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Disparity in use of modern combination chemotherapy associated with facility type influences survival of 2655 patients with advanced pancreatic cancer

Morten Ladekarl[a]*, Louise Skau Rasmussen[a], Jakob Kirkegård[b], Inna Chen[c], Per Pfeiffer[d]*, Britta Weber[e], Halla Skuladottir[f], Kell Østerlind[g], Jim Stenfatt Larsen[h], Frank Viborg Mortensen[b]*, Henriette Engberg[i] iD, Henrik Møller[i,j] and Claus Wilki Fristrup[k,l]

[a]Department of Oncology, Clinical Cancer Research Center, Aalborg University Hospital, Aalborg, Denmark; [b]Department of Gastrointestinal Surgery, Aarhus University Hospital, Aarhus, Denmark; [c]Department of Oncology, Herlev and Gentofte University Hospital, Copenhagen, Denmark; [d]Department of Oncology, Odense University Hospital, Odense, Denmark; [e]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; [f]Department of Oncology, Herning Hospital, Herning, Denmark; [g]Department of Oncology, North Zealand Hospital, Hillerød, Denmark; [h]Department of Oncology, Zealand University Hospital, Naestved and Roskilde, Denmark; [i]The Danish Clinical Quality Program and Clinical Registries (RKKP), Aalborg, Denmark; [j]Danish Center for Clinical Health Services Research, Aalborg University, Aalborg, Denmark; [k]Odense Pancreas Center (OPAC), Odense University Hospital, Odense, Denmark; [l]Danish Pancreatic Cancer Database (DPCD), Denmark

ABSTRACT

Aim: Academic and high volume hospitals have better outcome for pancreatic cancer (PC) surgery, but there are no reports on oncological treatment. We aimed to determine the influence of facility types on overall survival (OS) after treatment with chemotherapy for inoperable PC.

Material and methods: 2,657 patients were treated in Denmark from 2012 to 2018 and registered in the Danish Pancreatic Cancer Database. Facilities were classified as either secondary oncological units or comprehensive, tertiary referral cancer centers.

Results: The average yearly number of patients seen at the four tertiary facilities was 71, and 31 at the four secondary facilities. Patients at secondary facilities were older, more frequently had severe comorbidity and lived in non-urban municipalities. As compared to combination chemotherapy, mono-therapy with gemcitabine was used more often (59%) in secondary facilities than in tertiary (34%). The unadjusted median OS was 7.7 months at tertiary and 6.1 months at secondary facilities. The adjusted hazard ratio (HR) of 1.16 (confidence interval 1.07–1.27) demonstrated an excess risk of death for patients treated at secondary facilities, which disappeared when taking type of chemotherapy used into account. Hence, more use of combination chemotherapy was associated with the observed improved OS of patients treated at tertiary facilities. Declining HR's per year of first treatment indicated improved outcomes with time, however the difference among facility types remained significant.

Discussion: Equal access to modern combination chemotherapy at all facilities on a national level is essential to ensure equality in treatment results.

Introduction

Pancreatic cancer (PC) is presently the tenth most common cancer worldwide [1], and projected to become the second leading cause of cancer-related death in the US within the next ten years [2]. The prognosis is dismal with a 5-year survival rate of only 3–8% [3]. However, in the last decade large, randomized trials of combination chemotherapy compared with gemcitabine have shown improvements in short-term survival of patients with metastatic PC [4,5], and treatment with gemcitabine has become preferred only for patients unfit for combination chemotherapy [6,7].

For a number of complex surgical oncological procedures (e.g., pancreatectomy and esophagectomy), a higher volume at the hospital or physician level is associated with better

outcomes [8–10]. In addition, cancer patients surgically treated at academic versus nonacademic facilities may fare better [10–12]. Similar studies in the medical management of cancers are few and primarily confined to hematological malignancies of high complexity [13–16], however these studies also in general show improved survival at academic and high volume facilities.

The complexity of management in oncology is increasing, e.g., with introduction of new predictive markers, increasingly specific treatment guidelines and staging systems, more treatment options and advanced supportive care [6,17,18]. Access to multidisciplinary teams has been recognized as an important factor for optimizing treatment and outcome [19,20]. Therefore, a relation between degree of facility

specialization and outcome may also exist for the medical treatment of non-hematological cancers.

The Danish population of PC patients is well suited for studying treatment facility factors influencing outcome. All costs for patients at all facilities are covered by the public health system and registries are virtually complete. The treatment is regulated through national guidelines [7], there are centralized procedures for drug reimbursement, National Board of Health-determined 'cancer pathway packages' (to reduce delay in work-up and time to treatment start [21]), and governmental accreditation of units handling surgery and oncology. Moreover, the treatment of cancer patients is hierarchically organized. Surgical treatment of PC is considered a highly specialized field and is carried out at four certified university centers, whereas medical treatment of PC is categorized as a basic oncological service and is offered at eight oncological facilities. These include four units at larger hospitals with comprehensive diagnostic, surgical and oncological cancer care and other modalities of high specialization (tertiary facilities), and four units at smaller hospitals with standard oncological care (secondary facilities).

The treatment course and outcome of all Danish pancreatic cancer patients have been reported previously [22]. In the current study we aimed to investigate whether the type of oncological facility had an influence on survival of patients with inoperable PC treated with chemotherapy, and whether differences in distribution of treatment and patients' characteristics influenced outcome.

Material and methods

Data source

Diagnostic and treatment data were retrieved from the Danish Pancreatic Cancer Database (DPCD), a nationwide clinical quality database [23]. The DPCD combines data from The Danish Civil Registration System, The Danish National Patient Registry and The Danish Pathology Registry with supplementary manually recorded data. These registries have high validity and completeness [24]. In the DPCD, all patients in Denmark with a diagnosis of pancreatic or periampullary cancer, except patients with neuroendocrine tumors and patients diagnosed at autopsy, are included. The average yearly incidence in DPCD is almost 950 patients. The completeness of the registry has gradually improved from 76% the first year (2011) to 95–100% in 2018 [23,25].

Patients and variables

From 1 January 2012 to 31 December 2018, we prospectively registered in the DPCD 2,657 patients, who had received chemotherapy as their first treatment. According to national guidelines, all patients that received initial chemotherapy had non-resectable disease or were medically inoperable [7]. Therefore, none of the included patients had prior surgery or chemotherapy for pancreatic cancer. We excluded 2 patients due to emigration. Hence, 2,655 patients were included for final analysis. We classified patients according to the hospital facility at which their first oncological visit was registered. Only 39 patients (1.5%) were registered at more than one oncological facility during their disease course.

From DPCD we retrieved information on gender, age, pre-treatment clinical stage (cM0 or cM1), subsequent resection, participation in a standardized cancer pathway, type of 1st line chemotherapy and numbers of further lines of chemotherapy. Type of 1st line chemotherapy was defined by the first 3 series recorded. Chemotherapy was categorized into gemcitabine monotherapy, gemcitabine combination regimens, Folfirinox, and others. Treatment of 60 patients was at one institution erroneously registered as gemcitabine monotherapy wherefore data was manually corrected.

The Charlson Comorbidity Index (CCI) score [26] was calculated from the Danish National Patient Registry from each patient's medical history registered in the decade preceding their PC diagnosis. We defined three levels of comorbidity: low (CCI score 0), moderate (CCI score 1–2) and severe (CCI score >2). Performance status or tobacco use were not recorded.

The cM-stage was cross referenced with the National Pathology Registry. This resulted in a change of stage in a total of 626 patients (24%) to pathological M1 given malignant biopsies from a metastatic lesion at the time of diagnosis.

We also retrieved information on residential municipality at the time of cancer diagnosis. We used the official classification from the Danish Ministry of Environment and Food to classify patients into four types of municipalities: remote area, rural, regional and metropolitan municipality.

Treatment facility characteristics

Facilities were classified as either secondary or tertiary referral centers. In this aspect, the oncological unit at Herlev University Hospital, Copenhagen, and the surgical unit at Rigshospitalet, Copenhagen, were considered a common unit, geographically distributed only 10 km apart. There were 4 tertiary center facilities at larger hospitals with comprehensive diagnostic, surgical and oncological cancer care, all having inhouse pancreatic surgery, multidisciplinary team conferences and other highly specialized modalities. There were 4 secondary facilities at smaller hospitals with standard oncological care and without inhouse pancreatic surgery. One of these facilities first started treating patients in 2017.

Study outcome

The primary outcome of interest was overall survival (OS) measured from the date of the first chemotherapy. We followed each subject until death, emigration, or 15 June 2020, whichever occurred first. Ninety-two patients (3.5%) who had resection after chemotherapy were censored at the time of resection.

Statistical analyses

Categorical values are presented as numbers and percentage. Comparisons were made using Pearson's Chi square test. Continuous data were compared using Mann–Whitney U test.

For survival analysis unadjusted Kaplan–Meier functions were used to estimate OS, and a log-rank test to compare survival functions. For time specific survival the direct method was used. To illustrate time-trends in survival, the survival of patients treated the last two years was compared with the survival of patients treated the first five years. This cut point was arbitrarily chosen to provide sufficient statistical power.

We used Cox proportional hazards models to calculate hazard ratios (HRs) of PC survival in relation to facility type. A Wald test was used to test the difference in HRs between facilities. For time specific survival the direct method was used. In all analyses, the facility and type of facility were independent variables. In comparing relative risks of individual facilities, the one with the highest patient volume and thus most precisely estimated HR was used as reference. In a first step, estimates of death hazards were investigated by univariate analyses for each of the variables included. In a second step multivariate models were established with facility type as independent variable, adjusted for year of first treatment, age, gender, CCI score and M-stage. Since the use of chemotherapy varied between facilities and over time, a third model including type of chemotherapy was made. All variables were categorical except age. Entering age as a categorical variable, using 25 and 75% percentiles as cut points, produced equal results (data not shown). We checked the proportional hazards assumption by visual inspection of log-minus-log plots and a proportional hazard test. We did not find any significant violations of proportionality.

All tests of statistical significance were 2-sided, and a p-value < .05 was considered statistically significant. We performed analyses using Stata v. 16 (StataCorp LLC, Texas, USA).

Ethical considerations

No ethical board approval is needed in Denmark for this type of study and no consent from patients is needed to use this type of data. The study was approved by The Danish Data Protection Agency (2008-58-0028) and the Danish Patient Safety Authority (3-3013-1678/1/).

Results

Descriptive characteristics

Our cohort included 2,655 patients who were treated at eight oncological facilities in a seven-year period. The yearly median volume across all facilities was 43 patients, median for tertiary facilities 71 patients and 31 patients for secondary facilities.

The distribution of variables for the total population and according to facility category is shown in Table 1. In tertiary facilities more patients had low CCI score, were resected after chemotherapy, did not participate in the standardized cancer pathway, were treated with further lines of chemotherapy, and lived in metropolitan areas. More patients were among the 25% youngest and less patients among the 25% oldest, however the median ages were almost similar (68.5 versus 69.5 years, $p = .006$). Monotherapy with gemcitabine was used considerably less often (34%) in tertiary facilities compared with secondary (59%). The average time to

Table 1. Characteristics of all patients and of patients distributed according to oncological facility type (numbers and percent).

| Variable | Strata | All patients | | Patients according to facility type | | | | |
| | | | | Tertiary | | Secondary | | |
		N	%	N	%	N	%	p-value[a]
Gender	Male	1404	53	1010	54	394	50	0.10
	Female	1251	47	863	46	388	50	
Age (25 and 75%-percentiles)	<62 years	662	25	480	26	182	23	0.04
	62-74 years	1334	50	953	51	381	49	
	>74 years	659	25	440	23	219	28	
Charlsons Comorbidity Index	0	1140	43	845	45	295	38	<0.001
	1-2	928	35	660	35	268	34	
	>2	587	22	368	20	219	28	
Distant metastasis	Not present	995	37	700	37	295	38	0.87
	Present	1660	63	1173	63	487	62	
Pathologically verified diagnosis	No	138	5	90	5	48	6	0.16
	Yes	2517	95	1783	95	734	94	
Surgical resection after chemotherapy	No	2563	97	1793	96	770	98	<0.001
	Yes	92	3	80	4	12	2	
Cancer pathway participation	No	646	24	484	26	162	21	<0.01
	Yes	2009	76	1389	74	620	79	
Type of 1st line chemotherapy	Gemcitabine	1094	41	629	34	465	59	<0.001
	Gemcitabine combinations	814	31	662	35	152	19	
	Folfirinox	676	25	523	28	153	20	
	Other regimens	71	3	59	3	12	1	
Lines of chemotherapy in total per patient	1	1499	56	1000	53	499	64	<0.001
	2	614	23	455	24	159	20	
	>2	542	20	418	22	124	16	
Muncipality category[b]	Remote area	242	9	146	8	96	12	<0.001
	Rural	824	31	597	32	227	29	
	Regional	418	16	228	12	190	24	
	Metropolitan	1166	44	897	48	269	34	

[a]Results of Pearson Chi-square test for difference among facility types.
[b]Five patients with unknown municipality.

treatment start from diagnosis was longer (median 28 days (IQR 16–43 days) versus 25 days (IQR 14–37 days)) at tertiary facilities compared to secondary ($p < .001$).
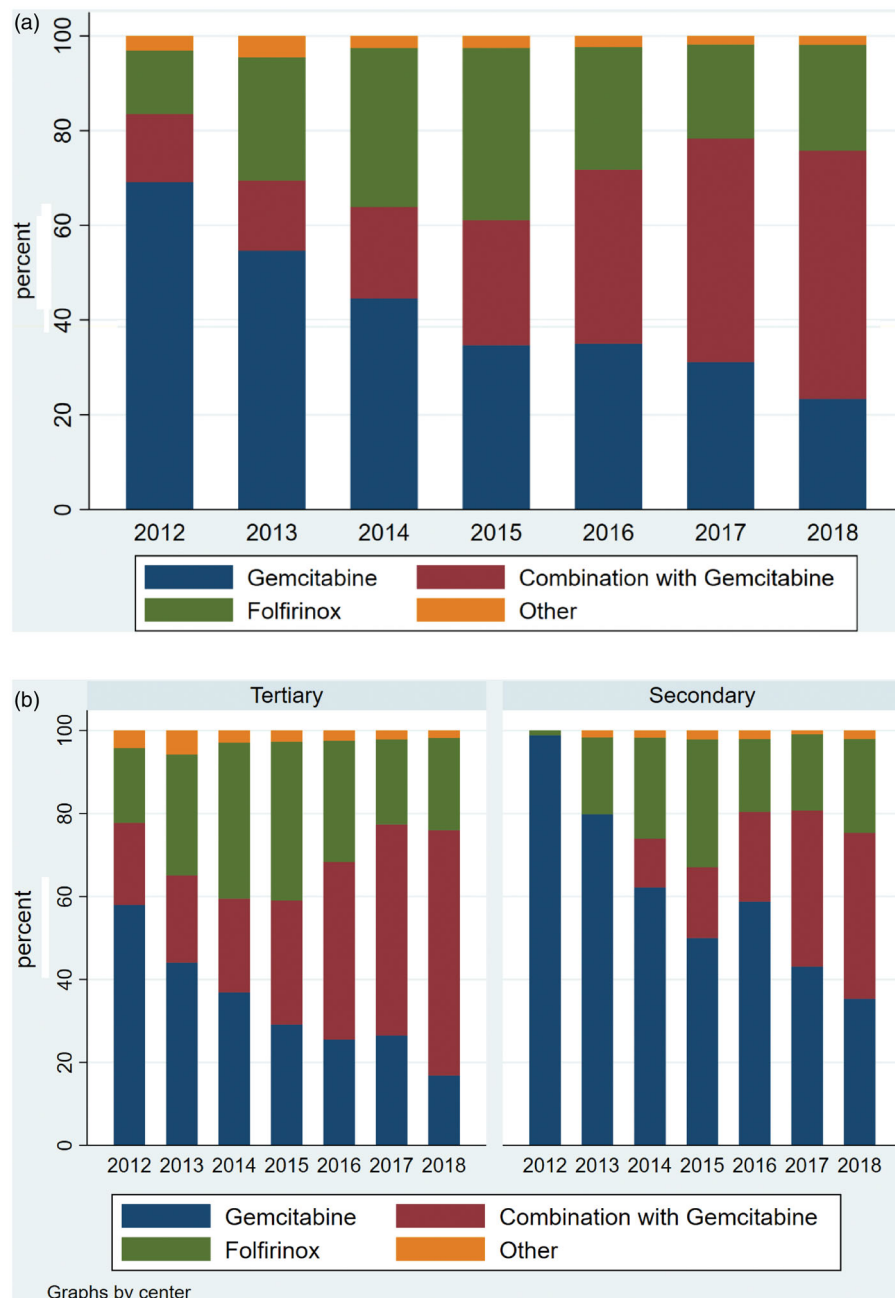
Evolution in use of chemotherapy regimens

We further explored the distribution of chemotherapy regimens used for first-line treatment according to year of treatment initiation (Figure 1). Gemcitabine monotherapy was used for 69% of patients in 2012 declining to 23% in 2018, whereas the use of gemcitabine combinations increased from 14 to 52%. The use of Folfirinox increased from 13% the first year to a maximum of 36% in 2015. Secondary facilities used monotherapy gemcitabine for virtually all patients in 2012, whereas this was the case for only 58% at tertiary

facilities. The fraction of patients treated with gemcitabine monotherapy generally decreased from 2013 and onwards, although in 2018 there was still a 18%-point difference among the facility types. The type of chemotherapy used for patients with or without distant metastases, distributed according to facility type and year of treatment initiation, showed similar trends (data not shown).

Difference in survival among facilities

Survival curves for patients distributed according to facility types are shown in Figure 2. A total of 91 patients were still alive with a median observation time of 27 months. The mOS was longer in patients treated at tertiary (7.7 months) as

Figure 1. (a) The distribution of chemotherapy regimens used for first line treatment according to year of treatment initiation. (b) The distribution of chemotherapy regimens used for first line treatment according to year of treatment initiation and facility type (tertiary and secondary).
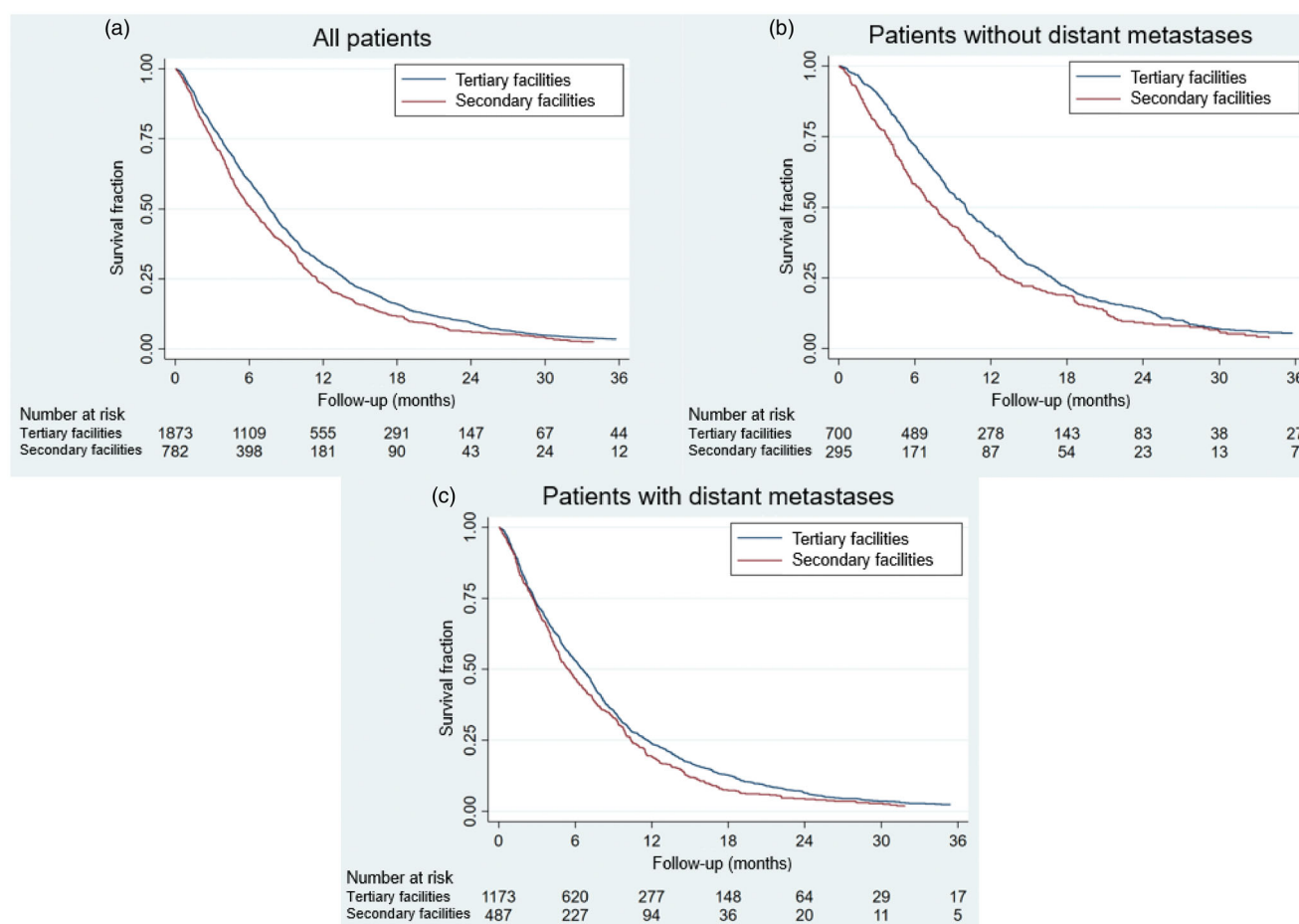
Figure 2. (a) The overall survival for patients with pancreatic cancer treated with chemotherapy as first line treatment according to facility type for all patients. The mOS was 7.7 and 6.1 months, respectively ($p = .0001$). (b) The overall survival for patients with pancreatic cancer treated with chemotherapy as first line treatment according to facility type for patients without distant metastases. The mOS was 10.0 and 7.7 months, respectively ($p = .001$). (c) The overall survival for patients with pancreatic cancer treated with chemotherapy as first line treatment according to facility type for patients with distant metastases. The mOS was 6.6 and 5.4 months, respectively ($p = .02$).

compared with secondary facilities (6.1 months), corresponding to an absolute difference in mOS of 1.6 months or 26%. IQR's were non-overlapping. For the subgroup of patients with non-metastatic disease the mOS was 10.0 months at tertiary facilities as compared with 7.7 months at secondary facilities and IQR's were non-overlapping, whereas patients with metastatic disease treated at tertiary facilities had a mOS of 6.6 months as compared with 5.4 months at secondary facilities (IQR's 2.8–11.7 months and 2.6–10.4 months, respectively).

The HRs for individual facilities were adjusted for year of first treatment, age, CCI score and M-stage. All secondary facilities, except the one with the highest volume, had significantly increased HRs compared to the reference facility (the largest), with an excess hazard of 27% (CI 7–50%), 47% (CI 12–92%) and 49% (CI 25–77%), respectively. All tertiary facilities had HRs not statistically different from the reference facility, except the one with the lowest volume, which had an excess hazard of 22% (CI 5–41%).

Given the major shift in chemotherapy regimens used over time, the survival analysis was repeated only to include the last two years (2017–2018). This analysis reproduced the finding of a significant difference in OS according to facility type for all patients ($p = .01$) and for the subgroup of

patients with distant metastases ($p = .04$), but not for patients with non-metastatic disease ($p = .10$) (Supplementary Figure). As illustrated in Figure 3, the survival for patients treated in 2017–2018 was improved compared to 2012–2016 with a mOS of 8.1 months (IQR 3.8–14.6 months) compared to 7.0 months (IQR 3.3–12.4 months)). Improvements with time were found both for the subgroup of patients treated at tertiary facilities (mOS 8.5 months compared to 7.3 months, $p = .0001$), and at secondary facilities (mOS 6.8 months compared to 5.8 months, $p = .03$).

In a multivariate Cox model with facility type as independent variable (Table 2) adjustment was made for the year of first treatment, age, gender, CCI score, and M-stage (Model 1). Gender had no independent prognostic significance. The adjusted HR of secondary facilities relative to tertiary was 1.16 (CI 1.07–1.27). The multivariate Cox model with further adjustment for the type of chemotherapy (Model 2) reduced the influence of facility type to 1.06 (CI 0.97–1.15) and the difference was not significant ($p = .23$). Together the two Cox models, indicate that the different distribution of type of chemotherapy used at secondary and tertiary facilities explains – at least in part – the observed difference in OS among facility types. Furthermore, the HRs

generally improved with time, especially in the latter two years. There was no survival difference according to municipalities in either univariate or multivariate analysis (data not shown).

Discussion

This study demonstrates an association between treatment facility characteristics and outcome for patients treated with chemotherapy for PC. We showed that patients treated at tertiary facilities had 1.6 month (26%) longer mOS compared to those treated at secondary facilities, corresponding to an increased, adjusted death intensity of 16% (CI 7–27%) for patients treated in secondary facilities. The difference in HRs was statistically significant in three of four secondary facilities and death intensity was almost 50% higher at two secondary centers compared to the largest reference center. Significant improvements in survival were observed for both facility

Figure 3. The overall survival for patients with pancreatic cancer treated with chemotherapy as first line treatment in 2012–2016 and in 2017–2018. The mOS was 8.1 and 7.0 months, respectively ($p < .0001$).

types with time, however, the difference in OS results among facility types was maintained.

Our study points to differences in the distribution of patient and treatment variables according to facility type that may influence survival. Patients treated at secondary facilities had more comorbidity and the age distribution was right skewed. However, we found that the effect of facility type on survival was maintained even after adjustment for these factors. We found that patients' residencies were highly different, but the municipality categories had no influence on survival.

Most striking, the use of multidrug chemotherapy was highly different among facility types. Of these, the Folfirinox regimen was introduced in Denmark at tertiary facilities in 2011 [27], whereas gemcitabine/nab-paclitaxel was used from 2012. Because combination chemotherapy has more side effects and is usually more expensive and logistically complex, the speed of introduction and use of such treatments may reflect quality of care and available resources. In our study we found both a longer delay in the introduction and a sustained reduced use of combination chemotherapy in secondary facilities. Interestingly, Canale et al. observed no difference in use of combination chemotherapy according to geography and found no disparities in survival among 659 patients with advanced PC treated in the British Colombia in Canada [28], whereas in a Danish study of PC in all stages, rural residency compared to urban was associated with a slightly worse outcome. This difference disappeared, however, after adjustment for cancer-directed treatment [29]. Similarly, in the current multivariate analysis with adjustment for type of chemotherapy, the prognostic influence of facility type became insignificant, indicating that the difference in use of combination chemotherapy in first line treatment at secondary and tertiary facilities was a major determinant for differences in outcome.

Other treatment related factors may apply; the dismal prognosis of inoperable PC imply that cure or long-term
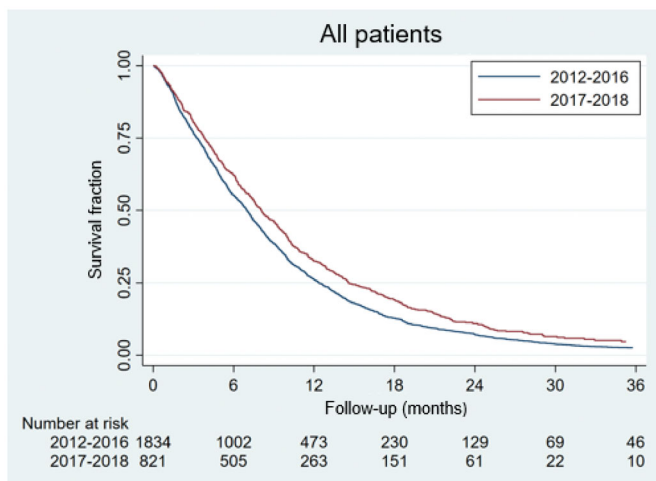
Table 2. Results of multivariate Cox regression analyses of survival with facility as independent variable, excluding (Model 1) and including type of chemotherapy (Model 2).

Variable	Strata	Model 1			Model 2		
		HR	(CI)	p-value	HR	(CI)	p-value
Type of chemotherapy	Gemcitabine			–	1.00		<.001
	Gemcitabine combinations				0.68	(0.61–0.76)	
	Folfirinox				0.59	(0.53–0.66)	
	Others				0.56	(0.43–0.71)	
Facility type	Tertiary	1.00		0.001	1.00		.23
	Secondary	1.16	(1.07–1.27)		1.06	(0.97–1.15)	
Age (years)	Continuos	1.02	(1.01–1.02)	<0.001	1.01	(1.00–1.01)	.004
Gender	Male	1.00		0.13	1.00		.13
	Female	0.94	(0.87–1.02)		0.95	(0.87–1.02)	
Charlson Comorbidity Index	0	1.00		0.04	1.00		.09
	1–2	1.02	(0.93–1.11)		1.01	(0.92–1.10)	
	>2	1.13	(1.03–1.26)		1.11	(1.00–1.23)	
Distant metastases	No	1.00		<0.001	1.00		<.001
	Yes	1.54	(1.41–1.67)		1.56	(1.43–1.69)	
Year of first treatment	2012	1.00		<0.001	1.00		.01
	2013	0.96	(0.83–1.11)		1.02	(0.89–1.19)	
	2014	0.84	(0.72–0.97)		0.94	(0.82–1.10)	
	2015	0.88	(0.76–1.03)		1.00	(0.86–1.17)	
	2016	0.85	(0.73–0.99)		0.98	(0.83–1.14)	
	2017	0.75	(0.65–0.88)		0.86	(0.74–1.01)	
	2018	0.67	(0.58–0.78)		0.80	(0.68–0.93)	

survival of even a minority of patients may have an influence on mOS of the population. Neoadjuvant therapy was not recommended [7], however, we identified 92 patients that had surgery after chemotherapy [30], casuistically with complete pathological response [31]. Resection was done twice as often in patients treated at tertiary facilities. We chose to censor these patients at the time of surgery, although this may contribute to underestimating the survival difference between facility types. The fraction of patients receiving second or further lines of chemotherapy was slightly higher at tertiary facilities compared to secondary (47 versus 44%), but this was unlikely to have a major influence on the results as the effect on survival is small [32].

Fewer patients were included in the standardized cancer pathway at tertiary centers compared to secondary centers (74 versus 79%). We hypothesize that patients at tertiary facilities may more often be diagnosed incidentally, thus not being registered for a cancer-specific pathway. This may imply a minor lead time bias favoring survival in tertiary facilities. The, on average, 3 day longer delay in treatment start observed at tertiary centers did not result in inferior survival measured from start of chemotherapy. Possible lead time bias prior to any contact of the patient with the health system (and its association with facility type) could not be assessed. The work up procedures and guaranteed waiting times in the standardized cancer pathway were, however, unchanged during the inclusion period, and we found no indications of diagnosis at an earlier stage with respect to stage (M-stage) during the latter years of the inclusion period for the whole cohort or according to facility type (data not shown).

In general, the data quality of the Danish national registers is high [24]. However, we found that M-staging was inadequate for 24% of patients, and type of chemotherapy had to be manually entered for 2.3% of patients. Pathological staging data are now automatically incorporated in the DPCD. Our study suggests an inverse correlation between HRs and number of patients treated per year at individual facilities. Studies in larger populations are needed to assess a minimum volume required for optimal results as has been done for several malignant diseases for which treatment has traditionally been regarded as more complex [11,14,16,33].

The strengths of our study are the inclusion of a large cohort of PC patients treated at all oncological departments in the country, the utilization of data in national health registries with standardized coding definitions and information on specific treatment. Nearly all patients in our study were treated at only one reporting facility and all patients were followed up.

The limitations of our study include the lack of some important individual-level prognostic data including performance status, tobacco use and weight loss, so residual confounding from these cannot be excluded. We did not include information on T- and N-stage or anatomical site of primary tumor, which have limited independent prognostic value in advanced disease and were not consistently reported in the database for inoperable patients. Furthermore, we had no available information on potential histopathological, genetic or biochemical prognostic or predictive factors such as tumor

grade, HRD mutational status, serum CA 19-9 or white blood cell counts [34]. Although residency was registered we lacked information on other socio-economical factors, which may be facility-dependent [35,36]. Others have shown that individuals living in rural areas with lower average income and level of education are more likely to receive less efficient treatment [29], whereas socio-economic deprivation may not influence treatment or treatment outcome when offered at a high-volume center [37]. We lacked data on the facility uptake-area-specific allocation of patients to surgery, chemotherapy and best supportive care, which may greatly influence survival [22,38,39]. We were unable to assess the recruitment of patients to facilities outside predetermined uptake areas, which might be skewed toward more patients with undisclosed favorable prognostic factors being treated at tertiary facilities. Finally, we did not study the influence of travel distance [28], as this presumably is of limited importance in a small country.

Although patient's preferences for certain treatments according to, e.g., logistics, quality of life and toxicity should be taken into account, together with efficacy, when discussing the optimal management of patients with PC, our study suggests an opportunity to improve the outcomes on a national level through proper use and fast introduction of evidence-based palliative treatments. Regulatory interventions, such as guarantied maximal waiting times to start on chemotherapy, may improve survival but may also contribute negatively to the selection of less complex care. Equal access to modern treatment at all facilities should be achievable with increased national collaboration and allocation of resources.

We used the STROBE cohort reporting guidelines [40] (included in supplementary material).

ORCID

Henriette Engberg http://orcid.org/0000-0003-1685-8434

Data availability statement

Patients are not completely anonymised and data can therefore not be shared. The data are extracted from the Danish healthcare registries by the Danish Health Data Authority. These data are available to researchers upon application and can only be obtained with permission from the Danish Data Protection Agency, who gave the permission to conduct this study.

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