Acinar Cell Carcinoma of the Pancreas: An Institutional Series of Resected Patients and Review of the Current Literature

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Abstract

Introduction Acinar cell carcinoma (ACC) is a rare, malignant neoplasm with a generally poor prognosis. We report our institutional series of 14 patients with ACC to determine current guidelines for their evaluation and treatment.

Materials and Methods The Johns Hopkins pathology prospective database was reviewed from 1988 to 2006 to identify patients with pancreatic neoplasms possessing features of acinar cell differentiation. Retrospective review and follow-up was performed for each patient.

Results Fourteen patients with ACC were identified with a median age of 57 years. All patients presented with abdominal pain or discomfort with none showing evidence of lipase hypersecretion syndrome. Each patient underwent surgical resection, including nine pancreaticoduodenectomies and five distal pancreatectomies. Median tumor size was 3.9 cm with 12 patients found to have stage IIB disease or worse. Four patients underwent neoadjuvant chemoradiation. Eight of the fourteen patients developed recurrent disease. Overall median survival and disease-free survival were 33 and 25 months, respectively, as compared to a median survival of 18 months for pancreatic adenocarcinoma.

Conclusion Acinar cell carcinomas are rare, aggressive neoplasms that are difficult to diagnose and treat. Operative resection represents the best first-line treatment. These lesions have a better prognosis than the more common pancreatic adenocarcinomas.

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Introduction

Acinar cell carcinomas (ACCs) are rare, malignant neoplasms of the exocrine pancreas accounting for approximately 1% of primary pancreatic neoplasms.[1–3] First described in 1908 by Berner,[4] they recapitulate the growth pattern and secretory products of normal pancreatic acini, often producing digestive enzymes such as trypsin, chymotrypsin, lipase, and amylase.[5–7] ACC can present with a variety of nonspecific symptoms including weight loss and abdominal pain, and less commonly with the jaundice that is classically seen in pancreatic adenocarcinoma.[3] A paraneoplastic syndrome of subcutaneous fat necrosis, polyarthralgia, and eosinophilia due to increased serum lipase has also been reported in some patients, now known as the lipase hypersecretion sydrome.[5,8–11] In general, the preoperative diagnosis of ACC is difficult, with computed tomography

Table 1 Current Acinar Cell Carcinoma Literature

Reference	No. of Pts	M/F	Pts with HOP tumor (%)	Median Survival (m)
[17]	12	6:6	50	5.0
[5]	28	24:4	56	18.0
[20]	4	2:2	50	21.5
[8]	39	31:8	53	19.0
[12]	10	7:3	60	18.8

HOP, head of pancreas; M/F, male/female; Pts, patients

(CT) only infrequently providing diagnostic clues. [12] Tissue diagnosis, given the similarity of ACC to endocrine tumors cytologically and histologically, often requires additional immunohistochemical assays or, rarely, electron microscopy for definitive confirmation. [5,13,14] Prognosis is generally poor, with patients frequently presenting with metastatic disease and having a high incidence of recurrence.[5,8]

Given its low incidence, characterizing the natural history of ACC and the appropriate therapeutic approach remains difficult with current guidelines based only on a limited number of small case series and anecdotal experiences.[5,8,11,17–20] Review of the literature (Table 1) demonstrates estimates of survival, ranging from 4 months to 7.5 years,[16] with the largest series to date reporting a median survival of 19 months.[8] In addition, the clinical course of ACC remains in question, with some series demonstrating it to be as aggressive as pancreatic adenocarcinoma[21,22] while others describe a more indolent pattern similar to lower-grade endocrine lesions.[5,23] Numerous reports have differentiated ACC from other more common pancreatic malignancies at a molecular and histologic level.[24–26] Nonetheless, a thorough description of its clinical manifestations and behavior as a distinct neoplasm remains incomplete.

In this study, we present our institutional experience of 14 patients with ACC, all of whom underwent surgical resection of their disease at the Johns Hopkins Hospital. We evaluate demographic factors, clinical and pathologic features, and outcomes in these patients, combining our results with a thorough literature review to both verify and expand upon current guidelines for the evaluation and treatment of these malignancies.

Materials and Methods

This study was approved by the Institutional Review Board of the Johns Hopkins Hospital. A retrospective review of prospectively collected data between 1988 and 2006 at the Johns Hopkins Hospital was performed for all patients having pancreatic neoplasms with features of acinar cell differentiation. The patients were identified using the Johns

Hopkins Pathology database, and tumor types included acinar cell carcinomas and mixed acinar-endocrine carcinomas. Only the patients with tissue specimens obtained during surgical resection or biopsy at our institution were included as part of the study. Surgical resectability was determined using preoperative abdominal CT scans. Resection of disease involved either a pancreaticoduodenectomy or distal pancreatectomy with splenectomy. For each patient, we recorded demographic information, existing comorbidities, preoperative symptoms and imaging results, operative and pathological findings, tumor staging, postoperative complications, and mortality. Follow-up was conducted using postoperative clinic notes to monitor recurrent disease and survival. Survival and disease-free probabilities were estimated using Kaplan-Meier methods.

Results

Retrospective review of the Johns Hopkins Pathology database revealed 14 patients with ACC from 1988–2006. Patients at our institution (Table 2) had a median age of 57 years (range 33–77) with 64% being female. Common preoperative comorbidities included hypertension (57%), diabetes (29%), and smoking (29%). Abdominal pain or discomfort was the most prevalent presenting symptom (100%), followed by weight loss (36%), nausea/vomiting (29%), and jaundice (21%). No patients presented with symptoms indicative of lipase hypersecretion syndrome. Four of fourteen (29%) patients (patients 2, 3, 5, 14) were initially considered to have unresectable disease due to

Table 2 Patient Characteristics and Symptoms

Characteristic	Value (%), $n=14$
Female gender	9 (64)
Age (years)	
Median	57
Range	33–77
Alcohol	1 (7)
Coronary artery disease	2 (14)
Diabetes	4 (29)
Hypertension	8 (57)
Obesity	0 (0)
Smoking	4 (29)
Abdominal pain/discomfort	14 (100)
Jaundice	3 (21)
Lipase hypersecretion syndrome (subcutaneous fat necrosis, polyarthralgia, eosinophilia)	0 (0)
Nausea/vomiting	4 (29)
Pancreatitis	2 (14)
Weight loss	5 (36)
Neoadjuvant chemoradiation	4 (29)

Table 3 Tumor Resection Characteristics

Pt	Rx	Size (cm)	+ LN (%)	TNM	Stage	Other features	F/U
1	P	3.5	2/18 (11)	T2N1Mx	IIB		DOD, 32 mo
2	P	2.5	2/12 (16)	T3N1Mx	IIB	Invasion of peripancreatic soft tissue	DOD, 33 mo
3	P	3.5	0/12 (0)	T2N0Mx	IB		A&W, 79 mo
4	P	0.7	6/19 (32)	T1N1Mx	IIB		DOD, 63 mo
5	D	2.5	0/5 (0)	T2N0M1	IV	Multiple liver lesions positive for tumor	DOD, 95 mo
6	D	3.4	0/14 (0)	T2N0M1	IV	Positive peritoneal nodule excised	A&W, 47 mo
7	P	3.0	8/16 (50)	T3N1Mx	IIB	Extension to distal CBD	A&W, 27 mo
8	D	8.0	5/13 (39)	T3N1Mx	IIB	Large vein invasion	DOD, 9 mo
9	P	5.0	0/29 (0)	T3N0Mx	IIA	Extension to distal CBD, wall of duodenum	DOD, 4 mo
10	P	4.2	10/12 (83)	T3N1Mx	IIB	Extension to distal CBD, positive hepatic artery LN	A&W, 17 mo
11	D	23.5	5/8 (63)	T3N1Mx	IIB	Extensive angiolymphatic and large vein invasion	A&W, 12 mo
12	P	6.5	4/20 (20)	T3N1Mx	IIB	Extension to wall of duodenum	DOD, 6 mo
13	D	12.5	1/11 (9)	T3N1Mx	IIB	MAEC, invasion of peripancreatic soft tissue	A&W, 5 mo
14	P	4.5	2/6 (33)	T3N1Mx	IIB	MAEC, extension to duodenal wall	A&W, 1 mo

A&W, alive and well; *CBD*, common bile duct; *DOD*, dead of disease; *D*, distal pancreatectomy; *F/U*, follow-up; *LN*, lymph node; *MAEC*, mixed acinar-endocrine carcinoma; *P*, pancreaticoduodenectomy; *Pt*, patient; *Rx*, resection

extensive tumor invasion of surrounding structures (e.g., transverse mesocolon, superior mesenteric vein encasement) or the presence of metastatic disease (e.g. multiple liver lesions, extensive regional lymphadenopathy). These patients underwent neoadjuvant chemoradiation in an effort to downstage previously unresectable disease, each utilizing gemcitabine, 5-fluorouracil, or adriamycin as part of their chemotherapy regimens. The patients were then reevaluated by CT scan for surgical resection. Each patient demonstrated an improvement in overall tumor burden enough to warrant surgical resection. Common features seen on preoperative CT scan include a hypodense-appearing neoplasm (six patients), a necrotic tumor core (five patients), a partially cystic structure (five patients), and ill-defined, thickened borders (three patients).

Table 3 describes the operative and pathological characteristics of each patient's tumor resection. All 14 patients had their disease surgically resected, with 9 patients undergoing a pancreaticoduodenectomy and 5 patients having a distal pancreatectomy with a concurrent splenectomy. Median tumor size was 3.9 cm (0.7 cm–23.5 cm). Patient 5 initially presented with multiple metastases to the liver that responded well to neoadjuvant chemoradiation, which allowed the patient to undergo operative resection of the lesion including a concurrent partial right hepatectomy. Patients 13 and 14 possessed features of ACC as part of a mixed acinar-endocrine carcinoma MAEC and were considered part of the group analysis given their similarity to pure ACC histologically and clinically.[25] Diagnostic immunohistochemistry was done in all 14 patients, revealing positive staining of tumor cells for trypsin and lipase in 9 and 5 patients, respectively. Further diagnostic confirmation through electron microscopy was done in three patients and demonstrated large, but varying, amounts of zymogen granules and rough endoplasmic reticulum within tumor cells. Using 2006 AJCC criteria, pathological staging of the resected specimens revealed only one patient to have a T1 lesion, while T2 and T3 lesions were present in four and nine patients, respectively. The majority of patients ($n=10$) had positive regional lymph node metastases. Meanwhile, only patients number 5 and 6, both of whom had negative regional lymph nodes, also had distant metastases. Overall TNM staging demonstrated 12 of 14 patients with stage I or II disease, while patients 5 and 6 possessed stage IV lesions given their M1 status.

Postoperative patient characteristics and survival data are displayed in Table 4. Median duration of hospital stay was 8 days (range 5–14 days) with delayed gastric emptying representing the only immediate postoperative complication (15%). Postoperative follow-up was available for all 14 patients with a median follow-up time of 15 months. Eight of fourteen patients (57%) developed recurrence of their disease, demonstrated on postoperative follow-up CT scans. Five patients recurred locally within the surgical bed, while seven patients had distant metastases to the lungs, liver, or other intraabdominal structures. Median disease-free survival for all patients was 25 months, with estimated disease-free survival at 1 year and 2 years being 64 and 55%, respectively. In addition, median survival for all patients was 33 months with actuarial survival at 1 year and 2 years estimated to be 75% each. When patients with MAECs were excluded, median survival and disease-free survival remained 33 and 25 months, respectively.

Discussion

Acinar cell carcinoma is a rare, malignant tumor of the exocrine pancreas that has only been studied in the

Table 4 Postoperative Characteristics and Survival

Characteristic	Value (%), $n=14$
Duration of stay (days)	
Median	8
Range	5–14
Delayed gastric emptying	2 (14)
Pancreatic leak	0 (0)
30-day mortality	0 (0)
Disease-free Survival	
Median (months)	25
1-year	64
2-year	55
5-year	34
Survival	
Median (months)	33
6-month	84
1-year	75
5-year	37
Recurrence	8 (57)

scientific literature through small retrospective case series and reports.[5,8,11,17–20] This study, involving a total of 14 patients with ACC within our institution, contributes to the limited amount of data currently available discussing these lesions. Further characterizing these neoplasms in terms of their potential etiology, clinical and histopathological manifestations, therapeutic approach, and prognosis will help distinguish these tumors from more commonly seen malignancies of the pancreas, such as adenocarcinoma and endocrine tumors.

Although 82% of the pancreas is occupied by acinar cells, ACC accounts for less than 1% of all pancreatic malignancies, as compared to pancreatic adenocarcinoma which represents 75%.[27] Despite the large volume of pancreatic operations performed at our institution, approximately 400 cases per year, the presence of only 14 patients with resected ACC over 18 years reinforces their low incidence. Consequently, only a small number of retrospective series have been able to characterize its demographics and clinical presentation. Holen et al. reported a median age of 60 (range: 15–87),[8] similar to that found by Klimstra et al. (mean: 62, range: 40 to 81),[5] and also in this study (median: 57, range: 33–77). These data suggest an overall younger age of presentation for ACC than pancreatic adenocarcinoma; however, very rarely have these lesions been recognized in children.[3,24] Meanwhile, the overwhelming dominance of ACC in males seen by Holen et al. (31:8 M:F ratio)[8] and Klimstra et al. (24:4 M:F ratio)[5] is in contrast to 64.3% of our patients being female. Whether or not sex is significant as an epidemiological factor for this tumor remains unknown.

Commonly reported presenting symptoms included abdominal pain, weight loss, and nausea/vomiting, similar to the distribution seen in our patients.[5,8] Jaundice is less frequently associated with ACC, seen in 21% of our patients and in only 12% of patients by Klimstra et al.[5] However, ACC tends to occur slightly less frequently in the head portion of the pancreas (64.3% in our study, 56% reported by Klimstra et al.,[5] 53% reported by Holen et al.[8], and 50% reported by Webb[17]) than the typical pancreatic neoplasm (70%).[28] Therefore, the lower incidence of jaundice in ACC patients might be explained by its increased frequency as a body and tail lesion, representing a possible distinguishing factor from pancreatic adenocarcinoma. Recognition of symptoms associated with lipase hypersecretion syndrome, including subcutaneous fat necrosis, polyarthralgia, and eosinophilia, may also help solidify a preoperative diagnosis given their specificity for ACC. Several of the first described cases of ACC were discovered through this unusual constellation of symptoms.[18] However, none of our patients presented with this syndrome, corresponding with the current literature that suggests that lipase hypersecretion syndrome is a distinctive but rare finding in these patients.[5,8,12]

Consistent with current practice guidelines for suspected pancreatic malignancy,[29] diagnostic tests such as carbohydrate associated antigen (CA 19-9) levels[30] and abdominal ultrasonography, CT, MRI, and endoscopic ultrasonography are useful in establishing both a preliminary diagnosis and treatment options. Although all of our patients underwent abdominal CT as part of their preoperative evaluation, establishing a diagnosis of ACC from this modality is difficult. Tatli et al. describe pure ACC as an exophytic, well-marginated, hypovascular mass on both CT and MRI, often either oval or round with cystic, necrotic areas when large.[31] Meanwhile, Chiou et al. concluded that ACCs are generally heterogeneous, hypodense masses on CT, notable for well-defined enhancing capsules, occasional internal calcification, and rare intratumoral hemorrhage. In addition, it is suggested that these tumors enhance at a level between pancreatic adenocarcinoma and endocrine tumors of the pancreas.[12] Reinforcing these findings, preoperative CT scans of our patients showed a number of hypodense lesions with or without a cystic structure, central necrosis, and ill-defined borders. In retrospect, none of our patients were definitively diagnosed preoperatively through CT, emphasizing that these descriptions are somewhat nonspecific and based on a limited number of cases. However, they may aid the experienced radiologist in suggesting ACC as part of a differential when a pancreatic neoplasm with these features is seen.

Currently, definitive diagnosis of ACC requires a thorough histopathological examination of tissue obtained through either biopsy or operative resection. Macroscopically, ACCs are generally large, well-circumscribed lesions, reportedly ranging in size from 2 to 30 cm. On gross

examination, they often appear yellowish or tan in color with a soft, lobulated consistency,[3] and tend to occur most frequently within the head of the pancreas.[5,8] Sporadic cases of ACC have also been found growing within pancreatic ducts,[32] arising in heterotopic pancreatic tissue within stomach,[33] and as cystic masses.[34] Consistent with previously reported data, our cases demonstrated a wide range of tumor sizes (0.7–23.5 cm), with several of our patients (62%) presenting with a mass in the pancreatic head or uncinate process, requiring a pancreaticoduodenctomy. At a cellular level, ACC exhibits acini with peripherally placed nuclei and small apical lumens (recapitulating the normal growth pattern of nonneoplastic pancreatic acini), trabeculae, glands, or diffuse sheets of cells separated by minimal fibrovascular stroma (Figure 1).[3] Cells generally display uniform nuclei with rare pleomorphism and prominent nucleoli.[5] Immunohistochemical markers for ACC include well-known digestive enzymes normally produced by the pancreas. Trypsin was found to be the most commonly expressed enzyme within the literature (97% of cases), followed by lipase (84.5%), chymotrypsin (66.1%), and amylase (14.3%), which is consistent with the trypsin- and lipase-rich staining pattern seen in our study group. The high frequency of trypsin reactivity in ACC, as opposed to its absence among endocrine tumors, makes it an attractive specific marker for distinguishing these otherwise similar appearing lesions.[3,7] Other smaller series have reported the production of alpha-fetoprotein (AFP) by ACC cells, proposing it as a possible marker of acinar differentiation within these tumors.[19,27,35] Similar to our results, electron microscopy
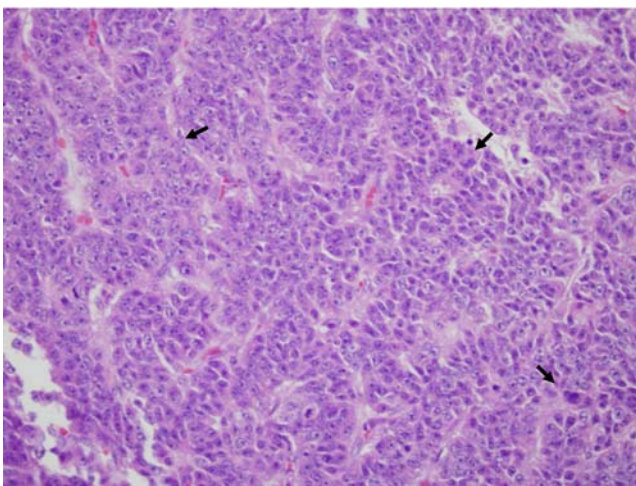
Figure 1 Acinar cell carcinoma, intermediate power view Intermediate power (400×) view of hematoxylin–eosin stained acinar cell carcinoma. The tumor grows in a trabecular pattern, and features uniform cells with amphophilic cytoplasm, round nuclei with vesicular chromatin and prominent nucleoli.

(EM) reveals zymogen granules in varying numbers among tumor cells, in contrast to relatively uniform amounts in nonneoplastic pancreatic acini.[36]

Another diagnostic consideration is the distinction between ACCs, mixed acinar-endocrine carcinomas (MAECs), and pure endocrine tumors. Ohike et al. compared patients with ACC and mixed acinar-endocrine carcinoma, demonstrating that they shared most clinicopathological features including histological differentiation, tumor size and location, and nuclear p53 expression, concluding that both may originate from a common precursor. In addition, even with large numbers of endocrine cells, MAECs rarely expressed one of the known pancreatic or gastrointestinal hormones.[25] These results justify the inclusion of the two mixed acinar-endocrine carcinoma patients within this study. However, our own comparison study of these two neoplasm types would be less informative given the disproportionate number of patients in the two groups. In addition, given the potentially better prognosis for pure endocrine tumors, it is important to distinguish these neoplasms from ACC so that the appropriate level of aggression is used in their oncologic management. Endocrine tumors have been reported to mimic ACCs due to cytologic and histologic subtleties seen in fine needle aspiration or resected specimens.[14] This diagnostic pitfall indicates why accurate diagnosis of ACC typically cannot be done by histology alone, instead requiring immunohistochemical staining or EM.[13] Given the nonspecific symptoms and imaging findings that are often seen with pancreatic neoplasms, this potential confusion between ACC and more common endocrine tumors provokes the question of whether the incidence of ACC is being underestimated. If the diagnosis of ACC is not considered, these lesions will likely be misdiagnosed as pancreatic endocrine neoplasms.

Operative resection remains the optimum therapy for patients presenting with ACC. Holen et al. reported a median disease-free survival of 14 months and a median actuarial survival of 36 months for those patients treated initially by operative resection (18 of 39 patients), as opposed to only 14 months overall survival for those who did not undergo resection.[8] In contrast, earlier work by Klimstra et al. demonstrated a more dismal survival of only 22.6 months in 18 resected patients.[5] All 14 patients in our study underwent surgical resection of their disease, demonstrating a median disease-free survival of 25 months and a median actuarial survival of 33 months, similar to that seen in surgically resected patients by Holen et al.[8] One of these patients (patient 5) required a concurrent right partial hepatectomy for distant metastases as well, after which the patient survived for 95 months, the longest among our patients. Furthermore, our estimated 5-year survival of 37% in resected patients is encouraging in comparison to values

of less than 10% seen in populations of surgical and nonsurgical ACC patients from other series.[5,8] Meanwhile, no large series exist describing the neoadjuvant or adjuvant treatment of ACC with radiation or chemotherapy, limiting our knowledge of their effectiveness. Anecdotal reports have discussed the use of drugs such as 5-fluorouracil, streptozotocin, cisplatin, and doxorubicin as part of their treatment regimens with variable success.[5,8,37,38] Riechel-mann et al. report the treatment of recurrent ACC in the form of pulmonary and abdominal metastases with weekly paclitaxel, demonstrating an unusual 4-year survival.[16] Contributing to these limited data, four of our patients underwent successful neoadjuvant chemoradiation treatment using either gemcitabine, 5-fluorouracil, or adriamycin, ultimately allowing for the resection of their tumors. However, the effectiveness of adjuvant chemoradiation is questionable given our recurrence rate of 57%, with six of the eight recurrences occurring within the first two disease-free years. In total, these data support the conclusion that surgical resection is the best first-line treatment for ACC if lesion resectability can be achieved.

The overall reported prognosis and survival of patients with ACC remains variable, with conflicting data on the indolence of ACC in comparison to pancreatic adenocarcinoma.[5,21–23] Holen et al. results showed an overall median survival of 19 months, including patients undergoing either surgical resection or adjuvant chemoradiation as their first-line treatment.[8] A similar median survival of 18.1 months was also reported by Klimstra et al.[5] These values both fall between the reported median survival of ductal adenocarcinoma (6 months)[39] and endocrine neoplasms of the pancreas (40–60 months).[40] When looking at surgically resected pancreatic adenocarcinoma with completely negative margins, our institution reports a median survival of only 18 months,[41] considerably less than the 33 months seen in this series of ACC patients. Although these data suggest ACC to be more indolent than pancreatic adenocarcinoma, it is important to recognize that patients still often present with disease metastatic to lymph nodes or other distant tissue such as the liver.[3] The large majority (12 of 14) of our patients presented preoperatively with disease stage IIB or higher, while four of our patients were deemed unresectable due to the size and extent of their disease on initial diagnosis. In addition, we observed a high recurrence rate of 57%, representing both local and distant metastases, similar to the 72% reported by Holen et al. in their resected patients. These high recurrence rates are suggestive that ACC is somewhat aggressive in nature, creating distant micrometastases not seen on presentation despite otherwise well-circumscribed local disease.[8] The role of neoadjuvant and adjuvant chemotherapy must be further studied in this setting to determine if they can improve on both the recurrence rate and survival of these patients.

As a rare neoplasm, acinar cell carcinoma remains a difficult malignancy to both study and treat. Unfortunately, this low incidence makes it difficult to perform larger, randomized trials looking at the clinical behavior of ACC. With only a limited amount of literature available, institutional series such as ours are useful in helping to characterize the origin, natural history, and appropriate treatment modalities for ACC. The data we have presented and reviewed suggest that definitive diagnosis and evaluation of ACC can be challenging. When possible, operative resection represents the best first-line treatment for resectable ACC due to its more favorable survival, which may be enhanced when combined with a planned neoadjuvant and/ or adjuvant chemoradiation regimen. The clinician must however be wary of the aggressive nature of this disease, demonstrated through frequent and significant metastatic spread and recurrence. This series of patients contributes useful clinical, pathological, and prognostic data that can be used by physicians to guide their decision-making when faced with a potential acinar cell carcinoma.

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