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415 Patients with Adenosquamous Carcinoma of the Pancreas: A Population-Based Analysis of Prognosis and Survival

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Background. Adenosquamous carcinoma of the pancreas is rare. Our understanding of the disease and its prognosis comes mainly from small retrospective studies.

Methods. Using the Surveillance, Epidemiology, and End Results (SEER) database (1988 to 2007), we identified patients with adenosquamous carcinoma ($n = 415$) or adenocarcinoma ($n = 45,693$) of the pancreas. The demographics, tumor characteristics, resection status, and survival were compared between the groups.

Results. Compared with patients with adenocarcinoma, patients with adenosquamous carcinoma were more likely to have disease located in the pancreatic body and tail (44.6% *versus* 53.5%, $P < 0.0001$). While the stage distribution was similar between the two groups, adenosquamous carcinomas were more likely to be poorly differentiated (71% *versus* 45%, $P < 0.0001$), node positive (53% *versus* 47%, $P < 0.0001$), and larger (5.7 *versus* 4.3 cm, $P < 0.0001$). For locoregional disease, resection increased over time from 26% in 1988 to 56% in 2007. The overall 2-y survival was 11% in both groups. Following resection, patients with adenosquamous carcinoma had worse 2-y survival (29% *versus* 36%, $P < 0.0001$). Resection was the strongest independent predictor of survival for patients with locoregional pancreatic adenosquamous carcinoma (HR 2.35, 95% CI = 1.47–3.76).

Conclusions. This is the first population-based study to evaluate outcomes in adenosquamous carcinoma of the pancreas. Compared with pancreatic adenocarcinoma, adenosquamous carcinoma was more likely to occur in the pancreatic tail, be poorly differentiated, larger, and node positive. The long-term survival following surgical resection is significantly worse for adenosquamous cancers; however, patients with adenosquamous carcinoma can still benefit from surgical resection, which is the strongest predictor of survival. © 2012 Elsevier Inc. All rights reserved.

Key Words: adenosquamous carcinoma; pancreas; survival; outcomes.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States, with approximately 43,140 new cases and 36,800 deaths in 2010 [1]. Adenocarcinoma accounts for approximately 90% of pancreatic malignancies [2]. Adenosquamous carcinoma of the pancreas, also referred to as adenoacanthoma, mixed squamous and adenocarcinoma, and mucoepidermoid carcinoma, accounts for 1%–4% of exocrine pancreatic malignancies [3]. Herxheimer first used the term "adenocancroid" when describing this entity in 1907 [4]. According to the Armed Forces Institute of Pathology, pancreatic adenosquamous carcinoma is defined as a neoplasm of the pancreas that is comprised of at least 30% malignant squamous cell carcinoma mixed with ductal adenocarcinoma [5].

Patients with adenosquamous carcinoma typically present with symptoms similar to adenocarcinoma of the pancreas, including abdominal pain, weight loss, anorexia, and jaundice [3, 6–8]. Diagnostic imaging can include computed tomography, endoscopic ultrasound, and endoscopic retrograde cholangiopancreatography (ERCP) [3]. Typically, one cannot differentiate adenosquamous carcinoma from adenocarcinoma radiographically [7]. When resected, adenosquamous carcinoma is frequently associated with positive lymph nodes, vascular and perineural invasion, and poor tumor cell differentiation [9].

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Because of its rarity, the majority of information on pancreatic adenosquamous carcinoma comes from small, single-institution and retrospective studies, with the largest study having 95 patients (Table 1) [3, 6–11]. In our literature search, we identified a total of 307 reported patients with adenosquamous carcinoma of the pancreas. A number of studies examined fewer than five patients each with adenosquamous carcinoma [12–26]. Table 1 (including studies with five or more patients) summarizes the number of patients, tumor location, resection status, and survival reported in previous studies.

Previous studies have demonstrated a poor prognosis for patients with pancreatic adenosquamous carcinoma. The reported overall median survival is less than 6 mo, and for patients who do not undergo surgical resection, median survival is even lower [8, 11]. Surgical resection with or without adjuvant chemotherapy has been shown to improve median survival from less than 6 mo to 11–20 mo in some studies, but in other studies, the median survival following resection was less than 8 mo [3, 6–8, 15, 18, 24, 27]. Resection margin status was shown to have prognostic significance in one small study, however, the small sample size in all previous studies does not allow for adequate evaluation of prognostic factors [11].

The goal of this study is to evaluate a large population-based cohort of patients with adenosquamous carcinoma of the pancreas. We will use Surveillance, Epidemiology, and End Results (SEER) database (1988–2007) to identify patients with adenosquamous carcinoma and adenocarcinoma of the pancreas. Specifically, we will compare patient characteristics, tumor characteristics, and outcomes between patients with adenosquamous carcinoma and adenocarcinoma of the pancreas, determine prognostic factors for adenosquamous carcinoma, and evaluate the benefit of surgical resection for patients with this histologic variant of pancreatic cancer.

METHODS

This study was approved by the Institutional Review Board at the University of Texas Medical Branch at Galveston.

Surveillance, Epidemiology, and End Results (SEER) Program

Developed by the National Cancer Institute, the SEER program collects information on cancer incidence and survival data from population-based cancer registries currently covering approximately 28% of the US population [28]. SEER provides information on patient demographics, primary tumor site, histology, stage of disease, first course of treatment, and survival status. The SEER database uses the best clinical information available, which is obtained from a variety of sources, including inpatient and outpatient hospital records [29]. We used the November 2009 submission, which has complete information on incidence from 1973–2007 and disease-specific survival through 2009.

SEER Patient Cohort

Our cohort included patients with a primary diagnosis of adenocarcinoma or adenosquamous carcinoma of the pancreas. International Classification of Disease for Oncology, 3rd edition (ICD-O-3) morphology codes included: adenocarcinoma (8000/3, 8010/3, 8020/3, 8021/3, 8022/3, 8050/3, 8140/3, 8141/3, 8230/3, 8260/3, 8450/3,

TABLE 1

Recent Literature on Adenosquamous Carcinoma with At Least Five Patients

Author	Year	Number of patients	Tumor location (%)	Resected (%)	Survival after resection	Overall survival
Yamaguchi et al. [30]	1991	8	Head (75) Body/tail (25)	8 (100)	6 mo	6 mo
Motojima et al. [31]	1992	6	Head (50) Body/tail (50)	3 (50)	5.7 mo	4.8 mo
Madura et al. [3]	1999	6	Head (50) Body/tail (50)	6 (100)	5 mo	5 mo
Kardon et al. [8]	2001	25	Head (68) Body/tail (32)	8 (32)	11.3 mo	4.5 mo
Rahemtullah et al. [27]	2003	14	Head (43) Body/tail (43)	2 (14.3)	Not reported	5.6 mo
Hsu et al. [6]	2008	12	Head (41.7) Body/tail (33.3)	7 (58.3)	6.5 mo	4.4 mo
Smoot et al. [11]	2008	23	Not reported	12 (52.2)	13.1 mo	Not reported
Okabayashi et al. [7]	2008	39	Head (76.9) Body/tail (23.1)	39 (100)	6.8 mo	6.8 mo
Brody et al. [32]	2009	8	Head (37.5) Body/tail (62.5)	8 (100)	5 mo	5 mo
Regi et al. [33]	2010	6	Head (100)	6 (100)	14.5 mo (with chemo)	14.5 mo
Voong et al. [9]	2010	38	Head (55) Body/tail (45)	38 (100)	17.9 mo	17.9 mo
Katz et al. [10]	2010	95	Not reported	31 (33)	12.0 mo	4.0 mo

8453/3, 8471/3, 8480/3, 8481/3, 8500/3, 8501/3, 8521/3) or adenosquamous cancer (8070/3, 8071/3, 8072/3, 8074/3, 8075/3, 8560/3, 8570/3). All SEER regions were included; as new SEER registries were added over the time periods, we did not attempt to evaluate time or geographic trends. Patients less than 18 and older than 100 years of age were excluded. Patients with *in situ* cancers and patients who did not have histologic confirmation of their cancer were excluded. The adenocarcinoma group included adenocarcinomas arising in intraductal papillary mucinous neoplasms. Patients with mucinous cystic neoplasms (8440, 8470) and neuroendocrine tumors (8150, 8151, 8152, 8153) were excluded.

Staging

The SEER program did not use AJCC TNM staging for pancreatic cancer before 2004. Therefore, patient stage was analyzed using SEER historic stage. The SEER historic stages were: (1) localized disease (AJCC 0, IA, IB), (2) regional disease (AJCC IIA, IIB, III), or (3) distant disease (AJCC IV). There were no noted changes in the historic coding system for cancer of the pancreas during our study period. Localized disease was defined as tumor *in situ* or tumor confined to the pancreas. Regional disease was defined as tumor invading adjacent structures including the duodenum, bile duct, ampulla of Vater, superior mesenteric vessels, hepatic artery, or locoregional lymph nodes. Distant disease required the presence of distant metastases (liver, lung) or metastases outside of the locoregional nodes. Initial SEER staging is derived from the best available information obtained within 4 mo of the date of diagnosis, including information from further studies, and excluding disease progression. Because of this, there is bias in the designation of local *versus* regional disease. In patients undergoing resection, full pathologic staging is available. In doing so, presumed local disease is often upstaged to regional disease. For this reason, locoregional disease is evaluated together. Patients with regional disease are technically resectable; those with tumor involving the superior mesenteric artery or celiac axis, or extensively involving the superior mesenteric vein and portal vein are not candidates for surgical resection.

For many patients, complete pathologic staging and data on tumor differentiation, lymph node status, and tumor size were not available. For these variables, the percentages are based on the denominator of patients with data available, and the number of patients with available data is reported. Resected patients were more likely to have accurate pathologic staging and were therefore analyzed separately to compare the above factors between adenocarcinoma and adenosquamous carcinoma patients.

Treatment

Because data on surgery of the primary site (within 4 mo of diagnosis) were available after 1988, we chose this as our start date. Over the time period 1988–2007, there were two different coding schemes for site-specific surgery. Patients were considered to have undergone potentially curative resection if they underwent partial or total pancreatectomy. For patients diagnosed between 1988 and 1997, this included "site specific surgery" codes 10, 20, 28, 30, 38, 40, and 50. For patients diagnosed after 1998, this included "surgery of primary site" codes: 10, 25, 30, 35, 36, 37, 40, 60, 70, 80.

To determine potential respectability, we used the SEER extent of disease (EOD) codes. Based on the "extension" portion of the code, cancers with invasion of the superior mesenteric/portal vein, celiac axis, or superior mesenteric artery and/or involvement of organs outside the usual resection field were considered unresectable. These codes changed over the time period and changes were taken into account.

While data on radiation (within 4 mo of diagnosis) are available in SEER, data regarding chemotherapy are not available. As such, we could not evaluate adjuvant or neoadjuvant therapy.

Statistical Analysis

The demographics, tumor stage, and resection status of the overall cohort were described. Bivariate statistics were performed to determine the unadjusted differences in these factors between the adenocarcinoma and adenosquamous carcinoma groups. χ^2 tests were used to compare all categorical variables and t-tests were used to compare all continuous variables in the univariate analysis. All means are expressed as mean $\pm$ standard deviation of the mean.

All analyses report overall disease-specific survival, with patients dying of non-cancer causes being censored at the time of death. Long-term survival was evaluated using the Kaplan-Meier method. As all patients had 2 y of follow-up, survival was evaluated at 2 y, with patients surviving more than 2 y censored as alive at the 2-year time point. We also performed survival analysis to 5 y and evaluated overall survival (not disease-specific), with no change in conclusions. Two-year survival is reported since our median follow-up is 26 mo. Comparisons of survival between groups (different tumor types, resection status) were performed using a logrank test. A Cox proportional hazards model was used to determine the independent effect of histology type (adenocarcinoma *versus* adenosquamous carcinoma) on survival. A second model was used to determine predictors of survival in patients with adenosquamous carcinoma. Categorical variables were modeled as a series of binary variables referenced to a single group specified for each variable. Statistical significance is accepted at the $P < 0.05$ level.

RESULTS

Overall Cohort (Table 2)

A retrospective review of the SEER database from 1988 to 2007 identified 415 patients with adenosquamous carcinoma and 45,693 patients with adenocarcinoma of the pancreas. Patient demographics and tumor characteristics are shown in Table 2. The age, gender, and race distributions were similar between the two groups, with a mean age of 66 years, a slight predominance of male patients, and approximately 80% of patients being white. While the stage at presentation was similar between the two groups, patients with adenosquamous carcinoma were more likely to have tumors in the body or tail of the pancreas (29.2% *versus* 19.0%) and less likely to have tumors located in the head of the pancreas (44.6% *versus* 53.5%, $P < 0.0001$) compared with patients with adenocarcinoma.

Tumor size was known in 26,123 patients, differentiation in 25,037 patients, and nodal status in 27,812 patients. Complete EOD codes to assess resectability were available in 40,376 patients. Patients with adenosquamous carcinoma had larger tumors than those with adenocarcinoma (5.7 $\pm$ 6.9 cm *versus* 4.3 $\pm$ 2.2 cm, $P < 0.0001$). In patients with known tumor differentiation ($n = 25,307$), 71.4% of patients with adenosquamous carcinoma had poorly-differentiated tumors, while only 45.0% of patients with adenocarcinoma had poorly-differentiated tumors ($P < 0.0001$). Of those patients whose nodal status was known, 52.8% of patients with adenosquamous carcinoma and 47.1% of patients with adenocarcinoma had positive lymph nodes ($P = 0.06$).

TABLE 2

Patient Demographics and Tumor Characteristics

Characteristics	Adenosquamous carcinoma ($n = 415$) n (%)	Adenocarcinoma ($n = 45,693$) n (%)	P value
Age (y), mean ± SD	66.6 ± 12.1	66.9 ± 11.8	0.41
Female gender	45.5%	49.4%	0.11
Race			
White	328 (79%)	36,855 (80.7%)	0.17
Black	60 (14.5%)	5,336 (11.7%)	
Other	27 (6.5%)	249 (7.7%)	
SEER stage			
Locoregional	176 (42.4%)	17,411 (38.1%)	0.16
Distant	220 (53%)	25,671 (56.2%)	
Unknown	19 (4.6%)	2611 (5.7%)	
Location			
Head	185 (44.6%)	24,432 (53.5%)	<0.0001
Body/tail	121 (29.2%)	8700 (19%)	
Other	109 (26.3%)	12,561 (27.5%)	
Size, median (SD) cm*	5.7 ± 6.9	4.3 ± 2.2	<0.0001
Differentiation*			
Well	7/241 (2.9%)	3042/24,796 (12.3%)	<0.0001
Moderate	62/241 (25.7%)	10,588/24,796 (42.7%)	
Poor	172/241 (71.4%)	11,166/24,796 (45.0%)	
Positive lymph nodes*	141/267 (52.8%)	12,696/27,545 (47.1%)	0.06
Resectable*	146/375 (38.9%)	16,245/40,001 (40.6%)	0.51
Resected (for those considered resectable)	90/146 (61.6%)	7502/16,245 (46.2%)	0.0002

*When denominator is provided, it reflects the number with available information.

Thirty-nine percent (38.9%) of patients with adenosquamous carcinoma and 40.6% with adenocarcinoma had tumors that were considered resectable ($P = 0.51$). Of those who were resectable by EOD codes, 46.3% of patients in the entire cohort underwent resection. Patients with resectable adenosquamous carcinoma were more likely to undergo surgical resection than patients with resectable adenocarcinoma (61.6% *versus* 46.2%, $P = 0.0002$).

Locoregional Disease (Table 3)

For the entire cohort, 17,587 patients had locoregional disease. Similar to all staged tumors, patients with adenosquamous carcinoma were less likely to have disease in the head of the pancreas compared with adenocarcinoma (59.7% *versus* 74.0%), and more likely to have disease in the body or tail of the pancreas (23.9% *versus* 10.6%, $P < 0.0001$). Tumors were larger in the patients with adenosquamous carcinoma (5.3 ± 2.4 cm *versus* 3.9 ± 1.9 cm, $P < 0.0001$). In the group of patients with locoregional adenosquamous carcinoma, 2.3% of patients had well-differentiated tumors and 49.4% of patients had poorly-differentiated tumors. This was statistically different from the patients with adenocarcinoma, of whom 10.3% and 27.2% had well- and poorly-differentiated disease, respectively ($P < 0.0001$). Patients with regional adenocarcinoma had positive lymph nodes in 48.4% of cases, while patients

with regional adenosquamous carcinoma had positive lymph nodes in 51.4% of cases ($P = 0.47$).

Of patients with locoregional disease only, 129 patients with adenosquamous carcinoma (73.7%, $n = 175$) and 12,926 patients with adenocarcinoma (75.7%, $n = 17,084$) had tumors that were considered resectable according to EOD coding ($P = 0.55$). Patients with resectable adenosquamous carcinoma were more likely to undergo surgical resection of their primary tumor (66.7% *versus* 56.8%, $P = 0.02$).

Long-Term Survival: Adenosquamous Carcinoma *Versus* Adenocarcinoma (Table 4)

The median follow-up for the entire cohort was 26 mo. The overall 1- and 2-y disease-specific Kaplan-Meier survival rates of patients with pancreatic adenosquamous carcinoma were 21.2% and 10.8%, respectively, with a median survival of 4 mo. This was similar to survival in patients with adenocarcinoma, whose 1-,and 2-y survival rates were 24.7% and 10.9%, respectively (median = 5 mo, $P = 0.08$, Fig. 1, Table 4). Following resection, patients with adenosquamous carcinoma had 1- and 2-y survival rates of 50.7% and 29%, respectively (median = 12 mo) compared with 1- and 2-y survival rates of 60.1% and 35.8% (median = 16 mo) in patients with pancreatic adenocarcinoma ($P < 0.0001$, Fig. 2, Table 4). An additional analysis was performed to evaluate 5-y survival for patients

TABLE 3

Tumor Characteristics: Locoregional Disease

Characteristics	Adenosquamous carcinoma (n = 176) N (%)	Adenocarcinoma (n = 17,411) N (%)	P value
Location			
Head	105 (59.7%)	12,878 (74.0%)	<0.0001
Body/tail	42 (23.9%)	1844 (10.6%)	
Other	29 (16.5%)	2689 (15.4%)	
Size, cm	5.3 ± 2.4	3.9 ± 1.9	<0.0001
Differentiation*			
Well	4/129 (2.3%)	1792/12,653 (10.3%)	<0.0001
Moderate	38/129 (21.6%)	6132/12,653 (35.2%)	
Poor	87/129 (49.4%)	4729/12,653 (27.2%)	
Positive lymph nodes*	75/146 (51.4%)	7188/14,863 (48.4%)	0.47
Resectable	129 (73.7%)	12,926 (75.7%)	0.51
Resected	86/129 (66.7%)	7335/12,926 (56.8%)	0.02

*When denominator is provided, it reflects the number with available information.

with available information, with sustained differences at 5 y (data not shown). Two-year disease-specific survival is reported.

Prognostic Factors for Adenosquamous Carcinoma

Overall, patients with locoregional adenosquamous cancer had 1- and 2-year disease-specific survival rates of 30.5% and 19.7%, respectively, and a median survival of 7 mo. The survival of patients with locoregional disease was, as expected, better than that of patients with distant disease, who had 1- and 2-year survival rates of 10.7% and 4.3%, respectively (median = 3 mo, P < 0.0001, Table 4). Patients with unstaged adenosquamous carcinoma had a median survival of 5 mo.

TABLE 4

Disease-Specific Survival

| Group	1-Y	2-Y	Median	P value
Adenosquamous (n = 415)	21.2%	10.8%	4 mo	0.08
Adenocarcinoma (n = 45.693)	24.7%	10.9%	5 mo	
Resected adenosquamous	50.7%	29.0%	12 mo	<0.0001
Resected adenocarcinoma	60.1%	35.8%	16 mo	
Adenosquamous carcinoma				
Locoregional (n = 145)	30.5%	19.7%	7 mo	<0.0001
Distant (n = 220)	10.7%	4.3%	3 mo	
Unstaged (n = 19)	15.8%	5.3%	5 mo	
Locoregional adenosquamous carcinoma				
Unresected (n = 77)	4.8%	4.8%	5 mo	<0.0001
Resected (n = 99)	54.1%	31.2%	13 mo	
Node negative (n = 71)	39.8%	25.1%	11 mo	0.46
Node positive (n = 75)	36.1%	21.2%	8 mo	
Size < 3 cm (n = 51)	29.3%	20.3%	7 mo	0.93
Size ≥ 3 cm (n = 125)	31.0%	19.5%	7 mo	
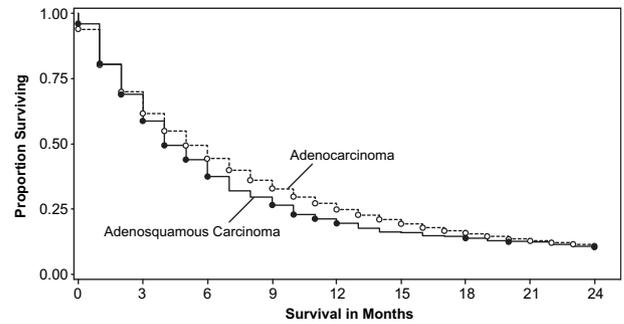
FIG. 1. The overall 2-y disease-specific Kaplan-Meier survival rates of patients with pancreatic adenosquamous carcinoma (solid line) and adenocarcinoma (dotted line, $P = 0.08$).

When looking specifically at patients with locoregional disease, there was a statistically significant difference between the survival rates of patients who underwent resection and those who did not. Median survival improved from 5 mo in patients who were not resected to 13 mo in patients who were resected. The 1- and 2-year survival rates of patients with locoregional disease who did not undergo resection were 4.8% and 4.8% compared to 54.1% and 31.2%, in patients who were resected (P < 0.0001, Fig. 3, Table 4).

Table 4 shows the survival rates by nodal status and tumor size. Nodal status did not have any bearing on survival in patients with locoregional adenosquamous carcinoma ($P = 0.46$). Similarly, size of the tumor did not have a statistically significant effect on survival ($P = 0.93$).

A multivariate survival analysis was performed for all patients with adenosquamous carcinoma of the pancreas. Table 5 shows the hazard ratios and 95% confidence intervals for various factors related to survival in these patients. As expected, older patients were more likely to die (HR 1.10, 95% CI 1.05-1.15). When compared to patients with locoregional disease, patients with distant disease were 1.58 times more likely to die (HR 1.58, 95% CI 1.23-2.03). The strongest predictor of survival among patients with adenosquamous
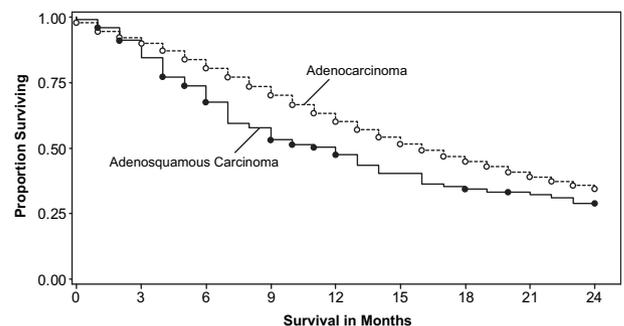

FIG. 2. Two-year disease-specific overall survival of patients with resected adenocarcinoma (dotted line) and adenosquamous carcinoma (solid line) of the pancreas (P < 0.0001).
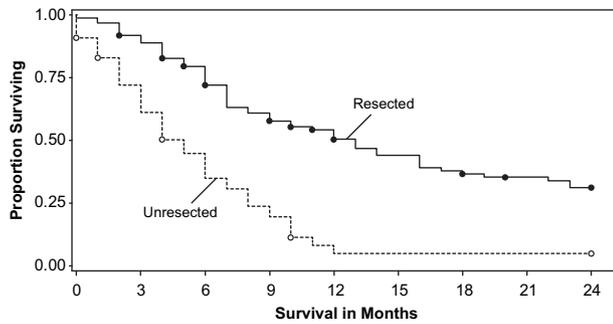
FIG. 3. Two-year disease-specific overall survival of patients with resected (solid line) and unresected (dotted line) locoregional adenosquamous carcinoma of the pancreas.

TABLE 5

Multivariate Survival Analysis: Adenosquamous Carcinoma

Factor (reference group)	Hazard ratio	95% Confidence interval
Overall cohort		
Age (per 5 y increase)	1.10	1.05–1.15
Resection (yes)	2.51	1.88–3.36
Distant (locoregional)	1.58	1.23–2.03
Locoregional only		
Age (per 5 y increase)	1.11	1.00–1.23
Resection (yes)	2.35	1.47–3.76
Size (per 10 cm increase)	1.09	1.00–1.18

carcinoma was resection status. Patients who did not undergo surgical resection were 2.51 times more likely to die than patients who were resected (HR 2.51, 95% CI 1.88-3.36).

When looking at patients with locoregional adenosquamous carcinoma of the pancreas only, similar results were obtained from the multivariate survival analysis. With increasing age, patients had a higher risk of death (HR 1.11, 95% CI 1.00-1.23). Patients with larger tumors also had an increased hazard of death (HR 1.09, 95% CI 1.00-1.18). Again, resection status was the strongest independent predictor of survival for patients with locoregional adenosquamous carcinoma. Patients who did not undergo surgical resection were 2.35 times more likely to die than patients who were resected (HR 2.35, 95% CI 1.47-3.76).

DISCUSSION

Our study is the largest population-based study to evaluate outcomes in patients with adenosquamous carcinoma of the pancreas. As such, it the largest series of patients with this rare disease and the first to be able to compare resection rates as well as long-term outcomes. When compared to patients with adenocarcinoma, patients with adenosquamous carcinoma of the pancreas present at a similar stage. However, patients with adenosquamous carcinoma are more likely to have tumors in the pancreatic tail and are more likely to be resected. In resected patients, adenosquamous carcinoma is more likely to be poorly differentiated, larger, and lymph node positive. Consistent with previous small studies, our population-based study demonstrates that the long-term disease-specific survival following surgical resection for patients with adenosquamous carcinoma of the pancreas is significantly worse when compared to patients with adenocarcinoma; however, surgical resection is the single strongest predictor of survival in patients with adenosquamous cancer and can be of benefit.

Because of the rarity of adenosquamous carcinoma, our knowledge of this disease is based on small retrospective studies, often with conflicting information derived from high-volume centers (Table 1). Katz et al. recently published a report of 95 patients with adenosquamous carcinoma of the pancreas using the California Cancer Registry [10]. This report also found that patients with adenosquamous carcinoma had tumors that were larger in size and more lymph node positive. Similar to our study, Katz and colleagues confirm that patients with adenosquamous carcinoma of the pancreas are more likely to undergo surgical resection than patients with adenocarcinoma. The comparability of our results and those of another population-based database give credibility to the information from the SEER database and also to the findings of our study.

Our study differs from many previous series in that we examined patients who did and did not undergo resection, and we were able to evaluate resectability based on SEER extent-of-disease coding. Approximately 40% of patients in both groups had tumors that were considered resectable using this coding system. However, among resectable patients, 61% of patients with adenosquamous carcinoma were resected, while only 46% of patients with adenocarcinoma underwent resection. This difference was also noted among patients with locoregional disease; 67% of patients with resectable adenosquamous and 57% of patients with resectable adenocarcinoma underwent resection. The higher incidence of body and tail cancers in patients with adenosquamous carcinoma may partially explain the observed differences in resectability. Distal pancreatectomy is technically easier and surgeons less experienced in pancreatic surgery may be more willing to attempt distal pancreatectomy than pancreaticoduodenectomy. In addition, in those pancreatic tumors that are diagnosed by biopsy, an inadequate sample may make it difficult for the pathologist to identify 30% squamous cells in the specimen. This may lead to an underestimation of the prevalence of adenosquamous carcinoma, and consequently, an overestimation of the

frequency of resection of adenosquamous carcinoma, as more unresected tumors are being classified as adenocarcinoma rather than adenosquamous carcinoma.

We are aware that our evaluation of resectability may be limited by the accuracy of information in the SEER extent-of-disease codes. Criteria for unresectability included vascular invasion and invasion of organs outside the resection field. It is possible that some surgeons may consider tumors that invade the superior mesenteric or portal vein as resectable. We used the standard extent-of-disease coding to allow for a conservative estimate of resectability.

Previous studies involving adenosquamous carcinoma, summarized in Table 1, have reported varying survival rates. Madura et al noted a median survival of 5.7 ± 4.1 mo for both resected and unresected patients [3]. Okabayashi reported 25.5% and 14% 1- and 2-year survival rates, respectively, for patients with resected adenosquamous carcinoma [7]. Our study is the only study to use disease-specific survival and demonstrates improved survival compared to this study. Our survival rates for 1- and 2-years are 51% and 29% after resection, respectively, with a median survival of 12 mo. These results are similar to studies by Kardon et al, Voong et al, and Smoot et al, who reported overall survival of 11.3 mo, 17.9 mo, and 13.1 mo after resection, respectively [8, 9, 11]. However, all these studies use very small populations, ranging from 6 to 39 patients with adenosquamous carcinoma. Again, in the study of 95 patients with adenosquamous carcinoma by Katz et al., overall survival was 4 mo, while survival after surgical resection was 12 mo [10]. Again, our study used disease-specific survival rather than disease-free survival. The results of our study would not change if disease-free survival, or time to recurrence, had been used.

Despite the decreased survival in patients with resected adenosquamous carcinoma compared to adenocarcinoma, surgical resection still offers the only chance for cure. In our study, surgical resection for locoregional adenosquamous carcinoma was the strongest predictor of survival. Patients with unresected locoregional adenosquamous carcinoma were 2.35 times more likely to die than those with locoregional disease who did undergo surgery.

Because we used registry data, we do not have information on presenting symptoms and radiologic findings. Previous smaller studies have examined these data [3, 6–8]. We are also limited by the lack of SEER data regarding chemotherapy, which restricts our ability to assess the role of adjuvant therapy. While radiation can be assessed, we did not evaluate this because we felt that the absence of chemotherapy data made the analysis meaningless. It is possible that the improved survival in patients with adenocarcinoma is due to higher rates of adjuvant therapy. However, rates of radiation were similar in the two groups (40% in adenosquamous and 39% in adenocarcinoma, $P = NS$). There is no current standard for the use of adjuvant therapy in patients with adenosquamous carcinoma, although one study did demonstrate a modest improvement in survival from 11 mo to 20 mo with the use of adjuvant chemotherapy after resection [8]. Katz et al. demonstrated an improvement in survival with the use of palliative radiation and chemotherapy, but there was no improvement in survival with the use of adjuvant chemoradiation [10]. Since adenosquamous carcinoma is uncommon, the role of chemoradiation in the treatment plan of these tumors remains unclear.

As with all registry studies, the staging and histology of tumors cannot be confirmed. Staging of all cancers is a complex process, and clinical staging often differs from pathologic staging. As a result, staging is fluid throughout a patient's course of illness. The SEER staging data are entered into the database based on the best available clinical data. This is based on a combination of pathologic observations, intraoperative observations, and clinical observations, in this priority order [29]. There is inherent upstaging observed when a tumor is pathologically staged when compared to clinically staged, which is why we evaluated local and regional disease together. The guidelines for implementing the SEER summary stage, which is used in our study, are updated regularly. As such, SEER accurately reflects the cancer stage to the best of the treating physician's knowledge.

In summary, patients with adenosquamous carcinoma of the pancreas present at a similar stage and resectability status as patients with adenocarcinoma. Adenosquamous carcinomas are more likely to occur in the pancreatic tail and are more often poorly-differentiated. Patients with adenosquamous carcinoma are more likely to undergo surgical resection than those with adenocarcinoma. Of those patients who did undergo resection, patients with adenosquamous carcinoma have a poorer prognosis than those with adenocarcinoma. However, surgical resection still offers the best chance at cure and long-term survival for patients with adenosquamous carcinoma. In the setting of resectable disease, these patients can still benefit from surgical resection.

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