Original Article

Adjuvant radiation provides survival benefit for resected pancreatic adenocarcinomas of the tail

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Background: The appropriate adjuvant treatment for resected pancreatic cancer remains a controversy. We sought to determine the effect of adjuvant treatment on overall survival (OS) in patients with pancreatic tail adenocarcinoma.

Methods: Retrospective review of patients with upfront surgically resected pancreatic tail cancer treated at our institution between 2000–2012 was performed to determine outcomes of patients treated with and without adjuvant radiation therapy (RT). Survival curves were calculated according to the Kaplan-Meier method. Univariate analysis (UVA) and multivariate analysis (MVA) were performed using the Cox proportional hazards model.

Results: Thirty-four patients met inclusion criteria. 79% received adjuvant chemotherapy, either concurrent with RT or alone. The groups were well matched, with the only significant difference being patient sex. On both UVA and MVA there was significantly worse survival in patients with a post-op CA19-9 >90 [hazard ratio (HR) 5.55; 95% confidence interval (CI): 1.20–25.7, P=0.03] and improved survival in patients treated with adjuvant RT (HR 0.15; 95% CI: 0.04–0.58, P=0.006). The median and 2-year OS were 21.6 months and 47% for patients treated with adjuvant RT compared with 11.3 months and 21% for those treated without RT.

Conclusions: Although few in patient numbers, this data suggests integration of adjuvant RT in resected pancreatic tail adenocarcinoma may improve OS.

Keywords: Pancreatic tail; adjuvant radiation; pancreatic cancer

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Introduction

Pancreatic cancer has one of the highest mortality to incidence ratios of all cancers, with one of the smallest clinical windows of intervention (1). By location, pancreatic cancers are found in the head, the uncinate, the body, and/or the tail, yet no data are available on whether location influences genomic characteristics of the individual tumor profile. Tumors located in the pancreatic tail are usually diagnosed incidentally, as they do not present with the "painless jaundice" seen in pancreatic head tumors (2). Their delayed presentation means that, if discovered, they are usually diagnosed as later stage cancers than the much more common tumors located in the pancreatic head. A recent SEER analysis suggested that in localized, resectable disease (per AJCC 8th edition staging), clinical outcomes are not significantly different based on tumor location (3). However, a National Cancer Database analysis reported a

significantly longer 5-year overall survival (OS) for tumors located in the tail (32% *vs.* 11%) in stage I pancreatic cancers (4). Over the past thirty years, there has been little progress in the high rates of distant failure in patients with pancreatic cancer. Ultimately, treatment strategies including surgical resection with negative margins provide the only chance for cure. The resected 5-year survival remains poor, with rates still in the 20–24% range overall, and subgroups of patients with node and margin negative resection up to 39% (5).

Adjuvant therapy strategies for pancreatic cancer remain controversial. In the era prior to gemcitabine chemotherapy, the GI Tumor Study Group (GITSG) completed a small randomized trial comparing pancreatic cancer surgery alone to surgery combined with adjuvant 5-FU based chemoradiation that was delivered with split course technique (6). The adjuvant arm had an improved median survival (20 *vs.* 11 months, P=0.035) and subsequent patients who were not randomized but were treated on the CRT arm also had median OS of 18 months supporting the seeming superiority of CRT (7). Over the years, subsequent European trials have attempted to confirm these findings but have been unable to do so (8), with results from the ESPAC-1 trial showing that CRT was inferior to chemotherapy alone (9). These results have been criticized by other investigators for inadequate radiation techniques (lack of quality assurance, split course regimens, non-standard RT dose) as well as having only 53% of the patients enrolled included in the final data analysis (10). Nonetheless, based on the superiority of chemotherapy alone reported in the European trials, the Charite Onkologie Clinical (CONKO-001) trial (11) subsequently compared gemcitabine as single agent with observation and reported superior outcomes with improved median survival of 22.8 *vs.* 20.2 months (P=0.005).

While CRT has been significantly displaced in Europe in favor of systemic gemcitabine chemotherapy alone as the standard adjuvant therapy recommendation, the role of radiation therapy (RT) has received further study in the U.S. The Radiation Therapy and Oncology Group (RTOG) 9704 study incorporated a continuous regimen of 50.4 Gy delivered in 28 daily fractions with 5-FU preceded by a randomization for either one cycle of gemcitabine or 5-FU. Following CRT, the same chemotherapy was delivered for an additional 3 months (12). In the updated 5-year analysis, Regine *et al.* reported a trend on multivariate analysis (MVA) for improved OS with the gemcitabine arm with a 5-year OS of 22% compared with 18% (13). Results from this trial showed that the site of first failure in the majority (73%) of patients was distant. Further analysis from this study indicated that positive lymph nodes (14) and postoperative CA 19-9 values ≥90 U/mL were associated with worse survival (15). The RTOG investigators also evaluated their outcomes with respect to adherence to protocol guidelines, reporting that patients who were not treated according to protocol had worse median survival (10). In addition, the outcomes of those patients were compared with the outcomes of patients with pancreatic head tumors on RTOG 9704 treated with gemcitabine who also had a post-operative CA 19-9 <90 U/mL. Median survivals were consistent with those reported in the CONKO-001 trial (16).

Recent molecular data suggests that biomarkers may be the key to differentiating tumors with a local *vs.* distant pattern of failure (17). Studies from rapid autopsy series have shown that 30% of patients die with locally destructive tumors compared to 70% with disseminated metastasis and that patients with intact SMAD4 (DPC4) on immunohistochemistry were more likely to die of local disease (18). These findings suggest that there may indeed be subsets of patients with pancreatic cancer who may benefit from adjuvant RT. Our institution previously reported (19) on the potential significance of the radiation sensitivity index (RSI), evaluated the effect of radiosensitive patients with adverse prognostic factors who received RT, and found an improved median survival (31.2 *vs.* 13.2 months, P=0.04) when compared with patients with radioresistant tumors (20).

Few data exist specifically evaluating outcomes of subsets of patients with pancreatic tail cancer. Whether tumor location in pancreatic cancers is a manifestation of variant biological behavior and whether patients should be risk stratified by such a categorization remains to be seen. Current National Comprehensive Cancer Network (NCCN) guidelines recommend either a clinical trial, chemotherapy alone, or a regimen including chemoradiation for adjuvant therapy in pancreatic cancers, regardless of location (21). We thus sought to evaluate our institutional experience with adjuvant RT in surgically resected pancreatic tail cancers.

Methods

Patient selection

After obtaining IRB approval, a retrospective review identified 34 patients with pancreatic cancers located in the tail that underwent distal pancreatectomy between

Table 1 Patient demographics and characteristics

Variable	Radiation	No radiation	P value
Median age (range) years	69 [37–81]	73 [43–91]	0.29
Gender			*0.03*
Male	16 (80%)	6 (42.9%)	
Female	4 (20%)	8 (57.1%)	
Median path tumor size (cm, range)	3.5 (0.1–14.7)	5.5 (2.0–8.0)	0.46
Pathologic tumor stage			0.24
1&2	6 (30%)	7 (50%)	
3&4	14 (70%)	7 (50%)	
Median nodes positive (range)	0 (0–7)	1 (0–4)	0.36
Median nodes removed (range)	6 (0–27)	10 [2–22]	0.59
Pathologic nodal stage			0.24
0	14 (70%)	7 (50%)	
1	6 (30%)	7 (50%)	
Tumor grade			0.76
Well/moderate	15 (78.9%)	10 (83.3%)	
Poor/undifferentiated	4 (21.1%)	2 (16.7%)	
Surgical margins			0.18
Negative	15 (75%)	13 (92.9%)	
Positive	5 (25%)	1 (7.1%)	
Post-op CA 19-9 >90			0.59
No	14 (77.8%)	4 (66.7%)	
Yes	4 (22.2%)	2 (33.3%)	

Statistically significant P value is in italic.

2002–2012 at Moffitt Cancer Center. Patients were treated per our institution's pancreatic cancer clinical pathway, which included the initial staging studies of endoscopic ultrasound (EUS), pancreas protocol computer tomography (CT), and Positron Emission Tomography (PET)/CT scan. The entire cohort was followed for a median duration of 18.2 months. Only those determined to have locally confined, non-metastatic disease amenable to distal pancreatectomy were included in this study. Additionally, patients with tumors located in the head or body of the pancreas, or underwent total pancreatectomy were also excluded. Patient characteristics are summarized in *Table 1*.

Statistical analysis

Patient characteristics were analyzed between patients treated with and without adjuvant RT with Pearson chi-square tests. The cutoff for CA 19-9 was set based on the findings from RTOG 97-04 (15). OS was evaluated using Kaplan-Meier survival functions. Significance was evaluated with Mantel-Cox log ranks. Significant predictors of survival functions were then further analyzed using multivariate Cox regression. For multiple variables that were significant, multivariate regression was performed. Statistical significance was set at $P<0.05$. All statistical analysis and figure artwork was performed and generated

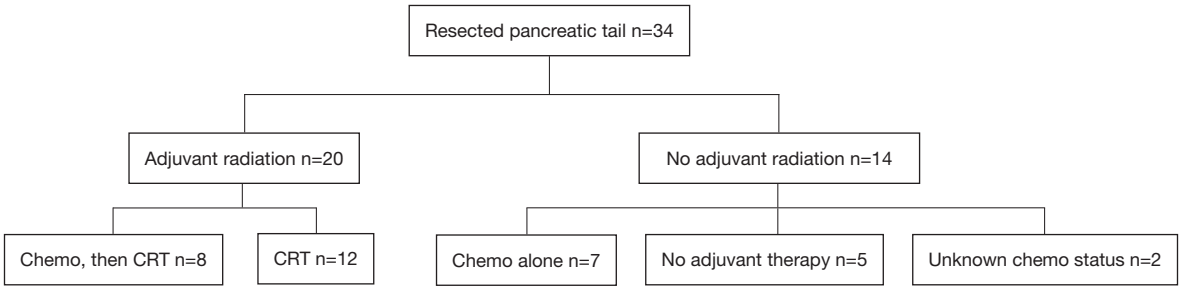


Figure 1 Distribution of chemotherapy regimens. CRT, chemoradiation therapy.

using SPSS v 23.0.0.2 (IBM, Armonk, NY, USA).

Results

Patient and tumor characteristics

After undergoing distal pancreatectomy, 20 patients received adjuvant radiation while 14 patients did not. Irradiated patients were treated to a median dose of 50.4 Gy in 28 fractions with concurrent 5-FU (fluorouracil) chemotherapy as the complete regimen in 12/20 (60%) and in addition to systemic gemcitabine therapy in 8/20 (40%). Of the 14 that did not receive adjuvant RT, 7 patients received chemotherapy alone with gemcitabine, 5 did not receive any adjuvant therapy and the chemotherapy status of 2 patients was unknown (*Figure 1*).

Patient demographics were well matched between the two groups except for gender. Notably, the majority of the patients receiving radiation had tumors with a post-operative CA 19-9 that was <90 and that were well to moderately differentiated with negative margins and nodes. Patients who received adjuvant radiation were much more likely to be male (80% *vs.* 42.9%, P=0.03). However, subsequent sub-group analysis for gender was not a confounder for survival outcomes. Otherwise, pathologic and surgical features were equally distributed between the two groups. Specifically, pathologic tumor size, stage, number of positive nodes, number of nodes removed, surgical margins, and post-operative CA 19-9 were not significantly different (*Table 1*).

OS

Univariate analysis (UVA) identified adjuvant radiation (HR =0.43, P=0.036) and post-operative CA 19-9 ≥90 (HR =5.37, P=0.003) as statistically significant predictors for survival (*Table 2*). In addition, removing ≥5 lymph nodes approached significance (HR =0.46, P=0.06). Therefore, all three variables were included in multivariate cox-regression analysis. However, only post-operative CA 19-9 <90 (HR =0.18, P=0.03) and adjuvant radiation (HR =0.15, P=0.006) remained statistically significant independent predictors for survival. Median survival in patients who received adjuvant radiation was 21.6 months, compared to 11.3 months in those who did not (*Figure 2*, P=0.03). Two-year OS were 47% and 21%, respectively.

Discussion

This study has shown that adjuvant RT containing regimens were associated with improved survival for pancreatic tail tumors. In our analysis, the majority of patients receiving adjuvant CRT regimens had a postoperative CA 19-9 <90 U/mL and underwent R0 resection for node negative tail tumors that were pathologic stage T3/4. The median survival of 21.6 months is concordant with the gemcitabine arm of the CONKO-001 trial and the RTOG 9704 analysis of pancreatic head tumors with CA 19-9 <90 U/mL that were treated according to protocol guidelines. In addition, 25% of the patients in the irradiated group in the present analysis had tumors resected with positive surgical margins, suggesting that adjuvant CRT may have obviated the adverse prognostic significance of R1 resection for these tail primary tumors.

The optimal adjuvant therapy regimen for resected pancreatic cancers remains controversial. GITSG 9731 provided some of the first prospective evidence that adjuvant chemoradiation improves survival after margin negative resection (6). However, in other clinical trials, the survival benefit of adjuvant radiation has been controversial, as seen in ESPAC-1 and EORTC 40013 (9,22). Criticisms for those early clinical trials include the anachronistic split dose fractionation scheme and the median 40 Gy

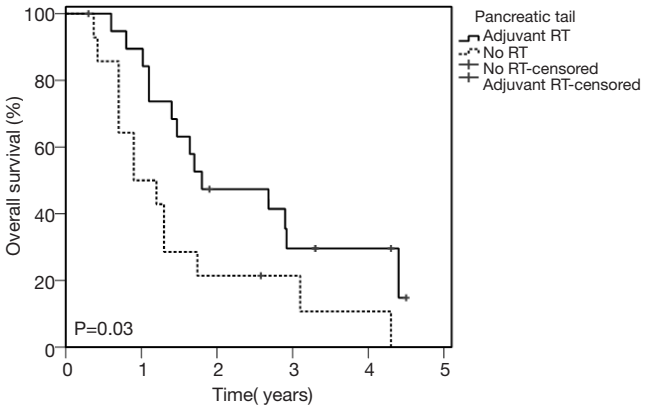
Table 2 Univariate and multivariate analysis for overall survival

Variable	Median OS (mo)	UV		MV	
		HR (95% CI)	P value	HR (95% CI)	P value
Age (years)			0.26		0.72
<70	21.6	ref.		ref.	
≥70	15.6	1.56 (0.72, 3.37)		0.81 (0.25, 2.63)	
Sex			0.93		0.22
Male	17.7	ref.		ref.	
Female	15.6	1.04 (0.46, 2.32)		0.54 (0.20,1.44)	
Pathologic AJCC tumor stage			0.64		0.13
T1/2	20.5	ref.		ref.	
T3/4	15.6	1.21 (0.55, 2.65)		2.56 (0.76, 8.63)	
Pathologic AJCC nodal status			0.35		0.09
N0	15.4	ref.		ref.	
N1	32.1	0.68 (0.31, 1.51)		0.25 (0.05, 1.25)	
Nodes removed			0.06		0.08
<5	12.2	ref.		ref.	
≥5	32.1	0.46 (0.21, 1.02)		0.31 (0.09, 1.15)	
Tumor grade					
Well/moderate	17.7	ref.		ref.	
Poor/undifferentiated	12.9	0.65 (0.22, 1.95)	0.44	0.59 (0.16, 2.20)	0.43
Unknown	20.9	1.20 (0.35, 4.09)	0.77	0.99 (0.25, 3.89)	0.98
Surgical margins			0.74		0.39
Negative	19.6	ref.		ref.	
Positive	12.7	1.18 (0.44, 3.19)		0.52 (0.12, 2.33)	
Post-op CA 19-9					
<90	32.1	ref.		ref.	
≥90	12.3	5.37 (1.74, 16.5)	0.003	5.55 (1.20, 25.7)	*0.03*
Unknown	11.1	2.11 (0.88, 5.06)	0.09	1.32 (0.42, 4.17)	0.64
Adjuvant radiation			0.036		*0.006*
No	11.3	ref.		ref.	
Yes	21.6	0.43 (0.20, 0.95)		0.15 (0.04, 0.58)	

Statistically significant P values are in italic. mo, month; UV, univariate; MV, multivariate; HR, hazard ratio; ref., reference.

delivered was likely an ineffectually low dose. Currently, NCCN guidelines still recommend adjuvant radiation as an acceptable means of management as level 2A evidence (21).

Current evidence is sparse with respect to adjuvant therapy outcomes specific to non-pancreatic head tumor locations. Ruess *et al.* found that resected pancreatic cancers in the tail were larger than those in the head, but they were also significantly less likely to have nodal metastasis (23). This



Adjuvant RT	Subjects	Events	Censored	Median survival (mo, 95% CI)
Yes	20	14	6	21.6 (4.5, 38.7)
No	14	13	1	11.3 (5.8, 16.8)

Figure 2 Kaplan-Meier overall survival in resected pancreatic tail tumors. RT, radiation therapy.

raises the possibility that pancreatic tail cancers may constitute a more favorable malignancy than those located in the head. This disparity based on location has been seen in other sites that have more anatomically distinct compartments, like in colorectal cancers (24). Right and left-sided colon cancers, as well as proximal and distal rectal cancers, have different biological profiles; the conditions necessary to produce malignant potential proximally are intrinsically different conditions than distally (25). Recent studies in pancreatic cancers suggest that the location of the primary tumor is also associated with inherent differences in biological aggressiveness, in terms of recurrence and micrometastatic potential (26,27). At present, evidence is lacking to support or undermine the hypothesis that pancreatic tail cancers are truly less aggressive; it could just be that they have a different, albeit predictable, pattern of progression.

Regardless, pancreatic cancers are associated with high rates of clinically undetectable, micrometastatic disease (28-30). Perhaps pancreatic tail cancers are intrinsically more likely to progress through local growth and invasion due to a higher incidence of tumors with intact SMAD4 profiles. This could explain the significant survival benefit conveyed from the addition of adjuvant radiation. Further, this data suggests that prioritizing strategies that focus on improved local control with modern RT modalities may be particularly important for tumors in the tail of the pancreas.

Our study faced certain limitations from its inherent retrospective nature and relatively small sample size. We recognize that the median survival of 11.3 months in those patients who did not receive adjuvant RT is low and could reflect a cohort with increased co-morbidities that precluded adjuvant therapy integration. Indeed, the group of 14 patients who did not receive RT included 5 patients who did not receive any adjuvant therapy at all. We attempted to perform sub-group analysis to separate adjuvant chemotherapy as a possible confounder, but our study was not designed to do so. While seven patients received chemotherapy alone, no patients received adjuvant radiation alone. One patient received a significantly lower dose of radiation at our institution (9 Gy) because he was previously treated at a community hospital, where he was treated with a split course fractionation scheme. Otherwise, the small sample size precludes the retrospective elucidation of individual effects from chemotherapy and radiation.

Current studies suggest patients with pancreatic head tumors that are node positive or resected with positive margins benefit from adjuvant regimens that contain chemoradiation (31). This small study suggests that there may be improved survival for tail tumors with adjuvant RT, even for R0 resected tumors that are node negative. Moreover, the majority of the patients receiving adjuvant RT did so without any additional systemic chemotherapy, suggesting there may be increased benefit to intensifying local therapy integration in this subset of patients. Further study of pancreatic tail tumors in the adjuvant setting is warranted.

Conclusions

This study showed an improvement in survival with the addition of adjuvant RT for pancreatic tail tumors. The data suggests that tumors of the pancreatic tail compared with other locations may have a different genetic tumor profile favoring a higher propensity for local rather than distant disease progression. These findings need further validation to identify the most appropriate patient selection factors for adjuvant RT regimens for resected tail tumors.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This research was approved by the ethics committee and informed consent was obtained from all patients per our IRB# Pro 00003328 (0.02).

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