

## Systematic Review and Case Series Report of Acinar Cell Carcinoma of the Pancreas

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**Background:** Acinar cell carcinoma of the pancreas is a rare malignancy representing less than 1% of all pancreatic malignancies.

**Methods:** We report on a case series of 21 patients with acinar cell carcinoma of the pancreas treated at a high-volume quaternary center. A systematic review of the medical literature was performed that described typical therapeutic management approaches for acinar cell carcinoma of the pancreas and reported on disease control and survival rates. Data for the case series were obtained from a prospective database.

**Results:** In our systematic review of 6 articles, study patients had a median age of 61 years, 66% were male, 52% had stage I/II disease, and 55% of lesions were located in the pancreatic head. The rates of median survival were approximately 47 months after resection with adjuvant therapy, 38 months for nonmetastatic, locally unresectable disease, and 17 months for metastatic disease treated with chemotherapy. Combination fluoropyrimidine-based chemotherapy regimens had better rates of disease control than other therapies. Our case series included 21 study patients, 14 of whom required resection and 7 who had metastatic disease. The rates of median survival were  $40.2 \pm 31.9$  months in those who underwent surgery and were treated with adjuvant therapy and  $13.8 \pm 11.3$  months for patients with metastatic disease.

**Conclusions:** Multidisciplinary treatment for acinar cell carcinoma of the pancreas should be considered due to the rarity of the disease and its lack of high-level therapeutic data. Progress in the molecular analysis of this tumor may improve outcomes through the use of personalized therapy based on underlying tumor mutations.

### Introduction

Acinar cell carcinoma of the pancreas is a rare exocrine malignancy representing less than 1% of all pancreatic neoplasms.<sup>1</sup> The exocrine pancreas is primarily composed of ductal cells and acinar cells. Acinar cells are enzyme-secreting cells that release amylase, lipases, and proteases. Debate exists regarding whether acinar cell carcinoma of the pancreas is unique from pancreatic ductal adenocarcinoma<sup>2,3</sup>; however, acinar cell carcinoma of the pancreas responds to treatment differently than pancreatic ductal adenocarcinoma and its rates of overall survival are not similar<sup>4</sup> — data sugges-

tive that it is a distinct entity.

The rarity of acinar cell carcinoma of the pancreas, lack of high-quality evidence, and its diagnostic difficulty have all limited consensus among authors regarding the most appropriate management of this disease.<sup>5-7</sup> Although patients who have undergone resection for acinar cell carcinoma of the pancreas may appear to have higher survival rates than patients with pancreatic ductal adenocarcinoma<sup>3,4</sup> — whose median survival rate is between 4 and 5 years<sup>1</sup> — the limited and selection-biased data make assertions difficult.

Nonsurgical treatment options for patients with acinar cell carcinoma of the pancreas include chemotherapy and radiotherapy. Use of various chemotherapeutic agents, including capecitabine monotherapy and folinic acid/fluorouracil/oxaliplatin (FOLFOX), have been reported in the literature.<sup>8,9</sup> Whether radiotherapy improves survival rates in patients with acinar cell carcinoma of the pancreas remains unclear.<sup>10-12</sup> Case reports of the use of radiotherapy to treat acinar cell carcinoma of the pancreas have noted an association with extended rates of survival.<sup>8,13</sup>

The patterns of genetic alterations and specific driver mutations in patients with acinar cell carcinoma of the pancreas are not well described in the literature. Studies have demonstrated lower rates of

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*EGFR* and *KRAS* mutations in acinar cell carcinoma of the pancreas than in pancreatic ductal adenocarcinoma.<sup>14</sup> Some have suggested that pancreatic ductal adenocarcinoma may develop from acinar cells that undermutate *p53* without evidence of developing acinar cell carcinoma of the pancreas.<sup>15</sup> In addition, nearly one-half of acinar cell carcinoma of the pancreas tumors have alterations in *APC*.<sup>16</sup>

Unlike pancreatic ductal adenocarcinoma, *KRAS* mutation is infrequently a driving force in acinar cell carcinoma of the pancreas; however, chromosomal imbalances are common in acinar cell carcinoma of the pancreas.<sup>14</sup> Whole-exome sequencing has revealed that mutations in *BRCA2* and the *FAT* family are common in patients with acinar cell carcinoma of the pancreas, but these mutations are not yet readily targetable.<sup>17</sup> *p53* expression has been demonstrated as both a positive and negative prognostic indicator in acinar cell carcinoma of the pancreas.<sup>18</sup> More than 70% of tumors of the acinar cell carcinoma of the pancreatic type demonstrated a decrease or complete loss of *DCC* expression on immunohistochemistry.<sup>14</sup> Bergmann et al<sup>14</sup> also suggested that *DCC* variation is an early genetic change in acinar cell carcinoma of the pancreas, whereas others have suggested that it is a late change in pancreatic ductal adenocarcinoma.<sup>19</sup>

## Purpose

The purpose of this systematic review is to delineate the most appropriate treatment and expected outcomes in patients diagnosed with acinar cell carcinoma of the pancreas. Our article focuses on adult patients because genetic mutations in childhood tumors suggest alternative etiologies.

## Methods

### Literature and Systematic Review

We searched the medical literature for studies describing typical therapeutic management approaches for acinar cell carcinoma of the pancreas and reported on disease control and survival rates. Studies were excluded during the initial search if they investigated fewer than 4 patients, focused on mixed carcinoma, were not written in English, did not include clinical data, were review articles, or were a technical manuscript on a surgical procedure alone. Case reports with fewer than 4 patients were also excluded due to lack of ability (too few patients to develop a systematic approach given the rarity of the malignancy). For studies that included previously published data, the most complete and most recent data were used for our systematic analysis. When studies listed patient-level data for multiple histologies, only data concerning acinar cell carcinoma of the pancreas were used. Rates of disease control were calculated using complete response in combination with partial response and stable disease (based on the definition used in each study). No stud-

ies were identified as having high-level evidence.

A total of 132 manuscripts were identified during the search, and 10 studies were included based on our inclusion/exclusion criteria.<sup>20</sup> Six studies were then identified and selected for summary analysis of response rates to chemotherapy and radiotherapy as well as to estimate the average median overall survival rate.<sup>3,21-25</sup> Four studies contained incomplete data or nonstandard treatment approaches and were excluded from the summary data analyses but were included in the systematic review.

## Case Series

We reviewed our records for patients with acinar cell carcinoma of the pancreas treated between 2004 and 2014 at the H. Lee Moffitt Cancer Center & Research Institute (Tampa, FL). Demographical, clinical, and pathological data were obtained from a retrospective database. Charts were reviewed to confirm data. The Institutional Review Board at our institution approved this research.

## Statistical Analyses

For the systematic review, summary clinical data from each study were averaged in a weighted fashion to determine the overall value for each characteristic (demographic, treatment, or survival data). STATA statistical software was utilized for analysis (StataCorp, College Station, Texas).

For the case series, data analyses were also performed with STATA (StataCorp), using  $\chi^2$ , Kaplan-Meier, and multivariate linear-regression techniques. Statistical significance was set to  $\alpha$  being equal to .05. Uncertainties are standard deviations of the mean unless otherwise specified.

## Results

A total of 68 patients identified from the systematic review had a median age of 61 years, and 66% were men (Table 1). These results are similar to other nonsystem-

**Table 1. — Characteristics of Patients With Acinar Cell Carcinoma of the Pancreas in Select Studies**

Study	No. of Study Patients	Median Age, y	Male, %	Stage I/II, %	Pancreatic Head, %
Butturini <sup>25</sup>	9	53	67	57	67
Holen <sup>21</sup>	39	60	77	46	44
Lowery <sup>24</sup>	40	65	73	55	55
Matos <sup>3</sup>	17	60	Unknown	59	76
Seki <sup>22</sup>	4	63	75	25	62
Seth <sup>23</sup>	14	57	33	86	64
Current series	21	64	76	33	66

atic analyses in which the male-to-female patient ratio is at least 2:1.<sup>3,18,21-26</sup> In our systematic review, 52% of patients with acinar cell carcinoma of the pancreas had resectable disease (stage I/II; see Table 1).<sup>3,21-25</sup> Nonspecific symptoms, such as nausea, abdominal pain, and weight loss, were observed in most patients.<sup>18</sup> We also found that 55% of patients with acinar cell carcinoma of the pancreas had tumors located in the pancreatic head. The data derived from the systematic review also demonstrated that most of the lesions described were generally well circumscribed without significant peritumoral stroma.<sup>3,25</sup>

### Diagnosis

The diagnosis of acinar cell carcinoma of the pancreas is confirmed by biopsy, such as fine needle aspiration, or resection of the pancreatic tumor — with the latter being more reliable than the other methods.<sup>27</sup> The highly cellular nodules of monotonous tumor cells have little to no stroma and lack a desmoplastic response (Fig 1). Therefore, tumor cells may be difficult to identify with fine needle aspiration alone but reliably seen on a resected specimen.<sup>1</sup> Tumor cells are arranged in solid sheets with spaces between the acinar structures and small lumens.<sup>18</sup> Cytologically, these cells exhibit basal polarization. Fig 1 also demonstrates that nuclei can range from moderate to marked atypia and contain a single, prominent nucleolus. In the apical region, the cells contain moderate to abundant eosinophilic cytoplasm rich in zymogen granules.

Other groups have utilized immunohistochemistry to confirm the diagnosis, and researchers have demonstrated that an antibody against a portion of the B-cell chronic lymphocytic leukemia/lymphoma 10 protein has utility in diagnosing acinar cell carcinoma of the pancreas.<sup>18</sup> In addition, immunohistochemistry staining for trypsin and chymotrypsin in

the acinar pattern and, typically, lack of staining for neuroendocrine neoplasm markers (neural cell adhesion molecule, chromogranin, synaptophysin) can confirm the diagnosis of acinar cell carcinoma of the pancreas.<sup>14</sup>

### Radiotherapy

Our systematic review revealed a modest response rate to radiotherapy in patients with localized acinar cell carcinoma of the pancreas. In several studies, a “major response” rate was seen in 25% to 35% of these patients.<sup>21,23</sup> However, if stable disease was included in the definition of response (ie, disease control rate), significantly higher response rates were seen in highly selected studies when radiotherapy was added (Table 2).<sup>3,21-25</sup> Radiotherapy is often used to “down-stage” or convert a tumor from being borderline resectable to resectable, and, in general, is provided with both conventional fractionation and hypofractionated stereotactic body radiotherapy (SBRT).<sup>25</sup> Lack of progression following neoadjuvant radiotherapy can help select patients who may benefit from resection.

### Chemotherapy

Significant heterogeneity was seen in the systematic review regarding specific chemotherapeutic protocols; however, most study patients received combination gemcitabine- or fluoropyrimidine-based chemotherapy protocols.<sup>23,25</sup> Indeed, Holen et al<sup>21</sup> and Lowery et al<sup>24</sup> concurred on the favored use of combination fluoropyrimidine-based therapies and radiotherapy in patients with acinar cell carcinoma of the pancreas. However, data regarding disease control rate (complete response + partial response + stable disease) are mixed (see Table 2).<sup>3,21-25,28</sup> Combination fluoropyrimidine-based chemotherapies were shown to be associated with higher rates of

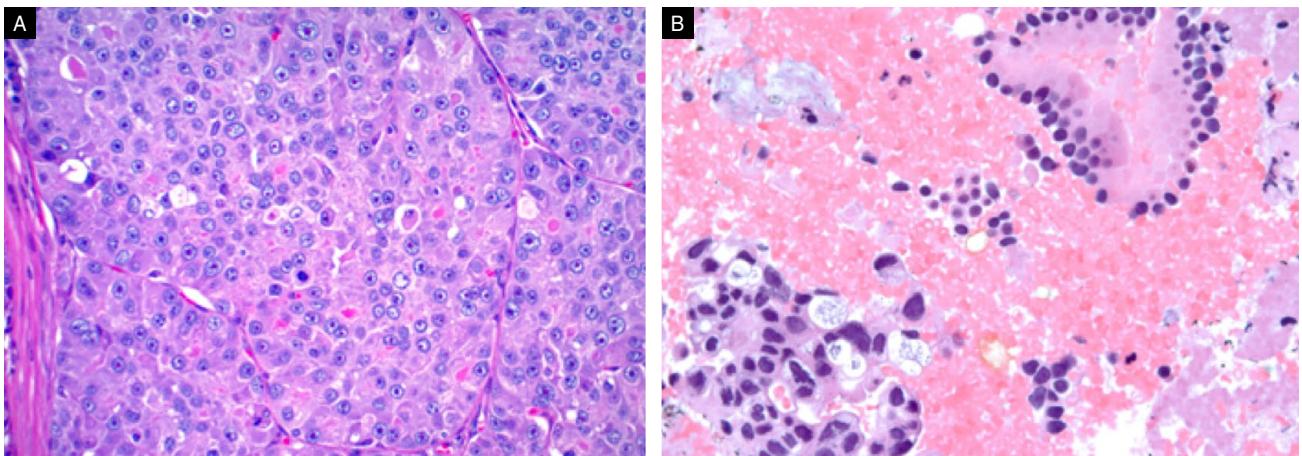


Fig 1A–B. — (A) Acinar cell carcinoma of the pancreas in a man aged 83 y and (B) pancreatic ductal adenocarcinoma in a woman aged 65 y. Hematoxylin and eosin stain,  $\times 20$ .

disease control (Table 3).<sup>3,21-25</sup> Therefore, FOLFOX or folinic acid/fluorouracil/irinotecan (FOLFIRI) is usually administered to patients with high performance status, whereas patients with a lower performance status usually receive gemcitabine/protein-bound paclitaxel.<sup>3,8,9,21-25</sup>

**Table 2. — Disease Control Rates of Chemotherapy and Radiotherapy in Select Series of Acinar Cell Carcinoma of the Pancreas**

Study	Type of Treatment	No. of Patients	Disease Control Rate, <sup>a</sup> %
Butturini <sup>25</sup>	Gemcitabine-based chemotherapy	7	29
Holen <sup>21</sup>	Fluoropyrimidine-based chemotherapy	22	41
	RT alone	1	100
	Fluoropyrimidine-based chemotherapy RT	4	100
Lowery <sup>24</sup>	Gemcitabine-based chemotherapy	20	35
Matos <sup>3</sup>	Mixed chemotherapy	4	50
	Mixed chemotherapy RT	2	100
Sekij <sup>22</sup>	Gemcitabine-based chemotherapy	1	0
	Fluoropyrimidine-/gemcitabine-based chemotherapy	3	33
Seth <sup>23</sup>	Mixed chemotherapy RT	4	100
Current series	Gemcitabine-based chemotherapy	6	50
	Fluoropyrimidine-based chemotherapy	6	67
	Mixed chemotherapy RT	5	100

Study patients not receiving chemotherapy are not included.

<sup>a</sup>Complete response + partial response + stable disease.

RT = radiotherapy.

**Table 3. — Summary of Select Disease Control Rates for the Nonsurgical Therapy of Acinar Cell Carcinoma of the Pancreas**

Treatment	No. of Patients	Disease Control Rate, <sup>a</sup> %
Any chemotherapy	79	55
Any radiotherapy	16	100
Gemcitabine-based chemotherapy	34	28
Fluoropyrimidine-based chemotherapy	35	60

<sup>a</sup>Complete response + partial response + stable disease.

Data from references 3 and 21 to 25.

## Surgery

Overall, surgical resection remains the mainstay of therapy for nonmetastatic disease, although adjuvant therapy is common. Most patients with acinar cell carcinoma of the pancreas undergo negative margin resection.<sup>3,21</sup> From our systematic review, we found that patients who underwent resection had an overall median survival rate of approximately 47 months (Table 4).<sup>3,21-25</sup> The contribution of adjuvant chemotherapy and radiotherapy has not been well investigated in the literature. Resection and adjuvant chemotherapy were associated with the longest rate of median overall survival (see Table 4).<sup>3,21-25</sup>

## Treatment at Our Institution

We identified 21 patients in a case series; 7 patients had metastatic disease based on imaging at the time of initial presentation (Table 5). Most patients were

**Table 4. — Systematic Review Summary of Survival Differences Between Select Patients With Resectable and Nonresectable Acinar Cell Carcinoma of the Pancreas**

Disease Status	Primary Treatment	Median Rate of Overall Survival, mos
Metastatic	Chemotherapy	17
Unresectable	Chemotherapy and radiotherapy	38
Resectable	Resection and adjuvant therapy	47

Data from references 3 and 21 to 25.

**Table 5. — Select Patient Characteristics From Current Patient Series**

Patient Characteristic	No. of Patients (%)
<b>Sex</b>	
Male	16 (76)
Female	5 (24)
<b>American Joint Committee on Cancer Stage</b>	
II	7 (33)
III	5 (24)
IV	9 (43)
<b>Site</b>	
Head	8 (38)
Neck/body	7 (33)
Tail	6 (29)
<b>Surgical Intervention</b>	
Whipple	6 (29)
Distal pancreatectomy	3 (14)
Total pancreatectomy	2 (10)
Unresectable	3 (14)
No surgery	7 (33)

Mean age ± standard deviation: 63.5 ± 14 y.

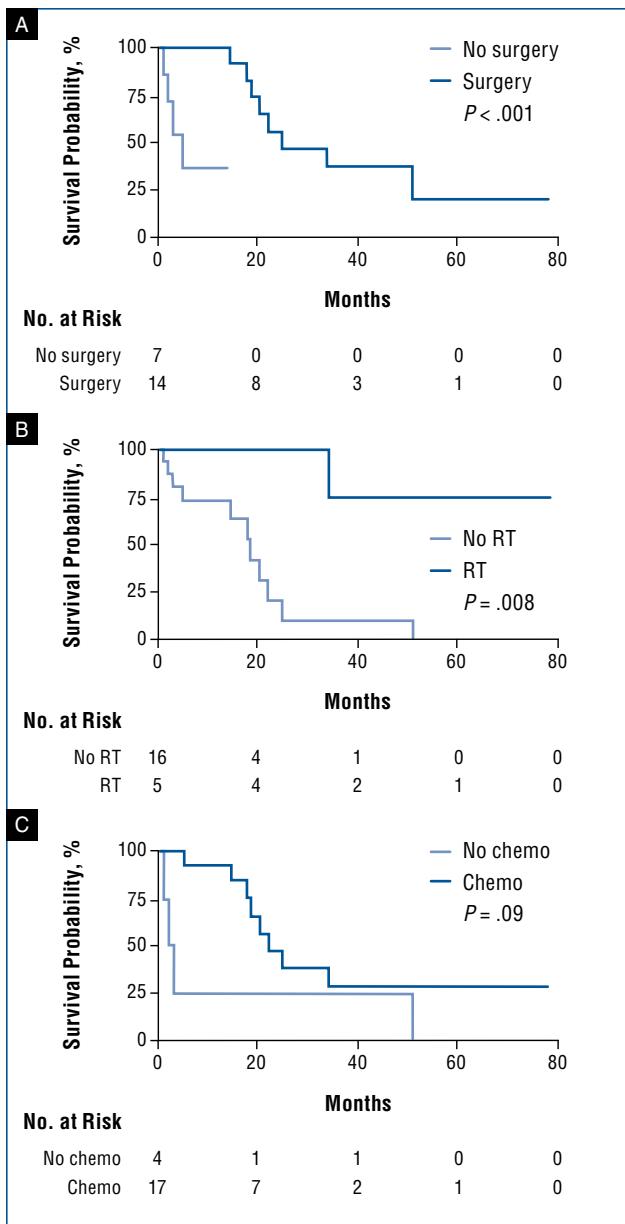


Fig 2A–C. — (A) Kaplan-Meier survival estimates based on surgery, (B) RT, and (C) chemotherapy. Patients with acinar cell carcinoma of the pancreas had significantly improved rates of survival following surgery ( $P < .001$ ) and RT ( $P = .008$ ) but not chemotherapy ( $P = .09$ ). RT = radiotherapy.

men. The average age was  $63.5 \pm 14.1$  years, and 38% of lesions were located in the pancreatic head. No patients had stage I disease. The median follow-up period was 1.2 years (range, 1 month to 6.5 years), and 62% of study patients were initially diagnosed elsewhere. Of the 21 patients, 14 were candidates for curative resection. Of those, 11 underwent R0 or R1 resections and 3 patients received R2 resection. At last follow-up, 43% of patients were alive; rates of actual 1- and 5-year survival were 67% and 5%, respectively. All patients who received radiotherapy lived for at

least 13 months after diagnosis.

Of the patients who underwent surgery, 1 patient also received neoadjuvant chemotherapy and 1 patient also received neoadjuvant radiotherapy. Eight patients received adjuvant chemotherapy, and 4 patients received adjuvant radiotherapy. More surgical patients received chemotherapy than nonsurgical patients (93% vs 57%;  $P < .05$ ), with 82% of those receiving a gemcitabine-based chemotherapy protocol. Five patients (24%) received radiotherapy, and all were surgical patients: 1 in a neoadjuvant and 4 in adjuvant settings.

Utilizing Kaplan-Meier analysis, we found rates of survival to be statistically associated with stage of disease ( $P = .005$ ), surgery (Fig 2A; log-rank  $P < .001$ ), and radiotherapy (Fig 2B; log-rank  $P = .008$ ), but not chemotherapy (Fig 2C; log-rank  $P = .09$ ). Patients who underwent resection followed by adjuvant radiotherapy had the longest survival (Fig 3). On multivariate Cox regression analysis, higher disease stage was associated with a shorter rate of survival (hazard ratio [HR] 6.70,  $P = .003$ ) and adjuvant radiotherapy was associated with longer survival (HR 0.05,  $P = .03$ ), but neither R0 margin nor adjuvant chemotherapy was statistically associated with improved rates of survival (0.70 and 0.30, respectively;  $P = .2$  for both).

## Discussion

Few large trials have studied acinar cell carcinoma of the pancreas because it is such a rare tumor. We were only able to identify 6 studies that fully met the criteria for our systematic review. Our institutional experience with 21 patients is the second largest case series in the literature. Because acinar cell carcinoma of the pancreas is treated similarly to pancreatic ductal adenocarcinoma, it is interesting to compare the outcomes. Analysis of Surveillance, Epidemiology, and End Results data

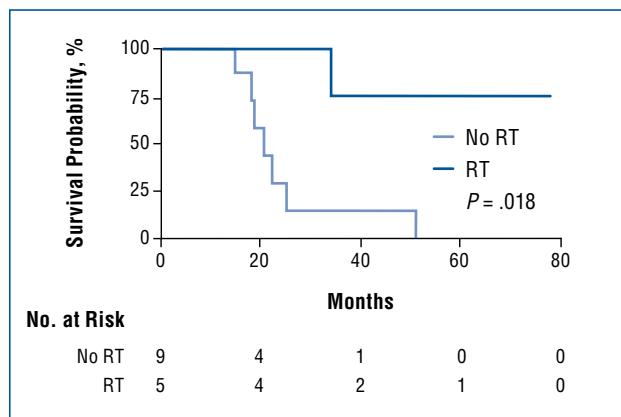


Fig 3. — Kaplan-Meier survival estimates among patients undergoing surgery and receiving RT. Surgical candidates with acinar cell carcinoma of the pancreas had significant improvement in their rates of survival probability when treated with RT.

RT = radiotherapy.

demonstrated higher rates of survival in acinar cell carcinoma of the pancreas compared with pancreatic ductal adenocarcinoma for both resected and unresected cases,<sup>1</sup> and analysis of the National Cancer Database demonstrated 5-year survival rates for patients with resected acinar cell carcinoma of the pancreas of 52%, 40%, 23%, and 17% for stages I, II, III, and IV, respectively.<sup>29</sup> Positive nodal disease was not associated with decreased rates of survival in patients with acinar cell carcinoma of the pancreas, but patients with high-grade acinar cell carcinoma of the pancreas had a 2-fold worse rate of 5-year survival ( $P = .003$ ).<sup>29</sup> Regarding margin status, negative microscopic margins were associated with 2-year median survival rates compared with 1-year median survival rates for patients with R1-/R2-positive margins ( $P < .02$ ).<sup>29</sup>

Debate exists as to whether pancreatic ductal adenocarcinoma is a radiosensitive tumor, but acinar cell carcinoma of the pancreas does appear to be radiosensitive based on the multivariate analysis and Kaplan-Meier survival curves presented here along with other published data.<sup>30</sup> Given the findings here and in the literature, it appears that, although acinar cell carcinoma of the pancreas and pancreatic ductal adenocarcinoma are similar exocrine pancreatic malignancies, they are distinct entities.<sup>29,30</sup>

This systematic review and case series illuminate 3 important findings. As expected, patients able to tolerate surgery live significantly longer than patients with unresectable disease.<sup>3,21-25</sup> Patients who undergo radiotherapy in combination with surgery also live significantly longer than those not receiving radiotherapy.<sup>3,21-25</sup> The biological mechanism of this result is unknown, but we hypothesize it is because acinar cell carcinoma of the pancreas is a radiosensitive tumor. This survival advantage of radiotherapy was seen despite 11 of 14 patients in our case series receiving surgery (R0/R1 resections), further suggesting that radiotherapy is valuable regardless of margin status. We did not find an association between use of chemotherapy and survival rate. This may be due to the low number of patients in the nonchemotherapy group, but lack of high-level evidence remains problematic given the overall poor prognosis of acinar cell carcinoma of the pancreas.

The cell of origin for acinar cell carcinoma of the pancreas is presumed to be the acinar cell, whereas the cell of origin for pancreatic adenocarcinoma is the duct epithelium.<sup>31-33</sup> However, controversy is ongoing regarding this assumption because it is based on the phenotype of pancreatic ducts in normal tissue, pancreatic intraepithelial neoplastic lesions, and carcinoma.<sup>31</sup> For example, injury to benign cells in the setting of malignancy (ie, enzyme-mediated cell destruction due to malignant local duct obstruction) may create a setting in which malignancy may appear to originate in a duct cell when in fact it actually originated in an aci-

nar cell.<sup>33</sup> An alternative pathway for carcinogenesis is described by *KRAS*-mediated acinar-ductal metaplasia and the subsequent development of pancreatic ductal adenocarcinoma.<sup>31,34</sup> In this setting, *KRAS* is hypothesized as being the driving force for the development of pancreatic ductal adenocarcinoma, as most commonly seen in the humans, whereas non-*KRAS*-mutated exocrine pancreatic carcinomas develop into acinar cell carcinoma of the pancreas.<sup>35-37</sup> Assuming this is true, then *KRAS* wild-type status would be a critical finding in distinguishing acinar cell carcinoma of the pancreas from pancreatic ductal adenocarcinoma.

Mutation of *DCC* may also serve as an early genetic change in acinar cell carcinoma of the pancreas; by contrast, it is a late change in pancreatic ductal adenocarcinoma. Furthermore, the rate of disease control was higher in patients with acinar cell carcinoma of the pancreas than in those with pancreatic ductal adenocarcinoma. This finding suggests that acinar cell carcinoma of the pancreas and pancreatic ductal adenocarcinoma are 2 distinct malignancies arising from similar cells but with important and early points of divergence (*KRAS* vs *DCC*). Other groups have demonstrated that acinar cell cystadenoma, a benign and rarely premalignant pancreatic lesion, may have genetic alteration patterns more similar to pancreatic ductal adenocarcinoma than to acinar cell carcinoma of the pancreas, suggesting that some genetic overlap may be present.<sup>38</sup>

At our institution, we favor the initial use of FOLFOX followed by FOLFIRI as second-line treatment for patients with acinar cell carcinoma of the pancreas and moderate to high performance status (Eastern Cooperative Oncology Group [ECOG] 0-1) either in the adjuvant setting or as systemic therapy (Fig 4). Use of folinic acid/fluorouracil/irinotecan/oxaliplatin (FOLFIRINOX) as first-line therapy for metastatic acinar cell carcinoma of the pancreas has been described in the literature, but whether the benefits of such an aggressive regimen outweighs the risks is unclear.<sup>39</sup> Because rates of disease control are higher with the use of combination, fluoropyrimidine-based chemotherapies, we also consider FOLFIRINOX in relatively young, very highly active individuals with ECOG performance status 0 (but rarely seen in our clinical practice). Among patients with moderate ECOG performance status 1 to 2, gemcitabine combined with protein-bound paclitaxel is our preferred chemotherapy regimen, with single-agent gemcitabine used for patients with poor performance status not wishing to enter hospice or palliative care.

In the neoadjuvant setting, our clinical approach for pancreatic cancer typically involves treating patients with SBRT who have borderline resectable or locally advanced disease. Therapy involves 5 days of fiducial marker-based radiotherapy applied to gross disease (median dose of 30 Gy and simultaneously

50 Gy to the area of vessel involvement/abutment) to help facilitate a negative margin resection.<sup>40,41</sup> In patients with acinar cell carcinoma of the pancreas, this general treatment approach could be considered given the high R0 resection rates and minimal rates of late

toxicity.<sup>30,42</sup> Based on data from the National Cancer Database, R0 resection has been shown to improve rates of overall survival on multivariate analysis, so neoadjuvant radiotherapy should be considered when a likelihood exists of positive margins.<sup>29</sup> Because patients with locally advanced tumors are unlikely to be candidates for resection, care must be taken to avoid late radiation-associated toxicities to the surrounding gastrointestinal organs. As such, intensity-modulated radiotherapy can be considered instead of SBRT for locally advanced acinar cell carcinoma of the pancreas.

### Limitations

Due to the rarity of this malignancy, we did not identify any prospective studies or large case-control studies to help guide clinical management. Likewise, oncologists are more familiar with the treatment protocols for pancreatic ductal adenocarcinoma, because this disease is more common, and, as such, these regimens are often utilized for acinar cell carcinoma of the pancreas despite the fact that evidence is lacking. The retrospective nature of this review also limits our interpretation of the results. Fundamentally, this limitation is also due to the rarity of the malignancy, thus limiting the initiation of prospective trials. Another important limitation relates to tumor response rates in retrospective studies. Oftentimes, the time to progression is based on when a patient is scheduled for his or her next imaging, not a pre-defined time point, as seen in a prospective study. As such, unless a patient is symptomatic, the time to progression may be partially related to an institutional bias. This is a difficult to quantify but important limitation.

### Future Research

Three critical inquiries must be explored to improve rates of survival among individuals with acinar cell carcinoma of the pancreas. Specific mechanisms (ie, gene muta-

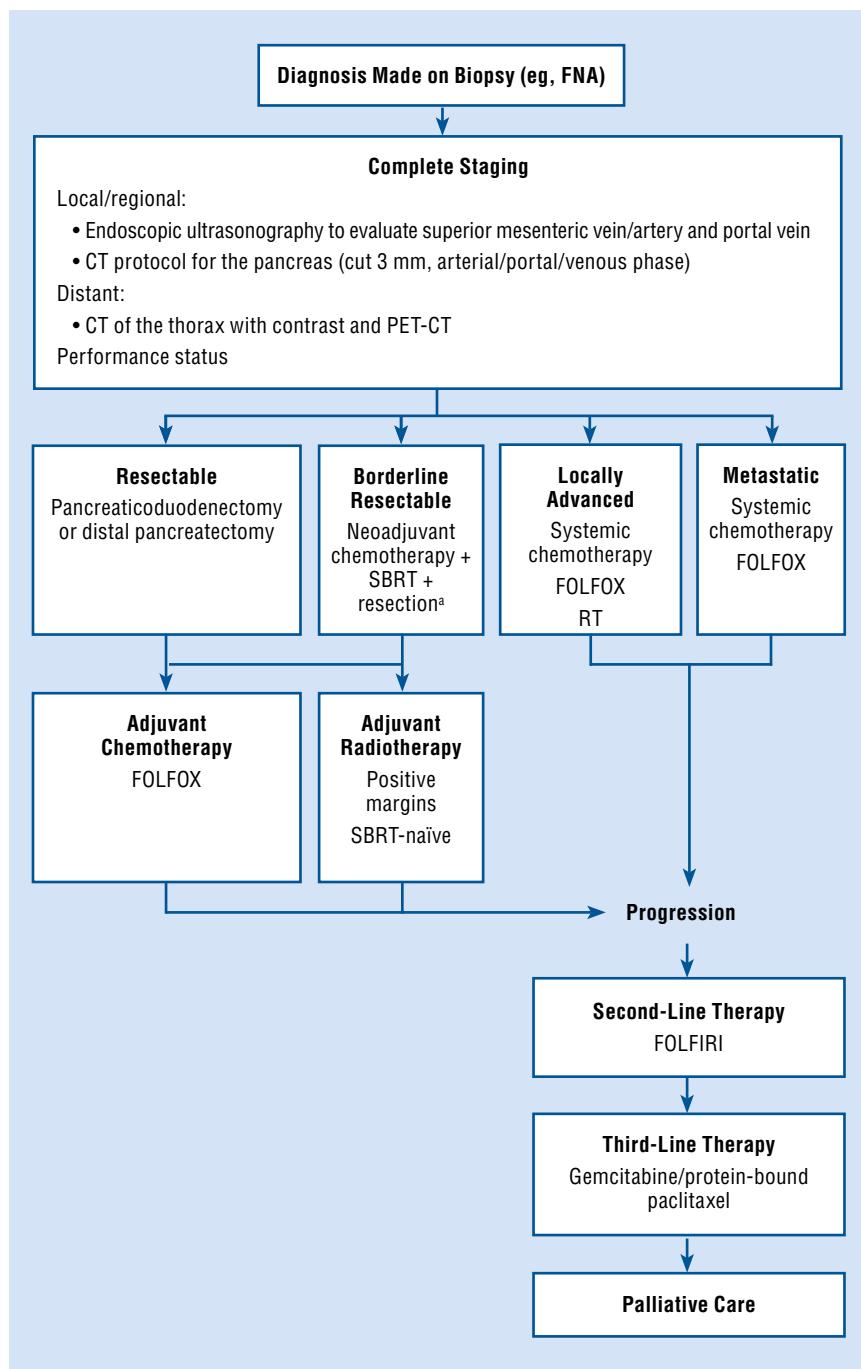


Fig 4. — Algorithm for the treatment of acinar cell carcinoma of the pancreas. This treatment plan is based on expert opinion and focuses on the importance of negative-margin resection coupled with RT.

CT = computed tomography, FNA = fine needle aspiration, FOLFIRI = folinic acid/fluorouracil/irinotecan, FOLFOX = folinic acid/fluorouracil/oxaliplatin, PET = positron emission tomography, RT = radiotherapy, SBRT = stereotactic body radiotherapy.

<sup>a</sup>If no progression on repeat staging.

tions) that lead to acinar cell carcinoma of the pancreas must be better elucidated to (theoretically) incorporate small molecule inhibitors into therapy. As demonstrated by the overall higher survival rates seen in acinar cell carcinoma of the pancreas (see Table 4), acinar cell carcinoma of the pancreas may likely be molecularly driven in a distinct way from pancreatic ductal adenocarcinoma.<sup>3,21-25</sup> The radiosensitivity of acinar cell carcinoma of the pancreas must also be investigated and modulated to optimize therapy. Our data suggest that acinar cell carcinoma of the pancreas is a radiosensitive tumor. Similar to many other malignancies, active chemotherapeutics also need identification. Whether current chemotherapy options add any improved likelihood of long-term survival remains unclear based on published data.

## Conclusions

Acinar cell carcinoma of the pancreas is a rare pancreatic malignancy with a prognosis slightly better than ductal adenocarcinoma. At Moffitt Cancer Center, our standard approach is surgical resection followed by adjuvant fluorouracil-based chemotherapy, radiotherapy, or both (see Fig 4). The utility of chemotherapy is uncertain; however, when it is used, a fluorouracil-based regimen is often proposed because of its higher rates of disease control when compared with gemcitabine or other chemotherapeutic agents. (However, this treatment plan is based on expert opinion and individualized for patient performance status.) Negative microscopic margins are the most important prognostic factor, because survival for patients with positive microscopic margins is generally as poor as those seen with positive gross margins.

Multidisciplinary management of pancreatic acinar cell carcinoma should be considered due to the lack of high-level data in treating this patient population. In addition, referral to a quaternary center is appropriate given the rarity of this malignancy. Despite the rarity of this disease, further investigation is needed to personalize care to improve long-term survival in these patients.

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