E, Jain S, Maggard MA, Ko CY, et al. Readmissions following pancreaticoduodenectomy for pancreas cancer: a population-based appraisal. Ann Surg Oncol. 2009;16(3):554-61.
11. Turrini O, Paye F, Bachellier P, Sauvanet A, Sa Cunha A, Le Treut YP, et al. Pancreatectomy for adenocarcinoma in elderly patients: postoperative outcomes and long term results: a study of the French Surgical Association. Eur J Surg Oncol. 2013;39(2):171-8.
12. van der Geest LG, Besselink MG, van Gestel YR, Busch OR, de Hingh IH, de Jong KP, et al. Pancreatic cancer surgery in elderly patients: Balancing between short-term harm and long-term benefit. A population-based study in the Netherlands. Acta Oncol. 2016;55(3):278-85.
13. Horowitz DP, Hsu CC, Wang J, Makary MA, Winter JM, Robinson R, et al. Adjuvant chemoradiation therapy after pancreaticoduodenectomy in elderly patients with pancreatic adenocarcinoma. Int J Radiat Oncol Biol Phys. 2011;80(5):1391-7.

14. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg. 1985;120(8):899-903.
15. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350(12):1200-10.
16. Neoptolemos JP, Stocken DD, Dunn JA, Almond J, Beger HG, Pederzoli P, et al. Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. Ann Surg. 2001;234(6):758-68.
17. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010;304(10):1073-81.
18. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007;297(3):267-77.
19. Yamagishi Y, Higuchi H, Izumiya M, Sakai G, Iizuka H, Nakamura S, et al. Gemcitabine as first-line chemotherapy in elderly patients with unresectable pancreatic carcinoma. J Gastroenterol. 2010;45(11):1146-54.
20. Heinemann V. Gemcitabine in the treatment of advanced pancreatic cancer: a comparative analysis of randomized trials. Semin Oncol. 2002;29(6 Suppl 20):9-16.
21. Versteijne E, Suker M, Groothuis K, Akkermans-Vogelaar JM, Besselink MG, Bonsing BA, et al. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. J Clin Oncol. 2020;38(16):1763-73.
22. Fest J, Ruiter R, van Rooij FJ, van der Geest LG, Lemmens VE, Ikram MA, et al. Underestimation of pancreatic cancer in the national cancer registry–Reconsidering the incidence and survival rates. Eur J Cancer. 2017;72:186-91.
23. Barbas AS, Turley RS, Ceppa EP, Reddy SK, Blazer DG, 3rd, Clary BM, et al. Comparison of outcomes and the use of multimodality therapy in young and elderly people undergoing surgical resection of pancreatic cancer. J Am Geriatr Soc. 2012;60(2):344-50.
24. Yeo CJ, Abrams RA, Grochow LB, Sohn TA, Ord SE, Hruban RH, et al. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. Ann Surg. 1997;225(5):621-33; discussion 33-6.
25. Klinkenbijl JH, Jeekel J, Sahmoud T, van Pel R, Couvreur ML, Veenhof CH, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg. 1999;230(6):776-82; discussion 82-4.
26. Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet. 2001;358(9293):1576-85.
27. Baldini C, Escande A, Bouche O, El Hajbi F, Volet J, Bourgeois V, et al. Safety and efficacy of FOLFIRINOX in elderly patients with metastatic or locally advanced pancreatic adenocarcinoma: A retrospective analysis. Pancreatology. 2017;17(1):146-9.

28. Extermann M, Balducci L. Optimizing cancer care in the elderly: progress in geriatric oncology. Cancer Control. 2003;10(6):440-1.
29. Vijayvergia N, Dotan E, Devarajan K, Hatahet K, Rahman F, Ricco J, et al. Patterns of care and outcomes of older versus younger patients with metastatic pancreatic cancer: A Fox Chase Cancer Center experience. J Geriatr Oncol. 2015;6(6):454-61.
30. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouche O, Guimbaud R, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. J Clin Oncol. 2013;31(1):23-9.
31. Chen H, Cantor A, Meyer J, Beth Corcoran M, Grendys E, Cavanaugh D, et al. Can older cancer patients tolerate chemotherapy? A prospective pilot study. Cancer. 2003;97(4):1107-14.
32. Gerstenhaber F, Grossman J, Lubezky N, Itzkowitz E, Nachmany I, Sever R, et al. Pancreaticoduodenectomy in elderly adults: is it justified in terms of mortality, long-term morbidity, and quality of life? J Am Geriatr Soc. 2013;61(8):1351-7.
33. Hardacre JM, Simo K, McGee MF, Stellato TA, Schulak JA. Pancreatic resection in octogenarians. J Surg Res. 2009;156(1):129-32.
34. Oguro S, Shimada K, Kishi Y, Nara S, Esaki M, Kosuge T. Perioperative and long-term outcomes after pancreaticoduodenectomy in elderly patients 80 years of age and older. Langenbecks Arch Surg. 2013;398(4):531-8.
35. Frakes JM, Strom T, Springett GM, Hoffe SE, Balducci L, Hodul P, et al. Resected pancreatic cancer outcomes in the elderly. J Geriatr Oncol. 2015;6(2):127-32.
36. Schnelldorfer T, Ware AL, Sarr MG, Smyrk TC, Zhang L, Qin R, et al. Long-term survival after pancreatoduodenectomy for pancreatic adenocarcinoma: is cure possible? Ann Surg. 2008;247(3):456-62.
37. Huang JJ, Yeo CJ, Sohn TA, Lillemoe KD, Sauter PK, Coleman J, et al. Quality of life and outcomes after pancreaticoduodenectomy. Ann Surg. 2000;231(6):890-8.
38. van de Water W, Bastiaannet E, Egan KM, de Craen AJ, Westendorp RG, Balducci L, et al. Management of primary metastatic breast cancer in elderly patients—an international comparison of oncogeriatric versus standard care. J Geriatr Oncol. 2014;5(3):252-9.


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