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Young Patients Undergoing Resection of Pancreatic Cancer Fare Better than their Older Counterparts

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Abstract

Background—The median age of pancreatic ductal adenocarcinoma (PDAC) patients is 71 years. PDAC rarely affects individuals under the age of 45. We investigated features of PDAC occurring in young patients (< 45 years) who underwent surgical resection in order to determine if any difference exists in comparison to elderly patients (> 70 years).

Methods—A retrospective analysis of patients with PDAC who were < 45 years on the date of surgery between 1975 and 2009 was performed. This cohort was compared with PDAC patients whose ages were over 70 years on the date of surgery over the same time interval. Information reviewed included demographics, Charlson Age–Comorbidity Index (CACI), pathological staging, surgical management, and death or last follow-up.

Results—Seventy five patients with PDAC of age < 45 years at surgery were identified. The reference group consisted of 870 patients with a median age of 75. The most common symptoms of young patients were jaundice (45 %), abdominal pain (32 %), or weight loss (33 %). This did not differ significantly from older patients. Among the younger patients, 7 (9 %) underwent total pancreatectomy, 60 (80 %) underwent pancreaticoduodenectomy, and 8 (11 %) had distal pancreatectomy. The distribution of type of surgery was similar between two groups. Fifty-two of the young patients (69 %) had an R0 resection and this did not differ from the older age group ($n=616$; 71 %). The rate of lymph node positivity was 68 % for younger patients and 74 % for older patients ($p=0.27$). Of the younger patients, 11, 13, 49, and 2 were classified as stage I, IIA, IIB, and III, respectively, and did not differ from the older age group. The median overall survival for the young patients cohort was 19 months (95 % CI 15–22 months) which is longer than 16 months (95 % CI 14–17 months) of the older group ($p=0.007$). The actual 5- and 10- year survival in young age group (24 and 17 %) was longer than that in old age group (11 and 3 %) ($p<0.05$). The median CACI of the younger patients was 0.5 and was lower than 4.1 of the older patients ($p<0.0001$).

Conclusions—The demographic, pathologic, and treatment characteristics of PDAC patients younger than 45 years were similar to those older than 70 years. Younger patients had fewer complications after curative resections. The better survival among younger patients is likely related to fewer comorbidities in this group. These findings will be useful in counseling young patients with resectable pancreatic cancer.

Keywords

Pancreas surgery; Morbidity; Mortality; Outcomes

Introduction

Pancreatic cancer (pancreatic ductal adenocarcinoma, PDAC) is a highly lethal disease that is characterized by early systemic spread and rapid progression following diagnosis. It is the fourth leading cause of cancer deaths in the US¹ with 43,920 new cases and 37,390 deaths estimated to have occurred in 2012 (<http://seer.cancer.gov/statfacts/html/pancreas.html>). Both the advanced stage at presentation and lack of effective systemic therapy contribute to the poor prognosis of this disease. Resection of localized disease offers the only chance for long-term survival. Prognostic factors following the resection of PDAC include tumor size, histologic grade, lymph node status, and margin status. Patients who undergo an R0 resection for PDAC with favorable tumor characteristic that include size less than 3 cm, well-differentiated tumors, and absence of nodal metastasis have a 5-year survival rate of approximately 40 %.²⁻⁴

The median age of diagnosis of PDAC in the USA is 71 years. Less than 3 % of patients diagnosed with PDAC are under the age of 45 years (accessed at July 12, 2012, <http://seer.cancer.gov/statfacts/html/pancreas.html>). Whether the age of onset affects long-term survival for patients with PDAC is not well-defined. Very little data exist regarding the clinicopathological features and treatment response of young patients with PDAC.⁵⁻⁸ Age of onset was not found to be a prognostic factor in several large cohort studies.^{2,9} In contrast, a population-based study using the SEER registry from 1988 through 2002 showed that younger patients (defined as less than age 49) with PDAC were more likely to undergo surgical treatment and had an associated higher 2-year survival rate as compared with patients age 80 years or older (36 vs. 10 %).¹⁰ Similarly, Duffy et al. reported a cohort of 35 young patients with PDAC who underwent curative resections achieved an impressive median overall survival of 41.8 months.⁶

In light of the potential differences in young patients who develop pancreatic cancers in comparison to a more typical age group, we sought to evaluate clinical and pathological features in these patients. The goal of this study was to characterize the outcome after curative surgery in young patients with PDAC. We performed a retrospective review of our pancreatic resection database, which covers a 34-year period, to characterize our experience with regard to the treatment of PDAC in a younger patient population.

Methods

A prospectively maintained database of patients undergoing pancreatic resection at the Johns Hopkins Hospital was reviewed to identify patients who underwent resection for a pathologically confirmed PDAC between 1975 and 2009. Patients with PDAC who were younger than 45 years or older than 70 years on the date of surgery were grouped into two cohorts. International patients who were not followed long-term after resection were excluded. Other common pathologic subtypes of pancreatic tumors in young patients including solid-pseudopapillary neoplasm, acinar cell carcinoma, neuroendocrine tumor, and pancreatoblastoma were excluded.

Patient demographics, Charlson Age–Comorbidity Index (CACI), tumor pathological staging, and surgical treatment-related variables were retrieved from the database and confirmed by chart review. Follow-up was obtained through office records and the social security death index. Patient factors evaluated included age, gender, and medical comorbidities. Treatment factors included the date of operation, type of operation, the estimated blood loss, length of stay (LOS), status at last follow-up, and whether adjuvant therapy was administered. Pathologic factors evaluated included tumor, nodes, and metastases stage, margin (positive or negative), and differentiation (well, moderate, or poor).

Margins assessed included the pancreatic resection margin, biliary margin, bowel margins, and uncinate margin. Maximal tumor size was determined and defined as the maximum diameter at pathological analysis.

CACI is a measure of comorbidity to standardize the evaluation of surgical patient and has been used to predict post-op mortality of patients undergoing surgery in many studies.¹¹ CACI score was calculated by weighing each preoperative comorbid disease separately and adding to the age factor as described by Charlson.¹² One point for each decade over the age of 50 was added.

Overall survival was computed from the time of operative resection to the date of last follow-up. Statistical Package for the Social Sciences software (SPSS V.16) was used to analyze data. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Continuous variables were expressed as median±standard deviation and were compared using Mann–Whitney test. Categorical variables were compared using a χ^2 test (or Fisher's exact test). Overall survival was computed from the time of operative resection to the date of last follow-up. A *p* value of less than 0.05 was considered significant. The institutional internal review board approved this study.

Results

Demographic Data

Data for patients with PDAC in each age group are presented in Table 1. At total of 945 patients were included in the study, 75 of whom were of age less than 45 years at surgery and 870 were older than 70 years. The median age of the young group was 41 years (range, 31–45). The median age of the old group was 75 years (range, 70–93). Patient demographics, including gender and race, were comparable between the two groups (Table 1). The percentage of patients with smoking history was similar between two groups. Other possible risk factors for PDAC, such as family history of pancreatic cancer¹³ and previous radiation exposure, were not investigated in this study.

The most common symptoms of young patients were jaundice (45 %), abdominal pain (32 %), or weight loss (33 %). This did not differ significantly from older patients (*p*=0.46).

The median CACI score was 0.5 (range, 0–2) for the younger group and 4.2 (range, 3–14) for the older group. Young patients had significant less preoperative comorbidities (*p*<0.0001).

Operative Data and Complications

In the younger cohort, 7 (9 %) underwent total pancreatectomy, 60 (80 %) underwent pancreaticoduodenectomy, and 8 (11 %) had distal pancreatectomy. Among these pancreatic operations, four (5 %) involved vein resection. This included three SMV resection and one portal vein resection. The type of pancreatic resection performed in young patients was not significantly different from those done in the older patient group. Fifty-two patients (69 %) in the young patient group underwent an R0 resection and this did not differ from the older age group (*n*=616; 71 %).

Delayed gastric emptying, pancreatic fistula, and wound infection are the most common complication after pancreatic surgery. Young patients had significantly lower incidence of postoperative pancreatic fistula (0 vs. 8 %; *p*=0.013) and delayed gastric emptying (5 vs. 15 %; *p*=0.017) in comparison to the older age group. The Clavien classification system has been widely used to grade surgical complications.^{14,15} In this system, grade III complication was defined as those requiring surgical, endoscopic, or radiological intervention. Fifteen of

75 (20 %) young patients had complications; five of them (33 %) were grade III or above. Two hundred seventy-one of 870 (31 %) old patients had complications, 111 of them (41 %) were grade III or above. The incidence of complication with grade III or above was not significantly different between young and old groups.

The median LOS was not significant different between two groups (9 vs. 9 days). Both groups had low perioperative mortality (young, 0 vs. old, 2 %).

Pathology Data

The rate of lymph node positivity was 68 % for younger patients and 74 % for older patients ($p=0.27$). Lymph node ratio (defined as ratio between positive lymph nodes and total excised lymph nodes) was also not significantly different between the two groups (0.14 vs. 0.14, $p=0.78$). Microvascular invasion was observed in 32 % of younger patients and 42 % of older patients ($p=0.1$). Perineural invasion was observed in 64 % of younger patients and 73 % of older patients ($p=0.09$). According to AJCC staging (seventh edition), 11 (15 %), 13 (17 %), 49 (65 %), and 2 (3 %) patients in young age group were in stage I, IIA, IIB, and III, respectively. This staging distribution did not differ from that in the older age group ($p=0.27$) (Fig. 1).

Survival Analysis

Most studies of patients undergoing resection for pancreatic adenocarcinoma reported estimated (actuarial) 5-year survival rates. Actual 5-year survival is rarely described. So we reported both estimated and actual survival data in this study.

The estimated median overall survival for the young patients cohort was 19 months (95 % CI: 15–22 months) which was significantly longer than that for the older group (16 months, 95 % CI: 14–17 months) ($p=0.007$) (Fig. 2). Subgroup analysis of patients with stage I/IIA disease showed the estimated median overall survival for the young patients cohort ($n=24$) was 27 months (95 % CI: 0–106 months) which was same as that for the older group (27 months, 95 % CI: 20–34 months) ($p=0.1$). However, for patients with stage IIB/IIIA disease, the estimated median overall survival for the young cohort ($n=51$) was 16 months (95 % CI: 12–21 months) which was significantly longer than that for the older group (14 months, 95 % CI: 13–15 months) ($p=0.046$).

Similarly, the actual 5- and 10-year survivals in young age group (24 and 17 %) were also significantly longer than those in old age group (11 and 3 %) ($p=0.005$ and $p<0.001$, respectively) (Table 1).

Stage I or IIA was strongly associated with 5-year actual survival rate in both age groups as compared to stage IIB and III (42 vs. 16 % in the young age group, $p=0.014$; 20 vs. 7 % in the old age group; $p<0.0001$) (Table 2).

Discussion

Except for prostate cancer,¹⁴ younger patients diagnosed with other common cancers tend to have higher survival rates than older patients in age-specific relative survival studies. (<http://info.cancerresearchuk.org/cancerstats/survival/age/>, accessed on October 22, 2012.) However, very little information is available regarding PDAC in young patients. Our hypothesis was that young patients with PDAC might have worse overall outcome comparing to the older patients even after curative surgery. However, our data showed the opposite. Young patients with PDAC actually do better in survival than their older counterparts.

Lüttges et al. analyzed the pathologic characteristics of six young patients with PDAC derived from a population of 439 reviewed.⁷ In this study, no difference in the expression of p53, MLH1, MSH2, and c-Erb-B2 were identified between young and older patients. Moreover, no unique immunohistochemical characteristics were found in younger patients. In addition, no familial component was identified by family history. However, literature review by Lüttges et al showed PDACs in patients with the age <40 years were commonly associated with risk factors such as Peutz-Jeghers syndrome, hereditary pancreatic cancer syndrome, and preceding radiotherapy.⁷ Similarly, Bergmann et al. studied the pathologic characteristics of seven patients with PDAC under the age of 40 (age range 35–40).⁵ The tumor grade, p53, Smad4, EGFR expression levels were comparable between young and older patients.

Most large series of resected PDAC have reported 5-year survival rates of 12–19 %, ^{2,15–17} and the factors associated with 5-year survival have been typically stage-related. Ferrone et al. reported that their patients resected for pancreatic adenocarcinoma experienced an actual 5-year survival of 12 % and a 10-year survival of 5 %.⁹ The median age in that study was 68 years. The factors found to be associated with survival endpoint were the stage of disease at presentation and the resection margin status. Our data are consistent with the literature. In this study, the actual 5- and 10-year survival rates for older age group (median age 75 years) were 11 and 3 %, respectively. In both age groups, stage I or IIA is associated with more actual 5-year survival as compared to stage IIB and III (Table 2).

To our knowledge, our study is the largest cohort of young patients undergoing resection for PDAC reported. We show that the actuarial overall survival and actual survival of the young cohort of patients was significantly better than those of their older counterpart (Table 1 and Fig. 2). Except for the lower incidence of postoperative pancreatic fistula and delayed gastric emptying in the young age group, the clinical characteristics of PDAC in both groups after resection were similar. Patients of both groups had similar demographic characteristics including gender, race, and smoking history. Their pathology results showed similar cancer staging and lymph node metastasis. They received similar pancreatic resection with similar rate of R0 resection, median LOS, and perioperative mortality. Taken together, the improved survival rate in the young group may reflect an overall better state of health and relative lower rate of comorbidities. This is supported by the significant difference of CACI between two groups.

These finding are useful in counseling young patients undergoing pancreatectomy for PDAC in that they have a better chance of survival than the most of the current reports available in the literature which are based on populations with an older median survival.

The major limitation of our study is the lack the data regarding disease-specific survival. This is of great importance for the cohort of old patients, where some long-term surviving patients might be dying from etiologies other than PDAC.

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Fig. 1.
Staging by age

Fig. 2.
Estimated overall survival by age, from time of first surgery. Deaths within 30 days of surgery were excluded

Table 1

Demographic and treatment data

	Age group		p
	18-45 (N=75)	>70 (N=870)	
Age at first surgery (median)	41	75	
Gender			
Female	33	44 %	450 52 %
Male	42	56 %	420 48 %
			0.20
Race			0.84
White	67	89 %	782 90 %
Black	3	4 %	42 5 %
Other	5	7 %	46 5 %
Smoker	28	37 %	355 41 %
			0.56
Presenting signs/symptoms			
Jaundice	34	45 %	354 41 %
			0.47
Abdominal pain	24	32 %	195 22 %
			0.06
Weight loss	25	33 %	342 39 %
			0.33
Type of surgery			0.31
Total pancreatectomy	7	9 %	45 5 %
Partial pancreatectomy	60	80 %	714 82 %
Distal pancreatectomy	8	11 %	107 12 %
Vein resection	4	5 %	34 4 %
			0.55
Morbidity			
Pancreatic fistula	0	0 %	66 8 %
			0.013
Wound infection	7	9 %	92 11 %
			0.74
Delayed gastric emptying	4	5 %	134 15 %
			0.017
Any Clavien grade	15	20 %	271 31 %
			0.05
Clavien grade III or above	5	7 %	111 13 %
			0.14
30-day mortality	0	0 %	14 2 %
			0.27
LOS (median)	9		9
Margin status			
Negative	52	69 %	616 71 %
			0.78

	Age group				<i>p</i>
	18-45 (N=75)	>70 (N=870)			
Positive	21	28 %	220	25 %	
Atypia or unknown	2	3 %	34	4 %	
Lymph node positivity	51	68 %	640	74 %	0.30
Microvascular invasion	24	32 %	362	42 %	0.10
Perineural invasion	48	64 %	636	73 %	0.09
LNR (median)	0.14		0.14		
Median OS (month)	19		16		0.007
Actual 5-year survival	18	24 %	92	11 %	0.005
Actual 10-year survival	13	17 %	27	3 %	<0.001

LOS length of stay, *LNR* lymph node ratio, *OS* overall survival

Table 2

Five-year actual survival analysis

	Young group, n (%)		Old group, n (%)	
	Yes	No	Yes	No
5-year survival				
Stage				
I/IIA	10 (42)	14 (58)	45 (20)	180 (80)
IIB/III	8 (16)	43 (84)	47 (7)	598 (93)

Stage I or IIA is strongly associated with 5-year survival rate in both age groups as compared to stages IIB and III (42 vs. 16 % in the young age group, $p=0.014$; 20 vs. 7 % in the old age group; $p<0.0001$)