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The treatment and survival of elderly patients with locally advanced pancreatic cancer: A post-hoc analysis of a multicenter registry

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ABSTRACT

Background: The treatment options for patients with locally advanced pancreatic cancer (LAPC) have improved in recent years and consequently survival has increased. It is unknown, however, if elderly patients benefit from these improvements in therapy. With the ongoing aging of the patient population and an increasing incidence of pancreatic cancer, this patient group becomes more relevant. This study aims to clarify the association between increasing age, treatment and overall survival in patients with LAPC.

Methods: Post-hoc analysis of a multicenter registry including consecutive patients with LAPC, who were registered in 14 centers of the Dutch Pancreatic Cancer Group (April 2015–December 2017). Patients were divided in three groups according to age (<65, 65–74 and ≥75 years). Primary outcome was overall

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Elderly
Best supportive care

survival stratified by primary treatment strategy. Multivariable regression analyses were performed to adjust for possible confounders.

Results: Overall, 422 patients with LAPC were included; 162 patients (38%) aged <65 years, 182 patients (43%) aged 65–74 and 78 patients (19%) aged ≥75 years. Chemotherapy was administered in 86%, 81% and 50% of the patients in the different age groups ($p<0.01$). Median overall survival was 12, 11 and 7 months for the different age groups ($p<0.01$). Patients treated with chemotherapy showed comparable median overall survival of 13, 14 and 10 months for the different age groups ($p=0.11$). When adjusted for confounders, age was not associated with overall survival.

Conclusion: Elderly patients are less likely to be treated with chemotherapy, but when treated with chemotherapy, their survival is comparable to younger patients.

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Introduction

In the Netherlands, overall survival of pancreatic cancer has hardly improved in the last decades [1]. It is predicted that pancreatic cancer will be the second most common cause of cancer related death in 2030 [2]. At presentation, only 10–20% of the patients are eligible for surgery and 30–35% of the patients are diagnosed with locally advanced pancreatic cancer (LAPC) [3–5]. The current standard first line treatment for patients with LAPC is chemotherapy [6]. The most frequently used regimens of chemotherapy are a (modified) combination of 5-fluorouracil, oxaliplatin, irinotecan and leucovorin (FOLFIRINOX), nab-paclitaxel plus gemcitabine (NABGEM), and gemcitabine monotherapy. FOLFIRINOX and NABGEM have shown their benefit in randomized trials in patients with metastatic disease [7,8]. Although no randomized trials have been reported for LAPC, several cohort studies suggested a survival benefit for these regimens as well [9–12]. The use of (chemo)radiation in LAPC is still controversial. Studies suggests that (chemo)radiation is safe and feasible, however, survival benefit has not yet been proven [5,9,13].

With the aging population and the increasing incidence of pancreatic cancer, advanced age in patients with pancreatic cancer becomes more relevant [14]. Limited data suggests that elderly patients with pancreatic cancer also benefit from chemotherapy [15,16]. Although an increased incidence of adverse events is seen, toxicity of the chemotherapeutic regimens seems to be acceptable in this patient group [17,18]. This, however, does not always translate to similar treatment strategies in the daily clinical practice [15,16]. Elderly patients are rarely included in clinical trials and are more often treated with best supportive care [15,19,20]. Moreover, elderly patients with pancreatic cancer are reported to have a worse prognosis in general [21]. It remains unclear, whether this worse prognosis is truly age dependent or due to retraining treatment, since data in the elderly patient population are scarce.

The present study aims to clarify the association between increasing age, primary treatment strategies and overall survival. A large unselected cohort of patients with LAPC representing daily clinical care for pancreatic cancer in the Netherlands was analyzed.

Methods

Study design and population

This is a post-hoc analysis of a multicenter registry including consecutive patients with LAPC, diagnosed between April 2015 and December 2017, in 14 centers collaborating in the Dutch Pancreatic Cancer Group.

All patients aged >18 years, diagnosed with LAPC were included. This diagnosis was based on radiologic examination or findings during upfront explorative laparotomy, according to the Dutch

Pancreatic Cancer Group criteria (Supplementary Table S1). All patients gave informed consent for registration and the Institutional Review Boards approved the registry within all participating centers. We adhered to the STROBE guidelines [22].

Data collection

Patient demographics, tumor characteristics, serum CA 19.9, treatment modalities, adverse events according to Common Terminology Criteria for Adverse Events version 4.0 [23] and survival were extracted from the retrospective database. For best supportive care, the registration included the reason why best supportive care was chosen (patient's choice or condition). Survival was measured from date of diagnosis (i.e. pathological proof or CT at diagnosis if no pathologic proof was available) to date of death from all causes. Patients still alive at follow-up were censored. Patients were divided in three age groups: <65 years, 65–74 years and ≥75 years; aiming for equal and clinically relevant proportions between the groups [15,24,25]. According to the World Health Organization (WHO) criteria patients aged over 65 years are defined as elderly [26]. This study defined the patients aged over 75 years as the true elderly.

Statistical analyses

Descriptive statistics were performed with IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Orchard Road Armonk, New York, US). Data are presented as mean ± standard deviation (SD), or median with interquartile range (IQR) when appropriate for continuous data and counts with percentage for categorical data. Differences in baseline characteristics were tested using Chi-square or Fisher exact test and continuous variables were compared using the One way ANOVA or Kruskal-Wallis H test. Overall survival was estimated with Kaplan Meier curves. Multivariable logistic regression was performed to assess the influence of age on the start of treatment with chemotherapy. Possible confounders that were corrected for included sex, World Health Organization performance score (WHO performance score), Charlson Comorbidity Index (CCI score), tumor size, tumor location, and baseline serum CA 19.9. Results are given as odds ratios (OR) with 95% confidence interval (CI). Multivariate Cox regression analysis was performed to assess the influence of age on overall survival. Possible confounders that were corrected for included sex, WHO performance score, CCI score, tumor size, tumor location, baseline serum CA 19.9 and treatment strategy. Results are given as hazard ratios (HR) with 95% CI. A sensitivity analysis was performed by excluding all patients with WHO performance score 2–3. A p -value <0.05 was considered statistically significant.

Results

Patient and tumor characteristics

Overall, 422 patients diagnosed with LAPC met our eligibility criteria, 162 patients (38%) aged <65 years, 182 patients (43%) aged 65–74 years and 78 patients (19%) aged ≥75 years. Patient and tumor characteristics are summarized in Table 1. The median age at diagnosis was 68 years (range 25–92). Patients had overall good clinical performance scores (WHO performance score 0–1 in 89%, 80% and 73% of patients aged <65, 65–74 and ≥75 years, respectively, $p<0.01$). Comorbidities were different between the age groups (median CCI score of 0, 1 and 1 in the three age groups, $p<0.01$). An increased age resulted in less often obtained pathological diagnosis (97%, 91% and 86% in patients aged <65, 65–74 and ≥75 years, respectively, $p<0.01$). The tumor location and tumor size were comparable between groups, with most tumors located in the pancreatic head.

Treatment strategy

Treatment modalities per age group are presented in Table 2. The primary treatment modality differed between the age groups ($p<0.01$). The majority of the patients aged <65 years and 65–74 years were treated with chemotherapy, as compared to only half of the patients aged ≥75 years (86%, 81% and 50% in patients aged <65, 65–74 and ≥75 years). Best supportive care was administered most often in the elderly patients (12%, 18% and 46% in patients aged <65 years, 65–74 years and ≥75 years, respectively, $p<0.01$). Reasons to chose for best supportive care were similar between age groups. Approximately half of the patients actively chose this approach, whereas the other half of the patients were treated with best supportive care because of a poor clinical condition. Chemotherapeutic regimens differed between the age groups ($p<0.01$). In patients aged <65 and 65–74 years FOLFIRINOX was the most frequently administered chemotherapy (in 78% and 63%, respectively), whereas in the patients aged ≥75 years Nab-paclitaxel plus gemcitabine or gemcitabine monotherapy were administered more often (both in 18% of the patients aged ≥75 years). Comparable results were seen in a sensitivity analysis for patients with WHO performance score 0–1, who were treated with chemotherapy or best supportive care. The proportion of patients with WHO

performance score 0–1 that was treated with chemotherapy differed with age (in the three age groups: 90%, 88%, and 60%, $p<0.01$). Of the patients aged ≥75 years, with WHO performance score 0–1 who were treated with chemotherapy, FOLFIRINOX was given in the minority (22%).

Grade 3 and higher adverse events associated with chemotherapy treatment occurred more often in younger patients (66% of patients aged <65 years, 61% of patients aged 65–74 years, and 34% of patients aged ≥75 years, $p<0.01$). Overall, the most common hematologic adverse event that occurred was neutropenia (32%). Furthermore, febrile neutropenia (6%), thrombocytopenia (3%), and anemia (3%) were reported. Non-hematologic adverse events that occurred often were diarrhea (13%), vomiting (7%), and thromboembolism (6%). The occurring of the most common adverse events in the different age groups is presented in Table 3 (all not significantly different).

A multivariable analysis on the influence of age on the probability for treatment with chemotherapy, adjusted for confounders, showed that each additional year in age was associated with a decreased probability to receive chemotherapy (OR 0.94, 95% CI 0.89–0.98, $p=0.01$).

Survival

In all age groups, patients treated with chemotherapy had longer median overall survival, as compared with patients treated with best supportive care (13 vs 6 months in patients <65 year, $p<0.01$; 14 vs 3 months in patients 65–74 year, $p<0.01$; and 10 vs 4 months in patients ≥75 year, $p<0.01$). Kaplan Meier survival curves are shown in Figs. 1 and 2. Patients aged ≥75 years had a lower median overall survival, compared to the younger patients groups (12 months in patients aged <65 years, 11 months in patients aged 65–74 years, and 7 months in patients aged ≥75 years, $p<0.01$). Survival did not differ significantly in patients treated with chemotherapy (in the three age groups: 13, 14, and 10 months, $p=0.11$). In patients treated with FOLFIRINOX chemotherapy median overall survival did not differ significantly as well (in the three age groups: 13, 15, and 20 months, $p=0.23$).

A multivariate Cox regression analysis on the influence of age on overall survival, adjusted for confounders, showed that an increase in age was not associated with a decrease in overall survival (HR 0.99, 95% CI 0.98–1.02, $p=0.83$).

Table 1
Patient and tumor characteristics in three age groups of patients with locally advanced pancreatic cancer.

	All n=422	(%)	Age <65 n=162	(%)	Age 65–74 n=182	(%)	Age ≥75 n=78	(%)	p-value
Age, median [range]	68	[25–92]	58	[25–64]	70	[65–74]	78	[75–92]	0.58
Gender									
Male	218	(52)	79	(49)	99	(54)	40	(51)	
Female	204	(48)	83	(51)	83	(46)	38	(49)	
CCI score, median [IQR] ^a	1	[0–2]	0	[0–1]	1	[0–2]	1	[0–2]	<0.01
WHO PS ^b									<0.01
0–1	313	(83)	133	(89)	131	(80)	49	(73)	
>1	66	(17)	16	(11)	32	(20)	18	(27)	
Pathologic confirmation									<0.01
Yes	390	(92)	157	(97)	166	(91)	67	(86)	
No	32	(8)	5	(3)	16	(9)	11	(14)	
Tumor location									0.12
Pancreatic head	285	(68)	103	(64)	122	(67)	60	(77)	
Pancreatic body/tail	137	(32)	59	(36)	60	(33)	18	(23)	
Tumor size, mm, median [IQR] ^c	41	[30–49]	42	[31–50]	40	[30–47]	40	[28–46]	0.49
CA 19.9, median [IQR] ^d	300	[52–1288]	228	[40–1243]	330	[99–1669]	173	[27–586]	0.04

CCI, Charlson Comorbidity Index; WHO PS, World Health Organization performance score; CA 19.9, carbohydrate antigen 19.9.

^a 1 missing.

^b 43 missing.

^c 12 missing.

^d 98 missing.

Table 2
First-line treatment strategies in three age groups of patients with locally advanced pancreatic cancer.

	All n=422	(%)	Age <65 n=162	(%)	Age 65–74 n=182	(%)	Age ≥75 n=78	(%)	p-value
Best supportive care	87	(21)	19	(12)	32	(18)	36	(46)	<0.01
Chemotherapy									
FOLFIRINOX	252	(60)	126	(78)	115	(63)	11	(14)	
NABGEM	33	(8)	8	(5)	11	(6)	14	(18)	
Gemcitabine	41	(10)	5	(3)	22	(12)	14	(18)	
Other	9	(2)	4	(2)	2	(1)	3	(4)	

NABGEM, Nab-paclitaxel plus gemcitabine.

Table 3
Adverse events grade 3 and 4 during chemotherapy, per age group.

	Age <65 n=139	(%)	Age 65–74 n=148	(%)	Age ≥75 n=39	(%)	p-value
Hematologic ^a							
Neutropenia	41	(30)	52	(35)	10	(26)	0.43
Febrile neutropenia	9	(7)	9	(6)	3	(8)	0.90
Thrombocytopenia	4	(3)	4	(3)	2	(5)	0.67
Anemia	4	(3)	3	(2)	3	(8)	0.14
Nonhematologic ^a							
Diarrhea	19	(14)	21	(14)	3	(8)	0.64
Vomiting	10	(7)	12	(8)	1	(3)	0.56
Thromboembolism	12	(9)	5	(3)	3	(8)	0.13
Fatigue	5	(4)	0	(0)	0	(0)	0.05
Sensory neuropathy	3	(2)	1	(1)	0	(0)	0.61
Elevated liver enzymes	2	(1)	3	(2)	1	(3)	0.85

^a 6 missing. **Fig. 1.** Kaplan Meier survival curve for overall survival in all patients with locally advanced pancreatic cancer, aged <65 years, 65–74 years, and ≥75 years, regardless of treatment.

Discussion

This multicenter cohort study aimed to clarify the association between increasing age, primary treatment strategies, and survival outcomes in consecutive patients with LAPC. Patients aged ≥75

years, with a good clinical condition, were less likely to be treated with chemotherapy. While treatment with chemotherapy showed an improvement in survival in elderly patients, similar to younger patients. Age was not independently associated with a decreased survival.

Fig. 2. Kaplan Meier survival curve for overall survival in patients with locally advanced pancreatic cancer, aged <65 years, 65–74 years, and ≥75 years, who were treated with chemotherapy.

The increasing life expectancy of the general population results in an increasing number of elderly patients with LAPC [27]. The importance and need to offer a meaningful treatment to this group is therefore increasingly relevant. With new chemotherapeutic regimens, the treatment options for patients with pancreatic cancer have improved [7,8]. Since elderly patients are underrepresented in most clinical studies, it is uncertain to which extent they benefit from these treatment regimens [28–30]. More data on the risks and benefit of chemotherapy will improve the complex process of shared decision-making in elderly patients with LAPC. In recent studies, the focus on elderly patients increased, suggesting that they might benefit from treatment with chemotherapy, even when receiving modified regimens [15,16,24,31]. Consistent with our findings, median overall survival up to 12 months in elderly patients (aged ≥70 years) treated with chemotherapy is described in previous studies [16,32–34]. More important, in our study, patients aged ≥75 years, who were treated with FOLFIRINOX, had a median overall survival up to 20 months. Although this group only consisted of 11 patients (with age 75–80 years, WHO performance score 0–1, and CCI score 0–2), these results suggest that highly selected, fit, elderly patients should be considered for treatment with FOLFIRINOX chemotherapy as well.

Even though more information about chemotherapy in elderly patients is becoming available, the risk and impact of toxicity in this patient group is still unclear. An increased number of adverse events is seen in elderly patients treated with chemotherapy, nevertheless toxicity is found acceptable in most studies [17,18,34]. In our study, the overall rate of adverse events was less in patients aged ≥75 years, as compared to younger patients. The occurrence of hematologic and nonhematologic adverse events did not differ in the age groups. This might be due to the administration of

gemcitabine with or without Nab-paclitaxel more often in this already selected patient group, since these chemotherapeutic regimens are less toxic compared to FOLFIRINOX [7]. It might also suggest that the toxicity of chemotherapy in elderly patients is acceptable.

It has been suggested that age itself is not a negative prognostic factor for survival [35,36]. The performance score and comorbidity (CCI score) are proven prognostic factors [37–40]. Age itself decreases the probability of receiving treatment, as seen in our results as well [19,41,42]. Literature reported that approximately half of the elderly patients are treated with chemotherapy, which is in line with our results [19,20]. Furthermore, we observed that about half of the patients treated with best supportive care specifically chose this treatment strategy over chemotherapy. Unfortunately, we do not know which factors contributed to this shared decision-making process. In previous studies, it was observed that elderly patients are not always properly informed of their diagnosis and sometimes they are treated according to their physicians or family's preferences [15,43]. In our cohort, all patients gave informed consent to participate in this study, so it is unlikely that they were not informed about their diagnosis and treatment options.

This study has several limitations. First, information about frailty in the elderly patients is lacking. Although this study reports about the clinical condition of all patients, due to the retrospective nature of this study frailty scores are not available. The Comprehensive Geriatric Assessment (CGA) is shown effective in geriatric oncology by identifying vulnerable elderly and optimizing cancer and overall treatment and should be recommended to use in the decision-making process [44]. Second, there might be referral bias. All included patients were presented at the multidisciplinary team meeting in the referral hospitals. There is a possibility that some

patients, especially those with a poor performance status or high age, were not referred to the participating expert pancreatic centers and could therefore not be included. Third, our true elderly population consists of patients aged 75 years and older. Currently, there is no consensus on who are the real elderly patients and different age thresholds are suggested in literature [45]. Some studies use the definition of octogenarians (≥ 80 years) to describe elderly patients. In our cohort, however, there were too few patients aged ≥ 80 years ($n=19$) for a valid analysis. Fourth, due to the retrospective nature of this study, there are missing data. Although we know if patients were treated with best supportive care due to a poor condition or by choice, we do not know the exact considerations leading to this decision.

In conclusion, in this multicenter LAPC cohort selected elderly patients, who are treated with chemotherapy, have similar survival as younger patients. Therefore, chemotherapy should probably be considered more often in fit elderly patients and be taken in account in the process of shared decision-making.

Author contribution

Study concepts and design: LJHB, MSW, HCVS, MGB, IQM.
Data acquisition: all authors.
Statistical analysis, data analysis and interpretation: LJHB, MSW.
Manuscript preparation: LJHB.
Manuscript editing and review: all authors.
Final approval of the manuscript: all authors.

Declaration of competing interest

The authors have no financial interests in relation to the work. Outside the work JdVG reports grants and non-financial support from Servier; IdH reports grants from Roche Pharmaceutical, QPS/RanD, and Medtronic; VEdM reports grants from Stichting Louise Vehmeijer and NWO and travel grants from Astellas, and from NeoVii; JWDG has received personal fees from Bristol-Myers Squibb, Roche, Pierre-Fabre, Servier, MSD, Novartis; MRM reports grants, personal fees and non-financial support from Angiodynamics, grants and personal fees from Medtronic Covidien, and non-financial support from Cascination; JWW reports research grants from Servier, Halozyme, Novartis, Celgene, Astra Zeneca, Pfizer, Roche, Amgen, Merck and a consulting/advisory role for Servier and Celgene; NHM reports advisory board fees for her institution from BMS, Eli Lilly, Servier, and MSD; HCVS, MGB and IQM have received research grants from the Dutch Cancer Society. For all other authors, there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pan.2020.11.012>.

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