Original Investigation

Characteristics of 10-Year Survivors of Pancreatic Ductal Adenocarcinoma

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IMPORTANCE To our knowledge, this study reports on the largest cohort of long-term survivors (LTSs) (≥10 years) following a diagnosis of pancreatic ductal adenocarcinoma (PADC) and identifies the characteristics associated with LTS.

OBJECTIVE To determine patient, tumor, surgical, and sociodemographic characteristics associated with LTS.

DESIGN, SETTING, AND PARTICIPANTS A nationwide retrospective cohort study of patients with invasive PADC (*International Classification of Diseases for Oncology, Third Edition* codes 8140/3, 8500/3, 8021/3, and 8035/3) was conducted using data collected in the National Cancer Database (NCDB). A multivariable logistic regression model of factors significantly associated with LTS was developed and used to generate a nomogram predicting the likelihood of surviving at least 10 years from initial diagnosis. Data collected from more than 1500 academic centers and community hospitals in the United States and Puerto Rico were assessed. Patients included were those with histologically proven PADC who underwent pancreatic surgical resection aimed at removal of the primary tumor between January 1, 1998, and December 31, 2002 (n = 11 917). The initial cohort (n = 70 915) excluded noninvasive tumors or tumors with unknown histology (n = 11 696) and was limited to patients who underwent surgical resection (n = 47 302 excluded). Analysis was conducted from January 1, 1998, to December 31, 2011.

EXPOSURES Pancreatic ductal adenocarcinoma.

MAIN OUTCOMES AND MEASURES *Long-term survival*, defined as surviving at least 10 years from initial diagnosis.

RESULTS Of the 11 081 patients with complete survival information, 431 individuals (3.9%) were LTSs. Significant predictors of LTS included (determined using odds ratio [OR]; 95% CI), in order of importance, lymph node positivity ratio (0%: 4.6; 3.4-6.4), adjuvant chemotherapy (2.4; 2.0-3.0), pathologic T stage (T1: 3.1; 1.8-5.6), patient age (50-60 years: 3.4; 1.8-6.7), tumor grade (well differentiated: 2.2; 1.5-3.0), surgical margin (negative: 1.9; 1.4-2.6), pathologic M stage (M = X: 5.6; 2.1-22.8), tumor size (<2 cm: 1.7; 1.2-2.5), educational level (>86% high school graduates: 1.7; 1.2-2.4), and insurance status according to the patient's zip code (private: 2.0; 95% CI, 0.9-5.1). The model C index was 0.768. Based on our nomogram, patients with the most favorable characteristics had an 18.1% chance of LTS. Furthermore, survival curves demonstrated that the probability of dying following initial diagnosis of PADC reached a plateau of approximately 10% per year after 7 years of survival.

CONCLUSIONS AND RELEVANCE Although PADC remains a deadly disease, long-term survival is possible, even beyond the 10-year mark. Our adjusted analysis identified lymph node ratio, administration of adjuvant chemotherapy, and pathologic T stage as being the top 3 variables associated with LTS of PADC. In addition, our easy-to-use nomogram may be able to identify potential LTS among patients with resected PADC.

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Pancreatic ductal adenocarcinoma (PADC) is the fourth leading cause of cancer death in North America.[1] During the past few decades, significant improvements in diagnostic modalities, standardization in surgical techniques, and advancement in neoadjuvant and adjuvant therapies have been accomplished.[2] Combinations of these factors have led to an acceptable perioperative mortality rate of 2% and some improvements in the 5-year survival rate of up to 27%.[3-5]

However, 5-year survival does not equate with definitive cure.[3,6] Disease recurrence, especially in the form of local recurrence or pulmonary metastatic lesions rather than hepatic lesions, has been increasingly recognized as the main tumor-related cause of death due to PADC in patients surviving at least 5 years.[5,6] Long-term survivors (LTSs) represent a particular subgroup of patients with PADC that remains poorly understood.

In recent years, several studies[3,7-9] have focused on LTSs (surviving ≥10 years) of PADC to characterize a subgroup of patients for whom definitive cure is possible. These studies are often single-institution reports analyzing a limited number of LTSs, often insufficient to reach definitive conclusions.

In this study, we present what we believe to be the largest report of PADC LTSs (>10 years since diagnosis). We used data collected in the National Cancer Database (NCDB).[10] The primary objective of our work was to identify patient, tumor, surgical, and sociodemographic characteristics associated with 10-year or longer survival following surgical resection for PADC.

Methods

The NCDB is a joint program of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The program is a nationwide oncology outcomes database that encompasses data from more than 1500 Commission on Cancer–accredited cancer programs in the United States and Puerto Rico. The NCDB captures approximately 70% of all newly diagnosed cases of cancer in the United States.[10] The University of Colorado institutional review board stated that no official waiver was needed since no patient, physician, or hospital identifiers were examined.

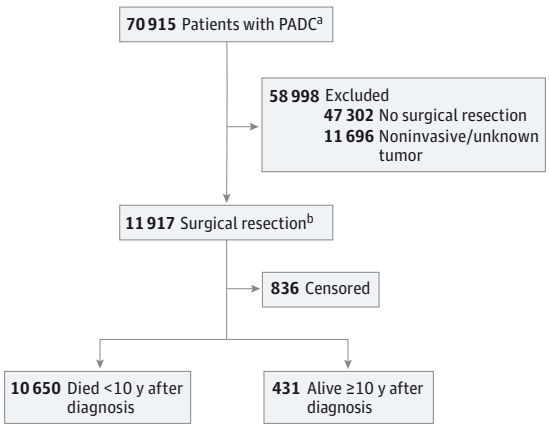
We identified patients with histology-proven PADC between 1998 and 2002, based on *International Classification of Diseases for Oncology, Third Revision*[11] histology codes 8140/3, 8500/3, 8021/3, and 8035/3. This initial selection resulted in a cohort of 70 915 patients. We excluded all cases classified histologically as noninvasive tumor or unknown histology (using the pathologic TNM [pTNM] stage [American Joint Commission on Cancer stage at the time of data collection]), excluding a total of 11 696 patients. For the purpose of this study, we considered *surgical resection* to be a pancreatic resection aimed at removal of the primary tumor. Furthermore, the presence of a reported pTNM stage was used as a confirmatory surrogate for surgical resection. Patients with incomplete or absent data on pTNM stage were excluded from the study on the assumption that such absence indicates that a pancreatic specimen was not collected (excluding a total of 47 302 patients). We used the NCDB codes corresponding to local or partial pancreatectomy (code 30) as well as pancreatectomy not otherwise specified (code 80), total pancreatectomy (codes 40 and 60), and pancreatoduodenectomy (codes 35, 36, 37, and 70). A total of 572 cases (5.2%) had surgical resection and documented pathologic stage IV disease, likely discovered intraoperatively.

The selected cohort (n = 11 917) was divided into 3 groups based on survival characteristics: alive at 10 years following initial diagnosis (431 [3.6%]), dead at 10 years following initial diagnosis (10 650 [89.4%]), and a censored group that was alive at last contact occurring before the 10-year mark (836 [7.0%]). Of the 11 081 patients with a potential follow-up period of 10 or more years (diagnosed before 2002 and with complete survival information), 431 individuals (3.9%) were LTSs (**Figure 1**).

Surgical resection margins were divided into 3 groups: negative margin (R0), positive margin (including microscopic [R1], macroscopic [R2], and positive [not otherwise specified]), and unknown margin status.

A new variable, termed *lymph node positivity ratio* (LNPR), was created. This variable represents the number of lymph nodes harboring a metastasis divided by the total number of nodes examined. Similar to the work done by Pawlik et al,[12] we used 4 levels for this categorical variable: negative nodes with a ratio of 0%, positive nodes with a ratio of 1% to 20%, positive nodes with a ratio of greater than 20%, and unknown (either missing the number of nodes examined or the node status of positive vs negative). The total number of nodes examined was transformed into a 4-level

Figure 1. STROBE Diagram: Patients' Selection Criteria



[a] Diagnosed before 2003. *International Classification of Disease for Oncology, Third Revision* (*ICD-O3*)[11] codes 8140/3, 8500/3, 8021/3, and 8035/3.

[b] The following codes for pancreatectomy represent surgical procedures that were selected for the study: local or partial pancreatectomy (*ICD-O3* code 30), pancreatectomy not otherwise specified (code 80), total pancreatectomy (codes 40 and 60), and pancreatoduodenectomy (codes 35, 36, 37, and 70). The presence of a reported pathologic TNM stage was used as an additional criterion to ensure that the surgical resection was done. PADC indicates pancreatic ductal carcinoma.

variable (0, 1-10, >10, and unknown). The continuous variable describing tumor size in the NCDB was transformed into a categorical variable with 4 levels (<2 cm, 2-4 cm, >4 cm, and unknown).

Patient race was categorized into 3 levels: white, black, and other. Additional demographic variables, such as educational level, insurance status, and income, were included in our analysis and used as provided by the NCDB (http://www.facs.org/cancer/coc/fordsmanual.html). Educational and income levels represent the population levels of those variables in the zip code of the patient. The primary end point of this study was long-term survival (≥10 years, yes or no). Patients who survived for 10 or more years were compared with patients who died within the first 10 years following the initial diagnosis. The Kaplan-Meier method was used to evaluate and plot overall survival.

To compare the mortality rate of this cohort with the background mortality rate, a projected life expectancy was generated for each member of the cohort by producing a random number between 0 and 1 for each patient. This value was considered the *percentile of survival*. The actual life expectancy for this percentile (including age and sex) was calculated using the 2009 life tables from the National Vital Statistics Reports.[13] These projected life expectancies were then compared with the actual life expectancies of the cohort using a log-rank test.

Descriptive statistics are reported as the number of events with corresponding percentage, mean (SD), or median with interquartile range unless otherwise specified. Differences between the 10-year survivors and nonsurvivors were assessed using the *t* test or Wilcoxon rank sum test for continuous variables and the χ^2 test or Fisher exact test for categorical variables. Statistical significance was set at $P < .05$. Factors that were statistically significant in bivariable analysis for the primary end point (survival ≥10 years) were selected for a forward-selection, stepwise multivariable logistic regression model. For each categorical predictor variable, the reference group was chosen to be the group with the smallest percentage of LTSs. Odds ratios (95% CIs) were calculated for each level of each predictor variable along with the cumulative C index at each step of the regression analysis. Multivariable logistic regression models were evaluated for discrimination using the cumulative C index and for calibration using the Hosmer-Lemeshow goodness-of-fit test. The C index is the proportion of all possible event-nonevent pairs for which the patient with the event has the higher probability of the event. The Hosmer-Lemeshow test evaluates the goodness of fit of the model by comparing observed and expected rates of long-term survival across deciles of risk of the patient pool.

A nomogram predicting the likelihood of surviving for 10 or more years from initial diagnosis of PADC was developed. The nomogram values were derived by multiplying the parameter estimates (β coefficients derived from the multivariable logistic regression equation) by 10/3 (empirically determined to optimize the spread of the final scores) and rounding to the nearest whole number.[14] Using this method, a risk score can be generated for any patient for whom data on the variables used in the model are available. A development model was first generated on two-thirds of the data, and the nomogram was applied to the remaining one-third of the data to validate the approach. Once this process was done, a new model was generated using the entire data set. All statistical analysis was conducted using SAS, version 9.2 (SAS Institute Inc).

Results

Factors Associated With 10-Year Survival

Characteristics of the study cohort are described in eTable 1 in the Supplement. **Table 1** compares patient characteristics between LTSs and nonsurvivors. Being an LTS was associated with patient sociodemographic factors (younger age, private insurance, and educational level within the patient's zip code), tumor characteristics (negative margin, well-differentiated tumor, small tumor size, smaller ratio of positive to examined lymph nodes, lower TNM scores, and lower American Joint Commission on Cancer stage), and adjuvant treatment (chemotherapy or radiotherapy).

Multivariable Logistic Regression Model

Our multivariable logistic regression model found that LNPR was the most important factor associated with LTS (**Table 2**). An LNPR equal to 0 (No disease) was identified in 220 patients (51.0%) of the LTS cohort. This factor resulted in more than a 4-fold increase in the chances of surviving at least 10 years following initial diagnosis compared with the chances in patients with an LNPR of greater than 20% (OR, 4.6; 95% CI, 3.4-6.4). The use of adjuvant chemotherapy in 269 patients (62.4%) was the second most important predictor variable associated with a survival advantage (OR, 2.4; 95% CI, 2.0-3.0).

Histopathologic tumor characteristics were included in our multivariable regression model evaluated using OR (95% CI). Tumors classified as pT3 were identified in 222 (51.5%) of the LTS cohort (1.8; 1.1-3.1). Although pT1 tumors were identified in only 80 cases (18.6%), the pT1 stage was strongly associated with LTS (3.1; 1.8-5.6).

Microscopic negative margins of resections were reported in 333 (77.3%) of the LTS cohort (OR, 1.9; 95% CI 1.4-2.6). Positive resection margins (R1 or R2) were present in 53 patients (12.3%) who were LTSs.

The absence of metastatic disease was an almost universal factor shared by patients in the LTS cohort. Three of 572 patients (0.52% survival rate) with synchronous metastatic spread at the time of surgical resection were alive at the 10-year mark. Although misclassification cannot be excluded, LTSs have been described[8] even in the presence of metastasis.

Tumor size at diagnosis ranged between 2 and 4 cm in 248 (57.5%) of the LTS cases (OR, 1.2; 95% CI, 0.9-1.5). Although smaller tumors (<2 cm) were present in only 87 cases (20.2%), this trait was significantly associated with long-term survival (OR, 1.7 95% CI, 1.2-2.5).

Educational level and insurance status were also included in the multivariable logistic regression model. In our LTS cohort,

Table 1. Bivariable Association Between Patient Characteristics and Long-term Survival

Variable	No. (%)		*P* Value
	Died (n = 10 650)	Survived (n = 431)	
Age, mean (SD), y	65.6 (10.7)	61.8 (10.6)	<.001
Sex			
Male	5443 (96.2)	217 (3.8)	.76
Female	5207 (96.0)	214 (4.0)	
Race			
Black	935 (96.9)	30 (3.1)	.06
White	9368 (96.1)	379 (3.9)	
Other	347 (94.0)	22 (6.0)	
Insurance status			
Not insured	252 (97.7)	6 (2.3)	<.001
Private	4251 (95.2)	214 (4.8)	
Medicaid	427 (96.2)	17 (3.8)	
Medicare	5231 (97.0)	163 (3.0)	
Status unknown	489 (94.0)	31 (6.0)	
Educational level (high school graduate)			
<71.0%	1613 (97.3)	45 (2.7)	.01
71.1%- 80.0%	2291 (95.9)	97 (4.1)	
81.1%- 86.0%	2506 (96.4)	95 (3.7)	
>86%	3712 (95.4)	178 (4.6)	
Unknown	528 (97.1)	16 (2.9)	
Income (quartile), $			
<30 000	1400 (96.9)	45 (3.1)	.09
30 000-34 999	1807 (96.6)	64 (3.4)	
35 000-45 999	2868 (96.0)	119 (4.0)	
>46 000	4047 (95.6)	187 (4.4)	
Not available	528 (97.1)	16 (2.9)	
Urban/rural			
Metropolitan	8315 (96.1)	337 (3.9)	.87
Urban	1544 (95.9)	66 (4.1)	
Rural	211 (96.8)	7 (3.2)	
Unknown	580 (96.5)	21 (3.5)	
Distance from hospital, mean (SD), miles	46.2 (217.2)	44.7 (126.5)	.82
Tumor site			
Head	8224 (96.1)	331 (3.9)	.84
Body and/or tail	2426 (96.0)	100 (4.0)	
Procedure			
Whipple	8774 (96.2)	345 (3.8)	.34
Distal pancreatectomy	1060 (95.3)	52 (4.7)	
Total pancreatectomy	816 (96.0)	34 (4.0)	
Margin			
Negative (R0)	6911 (95.4)	333 (4.6)	<.001
Positive (R1, R2, NOS)	2673 (98.1)	53 (1.9)	
Unknown	1066 (96.0)	45 (4.1)	
Grade, differentiated			
Well	991 (93.9)	64 (6.1)	<.001
Moderate	5070 (95.6)	234 (4.4)	
Poorly	3925 (97.4)	106 (2.6)	
Unknown	664 (96.1)	27 (3.9)	

(continued)

Table 1. Bivariable Association Between Patient Characteristics and Long-term Survival (continued)

Variable	No. (%) Died (n = 10 650)	No. (%) Survived (n = 431)	*P* Value
Tumor size, cm			
<2	1077 (92.5)	87 (7.5)	<.001
2-4	6134 (96.1)	248 (3.9)	
>4	2231 (97.3)	63 (2.8)	
Unknown	1191 (97.3)	33 (2.7)	
No. of nodes examined			
1-10	5653 (96.3)	217 (3.7)	.15
>10	3885 (95.7)	176 (4.3)	
0 or unknown	1112 (96.7)	38 (3.3)	
Ratio positive-examined nodes			
0%	3409 (93.9)	220 (6.1)	<.001
1%-20%	2508 (95.3)	125 (4.8)	
20%	3612 (98.7)	48 (1.3)	
Unknown	1121 (96.7)	38 (3.3)	
Pathologic T			
0/X	85 (97.7)	2 (2.3)	<.001
1	860 (91.5)	80 (8.5)	
2	2236 (95.4)	109 (4.7)	
3	6332 (96.6)	222 (3.4)	
4	1137 (98.4)	18 (1.6)	
Pathologic N			
0	3962 (94.1)	250 (5.9)	<.001
1	6559 (97.4)	177 (2.6)	
X	129 (97.0)	4 (3.0)	
Pathologic M			
1	569 (99.5)	3 (0.5)	<.001
X	10081 (95.9)	428 (4.1)	
Chemotherapy			
None	6169 (97.5)	157 (2.5)	<.001
Preoperative	139 (96.5)	5 (3.5)	
Postoperative	4342 (94.2)	269 (5.8)	
Radiotherapy			
None	5835 (97.3)	164 (2.7)	<.001
Preoperative	109 (94.8)	6 (5.2)	
Postoperative	4706 (94.8)	261 (5.3)	
AJCC staging group			
1A	504 (89.7)	58 (10.3)	<.001
1B	998 (92.8)	78 (7.3)	
2A	1910 (94.7)	107 (5.3)	
2B	5628 (97.2)	164 (2.8)	
3	973 (98.3)	17 (1.7)	
4	569 (99.5)	3 (0.5)	
Time from diagnosis to surgery, mean (SD), d	12.9 (25.5)	13.2 (29.6)	.86
Perioperative mortality (90 d)			
Alive	9382 (95.6)	431 (4.4)	<.001
Dead	1268 (100)	0	

Abbreviations: AJCC, American Joint Commission on Cancer; NOS, not otherwise specified.

178 patients (41.3%) were classified as residing in an area with more than 86% of high school graduates and represented a factor significantly associated with long-term survival (OR, 1.7; 95% CI, 1.2-2.4). In addition, most LTSs (214 [49.7%]; OR, 2.0; 95% CI, 0.9-5.1) were insured by private entities followed by Medicare (163 [37.8%]; OR, 2.0; 95% CI, 0.9-5.2).

Table 2. Multivariable Logistic Regression Model Predicting 10-Year Survival[a]

Step and Variable	10-y Survivors, No. (%)	OR (95% CI)[b]	Cumulative C Index
1. Lymph node ratio (positive-examined)			
>20%	48 (11.1)	1 [Reference]	0.645
1%-20%	125 (29.0)	3.5 (2.5-5.0)	
0%	220 (51.0)	4.6 (3.4-6.4)	
Unknown	38 (8.8)	3.0 (1.9-4.6)	
2. Chemotherapy			
None	107 (36.4)	1 [Reference]	0.701
Neoadjuvant	5 (1.2)	1.1 (0.4-2.5)	
Adjuvant	269 (62.4)	2.4 (2.0-3.0)	
3. Pathology T (TNM)			
T = 4	18 (4.2)	1 [Reference]	0.726
T = 3	222 (51.5)	1.8 (1.1-3.1)	
T= 2	109 (25.3)	2.4 (1.5-4.1)	
T= 1	80 (18.6)	3.1 (1.8-5.6)	
T= 0/X	2 (0.5)	2.4 (0.4-9.3)	
4. Age category, y			
>80	12 (2.8)	1 [Reference]	0.736
70-79	111 (25.8)	1.8 (1.0-3.4)	
60-69	126 (29.2)	2.0 (1.2-4.0)	
50-59	125 (29.0)	3.4 (1.8-6.7)	
<50	57 (13.2)	3.3 (1.8-6.9)	
5. Tumor grade, differentiated			
Poorly	106 (24.6)	1 [Reference]	0.746
Moderately	234 (54.3)	1.6 (1.3-2.0)	
Well	64 (14.9)	2.2 (1.5-3.0)	
Cell type NOS	27 (6.3)	1.6 (1.0-2.4)	
6. Surgical margin[c]			
Positive	53 (12.3)	1 [Reference]	0.754
Negative	333 (77.3)	1.9 (1.4-2.6)	
Unknown	45 (10.4)	1.8 (1.2-2.8)	
7. Pathology M (TNM)			
M = 1	3 (0.7)	1 [Reference]	0.761
M = X	428 (99.3)	5.6 (2.1-22.8)	
8. Tumor size, cm			
>4	63 (14.6)	1 [Reference]	0.764
2-4	248 (57.5)	1.2 (0.9-1.5)	
<2	87 (20.2)	1.7 (1.2-2.5)	
Unknown	33 (7.7)	0.9 (0.6-1.4)	
9. Educational level (% with high school diploma)			
<71.0%	45 (10.4)	1 [Reference]	0.766
71.1%-80.0%	97 (22.5)	1.5 (1.0-2.2)	
81.1%-86.0%	95 (22.0)	1.3 (0.9-1.9)	
>86.0%	178 (41.3)	1.7 (1.2-2.4)	
Not available	16 (3.7)	1.0 (0.6-1.8)	
10. Insurance status			
Not insured	6 (1.4)	1 [Reference]	0.768
Private	214 (49.7)	2.0 (0.9-5.1)	
Medicaid	17 (3.9)	1.6 (0.6-4.6)	
Medicare	163 (37.8)	2.0 (0.9-5.2)	
Unknown	31 (7.2)	3.2 (1.4-8.9)	

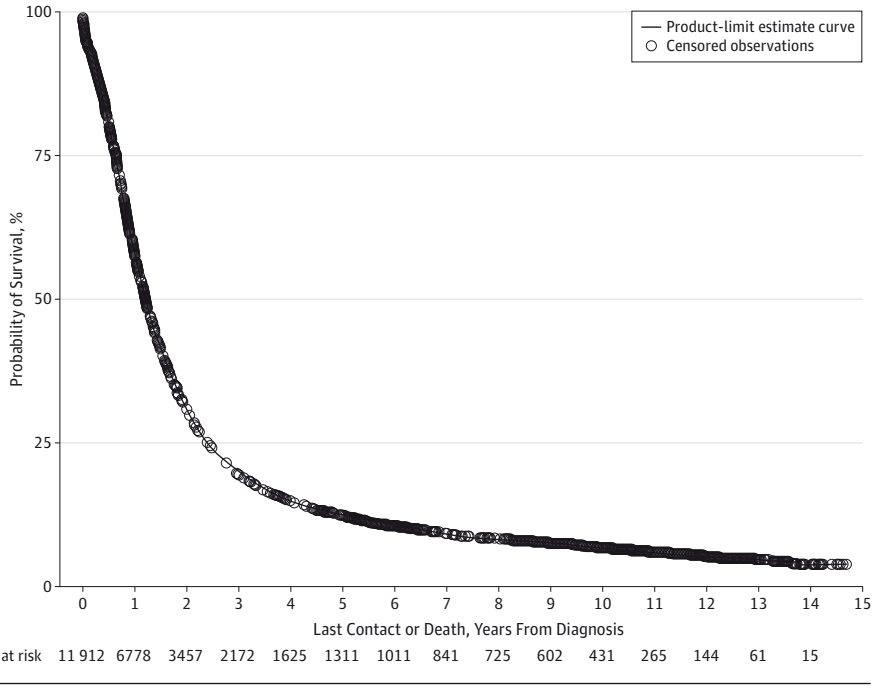
Abbreviations: NOS, not otherwise specified; OR, odds ratio.

[a] Total of 11 064 records, 431 events (17 records dropped out of the model owing to missing predictors).

[b] The group with the lowest probability of long-term survival (surviving ≥10 years from initial diagnosis) was selected as the reference frame.

[c] Surgical resection margins were divided into 3 groups: negative margin (R0), positive margin (including microscopic [R1], macroscopic [R2], and positive [NOS]), and unknown margin status.

Figure 2. Overall Survival of Patients Diagnosed With Pancreatic Ductal Adenocarcinoma



This figure was prepared using the initial cohort of 11 917 patients; 5 of these patients had no time to event and are not shown in the initial count. These 5 are part of the 836 patients (Figure 1) who were removed before models were run. The remaining 831 patients were censored and do not appear in the models but are shown here.

Finally, younger age was a significant predictor of 10-year survival. The 10 statistically significant predictor variables resulted in a predictive model with a moderately high C index of 0.768.

The Kaplan-Meier overall survival curve is shown in **Figure 2**. The probability of dying following initial diagnosis appears to reach a plateau at approximately 7 years. Although the yearly death rate declined from 47% to 15% during the first 6 years, it remained fairly constant at approximately 10% starting in the seventh year (eTable 2 in the Supplement). One possible explanation for this plateau is that death after year 7 is less likely due to tumor recurrence[7]; however, the annual death rate in the PADC group continued to be 2-fold higher than the mortality of an age- and sex-matched US general population (4.5%; $P < .001$) (eFigure in the Supplement).

Nomogram for 10-Year Survival

Based on our multivariable logistic regression model, each variable associated with long-term survival was assigned a specific score (**Table 3**). The sum of the score assigned to each variable, ranging from 0 to 35, can be used to predict LTS. The nomogram in **Figure 3** (see also eTable 3 in the Supplement) presents estimates of the probability of surviving for 10 or more years for different scores based on the scores given in Table 3. Inclusion or exclusion of patients with perioperative mortality did not change the performance of the model (C index, 0.767 vs 0.761) (eTable 4 in the Supplement).

For example, a 55-year-old patient (score, 4) with a well-differentiated tumor (score, 3), pT1 tumor (score, 4), tumor size of less than 2 cm (score, 2), LNPR of 0% (score, 5), negative margin (score, 2), no evidence of metastatic disease (score, 6), adjuvant chemotherapy (score, 3), educational level greater than 86% (score, 2), and any type of insurance (score, 2) would obtain a total score of 33 or a probability of 18.1% of LTS.

At the other extreme, a 65-year-old patient (score, 2), with a poorly differentiated tumor (score, 0), pT3 tumor (score, 2), tumor size of 3 cm (score, 0), LNPR of 20% (score, 0), negative margin (score, 2), no evidence of metastatic disease (score, 6), no chemotherapy (score, 0), educational level greater than 86% (score, 2), and any type of insurance (score, 2) would obtain a total score of 16 or a probability of LTS of less than 1.0%.

Validation of the model revealed that the C index for the developmental model applied to the developmental data set was 0.770 and decreased to 0.748 for the developmental model applied to the test data set. The Hosmer-Lemeshow goodness-of-fit test did not show statistical significance, both for the developmental model applied to the developmental data set ($P = .05$) and the developmental model applied to the test data set ($P = .20$).

Discussion

We have described what we believe to be the largest cohort of LTSs following surgical resection for PADC in the United States. We identified 431 LTSs (3.9%) and characterized clinical, histologic, and sociodemographic factors associated with LTS.

Schnelldorfer et al[7] described the characteristics associated with long-term survival in a cohort of 21 patients with PADC, reporting a disease-specific survival of 13%. Lymph node metastasis was the only variable significantly associated with LTS. Patients who survived at least 7.8 years from the initial diagnosis had no recurrence of disease. The inves-

Table 3. Scoring System for Nomogram Predicting Likelihood of 10 Years of Survival From Diagnosis

Variable	Full Model-Based Score
Lymph node ratio (positive-examined)	
>20%[a]	0
1%-20%	4
0%	5
Unknown	3
Chemotherapy	
None[a]	0
Neoadjuvant	0
Adjuvant	3
Pathology T (TNM)	
T = 4[a]	0
T = 3	2
T = 2	3
T = 1	4
T = 0/X	3
Age, y	
>80[a]	0
70-80	2
60-70	2
50-60	4
<50	4
Surgical margin	
Positive[a]	0
Negative	2
Unknown	2
Tumor grade, differentiated	
Poorly[a]	0
Moderately	2
Well	3
Cell type NOS	1
Pathology M	
M = 1[a]	0
M = X	6
Tumor size, cm	
>4[a]	0
2-4	0
<2	2
Unknown	0
Educational level (high school diploma)	
<71.0%[a]	0
71.1%-80.0%	1
81.1%-86.0%	1
>86.0%	2
Not available	0
Insurance status	
Not insured [a]	0
Private	2
Medicaid	2
Medicare	2
Unknown	4

Abbreviation: NOS, not otherwise specified.

[a] The model-based score was derived from the β coefficient • 10/3 and rounded down to the nearest integer.

tigators concluded that survival beyond 10 years could be indicative of cure.

In a study by Dusch et al,[3] a total of 22 patients with PADC survived 10 years, and 15 patients were alive 12 years after curative intent surgical resection. Lymph node ratio and blood transfusion were shown to be independent factors predicting long-term survival.

Our work overcomes some of the limitations of prior studies: small sample size and availability of long-term follow-up. In addition, we analyzed patients who underwent resection during a limited period (1998-2002). This limited time is advantageous because treatment strategies, surgical techniques, and perioperative mortalities remained fairly constant during the study.

We developed a simple nomogram. A score of 28 or more confers the highest likelihood of 10 or more years of survival following a diagnosis of PADC, although only 64 of 353 patients (18.1%) in this high-score subgroup went on to survive for 10 or more years. The presented nomogram can be used as an extension of the *American Joint Commission on Cancer Cancer Staging Manual*, seventh edition,[15] since it predicts survival beyond the conventional 5-year mark. Because several variables included in the nomogram are not available at the time of preoperative consultation, our nomogram is best used in the postsurgical setting.

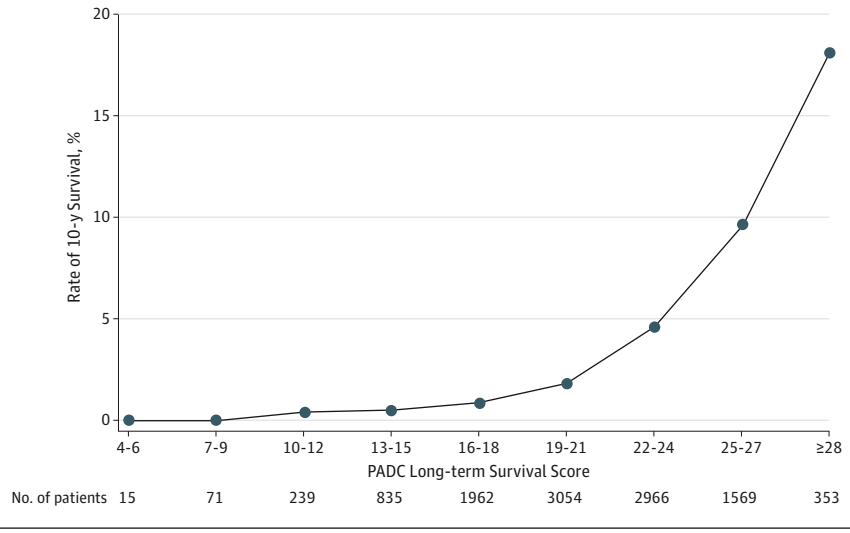
The absence of metastatic disease is an almost absolute prerogative for long-term survival and confers the highest score among all factors evaluated (6 points). Although metastatic disease was recorded in 3 cases (0.5%) of our LTS cohort, a misclassification error cannot be excluded.

The absence of nodal disease confers the second-highest score among all factors evaluated (5 points). Furthermore, LNPR is among the strongest predictors of LTS. Prior publications[12,16-18] have shown that LNPR is superior to the number of positive lymph nodes as a marker of overall survival especially when the number of nodes examined is low.

Systemic chemotherapy was used in only 40% of the entire PADC cohort. However, more than 60% of the LTS cohort received adjuvant chemotherapy, and its use conferred a substantial survival benefit (3 points). The positive association between the use of adjuvant therapy and LTS could be interpreted as a possible surrogate marker for a less-complicated postoperative course and better overall patient performance status,[19] even though a direct tumortoxic effect of chemotherapy is not excluded.[20,21] As expected, smaller tumor and younger age are positively associated with LTS: age younger than 60 years and T1 tumor stage each confer 4 points and are the most frequently represented categories in the LTS group.

Insurance status was among the selected factors included in our multivariable logistic regression model. With the exception of uninsured status, which was highly underrepresented in the entire cohort as well as in the LTS group (1.4%), we were not able to identify any significant effect of different types of insurance on LTS. Another socioeconomic factor evaluated was educational level, with higher levels of education being associated with the highest likelihood of

Figure 3. Nomogram Predicting the Likelihood of Surviving for 10 or More Years From Initial Diagnosis of Pancreatic Ductal Adenocarcinoma (PADC)



Score ranges obtained with the scoring system (Table 3) are represented on the x-axis with the likelihood of surviving for 10 or more years on the y-axis.

LTS. Prior studies[22-24] have identified higher socioeconomic status to be an independent predictor for access to care and likelihood of surgical resection. In our study this trend was confirmed since higher educational level could be seen as a surrogate of higher socioeconomic status.

This work has several limitations. First, the intrinsic nature of a population-based study does not allow reevaluation of histologic specimens. However, other authors[3] have noticed that histologic misclassification is identified in less than 6% of cases. Second, the NCDB does not collect information on which specific margins of resection were evaluated. Third, the lack of data on operative or postoperative complications limits our ability to evaluate the role of surgical morbidities on overall survival. Fourth, the NCDB does not collect data on disease recurrence; therefore, the possibility of disease recurrence in patients surviving for 10 or more years cannot be excluded. Furthermore, the survival data presented are not limited to cancer-related death, and patients in this study may have died for reasons unrelated to PADC. Fifth, the NCDB captures approximately 70% of patients with PADC in the United States, and we did not have information on the reminder of the patients. However, there are no reasons to believe that the missing data follow a specific pattern (ie, data missing not at random) that would change the overall conclusion of the data analysis. Finally, the NCDB does not provide information on the details of adjuvant therapy administered.

Conclusions

We have presented what we believe to be the largest study on LTSs with PADC in the United States. Although PADC remains a deadly disease, long-term survival is possible even beyond the 10-year mark. Our multivariable logistic regression model identified lymph node ratio, administration of adjuvant chemotherapy, and pathologic T stage as being the top 3 variables associated with LTS. In addition, we developed a simple nomogram to help identify potential LTSs for surgically resected PADC.

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Study concept and design: Paniccia, Henderson, Schulick, McCarter, Gajdos.
Acquisition, analysis, or interpretation of data: Paniccia, Hosokawa, Henderson, Schulick, Edil, Gajdos.
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Critical revision of the manuscript for important intellectual content: All authors.
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Invited Commentary

Long-term Survival After Pancreatic Cancer
Hope Has Arrived

Mu Xu, MD, PhD; O. Joe Hines, MD

Pancreatic cancer is the most lethal cancer with nearly every patient diagnosed dying within the ensuing 12 months. Pancreatic cancer is projected to become the second leading cause of cancer-related death in the United States by 2030.[1] Very rarely anecdotal reports on long-term survivors surface; however, such reports are becoming more common as new chemotherapeutic regimens have become used. However, long-term survivors (LTSs) (surviving ≥10 years) even with surgery are still rare, with a rate of only 6% at our institution: a tertiary center providing multidisciplinary treatment. Others[2,3] have found similar long-term survival rates.

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In this issue of *JAMA Surgery*, Paniccia et al[4] examined what appears to be the largest cohort to date: more than 11 000 patients who underwent surgical resection and found 431 LTSs (3.9%). Of note, among multiple predictors, such as adjuvant chemotherapy, low T stage, and R0 resection, the authors found a low positive lymph node ratio to be the most important predictor of long-term survival. The authors also developed a novel nomogram to predict the probability of long-term survival, with a projected 18.1% survival rate with the most favorable score.

A total of 51.0% of the LTSs in this study were node-positive at the time of surgery, and 12.3% of all LTSs underwent R1 or R2 resection. These findings underscore the importance of systemic therapy. This large cohort was treated between 1998 and 2002, before a wider application of chemotherapy. Only approximately 3% to 5% of LTSs in this study received neoadjuvant therapy. Neoadjuvant therapy is increasingly moving to the forefront of this disease and has been a paradigm shift for the management of borderline resectable or locally advanced tumors. Although the long-term effect of neoadjuvant therapy remains to be seen, we are hopeful that, as more effective treatments come on line, this approach will become standard as has been the case for many other solid malignant neoplasms.

Two other important factors that this study did not address are the ranges of perioperative carbohydrate antigen 19-9, and the presence or absence of perioperative complications, such as delayed gastric emptying, pancreatic leak, and pancreatic fistula. A low preoperative level of carbohydrate antigen 19-9 has been shown[5,6] to predict longer 5-year survival. Postoperative complications negatively affect patient recovery and nutritional status and directly delay adjuvant chemotherapy. Lowering postoperative morbidity through the consolidation of pancreatic cancer care to specialty centers is probably also contributing to improved long-term survival.

Overall, Paniccia et al[4] have presented a highly commendable retrospective study on the LTSs of pancreatic cancer. There is much to be learned from this cohort of patients regarding the clinical management and tumor biology of this group. With the advances in pancreatic cancer research and the growth of multidisciplinary management, we expect a growing number of patients will realize the benefits of incremental improvement in the management of this lethal disease.