Waiting time to surgery and pancreatic cancer survival: A nationwide population-based cohort study

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ABSTRACT

Introduction: The effect of waiting time to surgery on survival in pancreatic cancer patients is unclear. We examined this association in a nationwide population-based cohort study.

Materials and methods: A nationwide population-based cohort study of all patients undergoing surgery for pancreatic cancer (resection or a palliative procedure) registered in the Danish Pancreatic Cancer Database from May 2011 to May 2016. We defined waiting time to surgery in two ways: 1) from the date of entry into the National Cancer Pathway to the date of surgery and 2) from the date of the last pre-operative computed tomography (CT) or positron emission tomography (PET-CT) scan to the date of surgery. Waiting time was grouped into three groups: <28 days (<4 weeks), 28—55 days (4—8 weeks), and ≥56 days (≥8 weeks). We calculated median survival with associated 95% confidence intervals (CIs) for patients undergoing resection and for patients undergoing a palliative procedure.

Results: We included 873 patients. Mean age was 67 years (range: 35—86 years). Resection was performed in 701 patients (80%); the remaining 172 patients (20%) underwent an explorative laparotomy or palliative surgery. 652 patients (75%) had a registration in the National Cancer Pathway (median waiting time: 31 days, and 818 patients (94%) had registration of a preoperative CT or PET-CT scan (median waiting time: 32 days). We saw similar resection rates (~80%) and median survival (~22 months) in all thee groups.

Conclusion: In this study, waiting time to surgery did not affect survival in patients undergoing surgery for pancreatic cancer.

Introduction

Pancreatic cancer is a highly fatal malignancy and projected to be the second leading cause of cancer-related deaths by 2030 [1]. The majority of pancreatic cancer patients present with unresectable disease at the time of diagnosis [2]. As surgery is the only chance of cure, irresectability has a profound effect on the prognosis, leading to a dismal 5-year survival rate of less than 10% [3].

In cancer surgery, waiting time from diagnosis to surgery is perceived to be an important quality indicator. In Denmark, national measures to facilitate prompt cancer surgery has been implemented, such as the National Cancer Pathway [4]. These measures are, however, associated with substantial costs. Furthermore, it is unclear if survival from pancreatic cancer is influenced by the time elapsed between diagnosis and surgery. Previous studies have suggested that waiting time to surgery does not alone influence survival [5—7]. However, these studies were all conducted in small populations, and findings from one of the studies were ambiguous [6]. In contrast, a major cohort study from the United States found that patients operated in the period one to two weeks following diagnosis had a worse survival compared with the rest of the population.

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On one hand, increasing waiting time may render the tumor unresectable, as most pancreatic cancers have an aggressive biology [3]. On the other hand, political demands to lower the waiting time may impose unresolvable burdens on healthcare systems. Therefore, to guide political decision-making, the impact of waiting time to surgery on pancreatic cancer survival requires clarification.

Materials and methods

Setting and data sources

We conducted a nationwide, population-based cohort study of all patients undergoing surgery for pancreatic cancer (resection or a palliative procedure) registered in the Danish Pancreatic Cancer Database from May 2011 to May 2016. The Danish Pancreatic Cancer Database was established in 2011 and contains information such as date of diagnosis, tumor stage, comorbidity, and cancer-directed treatment [8]. In 2014, the completeness of data in the Danish Pancreatic Cancer Database was 83%. Since then, both historic and new data in the Danish Pancreatic Cancer Database has been enhanced with data from the Danish Civil Registration System [9], the Danish National Pathology Registry [10], and the Danish National Patient Registry [11]. Information from these registries can be linked at an individual level using the civil personal registration number, which is a unique 10-digit identification number assigned to all Danish residents at birth or immigration. This has improved the completeness of data in the Danish Pancreatic Cancer Database. Based on clinical validation of the latest data, the completeness is above 95%

Study population

We initially identified all patients registered with a pancreatic cancer diagnosis in the Danish Pancreatic Cancer Database during the study period (n = 4251). We excluded patients who did not undergo surgery (n = 3259), without a postoperative specimen registered in the Danish National Pathology Registry (n = 31), and patients receiving neoadjuvant chemotherapy (n = 88), thus leaving a study population of 873 patients. The initial treatment plan from the multidisciplinary conference was available for 2951 patients (69%) and for 786 (90%) of the study population. For flow-chart, see the Supplementary Information (Table A1).

Definition of waiting time to surgery

We defined waiting time to surgery in two ways. *First*, we calculated the time from the date of entry into the National Cancer Pathway to the date of surgery. In 2009, The National Cancer Pathways were implemented in Denmark to ensure timely cancer diagnosis and treatment within a prespecified time interval, which is based on the type of cancer [4]. For example, pancreatic cancer patients with a potentially resectable tumor are entitled to be operated within 10 days of decision to offer surgical treatment. As the National Cancer Pathway is not activated after neoadjuvant oncological treatment, an extended time before surgery was expected in these patients, which were therefore excluded. *Second*, we calculated the time to surgery from the date of the last preoperative computed tomography (CT), or positron emission tomography/computed tomography (PET-CT) scan to the date of surgery. Patients with missing information on waiting time were excluded from the analysis. Waiting time was grouped into three groups: less than 28 days (<4 weeks), 28–55 days (4–8 weeks), and 56 days or longer (≥8 weeks).

Statistical analysis

Descriptive variables are summarized using means and proportions. For each of the three waiting time groups, we calculated the resection rate, defined as the proportion of patients undergoing resection divided by the total number of patients. To examine the impact of waiting time to surgery on survival, we calculated median survival with associated 95% confidence interval (CI) for patients undergoing resection and for patients undergoing a palliative procedure. Survival was estimated using the Kaplan-Meier estimator. For the survival analyses, we followed patients from the date of surgery to death, emigration, or study end (31 October 2017) whichever occurred first. Statistical analyses were performed using Stata version 15 (StataCorp LP, College Station, TX, USA).

Ethical considerations

This study was approved by the Danish Data Protection Agency, Region of Southern Denmark (j.no. 18/24246). According to Danish law, ethical permission is not required to registry-based studies.

Results

Descriptive characteristics

We included 873 patients undergoing surgery for pancreatic cancer during the study period. Mean age was 67 years (range: 35–86 years), and approximately half were men (Table 1). The vast majority (92%) had a ductal adenocarcinoma. Resection was performed in 701 patients (80%); the remaining 172 patients (20%) underwent an explorative laparotomy or palliative surgery. Among the 701 patients undergoing resection, 484 (69%) had a Whipple procedure (Table 2). Seventy-four percent of the patients had stage IIb or stage III disease at pathological examination. We had information on preoperative T- and N-stage in approximately one-third of the population. "Overall, there were no major differences in the distribution of T- or N-stages regarding waiting

Table 1
Descriptive characteristics of 873 patients undergoing surgery for pancreatic cancer.

	N (%)
Age, *years*, mean (range)	67 (35–86)
Age group	
<50	43 (5%)
50-69	472 (54%)
70+	358 (41%)
Sex	
Men	476 (55%)
Women	397 (45%)
Charlson Comorbidity Index Score	
Low (0)	362 (41%)
Moderate (1–2)	310 (36%)
Severe (>2)	201 (23%)
Tumor histology	
Adenocarcinoma	804 (92%)
Mucinous adenocarcinoma	13 (1%)
IPMN	7 (1%)
Adenosquamous carcinoma	17 (2%)
Acinar cell carcinoma	2 (0%)
Undifferentiated carcinoma	12 (1%)
Malignant tumor cells	14 (2%)
Other	4 (0%)
Type of surgery	
Resection	701 (80%)
Exploration/palliative surgery	172 (20%)

Table 2
Characteristics of 701 patients resected for pancreatic cancer.

	N (%)
Procedure	
Pancreaticoduodenectomy (Whipple)	484 (69%)
Distal pancreatectomy	89 (13%)
Total pancreatectomy	127 (18%)
AJCC stage	
Stage Ia	20 (3%)
Stage Ib	37 (5%)
Stage IIa	133 (19%)
Stage IIb	391 (56%)
Stage III	30 (4%)
Missing	90 (13%)

time to surgery (Table 3).

Waiting time

National Cancer Pathway

In total, 652 patients (75%) had a registration in the National Cancer Pathway. Median waiting time to surgery was 31 days. Eighty-eight percent of the patients were resected within 55 days from diagnosis (Table 3). The proportion of patients older than 70 years was higher among patients waiting 28—55 days (45%) and 56 days or longer (53%) compared to patients waiting less than 28 days (37%). There was no difference in sex or Charlson Comorbidity Index score between the three groups. Resection rates and median survival were approximately the same in all three groups (Table 4 and Fig. 1).

Time from last CT/PET-CT

In total, 818 patients (94%) had registration of a preoperative CT and PET-CT scan in the Danish National Patient Registry. Median waiting time to surgery was 32 days. In 91% of the patients, the tumor was resected within 55 days from diagnosis (Table 3). There

was no sex difference between the three waiting groups, but the proportion of patients older than 70 years was higher among those waiting 28—55 days (43%) and 56 days or longer (51%) compared to patients who waited less than 28 days (36%), and so was severe comorbidity in the three groups (26%, 29% and 17%, respectively). Resection rates and median survival were approximately the same in all three groups (Table 4 and Fig. 2).

Multidisciplinary conference

Based on the partial data from the multidisciplinary conference, 888 patients were scheduled for surgery. Of these, 670 (75%) had tumor resection, 116 (13%) exploration/palliative procedure, and 102 (11%) never made it to surgery. Of the 102 patients, 51 (50%) had a new CT within 6 weeks of the multidisciplinary conference, whereas the remaining 51 patients had no further imaging within 6 weeks.

Discussion

In the present study of 873 patients undergoing resection or palliative surgery for pancreatic cancer within 8 weeks from diagnosis, no association between waiting time to surgery and survival was observed. Median survival rates were comparable to those previously reported following pancreatic cancer surgery [2]. Similarly, we observed no differences in resection rates between the three waiting time groups.

Because of the aggressive biology of pancreatic tumors [12], instant cancer surgery should be a priority for several reasons. Apart from the psychological factor and the stress patients may feel, the need to avoid progression and dissemination of the disease calls for an accelerated time to operation. However, our results did neither find a relation between the present time to surgery and the resectability nor the median survival. To some extent, our findings agree with some previous reports. Raptis et al. found that implementation of the National Cancer Waits Target of 62 days in the United Kingdom did neither improve operability, resectability, nor

Table 3
Preoperative T- and N-stage according to waiting time to surgery.

	National Cancer Pathway[a] (n = 652)			Time since last CT/PET-CT[b] (n = 818)		
	<28 days	28—55 days	≥56 days	<28 days	28—55 days	≥56 days
Total	278 (43%)	297 (46%)	77 (12%)	321 (39%)	420 (51%)	77 (9%)
T-stage						
T1	17 (12%)	7 (8%)	2 (7%)	19 (11%)	10 (10%)	3 (16%)
T2	51 (37%)	36 (40%)	8 (30%)	64 (35%)	39 (38%)	9 (47%)
T3	57 (42%)	39 (43%)	15 (56%)	84 (46%)	45 (44%)	6 (32%)
T4	12 (9%)	8 (9%)	2 (7%)	14 (8%)	9 (9%)	1 (5%)
N-stage						
N0	78 (70%)	44 (59%)	14 (64%)	110 (72%)	48 (56%)	11 (65%)
N1	34 (30%)	30 (41%)	8 (36%)	43 (28%)	37 (44%)	6 (35%)

[a] T-stage: Missing data on 47 patients, 351 patients staged as Tx; N-stage: Missing data on 47 patients, 397 patients staged as Nx.
[b] T-stage: Missing data on 82 patients, 433 patients staged as Tx; N-stage: Missing data on 82 patients, 481 patients staged as Nx.

Table 4
Resection and survival rates according to waiting time to surgery.

|	National Cancer Pathway (n = 652)			Time since last CT/PET-CT (n = 818)		
	<28 days	28—55 days	≥56 days	<28 days	28—55 days	≥56 days
Total	278 (43%)	297 (46%)	77 (12%)	321 (39%)	420 (51%)	77 (9%)
Surgery						
Resection	236 (85%)	248 (84%)	61 (79%)	254 (79%)	334 (80%)	63 (82%)
Exploration/palliation	42 (15%)	49 (17%)	16 (21%)	67 (21%)	86 (20%)	14 (18%)
Median survival, months						
Resection	22.3 (18.1—27.3)	25.1 (21.0—31.3)	20.7 (14.0—26.1)	22.1 (19.3—25.9)	22.0 (17.4—26.2)	21.8 (16.3—26.1)
Exploration/palliation	6.7 (5.5—9.8)	8.1 (6.3—9.3)	7.6 (2.9—12.2)	6.0 (3.7—8.3)	8.0 (6.2—9.3)	6.3 (1.3—9.1)
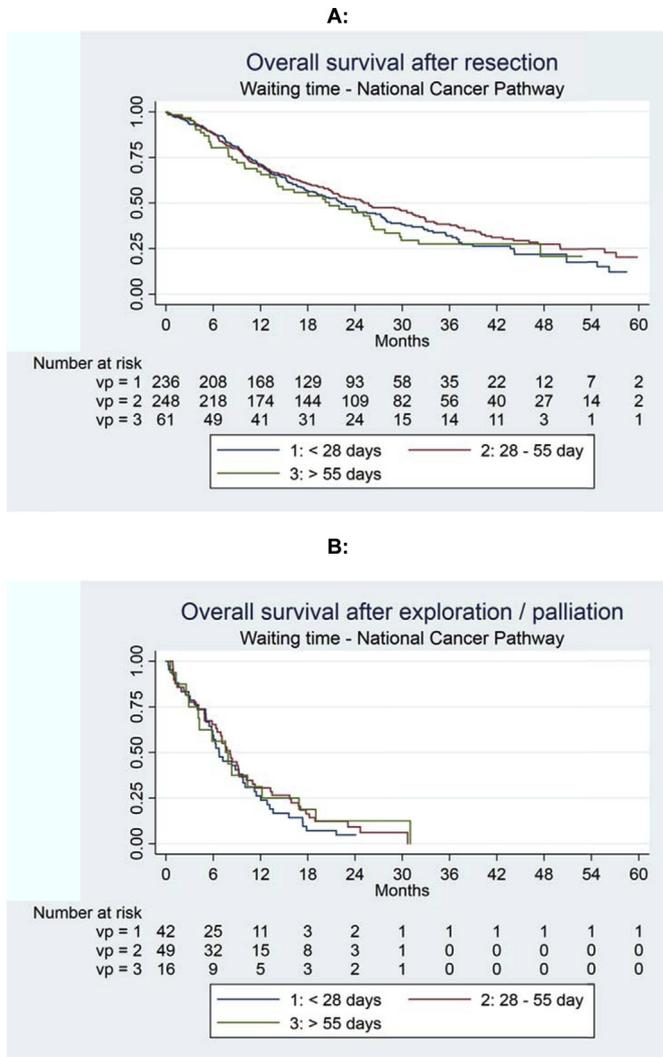
Fig. 1. Kaplan-Meier survival curves for patients registered in the National Cancer Pathway. A: Survival after resection; B: Survival after exploration or palliative surgery.

Figure 2. Kaplan-Meier survival curves for patients registered with a preoperative CT/PET-CT scan in the Danish National Patient Registry. A: Survival after resection; B: Survival after exploration or palliative surgery.

survival rates in 355 patients with pancreatic cancer [5]. Nor did McLean et al. observe a difference in resectability rates or survival according to waiting time in 119 patients who underwent operation for periampullary adenocarcinoma [7]. They did, however, show that the proportion of T4 tumors was higher in patients with waiting time more than 30 days. These findings agree with a study of 217 patients by Marchegiani et al., who also found that waiting time more than 30 days was associated with an increase in tumor size [6]. However, this did not translate into impaired survival in this study either. Contrary to these findings, Mirkin et al. in a cohort study of 14,807 patients with stage I-II pancreatic cancer found that a waiting time of 1−2 weeks was associated with poorer survival in a crude analysis, although the effect was modest (hazard ratio 1.12; 95% CI: 1.05−1.19) [13]. However, they did also find that patients waiting 8−12 weeks were less likely to have negative surgical margins or undergo adjuvant therapy, both of which potentially can affect prognosis. A major drawback of the study by Mirkin et al. is that they followed patients from the date of diagnosis rather than the day of surgery, introducing a classical example of immortal time bias [14]. Furthermore, they included histology codes for intestinal cancers and cholangiocarcinomas, thus limiting comparison to other studies.

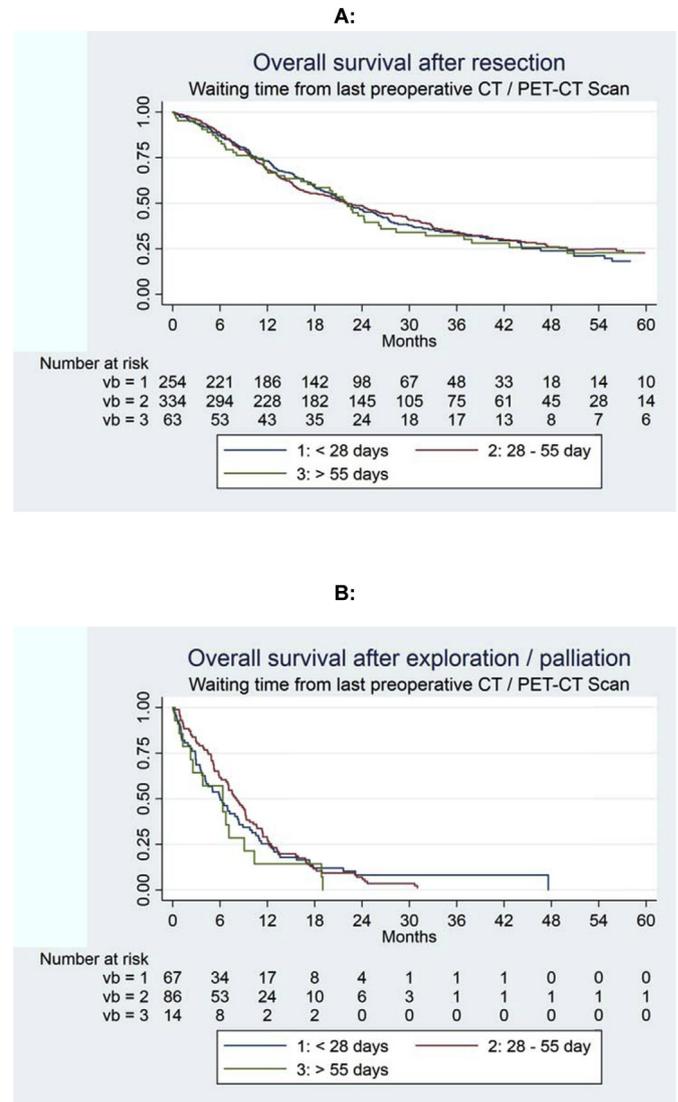The present study has some important strengths. We defined

waiting times in two way; by the National Cancer Pathway and by the last preoperative radiologic examination. Due to administrative causes, the National Cancer Pathway may remain inactivated in some patients (25% in this study). However, only 6% of the patients did not have registration of a preoperative radiologic examination. We observed similar resection and survival rates in both groups, limiting the risk of potential selection bias. Furthermore, the homogeneity in the National Cancer Pathways and the universal tax-financed healthcare system in Denmark also mitigates potential selection bias.

Some limitations should be noted. First, most importantly, some patients may have had their planned surgical procedure cancelled during the waiting time. Based on the partial data on multidisciplinary conference, this was the case for 11% of the patients. This could be caused by either tumor progression or clinical deterioration, both precluding surgical treatment. Given that the multidisciplinary conference is often based solely on imaging without full information on the patients, some will be found subsequently to be non-operable. It is not possible to fully distinguish between non-operability and progression based on data from the registry. But

the lack of further imaging in 50% of these patients indicates that they were more likely to be non-operable than having tumor progression. As we did not have clinical information of these patients, this could incur a selection bias, as patients in the long waiting time group may have smaller tumors, leading to a potential better prognosis. However, there were only minuscule differences in preoperative T- and N-stage between the three groups. Thus, the potential selection bias caused by such a difference is of limited concern, but not eliminated as we only had information on preoperative T- and N-stage in around one-third of the patients. Second, we had no information on other factors such as resection margins, lymph node status, tumor differentiation, and performance status, which affect prognosis and may be skewedly distributed between the waiting time groups [15,16]. Third, we did not have information on the reasons for the waiting time (*e.g.* preoperative optimization, additional diagnostic workup, administrative reasons etc.).

Our study has substantial clinical implications. Despite patients' and physicians' perceptions of the opposite, resection rates and survival rates were unaffected by waiting time to surgery in patients undergoing pancreatic cancer surgery. We emphasize that healthcare policies by political decision-makers should be based on available evidence rather than subjective opinions. The substantial psychological distress of the waiting time to surgery for patients with a highly malignant disease and their relatives [17] should however not be disregarded as an important factor when planning surgery.

Conclusion

In conclusion, our findings suggest that longer waiting times to surgery within 8 weeks from diagnosis do not affect the survival of patients undergoing surgery for pancreatic cancer.

Declarations of interest

None declared.

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Authorship contribution

Study design and conception: CF.
Acquisition, analysis, and interpretation of data: JK, FVM, CPH, MBM, MS, CF.
Manuscript drafting: JK, FVM, CF.
Critical revisions of manuscript: JK, FVM, CPH, MBM, MS, CF.
All authors approved the final paper.

6. Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.05.029.

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