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## Consensus Statement on the Pathology of IgG4-Related Disease

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## Pancreatic ductal adenocarcinoma: Long-term survival does not equal cure

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### Abstract

**Background**—Pancreatic ductal adenocarcinoma represents 90% of pancreatic cancers and is an important cause of cancer death in the United States. Operative resection remains as the only treatment providing prolonged survival, but even after a curative resection, 5-year survival rates are low. Our aim was to identify the prognostic factors for long-term survival after resection of pancreatic ductal adenocarcinoma related to patients, treatments, and tumor biology.

**Methods**—Retrospective review identified 959 patients who underwent resection of their pancreatic adenocarcinoma between February 1985 and December 2010, of whom 499 were resected before November 2006 and represent the cohort we describe in this study. Patient, tumor, and treatment-related variables were assessed for their associations with 5- and 10-year overall survival.

**Results**—Of the 499 patients, 49% were female and median age was 65 years. The majority of patients had stage IIb disease (60%). Actual 5-year survival after resection of pancreatic adenocarcinoma was 19% (95/499), and actual 10-year survival was 10% (33/329). Significant clinicopathologic factors predicting 5- and 10-year survival were negative margins and negative nodal status. Interestingly, 41% (39/95) of long-term survivors had positive nodes and 24% (23/95) had positive margins.

**Conclusion**—Pancreatic ductal adenocarcinoma demonstrates a very heterogeneous biology, but patients with negative resection margins and node negative cancers are more likely to survive 5 years after resection. However, our series demonstrates that the biology of the cancer rather than simple pathologic factors determine a patient's prognosis.

Recently, the American Cancer Society reported that during the last decade overall rates of cancer and cancer death have dropped.<sup>1</sup> This is believed to be largely because of a decrease in cigarette smoking and an increase in cancer screening. Conversely, pancreatic cancer rates are on the rise.<sup>2</sup> This fact, in combination with the dismal prognosis and lack of early detection, make pancreatic cancer a growing concern. Additionally, societal awareness of

pancreas cancer has been heightened owing to numerous celebrities who have recently died of the disease.

The American Cancer Society estimates that there will be 44,030 new cases of pancreatic cancer diagnosed in 2011. This is an increase of almost 19% from 2007.<sup>2</sup> The American Cancer Society also estimates that there will be 37,660 deaths from pancreatic cancer in 2011, making it the fourth leading cause of cancer-related death among men and the third leading cause of cancer-related death among women in the United States.<sup>3</sup> An estimated \$1.9 billion is spent on the disease each year.<sup>3</sup> Despite progress in our understanding of pancreatic cancer, the 5-year survival for all-comers remains 5% and has not changed over the past 3 decades.<sup>4</sup> Even after operative resection, actual 5-year survival is only 12% in other series.<sup>5</sup>

The aims of this study were to evaluate the actual 5- and 10-year overall survivals of patients who have undergone operative resection of pancreatic ductal adenocarcinoma. The second aim was to evaluate clinicopathologic factors predicting long-term survival.

## METHODS

We retrospectively reviewed a database of all patients who underwent pancreatic resection at the Massachusetts General Hospital between February 1985 and November 2006 and identified 499 patients who underwent resection for pathologically confirmed pancreatic ductal adenocarcinoma.

Patient-, tumor-, and treatment-related variables were evaluated. Patient factors evaluated included age, gender, smoking status, and family history. Treatment factors included the type of operation, adjuvant therapy, and status at last follow-up. Pathologic factors included tumor size, nodes, metastases, TNM stage, margin (positive or negative), and vascular, lymphatic, and perineural invasion and differentiation (well, moderate, or poor). Maximal tumor size was determined and defined as the maximum diameter at pathological analysis. Follow-up was obtained through office records and the social security death index.

Patients were divided into short-term survivors (3– 20 months), intermediate term survivors (>20–<60 months), and long-term survivors (>60 months). There were 17 perioperative mortalities within 90 days of operative resection that were not included in Table I. Utilizing SAS Version 9.2 (SAS, Inc, Chicago, IL), both univariate and multivariate modeling were performed. Continuous variables were expressed as median or mean values  $\pm$  standard deviation and were compared using an independent samples *t*-test. Chi-square *P*-values were calculated for the comparison of clinical characteristics between survivorship groupings (Table I). Cox regression modeling was used to determine the effect of prognostic factors on overall survival. We calculated odds ratios using logistic regression modeling to determine factors associated with short- and long-term (Tables II and III) survivorship. Both univariate and multivariate models were created. Kaplan–Meier methodology was used for the overall survival curve and it was computed from the time of operative resection to the date of last follow-up. The institutional internal review board approved this study, and none of the authors have any conflict of interest.

## RESULTS

### Clinicopathologic factors

Between February 1985 and November 2006, 499 patients underwent complete gross resection of a pathologically confirmed pancreatic ductal adenocarcinoma. The cohort was approximately half female (49%) with a median age at diagnosis of 65 years (range, 31–91).

The majority of patients (84%) underwent pancreaticoduodenectomy and had stage IIB disease (60%). One third of the patients 35% (174/499) received chemotherapy and 66% (329/499) received radiotherapy with chemotherapy. Even though receiving chemotherapy is a time-dependent covariate, not receiving chemotherapy was independently associated with decreased survival after the pancreatic operation ( $P = .04$ ). The clinicopathologic characteristics of the overall cohort are listed in Table I.

### Overall survival

Patients were divided into short-term survivors (3–20 months), intermediate term survivors (>20–<60 months), and long-term survivors (>60 months). The final cohort contained 499 patients, including 243 short-term survivors, 144 intermediate term survivors, and 95 long-term survivors. The median follow-up for the entire cohort was 19 months (range, 1–271). The overall postoperative mortality at 90 days was 3.4% (17/499). The postoperative mortality after pan-creaticoduodenectomy was 16/418 (3.8%) and after distal pancreatectomy 1/66 (1.5%). The 14 perioperative mortalities were included in the short-term survivor group. Overall survival for the entire cohort is demonstrated in the Figure. The actual 5-year survival was 19% (95/499). Almost 1/3 of patients survived between 20 and 60 months and 49% survived less than 20 months. Within the group of 95 patients who survived 5 years, 41% had stage IIB, 31% stage IIA, 15% stage IB, and 14% stage IA cancers. Unfortunately, 5-year survival does not represent cure, with 13% (12/95) of the patients dying of disease after this time. Currently, 62 patients have survived between 5 and 10 years of whom 56 are still alive. The longest survivor is alive 22.5 years after her operation. Actual 10-year survival was 10% (33/329).

### Prognostic factors

Short-term, intermediate, and long-term survivors had significant differences in their R0/R1 status, histologic tumor grade, lymph node status, and TNM staging on univariate analysis (Table I). Patients with negative margins, well-differentiated tumors, negative nodes and a lower TNM stage were more likely to experience long-term survival. When comparing patients who survived 5–10 years with those who survived <10 years, the only significant difference was the percentage of R0 resections ( $P = .01$ ). Otherwise, the differences in clinical characteristics between the 2 survivorship groups were not statistically significant (Table IV).

Univariate logistic regression models built to predict overall survival from the date of resection demonstrated that positive margins, higher stage, positive nodes, and increased tumor size were independently associated with decreased overall survival (Table II). Multivariate analysis demonstrates that negative margins and negative nodes were independently associated with longer survival (Table III).

## DISCUSSION

Most pancreatic cancers are diagnosed at an advance stage. This, together with the aggressiveness of the disease and the lack of effective systemic therapies, results in low rates of overall survival. Operative resection remains the only chance for long-term survival, despite advances in adjuvant and neoadjuvant therapies. The perioperative morbidity and mortality of pancreatic surgery has decreased to 24% and 2%, respectively, over the last 30 years.<sup>6–8</sup> Despite all of these improvements, the overall survival of patients with pancreatic adenocarcinoma remains low. In our cohort of 499 patients resected between 1985 and 2006, the actual 5- and 10-year overall survivals were 19% and 10%, respectively. The actual 5-year overall survival of 19% is 2% higher than what we reported in 1992.<sup>9</sup> Although these results are better, survival remains low. Series from John Hopkins University and Memorial

Sloan Kettering Cancer Center report a similar 5-year overall survival of 18% and 12%, respectively (Table V).

Analysis of clinicopathologic variables in our 5-year survivors demonstrates the challenges in prognosis for an individual patient with this disease. Increased tumor size, R1 status, positive nodes, advanced stage disease, and not receiving chemotherapy were independently associated with decreased survival after resection on univariate analysis. Only N stage and margin status were significant predictors of long-term survival in our cohort. Similarly, other large series identified margin status as a predictor of long-term survival.<sup>5,7,10</sup> Unfortunately, margin status is often affected by the location and size of the tumor. However, positive margins do not preclude long-term survival, because 25% of the 5-year survivors in our series had an operation with positive margins. Negative nodes also emerged as a prognostic factor for long-term survival in our series. Multiple studies identify stage as a prognostic marker. We did not identify stage, but clearly nodal status and American Joint Committee on Cancer stage are closely linked. In our cohort 41% (39/95) of 5-year survivors and 44% (14/33) of 10-year survivors had positive lymph nodes at the time of operative resection. These node-positive, long-term survivors exemplify the heterogeneous tumor biology of pancreatic cancer.

The use of adjuvant chemotherapy has increased during the last 2 decades in the United States.<sup>11</sup> Although the aim of our study was not to measure the benefit conferred by adjuvant therapy, we did notice that between the first 10 years of our study (1985–1995) only 1.4% of the patients received chemotherapy, compared to 47.7% between 1995 and 2006. Some of the long-term survivors may have benefited from adjuvant therapy because chemotherapy improved survival in our series and has been demonstrated to improve disease-free survival after operative resection by about 10% in a randomized, controlled trial.<sup>12</sup> Despite a shift in adjuvant chemotherapy from 5-fluorouracil to gemcitabine over the last 2 decades, these 2 agents have demonstrated equivalent efficacy on disease-free and overall survivals.<sup>13,14</sup> Therefore, the increased use of chemotherapy over time in our series most likely improved the time to recurrence rather than the specific agent used.

Overall survival did not change significantly during the 2-decade study period; however, perioperative 90-day mortality decreased by half from 5% to 2.5% between the first and second decade. Perioperative mortality has been reported at most centers around 5%.<sup>8,15</sup> We report in this study a 3.2% perioperative 90-day mortality rate for the entire cohort. This decrease in mortality is multi-factorial, to which the development of tertiary care centers with multidisciplinary teams and the specialization of surgeons in pancreas surgery has contributed.<sup>16,17</sup>

Long-term survivors present a unique cohort of patients to study. Despite positive margins and/or positive nodes some patients are still alive. Whereas 66% of the short-term survivors and 63% of the intermediate survivors had stage IIB disease, 41% of the 5-year survivors had positive nodes. Conversely, 28% (17/61) of patients with stage I disease died of the disease within 20 months, and only 44% (27/61) lived beyond 5 years. Therefore, stage alone is unable to reliably predict prognosis. Positive margins were demonstrated in 47% of short-term survivors and 31% of intermediate survivors, yet 24% of 5-year survivors also underwent an R1 resection. Although these differences are significant they highlight that the pace of progression is heterogeneous and determined by biology rather than pathology. These tumors may have a lower number of cancer-initiating cells (aldehyde dehydrogenase-high), cells that possess properties of self-renewal, tumor initiation, and differentiation.<sup>18</sup> Other series have demonstrated a worse prognosis in patients who have more mesenchymal tumors, which express vimentin, fibronectin, and N-cadherin,<sup>18–20</sup> so perhaps these long-term survivors may have tumors with more epithelial features. Although many gene

amplifications and deletions, epigenetic changes, and proteomic abnormalities have been identified, the biology of pancreatic cancer is currently still poorly understood.

Interestingly, 5-year survival is not consistent with cure as an additional 23 patients died 5 years after their operation. Of these patients 12 died of disease, 10 patients died of unknown causes, and 1 patient died of a non-cancer-related cause. Therefore, of our 5-year survivors, 58% (55/95) are still alive. Several patients in our cohort have relapsed >10 years after the resection of their primary pancreatic adenocarcinoma. Two patients developed isolated lung metastases and underwent pulmonary resections to help control their disease. This late relapse perhaps suggests that the interaction of the immune system with the tumor varies over time and during the progression of the malignancy. The cells we later identify as recurrences may have been controlled by the immune system from the time of the resection of the primary cancer. This phenomenon of tumor escape can occur through a variety of mechanisms, including inhibition or suppression of T-cell recognition, an increase in regulatory T cells, alterations in the immunologic checkpoints resulting in downregulation of T cells, and many others.<sup>21–23</sup> By studying this cohort of patients, we hope to elucidate some of the contributing factors to recurrence.

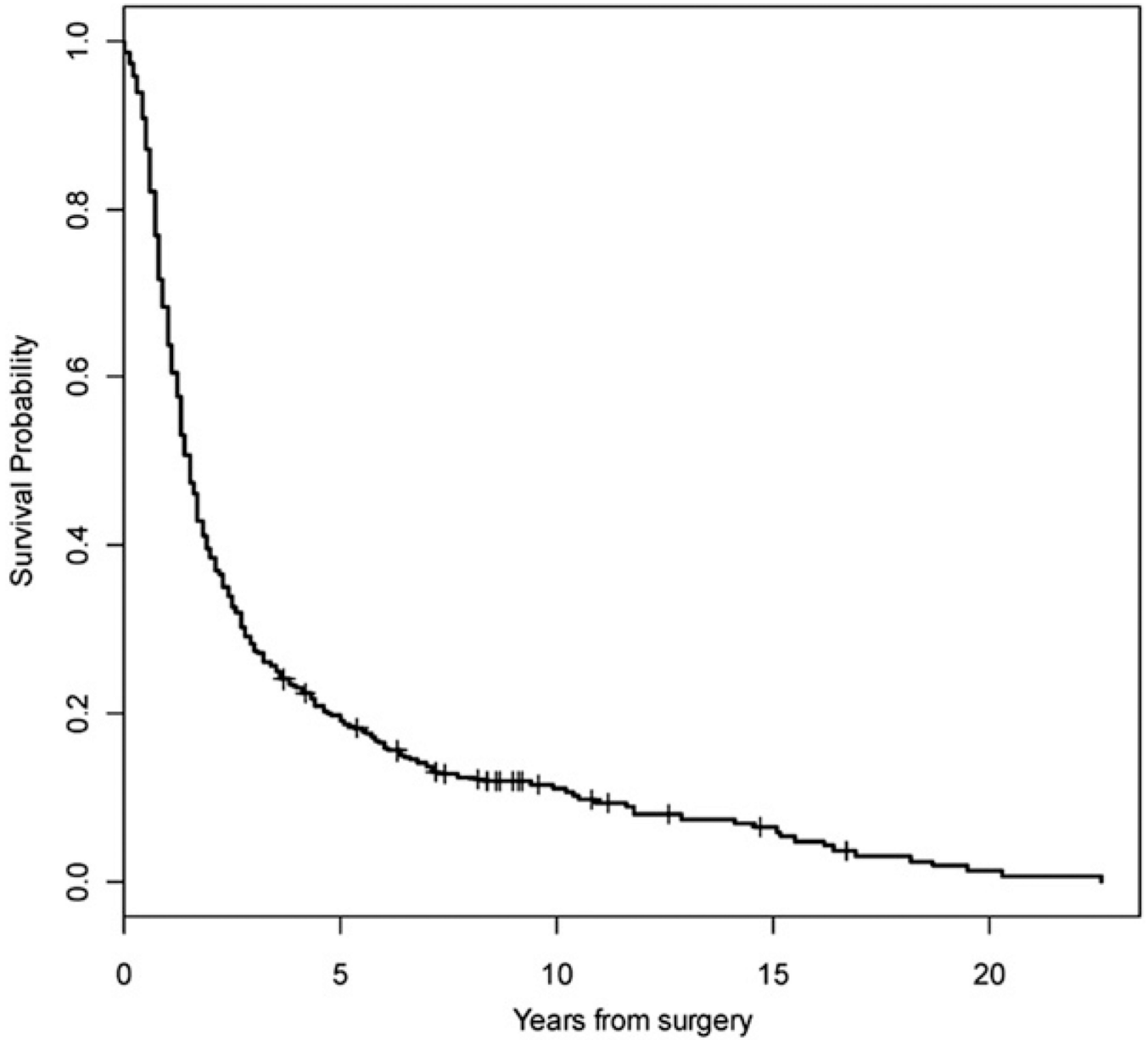
In conclusion, this series confirms that ductal adenocarcinoma of the pancreas has an implacable prognosis, even after resection, with actual 5- and 10-year survivals of 19% and 10%, respectively. However, our series exemplifies that a patient's prognosis is determined by tumor biology rather than clinicopathologic factors, because there is a striking discordance between pathology, stage, and survival. Additional efforts are needed to decrease morbidity associated with pancreatic resection and improve screening for early detection; however, mostly we need to intensify the search for new and effective therapies by understanding the diverse biology of the long-term survivors.

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### Overall survival from date of first surgery



**Figure.**  
Overall survival for all patients (Kaplan–Meier).



**Table 1**  
 Clinicopathologic factors of patients who underwent resection of pancreatic adenocarcinoma

	Overall, n (%) (n = 499)	Short-term survivor, n (%) (n = 243)	Intermediate-term survivor, n (%) (n = 144)	Long-term survivor, n (%) (n = 95)	Chi-square P-value
Gender					NS
Female	242 (49)	131 (54)	62 (43)	42 (45)	
Male	257 (51)	112 (46)	82 (57)	53 (55)	
Tumor location					NS
Head	420 (85)	205 (84)	125 (87)	77 (81)	
Body	23 (5)	9 (4)	7 (5)	7 (7)	
Tail	51 (10)	29 (12)	12 (8)	8 (9)	
Operation					NS
Pancreaticoduodenectomy	418 (84)	199 (81)	125 (88)	79 (83)	
Distal pancreatectomy	66 (13)	37 (16)	16 (11)	11 (12)	
Total pancreatectomy	15 (3)	7 (3)	2 (1)	5 (5)	
Stage of resected patients					<.001
IA	19 (4)	2 (1)	4 (3)	13 (14)	
IB	42 (8)	15 (6)	13 (9)	14 (15)	
IIA	115 (23)	47 (19)	34 (22)	29 (31)	
IIB	300 (60)	160 (66)	89 (63)	39 (41)	
III	18 (4)	14 (6)	4 (3)	0 (0)	
IV	5 (1)	5 (2)	0 (0)	0 (0)	
pT					<.001
1	25 (9)	6 (2)	6 (4)	13 (14)	
2	75 (15)	31 (13)	24 (17)	18 (19)	
3	379 (76)	190 (78)	110 (76)	64 (67)	
4	20 (4)	16 (7)	4 (3)	0 (0)	
pN					<.001
0	187 (37)	71 (29)	54 (37)	56 (59)	
1	312 (63)	171 (71)	90 (63)	39 (41)	
Margin (R0R1)					<.001
Negative	310 (60)	129 (53)	100 (69)	72 (76)	

	Overall, n (%) (n = 499)	Short-term survivor, n (%) (n = 243)	Intermediate-term survivor, n (%) (n = 144)	Long-term survivor, n (%) (n = 95)	Chi-square P-value
Positive	189 (40)	114 (47)	44 (31)	23 (24)	
Perineural invasion					NS
No	125 (25)	63 (26)	36 (25)	23 (25)	
Yes	334 (67)	167 (69)	96 (67)	56 (60)	
Unknown	40 (8)	12 (5)	12 (8)	16 (15)	
Perivascular invasion					NS
No	191 (38)	89 (37)	56 (39)	32 (34)	
Yes	154 (31)	84 (35)	42 (29)	22 (23)	
Unknown	154 (31)	68 (28)	46 (32)	41 (43)	
Grade					.002
Moderately differentiated	265 (53)	133 (55)	84 (58)	40 (42)	
Poorly differentiated	190 (38)	102 (42)	46 (32)	39 (37)	
Undifferentiated	4 (1)	0 (0)	4 (3)	0 (0)	
Well differentiated	23 (5)	8 (3)	6 (4)	10 (10)	

**Table II**

Univariate logistic regression model predicting long-term survival

Long-term univariate	Odds ratio (95% confidence interval)	P-value
Head	0.712 (0.40–1.28)	.258
Male	1.232 (0.78–1.94)	.368
Pancreaticoduodenectomy	0.911 (0.50–1.67)	.763
ROR1:R1	0.447 (0.27–0.75)	.002
Age/10	1.009 (0.81–1.26)	.936
Received chemo	1.499 (0.94–2.39)	.089
H vs D:H	0.851 (0.46–1.59)	.612
pN	0.318 (0.20–0.51)	<.001
Poorly differentiated	1.142 (0.72–1.81)	.572
Tumor size	0.774 (0.64–0.94)	.010
Stage 3–4*	NA	—
T stage 3–4	0.434 (0.26–0.72)	.001

\* Because there were no stage 3–4 patients in the long-term survivor group, this effect was not analyzable (NA).

**Table III**

Multivariate logistic regression model predicting long-term survival

<b>Multivariate</b>	<b>Odds ratio (95% confidence interval)</b>	<b>P-value</b>
R0/R1:R1	0.472 (0.27–0.82)	.008
pN	0.300 (0.18–0.50)	<.001

Table IV

Patients characteristics of long-term survivors by length of survival time

Variable	Long-term survivors (overall), n (%) (n = 95)	5- and <10-year survivorship, n (%) (n = 62)	10-yr survivorship, n (%) (n = 33)	Chi-square P-value
Gender				NS
Female	42 (45)	30 (48)	12 (37)	
Male	53 (55)	32 (52)	21 (63)	
Tumor location				NS
Head	77 (81)	51 (82)	26 (79)	
Body	7 (7)	5 (8)	2 (6)	
Tail	8 (9)	4 (7)	4 (12)	
Operation				NS
Pancreaticoduodenectomy	79 (83)	53 (86)	26 (79)	
Distal pancreatectomy	11 (12)	7 (11)	4 (12)	
Total pancreatectomy	5 (5)	2 (3)	3 (9)	
Stage of resected patients				NS
IA	13 (14)	9 (15)	4 (12)	
IB	14 (15)	7 (11)	7 (21)	
IIA	29 (31)	22 (35)	7 (21)	
IIB	39 (41)	24 (39)	15 (46)	
pT				NS
1	13 (14)	9 (15)	5 (13)	
2	18 (19)	8 (13)	10 (31)	
3	64 (67)	45 (72)	18 (56)	
pN				NS
0	56 (59)	38 (61)	19 (56)	
1	39 (41)	24 (39)	14 (44)	
Margin (R0R1)				.014
Negative	72 (76)	42 (68)	30 (91)	
Positive	23 (24)	20 (32)	3 (9)	
Perineural invasion				NS
No	23 (25)	14 (22)	9 (29)	
Yes	56 (60)	42 (68)	14 (45)	
Unknown	16 (15)	6 (10)	9 (26)	
Perivascular invasion				NS
No	32 (34)	18 (29)	13 (42)	
Yes	22 (23)	17 (28)	4 (13)	
Unknown	41 (43)	27 (43)	15 (45)	
Grade				NS
Moderately differentiated	40 (42)	25 (40)	15 (46)	
Poorly differentiated	39 (37)	25 (40)	14 (42)	
Well differentiated	10 (10)	9 (14)	2 (6)	

**Table V**

Comparison of other series with actual 5-year survivors of pancreatic adenocarcinoma

	Number of patients	Female (%)	Whipple (%)	Median survival (mos)	Actual 5-year survival (%)	Actual 10-year survival (%)	Predictors of survival
Ahmad et al <sup>24</sup>	116	54	95	16	19	11 (7 yrs)	Adjuvant therapy
Cleary et al <sup>25</sup>	123	43	91	14	14	4	AJCC stage, grade
Winter et al <sup>10</sup>	1,175	46	100	18	18	11	Tumor size, lymph node, margin, histological grade, COPD, bile leak, adjuvant therapy
Han et al <sup>7</sup>	123	29	81	15	12	—	AJCC stage, margin
Ferrone et al <sup>5</sup>	618	50	85	85	12	5	Negative margins, AJCC stage
Present (2011)	499	49	84	19	19	10	Negative margins, pN stage

AJCC, American Joint Committee on Cancer.