Improving outcomes of pancreatic surgery

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PART I

INTERNATIONAL EVALUATION OF CLINICAL PRACTICE IN PANCREATIC SURGERY

CHAPTER 2

Differences in treatment and outcome of pancreatic adenocarcinoma stage I & II in the EURECCA Pancreas consortium

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Ann Surg Oncol. 2018 Nov;25(12):3492-3501. doi: 10.1245/s10434-018-6705-1. Epub 2018 Aug 27. PMID: 30151560.

ABSTRACT

Background: The EUropean REgistration of Cancer CAre (EURECCA) consortium aims to investigate differences in treatment and to improve cancer care through Europe. The aim of this study was to compare neo –and adjuvant chemotherapy (ACT) and outcome after tumor resection for pancreatic adenocarcinoma stage I & II in the EURECCA Pancreas consortium.

Methods: The eight collaborating national, regional and single center partners shared their anonymized dataset. Patients diagnosed in 2012-2013 who underwent tumor resection for pancreatic adenocarcinoma stage I & II were investigated with respect to treatment and survival and compared using uni- and multivariable logistic -and Cox regression analyses. All comparisons were performed separately per registry type: national, regional- and single center registries.

Results: In total, 2052 patients were included. Stage II was present in the majority of patients. The use of neo-ACT was limited in most registries (range: 2.8%-15.5%) and only different between Belgium and the Netherlands after adjustment for potential confounders. The use of ACT was different between the registries (range: 40.5%-70.0%), even after adjustment for potential confounders. Ninety-day mortality was also different between the registries (range: 0.9%-13.6%). In multivariable analyses for overall survival, differences were observed between the national –and regional registries, furthermore patients in ascending age groups and patients stage II showed a significant worse overall survival.

Conclusions: This study provides a clear insight in clinical practice in the EURECCA Pancreas consortium. The differences observed in (neo-)ACT and outcome give us the chance to further investigate the *best practices* and improve outcome of pancreatic adenocarcinoma.

INTRODUCTION

Pancreatic cancer (PC) is one of the few types of cancer with increasing incidence and mortality rates.[1] In 2017, the number of annual deaths in the European Union due to PC will exceed the number of death due to breast cancer.[2] Resection is the only chance for prolonged survival, unfortunately only 15-20% of PC patients are eligible for resection due to advanced -or metastatic disease at diagnosis.[3] Tumor/node/metastases (TNM) stage I & II PC are generally considered eligible for resection.[4] The European Society of Medical Oncology (ESMO) guidelines, during the study period and most recent, state that patients with a borderline resectable or locally advanced tumor should be treated with neoadjuvant chemotherapy (neo-ACT) in clinical trials whenever possible and that adjuvant chemotherapy (ACT) is considered as standard of care after curative resection for PC.[5,6] Recently, the ESPAC-4 trial showed a survival benefit in patients treated with adjuvant gemcitabine and capecitabine compared to gemcitabine alone.[7] Despite advances in (neo)-ACT, the median survival for patients with an initial resectable tumor is only 23.3 (range: 12-54) months.[8]

Previous studies have reported variations in incidence, mortality and survival in PC between countries.[9-12] The EUropean REgistration of Cancer CAre (EURECCA) consortium, established by the European CanCer Organisation (ECCO), aims to investigate differences in treatment and to improve cancer care through Europe.[13] International comparisons of (neo–)ACT and outcome in surgically treated patients with PC are sparse. Therefore, the aim of this study was to describe and compare (neo–)ACT and outcome of patients who underwent tumor resection for resectable (TNM stage I & II) pancreatic adenocarcinoma in the EURECCA Pancreas consortium.

MATERIALS AND METHODS

Study design & data preparation

This is an observational cohort study of eight partners (registries) in the EURECCA Pancreas consortium (national: Belgium (BE), the Netherlands (NL), Slovenia (SLO), Ukraine (UA) and Bulgaria (BG); regional: Catalonia (Spain) (CAT(E)) and Munich (Germany) (MU(D); and single center: Milan (Italy) (MIL(I))) who shared their anonymized dataset. Detailed description of the registries is provided in Table S1 (Supplementary). The American Joint Committee on Cancer and International Union Against Cancer TNM 7th Edition classification were used to describe stage.[4,14] In case pathology TNM variables were not informative (missing or X), clinical TNM variables were used as replacement. In case clinical TNM variables were also not informative (missing or X), pathology TNM variables were considered to be '0'. The 3rd edition of the International Classification of

Disease for Oncology was used for topographical- and morphological (i.e. pathologic diagnosis) coding.[15] Age was categorized as <65 years, 65-75 years and >75 years. Overall survival (OS) was calculated from date of surgery until date of death (event) or last follow-up (censored). Ninety-day mortality was calculated to distinguish surgery-related from disease-related death.[16]

Patient selection

All patients with pancreatic tumors (included codes: C25.0-C25.9; excluded: C25.4),[15] diagnosed in 2012-2013 (present in all registries), undergoing tumor resection, for adenocarcinoma (included codes: 8140-8380, 8500-8585; excluded: 8150-8158, 8240-8249), [15] stage I & II were included. Patients with a history of other malignancies were not excluded, since PC is most often determinative for the prognosis. BG could not confirm tumor resection and was only used in descriptive statistics in Table S2 (Supplementary). SLO and UA were not included in analyses of neo-ACT since no information was available. CAT(E) and UA were not included in analyses of ACT since no information was available.

Statistical analyses

Statistical analyses were performed using SPSS Inc. for Windows (version 23.0). Numerical data are reported as mean (standard deviation (SD)) and compared using the one-way ANOVA test. Categorical data are reported as absolute numbers (percentages) and compared using the Chi-square test. Multivariable logistics regression analyses (adjusted for sex, age group and stage) where performed for neo-ACT, ACT and 90-day mortality. Kaplan-Meier curves, Log-Rank tests and multivariable Cox regression analyses (adjusted for sex, age group, stage) where used to compare OS. For multivariable comparisons between registries, BE (national) and CAT(E) (regional) were used as reference groups (first in alphabetic order). For reasons of bias, comparisons were performed separately per registry type: national, regional- and single center registries. To assess the risk of missing data bias, sensitivity analyses were conducted by adding patients with 'unknown' stage to the original analyses. To assess the influence of 90-day mortality on the use of ACT, multivariable sensitivity analysis were performed with 90-day mortality as covariate. To assess the influence of use of (neo-)ACT on OS, multivariable sensitivity analysis were performed with (neo-)ACT as covariates. The original results were considered robust if the sensitivity analyses showed similar results. A P <0.05 was considered statistically significant for all analyses.

RESULTS

Patient & tumor characteristics

Figure S1 (Supplementary) illustrates the inclusion of patients in this study. In total, 2052 patients diagnosed in 2012-2013 underwent tumor resection for pancreatic adenocarcinoma stage I & II were included (Table 1). Distribution of males/females was largely comparable between the registries. The mean (SD) age differed between the national registries, ranging from 57.5 (11.8) years in UA to 66.7 (10.0) years in BE, and the regional registries, 67.4 (9.6) years in CAT(E) and 69.3 (9.2) years in MU(D). In all registries, stage II patients were the majority of patients undergoing tumor resection, ranging from 78.5% (UA) to 98.2% (MIL(I)). Overall, tumors were most often (73.6%) located in 'head of pancreas' and 'pancreaticoduodectomy' was performed in majority (81.2%) of patients, excluding SLO who did not specify type of resection. Table S2 (Supplementary) shows characteristics of patients for BG, who could not confirm tumor resection.

Neoadjuvant chemotherapy

Overall, the use of neo-ACT ranged from 2.8% in NL - 15.5% in MIL(I). There were no differences between the national and regional registries (Figure 1a-b).

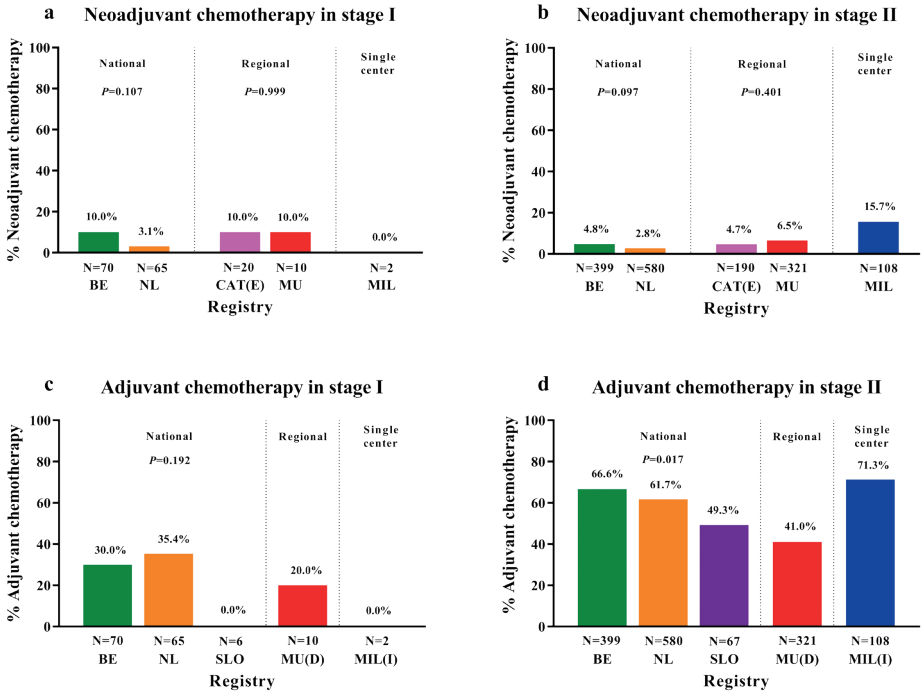

Figure 1a-d. Neo- and adjuvant chemotherapy per registry in (a) neoadjuvant chemotherapy in stage I, (b) neoadjuvant chemotherapy in stage II, (c) adjuvant chemotherapy in stage I, (d) adjuvant chemotherapy in stage II.

Table 1. Patient & tumor characteristics.

		Registry														
		National									Regional					Single center
		Belgium (*N*=469)		**The Netherlands (*N*=645)**		**Slovenia (*N*=73)**		**Ukraine (*N*=214)**			**Catalonia (*N*=210)**		**Munich (*N*=331)**			**Milan (*N*=110)**	
		N	**%**	***N***	**%**	***N***	**%**	***N***	**%**	**p-value**	***N***	**%**	***N***	**%**	**p-value**	***N***	**%**
Sex	Male	256	54.6%	329	51.0%	39	53.4%	130	60.7%	0.098	116	55.2%	161	48.6%	0.135	60	54.5%
	Female	213	45.4%	316	49.0%	34	46.6%	84	39.3%		94	44.8%	170	51.4%		50	45.5%
Age	Mean (SD)	66.7 (10.0)		66.0 (9.0)		65.6 (10.2)		57.5 (9.8)		<0.001	67.4 (9.6)		69.3 (9.2)		0.020	68.3 (9.8)	
Stage	I	70	14.9%	65	10.1%	6	8.2%	46	21.5%	<0.001	20	9.5%	10	3.0%	0.001	2	1.8%
	II	399	85.1%	580	89.9%	67	91.8%	168	78.5%		190	90.5%	321	97.0%		108	98.2%
Location	Head of pancreas	287	61.2%	525	81.4%	56	76.7%	145	67.8%	<0.001	176	83.8%	252	76.1%	<0.001	70	63.6%
	Body of pancreas	25	5.3%	18	2.8%	8	11.0%	20	9.3%		27	12.9%	16	4.8%		0	0.0%
	Tail of pancreas	35	7.5%	47	7.3%	6	8.2%	16	7.5%		7	3.3%	27	8.2%		0	0.0%
	Other pancreas	122	26.0%	55	8.5%	3	4.1%	33	15.4%		0	0.0%	36	10.9%		40[1]	36.4%
Type of surgery	Pancreatico-duodenectomy	377	80.4%	571	88.5%	0	0.0%	149	69.6%	<0.001	200	95.2%	240	72.5%	<0.001	70	63.6%
	Other[2]	92	19.6%	73	11.3%	0	0.0%	65	30.4%		10	4.8%	91	27.5%		40	36.4%
	Unknown	0	0.0%	1	0.2%	73[3]	100.0%	0	0.0%		0	0.0%	0	0.0%		0	0.0%

[1]Includes tumours from body- and tail of pancreas
[2]Other types of pancreatectomy (e.g. total- and distal pancreatectomy or enucleation)
[3]Authors confirmed these patients underwent oncological resections

Table 2. Multivariable analyses of (neo-)adjuvant chemotherapy, 90-day mortality and overall survival.

			Use of neoadjuvant chemotherapy			Use of adjuvant chemotherapy			Ninety-day mortality			Overall survival		
			Odds ratio[1,2]	95% confidence interval	p-value	Odds ratio[1,2]	95% confidence interval	p-value	Odds ratio[3]	95% confidence interval	p-value	Hazard ratio[1]	95% confidence interval	p-value
National	Registry	BE	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
		NL	0.48	0.29-0.89	0.020	0.70	0.53-0.93	0.012	0.56	0.35-0.89	0.014	1.11	0.96-1.28	0.177
		SLO	-	Not in analysis	-	0.32	0.19-0.56	<0.001	0.59	0.20-1.71	0.329	1.23	0.94-1.62	0.139
		UA	-	Not in analysis	-	-	Not in analysis	-	2.21	1.23-3.68	0.007	2.29	1.83-2.85	<0.001
	Sex	Male	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
		Female	0.97	0.53-1.79	0.928	1.16	0.89-1.49	0.273	0.36	0.23-0.56	<0.001	0.77	0.68-0.87	<0.001
	Age group	<65 years	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
		65-75 years	0.84	0.44-1.58	0.583	0.41	0.31-0.55	<0.001	2.01	1.25-3.26	0.004	1.16	1.01-1.34	0.040
		>75 years	0.40	0.13-1.20	0.101	0.08	0.05-0.12	<0.001	3.66	2.05-6.54	<0.001	1.75	1.44-2.12	<0.001
	Stage	I	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
		II	0.55	0.26-1.18	0.126	4.68	3.11-7.04	<0.001	1.26	0.69-2.30	0.446	1.86	1.49-2.31	<0.001
Regional	Registry	CAT(E)	1.00	Reference	-	-	Not in analysis	-	1.00	Reference	-	1.00	Reference	-
		MU(D)	1.43	0.66-3.06	0.363	-	-	-	1.63	0.79-3.37	0.189	1.29	1.03-1.61	0.026
	Sex	Male	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
		Female	0.92	0.45-1.88	0.821	1.36	0.87-2.12	0.181	0.87	0.50-1.68	0.671	1.01	0.81-1.25	0.929
	Age group	<65 years	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-

Table 2. Continued

		65-75 years	0.57	0.25-1.27	0.166	0.68	0.40-1.15	0.152	0.82	0.37-1.82	0.629	1.04	0.80-1.36	0.747
		>75 years	0.54	0.21-1.38	0.198	0.52	0.29-0.95	0.033	1.13	0.49-2.62	0.772	1.43	1.08-1.90	0.013
	Stage	I	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
		II	0.51	0.14-1.83	0.299	2.61	0.54-12.72	0.235	2.05	0.27-15.71	0.489	1.29	0.80-2.09	0.304
Single center	Registry	MIL(I)	-	-	-	-	-	-	-	-	-	-	-	-
	Sex	Male	1.00	Reference	-	1.00	Reference	-	-	-	-	1.00	Reference	-
		Female	1.10	0.38-3.16	0.859	1.04	0.40-2.72	0.936	-	-	-	0.82	0.53-1.27	0.365
	Age group	<65 years	1.00	Reference	-	1.00	Reference	-	-	-	-	1.00	Reference	-
		65-75 years	0.75	0.24-2.32	0.617	0.19	0.04-0.94	0.194	-	-	-	0.99	0.59-1.66	0.965
		>75 years	0.30	0.06-1.56	0.151	0.04	0.01-0.19	<0.001	-	-	-	1.62	0.92-2.85	0.094
	Stage	I	1.00	Reference	-	1.00	Reference	-	-	-	-	1.00	Reference	-
		II	-	-	0.999	-	-	0.999	-	-	-	-	-	0.963

BE, Belgium; *NL*, The Netherlands; *SLO*, Slovenia; *UA*, Ukraine; *CAT(E)*, Catalonia (Spain); *MU(D)*, Munchen (Germany); *MIL(I)*, Milan (Italy)

[1]UA provided no data on adjuvant chemotherapy therefore excluded from analyses of national registries

[2]CAT(E) provided no data on adjuvant chemotherapy therefore excluded from analyses of regional registries

[3]Multivariable analyses in the single center registry was not possible due to low number of events

Multivariable analyses showed differences in odds ratios (OR) for the use of neo-ACT between the national registries: patients in NL were less likely to receive neo-ACT compared to BE (NL: OR=0.48, 95% CI=0.29-0.89, P=0.020, Table 2). No other predictive factors where identified in the national, regional or single center registries. Sensitivity analyses with patients with 'unknown' stage added to the multivariable analyses showed similar OR.

Adjuvant chemotherapy

Overall, the use of ACT ranged from 40.5% in MU(D) - 70.0% in MIL(I). A higher proportion of ACT in stage II *versus* stage I was observed in all registries (Figure 1c-d). The proportion of patients with stage II receiving ACT varied between the national registries (*P*=0.017).

Multivariable analyses showed considerable differences in OR for the use of ACT between the national registries (Table 2). Patients in NL and SLO were significantly less likely to receive ACT compared to BE (NL: OR=0.70, 95% CI=0.53-0.93, *P*=0.012; SLO: OR=0.32, 95% CI=0.19-0.56, *P*<0.001). Furthermore, patients in ascending age group and patients with stage I were less likely to receive ACT in the national registries. In the regional- and single center registry patients in age group >75 years were also less likely to receive ACT. Sensitivity analyses with patients with 'unknown' stage added to the multivariable analyses showed similar results, except that in regional –and single center registries each ascending age group was significantly less likely to receive ACT. Sensitivity analyses with 90-day mortality as covariate in the multivariable analyses showed similar OR.

Ninety-day mortality

Ninety-day mortality differed between the national registries (*P*=0.001, Figure 2). UA (13.6%) and MU(D) (8.5%) had the highest 90-day mortality in the national –and regional registries respectively, whereas overall MIL(I) (single center registry) had the lowest 90-day mortality (0.9%).

Multivariable analyses showed considerable differences in OR for 90-day mortality between the national registries (Table 2). Compared to BE, patients in NL had lower 90-day mortality (OR=0.56, 95% CI=0.35-0.89, *P*=0.014) and patients in UA (OR=2.21, 95% CI=1.23-3.68, *P*=0.007) had higher 90-day mortality. Female and younger age group were significant protective factors for 90-day mortality in the national registries. No predictive factors where identified in the regional registries. Multivariable analyses in the single center registry was not possible due to low number of events. Sensitivity analyses with patients with 'unknown' stage added to the multivariable analyses showed similar OR.

Overall survival

OS was significantly different in the national (P<0.001) and regional (P=0.005) registries (Figure 3a-c). In multivariable analysis for OS in the national registries, UA showed a significantly different OS compared to BE (Hazard Ratio (HR)=2.29, 95% CI=1.83-2.85, P<0.001, Table 2). Female sex was a significant protective factors for OS (HR=0.77, 95% CI=0.68-0.87, P<0.001). Patients in each ascending age group (65-75 years: HR=1.16, 95% CI=1.01-1.34, P=0.040; >75 years: HR=1.75, 95% CI=1.44-2.12, P<0.001) and stage II (HR=1.86, 95% CI=1.69-2.31, P<0.001) showed worse OS. In the regional registries, MU(D) showed a significantly different OS compared to CAT(E) (HR=1.29, 95% CI=1.03-1.61, P=0.026). Age group >75 years was a significant factor with worse OS compared to age group <65 years (HR=1.43, 95% CI=1.08-1.90, P=0.013), whereas age group 65-75 years was not. Also sex and stage were not significant factors for OS. In the single center registry, only age group >75 years was a borderline significant factor with worse OS compared to age group <65 years (HR=1.62, 95% CI=0.92-2.85, P=0.094).

In addition, median (95% CI) survival of patients who received ACT was: 20.1 (18.5-21.7) months in the national-, 19.0 (15.6-22.4) months in the regional-, and 30.0 (24.4-35.6) months in the single center registries and median (95% CI) survival of ACT naïve patients: 12.1 (10.3-13.9) months in the national-, 14.0 (11.2-16.8) months in the regional-, and 19.0 (11.1-26.8) months in the single center registries, although a direct comparison is not possible.

Sensitivity analyses with patients with 'unknown' stage added to the multivariable analyses showed similar HR. Sensitivity analyses with ACT added to the multivariable analyses showed similar HR.

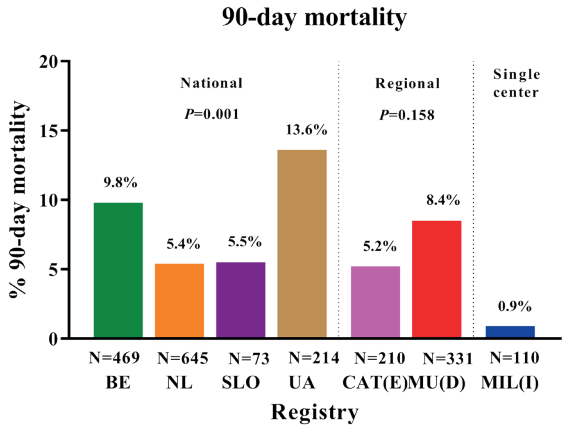

Figure 2. Ninety-day mortality rates per registry.

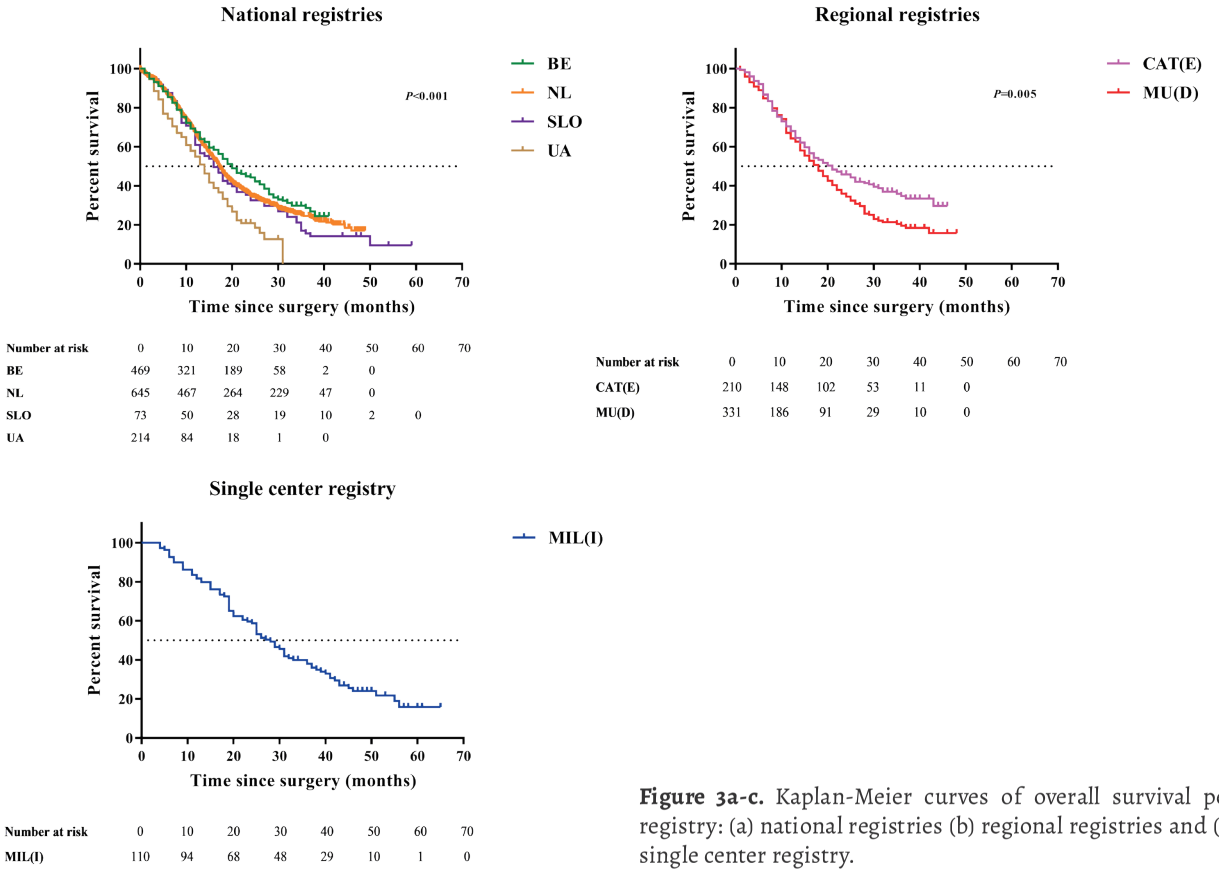

Figure 3a-c. Kaplan-Meier curves of overall survival per registry: (a) national registries (b) regional registries and (c) single center registry.

DISCUSSION

The main aim of this study was to describe and compare (neo–)ACT and outcomes of patients who underwent tumor resection for stage I & II pancreatic adenocarcinoma in the EURECCA consortium. There were some differences in the use of neo-ACT. Although the ESMO guidelines, during the study period and most recent, recommended the use of ACT, variations were observed in OR for ACT usage between national registries.[6] Also large variations in 90-day mortality and OS were observed between the registries included in this study.

Previous studies from the EURECCA consortium showed variations in the use of chemo(radiation)therapy in colon-, rectal- and breast cancer patients.[17-19] The observed variations in neo-ACT, but mainly ACT, between the registries in this study are in concordance with a recent large-scale international study of resected PC patients.[20] A possible explanation for the variations can be differences in adherence to (inter)national guidelines.[18,19] Also, cultural, socioeconomic and health-care differences may play a role in the use of (neo-)ACT.[21-23] The observation that few patients received neo-ACT was probably due to the statement by the ESMO guidelines (during the study period) that neo-ACT should be used in clinical trial settings.[6] Clinical trials are more easily accessible in specialized centers which explains the greater use of neo-ACT in the (specialized) single center registry compared to the national –and regional registries. A recent meta-analysis has shown the benefit of neo-ACT over upfront surgery.[24] An interesting international comparison would be how these results are implemented in more recent practice. A complicated postoperative course can delay or omit the use of ACT.[25] In a sensitivity analyses with 90-day mortality added to the multivariable analyses for the use of ACT, we confirmed that differences in 90-day mortality were not of influence on the differences in the use of ACT between the registries. The use of ACT decreased per ascending age group and patients in age group >75 years showed a significant worse OS in multivariable analyses in the national, regional –and single center registries. As previously investigated, elderly patients are at higher risk of postoperative complications.[26] Although centralization improved outcome of pancreatic surgery in elderly patients in a recent study, further research is needed to gain knowledge on this matter.[27]

Variations in 90-day mortality were observed between the national registries, even after adjustment for sex, age group and stage. Multiple studies have shown a lower postoperative mortality after pancreatic surgery in high- compared to low-volume hospitals.[28,29] In our study this could not be assessed, because the annual hospital volumes were not available. Nonetheless, BE and MU(D) showed a high 90-day mortality and centralization of pancreatic surgery was not implemented there during the study

period. Caution has to be taken with this statement as detailed information about perioperative treatment, likely to affect 90-day mortality, was not available.

This study showed a better survival in patients receiving ACT compared to naïve patients in the national, regional –and single center registries. This can very well be explained by confounding by indication (fit patients with a good prognosis are generally more likely to receive ACT) and therefore a justifiable comparison is not possible. The recent ESPAC-4 trial (2017), showed a significant better survival for patients treated with adjuvant gemcitabine and capecitabine compared to gemcitabine alone (28.0 (95% CI=23.5-31.5 months *versus* 25.5 (95%CI=22.7-27.9) months) after resection for PC.[7] Considering the randomized ESPAC-trial has strict inclusion criteria (e.g. full recovery after surgery, creatinine clearance ≥50 mL/min) and our study is mainly population-based, the results are largely comparable. Still, direct comparison is hampered by the differences in study design. In a sensitivity analyses with (neo-)ACT added to the multivariable analyses for OS, we confirmed that differences in ACT were not of influence on the differences in OS between the registries. Definite conclusions cannot be drawn from this sensitivity analysis since immortal time bias and confounding by indication cannot be ruled out.

Our study has several limitations. First, caution has to be taken with interpretation of the results as differences in (unmeasured) patient characteristics (e.g. patient selection for tumor resection) might have been of influence. Nevertheless, analyses were adjusted for important factors (sex, age group, stage) and still showed differences between the registries. Second, due to inherent differences between national, -regional and single center registries, which also explain the observed inter-registry-type variations, analyses had to be performed separately per registry type and lowered the statistical power (e.g. multivariable analyses for 90-day mortality was not possible in the single center registry). Third, due to missing data this study excluded some patients (e.g. 'unknown' stage or tumor resection) and registries (e.g. SLO and UA did not provide data on neo-ACT, CAT(E) and UA did not provide data on ACT and the dataset from BG could not confirm tumor resection) from certain analyses. A possible explanation for this is that the provided datasets may originally have been established for other intentions (e.g. Cancer Registry or Clinical/Surgical Audit) and thus focussed on completeness of certain (other) variables. Although most included registries are surgically driven and therefore very comparable, this probably introduced missing data bias.[30] Sensitivity analyses with patients with 'unknown' stage added to the analyses confirmed the robustness of the results of this study. Still, variables as stage and tumor resection are pivotal when investigating treatment and outcome in cancer patients. Future registration should focus on completeness and uniform use of definitions as previously stated by other member of the EURECCA consortium.[13,17] Nonetheless, this study is the first in describing

and comparing (neo-)ACT and outcome of patients undergoing tumor resection for pancreatic adenocarcinoma stage I & II in eight different European registries.

In conclusion, the results of this study give a clear insight in the clinical practice of the partners in the EURECCA Pancreas consortium. Overall, the variations illustrate the difference in implementation of universally accepted and used guidelines for treatment of pancreatic adenocarcinoma stage I & II. The differences in the use of (neo-)ACT and outcome provide us the chance to further investigate the *best practices*. Moreover, the EURECCA Pancreas consortium underlines the need for uniform registration as international comparisons will become increasingly important pillars of international guidelines.

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SUPPLEMENTARY MATERIAL

Table S1. Description of registries.

	Registry							
	National					**Regional**		**Single center**
	Belgium	**The Netherlands**	**Slovenia**	**Bulgaria**	**Ukraine**	**Catalonia**	**Munich**	**Milan**
Registry	BCR: Belgian Cancer Registry	NCR: Netherlands Cancer registry	Cancer Registry of Republic of Slovenia	BNCR: Bulgarian National Cancer Registry	NCRU: National Cancer Registry of Ukraine	Pancreatic Surgery Clinical Audit Catalonia	MCR: Munich Cancer Registry	ICH pancreatic surgery registry
Organisation	Population based	Cancer registry	Population based	Population based	Regions and central database	Clinical audit	Clinical Cancer Registry	Surgical Audit
Inhabitants (x10^6)	11	17	2	7.3	45	7.5	4.7	3.2
Incidence years in provided dataset	2004-2013	2010-2013	2012-2014	2012-2013	2012-2013	2012-2013	2010-2014	2010-2017
Coverage of national, regional or single center data	>98%	>95%	>95%%	95%	100%	100%	>95%	100%
Collection of data	Per center, data managers, pathology laboratories and use of medical claims data	Per center, data manager	Per center, data manager	13 regional centers, 1 central database	Regional center, registrars	Per center, data manager	Central data management of information provided from cancer units	Surgical staff

Table S1. Continued

Collection of survival data until	01-07-2015	01-02-2016	01-06-2017	12-01-2016	19-02-2015	01-01-2016	15-04-2016	03-08-2017
Centralisation of surgery	No	20 hospitals	2 hospitals	No	40 hospitals	10 hospitals	27 hospitals, 60% in 4 hospitals	Not applicable

Table S2. Patient & tumor characteristics from Bulgaria.

		Registry	
		National	
		Bulgaria (*N*=2496)	
	N	**%**	
Sex	**Male**	1439	57.7%
	Female	1057	42.3%
Age	**Mean (SD)**	68.1 (11.3)	
Year of diagnosis	**2012**	1240	49.7%
	2013	1256	50.3%
Stage	**0**	0	0.0%
	I	120	4.8%
	II	334	13.4%
	III	302	12.1%
	IV	1130	45.3%
	Unknown	610	24.4%
Location	**Head of pancreas**	1220	48.9%
	Body of pancreas	272	10.9%
	Tail of pancreas	140	5.6%
	Other pancreas	864	34.6%
Pathology	**Carcinoma non classified**	1187	47.6%
	Adenocarcinoma	1160	46.5%
	Neuro-endocrine	30	1.2%
	Cystic / mucinous / serous	78	3.1%
	Other[1]	41	1.6%
	Unknown	0	0.0%
Surgery[2]	**No**	1658	66.4%
	Yes	838	33.6%

[1]Includes e.g.: squamous cell carcinoma, melanoma (metastatic), liposarcoma, leiomyosarcoma, lymphomas, Gastrointestinal Stromal Tumor, pancreatoblastoma
[2]Tumor resection could not be confirmed

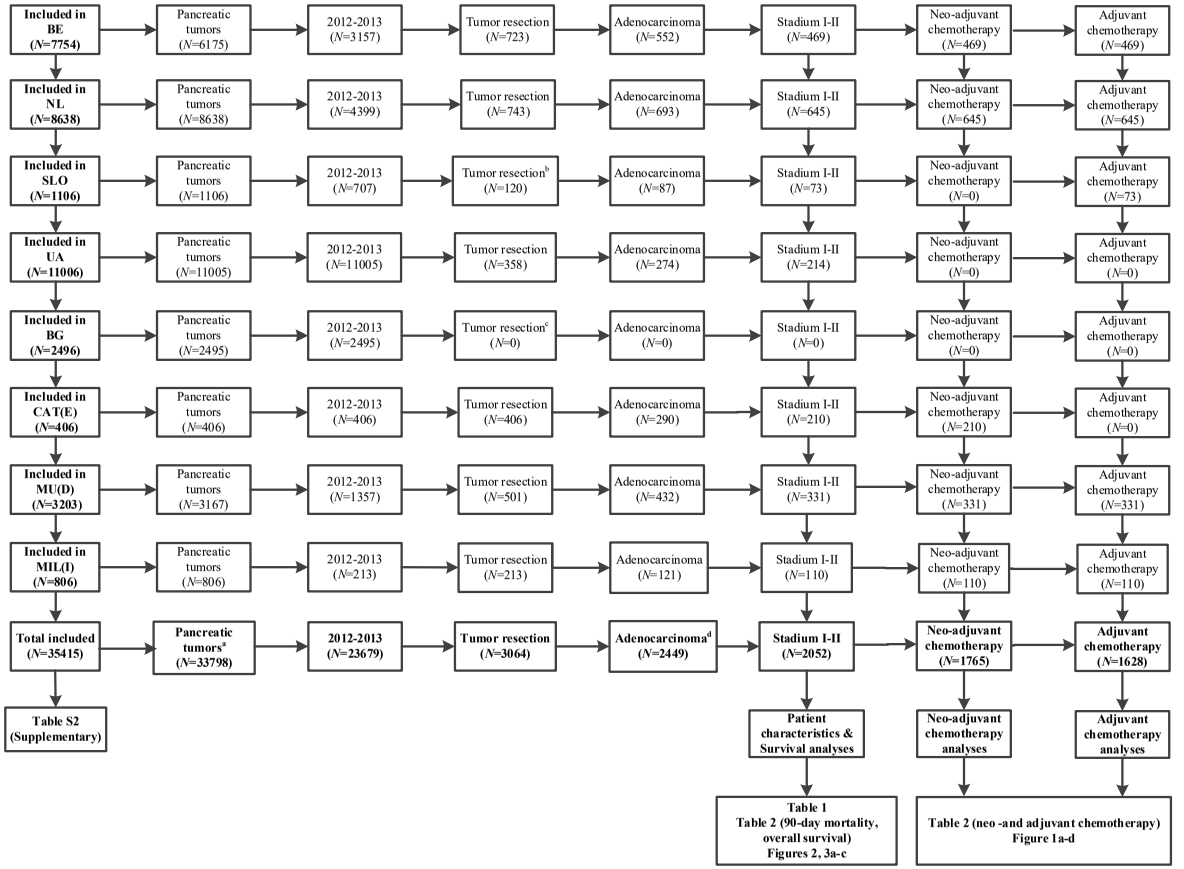

Figure S1. Flow chart of inclusion of patients per registry. [a]Included: C25.0-C25.9; excluded: C25.4.[14] [b]Includes only oncological resections. [c]Unable to confirm if patients underwent tumor resection and therefore only used in patient & tumor characteristics description.[d] Included: 8140-8380, 8500-8585; excluded: 8150-8158, 8240-8249.[14]