

Early onset pancreatic cancer: a controlled trial

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Abstract

Background Pancreatic ductal adenocarcinoma (PDAC) represents the fourth cause of death in cancer with a 5-year survival rate of less than 1-2%. Early onset pancreatic cancer (EOPC), i.e. patients below 50 years of age, is infrequently described. The present study aimed to determine the epidemiology, demographic incidence and prognosis of EOPC and to identify the characteristics that might distinguish EOPC.

Methods 576 consecutive patients with PDAC diagnosed from January 1993 to December 2008 at the University Hospital of Lund, Sweden. 65 different parameters were compared with a historic cohort of pancreatic cancer patients as well as with matched controls.

Results 33 patients (5.7%) with PDAC were 50 years or younger. The overall survival was 170 days compared to 240 days for matched controls ($p=n.s.$). Patients with EOPC were diagnosed at a significantly more advanced stage, i.e. distant metastasis, (52%) as compared to matched controls (30%; $p=0.04$). EOPC-patients received more treatment than the compared PDAC-cohort.

Conclusion EOPC constituted 5.7 % of all PDAC, presenting at an advanced stage with frequent metastases and poor survival. The role of genetic alterations and the potential influence of environmental factors for EOPC are to be further investigated.

Keywords pancreatic cancer, early onset, matched controls, outcome

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Introduction

Pancreatic cancer is the thirteenth most common cancer worldwide with an incidence of about 8 to 10 cases per 100,000 population per year in the developed world. The prognosis is dismal with a mere 1-2% overall 5-year survival rate, making pancreatic cancer the fourth most common cause of cancer-related death in the US [1,2].

Following best treatment, with R0 resection and adjuvant chemotherapy, a 5-year survival rate of up to 20% is possible [3], but for patients with metastatic disease the median survival is below 6 months [4].

In Sweden the median age of onset of pancreatic cancer is 72 years [5]. In a subgroup of patients pancreatic cancer manifests before 50 years of age, defined as early onset pancreatic cancer (EOPC). Epidemiological studies propose that this subgroup

is approximately 5-10% of all pancreatic cancers and carries a large burden, one third, of years-of-potential-life-lost of the total mortality burden of pancreatic cancer [6]. The same study also states that smokers could be overrepresented in EOPC [6]. In the largest demographic study so far with 136 patients reported from Memorial Sloan Kettering (<45 years at diagnosis) no differences could be noted in smoking, hereditary burden or survival when compared to other pancreatic cancer studies or registers [7].

Altogether there is scarce information and data of EOPC regarding biology and etiology and it would be of interest to elucidate potential risk factors and to establish prognosis regarding survival in this subgroup of pancreatic cancer since the years-of-potential-life-lost is great considering the poor prognosis.

We performed a retrospective analysis of the pancreatic cancers from 1993 through 2008 at the Lund University Hospital, Sweden, and compared EOPC with matched controls with the aim to identify possible differences as compared to the whole group of pancreatic cancer.

Patients - Methods

A retrospective analysis was performed in all patients with pancreatic cancer, according to ICD-9 and ICD-10, at the

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Conflict of Interest: None

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Department of Surgery, Lund University Hospital, Sweden between January 1993 and December 2008. The hospital covers an area of 270,000 inhabitants and also functions as a referral center for Southern Sweden. 576 patients with pancreatic cancer were identified and 45 patients were below the age of 50 years (7.8%). Of these 45 patients, 12 were excluded due to other pancreatic neoplasms such as endocrine tumors, intraductal papillary mucinous neoplasms, pseudopapillary and acinar cell carcinomas, thus leaving 33 (5.7%) patients for analysis.

All 33 patients had a histopathologically confirmed diagnosis of ductal pancreatic adenocarcinoma (PDAC) either on resected specimen, true-cut biopsies or fine-needle aspiration. Date of diagnosis was set to be the date of surgery or biopsy.

Sixty-five unique parameters were collected from the medical charts of the patients, including basic demographic data, background medical history and heredity, as well symptoms, clinical and laboratory signs at the time of diagnosis, clinical stage at diagnosis, treatment, therapy and outcome.

Controls were collected from our pancreatic cancer database. We used 129 patients with histopathologically confirmed PDAC from 1999-2002, situated in the middle of the time span of the investigated cohort. The EOPC group was compared both to this group and matched controls from this group. Matching was performed for the following parameters: sex, resection, tumor size, chemotherapy and radiotherapy. These parameters were chosen since they correlate best with survival. It was not possible to match for histopathological differentiation due to the lack of patients that were graded in the EOPC group (9 patients). The EOPC group and controls were considered comparable since there was no statistically significant difference detected in the matched parameters.

Statistical analysis

A standardized form for database collection was used (Microsoft Excel, Microsoft, Redmond Washington, USA). Mann-Whitney U-test and Fisher's exact test was used to compare groups and Kaplan-Meier method to estimate survival. All statistical analyses were performed using SPSS v17.0 (SPSS Inc, Chicago, Ill, USA).

Results

Of the 33 patients that constitute the cohort, 20 (61%) were male and 13 (39%) were female. Median and mean ages at diagnosis was 46.5 years (range 30-50 years) and 44.8 years, respectively. Seven patients (21%) with EOPC were between 30 and 40 years at the time of diagnosis and 26 patients (69%) were between 40 and 50 years of age.

During the study period there was a non-significant decrease in patients with EOPC, 21 patients in the first 8

years and 12 patients in the last 8 years. This however, did not reach statistical significance. This decline is also noticed in the Swedish Cancer Database covering all cancers from 1970-2009.

History and symptoms

Data regarding medical and hereditary characteristics as well as symptoms and clinical signs are shown in Table 1.

Family history in the EOPC group revealed only one patient (3%) with a relative with pancreatic cancer. There was no evidence for familial pancreatitis or other hereditary diseases. In the EOPC cohort, 13 patients (40%) were previously diagnosed with biliary-pancreatic diseases. There was no difference in the frequency of chronic pancreatitis between groups, ($p=1.0$).

Present alcohol consumption prior to diagnosis is shown in Table 1.

In the EOPC group 73% were smokers or had recently quit smoking, but it was not possible to obtain pack years. In the matched group the corresponding figure was 54%. During this period the percentage of smokers in Sweden was approximately 20%. Present consumption of cigarettes at time of diagnosis is outlined in Table 1.

In the EOPC group only 3 (9%) were obese [body mass index (BMI) >30] before weight loss compared to the matched group of 4 (12%), ($p=1.0$), and the general population at the time with 12% having a BMI>30. C-reactive protein (CRP) was measured at the time of diagnosis and no statistical difference was found between groups ($p=0.16$).

Regarding the presenting symptoms, no significant changes were noted in presence of jaundice, abdominal pain, weight loss, recent onset diabetes, nausea or diarrhea.

Time from first contact with health care to diagnosis was 27 days in mean and 23 (2-93) days in median. The corresponding time for the matched controls was both in mean and median 25 (2-75) days, $p=0.75$. It was not feasible to obtain data on possible patient delays.

Tumor-specific characteristics and treatment

The location of the cancer in the EOPC group was as follows; the pancreatic head in 26 (79%), the body in 4 (12%) and the tail in 3 (9%) and the median tumor size was 4.0 cm. Clinical stages at presentation were local only in 6 patients (18%), locoregional lymph nodes were involved in 10 patients (30%), and distant, i.e. liver metastases, in 17 patients (52%). The proportion of distant metastases at diagnosis was significantly higher in the EOPC group as compared with both matched controls ($p=0.04$) and the entire cohort ($p<0.001$) (Table 2).

Histopathological grading was performed in 20 of 33 patients in the EOPC group where 20% was highly, 45% moderately and 25% poorly differentiated.

The resection rate was higher in the EOPC group, 27%,

Table 1. History and symptoms at the time of diagnosis.

Investigated parameters	EOPC group n=33	Matched controls n=33	p-value
Symptoms and Clinical signs			
Jaundice	61% (0)	73% (0)	0.43
Weight loss <10%	55% (4)	33% (2)	0.13
Pain	91% (0)	61% (5)	0.001
Recent onset diabetes (<12 months)	21% (0)	15% (2)	0.75
CRP at diagnosis (median)	9 (range 1-204)	14 (1-185)	0.16
Hemoglobin at diagnosis (median)	131 (range 102-167)	125 (98-160)	0.34
Elevated s-amylase (>0.8 μ kat/L)	21% (7)	9% (11)	0.43
BMI >30	9% (0)	12% (0)	1
History			
Chronic pancreatitis	12% (0)	9% (2)	1
Gallstone disease	24% (0)	18% (0)	0.76
Diabetes (>12 months)	3% (0)	6% (2)	0.61
Previous cancer in other organ	3% (3)	3% (0)	1
Smoking 1pack/day or more	48% (0)	53% (2)	0.63
Alcohol	21% (5)	19% (7)	1
Female >14 units or Male >21 units/week			
Hereditary*			
Pancreatic cancer	3% (0)	0% (2)	p=1
Pancreatic disease	6% (0)	6% (2)	p=1
Gynecological cancer	3% (0)	0% (0)	p=1

*First-degree relatives only

Patients with missing data in parenthesis

Fisher's exact test, two tailed and Mann-Whitney U test

BMI, body mass index

vs. 10% in the entire cohort ($p=0.01$), but not different when compared to the matched control group. In the EOPC group, 15 patients received chemotherapy (Gemcitabine or 5-FU/Leucovorine) administered as adjuvant or palliative treatment and also significantly more radiotherapy (both intra- and post-operatively) was given to the EOPC group as compared to the entire cohort (36% vs. 9%) ($p=0.002$).

Comparisons with the PDAC group and the matched controls are shown in Table 2.

Survival

Median survival in patients with EOPC was 170 (95% CI: 59-281 days) days compared to 158 days (95% CI: 122-193 days) ($p=0.84$) for the entire cohort of patients with pancreatic ductal adenocarcinoma, despite a significantly higher rate of treatment with both resection and radiotherapy. When compared with matched controls the survival had a tendency

to be shorter for the EOPC group although not significant, i.e. 170 days (95% CI: 59-281 days) as compared to 240 days (95% CI: 91-388 days), ($p=0.12$) (Fig. 1).

Five-year survival was 3.3% for the EOPC patients and 2.3% for the entire cohort and the matched controls had a five-year survival rate of 0%.

Discussion

Pancreatic cancer is a disease of the elderly with a median age at diagnosis ranging between 68-72 years [8-10]. A subgroup of these patients is younger than 50 years and limited information has been presented about this subgroup. In the largest descriptive study previously presented, it was proposed that there might be a better survival in the earlier stages of the disease in younger patients, but this could be reflected by lack of co-morbidities in younger patients. Other

Table 2. Comparison of tumor appearance and treatment.

		EOPC n=33	PDAC matched controls n=33	p-value	PDAC n=129	p-value
Sex	<i>Male</i>	20 (61%)	20 (61%)	0.50	52 (40%)	0.02
	<i>Female</i>	13 (39%)	13 (39%)	0.50	77 (60%)	0.02
Median (range) age		46.5 (30-50)	68 (50-90)		72 (39-95)	
Tumor location						
	<i>Head</i>	26 (79%)	27 (82%)	0.50	109 (84%)	0.29
	<i>Body</i>	4 (12%)	3 (9%)	0.50	12 (9%)	0.41
	<i>Tail</i>	3 (9%)	3 (9%)	0.50	8 (6%)	0.39
Tumor size						
	<i><2 cm</i>	2 (6%)	1 (3%)	0.50	5 (4%)	0.43
	<i>2-5 cm</i>	24 (73%)	28 (85%)	0.36	94 (73%)	0.60
	<i>> 5 cm</i>	7 (21%)	4 (12%)	0.50	30 (23%)	0.67
	<i>Median size (cm)</i>	4.0	4.1	0.46	4.0	0.50
Clinical Stage						
	<i>Localized</i>	6 (18%)	7 (21%)	0.99	26 (20%)	0.68
	<i>Locoregional</i>	9 (27%)	16 (49%)	0.12	72 (56%)	0.005
	<i>Metastatic</i>	18 (52%)	10 (30%)	0.04	31 (25%)	0.001
Resection rate		9 (27%)	8 (24%)	0.50	13 (10%)	0.01
Chemotherapy		15 (45%)	20 (61%)	0.32	45 (35%)	0.17
Radiotherapy		12 (36%)	7 (21%)	0.13	12 (9%)	0.002

EOPC, early onset pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma.

authors have suggested that survival rates are difficult to compare since younger patients are more likely to undergo resective surgery for their tumors [10].

We could not investigate or sub analyze survival in the different stages due to a limited number of resected patients (n=9) in the present study, but we tried to match for tumor size and treatment which both correlate very well to survival in large studies.

In this retrospective study, we tried to compare characteristics and results for the EOPC group with a large cohort of patients at the same institution, as well as with matched controls.

Compared with the large cohort of consecutive patients with pancreatic ductal adenocarcinoma, it is evident that the younger patients have a higher resection rate and receive more radio-chemotherapy. Despite this fact, there is no difference in survival between the groups, 170 days (PDAC) vs. 158 days (EOPC) in median survival. When the rates for resection and therapy, as well as tumor size, were compared with matching controls, the average survival was 70 days lower in the EOPC group than in the matched controls 170 vs. 240 days), not reaching statistical significance.

This is could possibly be due to the fact that EOPC

patients were diagnosed at a more advanced stage in this study. EOPC patients had metastatic disease to a significantly larger extent than matched controls, despite matching also for tumor size. Tumor is often well correlated to the time point of metastasis as suggested in a recent paper by Yachida et al [11], therefore the matching was performed according to size and not to TNM stage.

There was no difference in doctors' delay in these patients, but whether a patient's delay was present was not possible to investigate and the reason for the significant difference in metastatic disease at presentation needs to be elucidated, i.e. whether it is due to tumor biology, invasiveness, immunological factors or patients' delay.

Smoking is an established risk factor for pancreatic ductal adenocarcinoma, increasing the risk by 2-3 fold and this is also suggested in the EOPC subgroup [6]. Smoking itself is associated with a younger age at presentation by approximately 8 years [12] and smoking is an even stronger predisposing factor in patients with familial clustering or hereditary pancreatitis [13-15]. The incidence of pancreatic cancer also shows signs of declining in this young patient group suggested to be related to decreased smoking [16]. This was also shown in the present study with a decline, however non-significant, comparing

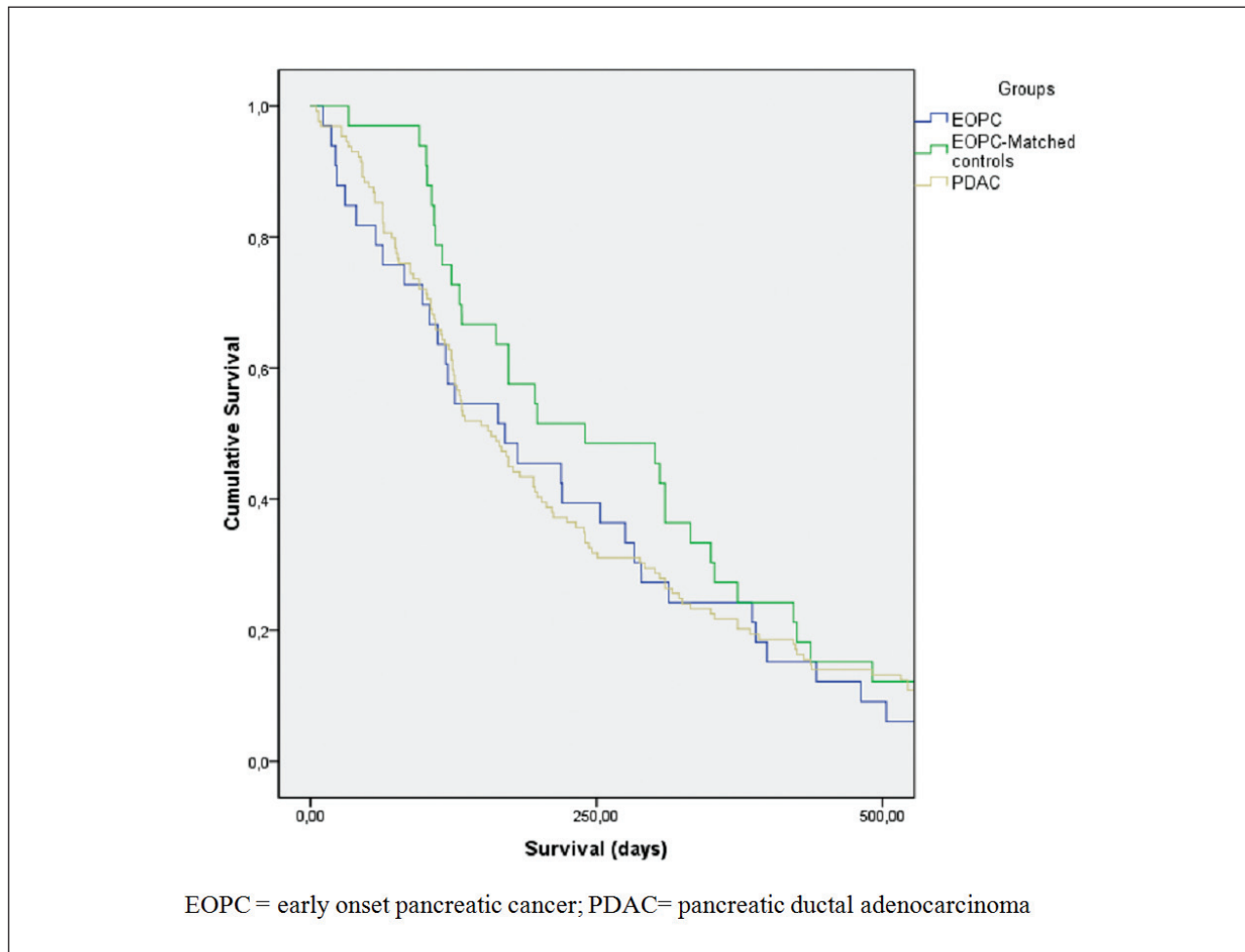


Figure 1 Survival of patients and controls

the periods 1993-2000 and 2001 and 2008. During the last decades smoking in Sweden has greatly declined from 24% in 1970 to 11% in 2008.

Smoking, however, is not the only predisposing factor. Dietary factors and obesity have also been discussed [17,18]. Obesity (BMI>30) at a younger age (20-49 years) is associated with an earlier onset of their pancreatic cancer by 2-6 years [19].

In the present study, the smoking frequency was high as compared to the whole population [20] (73% vs. 20%), supporting data that smoking has an important predisposing role. There was, however, no difference in the obesity ratio in this study as compared to the general population (9 vs. 12%).

Genetic factors have been discussed as a plausible explanation for EOPC. In this study fewer patients with possible hereditary cancer were found compared to other reports [7,21]. In larger studies on ductal adenocarcinoma an incidence of hereditary pancreatic ductal adenocarcinoma are found in 5-10%. In this study we only found one (3%) such patient. This could be due to the small sample size and the retrospective design but also to the fact that genetic analysis was more uncommon in the early period of this study's time span.

Individuals carrying various mutations in suppressor genes, such as *CDKN2A/p16* and *LKB1/STK11*, are predisposed for EOPC [22,23], and patients with alterations in *BRCA 1* [24] and *BRCA 2* [25] also have a higher risk of developing pancreatic cancer. In this study we only found one young patient with a first-degree relative that had suffered gynecological cancer; ovarian cancer. Furthermore, the average onset age of pancreatic cancer in *BRCA 1* and *2*-positive patients is 65 and 66 years [26].

Other studies, however, with a limited number of patients (n=10 and n=7), analyzed histopathological characteristics in the EOPC subgroup, but found no evidence of immunohistochemical differences including p53, MLH1, MSH2, c-erb-B2, Smad4 or EGFR expression [27,28]. Mutations in the *K-ras* gene at codon 12 have been thought of as markers for PDAC [29, 30], but their value has been debated [31].

Regarding metastatic pancreatic cancer, recent work offers interesting possibilities in an explanatory model for pancreatic cancer development and these new findings include the plasma cytokeratin 18 (CK18), interleukin 13 receptor $\alpha 2$ (IL-13R $\alpha 2$) and protein kinase C delta (PKCdelta) [32-34]

as markers for a more aggressive disease and malignant phenotype. An *in vitro* study by Melisi *et al* [35] also offers a possible link between cancer and inflammation and metastatic disease through interleukin-1 α by constitutive activation of nuclear factor κ B. In the present study we could only measure inflammation expressed by CRP at the time of diagnosis and it did not reveal any differences. All of these markers offer an interesting view and merit more studies, also with respect to the EOPC group that might have a more aggressive phenotype.

In summary, we investigated EOPC, all with histopathologically-proven PDAC. This was a retrospective study with all the obvious pitfalls. We also investigated a small cohort with the possibility of type 2 errors; hence conclusions should be made with caution. We have, however, found that the subgroup of young patients are diagnosed at a more advanced stage and have significantly more metastases. They also receive more therapy, both surgical and non-surgical. This, however, was not reflected in survival which was similar to that of the entire cohort of pancreatic ductal adenocarcinoma patients. Studies are ongoing and planned to compare immunological features of these patients and their metastasizing potential.

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Summary Box

What is already known:

- Early onset pancreatic cancer (EOPC) constitutes a subgroup of pancreatic adenocarcinoma manifesting before 50 years of age.
- Smoking and obesity have been debated to increase the risk of EOPC.
- Survival in EOPC is most likely similar to other pancreatic adenocarcinoma.

What the new findings are:

- Patients with EOPC present at a later stage with more metastases.
- Younger patients receive more therapy than older than older matched controls.
- Survival tends to be shorter when compared to tumor size and therapy-matched controls.

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