Int J Clin Exp Med 2017;10(6):9416-9423
www.ijcem.com /ISSN:1940-5901/IJCEM0045614

Original Article

Risk factors for early-onset pancreatic cancer patients, and survival analysis

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Received October 24, 2016; Accepted February 17, 2017; Epub June 15, 2017; Published June 30, 2017

Abstract: Background: The median age of patients with pancreatic ductal adenocarcinoma (PDAC) is approximately 70 years, and it rarely affects individuals younger than 45 years, when it is defined as early-onset pancreatic cancer (EOPC). Little is known about risk factors and outcomes for EOPC patients. Aim: To evaluate the clinico-pathological features, risk factors, and outcomes of EOPC. Methods: A retrospective analysis of pancreatic cancer patients diagnosed between January 1999 and December 2014 was performed. Information about environmental risk factors, clinical characteristics, treatment, and survival was collected. The risk factors of EOPC patients were compared to normal-onset pancreatic cancer (NOPC) patients. Results: Of 1789 patients with pathologically proven PDAC, 156 (8.7%) had EOPC. There was no difference regarding alcohol use, BMI, weight loss, and tumor location between EOPC and older subjects. EOPC patients were more likely to be male (75 vs. 63.9%) and to have a history of tobacco use (34.6% vs. 25.9%), compared NOPC patients. Among the 156 EOPC patients, there were 117 (75%) males, and 39 (25%) females, from 17 to 45 years old. Fifty-four (34.6%) had a smoking history, 55 had used alcohol, and 27 (17.3%) had a family history of cancer. For treatment, 32 underwent surgery to attempt curative resection of localized disease and 74 had palliative surgery. The median overall survival for the 156 EOPC patients was 8±0.5 months, with 1.2 years survival rates of 25.4 and 8%, respectively. For EOPC patients, the median overall survival of the patients treated with radical resection, palliative surgery, and medical treatment was 19±2.5, 8±0.6 and 6±0.3 months, respectively. The 1-year survival rates were 77.5, 17.6 and 4%, respectively. Survival analysis showed that the tumor size, tumor location, differentiation, treatment procedure, TNM stage, and first symptoms were associated with the overall survival ($P < 0.05$). Cox regression revealed that the TNM stage (RR=3.427; 95% CI: 1.802-6.519) and tumor size (RR=1.911; 95% CI: 1.054-3.463) are independent prognostic factors for EOPC patients. Conclusion: EOPC was associated with male gender and smoking history. Although EOPC patients display aggressive disease and have a worse outcome, radical resection is the best treatment. The TNM stage and tumor size are independent prognostic factors.

Keywords: Pancreatic cancer, early onset, smoking, survival analysis, risk factors

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is usually a lethal disease and is characterized by late diagnosis and rapid progression. According to cancer statistics for China, the incidence and mortality of pancreatic cancer was 52,200 and 45,600 for males, 37,900 and 33,800 for females. PDAC is the 7th most common cancer type by incidence and the 6th cause of cancer-related death in China [1]. The incidence is even higher in more developed countries [2]. Usually, PDAC affects people in their late adult life. The median onset age of PDAC is between 65 and 75 years, and patients younger than 45 years are identified as having early-onset pancreatic cancer (EOPC). Around 5% of newly diagnosed PDAC patients are < 45 years old in the USA [3]. Cancer statistics in Japan indicate that 1.0% of PDAC patients are younger than 45 years of age [4]. Although the rate is low, EOPC contributes significantly to the total burden of PDAC because it confers a greater number of years of potential life lost.

Given the rarity of EOPC, its risk factors are not well known and there is a dearth of available data concerning survival in these patients. To

Table 1. Comparison of environmental risk factors and tumor characteristics between EOPC patients and NOPC patients

	EOPC (n=156)	NOPC (n=1633)	*p* value
Age (year)	41±4.7	62±9.7	-
Sex			0.006
Male	117 (75%)	1044 (63.9%)	
Female	39 (25%)	589 (36.1%)	
Ever smoker	54 (34.6%)	423 (25.9%)	0.024
Consumption per day	19.3±8.6	18.1±9.0	0.709
Drinking history	55 (35.3%)	479 (29.3%)	0.122
Mean alcohol per day	3.4±2.9	3.8±2.8	0.697
Obesity (BMI > 28)	26 (16.7%)	226 (13.8%)	0.317
Mean BMI	24.28±3.50	24.51±8.80	0.826
Weight loss	72 (46.2%)	653 (40.0%)	0.134
Tumor location			0.235
Head and neck	109 (69.9%)	1174 (71.9%)	
Body and tail	47 (30.1%)	436 (26.7%)	
Diffuse	0	23 (1.4%)	
Clinical stage			0.129
Potentially resectable	45 (28.8%)	357 (21.87%)	
Locally advanced	53 (34.0%)	574 (35.15%)	
Metastasis	58 (37.2%)	702 (42.99%)	

the best of our knowledge, no reports concerning Chinese EOPC patients have been published. Therefore, we conducted a retrospective review of the National Cancer Center of China database over a 16-year period, in order to characterize clinical experience with EOPC, and to elucidate risk factors and survival characteristics of these patients.

Materials and methods

Patients

The medical records of all patients diagnosed with PDAC from January 1999 to December 2014 in the Cancer Hospital, Chinese Academy of Medical Science, Peking Union Medical College, were studied by retrospective chart review, as approved by the Institutional Review Board. All patients had a histological diagnosis of pancreatic ductal adenocarcinoma confirmed by pathology. Other histologic subtypes, including cystic, colloid, acinar, and solid-pseudopapillary, were excluded. For the whole cohort, the extracted information included demographics (age, gender) and epidemiologic and genetic information-tobacco history, alcohol use history, family history of cancers, and BMI. Subjects reporting > 6 months of smoking or > 100 cigarettes during their lifetime were classed as "ever smokers". The mean number of cigarettes smoked per day was recorded. Regarding alcohol history, "everdrinkers" were defined as those who drank a mean of at least 12.5 g of alcohol per day for at least 1 year, or a lower amount for > 1 year. The mean number of alcohol units per day consumed by each of the EPOC subjects was recorded. BMI at 1 year prior to diagnosis was recorded according to the Asia Standard, with any weight changes also recorded. Clinical data collected included: tumor location, size, and clinical stage at presentation.

EOPC patients

EOPC patients were defined as those who were 45 years or younger on the date of the diagnostic biopsy, and all treatments for this group were recorded. Curative surgical treatment consisted of pancreaticoduodenectomy or distal pancreatectomy. Palliative surgical treatment was bilio-digestive drainage. The following information was also recorded: initial symptoms; tumor differentiation; CEA level; CA19-9 level; CA242 level; treatment methods; number of lymph nodes resected; local recurrence and evidence of metastases, perineural invasion and vascular invasion; and adjuvant therapy. Follow-up information was obtained by telephone interviews, as well as from any records of outpatient follow-up. The primary outcome variable was overall survival, defined for EOPC patients as the period from date of initial treatment to date of death.

Statistical analysis

Data were analyzed using SPSS software (version 14.0; SPSS, Inc., Chicago, IL, USA). Differences between EOPC and normal-onset pancreatic cancer (NOPC) risk factors were analyzed. Chi-squared tests for comparison of proportions of categorical variables, and Student's t-test or Mann-Whitney test for continuous variables were employed. Multiple logistic regression analysis was employed to investigate factors associated with risk of EOPC. Survival analysis was performed utilizing the Kaplan-

Table 2. Clinical characteristics and survival analysis of 156 EOPC patients

Characteristic factors	Number	Median survival time (month)	X^2	*P* value
Gender			0.226	0.635
Male	117	8		
Female	39	9		
Tumor location			5.445	0.020
Head and neck	109	9		
Body and tail	47	6		
Tumor size			23.243	0.000
≥ 5 cm	76	7		
< 5 cm	80	11		
Treatment			69.443	0.000
Radical resection	32	19		
Palliative surgery	74	8		
No surgery	50	6		
CA 19-9 level			0.819	0.365
Elevated	108	8		
Normal	33	8		
CEA level			1.510	0.219
Elevated	50	8		
Normal	84	9		
CA 242 level			1.342	0.247
Elevated	65	9		
Normal	51	9		
TNM stage			78.826	0.000
I	2	Not calculated		
II	12	19		
III	84	9		
IV	58	5		
Differentiation			13.889	0.001
High	6	10		
Middle	23	15		
Low	41	9		
Cancer History			0.653	0.419
Yes	27	9		
No	128	8		
Smoking			0.058	0.810
Yes	54	8		
No	102	8		
Drinking			0.508	0.476
Yes	55	8		
No	101	8		
Weight loss			0.004	0.948
Yes	72	9		
No	84	8		
BMI			1.903	0.168
≥ 28	26	7		
< 28	127	9		
Initial symptom			18.814	0.001
Abdominal discomfort	97	8		
Jaundice	29	11		
Backache	15	5		
Other	15	8		

Meyer method. Possible prognostic factors influencing survival were first evaluated by univariate analysis (log-rank test). Only parameters which showed significance by univariate analysis were further analyzed by multivariate analysis (Cox proportional hazards test, method forwardconditional). Statistical significance was defined as a *p* value of less than 0.05.

Results

PDAC subjects

Data from a total of 1789 subjects with PDAC were extracted. A histological or cytological diagnosis was obtained in all cases, either from the primary pancreatic lesion or from metastases. The pathology was confirmed by two pathologists. Of the 1789 subjects, 1161 (64.9%) were male, with a median age of 62 years (**Table 1**); in 1283 (71.7%) subjects, the tumor was located in the pancreatic head. According to the clinical symptoms and image data, 402 subjects had potentially resectable tumors at time of diagnosis, 627 had locally advanced disease, and 760 had distant metastasis. EOPC was present in 156 subjects who were ≤ 45 years of age, and represented 8.72% of all PDAC cases.

Risk factors assessment

We compared environmental risk factors and the tumor characteristics of the EOPC patients and the NOPC patients. The EOPC group had a higher fraction of males (75%) and “ever smokers” (34.6%) than the NOPC group (63.9% and 25.9%, respectively) ($P < 0.05$). Daily cigarette consumption did not differ between the two groups (19.3±8.6 vs. 18.1±9.0 per day, P=0.709). The percentage of “ever drinkers” in the EOPC group was higher than in the NOPC group (35.3% of EOPC vs. 29.3% of NOPC,

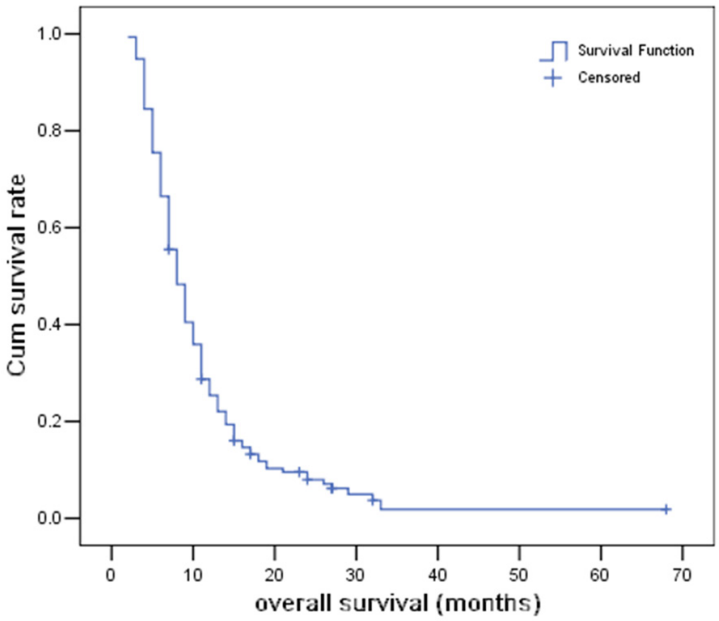

Figure 1. Overall survival of the 156 EOPC patients.

P=0.122). The different gender distribution may play a role, but the mean number of alcohol units consumed per day was not different between the EOPC (3.4±2.9) and the NOPC groups (3.8±2.8) (P=0.679).

We also calculated the changes in BMI over the year before diagnosis; this indicated that 16.7% of EOPC subjects were obese, whereas 13.8% of NOPC subjects were obese. Nearly half of the subjects had weight loss before the final diagnosis. But there was no difference in BMI, weight loss, or obesity between the EOPC and NOPC patients (**Table 1**).

Characteristics of EOPC patients

EOPC was identified in 156 patients in our medical center (shown in **Table 2**). The mean age was 41 years (range: 17 to 45), and 117 (75%) patients were male. Pre-existing diabetes mellitus occurred in 18 patients. Also, 27 patients had a first degree familial cancer history, six of whom had pancreatic cancer. Initial symptoms included abdominal pain in 97 and jaundice in 29 patients; bile drainage was performed prior to systematic treatment in 14, for severe jaundice. Nearly half (46.2%) of the subjects had weight loss before final diagnosis. The mean BMI of all the patients was 24.28±3.50, but 26 patients were obese according the Asia database. The tumor was located at the head or neck of the pancreas in 109 patients. The other patients presented with a mass in the pancreatic body or tail. The mean tumor diameter was 4.65 cm (range: 1.5 to 12 cm). Serum tumor marker analysis showed elevated levels of CA19-9 in 108 patients, of CEA in 50 patients, and of CA242 in 65 patients. Histopathological grading was performed for 70 of the 156 EOPC surgical biopsies; 8.6% were highly, 32.8% were moderately, and 58.6% were poorly differentiated.

Treatment and survival analysis

Of these 156 EOPC subjects, a potentially curative operation was performed on 32 (20.5%), and 74 (47.4%) were treated with palliative bilio-digestive drainage surgery. Potentially curative surgical treatment consisted of pancreaticoduodenectomy or, if appropriate, distal pancreatectomy. Beyond palliative surgery, 13 subjects with locally advanced pancreatic cancer received intraoperative radiation treatment. Finally, 50 patients were not surgical candidates because of distant metastasis at diagnosis, or high surgical risk as a result of poor physical condition. These patients received *supportive medical care and symptom management*. Most patients presented with stage III disease (stage I, 1.3%; stage II, 7.7%; stage III, 53.8%; and stage IV, 37.2%).

The estimated median overall survival for the EOPC cohort was 8±0.5 months, with a 1.2-year survival rate of 25.4% and 8%, respectively (**Figure 1**). The median overall survival for those who underwent radical resection, palliative surgery, and supportive medical treatment were 19±2.5, 8±0.6 and 6±0.3 months, with 1 year survival rates of 77.5, 17.6 and 4%, and 2-year survival rates of 32.8, 0, and 0%, respectively. Survival analysis showed that a tumor size ≥ 5 cm, tumor located at the distal part of the pancreas, lower-grade differentiation, higher TNM stage, palliative treatment procedure

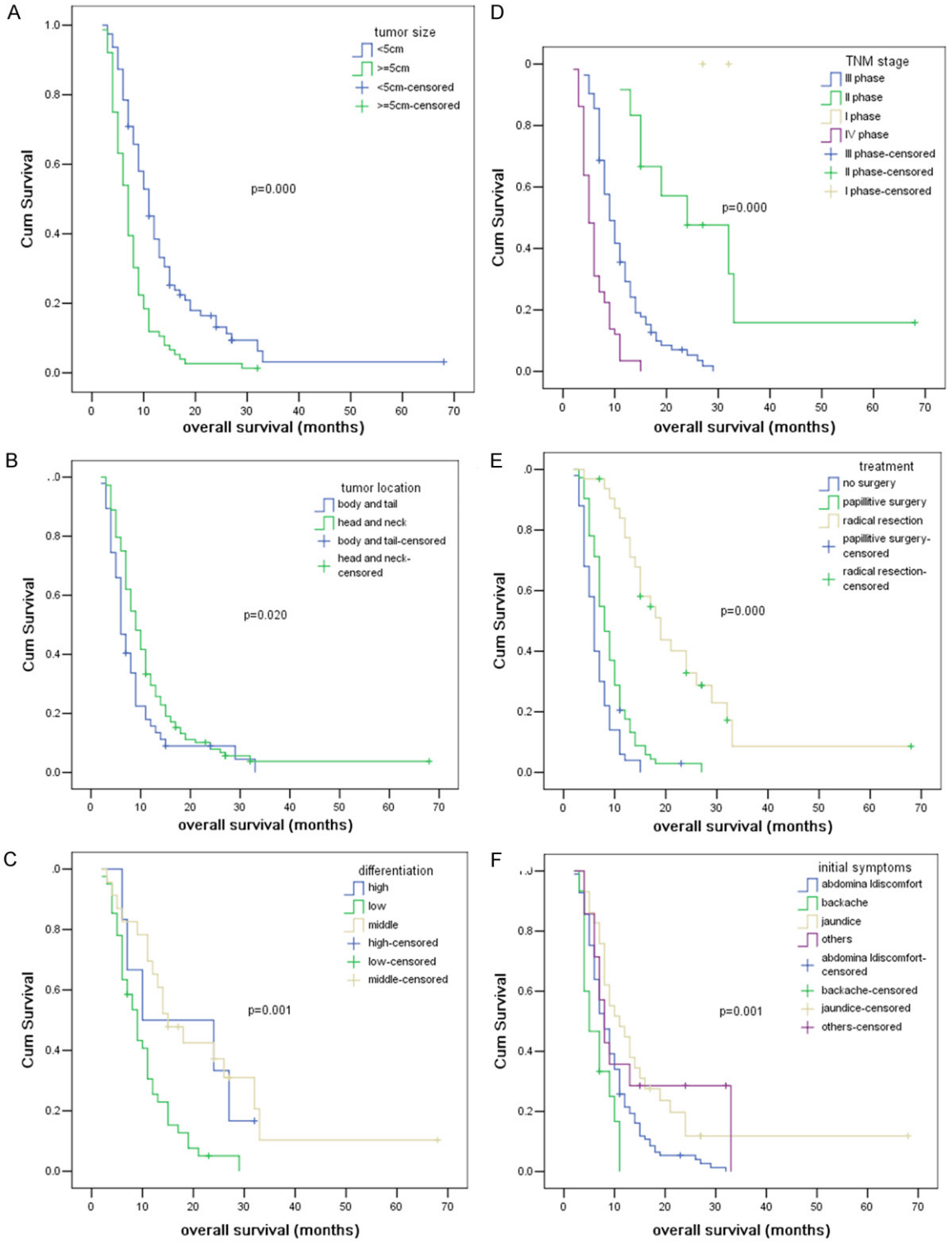

Figure 2. Survival analysis showed risk factors associated with the overall survival of EOPC patients ($P < 0.05$). A: Tumor size ≥ 5 cm was associated with poorer overall survival. B: Tumor located at the distal portion of the pancreas was associated with poorer overall survival. C: The differentiation of the tumor cells is the significant risk factor for the overall survival. D: The TNM stage is the significant risk factor for the overall survival. E: Radical resection can significantly improve the prognosis of EOPC patients. F: The first symptom is associated with poorer overall survival.

Table 3. Multivariate Cox regression of factors associated with EOPC patients' survival (n=156)

Characteristics	B	SE	Wald	df	p	RR	95.0% CI for RR	
							Lower	Upper
TNM stage	1.232	0.328	14.093	1	0.000	3.427	1.802	6.519
Differentiation	-0.326	0.224	2.113	1	0.146	0.722	0.466	1.120
Treatment procedure	0.301	0.254	1.407	1	0.236	1.352	0.822	2.224
Tumor size	0.648	0.303	4.558	1	0.033	1.911	1.054	3.463
Location	-0.188	0.314	0.358	1	0.550	0.829	0.448	1.533
Initial Symptoms	0.067	0.150	0.199	1	0.656	1.069	0.796	1.436

and a backache first symptoms were associated with worse overall survival ($P < 0.05$) (**Figure 2**). Other clinical characteristics such as gender, CA19-9 level, CEA level, CA242 level, cancer history, tobacco and alcohol history, BMI and weight loss did not influence the prognosis. Cox regression revealed that the TNM stage (RR=3.427; 95% CI: 1.802-6.519) and tumor size (RR=1.911; 95% CI: 1.054-3.463) are independent prognostic factors for EOPC patients (**Table 3**).

Discussion

About 80% of pancreatic cancers are diagnosed in patients between 60 and 80 years of age, in late adult life [5]. Early-onset pancreatic cancer diagnoses comprise 1 to17% of cases [4, 6]. Clinicopathologic features of PDAC occurring in young patients (EOPC) have been little investigated because of their relative rarity [7]. We conducted a retrospective study of EOPC treated at the National Cancer Center of China in Beijing. To the best of our knowledge, these results are from the largest cohort of young PDAC patients yet reported from China.

The association of PDAC with cigarette smoking has been evaluated in multiple reports and case-control studies [8-12]. Several studies have demonstrated that the mean age at diagnosis of pancreatic cancer is earlier in smokers than in nonsmokers [13-16]. Early exposure to tobacco smoke might be a significant risk factor for early onset of PDAC. Raimondi et al. [17] suggested that smoking is the major identified risk factor and seems to be even more important for EOPC than for PC in older age groups. Furthermore, Brand et al. [13] reported that cigarette smoking and alcohol consumption were associated with younger age at pancreatic cancer presentation and even have a combined effect on age of diagnosis. But Duffy [7] reported that smoking did not appear to influence the occurrence of pancreatic cancer in young patients, or at least did not play a major role as a risk factor. Therefore, debate continues on the role of smoking in EOPC patients. In this study, smoking frequency was higher than in the general population (34.6 vs. 25.9%), supporting the hypothesis that smoking is a predisposing factor for pancreatic cancer. However, there was no difference in the mean BMI and drinking history of EOPC compared to the NOPC subjects. A role for alcohol intake in EOPC has been indirectly suggested by Raimondi et al. [13]. Other studies showed that obesity (BMI > 30) at a younger age (20 to 49 years) is associated with an earlier onset of pancreatic cancer by 2-6 years [18]. Our criterion for obesity in men is a BMI > 28 according to the Asia Obesity Standard, which is different from the previous study. EOPC occurred more frequently in males; in China, the majority of smokers are men. Our results thus support the hypothesis that tobacco smoking plays a role in the early onset of pancreatic cancer.

Pancreatic ductal adenocarcinoma has the poorest 5-year survival rate of all malignancies [19]. The diagnosis of this cancer is frequently delayed because it generally has a non-specific clinical presentation [20]. The effect of age on the prognosis of this cancer is not well established [21]. Because of the rarity of this cancer, there is a dearth of survival data on EOPC patients. Duffy published a large retrospective review of 136 patients under the age of 45 years with a diagnosis of pancreatic ductal adenocarcinoma; he found that the EOPC patients with stages I-II disease have a favorable prognosis. However, patients with stage III-IV EOPC appeared to have a prognosis as grave as that of the NOPC population with stage III-IV pancreatic cancers. The median survival time of EOPC

patients after radical resection can reach 41.8 months [7]. A survival study from Johns Hopkins University School of Medicine showed that the demographic, pathologic, and treatment characteristics of EOPC patients were similar to those of NOPC patients older than 70 years. In this study, younger patients had fewer complications after curative resections and better survival [22]. In fact, younger patients were more likely to be candidates for curative surgery and combination therapies, and their prognosis may be better [23]. In our study, the median survival of 32 EOPC patients who underwent curative resection was 19 months, similar to that in older patients but less than previous reports. A higher rate of low-grade tumor differentiation in our cohort may explain this difference.

Our survival analysis also showed that tumor size, tumor location, differentiation, treatment procedure, TNM stage, and first symptoms are all associated with overall survival. TNM stage and tumor size are independent prognostic factors for EOPC patients.

The current analysis has several limitations: it is a single-institution retrospective study, and it lacks a survival comparison with NOPC patients.

Conclusion

In summary, this report documents the clinical experience with PDAC at our institution, in a population of younger patients, over a 16-year period. To the best of our knowledge, this is the largest study evaluating outcomes in Chinese EOPC patients, and it supports the hypothesis that this cancer is related to male gender and smoking history; TNM stage and tumor size are independent prognostic factors. Although EOPC is characterized by aggressive progression and poor outcomes, radical resection is the best treatment.

Disclosure of conflict of interest

None.

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