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Relationship between tumour size and outcome in pancreatic ductal adenocarcinoma

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Background: **The size of pancreatic ductal adenocarcinoma (PDAC) at diagnosis is an indicator of outcome. Previous studies have focused mostly on patients with resectable disease. The aim of this study was to investigate the relationship between tumour size and risk of metastasis and death in a large PDAC cohort, including all stages.**

Methods: **Patients diagnosed with PDAC between 1988 and 2013 were identified from the Surveillance, Epidemiology, and End Results (SEER) database. Tumour size was defined as the maximum dimension of the tumour as provided by the registry. Metastatic spread was assessed, and survival was calculated according to size of the primary tumour using the Kaplan–Meier method. Cox proportional regression modelling was used to adjust for known confounders.**

Results: **Some 58 728 patients were included. There were 187 patients (0·3 per cent) with a tumour size of 0·5 cm or less, in whom the rate of distant metastasis was 30·6 per cent. The probability of tumour dissemination was associated with tumour size at the time of diagnosis. The association between survival and tumour size was linear for patients with localized tumours, but stochastic in patients with regional and distant stages. In patients with resected tumours, increasing tumour size was associated with worse tumour-specific survival, whereas size was not associated with survival in patients with unresected tumours. In the adjusted Cox regression analysis, the death rate increased by 4·1 per cent for each additional 1-cm increase in tumour size.**

Conclusion: **Pancreatic cancer has a high metastatic capacity even in small tumours. The prognostic impact of tumour size is restricted to patients with localized disease.**

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is associated with an overall 5-year survival rate of less than 7 per cent[1]. Multiple factors are responsible for the poor prognosis, including late presentation, aggressive tumour biology and the lack of effective systemic therapies[2]. Although surgery provides a chance of cure, the 5-year survival rate after surgery is only 20 per cent[3].

PDAC is believed to arise from non-invasive precursor lesions including pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasm and mucinous cystic neoplasm[4]. Progression of precursor lesions to invasive PDAC is likely to be a slow process that develops over years, or even decades[5]. Some studies[6,7] have suggested that, once cancer has developed, progression from an early to a more advanced stage can occur quickly. Small tumours may already have distant metastases at the time of diagnosis[8].

Traditionally, tumour size has been viewed as an important prognostic factor. According to the TNM classification system, T1 tumours are defined as lesions with a size of 2 cm or less confined to the pancreas[9,10]. These small tumours are considered to be at an early stage of the disease and have a favourable prognosis[11]. The development of metastasis is mostly considered as a late event in the progression of PDAC, occurring mainly in larger tumours[5,8,12,13]. Several studies[6,14–16], however, have suggested that even small tumours are associated with disseminated disease, sometimes even before PDAC has reached the detection limit.

The aim of this study was to investigate the relationship between primary tumour size and metastatic rates

and survival in patients with PDAC. It was hypothesized that tumours no larger than 0·5 cm in diameter are already associated with locoregional and distant metastases.

Methods

The National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database is a national programme of 18 regional or statewide cancer registries in the USA. Data were obtained from all US cancer registries participating in the SEER programme using SEER*Stat version 8.3.2[17]. The Ethics Committee for Clinical Research at Lund University, Sweden, approved the study protocol (2016/100). The study followed the STROBE guidelines[18].

Patients and study design

The study group included all patients with pancreatic cancer registered in the SEER database between 1988 and 2013. Patients were identified on the basis of the ICD for Oncology, third edition (ICD-O-3) for tumours of the exocrine pancreas: C25.0, C25.1, C25.2, C25.3, C25.7, C25.8 and C25.9. Only patients with microscopically confirmed infiltrating pancreatic adenocarcinoma or PDAC (ICD-O-3 histology codes 8140 and 8500 respectively) were selected. Patients with non-invasive tumours, mucinous cystic neoplasms or histological variants, such as adenosquamous carcinoma, colloid carcinoma or hepatoid adenocarcinoma, were excluded. Tumour size was measured as the maximum length of the tumour based on the pathological, operative or radiological report, in this order of priority. Patients were excluded when tumour size was not defined or the value recorded was greater than 20 cm. Patients with incomplete follow-up were also removed. Disease-specific survival was calculated from diagnosis to date of death, last date known to be alive, or until last follow-up (November 2015). Individuals who died from causes other than pancreatic cancer were censored.

To ensure a coherent cancer staging classification across the study period, the SEER historical stage A was used, which provides a consistent definition over time. The AJCC staging system, which is used more widely in clinical settings, was not accessible for many of the annual data sets analysed. The SEER historical stages were outlined as localized (limited to the pancreas; AJCC IA or IB), regional (tumour invading adjacent structures or spread to regional lymph nodes; AJCC IIA, IIB or III) or distant (presence of distant metastasis; AJCC IV).

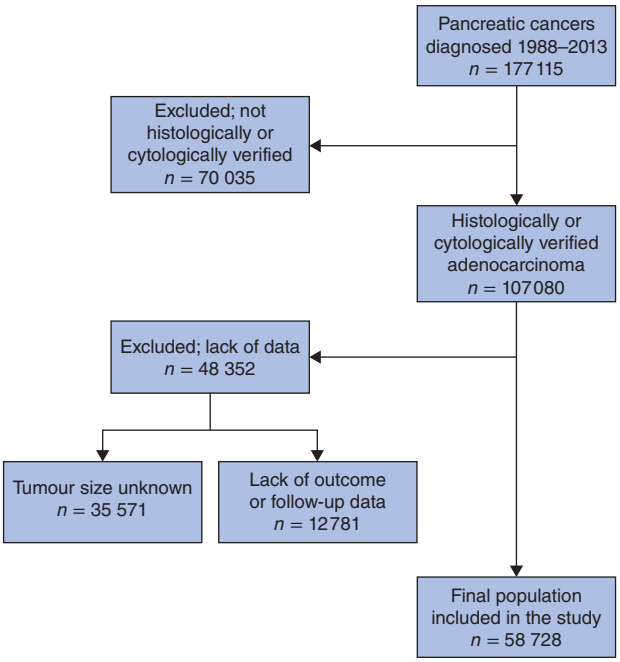

Fig. 1 Flow diagram for the study

Statistical analysis

Data were analysed using Stata® MP 14.1 software (StataCorp, College Station, Texas, USA). Survival curves were calculated using the Kaplan–Meier method. The Cox proportional hazards model was used to adjust for confounding variables. Proportional hazards assumptions were checked, giving more weight to the graphical tests than the statistical ones because of the large sample size. A Poisson model was used to verify the results, with survival time as an offset.

Factors of interest were: age, sex, tumour stage, histological grade, tumour location, surgical resection, radiation therapy, chemotherapy and year of diagnosis. Variable selection was determined by the literature and background medical knowledge; collinearity was checked and variables removed if collinearity was deemed problematic, resulting in the main effect model with no interaction terms. Hazard ratios are presented with 95 per cent confidence intervals.

Missing values were imputed using the multiple imputation with chained equations technique, as described by White and colleagues[19]. The imputation method was predictive mean matching. The number of iterations for each chain was ten, as was the number of imputed data sets.

Results

In total, 177 115 patients with pancreatic cancer were registered in the SEER database. Some 118 387 patients did

Table 1 Cohort characteristics

	No. of patients* ($n = 58\,728$)
Age (years)†	67·0(11·5)
Sex ratio (F : M)	29 003 : 29 725
Tumour size (cm)	
≤ 0·5	187 (0·3)
0·6–1·0	430 (0·7)
1·1–1·5	1349 (2·3)
1·6–2·0	3791 (6·5)
> 2·0	52 971 (90·2)
Histological grade	
Well differentiated	3142 (5·4)
Moderately differentiated	12 409 (21·1)
Poorly differentiated	11 484 (19·6)
Anaplastic	470 (0·8)
Unknown	31 223 (53·2)
Tumour location	
Head	34 792 (59·2)
Body	7564 (12·9)
Tail	7470 (12·7)
Pancreatic duct	356 (0·6)
Other specified parts of pancreas	758 (1·3)
Overlapping	4752 (8·1)
Pancreas, NOS	3036 (5·2)
Stage	
Localized	4777 (8·1)
Regional	23 579 (40·2)
Distant	29 128 (49·6)
Unknown	1244 (2·1)
Surgical resection	
No	43 182 (73·5)
Yes	15 398 (26·2)
Unknown	148 (0·3)
Radiation therapy	
No	43 011 (73·2)
Yes	15 717 (26·8)
Chemotherapy	
No‡	26 592 (45·3)
Yes	32 136 (54·7)
Time period	
1988–2006	27 601 (47·0)
2007–2013	31 127 (53·0)

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.). ‡No evidence of chemotherapy found in the medical records examined. NOS, not otherwise specified.

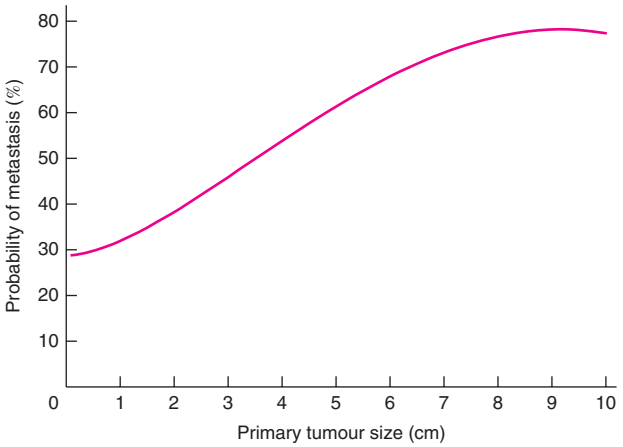

Fig. 2 Fractional polynomial plot illustrating rate of distant metastasis in relation to tumour size at the time of diagnosis

Table 2 Tumour size and survival according to disease stage

Tumour size (cm)	No. of patients	Survival (%)*	
		3 years	5 years
All stages	58 728 (100)	8·4	5·4
≤ 0·5	187 (0·3)	26·7	23·1
0·6–1·0	430 (0·7)	26·6	20·4
1·1–1·5	1349 (2·3)	24·9	17·3
1·6–2·0	3791 (6·5)	16·9	11·3
> 2·0	52 971 (90·2)	7·1	4·4
Localized disease	4777 (100)	20·3	16·0
≤ 0·5	66 (1·4)	63	57
0·6–1·0	128 (2·7)	49·3	39·7
1·1–1·5	265 (5·5)	39·7	27·5
1·6–2·0	570 (11·9)	31·2	26·8
> 2·0	3748 (78·5)	15·4	12·0
Regional disease	23 579 (100)	13·5	8·2
≤ 0·5	59 (0·3)	14	7
0·6–1·0	152 (0·6)	30·3	22·7
1·1–1·5	650 (2·8)	29·9	21·2
1·6–2·0	1765 (7·5)	23·1	14·5
> 2·0	20 953 (88·9)	11·9	7·1
Distant metastases	29 128 (100)	2·2	1·1
≤ 0·5	55 (0·2)	0	0
0·6–1·0	148 (0·5)	3·2	2·1
1·1–1·5	411 (1·4)	7·4	3·2
1·6–2·0	1364 (4·7)	3·4	1·5
> 2·0	27 150 (93·2)	2·0	1·1

Values in parentheses are percentages. *Calculated by Kaplan–Meier analysis.

not fulfil the inclusion criteria and were excluded. Histological or cytological confirmation of the tumour was not available in 70 035 patients. Tumour size was not defined in 35 571 patients and data on outcome or follow-up was not available for 12 781. The study group consisted of 58 728 patients (*Fig. 1*).

Some 8·1 per cent of the patients had localized disease only, 40·2 per cent had regional disease, 49·6 per cent had distant disease and in 2·1 per cent of patients the disease stage was unknown (*Table 1*).

Median tumour diameter was 3·9 (range 0·1–20·0) cm (*Fig. S1*, supporting information). Only 0·3 per cent of the tumours had a diameter of 0·5 cm or less and 90·2 per cent of the tumours were larger than 2 cm (*Table 1*). Median follow-up time was 5 (range 0–301) months.

Association between tumour size and distant metastasis

The risk of distant metastasis at diagnosis increased in a non-linear fashion with increasing primary tumour burden (*Fig. 2*). Tumour stage distribution according to tumour size is shown in *Fig. S2* (supporting information). When the tumour size was no more than 0·5 cm, the rate of distant

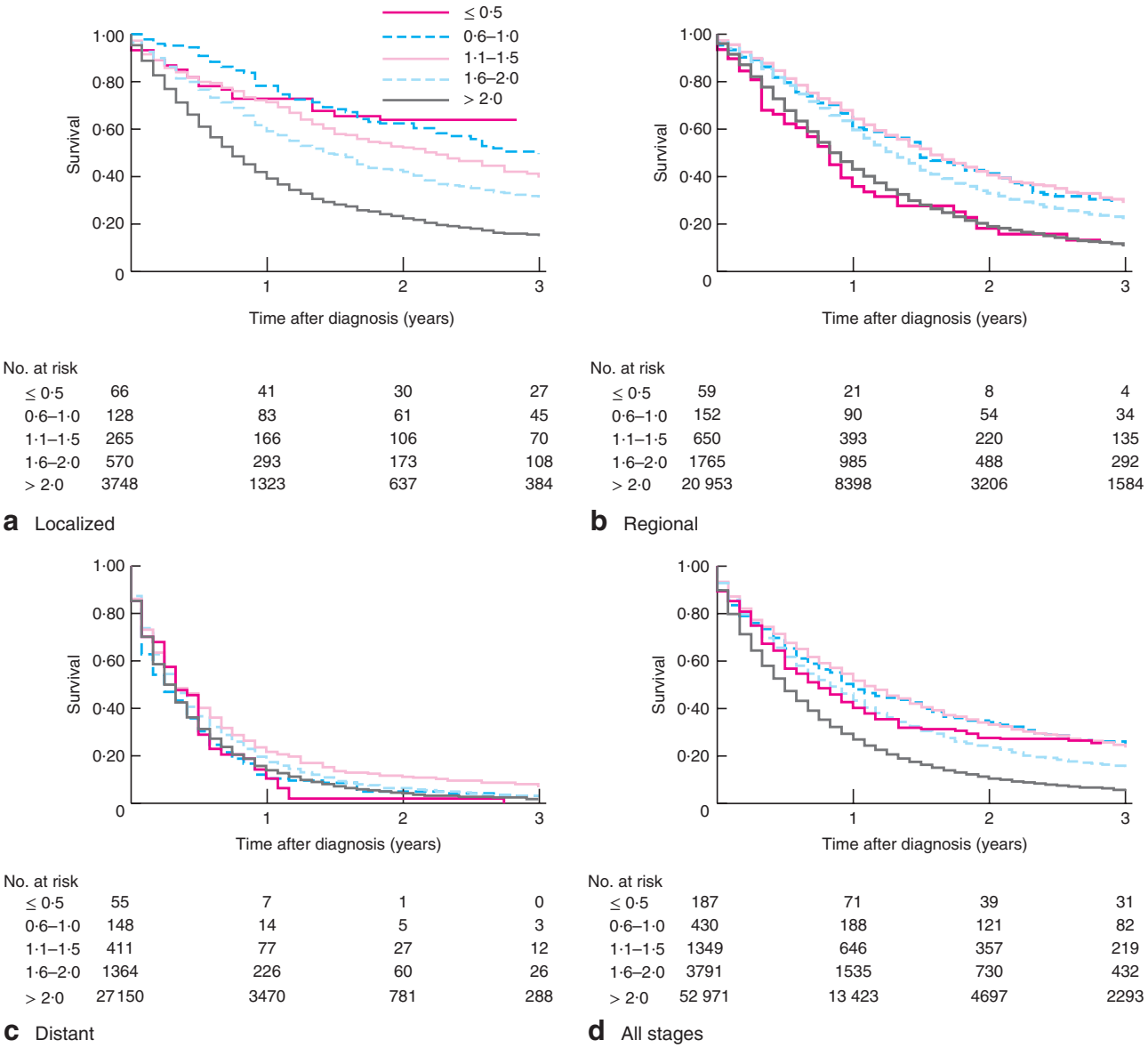

Fig. 3 Kaplan–Meier curves illustrating survival by tumour size (cm) and stage of disease: **a** localized, **b** regional, **c** distant and **d** all stages

metastasis was 30·6 per cent, increasing to 73·9 per cent when the tumour size was 10 cm.

Survival according to tumour size and stage

The 5-year survival rate for the study group was 5·4 per cent. For tumours no larger than 0·5 cm the 5-year survival rate was 23·1 per cent. Survival decreased with increasing tumour size (*Table 2*). Among 4777 patients with local disease only, the 5-year survival rate was 16·0 per cent; it was 57 per cent for patients with tumours of 0·5 cm or less in diameter, decreasing to 12·0 per cent for those with tumours larger than 2 cm. In patients with regional disease or distant metastases, survival was similar across tumour size categories. The relationship between tumour size and survival, stratified by stage, is shown in *Fig. 3* and *Fig. S3* (supporting information).

Survival in patients who underwent surgery

Some 15 398 patients underwent surgical resection. The 5-year survival rate was 16·1 per cent after surgery compared with 1·2 per cent for patients who were not operated on. When surgery was performed, patients with tumours

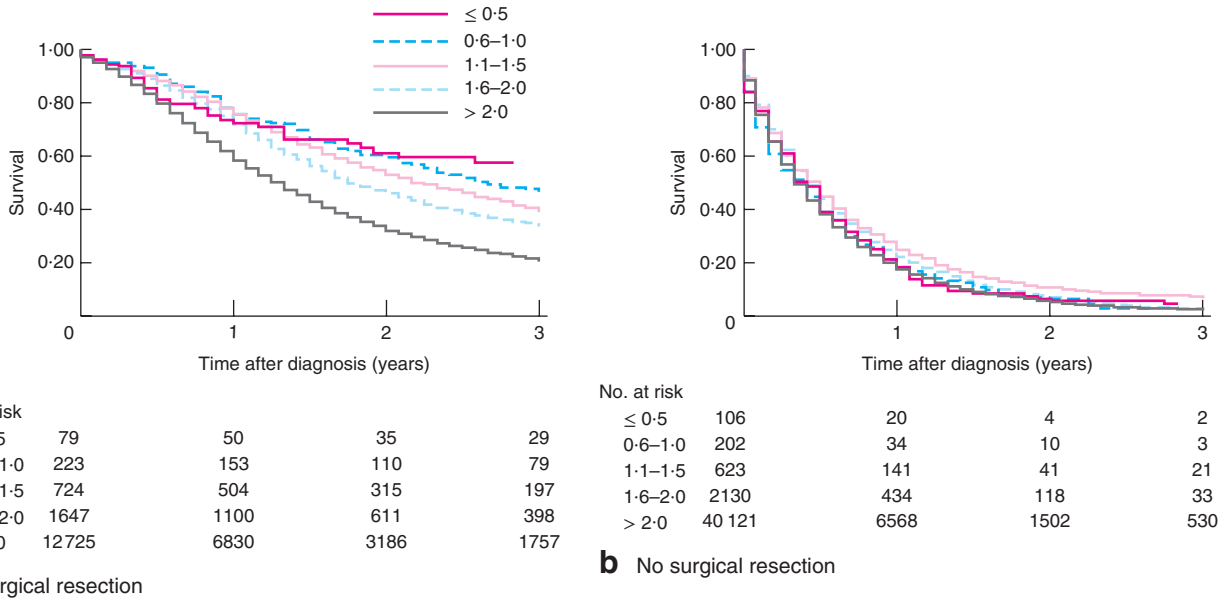

Fig. 4 Kaplan–Meier survival curves showing survival by tumour size (cm) **a** with or **b** without surgical resection

Table 3 Predictors of survival identified by multivariable Cox regression analysis

	Hazard ratio	*P*
Age (per year)	1·01 (1·01, 1·01)	< 0·001
Male sex	1·03 (1·01, 1·05)	0·001
Size (per cm)	1·04 (1·04, 1·05)	< 0·001
Grade		
Well differentiated	1·00 (reference)	
Moderately differentiated	1·21 (1·16, 1·26)	< 0·001
Poorly differentiated	1·52 (1·45, 1·59)	< 0·001
Anaplastic	1·49 (1·32, 1·68)	< 0·001
Stage		
Localized disease	1·00 (reference)	
Regional disease	1·32 (1·27, 1·37)	< 0·001
Distant metastases	2·07 (1·99, 2·15)	< 0·001
Location (head of pancreas *versus* other sites)	0·96 (0·94, 0·98)	< 0·001
Surgery	0·43 (0·42, 0·44)	< 0·001
Radiation therapy	0·90 (0·88, 0·93)	< 0·001
Chemotherapy	0·58 (0·57, 0·59)	< 0·001
Time interval (2007–2013 *versus* 1988–2006)	0·87 (0·85, 0·88)	< 0·001

Values in parentheses are 95 per cent confidence intervals.

Table 4 Subgroup analyses of survival according to size and stage

Tumour size (cm)	Hazard ratio*	*P*
Localized disease		
≤ 0·5	1·00 (reference)	
0·6–1·0	1·57 (0·94, 2·62)	0·085
1·1–1·5	2·10 (1·31, 3·37)	0·002
1·6–2·0	2·31 (1·46, 3·65)	< 0·001
> 2·0	3·38 (2·16, 5·30)	< 0·001
Regional disease		
≤ 0·5	1·00 (reference)	
0·6–1·0	0·74 (0·52, 1·05)	0·088
1·1–1·5	0·73 (0·54, 1·00)	0·047
1·6–2·0	0·88 (0·65, 1·18)	0·398
> 2·0	1·09 (0·82, 1·46)	0·550
Distant metastases		
≤ 0·5	1·00 (reference)	
0·6–1·0	1·01 (0·71, 1·44)	0·964
1·1–1·5	0·77 (0·56, 1·06)	0·113
1·6–2·0	0·87 (0·64, 1·18)	0·364
> 2·0	0·97 (0·72, 1·31)	0·840

Values in parentheses are 95 per cent confidence intervals.
*Multivariable Cox regression analysis, adjusted for age, male sex, grade, tumour location, surgery, radiation therapy, chemotherapy and time interval.

no larger than 0·5 cm had better survival than those with larger tumours (*Fig. 4*). In contrast, in the absence of tumour resection, overall 5-year survival was not associated with tumour size.

Predictors of survival

All factors considered in the multivariable Cox regression analysis, including age, sex, tumour size, grade, stage, tumour location, surgical resection, radiation therapy and chemotherapy, were associated with cancer-specific survival. For each additional 1-cm increase in tumour size, the rate of death increased by 4·1 per cent (*Table 3*).

Subgroup analyses were undertaken to determine whether the prognostic impact of tumour size was

Table 5 Subgroup analyses of survival by size, with or without surgical resection

Tumour size (cm)	Hazard ratio*	*P*
Surgical resection		
≤ 0·5	1·00 (reference)	
0·6–1·0	1·25 (0·83, 1·87)	0·283
1·1–1·5	1·47 (1·01, 2·14)	0·044
1·6–2·0	1·73 (1·20, 2·50)	0·003
> 2·0	2·33 (1·62, 3·36)	< 0·001
No surgical resection		
≤ 0·5	1·00 (reference)	
0·6–1·0	1·04 (0·79, 1·37)	0·762
1·1–1·5	0·82 (0·65, 1·05)	0·116
1·6–2·0	0·93 (0·74, 1·16)	0·504
> 2·0	1·05 (0·84, 1·31)	0·679

Values in parentheses are 95 per cent confidence intervals. *Multivariable Cox regression analysis, adjusted for age, male sex, grade, tumour location, stage, radiation therapy, chemotherapy and time interval.

consistent across stage and treatment categories, adjusting for the same co-variables as the main Cox regression model. Tumour size was associated with an increase in the hazard ratio for death in patients with localized disease. However, no such association could be found for patients with regional disease or distant metastases (*Table 4*). Increasing tumour size was associated with worse survival in patients with resected tumours, but not in those with unresected disease (*Table 5*).

Discussion

In the present study of patients with histologically or cytologically confirmed PDAC, distant metastases were present in almost one-third of patients with tumours of 0·5 cm or less in diameter. This finding may influence staging and treatment of the disease. Identification of new biomarkers for the detection of early disease and targets for treatment is needed.

The present study also revealed a stage-dependent relationship between tumour size and survival. The association between small tumour size and prolonged survival was confirmed only in the subgroup of patients with localized cancer. Once the cancer had disseminated, tumour size was no longer an important predictive factor for long-term survival. In some patients, small tumours with regional or distant spread were even associated with a worse prognosis than larger tumours. This suggests that PDAC is a systemic disease already in the early stages of cancer development. PDAC has a high metastatic potential regardless of tumour size. An important observation from the present data is that patients with PDAC had a poor prognosis, even when the disease seemed to be limited to the pancreas. The poor survival in patients diagnosed with localized tumours is generally attributed to early vascular dissemination and metastasis in combination with the insensitivity to adjuvant therapy[20,21]. In a previous study[22], the 5-year survival rate for patients with small localized lesions (less than 2 cm in diameter) was estimated to reach 40 per cent at most. The present results indicate that the survival rate is even lower at a population level.

The most common cause of death for patients with resected pancreatic tumours is systemic recurrence rather than local disease[23,24], which supports the hypothesis that PDAC is a systemic disease at the time of diagnosis in the majority of patients. Yet, not all PDACs show such aggressiveness at an early stage. PDAC is a heterogeneous disease, and it may be speculated that there are biological differences between tumours that metastasize early and those that behave in a more indolent fashion. Integrated analysis of genomic, epigenomic and transcriptomic data has revealed distinct molecular subtypes of PDAC with different histopathological characteristics and prognosis[25].

The initiation and progression of PDAC probably take place over years and involve the accumulation of multiple genetic or epigenetic alterations within the cells, resulting in uncontrollable cell expansion with subsequent acquisition of migratory properties and metastatic disease[5,26,27]. According to a previous study[28] that predicted the metastatic capability of PDAC using a mathematical model, the probability of tumour dissemination is dependent on the size of the primary tumour at the time of diagnosis. The present clinical data confirm the relationship between size and dissemination, but indicate a higher rate of small tumours presenting with widespread disease (*Fig. 2*).

Early metastatic spread has long been recognized as an indicator for the poor prognosis of PDAC and, when detected, is a critical variable in the AJCC/TNM classification system on which treatment planning is based. Current clinical practice for PDAC recommends surgical resection of the primary tumour followed by adjuvant chemotherapy in patients with a resectable tumour. Based on the findings of the present study, early-stage tumours should also be considered high-risk lesions, with a high probability of systemic metastasis for which systemic treatment may be indicated. Such treatment would target micrometastases that go undetected by imaging. Accordingly, it was reported recently that patients with PDAC receiving neoadjuvant therapy before surgery showed clear improvement in median overall survival compared with patients treated by a 'surgery-first' approach[29].

The study has limitations given its retrospective design and the use of a national registry. The SEER historical

stage A was used, which is different from the AJCC staging system and probably of less clinical relevance. However, this classification allowed uniform staging during the study period. Lack of central pathological review is a limitation of the SEER database. However, previous studies have found good agreement between the histological subtypes of cancer reported by SEER and those assigned by independent reviewers[30]. Another limitation of SEER data is related to registration of the use of chemotherapy. The completeness of the registration and the potential biases associated with reasons for receiving or not receiving chemotherapy have been addressed previously[31]. Missing values in this study were handled by a multiple imputation technique, which is probably the best method available today[32]. This approach reduces selection bias and improves generalizability, but necessitates caution when interpreting the results. In the future, the addition of specific tumour cell phenotypes may improve risk stratification for predicting metastatic disease and survival in patients with PDAC.

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Fig. S1 Size distribution of tumours in the cohort (Word document)

Fig. S2 Stage distribution according to tumour size (Word document)

Fig. S3 Survival time according to tumour size and stage (Word document)