Improving outcomes of pancreatic surgery

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CHAPTER 3

Treatment and survival of elderly patients with stage I-II pancreatic cancer: a report of the EURECCA Pancreas Consortium

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ABSTRACT

Background: Elderly patients with pancreatic cancer are underrepresented in clinical trials resulting in a lack of evidence. The aim of this study was to compare treatment and overall survival (OS) of patients ≥70 years with stage I-II pancreatic cancer in the EURECCA Pancreas Consortium.

Methods: This was an observational cohort study of the Belgian (BE), Dutch (NL) and Norwegian (NOR) cancer registries. The primary outcome was OS. Secondary outcomes were resection, 90-day mortality after resection, and (neo)adjuvant and palliative chemotherapy.

Results: In total, 3624 patients were included. Resection (BE: 50.2%; NL: 36.2%; NOR: 41.3%; P<0.001), use of (neo)adjuvant chemotherapy (BE: 55.9%; NL: 41.9%; NOR: 13.8%; P<0.001) and palliative chemotherapy (BE: 39.5%; NL: 6.0%; NOR: 15.7%; P<0.001) differed. Ninety-day mortality differed (BE: 11.7%; NL: 8.0%; NOR: 5.2%; P<0.001). Median OS in patients with resection (BE: 17.4; NL: 15.9; NOR: 25.4 months; P<0.001) and in patients without resection (BE: 7.0, NL: 3.9, NOR: 6.5 months; P<0.001) differed.

Conclusions: Differences were observed in treatment and OS in patients ≥70 years with stage I-II pancreatic cancer between the population based cancer registries. Future studies should focus on selection criteria for (non)-surgical treatment in older patients, so that clinicians can tailor treatment.

INTRODUCTION

For pancreatic cancer, very little progress has been made in terms of mortality rates over the past decades.[1] Resection combined with systemic treatment offers the best chance for prolonged survival. Resectability is mainly determined by contact between the tumor and the venous and arterial vasculature.[2] Patients with stage I-II pancreatic cancer are generally considered eligible for resection. Unfortunately, about 20% of all patients are resectable due to advanced or metastatic disease at diagnosis.[3] Still, even after tumor resection of stage I-II pancreatic cancer, prognosis is poor with a median overall survival (OS) of 17-30 months.[4]

The most recent European Society of Medical Oncology (ESMO) guideline does not consider advanced age a contra-indication for resection, but states that comorbidities and poor functional status can be a reason to refrain from resection.[5] The National Comprehensive Cancer Network (NCCN) guideline is largely similar to the ESMO guideline.[6] Although no statements are made regarding advanced age directly, the guideline states that performance status should be taken into account when considering treatment strategy. Older cancer patients are often underrepresented in clinical trials, possibly due to the strict inclusion criteria.[7] Recently, a study with population-based data of multiple pancreatic cancer registries, showed that the median age at diagnosis is 70 years.[8] This clearly differs from large randomized controlled trials in pancreatic cancer in which the median age is 61-65 years.[9-12] There is a lack of evidence on treatment and survival of elderly patients with pancreatic cancer.

The EUropean REgistration of Cancer CAre (EURECCA) consortium, established by the European CanCer Organisation (ECCO), investigates differences in treatment and outcomes of patients in a real world scenario by using cancer registry data.[13] Previous studies from the EURECCA Pancreas Consortium showed considerable variations in treatment and outcomes.[14,15]

The aim of this study was to compare treatment strategies and survival outcomes of patients ≥70 years with stage I-II pancreatic cancer in the Belgian (BE), Dutch (NL) and Norwegian (NOR) national cancer registries from the EURECCA Pancreas Consortium.

METHODS

Design and patient selection

This is an observational cohort study of three cancer registries in the EURECCA Pancreas Consortium reported according to the STROBE criteria.[16] The BE, NL and NOR national cancer registries were selected because of data quality, data availability and similarity regarding design and organization (Table S1; Supplementary Material). Also cancer incidence and life expectancy are largely similar between the national cancer registries.[17] Patients ≥70 years with pancreatic adenocarcinoma stage I-II, diagnosed from 2012 through 2016 (2012 through 2015 for BE), were included. Patients ≥70 years were included according to the definitions of 'elderly' of the International Society of Geriatric Oncology (http://siog.org/content/defining-elderly). An overview of stage distribution per cancer registry is provided in Table S2 (Supplementary Material). Patients with other malignancies were not excluded, because pancreatic cancer is often determinative for the prognosis. In case of synchronous pancreatic cancer, the tumor with the highest known stage was used.

Data collection, definition and preparation

Anonymous data obtained from the cancer registries were: 1) patient and tumor related variables: sex, age, tumor topography, tumor morphology, tumor stage; 2) treatment related variables: tumor resection, chemotherapy, radiotherapy; and 3) outcome related variables: vital status, follow-up.

Patients were divided into age groups: 70-74, 75-79 and ≥80 years. The International Classification of Disease for Oncology (ICD-O-3) was used for tumor topography and morphology.[18] Pancreatic cancer were identified through tumor topography codes (C25.0, C25.1, C25.2, C25.3, C25.7, C25.8, C25.9) and morphological codes (8000-8009, 8010-8012, 8014-8049, 8050-8089, 8140-8149, 8154, 8158, 8159, 8161, 8163-8169, 8171-8179, 8181-8239, 8244-8245, 8250-8311, 8313-8389, 8440-8499, 8500-8549, 8550-8559, 8560-8579). For NOR, also morphological codes 690099 and 699999 (no or unknown microscopic examination) were included, since similar patients are coded as 8000 in the BE and NL cancer registry. Unless patients with codes 690099 and 699999 were diagnosed by death certificate only, these patients are not included in the BE and NL cancer registry.

The seventh edition of the TNM classification was in use during the study period and was therefore used for tumor staging in BE and NL.[19] The pTNM stage was used in patients who underwent tumor resection and the cTNM stage was used in patients who did not undergo tumor resection. In case of missing pTNM stage variables for patients who underwent tumor resection, cTNM stage variables were used when available. In NOR tumor stage was categorized as localized, regional or distant disease. For analyses,

localized and regional tumor disease were included. In case of missing data on tumor resection, chemotherapy and radiotherapy it was considered as 'no'. No distinction was made between neo- and adjuvant non-surgical treatment since this data was not available for NOR. OS was calculated from the day of diagnosis or tumor resection until the date of death or last follow-up.

Outcomes and comparisons

The primary outcome was OS. Secondary outcomes were tumor resection and 90-day mortality after tumor resection, use of non-surgical treatment strategies ((neo)adjuvant and palliative chemotherapy and radiotherapy). The main comparison was focused at assessing differences in the three cancer registries. Subgroup analyses were performed comparing per age group between the cancer registries (in case of ≥60 events).

Statistical analyses

Statistical analyses were performed using SPSS Inc. for Windows (version 23.0). Categorical data were reported as numbers (percentages) and compared using the Chi square test. Multivariable binary logistics regression was used to assess predictive factors (cancer registry, age group) for tumor resection and 90-day mortality after tumor resection and use of non-surgical treatment strategies ((neo)adjuvant and palliative chemotherapy and radiotherapy) (in case of ≥60 events). Survival analyses were performed separately for patients who underwent tumor resection and patients who did not undergo tumor resection. Kaplan-Meier curves were used to estimate median OS and the 95% confidence interval (CI) and log-rank tests were used to compare OS. Multivariable Cox regression were used to assess predictive factors (cancer registry, age group) for OS. BE and age group 70-74 were the reference categories in the multivariable analyses. Sensitivity analyses were performed, excluding patients who deceased within 90 days after tumor resection or diagnosis and including chemotherapy as additional factor to assess the influence on OS and minimize confounding by indication. In patients who did not undergo tumor resection, a sensitivity analysis was performed only with patients in which the tumor was pathologically confirmed. The original results were considered robust if the sensitivity analyses showed similar results. A $P<0.05$ was considered as statistically significant for all analyses.

RESULTS

Patient and tumor characteristics

In total, 3624 patients were included: 1002 (27.6%) from BE, 1973 (54.4%) from NL, and 649 (17.9%) from NOR (Table 1). Distribution of sex was comparable between the cancer registries. Age group distribution was largely similar. Most tumors were stage II/ regional stage (72.1% in BE; 67.4% in NL; 72.0% in NOR).

Table 1. Patient and tumor characteristics by cancer registry.

		Cancer registry					
		BE		NL		NOR	
		N	%	N	%	N	%
Total		**1002**	**27.6**	**1973**	**54.4**	**649**	**17.9**
Age group	**70-74**	300	29.9	545	27.6	216	33.3
	75-79	310	30.9	564	28.6	166	25.6
	≥80	392	39.1	864	43.8	267	41.1
Sex	**Male**	458	45.7	894	45.3	295	45.5
	Female	544	54.3	1079	54.7	354	54.5
Stage[a]	**IA**	79	7.9	158	8.0	182	28.0
	IB	201	20.1	485	24.6		
	IIA	226	22.6	552	28.0	467	72.0
	IIB	496	49.5	778	39.4		

[a]For NOR, no distinction was made for stage IA/IB and IIA/IIB.

Treatment strategies

Tumor resection

The tumor resection rate differed between the cancer registries: 50.2% in BE, 36.2% in NL, and 41.3% in NOR (P<0.001; Figure 1A). Subgroup analysis showed a similar tumor resection rate in age group 70-74 (P=0.424) and different tumor resection rates in the higher age groups between the registries (both P<0.001).

In multivariable analyses, patients in NL (OR=0.54, 95% CI=0.46-0.65) and NOR were less likely (OR=0.65, 95% CI=0.52-0.81) to undergo tumor resection compared to BE (Table 2). Patients in age group 75-79 (OR=0.61, 95% CI=0.51-0.73) and age group ≥80 (OR=0.10, 95% CI=0.09-0.13) were less likely to undergo tumor resection compared to age group 70-74.

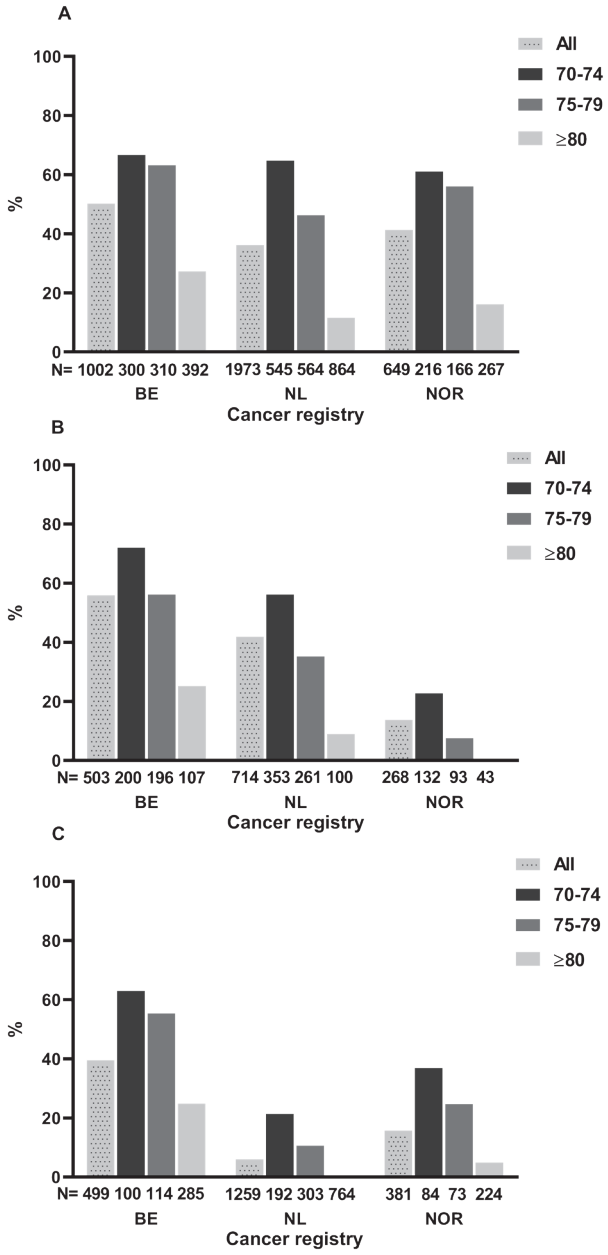

Figure 1 A-C. Treatment strategies: (A) tumor resection by cancer registry and age group, (B) (neo-)adjuvant chemotherapy by cancer registry and age group, (C) palliative chemotherapy by cancer registry and age group.

Table 2. Multivariable analyses for treatment strategies.

		Tumor resection[a]		(Neo)adjuvant chemotherapy[b]		Palliative chemotherapy[c]	
		OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Cancer registry	**BE**	**Reference**		**Reference**		**Reference**	
	NL	0.54 (0.46-0.65)	<0.001	0.43 (0.34-0.56)	<0.001	0.08 (0.05-0.10)	<0.001
	NOR	0.65 (0.52-0.81)	<0.001	0.09 (0.06-0.13)	<0.001	0.22 (0.15-0.32)	<0.001
Age group	**70-74**	**Reference**		**Reference**		**Reference**	
	75-79	0.61 (0.51-0.73)	<0.001	0.43 (0.34-0.55)	<0.001	0.54 (0.38-0.75)	<0.001
	≥80	0.10 (0.09-0.13)	<0.001	0.10 (0.07-0.15)	<0.001	0.10 (0.07-0.14)	<0.001

OR: odds ratio; CI: confidence interval
[a]Tumor resection in the total cohort (N=3624).
[b]Chemotherapy before or after tumor resection or both (N=1485).
[c]Chemotherapy in patients who did not undergo tumor resection (N=2139).

Non-surgical treatment in patients who underwent tumor resection

The use of (neo)adjuvant chemotherapy differed between the cancer registries: 55.9% in BE, 41.9% in NL and 13.8% in NOR (P<0.001; Figure 1B). Subgroup analysis showed that in all age groups the use of (neo)adjuvant chemotherapy differed between the cancer registries (all P<0.001). In multivariable analyses, patients in NL (OR=0.43, 95% CI=0.34-0.56) and NOR (OR=0.09, 95% CI=0.06-0.13) were less likely to receive (neo)adjuvant chemotherapy compared to BE (Table 2). Patients in age group 75-79 (OR=0.43, 95% CI 0.34-0.55) and age group ≥80 (OR=0.10, 95% CI=0.07-0.14) were less likely to receive (neo)adjuvant chemotherapy compared to age group 70-74.

The use of (neo)adjuvant radiotherapy was similar between the cancer registries: 4.0% in BE, 2.2% in NL, and 3.7% in NOR (P=0.183).

Non-surgical treatment in patients who did not undergo tumor resection

The use of palliative chemotherapy differed between the cancer registries: 39.5% in BE, 6.0% in NL and 15.7% in NOR (P<0.001; Figure 1C). Subgroup analysis showed that in all age groups the use of palliative chemotherapy differed between the cancer registries (all P<0.001). In multivariable analyses, patients in NL (OR=0.08, 95% CI=0.05-0.10) and NOR (OR=0.22, 95% CI=0.15-0.32) were less likely to receive palliative chemotherapy compared to BE (Table 2). Patients in age group 75-79 (OR=0.54, 95%CI=0.38-0.75) and age group ≥80 (OR=0.10, 95% CI=0.07-0.15) were less likely to receive palliative chemotherapy compared to age group 70-74.

The use of palliative radiotherapy differed between the cancer registries: 7.4% in BE, 1.6% in NL, and 0.7% in NOR (P<0.001).

Survival

Ninety-day mortality after tumor resection

Ninety-day mortality after tumor resection differed between the cancer registries: 11.7% in BE, 8.0% in NL, and 5.2% in NOR (P<0.001; Figure 2). Subgroup analysis showed different 90-day mortality after tumor resection in age group 70-74 (P=0.012) and similar 90-day mortality after tumor resection in age group 75-79 (P=0.138) and age group ≥80 (P=0.324) between the cancer registries. In multivariable analyses, patients in NL (OR=0.64, 95% CI=0.43-0.95) and NOR (OR=0.38, 95% CI=0.20-0.72) were less likely to experience 90-day mortality after tumor resection compared to BE (Table 3). Age group was not a significant predictive factors for 90-day mortality after tumor resection.

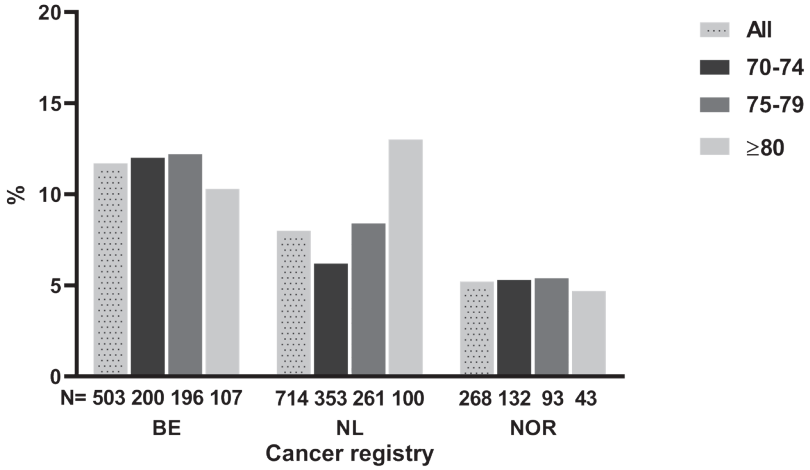

Figure 2. Ninety-day mortality after tumor resection by cancer registry and age group.

Overall survival of patient who underwent tumor resection

Median OS in patients who underwent tumor resection differed between the cancer registries: 17.4 (15.3-19.4) months in BE, 15.9 (14.4-17.5) months in NL, and 25.4 (21.6-29.2) months in NOR (P<0.001; Figure 3A). Subgroup analysis showed different OS in age group 70-74 between the cancer registries and similar OS in age group 75-79 and age group ≥80 (Figure S1A-C). In multivariable analyses, patients in NL showed similar OS (HR=1.07, 95% CI=0.93-1.22) and patients in NOR showed better OS (HR=0.72, 95% CI=0.60-0.87) compared to BE (Table 3). Patients in age group 75-79 (HR=1.23, 95% CI 1.07-1.40) and age group ≥80 (HR=1.30, 95% CI=1.10-1.54) showed worse OS compared to age group 70-74.

In the sensitivity analysis without patients who deceased within 90 days after tumor resection, patients who received (neo)adjuvant chemotherapy showed better OS compared to (neo)adjuvant chemotherapy naïve patients and the results for cancer registry and age group were robust (Table 4 and Table S3, Supplemental Material). Detailed analyses by cancer registry and age group showed inconsistent results of OS of patients who received (neo)adjuvant chemotherapy versus (neo)adjuvant chemotherapy naïve patients (Table S4, Supplemental Material).

Overall survival of patients who did not undergo tumor resection

Median OS in patients who did not undergo tumor resection differed between the cancer registries: 7.0 (6.2-7.8) months in BE, 3.9 (3.5-4.3) months in NL, and 6.5 (5.0-8.0) months in NOR (P<0.001; Figure 3B). Subgroup analysis showed different OS in all age groups between the cancer registries (Figure S2A-C). In multivariable analyses, patients in NL (HR=1.46, 95% CI=1.31-1.62) and NOR (HR=1.35, 95% CI=1.18-1.55) showed worse OS compared to BE (Table 3). Patients in age group 75-79 showed similar (HR=1.12, 95% CI 0.97-1.29) and age group ≥80 showed worse OS (HR=1.28, 95% CI=1.14-1.44) compared to age group 70-74.

In the sensitivity analysis without patients who deceased within 90 days after diagnosis, patients who received palliative chemotherapy did not show better OS compared to palliative chemotherapy naïve patients and the results for cancer registry and age group were robust (Table 4 and Table S3, Supplemental Material). Detailed analyses by cancer registry and age group showed inconsistent results of OS of patients who received palliative chemotherapy versus palliative chemotherapy naïve patients (Table S4, Supplemental Material). In the sensitivity analysis, with patients in which the tumor was pathologically confirmed, results regarding cancer registries, age group and palliative chemotherapy were robust.

Table 3. Multivariable analyses for survival.

		90-day mortality after tumor resection[a]		Overall survival of patients who underwent tumor resection[b]		Overall survival of patients who did not undergo tumor resection[c]	
		OR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Cancer registry	**BE**	Reference		Reference		Reference	
	NL	0.67 (0.45-0.98)	0.040	1.07 (0.93-1.22)	0.340	1.46 (1.31-1.62)	<0.001
	NOR	0.42 (0.23-0.77)	0.005	0.72 (0.60-0.87)	0.001	1.35 (1.18-1.55)	<0.001
Age group	**70-74**	Reference		Reference		Reference	
	75-79	1.18 (0.79-1.76)	0.433	1.23 (1.07-1.40)	0.001	1.12 (0.97-1.29)	0.111
	≥80	1.30 (0.79-2.13)	0.307	1.30 (1.10-1.54)	0.002	1.28 (1.14-1.44)	<0.001

OR: odds ratio; CI: confidence interval; HR: hazard ratio
[a]Ninety-day mortality in patients who underwent tumor resection (N=1485).
[b]Overall survival of patients who underwent tumor resection (N=1485).
[c]Overall survival of patients who did not undergo tumor resection (N=2139).

Table 4. Sensitivity analyses for overall survival, excluding patients who deceased within 90 days after diagnosis or tumor resection, by age group and treatment strategy.

					Age group								
Treatment strategy	**Total**			**70-74**			**75-79**			**≥80**			
	N	**%**	**OS (95%CI)[a]**	**N**	**%**	**OS (95%CI)[a]**	**N**	**%**	**OS (95%CI)[a]**	**N**	**%**	**OS (95%CI)[a]**
Tumor resection + (neo)adjuvant chemotherapy	602	23.2	22 (19-25)	366	41.6	24 (20-28)	200	24.8	20 (18-23)	36	3.9	21 (13-30)
Tumor resection alone	752	28.9	18 (17-20)	266	30.3	22 (18-26)	298	37.0	16 (14-18)	188	20.5	17 (15-19)
Palliative chemotherapy	293	11.3	9 (8-11)	118	13.4	11 (9-13)	101	12.5	7 (2-12)	74	8.1	10 (8-11)
No treatment	951	36.6	8 (7-9)	129	14.7	12 (10-13)	205	25.5	8 (7-9)	617	67.4	8 (7-9)
Total	**2599**	**100**	**13 (12-14)**	**879**	**100**	**18 (17-20)**	**805**	**100**	**14 (12-15)**	**915**	**100**	**10 (9-10)**

[a]Median overall survival in months after tumor resection (patients who underwent tumor resection) or after diagnosis (patients who did not undergo tumor resection) and 95% confidence interval

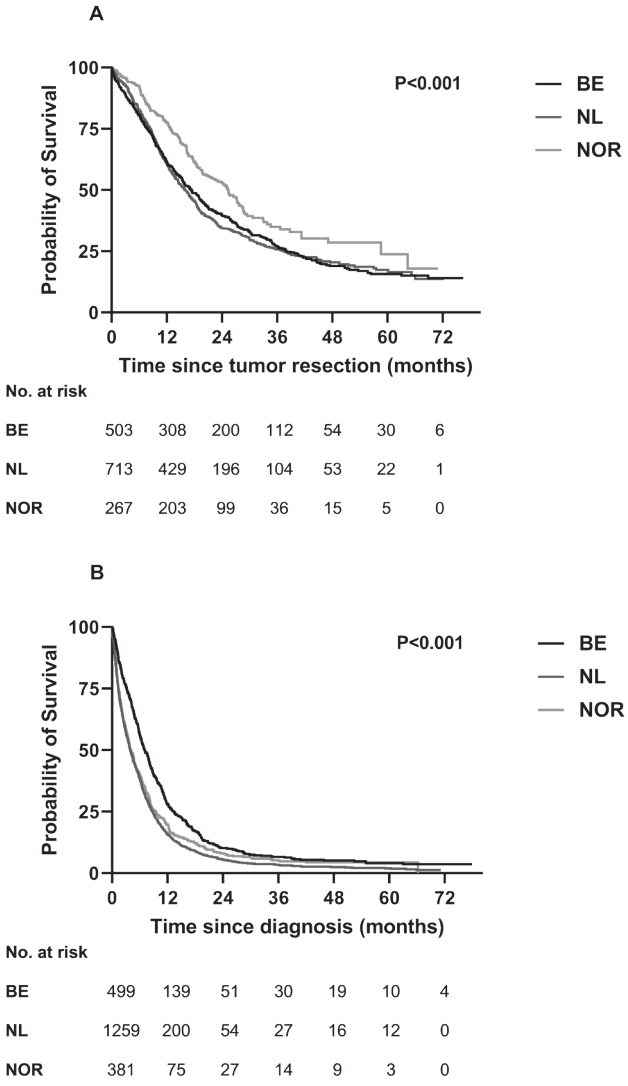

Figure 3 A-B. Overall survival by cancer registry: (A) patients who underwent tumor resection, (B) patients who did not undergo tumor resection.

DISCUSSION

In this study, treatment and survival of patients ≥70 years with stage I-II pancreatic cancer were evaluated in three European population based cancer registries. Variations were observed for tumor resection rate (ranging 36-50%), (neo)adjuvant chemotherapy (ranging 14-56%) and palliative chemotherapy (ranging 6-40%). Subgroup analysis showed

that patients in the age group 70-74 had a similar tumor resection rate between the cancer registries, which was different in the older age groups. The use of (neo-)adjuvant and palliative chemotherapy was different in all age groups between the cancer registries. The use of (neo-)adjuvant and palliative radiotherapy was low. Ninety-day mortality after tumor resection was lower in NL and NOR compared to BE. In patients who underwent tumor resection, OS in NOR was better compared to BE and NL was similar to BE. Overall, a better OS was observed in patients who received (neo)adjuvant compared to chemotherapy naïve patients. In patients who did not undergo tumor resection, OS in BE was better compared to NL and NOR.

Although the TNM staging system is not directly translatable to widely used resectability criteria[5], the low resection rate in this study, compared to previously reported[20], is noteworthy and could be explained by the inclusion of patients ≥70 years. Also, some patients with may have anatomically resectable disease, yet have unfavourable biological (high CA19.9) and conditional (poor functional status) factors.[21] An important observation is that only in the age group 70-74 tumor resection rate was similar between the cancer registries. According to the ESMO and NCCN guideline, a poor functional status, and not advanced age only, can be a good reason to be more retained by clinicians or patients.[5,6] Unfortunately, no data (e.g. ASA, ECOG score) were available to investigate this. Variation between the cancer registries regarding the cultural factors that influence the decision making for treatment in elderly patients might also be an explanation.[22,23] Despite the higher tumor resection rates in BE and NOR in the older age groups, which could have illustrated poor patient selection, 90-day mortality after resection was similar. Only in NL, 90-day mortality after resection increased with ascending age groups. Possibly the transparent outcome indicators (mortality) in the Dutch Pancreatic Cancer Audit[24], refrains clinicians in NL in performing more tumor resections. A recent meta analyse showed elderly patients have more comorbidities, more overall complications (mainly respiratory), though a comparable mortality compared to younger patients.[25] Adequate patient selection, prehabilitation, enhanced recovery protocols, and centralization of pancreatic surgery for elderly patients might improve outcomes.[26-30] Others have advocated a multidisciplinary approach to high-risk elderly patients undergoing major surgery.[31] Several studies have illuminated the importance of geriatric assessment to improve outcomes of cancer treatment.[32,33] However, high level evidence of functional recovery of elderly patients undergoing pancreatic surgery is lacking. Surprisingly, age was not a predictive factor for functional recovery in a Canadian population-based cohort study.[34]

The use of (neo)adjuvant chemotherapy was different between the cancer registries, comparable with previous international studies.[8,15] Still, this is notable since adjuvant chemotherapy is the standard treatment.[5,6] Morbidity after surgery is not uncommon in

elderly patients and may cause omission of chemotherapy.[25,26,35] Unfortunately, these data were not available in present study. No distinction was made between neo- and adjuvant chemotherapy because NOR did not provide this. This was accepted since the use of neoadjuvant therapy was expected to be low, as the ESMO and NCCN guidelines stated that neoadjuvant therapy should be used in clinical trials and elderly patients are often not included. The sensitivity analyses showed that the differences between the cancer registries in OS after tumor resection cannot be explained by the differences in the use of (neo)adjuvant chemotherapy. It remains unknown which other factors also contribute to the differences in OS.

The largest observed difference was in the use of palliative chemotherapy between BE (40%) and NL (6%). This can be explained by the fact that the ESMO and NCCN guidelines state that palliative treatment can be considered depending on the performance status of the patient.[5] Differences can also be explained by variations in nihilistic attitudes of clinicians and patients regarding the small benefit of palliative chemotherapy in elderly pancreatic cancer patients.[36] Multiple randomized controlled trials showed improved OS and quality of life with palliative chemotherapy, but adverse events are not rare.[9,10] Exemplified by the present study, results from randomized controlled trials cannot directly be extrapolated to the elderly population due to the strict inclusion criteria. These factors should be discussed with the patient before a shared decision on treatment strategy can be made. In the sensitivity analyses, patients from BE had a better OS compared to NL and similar to NOR, which suggests that the differences in the use of palliative chemotherapy do not explain the observed differences in OS. Furthermore, palliative chemotherapy was not a significant predictive factor for OS in sensitivity analyses. The unclear pattern between (neo)adjuvant and palliative chemotherapy and OS in subgroup analyses suggests that better patient selection is needed to improve resource utilization and OS. But the results also show that tumor resection, (neo)adjuvant and palliative chemotherapy, in correctly selected patients, can provide prolonged survival.

This study has several limitations. First, although the design and organization of the national cancer registries was similar, differences in the completeness of data and patients, which could have influenced the baseline characteristics and results, have to be considered. Baseline characteristics are of paramount importance for external validity of study results and should be studied carefully.[17,37] Our findings may possibly be influenced by differences in (under)-registration of elderly patients with pancreatic cancer.[38] On the other hand, age distribution was similar in the cancer registries. Furthermore, the number of included patients per cancer registry was similar to the expected amount of patients based on the size of the cancer registry population, incidence of pancreatic cancer and the provided incidence years. The proportion of 'unknown' stage differed between the cancer registries. We hypothesized that this only marginally has influenced

our results. The majority of patients with 'unknown stage' are likely to have stage III-IV disease and do not undergo further diagnostic procedures due to poor prognosis at time of diagnosis. Also, the distribution of 'known' stages was similar between the cancer registries. Second, the seventh instead of the eighth edition of the TNM classification was used in the analyses due to data availability. As showed by external validation studies, the eight edition has more prognostic significance.[39,40] On the other hand, the eight edition was not yet in use during the study period (2012-2016). Third, this study included adjusted analyses for age group nevertheless, residual confounding cannot be ruled out. Due to the low the use of radiotherapy, adjusted analyses were not performed. In the sensitivity analyses, patients who deceased within 90 days after diagnosis or tumor resection were excluded and treatment strategies were re-investigated. In patients who did not undergo tumor resection, also the influence of patients without pathological confirmation was investigated. The sensitivity analyses showed that the original results were robust. Caution has to be taken with drawing of conclusions and indicating causal relations regarding the treatment strategies, since treatment selection bias cannot be ruled out.

To the best of our knowledge, this is the first study on elderly patients with stage I-II pancreatic cancer, in three European cancer registries, that gives insight in real world data of treatment strategies and survival. These outcomes are relevant since the pancreatic cancer population is increasing in age and these patients are underrepresented in clinical trials.[7,41] Future studies should focus on selection criteria for (non)-surgical treatment, so that clinicians can offer uniform and tailored treatment across countries and in (inter-) national randomized trials. In this tailored treatment, quality of life plays an pivotal role and studies like the Dutch Pancreatic Cancer Project (PACAP) will provide valuable data.[42]

In conclusion, treatment and survival of patients ≥70 years with stage I-II pancreatic cancer in the EURECCA Pancreas Consortium showed substantial variations between three European registries. This included the rate of tumor resection, (neo)adjuvant chemotherapy and palliative chemotherapy. The use of radiotherapy was limited. Survival of patients who underwent tumor resection and who did not undergo tumor resection also differed between the cancer registries. The findings of this study suggest that patients aged 70 years and older with stage I-II pancreatic cancer benefit of a higher tumor resection and chemotherapy administration rate.

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SUPPLEMENTARY MATERIAL

Table S1. Description of cancer registries.

	Cancer registry		
	BE	**NL**	**NOR**
Registry	Belgian Cancer Registry	Netherlands Cancer registry	Cancer Registry of Norway
Organisation	Population based	Population based	Population based
Inhabitants (x10^6)	11	17	5
Incidence years in provided dataset	2012-2015	2012-2016	2012-2016
Coverage of data	>98%	>95%	>98%
Sources of data	Pathology laboratories and use of medical claims data	Nationwide automated pathological archive (PALGA), National Registry of Hospital Discharge Diagnoses	Electronic reporting by physicians, reports from pathology laboratories, discharge and outpatient data, death registry
Collection of survival data until	01-07-2018	31-01-2018	31-12-2017
Centralisation of surgery	No	18 hospitals	No

Table S2. Distribution of stages in registries.

		Cancer registry					
		BE[a]		**NL[a]**		**NOR**	
		N	**%**	**N**	**%**	**N**	**%**
Stage/Extent	**IA**	104	2.9	167	2.6	Localised	
	IB	221	6.2	491	7.6	182	8.3
	IIA	231	6.5	564	8.7	Regional	
	IIB	513	14.4	792	12.3	465	21.1
	III	273	7.6	781	12.1	Distant	
	IV	1410	39.5	3392	52.6	1008	45.7
	Unknown	822	23.0	264	4.1	551	25.0

[a]Data from dynamic databases, numbers slightly differ from cohort included in study

Table S3. Multivariable sensitivity analyses for overall survival, excluding patients who deceased within 90 days after diagnosis or tumor resection, including cancer registry, age group and chemotherapy as factors.

		Overall survival of patients who underwent tumor resection (N=1354)		Overall survival of patients who did not undergo tumor resection (N=1243)	
		HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Cancer registry	**BE**	**Reference**		**Reference**	
	NL	1.10 (0.95-1.27)	0.127	1.29 (1.11-1.49)	0.001
	NOR	0.70 (0.57-0.87)	0.001	1.12 (0.93-1.35)	0.217
Age group	**70-74**	**Reference**		**Reference**	
	75-79	1.19 (1.03-1.38)	0.018	1.16 (0.97-1.39)	0.099
	≥80	1.20 (0.99-1.45)	0.070	1.19 (1.00-1.40)	0.040
(Neo)adjuvant chemotherapy[a]	**No**	**Reference**		-	-
	Yes	0.82 (0.71-0.94)	0.007	-	-
Palliative chemotherapy[b]	**No**	-	-	**Reference**	
	Yes	-	-	1.08 (0.92-1.27)	0.332

HR: hazard ratio; CI: confidence interval
[a]Chemotherapy before or after tumor resection or both
[b]Chemotherapy in patients who did not undergo tumor resection

Table S4. Sensitivity analyses for overall survival, excluding patients who deceased within 90 days after diagnosis or tumor resection, by cancer registry, age group and treatment strategy.

		Total			Cancer registry								
					BE			NL			NOR		
Age group	**Treatment strategy**	**N**	**%**	**OS (95%CI)[a]**	**N**	**%**	**OS (95%CI)[a]**	**N**	**%**	**OS (95%CI)[a]**	**N**	**%**	**OS (95%CI)[a]**
Total	**Tumor resection + (neo)adjuvant chemotherapy**	602	23.2	22 (19-25)	271	33.7	21 (17-25)	296	22.2	23 (19-27)	35	7.6	27 (14-40)
	Tumor resection alone	752	28.9	18 (17-20)	173	21.5	19 (15-24)	360	27.0	15 (12-17)	219	47.3	26 (23-28)
	Palliative chemotherapy	293	11.3	9 (8-11)	173	21.5	11 (10-12)	67	5.0	9 (8-11)	53	11.4	9 (8-11)
	No treatment	951	36.6	8 (7-9)	188	23.4	9 (7-11)	607	45.6	8 (8-9)	156	33.7	8 (7-9)
	Total	**2599**	**100**	**13 (12-14)**	**805**	**100**	**15 (13-16)**	**1331**	**100**	**12 (11-12)**	**463**	**100**	**16 (14-19)**
70-74	**Tumor resection + (neo)adjuvant chemotherapy**	366	41.6	24 (20-28)	140	55.1	25 (19-31)	198	44.6	24 (18-29)	28	15.5	27 (9-45)
	Tumor resection alone	266	30.3	22 (18-26)	36	14.2	26 (17-35)	133	30.0	16 (13-19)	97	53.6	34 (23-44)
	Palliative chemotherapy	118	13.4	11 (9-13)	56	22.0	12 (9-14)	36	8.1	11 (8-13)	26	14.4	10 (8-11)
	No treatment	129	14.7	12 (10-13)	22	8.7	9 (5-14)	77	17.3	7 (6-8)	30	16.6	12 (10-13)
	Total	**879**	**100**	**18 (17-20)**	**254**	**100**	**18 (16-21)**	**444**	**100**	**16 (14-18)**	**181**	**100**	**25 (19-32)**
75-79	**Tumor resection + (neo)adjuvant chemotherapy**	200	24.8	20 (18-23)	104	40.5	20 (17-24)	89	21.5	20 (15-26)	7	5.2	27 (12-42)
	Tumor resection alone	298	37.0	16 (14-18)	68	26.5	16 (10-22)	149	36.0	13 (10-16)	81	60.4	22 (17-27)
	Palliative chemotherapy	101	12.5	7 (2-12)	53	20.6	11 (10-13)	30	7.2	9 (7-11)	18	13.4	7 (2-12)
	No treatment	205	25.5	8 (7-9)	32	12.5	12 (10-14)	145	35.0	8 (7-9)	28	20.9	8 (6-9)
	Total	**805**	**100**	**14 (12-15)**	**257**	**100**	**16 (13-19)**	**414**	**100**	**11 (10-13)**	**134**	**100**	**18 (14-21)**
≥80	**Tumor resection + (neo)adjuvant chemotherapy**	36	3.9	21 (13-30)	27	9.2	26 (9-21)	9	1.9	20 (19-21)	0	0.0	-
	Tumor resection alone	188	20.5	17 (15-19)	69	23.5	17 (11-24)	78	16.5	16 (12-19)	41	27.7	20 (11-29)
	Palliative chemotherapy	74	8.1	10 (8-11)	64	21.8	10 (8-12)	1	0.2	4	9	6.1	8 (7-10)
	No treatment	617	67.4	8 (7-9)	134	45.6	8 (7-10)	385	81.4	9 (8-9)	98	66.2	8 (7-9)
	Total	**915**	**100**	**10 (9-10)**	**294**	**100**	**11 (9-12)**	**473**	**100**	**9 (9-10)**	**148**	**100**	**10 (8-12)**

[a]Median overall survival in months after tumor resection (patients who underwent tumor resection) or after diagnosis (patients who did not undergo tumor resection) and 95% confidence interval

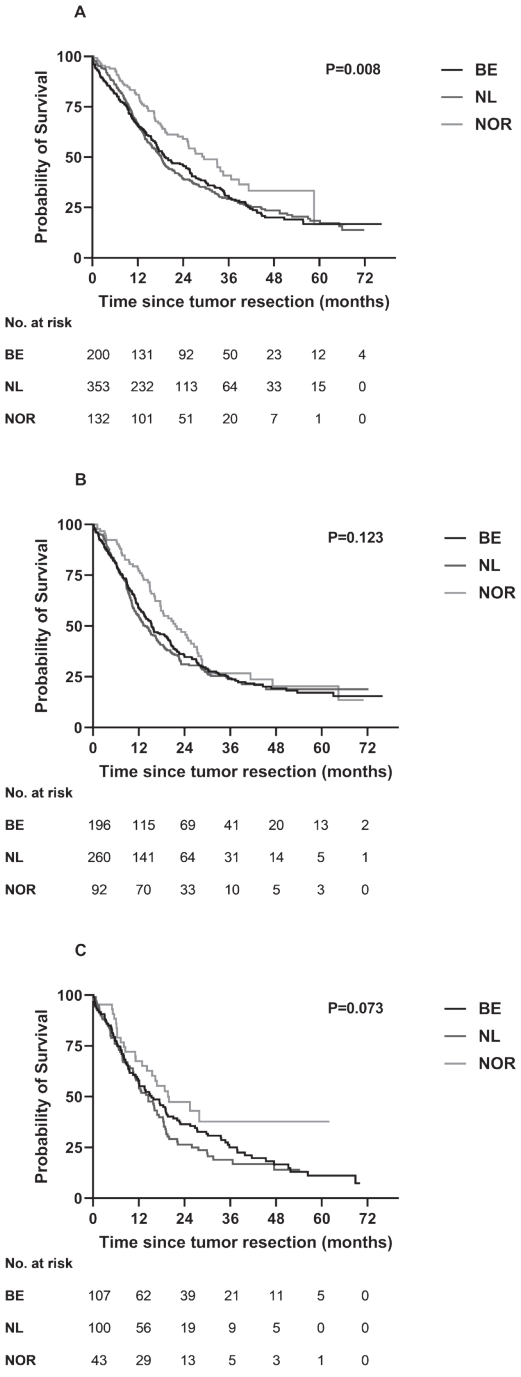

Figure S1 A-C. Overall survival of patients who underwent tumor resection by cancer registry for: (A) age group 70-74 years, (B) age group 75-79 years, (C) age group ≥80 years.

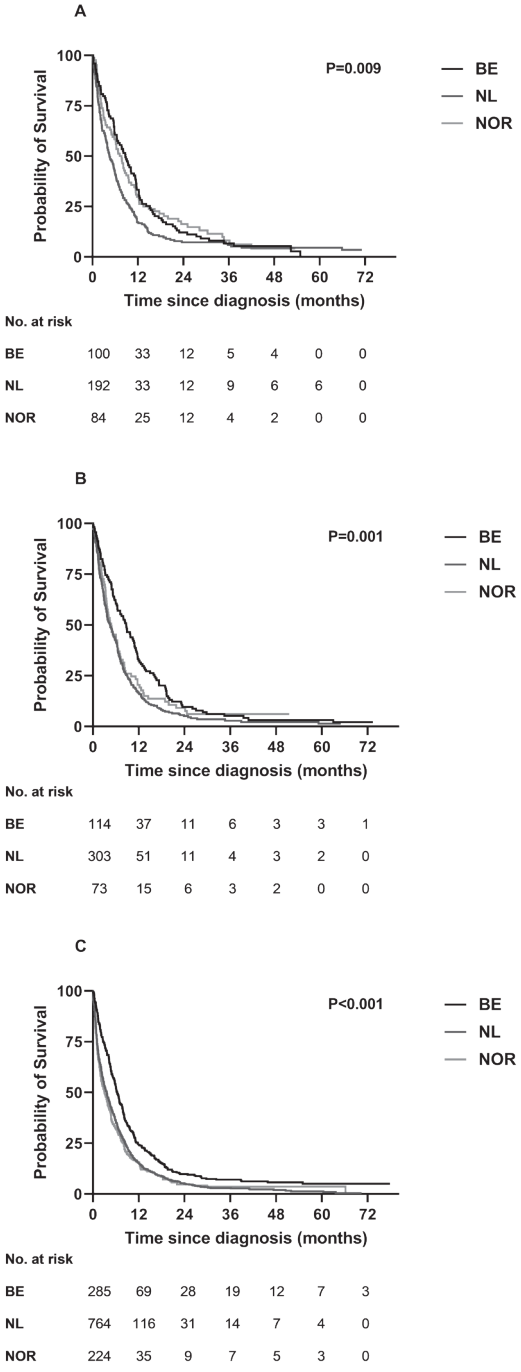

Figure S2 A-C. Overall survival of patients who did not undergo tumor resection by cancer registry for: (A) age group 70-74 years, (B) age group 75-79 years, (C) age group ≥80 years.

ASO Author Reflections: Can Utilization of Cancer Registry Data Contribute to Solving the Lack of Evidence for Older Pancreatic Cancer Patients?

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To The Editor

PAST

Pancreatic cancer has a poor prognosis with a 5-year survival of approximately 7%.[1] Only patients with stage I-II (localized disease) have a chance for long-term survival after resection. Recently, some advances were made in patients with localized disease who were treated with neoadjuvant chemoradiation therapy[2] or adjuvant FOLFIRINOX[3]. Unfortunately, the median age of patients included in these randomized controlled trials (63-67) are not representative for the general pancreatic cancer population.[4] Older patients are often not included in clinical trials, leading to a knowledge gap in treating older patients. The international EURECCA (European Registration of Cancer Care) project is a research committee supported by the European Society of Surgical Oncology. The aim of EURECCA is to utilize cancer registry data to compare and improve treatment strategies.[5]

PRESENT

In this international EURECCA study[6], treatment strategies and survival outcomes of patients 70 years and older with stage I-II pancreatic cancer were compared in the Belgian, Dutch and Norwegian national cancer registries. Large differences were observed in the use of surgery and (neo)adjuvant and palliative chemotherapy. Only 23% of patients received the current standard-of-care (tumor resection preceded or followed by chemotherapy). Even stratified for treatment strategy, overall survival differed significantly between the cancer registries. Although this study provides no insight in quality of life, it appears that adequately selected older patients and more aggressive treatment can result in better overall survival.

FUTURE

Although the quantity and quality of randomized clinical trials is increasing[7], we still expect that elderly patients will often be excluded. Therefore, the utilization of cancer registry data offers a solution in research of elderly patients. Another advantage over randomized clinical trials data, is that cancer registry data is readily available and population-based, thereby minimizing selection bias. EURECCA also aims to create awareness of the large variation in treatment strategies between cancer registries and generate new hypotheses for future research.[5] Future studies are needed to identify selection criteria for local and systemic treatment, so that clinicians can offer tailored treatment to older patients with pancreatic cancer.

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