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Surgical resection improves survival in pancreatic cancer patients without vascular invasion- a population based study

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Abstract

Aim To investigate the effect of surgery on overall survival (measured from the time of diagnosis) in pancreatic cancer without vascular invasion (stage 1, 2A and 2B). We also sought to investigate factors that predict survival in patients who elected to undergo surgery and factors that affect the decision to undergo surgery.

Methods The Surveillance Epidemiology and End Results (SEER) database was queried for microscopically confirmed cases of stage 1,2A and 2B pancreatic ductal adenocarcinoma diagnosed between 1973-2009. Survival analysis was carried out by univariate and multivariate analysis. Logistic regression was employed to identify factors that predict decision to undergo surgery.

Results 1,759 patients with microscopically confirmed pancreatic cancer with stage 1-2B at the time of diagnosis were recorded in the SEER database. 92.6% patients underwent pancreatic cancer-directed surgery. Patients undergoing surgery had a significantly lower mean age at the time of diagnosis (65.8 vs. 69.9 years, P=0.002) and a longer median survival (18 vs. 7 months) compared to those who did not undergo surgery. Surgical resection was a significant predictor of overall survival upon both univariate and multivariate analysis. Younger age at the time of diagnosis, non-white, non-black race, tumor size <40 mm and tumor located in the tail of the pancreas were factors significantly associated with a chance of pancreatic cancer-directed surgery.

Conclusion Surgery improves survival in pancreatic cancer patients where the tumor has not involved the vasculature. Younger patients, those with smaller tumors located in the tail of the pancreas were most likely to undergo surgical resection.

Keywords Pancreatic cancer, vascular invasion, survival

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Introduction

It is estimated that about 43,920 patients will develop malignancy of the exocrine pancreas each year in the United States. The most common type of exocrine pancreatic cancer is infiltrating ductal adenocarcinoma. Stage of the disease, particularly vascular invasion has an important bearing on the treatment of pancreatic cancer. Currently, the only potentially curative treatment is surgery. Tumors with venous involvement (portal vein and superior mesenteric vein) can be resected. However, a survival benefit is not achieved by such curative resection in patients with pancreatic cancer and vascular involvement. Involvement of the celiac axis or superior mesenteric artery constitutes stage III pancreatic cancer and is considered unresectable. In the present study, we employed the SEER database to investigate impact of surgery on survival in pancreatic cancer patients without vascular involvement. Further, we also investigated the patient, tumor and treatment related factors that impact survival in these patients.

Materials and methods

The case listing function of the SEER database containing data from 17 registries from 1973-2008 was queried for microscopically confirmed cases of pancreatic ductal adenocarcinoma (ICD-O-3 code 8500/3) diagnosed between 1973-2009 using the SEER Stat software version 7.0.5 (http://seer.cancer.gov/seerstat/) [1,2]. The SEER database codes

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Conflict of Interest: None

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histologic type of tumor using the Third Edition of the International Classification of Diseases (ICD-O codes) for Oncology. Statistical analysis of case records was carried out using the PASW Statistics package version 18.0.

A total of 7,717 cases were retrieved using the criteria mentioned above. From these, we selected cases where the tumor did not involve the vessels (celiac axis and superior mesenteric vessels), i.e. patients with tumor stage 1, 2A and 2B (N=2533 patients). Next, we excluded patients with more than one primary tumor (N=500) leaving 2,033 patients. Patients in whom grade of the tumor was unknown were excluded (N=143) leaving 1,886 cases. Then, we selected cases in whom the cause of death was coded as "pancreas" (N=1,762). Patients in whom there was no information on the use of radiation therapy or surgery were also excluded. Finally, 1,759 patients were left for final analysis. These were all patients with stage 1-2B tumors. We compared the survival of patients who did vs. those who did not receive surgery and investigated factors that affect survival in these patients. Age, tumor size, number of regional lymph nodes positive were considered as continuous variables while race, gender, location and grade of the tumor, surgery and radiation therapy were considered as categorical variables.

An independent samples t-test employing Levine's test for equality of variances was used to compare the mean values for continuous variables while the Mann-Whitney U test was applied to categorical variables. Kaplan-Meier survival analysis was used to examine the effect of individual factors on the survival of pancreatic cancer patients in the two groups (i.e., no surgery vs. cancer-directed surgery). All tests were carried out with 95% confidence intervals. A P-value <0.05 was considered significant.

Results

Overall, the ratio of males to females was 49:51. The mean age of patients in the study population was 66.6 years (SD 10.7) and ranged from 29-94 years. Nearly 82% of patients were whites. The majority of tumors were moderate (54%) or poorly differentiated (35%) at the time of diagnosis. Location-wise, they were commonest in the head of the pancreas (76%). Median tumor size at the time of diagnosis was 31 mm. Compared to patients who did not receive surgery, those who underwent pancreatic cancer-directed surgery were significantly younger (mean age 65.8 vs. 69.9 years, P<0.0001). They also had a higher proportion of females (50% vs. 43%, P>0.05) but a lower percentage of well and moderately differentiated tumors (64% each). Patients undergoing surgery also had a longer mean (15.7 vs. 8.4 months) survival time (P<0.0001) (Table 1).

Univariate analysis revealed that the age at the time of diagnosis of pancreatic cancer, grade of tumor, number of lymph nodes removed at the time of surgery, size of the primary tumor and the administration of radiation and surgery were

Table 1 Resectable pancreatic cancer- comparison of "no surgery" vs. "surgery" groups

Variable	Overall	Did not undergo cancer-directed surgery (N=129)	Underwent pancreatic cancer-directed surgery (N=1630)
Mean (±SD) age in years at diagnosis [range]	66.1 (±10.7) [29-94]	69.9 (±12.5) [37-94]	65.8 (±10.5) [29-93]*
Male: Female ratio	49:51	43:57	50:50
Race			
White	82.3%	80.6%	82.4%
Black	9.3%	14.0%	9.0%
Others	8.4%	5.4%	8.6%
Grade of tumor			
Well differentiated	10.2%	19.4%	9.4%[a]
Moderately differentiated	53.9%	45.0%	54.7%
Poorly differentiated	35.0%	34.0%	35.2 %
Undifferentiated	0.9%	1.6%	0.7%
Location of tumor			
Head	76.3%	72.79	77.7%
Body	6.8%	15.5%	5.3%
Tail	7.4%	2.3%	6.6%
Others	9.5%	9.3%	10.4%
Median tumor size in mm	31.0	40.0	30.0
Mean survival (±SD) survival in months	13.8 (±10.2)	8.4 (±7.8)	15.7 (±13.1) [a]

**P=0.002 by independent samples t-test assuming unequal variances*
[a]P<0.0001 by independent samples t-test assuming unequal variances

factors that significantly influenced survival in pancreatic cancer patients with stage 1-II B tumors (Table 2). Patients who underwent surgery had a significantly longer median survival (18 months) compared to those who did not undergo surgery (7 months) and this was significant by Log-rank test (P<0.0001, Fig. 1). In multivariate analysis, pancreatic cancer-directed surgery, tumor size and grade, age at the time of diagnosis, number of positive lymph nodes and radiation therapy were factors that were significantly associated with survival in these patients (Table 3).

Using logistic regression analysis, we explored the factors that could be significant predictors of a patient with stage IA-IIB pancreatic cancer undergoing a cancer-directed surgery. As shown in Table 4, younger age at the time of diagnosis of the cancer, non-white, non-black race, tumor size <40 mm, and tumors located in the tail of the pancreas were significantly associated with a chance of patients undergoing cancer directed surgery. Males appeared to be slightly more likely than females to undergo surgery (P=0.32). Compared to patients diagnosed in 2008 and later, patients diagnosed earlier were less likely to undergo pancreatic cancer directed surgery (P=0.002).

Having noted the improved survival with smaller tumors, we next hypothesized that this could either be due to an increase in cancer directed surgery, fewer positive lymph nodes or increase in number of patients receiving radiation therapy. To investigate this, we examined the correlation between tumor size and the three variables. As shown in Table 5, patients with smaller tumors (particularly less than 2cm) underwent cancer directed surgery more often and also had significantly fewer cancer positive lymph nodes.

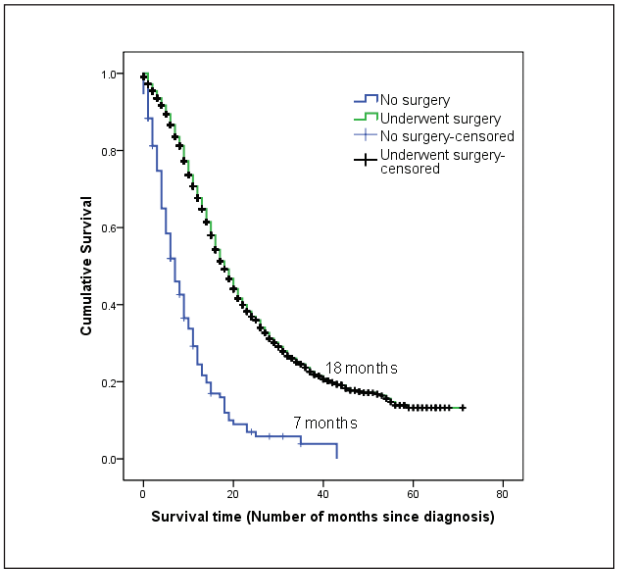

Figure 1 Kaplan-Meier analysis demonstrating effect of surgical resection on survival of patients with resectable pancreatic cancer. Patients who underwent surgery had a significantly longer median survival (18 months) compared to those who did not undergo surgery (7 months) (P<0.0001 by Log rank test)

Discussion

Ductal adenocarcinoma of the pancreas is currently staged according to the TNM (tumor grade, nodal status and metastases) system wherein T1-T3 constitutes a resectable tumor. T4 indicates a tumor that has invaded either the superior mesenteric artery or the celiac artery and such tumors are considered unresectable. T1-T3 (with or without nodal involvement) comprise stages IA-IIB in the TNM staging system. The main objective of our present study was to compare survival among patients with stage IA-IIB ductal adenocarcinomas of the pancreas that either did or did not undergo cancer-directed surgery. We observed that those patients who underwent surgery had a significantly longer median survival than those who did not (18.0 vs. 7 months). Further, we sought to determine factors (including surgery) that predict survival in these patients. We observed that age <70 years, tumor size <40 mm at the time of diagnosis, well or moderately differentiated tumors, sampling of regional lymph nodes for detecting tumor spread, presence of nodes positive for tumor and cancer-directed surgery or radiation therapy were all associated with an improved survival in patients with stage IA-IIB pancreatic ductal carcinomas. In multivariate analysis however, only age at the time of diagnosis, tumor size, degree of differentiation and cancer-directed surgery and radiation therapy remained as independent predictors of survival in these patients. Having observed that cancer-directed surgery improved survival in this subset of pancreatic cancer patients, we also sought to identify factors that predict the likelihood of a patient with stage IA, IB, IIA or IIB pancreatic cancer undergoing cancer-directed surgery. Using logistic regression we identified age (but not race or gender), tumor size, and degree of differentiation, grade and location in the pancreas as all being significant predictors of cancer directed surgery. The study reiterates two key aspects in pancreatic cancer management, early diagnosis using high-resolution multi detector CT and accurate staging both by imaging and at the time of surgery by sampling regional lymph nodes [3]. Both these factors are associated with improvement in survival. It also supports previous studies that have identified tumor size, lymph node status and degree of differentiation as significant predictors of survival in pancreatic cancer [4]. Curative resection has been shown to be the single most effective way to treat pancreatic cancer. Wagner and colleagues observed that pancreatic cancer patients who had curative resection (defined as clear resection margins with no gross tumor mass at the site of the operation or in other organs) had a 5-year survival of 24.2%. Patients whose lymph nodes were negative for cancer had a 5-year survival of 31.6% after surgery. Overall 5-year survival after surgery was 19.8% in their patients [5]. Currently, surgery is rarely used alone due to better survival with adjuvant or neoadjuvant chemotherapy with or without radiation. Furthermore, improvements in radiation therapy in the last 2 decades including abandonment of split course radiation, identification of optimal radiation dose for upper GI cancers and wider use of CT to define the radiation boundaries have meant that treatment for resectable pancreatic cancer

Table 2 Univariate analysis of factors influencing survival in pancreatic cancer patients without vascular invasion

Variable	Median (SE) survival	95% C.I.	P-value (log rank test)
Age groups (%)			<0.0001
0-50 yrs	18.0 (0.94)	16.2-19.8	
31-70 yrs	18.0 (0.75)	16.5-19.5	
71 and above	15.0 (0.70)	13.6-16.4	
Gender			0.095
Male	17.0 (0.6)	15.8-18.2	
Female	18.0 (0.75)	16.5-19.5	
Race			0.675
White	17.0 (0.53)	16.0-18.0	
Black	16.0 (1.78)	12.5-19.5	
Other (American Indian/AK Native, Asian/Pacific Islander)	15.0 (1.20)	12.6-17.4	
Location			0.237
Head of pancreas	17.0 (0.56)	15.9-18.1	
Body of pancreas	15.0 (1.8)	11.4-18.6	
Tail of pancreas	20.0 (2.6)	14.8-25.2	
Other	15.0 (1.2)	12.6-17.4	
Scope of lymph node surgery			<0.0001
None	7.0 (0.82)	5.4-8.6	
1-3 regional nodes removed	18.0 (2.0)	14.0-22.0	
≥4 nodes removed	18.0 (0.52)	16.9-19.0	
Number of positive lymph nodes			<0.0001
No positive nodes	22.0 (1.2)	19.6-24.2	
1-97	16.0 (0.52)	15.0-17.0	
No nodes examined	7.0 (0.81)	5.4-8.6	
Size of tumor (mm)			<0.0001
0-20	25.0 (3.1)	18.9-31.1	
21-40	18.0 (0.62)	16.8-19.2	
41-60	13.0 (1.0)	11.0-14.9	
≥60	13.0 (0.99)	11.0-14.9	
Radiation therapy			<0.0001
None	15.0 (0.63)	13.8-16.2	
Received radiation	20.0 (0.81)	18.4-21.6	
Cancer directed surgery			<0.0001
Not performed	7.0 (0.85)	5.3-8.7	
Performed	18.0 (0.51)	16.9-19.0	
Tumor grade			<0.0001
Well differentiated	23.0(2.9)	17.4-28.6	
Moderately differentiated	19.0 (0.67)	17.7-20.3	
Poorly differentiated	13.0 (0.61)	11.8-14.2	
Undifferentiated	14.0 (3.7)	6.7-21.3	

now offers a wider choice [6]. Chemotherapy has not been shown to be of clear benefit in resectable pancreatic cancer. Gemcitabine has been the first line chemotherapy agent for patients with locally advanced or metastatic pancreatic cancer after a randomized trial showed significant improvement in the median overall survival as compared with 5-fluoruracil (5.6 vs. 4.4 months, P=0.002) [7]. Over the last several years single agent gemcitabine therapy has been the accepted standard of care. Addition of other agents to gemcitabine has not yielded significant survival benefit. However, recent randomized trial of combination chemotherapy regimen of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) compared with gemcitabine as first-line therapy in patients with metastatic pancreatic cancer showed improvement in median overall

Table 3 Multivariate analysis of factors influencing survival in patients with resectable pancreatic ductal adenocarcinoma

Factor	H.R. (95% CI)	P-value
Age at diagnosis	1.02 (1.004-1.03)	0.006
Age group		0.12
0-50 years	1.0 (reference)	
51-70 years	0.73 (0.53-0.99)	0.045
≥71 years	0.69 (0.43-1.10)	0.12
Race		0.11
White	1.0 (reference)	
Black	1.15 (0.92-1.43)	0.23
Others	1.22 (0.98-1.52)	0.07
Gender		
Male	1.0 (reference)	
Female	0.89 (0.79-1.02)	0.08
Tumor size (in mm)		<0.0001
0-20	1.0 (reference)	
21-40	1.34 (1.10-1.62)	0.003
41-60	1.76 (1.41-2.2)	<0.0001
≥61	1.80 (1.37-2.38)	<0.0001
Tumor location		0.57
Head	1.0 (reference)	
Body	1.08 (0.83-1.4)	0.56
Tail	0.88 (0.67-1.15)	0.34
Others	1.09 (0.88-1.34)	0.45
Tumor grade		<0.0001
Well differentiated	1.0 (reference)	
Moderately differentiated	1.40 (1.10-1.78)	0.005
Poorly differentiated	1.89 (1.48-2.41)	<0.0001
Undifferentiated	2.13 (1.16-3.93)	0.015
Number of regional lymph nodes sampled		0.08
None	1.0 (reference)	
1-3 nodes removed	0.71 (0.38-1.32)	0.28
≥4 nodes removed	0.59 (0.32-1.06)	0.079
Number of regional nodes positive		<0.0001
None	1.0 (reference)	
1-97	1.5 (1.29-1.76)	<0.0001
Not sampled	1.02 (0.59-1.79)	0.93
Pancreatic cancer directed surgery		
Not performed	1.0 (reference)	
Performed	0.41 (0.26-0.62)	<0.0001
Radiation therapy		
Did not receive radiation therapy	1.0 (reference)	
Received radiation therapy	0.69 (0.61-0.79)	<0.0001

survival for FOLFIRINOX group (11.1 vs. 6.8 months) [8]. This combination regimen did have higher incidence of adverse events and was suggested as first-line treatment option for metastatic pancreatic cancer in younger patients with good performance status. Despite these advancements, the prognosis of pancreatic cancer remains grim. The optimum treatment for this malignancy remains a matter of controversy chiefly due to its aggressive spread and recurrence despite aggressive treatment. However, with advancements in molecular biology, our knowledge about the factors responsible for the tenacity of pancreatic cancer cells is slowly emerging. While surgical resection remains the definitive treatment of

Table 4 Logistic regression analysis of factors significantly associated with chance of getting surgery in pancreatic cancer

Factor	X2 statistic	Odds ratio	P-value
Age at diagnosis of PC	9.77	0.94 (0.91-0.98)	0.002
Age groups	4.89		0.086
0-50 years		1.83 (0.86-3.88)	0.12
51-70 yrs		2.13 (1.4-3.2)	<0.0001
≥71 years		1.0 (reference)	
Race	8.1		0.017
White		0.59 (0.26-1.32)	0.19
Black		0.28 (0.11-0.73)	0.009
Other		1.0 (reference)	
Gender	0.97		0.32
Male		1.22 (0.82-1.79)	0.32
Female		1.0 (reference)	
Tumor size	45.6		<0.0001
0-20		7.5 (3.45-16.61)	<0.0001
21-40		4.6 (2.64-7.97)	<0.0001
41-60		1.65 (0.92-2.97)	0.095
61		1.0 (reference)	
Tumor grade	9.53		0.023
Well differentiated		0.79 (0.15-4.20)	0.78
Moderately differentiated		1.87 (0.37-9.56)	0.45
Poorly differentiated		1.68 (0.33-8.70)	0.53
Undifferentiated		1.0 (reference)	
Tumor location	20.4		<0.0001
Head		0.83 (0.43-1.59)	0.57
Body		0.43 (0.19-0.96)	0.04
Tail		4.8 (1.27-17.9)	0.02
Others		1.0 (reference)	
Year of diagnosis	18.9		0.002
2004		0.29 (0.15-0.60)	<0.0001
2005		0.38 (0.19-0.75)	0.006
2006		0.33 (0.17-0.64)	0.001
2007		0.46 (0.23-0.92)	0.028
2008		0.69 (0.34-1.43)	0.32
2009		1.0 (reference)	

Table 5 Relationship between tumor size, cancer directed surgery, lymph node positivity, radiation and survival

Tumor size	Median survival (months)	Percentage cases where cancer directed surgery was performed	Percentage with tumor positive lymph nodes †	Percentage patients who received radiation therapy
Less than 2cm	28	90.2	50.6	35.8
2 to <3cm	20	70.3	61.4	40.8
3 to <4cm	18	89.2	70.9	37.7
4 to <5cm	17	82.8	73.4	41.8
5 to <6cm	15	83.2	79.9	42.8
6 cm and larger	14	84.3	68.5	39.1
P value	<0.0001*	0.06	<0.0001	0.53

**By log rank test*

†There was a significant positive correlation between tumor size and the number of positive lymph nodes (Spearman's coefficient of correlation 0.18, P<0.0001). For comparisons between groups we used the chi-square test

resectable pancreatic cancer, newer molecular therapies are being developed that will hopefully improve long-term survival. The present study was limited by lack of information on other co-morbidities that could have impacted the decision of patients not to opt for surgery. This is a limitation of the study design but the question can be explored by future hospital-based studies that provide greater information regarding laboratory values and co-existing medical conditions.

Summary Box

What is already known:

- Surgery is the only potentially curative treatment of pancreatic cancer
- Stage 1, 2A and 2B pancreatic cancer is considered resectable

What the new findings are:

- Pancreatic cancer-directed surgery is associated with improved survival for stages 1-2B
- Age less than 50 years, tumor less than 20 mm in diameter, absence of lymph node positivity, radiation therapy, degree of tumor differentiation (well-moderately differentiated) are associated with significantly improved survival in patients with stages 1-2B
- Age younger than 71 years, non white non-black race, tumor diameter 40 mm or smaller, tumor located in the tail of the pancreas were the patient- and tumor-associated factors related with a greater chance of getting pancreatic cancer-directed surgery

References

1. Chakraborty S, Hauke RJ, Bonthu N, Tarantolo SR. Increased incidence of a second lymphoproliferative malignancy in patients with multiple myeloma - a SEER based study. *Anticancer Res* 2012;**32**:4507-4515.
2. Baine M, Sahak F, Lin C, Chakraborty S, Lyden E, Batra SK. Marital status and survival in pancreatic cancer patients: a SEER based analysis. *PLoS One* 2011;**6**:e21052.
3. Vargas R, Nino-Murcia M, Trueblood W, Jeffrey RB, Jr. MDCT in Pancreatic adenocarcinoma: prediction of vascular invasion and resectability using a multiphasic technique with curved planar reformations. *Am J Roentgenol* 2004;**182**:419-425.
4. Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J *Gastrointest Surg* 2006;**10**:1199-1210.
5. Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Buchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. *Br J Surg* 2004;**91**:586-594.
6. Goodman KA, Hajj C. Role of radiation therapy in the management of pancreatic cancer. *J Surg Oncol* 2013;**107**:86-96.
7. Freelove R, Walling AD. Pancreatic cancer: diagnosis and management. *Am Fam Physician* 2006;**73**:485-492.