University of Kentucky
UKnowledge

Radiation Medicine Faculty Publications | Radiation Medicine

4-2019

Initial Results of a Prospective Study of Adjuvant Pancreatic Stereotactic Body Radiation Therapy for Close or Positive Margins

Mark E. Bernard
University of Kentucky, Mark.Bernard@uky.edu

Philip A. Sutera
University of Pittsburgh

Nicholas A. Iarrobino
University of Pittsburgh

Kimmen Quan
University of Pittsburgh

Steven A. Burton
University of Pittsburgh

See next page for additional authors
Follow this and additional works at: https://uknowledge.uky.edu/radmed_facpub

 Part of the Oncology Commons, and the Radiology Commons

Right click to open a feedback form in a new tab to let us know how this document benefits you.

Repository Citation

Bernard, Mark E.; Sutera, Philip A.; Iarrobino, Nicholas A.; Quan, Kimmen; Burton, Steven A.; Bahary, Nathan; Hogg, Melissa; Zureikat, Amer; and Heron, Dwight E., "Initial Results of a Prospective Study of Adjuvant Pancreatic Stereotactic Body Radiation Therapy for Close or Positive Margins" (2019). *Radiation Medicine Faculty Publications*. 22.
https://uknowledge.uky.edu/radmed_facpub/22

This Article is brought to you for free and open access by the Radiation Medicine at UKnowledge. It has been accepted for inclusion in Radiation Medicine Faculty Publications by an authorized administrator of UKnowledge. For more information, please contact UKnowledge@lsv.uky.edu.

Initial Results of a Prospective Study of Adjuvant Pancreatic Stereotactic Body Radiation Therapy for Close or Positive Margins

Digital Object Identifier (DOI)
https://doi.org/10.1016/j.adro.2018.11.007

Notes/Citation Information

Published in *Advances in Radiation Oncology*, v. 4, issue 2, p. 294-301.

© 2018 The Author(s). Published by Elsevier Inc. on behalf of American Society for Radiation Oncology.

This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Authors

Mark E. Bernard, Philip A. Sutera, Nicholas A. Iarrobino, Kimmen Quan, Steven A. Burton, Nathan Bahary, Melissa Hogg, Amer Zureikat, and Dwight E. Heron

This article is available at UKnowledge: https://uknowledge.uky.edu/radmed_facpub/22

Advances in Radiation Oncology (2019) **4**, 294-301

advances
in radiation oncology

www.advancesradonc.org

Scientific Article

Initial Results of a Prospective Study of Adjuvant Pancreatic Stereotactic Body Radiation Therapy for Close or Positive Margins

Mark E. Bernard MD [a,b], Philip A. Sutera BS [a], Nicholas A. Iarrobino BS [a], Kimmen Quan MD [a], Steven A. Burton MD [a], Nathan Bahary MD [c], Melissa Hogg MD [d], Amer Zureikat MD [d], Dwight E. Heron MD, MBA, FACRO, FACR [a,*]

[a]*Department of Radiation Oncology, UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania;* [b]*Department of Radiation Medicine, University of Kentucky, Lexington, Kentucky;* [c]*Department of Medical Oncology, UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania;* [d]*Department of Surgical Oncology, UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania*

Received 9 August 2018; accepted 16 November 2018

Abstract

Purpose: Patients with close or positive margins after surgery for pancreatic carcinoma are at a high risk for recurrence. Stereotactic body radiation therapy (SBRT) allows for safe dose escalation with great conformity and short duration of treatment. Herein, we report the initial results of a prospective observational study that evaluated the efficacy and safety of this treatment option.

Methods and Materials: Patients eligible for the study had pathologically proven T1-4N0-1M0 pancreatic adenocarcinoma with a positive margin ($\leq$1 mm) or a close margin defined as $<$2.5 mm. Patients were treated with either neoadjuvant or adjuvant chemotherapy, if eligible for systemic therapy. All patients received 36 Gy in 3 fractions to the close or positive margin site.

Results: From February 2013 to January 2018, 50 patients were enrolled with 49 patients treated on protocol and included in the analysis. The median age was 71 years. The median clinical target volume was 11.3 cc and median planning target volume 22.0 cc. The median overall survival was 23.7 months (95% confidence interval, 13.6-33.8). Local progression-free survival at 1 and 2 years was 85% and 77%, respectively. Regional progression-free survival at 1 and 2 years was 73% and 73%, respectively. Distant metastases-free survival was 57% and 49% at 1 and 2 years, respectively. Grade 3+ radiation toxicity was only 4.1% and occurred in 2 patients.

Conclusions: Adjuvant pancreatic SBRT was shown to be a safe and feasible treatment option for patients with high-risk pancreatic adenocarcinoma and close or positive margins. This is the first prospective study of SBRT in high-risk postoperative pancreatic cancer. Our results yielded significant local and regional control with low rates of acute toxicity. This technique does not interrupt the administration of systemically dosed multiagent chemotherapy and can be safely interdigitated between cycles because SBRT is only 1 week of treatment.

Sources of support: This work had no specific funding.

Conflicts of interest: The authors have no conflicts of interest to disclose.

* Corresponding author. Department of Radiation Oncology, UPMC Hillman Cancer Center, 5230 Centre Ave, Suite 544, Pittsburgh, PA 15232.
E-mail address: herond2@upmc.edu (D.E. Heron).

https://doi.org/10.1016/j.adro.2018.11.007

2452-1094/© 2018 The Author(s). Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

© 2018 The Author(s). Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Surgery remains the standard of care for patients with resectable pancreatic adenocarcinoma.[1,2] Adjuvant therapy consists of chemotherapy, with the addition of adjuvant radiation reserved for select cases.[1–3] Even for patients who receive surgical resection and adjuvant therapy, outcomes remain poor with a median survival of 28 months and a 5-year overall survival (OS) of approximately 20% to 25%.[1–3]

Prognostic factors associated with outcomes for surgically staged patients include tumor grade, tumor size, lymph node status, surgical margin status, and perineural or blood vessel invasion.[4] Numerous reports have demonstrated that patients who receive an R1 resection with margins $\leq$1 mm are at an increased risk of recurrence with worse survival rates.[3–6] The impact that margin status has on survival is evident, even with dual-agent chemotherapy, and necessitates additional therapy.[1]

Multiagent adjuvant chemotherapy has been shown to improve survival, but the addition of radiation therapy is controversial, and prior studies have shown conflicting results.[7,8] However, patients with less than an R0 resection margin may likely benefit from further local therapy. If adjuvant chemoradiation is administered, treatment usually involves conventional fractionation that consists of approximately 5 to 6 weeks of treatment with concurrent chemotherapy.[8,9] However, this regimen may result in delays in systemic dosing of chemotherapy, which theoretically could increase the risk of distant metastasis.

Adjuvant stereotactic body radiation therapy (SBRT) presents a great opportunity to adequately treat patients with close or positive margins. The highly conformal nature of SBRT allows for a higher dose to be administered within 3 to 5 treatments while minimizing doses to surrounding critical structures.[10,11] In addition, the abbreviated treatment course prevents long delays for the initiation of systemically dosed chemotherapy, which may assist in reducing the risk of distant metastasis.

Pancreatic SBRT has been shown to be efficacious in the borderline-resectable and locally advanced setting.[10,11] We previously conducted a retrospective review of adjuvant pancreatic SBRT for close or positive margins.[3] We now report the initial results of a prospective observational study that evaluated the use of SBRT in the adjuvant setting for this high-risk subset of patients.

Methods and Materials

Enrollment and eligibility

All patients had pathologically proven T1-4N0-1M0 pancreatic adenocarcinoma with a positive margin (direct positive and $\leq$1 mm) or a close margin defined as $<$2.5 mm. Patients were age $\geq$18 years, had an estimated life expectancy of $>$12 weeks, and a Karnofsky performance status score of $\geq$70 (Eastern Cooperative Oncology Group score 0-1). Other criteria included adequate renal function, adequate hepatic function, being able to swallow enteral medications with no feeding tube, no uncontrolled intercurrent illness, and not pregnant or nursing. All patients were treated with surgical resection and had either neoadjuvant chemotherapy or adjuvant chemotherapy if eligible to receive systemic therapy. All patients were treated at UPMC Hillman Cancer Center, Department of Radiation Oncology with approval from an institutional review board to conduct the study. This trial was prospectively registered with ClinicalTrials.gov identifier NCT01357525.

Pancreatic stereotactic body radiation therapy planning

Contrast-enhanced computed tomography (CT)-based simulations were obtained before any adjuvant treatment (2-4 weeks postoperative, depending on healing). The treatment volume was contoured on axial CT images obtained at 1.25 mm slice thickness. The volumes were then reconstructed into a 3-dimensional image set for SBRT planning. Subjects were simulated in the treatment position (ie, supine with arms raised) on the CT scanner table with the appropriate immobilization and a vacuum lock bag. Optiray contrast (125 mL Optiray 350; 350 mg/mL organically bound iodine; Ioversol; Mallinckrodt Inc, St. Louis, MO) was administered intravenously at a flow rate of 2.5 mL/s. A helical CT scan of the abdomen was acquired with intravenous contrast starting 30 seconds before CT acquisition.

Four-dimensional CT data acquisition for the same axial extent was also obtained. Based on the axial CT images, fiducial marker placement (ie, 3 fiducials placed at the discretion of the surgeon), review of the pathology report, and a detailed discussion with the operating surgeon, the contours were drawn of the clinical target volume (CTV), which was defined as the area at risk for

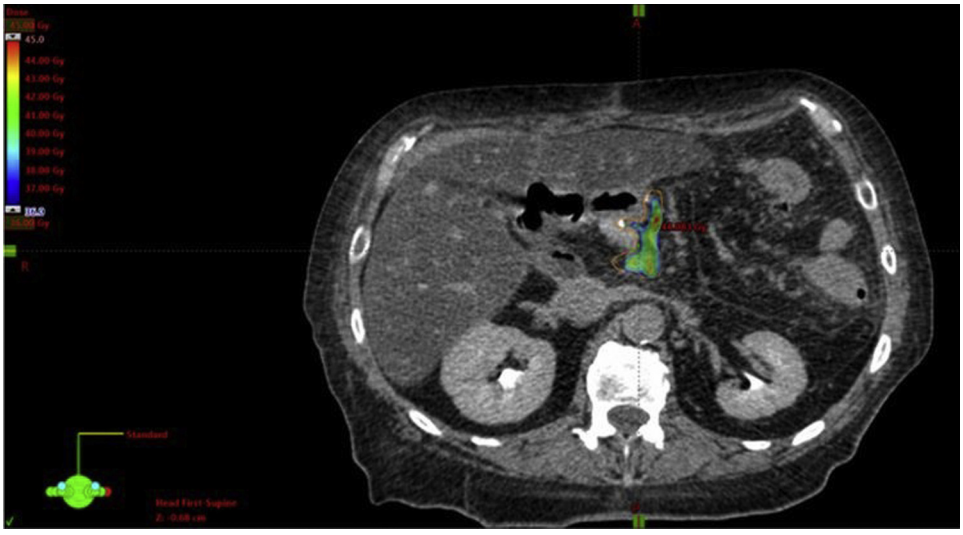

Figure 1 Example of a stereotactic body radiation therapy treatment plan. The orange volume represents the planning target volume (PTV). Of note, the dose to the small bowel takes priority of the PTV coverage. Also, the PTV is the same as the clinical target volume for areas that touch the bowel.

microscopic disease based on the pathology report and per the surgeons as marked by clips and fiducials. The CTV only included the area of the close or positive margin and was not altered for nodal status. Preoperative tumor volume was not used to determine the CTV. The planning target volume (PTV) was the CTV + 2 mm, unless motion was detected on the 4-dimensional motion study. In addition, no margin was added to the CTV if it was adjacent to the bowel. If there was motion, the margin given was the amount of motion in the superior–inferior, lateral, and anterior–posterior directions. The surrounding normal and critical structures were also contoured by the treating radiation oncologist, including the kidneys, liver, small bowel, spinal cord, and stomach if necessary.

Patients were treated with a dose of 36 Gy in 3 fractions, with 12 Gy per fraction prescribed to the PTV (Fig 1) every other day. This dose regimen was chosen based on our prior institutional experience with multifractionated pancreatic SBRT.[12] Patients were treated either using volumetric modulated arc therapy or static field intensity modulated radiation therapy with image guidance, using daily cone beam CT with localization of fiducials. No more than 2% of the PTV could receive <93% of the prescribed dose. The maximum dose (in 3 fractions) was limited to sensitive critical structures, including the liver (15 Gy), kidney (15 Gy), spinal cord (18 Gy), stomach (30 Gy), and small bowel (30 Gy). Patients were followed up 10 to 12 weeks after SBRT, then every 3 months, and thereafter for up to 24 months, with CT scans obtained at each follow-up visit.

Primary endpoints

Our primary, prospectively defined endpoint was local progression-free survival (LPFS). Secondary endpoints include OS, regional progression-free survival (RPFS), distant metastases-free survival (DMFS), toxicity, and quality of life. OS was measured from enrollment, and LPFS, RPFS, and DMFS were all measured from completion of the SBRT. Local progression was defined as disease recurrence detected on follow-up imaging (CT or 18-fluoro-deoxyglucose positron emission tomography/CT) that was located with the SBRT target volume. Regional failure was defined as disease progression to the regional nodes, defined as N1, N2, or N3 by the Japan Pancreas Society classification[13,14] (or new tumor growth within the pancreas outside of the radiation field). Toxicity was graded and recorded prospectively with the Common Terminology Criteria for Adverse Events, version 4.0 at each follow-up visit. Patient-reported quality of life was assessed with the Functional Assessment of Cancer Therapy-General questionnaire before and within 3 months of completion of the SBRT.

Statistical analysis

Continuous variables were summarized with median and interquartile range. Categorical variables were summarized with frequency and percentage. Median follow-up was calculated with reverse Kaplan-Meier.[15] The survival endpoints (OS and time to progression) were analyzed with the Kaplan-Meier method. The association of these survival endpoints with risk factors was studied with univariate Cox proportional hazards models. To build the multivariable Cox models for the survival endpoints, a stepwise variable selection was performed. All variables from the univariate models that had $P < .1$ were included as potential predictors. Variables were removed from the multivariable model if

Table 1 Patient characteristics

Characteristics	No (%) (n = 49 lesions)
Age (median years, range)	69.9 (62.2-75.6)
Sex	
Female	23 (46.9)
Male	26 (53.1)
Stage	
T3N0	13 (26.5)
T3N1	36 (73.5)
Grade	
Well	0 (0)
Moderate	33 (69.4)
Poor	14 (28.6)
Undifferentiated	1 (2.0)
Resectability at time of diagnosis	
Resectable	27 (55.1)
Borderline resectable	21 (42.9)
Locally advanced	1 (2.0)
SMAD4 status	
Preserved	17 (34.7)
Lost	26 (53.1)
Unknown	6 (12.2)
Cancer antigen 19-9 value (median value, IQR)	
Diagnosis	120.6 (36.0-379.5)
Postoperative	20.3 (8.8-71.6)
Post-SBRT	26.5 (11.3-96.1)
Post-SBRT cancer antigen 19-9 normalization	
Yes	10 (22.0)
No	11 (20.0)
Unknown	29 (58)
Margins	
Close	11 (22.4)
Positive	38 (77.6)
Location	
Head/uncinate	40 (81.6)
Body	9 (18.4)
Treatment platform	
True beam	29 (59.2)
Trilogy	20 (40.8)
Chemotherapy	
Neoadjuvant	32 (65.3)
Gemcitabine	2 (4.1)
Gemcitabine + Pb-paclitaxel	25 (51)
Folfirinox	5 (10.2)
Median duration of neoadjuvant, days (IQR)	44 (37.5-67)
Adjuvant	40 (81.6)
Gemcitabine	11 (22.4)
Gemcitabine + Pb-paclitaxel	11 (22.4)
Gemcitabine + capecitabine	8 (16.3)
5-fluorouracil based	6 (12.2)
Other	4 (8.2)
Median duration of adjuvant, days (IQR)	126 (91-150)
Median duration from SBRT to start of adjuvant, days (IQR)	7 (−7 to 18)
Clinical target volume, cc (median, IQR)	11.3 (7.0-15.7)
Planning target volume, cc (median, IQR)	22.0 (15.1-27.7)
Dose (median, range)	36 (30-36)
Interval from surgery (median days, IQR)	63 (48-84)

Abbreviations: IQR = interquartile range; SBRT = stereotactic body radiation therapy.

$P > .05$. All P-values reported are 2-sided. For the quality of life analysis, the total Functional Assessment of Cancer Therapy-General score was compared using the Wilcoxon signed rank test between pre- and post-SBRT.

Results

Patient characteristics and treatment delivery

A detailed list of patient characteristics can be found in Table 1. From February 2013 to January 2018, 50 patients were enrolled and 49 patients were treated. One patient was unable to receive SBRT owing to treatment not covered by insurance; therefore, the patient was excluded from the analysis. The median age was 69.9 years (range, 62.2-75.6 years). Male patients comprised 53.1% of our cohort. The tumors were located in the pancreatic head or uncinate process in 81.6% and body in 18.4% of patients. At the time of diagnosis, patients had either resectable (55.1%), borderline resectable (42.9%), or locally advanced (2.0%) disease. Patients received neoadjuvant (65.3%) and adjuvant (81.6%) chemotherapy. After resection, 38 patients (77.6%) had a positive margin ($\leq$1 mm) and 11 patients (22.4%) had a close margin (median: 2 mm; range, 1.5-2.0). The median CTV and PTV were 11.3 cc and 22.0 cc, respectively. One patient received 30 Gy in 10 fraction because dose constraints could not be met with 36 Gy. The interval from surgery was 63 days (interquartile range, 48-84 days). SMAD4 was obtained for all patients, except 6, and lost in 53.1% of patients. The median follow-up time was 31.2 months (95% confidence interval [CI], 13.7-48.7 months).

Overall survival

The median survival for the entire cohort was 20.03 months (95% CI, 12.8-27.3 months). The 1- and 2-year OS rates were 68% and 50%, respectively (Fig 2). No variables were found to be associated with OS on the

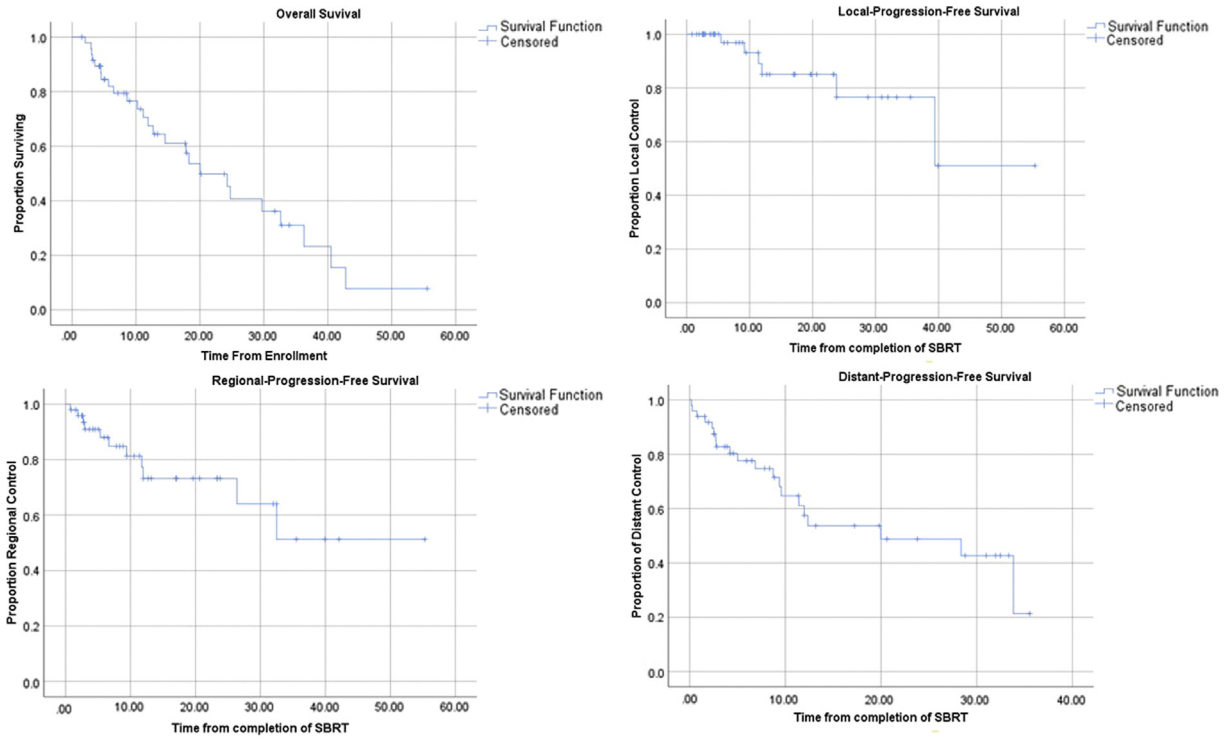

Figure 2 Kaplan-Meier curves of overall survival, local progression-free survival, regional progression-free survival, and distant progression-free survival

univariate cox regression analysis (Table 2). No significant difference in OS was observed between close (median OS: 32.6 months) and positive margins (median OS: 17.8 months), but OS trended toward significance on the log rank ($P = .066$; $\chi^2 = 3.374$).

Local progression-free survival

Local failure was observed in 6 patients (12.5%), and the median time to local progression was not reached. The 1- and 2-year LPFS were 85% and 77%, respectively (Fig 2). On univariate analysis, no predictors were significantly associated with LPFS, but CTV (continuous; $P = .051$; hazard ratio [HR]: 1.050; 95% CI, 1.000-1.103) and neoadjuvant chemotherapy ($P = .071$; HR: 0.129; 95% CI, 0.014-1.196) demonstrated a trend toward significance (Table 2). The multivariate analysis using predictors that trended toward significance on univariate analysis identified increased CTV ($P = .038$; HR: 1.095; 95% CI, 1.005-1.193) associated with inferior LPFS.

Regional progression-free and distant metastasis-free survival

The median time-to-regional progression was not reached; however, the 1- and 2-year RPFS rates were 73% and 73%, respectively (Fig 2). On univariate analysis, undifferentiated versus moderately differentiated pancreatic cancer ($P = .009$; HR: 28.171; 95% CI, 2.343-338.755) was associated with inferior RPFS (Table 3). A multivariate model was unable to be generated. The median DMFS was 20.0 months (95% CI, 0.0-40.0) with 1- and 2-year DMFS rates of 57% and 49%, respectively (Fig 2). The median time-to-distant metastasis was 20.0 months (95% CI, 0.0-40.0 months). Post-SBRT cancer antigen 19-9 ($P = .002$; HR: 1.001; 95% CI, 1.000-1.001), cancer antigen 19-9 normalization ($P = .025$; HR: 0.084; 95% CI, 0.010-0.731), and undifferentiated versus moderately differentiated ($P = .038$; HR: 9.965; 95% CI, 1.133-87.638) were found to be significantly associated with distant metastases (Table 3). No variables were found to be predicative of DMFS on multivariate analysis.

Radiation toxicity and quality of life

Two patients (4.1%) experienced acute grade 3 + radiation toxicity. Toxicity included grade 3 abdominal pain (n = 1) and hyperglycemia (n = 1), which both required hospitalization within 1 week after treatment. No patients experienced late grade 3+ toxicity. After treatment, there was no significant difference in patient-reported quality of life ($Z = -0.700$; $P = .484$).

Discussion

Surgery remains the standard of care for resectable pancreatic adenocarcinoma, but adjuvant radiation has

Table 2 Univariate and multivariate analysis for OS and FFLP

Factor	OS HR (95% CI)	*P*-value	FFLP HR (95% CI)	*P*-value
Univariate				
Age	1.001 (0.978-1.043)	.5504	0.947 (0.883-1.015)	.124
Pretreatment CA 19-9 at time of diagnosis (continuous)	1.000 (1.000-1.000)	.742	1.000 (1.000-1.000	.108
Postoperative CA 19-9 (continuous)	1.000 (0.999-1.002)	.806	1.003 (0.997-1.009)	.345
Post-SBRT CA19-9 (continuous)	1.000 (1.000-1.000)	.265	1.00 (1.00-1.001)	.360
CA 19-9 normalization	0.381 (0.062-2.332)	.297	0.009 (0.000-1356.451)	.437
Tumor stage: T3N1 vs T3N0	1.997 (0.678-5.885)	.209	3.009 (0.348-26.036)	.317
Grade: Poor vs moderate	1.918 (0.825-4.460)	.130	1.696 (0.267-10.755)	.575
Neoadjuvant chemotherapy	0.618 (0.367-1.815)	.618	0.129 (0.014-1.196)	.071
Adjuvant chemotherapy	0.938 (0.345-2.547)	.899	0.552 (0.062-4.954)	.596
Positive vs close margins	2.685 (0.901-8.000)	.076	0.401 (0.067-2.403)	.317
Lymphovascular invasion: Yes vs no	1.046 (0.354-3.086)	.935	0.801 (0.089-7.244)	.843
Clinical target volume (continuous)	0.993 (0.958-1.029)	.689	1.050 (1.000-1.103)	.051
Planning target volume (continuous)	0.968 (0.921-1.017)	.192	1.032 (0.938-1.135)	.520
SMAD4 intact: Yes vs no	0.982 (0.421-2.292)	.966	1.334 (0.243-7.326)	.740
Multivariate				
Clinical target volume	-	-	1.095 (1.005-1.193)	.038

Abbreviations: CA = cancer antigen; CI = confidence interval; FFLP = freedom from local progression; HR = hazard ratio; OS = overall survival; SBRT = stereotactic body radiation therapy.

remained controversial.[16–18] However, studies that addressed the role of adjuvant radiation used outdated techniques and included patients with both R0 and R1 resection. Margin status remains a potent predictor for recurrence and survival.[3–6] We recognize that there is no standard definition for close margins in the pancreatic adenocarcinoma literature. Close margin has been reported as >1 to ≤ 2.5 mm.[3,19] Our definition of close margins was based on our previous retrospective report.[11] Adjuvant chemotherapy has been shown to reduce recurrence, and improve survival for resectable pancreatic adenocarcinoma; however, even after aggressive systemic therapy, a positive margin is associated with poor outcomes.[1,2] SBRT represents a promising modality to provide additional local control and improve outcomes.

Table 3 Univariate analysis for FFRP and FFDM

Factor	FFRP HR (95% CI)	*P*-value	FFDM HR (95% CI)	*P*-value
Univariate*				
Age	1.024 (0.964-1.087)	.443	0.983 (0.944-1.025)	.426
Pretreatment CA 19-9 (continuous)	1.000 (1.000-1.000)	.175	1.000 (1.000-1.000)	.284
Postoperative CA 19-9 (continuous)	1.001 (0.999-1.003)	.381	1.001 (1.000-1.003)	.098
Post-SBRT CA 19-9 (continuous)	1.000 (1.000-1.000)	.758	1.001 (1.000-1.001)	.002
CA 19-9 Normalization	0.209 (0.021-2.063)	.180	0.084 (0.010-0.731)	.025
Borderline resectable vs resectable	1.638 (0.471-5.696)	.437	1.832 (0.755-4.445)	.181
Tumor stage: T3N1 vs T3N0	0.860 (0.249-2.973)	.811	2.872 (0.822-10.029)	.098
Grade: Poor vs moderate	1.992 (0.525-7.558)	.311	2.451 (0.930-6.459)	.070
Grade: Undifferentiated vs moderate	28.171 (2.343-338.755)	.009	9.965 (1.133-87.638)	.038
Neoadjuvant chemotherapy	1.439 (0.370-5.598)	.600	1.029 (0.403-2.628)	.952
Adjuvant chemotherapy	0.779 (0.168-3.622)	.751	1.143 (0.325-4.013)	.835
Positive vs close margins	1.079 (0.228-5.017)	.924	1.482 (0.430-5.103)	.533
Treatment platform: trilogy vs true beam	0.537 (0.142-2.028)	.359	1.701 (0.700-4.130)	.241
Lymphovascular invasion: Yes vs no	1.714 (0.217-13.546)	.610	3.838 (0.511-28.796)	.191
Clinical target volume	1.029 (0.991-1.068)	.134	0.987 (0.936-1.041)	.629
Planning target volume	1.021 (0.958-1.088)	.522	0.955 (0.905-1.007)	.091
SMAD4 intact: Yes vs no	0.896 (0.238-3.378)	.871	0.824 (0.324-2.096)	.684

Abbreviations: CA = cancer antigen; CI = confidence interval; FFDM = freedom from distant metastases; FFRP = freedom from regional progression; HR = hazard ratio; OS = overall survival; SBRT = stereotactic body radiation therapy.

* No multivariate model was found for FFRP or FFDM.

Delpero et al conducted a prospective multicenter study to determine impact of resection margin status after pancreaticoduodenectomy.[20] The prospective study accrued 150 patients between 2008 and 2010. As expected, patients with a least one R1 margin status had a lower median survival rate than those with an R0 margin status (17.7 vs 32.9 months) and a lower median progression-free survival rate (10.5 vs 19.5 months).

The Massachusetts General Hospital conducted a retrospective review of 1705 patients with pancreatic ductal adenocarcinoma to determine whether margin status had any prognostic significance.[19] They included R0-close, which was a margin status of $\leq$1 mm. The results showed a survival difference between R0 versus R1 (24 vs 14 months). Although there was no difference in survival time between R0-close and R1, an R0-wide margin of $>$1 mm was associated with a longer survival time compared with R1 or R0-close (34 vs 14 vs 16 months).

Washington University also conducted a retrospective review of 285 patients between 1997 and 2008 who were postpancreaticoduodenectomy to correlate margin status with survival and recurrence.[21] The results also showed that R1 resections were associated with a lower median survival time compared with R0 resections (16.4 vs 21.7 months) and a lower local recurrence-free survival rate. A subset analysis showed that a posterior positive margin was the only site to increase the risk for lower local recurrence-free survival. However, how many patients received adjuvant chemotherapy is unclear, and whether the optimized regimens used in the modern era is also unsure.

ESPAC-4 was a recent randomized controlled trial that compared adjuvant gemcitabine with or without capecitabine for resected pancreatic adenocarcinoma.[1] The study allowed both R0 and R1 resections to be included. Although the addition of capecitabine improved the median survival time, there was a difference in outcomes for patients who received an R0 or R1 resection. In the multiagent chemotherapy group, patients with an R1 resection had a statistically significant lower median overall survival time compared with those who received an R0 resection (23.7 vs 39.5 months). Among all patients who received dual chemotherapy, 46% experienced a local relapse. Our results demonstrated a similar survival time but significantly improved local control with only 12% of patients experiencing local recurrence.

Rwigema et al previously reported on a retrospective review of 24 patients who were treated with adjuvant SBRT for resected pancreatic cancer with close or positive margins. In a median follow-up period of 12.5 months, the 2-year OS and freedom-from-local-progression rates were 57.2% and 44%, respectively. No patients experienced grade 3+ toxicity.[3] Our study demonstrated significantly better local control rates with 77% LPFS at 2 years. Suss et al reported on 1392 patients who were treated with either chemoradiation or chemotherapy. Radiation improved the median survival time from 15.2 to 17.5 months. The addition of adjuvant radiation did not significantly change the median survival time among patients with node-negative disease (22.5 vs 23.6 months).[22]

To date, this is the first prospective report to show the feasibility of adjuvant SBRT for patients with pancreatic carcinoma and close or positive margins. Grade $\geq$3 toxicity occurred in 2 patients (4.1%), and local control remained high at 77% at 2 years. This local control rate is comparable with the rates reported in Radiation Therapy Oncology Group (RTOG) study 9704 that assessed adjuvant chemoradiation, including patients with both positive and negative margins (72%-77%).[23] Of note, adjuvant chemoradiation is controversial, and randomized controlled trials have demonstrated a range from no benefit to a detriment on OS.[16,24] These trials have since been subjected to numerous criticisms, and the RTOG 0848 study is currently ongoing to clarify the role of chemoradiation in patients with R0/R1 resection.

Our low toxicity profile is comparable with the profiles of other prospective trials that utilized conventional chemoradiation. RTOG 9704 was a randomized control trial that evaluated the addition of gemcitabine to fluorouracil chemotherapy for resected pancreatic adenocarcinoma. Grade $\geq$2 toxicity ranged between 15% and 21%.[23] GITSG 9173 was another randomized control trial that evaluated surgery with or without postoperative chemoradiation for pancreatic adenocarcinoma. The chemoradiation was administered in a split course fashion, consisting of 2 courses of 20 Gy separated by 2 weeks. The results showed that 14% of patients had hematologic toxicity, and 20% in the registered phase had severe leukopenia. Our grade $\geq$3 was only 4.1%, demonstrating that a high dose of radiation therapy can be safely delivered without causing significant morbidity. Of note, a large component of the toxicities reported in these trials were secondary to chemotherapy, which was not standard in the present report.

Conclusions

Adjuvant pancreatic SBRT is a safe and feasibility option for patients with pancreatic carcinoma and close or positive margins, because of its systemic dosing of chemotherapy without interruption. The technique can also be interdigitated safely between chemotherapy cycles because adjuvant SBRT can be delivered in 1 week. Although there is no apparent addition to any survival benefit from chemotherapy alone, adjuvant SBRT appears to improve local control without an adverse effect on patient-reported quality of life. Further prospective trials, including phase 3 trials, will needed to be performed to allow for the implementation of this technique at other institutions.

References

1. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): A multicentre, open-label, randomised, phase 3 trial. *Lancet (London, England)*. 2017;389:1011-1024.
2. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: A randomized controlled trial. *JAMA*. 2007;297:267-277.
3. Rwigema JC, Heron DE, Parikh SD, et al. Adjuvant stereotactic body radiotherapy for resected pancreatic adenocarcinoma with close or positive margins. *J Gastrointest Cancer*. 2012;43:70-76.
4. Garcea G, Dennison AR, Pattenden CJ, et al. Survival following curative resection for pancreatic ductal adenocarcinoma. A systematic review of the literature. *JOP*. 2008;9:99-132.
5. Swartz MJ, Hsu CC, Pawlik TM, et al. Adjuvant chemoradiotherapy after pancreatic resection for invasive carcinoma associated with intraductal papillary mucinous neoplasm of the pancreas. *Int J Radiat Oncol Biol Phys*. 2010;76:839-844.
6. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: Results of a large, prospectively collected database at the Johns Hopkins Hospital. *J Clin Oncol*. 2008;26:3503-3510.
7. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004;350:1200-1210.
8. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg*. 1985;120:899-903.
9. Regine WF, Winter KA, Abrams R, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. *Ann Surg Oncol*. 2011;18:1319-1326.
10. Herman JM, Chang DT, Goodman KA, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. *Cancer*. 2015;121:1128-1137.
11. Quan K, Sutera P, Xu K, et al. Results of a prospective phase 2 clinical trial of induction gemcitabine/capecitabine followed by stereotactic ablative radiation therapy in borderline resectable or locally advanced pancreatic adenocarcinoma. *Pract Radiat Oncol*. 2018;8:95-106.
12. Sutera PA, Bernard ME, Gill BS, et al. One- vs. three-fraction pancreatic stereotactic body radiation therapy for pancreatic carcinoma: Single institution retrospective review. *Front Oncol*. 2017;7:272.
13. Yamada S, Fujii T, Hirakawa A, et al. Lymph node ratio as parameter of regional lymph node involvement in pancreatic cancer. *Langenbecks Arch Surg*. 2016;401:1143-1152.
14. Isaji S, Kawarada Y, Uemoto S. Classification of pancreatic cancer: Comparison of Japanese and UICC classifications. *Pancreas*. 2004;28:231-234.
15. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17:343-346.
16. Evans DB, Hess KR, Pisters PW. ESPAC-1 trial of adjuvant therapy for resectable adenocarcinoma of the pancreas. *Ann Surg*. 2002;236:694. author reply -6.
17. de Geus SW, Bliss LA, Eskander MF, et al. A Tale of two cities: Reconsidering adjuvant radiation in pancreatic cancer care. *J Gastrointest Surg*. 2016;20:85-92. discussion.
18. Morganti AG, Falconi M, van Stiphout RG, et al. Multi-institutional pooled analysis on adjuvant chemoradiation in pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2014;90:911-917.
19. Konstantinidis IT, Warshaw AL, Allen JN, et al. Pancreatic ductal adenocarcinoma: Is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a "true" R0 resection? *Ann Surg*. 2013;257:731-736.
20. Delpero JR, Bachellier P, Regenet N, et al. Pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: A French multicentre prospective evaluation of resection margins in 150 evaluable specimens. *HPB (Oxford)*. 2014;16:20-33.
21. Gnerlich JL, Luka SR, Deshpande AD, et al. Microscopic margins and patterns of treatment failure in resected pancreatic adenocarcinoma. *Arch Surg*. 2012;147:753-760.
22. Suss NR, Talamonti MS, Bryan DS, et al. Does adjuvant radiation provide any survival benefit after an R1 resections for pancreatic cancer? *Surgery*. 2018;163:1047-1052.
23. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: A randomized controlled trial. *JAMA*. 2008;299:1019-1026.
24. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: Phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg*. 1999;230:776-782. discussion 82-84.