A Time-Trend Survival Analysis of Elderly Resectable Pancreatic Cancer Patients

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Research

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Abstract

Background: The time-trend in the survival of elderly pancreatic cancer patients was still unclear. Thus, the aim of this study was to compare the survival benefit of young and elderly pancreatic cancer patients by a time-trend analysis.

Methods: From 2004-2013, we obtained 5,341 of young patients (< 80 years) and 569 elderly patients ($\geq$ 80 years) from the Surveillance, Epidemiology, and End Results (SEER) database, and the overall survival of these patients were analyzed by Kaplan-Meier estimator. The independent factors which could predict the survival of patients were determined by cox proportional hazards model.

Results: We observed that the median overall survival of the young patients in 2004-2008 cohort was significantly ($P < 0.001$) increased when compared to that in the 2009-2013 cohort. However, we did not observe the survival benefit for the elderly patients. The Cox proportional hazards model demonstrated that the tumor size, lymph node ratio, grade, and AJCC TNM stage were independent factors of survival.

Conclusions: This study demonstrated that compared to 2004-2008, the survival of elderly patients in 2009-2013 was not significantly improved. Thus, the clinicians still need to administer more care to elderly patients.

Introduction

It is reported that pancreatic cancer will surpass colorectal, breast, and prostate cancer to be the second leading cause of cancer-related deaths after lung cancer by 2030 [1, 2]. In 2050, the elderly population (age $\geq$ 80 years) is projected to be 30.9 million, almost three-fold more than that in 2012 (11.6 million) [3]. There will be an increasing number of elderly patient inevitable requiring surgical interventions in the future.

Pancreaticoduodenectomy (PD) or Whipple's procedure is currently the only potentially definitive treatment for pancreatic cancer [4]. Usually, the advanced age of patients is considered as a contraindication to PD, because surgery increased the perioperative mortality of patients [5]. However, recently some studies suggest that the survival of elderly patients, who underwent PD, was significantly longer than those who were not treated by resection of tumor [6–8].

Some population-based studies proved that with the advancements in surgical techniques and adjuvant therapy, the overall survival of pancreatic cancer patients has been improved over time [9, 10]. However, no time-trend analysis has so far explored if the survival time of elderly patients is improved over period. Thus, the present study used a long-term follow-up database, Surveillance, Epidemiology, and End Results (SEER), to compare the survival over time between the young (age < 80 years) and the elderly (age $\geq$ 80 years) population.

Materials And Methods

Database

We used the SEER database to analyze the data of patients with pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer [11]. The database includes patients of 18 registries in the USA from 1973–2013, encompassing approximately 28% of the USA population. All the malignant cases were followed-up annually to determine vital status.

Patient Population

All the variables' definitions are encoded in the SEER database. To identify the PDAC cases, site codes (C25 pancreas, C25.0-C25.9) and histology codes (8140 adenocarcinoma, 8500 infiltrating duct carcinoma) based on the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) were used [12]. Only cases that underwent PD and microscopically confirmed were included.

Outcome Variables

We only included those PDAC patients that underwent PD with precise data available for the following variables: age at diagnosis, year of diagnosis, gender, race, tumor site, tumor size, regional nodes positive, regional nodes examined, grade, stage, vital status, and survival months.

In order to compare the long-term survival between young and elderly patients, all cases were divided into two group age < 80 years and age $\geq$ 80 years. Since 2004, the AJCC 6th stage has been used in the SEER database. Thus, the diagnosis years of the cases included in our study ranged from 2004–2013. To analyze the median overall survival between different time periods, we divided the year of diagnosis into two groups: 2004–2008 year and 2009–2013. Furthermore, we also divided the tumor size into three groups: $\leq$ 2 cm, 2–4 cm, and > 4 cm. The lymph node ratio (LNR) is considered a robust prognostic factor after resection of pancreatic cancer and was estimated using regional nodes positive divided by regional nodes examined [13]. LNR was then categorized into three groups: 0%, 1–50%, > 50%.

Data Analysis And Statistics

The patients' clinical and pathology characteristics were summarized with descriptive statistics. Normally distributed continuous variables were presented as mean $\pm$ standard deviation and Student's *t*-test was used to evaluate these variables. In the case of non-normal distribution, the continuous variables were expressed as median (interquartile range, IQR) and analyzed using Mann–Whitney *U* test. The categorical and ordinal variables were presented as frequencies and proportions. Chi-square or Mann–Whitney *U* tests were used independently for categorical or ordinal variables, respectively, to investigate the differences between the two groups. Survival was analyzed using the life-table curve, and Gehan–Wilcoxon test was used to compare these curves. Univariate and multivariate Cox proportional hazards

model (enter method) was used to identify the independent factors associated with prognosis in elderly patients. All statistical analyses were performed using SPSS version 19.0 (IBM Corporation. Armonk, NY, USA). P -value ≤ 0.05 was considered statistically significant.

Results

Patient Characteristics

From 2004–2013, a total of 5,910 patients (3,005 males and 2,905 females) were microscopically diagnosed as PDAC and underwent PD. The patients' characteristics were summarized in Table 1. The median age of all patients was 67.00 years (IQR, 59.00 years-74.00 years). 5,341 patients (90.32%) were included in the young cohort (aged < 80 years) and 569 were included in the elderly cohort (aged $\geq$ 80 years). A statistical difference between these two cohort was not observed with respect to the tumor size ($P = 0.225$) and LNR ($P = 0.301$). In addition, no statistically significant differences were observed between these two cohorts in the diagnosis period (2004 years-2008 years and 2009 years-2013 years, $P = 0.134$), tumor site (head, body, tail, pancreatic duct and neck, overlapping lesion, unspecified site $P = 0.341$), grade (grade I, II, III, and IV, $P = 0.325$), AJCC TNM stage (stages I, II, III, and IV, $P = 0.612$). However, the gender composition was significantly ($P < 0.004$) different between young cohort (51.50% males) and elderly cohort (45.20% males). The composition of the race also differed significantly between the two cohorts ($P < 0.001$).

Table 1
Baseline characteristics of the younger and the elderly patients

Variable	Age < 80 years (N = 5341) n (%) ^a	Age ≥ 80 years (N = 569) n (%) ^a	P-value
Age	65.00 years (58.00 years-72.00 years)	82.00 years (81.00 years – 84.00 years)	-
Tumor Size	3.00 cm (2.40cm,4.00cm)	3.00 cm (2.50cm,4.00cm)	0.225 ^{\$}
Lymph Nodes Ratio	11.54% (0.00%, 26.67%)	10.34% (0.00%, 25.00%)	0.305 ^{\$}
Year of Diagnosis			
2004–2008	2334(43.70%)	230(40.40%)	0.134 [#]
2009–2013	3007(56.30%)	339(59.60%)	
Gender			0.004[#]
Male	2748 (51.50%)	257 (45.20%)	
Female	2593 (48.50%)	312 (54.80%)	
Race			< 0.001[#]
White	4430 (82.94%)	491 (86.30%)	
Black	540 (10.11%)	26 (4.60%)	
Others^b	371 (6.95%)	52 (9.10%)	
Tumor Site			0.341 [#]
Head	4782 (89.53%)	502 (88.22%)	
Body	108 (2.02%)	12 (2.11%)	
Tail	111 (2.08%)	17 (2.99%)	
Pancreatic duct	60 (1.12%)	4 (0.70%)	
Neck of pancreas	29 (0.54%)	6 (1.05%)	
Overlapping lesion	120 (2.25%)	10 (1.76%)	
Unspecified site	131 (2.45%)	18 (3.16%)	

a. Number of patients (constituent ratio); b. American Indian/Alaska Native, Asian or Pacific Islander; c. American Joint Committee on Cancer: AJCC Cancer Staging Manual; \$ Mann–Whitney *U* test; # Chi square test. Variables and values in bold means statistically significant.

Variable	Age < 80 years (N = 5341) n (%) ^a	Age ≥ 80 years (N = 569) n (%) ^a	P-value
Grade			0.325 ^{\$}
I	548 (10.26%)	58(10.19%)	
II	2808(52.57%)	284 (49.91%)	
III	1942 (36.36%)	225 (39.54%)	
IV	45 (0.84%)	2 (0.35%)	
Tumor Stage (AJCC 6th) ^c			0.612 ^{\$}
I	453 (8.48%)	51 (8.96%)	
II	4431 (82.96%)	472 (82.95%)	
III	216 (4.04%)	20 (3.51%)	
IV	241 (4.51%)	26 (4.57%)	
a. Number of patients (constituent ratio); b. American Indian/Alaska Native, Asian or Pacific Islander; c. American Joint Committee on Cancer: AJCC Cancer Staging Manual; \$ Mann–Whitney <i>U</i> test; # Chi square test. Variables and values in bold means statistically significant.			

Survival Analysis

The overall survival of all patients was 15.00 months (IQR, 7.00 months-26.00 months). In addition, we observed that the median overall survival of young cohort was significantly ($P < 0.001$) longer than that of elderly cohort (young cohort vs. elderly cohort, 18.83 months vs. 14.68 months, Fig. 1A). Notably, compared 2004–2008 years to 2009–2013 years, the overall survival of all patients significantly ($P < 0.001$) increased from 17.19 months to 19.55 months (Fig. 1B). A significant ($P < 0.001$) increase was also observed in young cohort, from 17.49 months to 20.09 months (Fig. 1C), but only a minor ($P = 0.498$) increase was observed in elderly cohort, from 14.59 months to 14.63 months (Fig. 1D).

The univariate and multivariate analysis of elderly patients were presented in Table 2. Only two patients were diagnosed with grade IV and were excluded from analysis. The results showed that age, year of diagnosis, gender, race and tumor primary site were not significantly independent risk factor for elderly PDAC patients after PD. Compared to the reference, the tumor size [2.0 cm-4.0 cm or > 4.0 cm vs. reference (< 2.0 cm)], LNR [1–50%, > 50% vs. reference (0%)], grade [III vs. reference(I)] and TNM stage [II, III, IV vs. reference (I)] were associated with short survival time of elderly patients (Fig. 2).

Table 2
Univariate and multivariate analysis in patients aged 80 and older

Variable	Median	Univariate			Multivariate		
	(Months)	HR	95%CI	<i>P</i>	HR	95%CI	<i>P</i>
Age	14.68	1.039	1.001–1.079	0.045	1.028	0.990–1.068	0.154
Year							
2004–2008	14.59	Reference			0.975	0.937–1.015	0.218
2009–2013	14.63	1.023	0.841–1.244	0.820			
Gender					0.994	0.816–1.210	0.949
Male	16.29	Reference					
Female	13.71	1.001	0.826–1.214	0.989			
Race							
White	15.03	Reference			1.050	0.886–1.244	0.575
Black	12.88	1.237	0.788–1.941	0.355			
Others ^a	13.26	1.083	0.762–1.540	0.657			
Tumor Site							
Head	14.67	Reference			0.984	0.936–1.036	0.544
Body	22.49	0.651	0.291–1.450	0.297			
Tail	10.30	1.141	0.565–2.306	0.713			
Neck	15.50	0.840	0.269–2.622	0.765			
Duct	14.00	1.092	0.407–2.928	0.862			
Other ^b	10.05	0.864	0.545–1.370	0.534			
Tumor Size					1.012	1.004–1.019	0.002
≤2.0 cm	20.51	Reference					
2.1cm-4.0 cm	14.96	1.397	1.074–1.816	0.013			
> 4.0 cm	10.67	1.962	1.428–2.695	<0.001			
LNR^c					1.008	1.004–1.012	<0.001

a. American Indian/Alaska Native, Asian or Pacific Islander; b. Overlapping lesion and unspecified site; c. LNR lymph node ratio; d. American Joint Committee on Cancer: AJCC Cancer Staging Manual. Variables and values in bold means statistically significant.

Variable	Median	Univariate	Multivariate		
0%	19.62	Reference			
1%-50%	13.87	1.436	1.161–1.776	0.001	
> 50%	11.15	1.911	1.343–2.719	< 0.001	
Grade				1.311	1.122–1.531
I	22.19	Reference			
II	15.95	1.289	0.918–1.811	0.142	
III	10.96	1.969	1.395–2.781	< 0.001	
IV	-	-	-	-	
Tumor Stage (AJCC^{6th})				1.298	1.076–1.565
I	15.93	Reference			
II	15.48	1.435	1.01–2.04	0.043	
III	12.82	2.167	1.14–4.12	0.018	
IV	5.18	2.943	1.74–4.99	< 0.001	
a. American Indian/Alaska Native, Asian or Pacific Islander; b. Overlapping lesion and unspecified site; c. LNR lymph node ratio; d. American Joint Committee on Cancer: AJCC Cancer Staging Manual. Variables and values in bold means statistically significant.					

Discussion

PD is the optimal curative intervention for pancreatic cancer [14, 15]. However, the benefit of PD in elderly patients, especially ≥ 80 years is yet controversial. A previous meta-analysis showed that patients aged 80 years or older present an increased incidence of postoperative mortality and morbidity than the younger patients [16]. Nevertheless, the definitions of complications among the included studies were often not reported or different in the various studies. In addition, most studies comprised of limited sample size in the elderly group (median 53, IQR 24–136) and included heterogeneous patient population (different types of pancreatic malignancies, periampullary cancers, and benign pancreatic diseases). Moreover, some of those studies included patients that underwent PD or a distal pancreatectomy.

In the present study, only histological diagnosis of PDAC patients and those that underwent PD resection was included. The results proved that the overall survival of elderly patients was significantly shorter than the younger (14.68 months vs. 18.83 months, $P < 0.001$), while age is not the independent risk factor for elderly PDAC patients undergoing PD. This result was in agreement with some previous studies [16–18]. For example, Park et al. demonstrated that surgical resection significantly increased the survival of elderly patients when compared to non-surgical resection patients [18].

Some studies reported that the mortality after PD decreased significantly over the last few years [19–21]. Indeed, this study also reported that the overall survival of entire cohort (Fig. 1B) or the young cohort (Fig. 1C) has improved during the time period of 2009–2013. This benefit may result from the improvements of high-quality imaging techniques [19] and the multidisciplinary team management of pancreatic cancer [22]. Unfortunately, we did not observe the survival benefit in elderly patients. This suggests that how to improve the survival of resectable elderly pancreatic cancer patients is still a changeling for clinicians. It has been reported that PD can cause pancreatic fistula, a fatal complication of elderly patients [23]. In addition, some complications, such as intra-abdominal abscess, sepsis and organ failure are more frequently in elderly patients [9]. Thus, several studies recommend that the elderly pancreatic cancer patients should be treated in high volume hospitals and requires multidisciplinary team management.

In conclusion, the present study demonstrated that the overall survival of young pancreatic cancer patient was improved over the time, however, the survival benefit of elderly patients was not observed. Therefore, great care must be administered in elderly pancreatic cancer patients who treated by surgery.

Abbreviations

SEER Surveillance, Epidemiology, and End Results

AJCC American Joint Committee on Cancer

PD Pancreaticoduodenectomy

PDAC pancreatic ductal adenocarcinoma

ICD-O International Classification of Disease for Oncology

LNR The lymph node ratio

Declarations

Acknowledgement

Not applicable

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Author Contributions

RJ, GS and XB designed the study. RJ and YS obtained the data from SEER. RJ and BL performed the analysis and interpreted the results. RJ wrote the manuscript. All authors read and revised the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the institutional review board and was also conducted in accordance with the Declaration of Helsinki and all patients signed the informed consent.

Consent for publication

Not applicable

Competing Interests

The authors declare that they have no conflicts of interest.

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Figures

Figure 1

(A) Survival curve of young (aged <80 years) and elderly (aged ≥80 years) pancreatic ductal adenocarcinoma (PDAC) patients; (B) Survival curve over time (2004-2008 vs. 2009-2013) of all PDAC patients; (C) Survival curve over time (2004-2008 vs. 2009-2013) of young PDAC patients; (D) Survival curve over time (2004-2008 vs. 2009-2013) of elderly PDAC patients.

Figure 2

Survival curve of elderly (aged ≥ 80 years) PDAC patients with distinct of tumor size (A), lymph nodes ratio (B), grade (C), and tumor stage (D)