Patterns of Failure After Adjuvant Stereotactic Body Radiation Therapy for Pancreatic Cancer With Close or Positive Margins

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Received 4 March 2020; revised 31 July 2020; accepted 19 August 2020

Abstract

Purpose: There is no consensus on treatment volumes for adjuvant stereotactic body radiation therapy (SBRT) for pancreatic cancer. Herein, we report patterns of failure after pancreatic SBRT for close/positive margins, which may inform target volume design.

Methods and Materials: An institutional review board-approved retrospective review of patients with pancreatic adenocarcinoma treated with adjuvant SBRT for close/positive margins from 2009 to 2018 was conducted. Patterns of failure were defined as local (LF) within the tumor bed, regional (RF) within lymph nodes or anastomoses, or distant (DF). The cumulative incidence of locoregional failure was calculated using the cumulative incidence function accounting for the competing risk of death. LFs were mapped to the planning target volume (PTV) and classified as in-field (completely within the PTV), marginal (partially within the PTV), or out-of-field (completely outside the PTV). The location of LFs was compared with the Radiation Therapy Oncology Group 0848 contouring atlas to determine whether standard postoperative radiation therapy volumes would have included the LF.

Results: Seventy-six patients were treated with adjuvant SBRT for close (51.3%) or positive (48.7%) margins. Most (81.6%) received 36 Gy in 3 fractions, with a median PTV volume of 17.8 cc (interquartile range, 12.1-25.6). With a median follow-up of 17.0 months (interquartile range, 7.3-28.4), crude rates of first isolated LF, isolated RF, and DF +/− LF or RF were 9.2%, 6.6%, and 56.6%, respectively. Two-year cumulative incidences of LF, RF, locoregional failure, and DF were 34.9%, 30.8%, 49.2%, and 60.4%, respectively. Of 28 reviewable LFs, 21.4% were in-field while the remainder were completely outside (60.7%) or partially outside (17.9%) the PTV. Most LFs (92.9%) would have been encompassed by the Radiation Therapy Oncology Group consensus target volumes.

Conclusions: After adjuvant pancreatic SBRT for close/positive margins, the majority of LFs were outside the PTV but within contemporary target volumes for conventional radiation therapy.

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Introduction

Pancreatic cancer is a highly lethal malignancy, responsible for the fourth-highest cancer death rate in the United States. Despite advances in management, 5-year overall survival (OS) remains dismal at 9%. Resection remains the most important curative modality; however, 80% to 85% of patients are unresectable at presentation. Of resectable patients, 20% to 30% have positive margins (R1) and fare worse than patients with negative margins (R0), even with adjuvant chemotherapy. Adjuvant radiation therapy (RT) may thus have a role after R1 resection and for other high-risk patients; however, studies examining adjuvant RT have produced conflicting results. The role of adjuvant RT is currently being examined in Radiation Therapy Oncology Group (RTOG) 0848.

One concern with adjuvant conventionally fractionated RT is the delay to initiating systemic chemotherapy, owing to time needed to deliver RT over 5 to 6 weeks as well as potential interruptions in treatment from treatment-induced toxicities. Micrometastatic spread before adjuvant chemotherapy may offset any locoregional control benefits with adjuvant RT. For these reasons, adjuvant stereotactic body radiation therapy (SBRT) delivered over a few fractions may be an attractive option for select patients. Definitive pancreatic SBRT provides local control rates of 70% to 80%. Adjuvant pancreatic SBRT provides similar local control with mild toxicities, though the body of evidence for adjuvant SBRT is limited. A previous report of a prospective trial from our institution involving 50 patients who received adjuvant pancreatic SBRT for close/positive margins showed 2-year local and regional control of 77% and 73%, respectively. Acute grade 3+ toxicity was 4.1%, and no late grade 3+ toxicity or changes in patient-reported quality of life were evident.

Although SBRT may provide some advantages over conventionally fractionated RT, 1 disadvantage to SBRT is the size limit on treatment volumes. Dose constraints of adjacent organs, chiefly the duodenum, limit the ability to dose-escalate in this region. Thus, SBRT target volumes are often limited to areas of highest risk of recurrence (ie, the positive margin or critical vascular interfaces); coverage of regional lymph nodes (LNs) and other areas at risk for harboring microscopic disease are usually omitted. Furthermore, although guidelines exist to standardize treatment volumes with adjuvant conventionally fractionated RT, no such consensus has been reached for pancreatic SBRT volumes. Contouring guidelines for postoperative conventionally fractionated RT were developed based on studies examining patterns of failure (POF), and recommend inclusion of surgical anastomoses and regional LNs (Table 1). Limited treatment volumes with SBRT that omit areas adjacent to the tumor or tumor bed may not be adequate in preventing adjacent local or regional recurrences.

Few studies have reported POF after pancreatic SBRT to inform appropriate treatment volumes. No studies, to our knowledge, have examined failure locations relative to treatment volumes after adjuvant pancreatic SBRT. Herein we report POF in patients treated with adjuvant pancreatic SBRT for close/positive margins.

Methods and Materials

Eligibility

An institutional review board-approved retrospective review of consecutive patients treated between October 2009-February 2018 with adjuvant pancreatic SBRT for close/positive margins was conducted. During this time, many patients were treated in a prospective observational trial at our institution, results of which have been previously reported. Patients in this trial were included in this retrospective review if they met inclusion criteria. Demographic, clinical, pathologic, and treatment details were collected. Included patients had resectable or borderline resectable pancreatic adenocarcinoma and were treated with resection and adjuvant pancreatic SBRT for close/positive margins. Resectability definitions were based on National Comprehensive Cancer Network guidelines available at the time of treatment. Generally, resectable patients had no arterial tumor contact and/or ≤180° venous tumor contact without vein contour irregularity, while borderline resectable patients had arterial tumor contact ≤180° and/or venous tumor contact >180° or ≤180° with contour irregularity that was amenable to vein reconstruction. Patients underwent pancreaticoduodenectomy or distal pancreatectomies for pancreatic tail tumors ± robotic assistance. Positive surgical margins included viable tumor cells present at any resection margin. Close margins included viable tumor cells present within 2 mm of any resection margin. Patients received adjuvant or neoadjuvant chemotherapy or both per physician discretion and patient tolerance. Experimental systemic therapy was allowed in institutional protocols based on eligibility and patient/physician preference.

Stereotactic body radiation therapy

Patients were simulated supine with arms raised and vacuum lock bag immobilization. Axial computed tomography (CT) images with 1.25 mm slice thickness were obtained. Intravenous and/or enteral contrast was administered per physician discretion. Four-dimensional CT data were acquired to evaluate target motion. The clinical target volume (CTV) was delineated in
Endpoints and statistical analysis

Clinical notes and radiologic images/reports were reviewed to capture recurrences. For patterns of failure analysis, failures were classified as local (LF), regional (RF), locoregional (LRF), or distant (DF) as deemed by the reading radiologist and/or treating physician in radiology reports and/or clinical notes. LFs were recurrences within the operative bed. RFs were recurrences within the regional LNs (new or enlarging LNs) or anastomosis. LRFs were defined as local and/or regional failures. DFs were recurrences in nonregional LNs or distant organs. The date of recurrence was backdated to the initial imaging study demonstrating any radiographic evidence of progression. Both the site of first failure and the cumulative incidence of all failure types were collected. All patients were evaluated for LF and RF from SBRT completion to death or loss of follow-up, regardless of progression at other sites.

SBRT treatment plans were accessed to map LFs relative to the PTV. In-field LFs were LFs completely within the PTV. Marginal failures were LFs partially within the PTV, and out-of-field were LFs completely outside the PTV. The location of LFs and RFs was compared with the RTOG 0848 consensus volumes for postoperative treatment of pancreatic cancer\(^2\) to determine whether consensus volumes for conventionally fractionated postoperative RT would have included the LF or RF. Recommended contours of each region of interest and CTV expansions were considered when determining whether an LF/RF would have been encompassed by the RTOG consensus volumes (Table 1). To successfully map LFs and RFs relative to the PTV and the RTOG consensus volumes, the location of each failure relative to the preoperative tumor location and measured distances between the edge of failures and prominent abdominal anatomy (eg, celiac artery [CA], superior mesenteric artery [SMA], portal vein, anastomoses) were recorded and compared with the location and measured distances of the PTV volumes and RTOG consensus volumes relative to the same anatomic landmarks. Patients without available SBRT plans or imaging evidence of LF/RF were excluded from analysis of failure location.

Crude failure rates were calculated from the number of each failure type within the cohort. Time-to-event analysis was calculated from the date of SBRT completion to the date of the event. OS was calculated using Kaplan-Meier methods. The cumulative incidence function was used to calculate the cumulative incidence of LF, in-field LF, marginal LF, out-of-field LF, RF, LRF, and DF +/− LF or RF from the last day of SBRT treatment to the date of failure, accounting for the competing risk of death.\(^31-33\) Differences in time to LF by type of LF were analyzed with the log-rank test. Cox proportional hazards regression was used to test the effect of demographic, clinical, pathologic, and SBRT treatment details on the risk of LF and in-field LF. Log-minus-log plots were used to confirm the proportional hazards assumption. As a sensitivity analysis, continuous variables were also tested as binary categorical variables stratified by the median value. Variables with \(P\) values < .10 on univariate analysis were entered into the multivariate model, which was run with backward stepwise selection. \(P\) values < .05 were considered statistically significant. Statistical analysis was conducted with Statistical Package for the Social Sciences (SPSS) Statistics for Windows version 25.0 (SPSS Inc, Chicago, IL) and R version 3.6.2.\(^34\)

Results

Seventy-six patients were treated with adjuvant SBRT for close/positive margins. Table 2 outlines cohort characteristics. Most patients (56.6%) were male and had pancreatic head tumors (80.3%). Most (59.2%) received neoadjuvant chemotherapy, most commonly gemcitabine/nab-paclitaxel (48.9%). The majority (81.6%) received adjuvant chemotherapy, most commonly gemcitabine (41.9%).

Three-quarters of patients were resectable and 25.0% were borderline resectable. Most patients (86.8%) underwent pancreaticoduodenectomy. Close margins were seen in 51.3%; positive margins were seen in 48.7%. The most common positive/close margin was retroperitoneal (52.6%). Twenty patients (26.3%) had multiple positive/close margins. More than 3/4 (77.6%) had pathologic T2 disease. Pathologic nodal staging was variable: pN0, pN1, and pN2 was seen in 26.3%, 39.5%, and 34.2%, respectively.

Adjuvant SBRT was delivered a median 2.2 months after surgery (interquartile range [IQR], 1.7-3.0). Most patients (81.6%) received 36 Gy in 3 fractions. Median PTV was 17.8 cc (IQR, 12.1-25.6). Median equivalent
Table 1  Radiation Therapy Oncology Group consensus treatment volumes for conventionally fractionated postoperative pancreatic radiation therapy.  

| Region of interest            | RTOG* recommendations for volume delineation                                                                 | Expansions for CTV                     |
|-------------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Postoperative bed             | Based on preoperative tumor location and pathology reports; include surgical clips.                               | ±0.5-1.0 cm                            |
| Anastomoses                   | Pancreaticojejunostomy (PJ), choledochojejunosomy, or hepaticojejunostomy. Do not include pancreaticogastrostomy if present. | 0.5-1.0 cm                             |
| Abdominal nodal regions       |                                                                                                                |                                        |
| Celiac artery (CA)            | Most proximal 1.0-1.5 cm                                                                                      | 1.0-1.5 cm                             |
| Superior mesenteric artery (SMA) | Most proximal 2.5-3.0 cm (includes peripancreatic nodes)                                                      | 1.0-1.5 cm                             |
| Porta hepatic                 | Portal vein (PV) segment that runs anterior and anteromedial to the inferior vena cava.                        | 1.0-1.5 cm                             |
| Para-aortic                   | Aorta from most cephalad aspect of CA, PJ, or PV (whichever is most cephalad), to bottom of L2; cover to bottom of L3 if needed to encompass extent of preoperative tumor. | 2.5-3.0 cm to the right, 1.0 cm to the left, 2.0-2.5 cm anteriorly, and 0.2 cm posteriorly toward the anterior edge of the vertebral body. |

Abbreviations: CTV = clinical target volume; RTOG = Radiation Therapy Oncology Group (RTOG).

dose in 2-Gray-per-fraction using alpha:beta = 10 and biologically effective dose using alpha:beta = 10 was 66.0 Gy (IQR, 66.0-66.0) and 79.2 Gy (IQR, 79.2-79.2), respectively. No patient had a significant interruption during SBRT; the median time elapsed during the SBRT course was 6.0 days (IQR, 5.0-7.0).

Median follow-up after SBRT completion was 17.0 months (IQR, 7.3-28.4). Median OS was 17.3 months (95% confidence interval, 11.0-23.5 months). Fifty-seven patients (75.0%) experienced a recurrence at any site during follow-up. Table 3 outlines POF. Upon examination of sites of first failure, isolated DF was predominant (30.2%, n = 23). LF was a component of first failure in 23 patients. Crude rates of isolated LF, isolated RF, and DF +/− RF or LF at first failure were 9.2%, 6.6%, and 56.6%, respectively. A total of 32 (42.1%), 24 (31.6%), 42 (55.3%), and 50 patients (65.8%) developed a LF, RF, LRF, or DF, respectively, during follow-up. Upon examination of LF or RF, 18 patients (23.7%) had an LF ± DF but without RF, 10 patients (13.2%) had an RF ± DF but without LF, and 14 patients (18.4%) had both LF and RF ± DF. The 2-year cumulative incidence of LF, RF, LRF, or DF, accounting for the competing risk of death, was 34.9%, 30.8%, 49.2%, and 60.4%, respectively (Fig 1). Univariate Cox regression did not reveal any statistically significant predictors of LF (Table 4), although a trend was seen for positive pancreatic neck margin (P = .056).

Of 32 patients with an LF during follow-up, 3 patients had unavailable imaging of the LF, and 1 patient had an unavailable SBRT plan. Thus, 28 of 32 patients (87.5%) were analyzed for POF relative to treatment volumes. Only 21.4% (n = 6) of LFs were in-field; the remaining were out-of-field (60.7%, n = 17) or marginal (17.9%, n = 5). The 2-year cumulative incidence of in-field, marginal, and out-of-field LFs was 7.3%, 5.8%, and 17.9%, respectively. There were no differences in time to LF based on type of LF: median time to failure for in-field, marginal, and out-of-field LFs was 5.0, 6.0, and 11.8 months, respectively (P = .477). All 6 patients with an in-field LF received 36 Gy in 3 fractions and had larger CTV (median, 15.2 cc; IQR, 12.4-16.7) and PTV (median, 27.5 cc; IQR, 22.0-33.9) volumes relative to the entire cohort. However, no variables correlated with risk of in-field LF (Table 4).

Because RTOG consensus volumes cover areas at risk for LF and RF, every LF (n = 28) and RF (n = 24) with available imaging was examined to assess its location relative to recommended RTOG consensus volumes. Most LFs (92.9%, n = 26) would have been encompassed by the RTOG consensus volumes for postoperative conventional RT. Two LFs (7.1%) were deemed to be outside RTOG consensus volumes. Both were infiltrative masses that spread along and cuffed the distal SMA >5 cm beyond the SMA origin from the aorta, and thus outside the caudal extent of the recommended SMA target volume.

Upon examination of RFs, 62.5% (n = 15) would have been encompassed by RTOG consensus volumes. Of 9 RFs deemed to be outside RTOG consensus volumes, 5 were in high para-aortic or gastrohepatic LNs located ≥1 cm above the recommended cephalad border of the para-aortic LN target volume, 2 were in para-aortic LNs below the recommended caudal extent of the para-aortic LN volume, and 2 were in mesenteric LNs in the
anterior or lower abdomen along the distal SMA, beyond the recommended SMA nodal target volume. The 2-year cumulative incidence of LRF within RTOG consensus volumes was 39.3%.

**Discussion**

In this single-institution retrospective analysis of adjuvant pancreatic SBRT for close/positive margins, we identified a high rate of LRF outside the SBRT PTV but within contemporary RT target volumes. Although the predominant POF at first failure was isolated DF (30.2%), 42.1% of patients developed an LF during follow-up. The 2-year cumulative incidence of LF was 34.9%. Thus, despite macroscopic resection, targeted RT, and systemic therapy, patients with close/positive margins were at substantial risk for developing an LF. LFs within the PTV were infrequent (6 of 28 patients); the 2-year cumulative incidence of in-field LFs was 7.3%. Most LFs were completely outside the PTV (60.7%). Over 90% of LFs would have been encompassed by RTOG consensus volumes for postoperative conventionally fractionated RT.

This study is the first, to our knowledge, that describes POF after adjuvant SBRT. Published studies examining POF with pancreatic SBRT are limited to patients treated in the definitive or neoadjuvant setting, and few studies have detailed examination of failures relative to treatment volumes or abdominal vasculature. A Chinese study of >500 medically inoperable patients treated with pancreatic SBRT revealed that most LFs occurred near the CA, SMA, or splenic artery for pancreatic tail tumors; 80% and 95% of failures near the CA or SMA occurred within 11 and 13 mm of the vessel, respectively. These failures likely would have been included within the consensus postoperative target volumes for conventionally fractionated RT. In-field failures (>80% of volume...
within the prescription isodose) occurred in 22.9%; this number mirrors the in-field failure rate in this study of 21.4%. The distance from primary tumors to retroperitoneal recurrences was larger than the distance from primary tumors to the CA (11.7 vs 9.0 mm, respectively), suggesting that asymmetrical expansion of SBRT target volumes to include the local retroperitoneal space may be warranted. Kharofa et al\textsuperscript{30} reported POF in 18 resectable or borderline resectable patients treated with neoadjuvant pancreatic SBRT (33 Gy in 5 fractions) to the tumor and entire circumference of the abutting vessel. After interim analysis showed 2 of 8 patients failed locally at the vessel at the PTV margin, the remaining patients received 25 Gy in 5 fractions simultaneously to an additional PTV covering the entire pancreatic head/body, with extension of vessel coverage to the CA origin and SMA. With the limitations of a small sample size, the combined PTV approach led to longer 1-year PFS (60% vs 25%; $P = .03$), 2-year OS (67% vs 25%; $P = .03$), and lower 1-year cumulative incidence of LF (38% vs 70%; $P = .45$), raising the question of whether elective coverage of vessel origins with SBRT reduces the risk of failures at the margin of the primary PTV.

There are no consensus pancreatic SBRT volumes. Results from our study support consideration for expanding treatment volumes if feasible. Indeed, initial results from our institutional prospective trial of adjuvant pancreatic SBRT for close/positive margins found CTV volume was the only predictor for freedom from LF on multivariate analysis (hazard ratio, 1.095; 95% confidence interval, 1.005-1.193; $P = .038$).\textsuperscript{25} However, the tradeoff between expanding target volumes and irradiating more normal tissue must be carefully evaluated. A study by Dholakia et al\textsuperscript{36} generated hypothetical adjuvant intensity modulated radiation therapy and SBRT volumes encompassing the majority of LFs in >200 patients after pancreaticoduodenectomy. CTV volumes encompassed either 90% of LFs (CTV90) or 80% of LFs (CTV80) based on specific asymmetrical expansions around CA and SMA contours. With no further margins for setup error, PTV80 and PTV90 volumes ranged from 123.0 to 139.6 cc and 183.2 to 215.7 cc, respectively. These volumes are significantly larger than those in our study but may represent a practical strategy to expand treatment volumes while minimizing irradiation of normal tissue. Although the authors report critical structure dose constraints were met with 25 Gy in 5 fractions to the PTV90 with a simultaneous integrated boost to 33 Gy to PTV80, no patients were actually treated using the hypothetical plans.

The aforementioned studies highlight the commonality of LFs along vessels after SBRT and underline the importance of detailed POF examinations. Studies reporting LFs after pancreatic SBRT use different LF definitions, which may inadvertently include nodal failures — the Chinese and Dholakia studies defined LFs as

| Location of failure based on clinical documentation (n = 76) | Crude rates | Cumulative incidence (95% CI) |
|---|---|---|
| No failure | 19 (25.0) | 17.2% (9.7-26.5) | 29.3% (19.5-39.8) | 34.9% (24.3-45.8) |
| Local failure | 32 (42.1) | 26.3% (17.0-36.6) | 40.8% (29.7-51.5) | 49.2% (37.4-59.9) |
| Regional failure | 24 (31.6) | 26.3% (17.0-36.6) | 40.8% (29.7-51.5) | 49.2% (37.4-59.9) |
| Locoregional | 42 (55.3) | 33.1% (22.7-43.4) | 50.5% (38.7-61.2) | 60.4% (48.2-70.5) |

| Location of local failure in patients with available plans and imaging (n = 28) | | |
|---|---|---|
| In-field | 6 (21.4) | 4.2% (1.1-10.8) | 5.7% (1.8-12.9) | 7.3% (2.7-15.2) |
| Marginal | 5 (17.9) | 2.9% (0.1-8.9) | 5.8% (1.9-13.2) | 5.8% (1.9-13.2) |
| Out-of-field | 17 (60.7) | 8.0% (3.3-15.6) | 14.8% (7.8-23.9) | 17.9% (10.1-27.6) |

Abbreviations: CI = confidence interval; SBRT = stereotactic body radiation therapy.

Figure 1 Cumulative incidence of local failure (LF), regional failure (RF), and distant failure (DF).
failures in between the diaphragm and bottom of L3, while Kharofa et al considered LFs as failures within the SBRT volume or within institutional fractionated volumes that electively covered the regional vasculature. In our analysis, because no elective nodal volumes were treated, we constrained the definition of LF to failures within the operative bed based on preoperative tumor location to minimize inclusion of nodal failures. Despite this constrained definition, LFs were identified in 42.1% of patients after SBRT targeted to close/positive margins. Thus, true LFs occur in a significant proportion of patients, despite SBRT targeting the areas of highest risk of recurrence. Of 72 patients with available imaging and SBRT plans, only 6 (8.3%) experienced an LF within the treatment volume; the majority of LFs were outside or marginal to the treatment volume. This suggests issues

### Table 4

| Variable                                      | HR for LF (95% CI) | P value | HR for in-field LF (95% CI) | P value |
|-----------------------------------------------|--------------------|---------|----------------------------|---------|
| Age at diagnosis                              | 1.00 (0.96-1.03)   | .769    | 1.06 (0.96-1.17)            | .259    |
| Sex                                           | Male Reference     | .565    | Female 0.81 (0.40-1.66)     | .88 (0.38-9.42) |
| Tumor location                                | Body Reference .999|         | Head 1.05 (0.36-3.04)       | 0.33 (0.06-1.81) |
|                                              | Tail 1.44 (0.16-13.04) |       | UNCINATE PROCESS 1.05 (0.19-5.80) | NR |
|                                              | Neck NR NR         |         |                            |         |
| Resectability                                 | .127               |         | Reference 1.83 (0.84-3.96)  | 1.17 (0.21-6.60) |
| Surgery type                                   | Pancreaticoduodenectomy Reference | .600 | Distal pancreatectomy 1.27 (0.52-3.10) | 1.79 (0.33-9.82) |
| Margin status                                 | Positive Reference .862 |       | Close (1 mm) 0.87 (0.42-1.78) | 0.87 (0.14-5.29) |
|                                              | Close (2 mm) 0.62 (0.08-4.79) |       | Retroperitoneal margin Negative Reference 1.48 (0.73-3.03) | 1.89 (0.34-10.51) |
|                                              | Negative Reference | .279 | Vascular groove margin Reference 1.48 (0.73-3.03) | 1.89 (0.34-10.51) |
|                                              | Positive/close 0.66 (0.32-1.35) | .256 | Pancreatic neck margin Reference 1.48 (0.73-3.03) | 1.89 (0.34-10.51) |
|                                              | Negative Reference | .565 | Positive/close 0.66 (0.32-1.35) | 0.73 (0.13-4.02) |
| Pancreatic neck margin                        | Negative Reference | .565 | Positive/close 0.66 (0.32-1.35) | 0.73 (0.13-4.02) |
| Pathologic tumor size (cm)                    | 1.10 (0.82-1.46)   | .538    | 0.39 (0.11-1.43)            | .155    |
| Neoadjuvant chemotherapy                      | .624               | .390    |                            |         |
|                                              | No Reference       | .84 (0.42-1.70) | Yes 2.30 (0.98-5.42) | 0.81 (0.09-7.08) |
| Adjuvant chemotherapy                         | No Reference       | .84 (0.42-1.70) | Yes 2.30 (0.98-5.42) | 0.81 (0.09-7.08) |
|                                              | Yes Reference      | 2.25 (0.68-7.42) | NR 2.57 (0.30-22.07) | .183    |
| CTV volume (cc)                               | 1.02 (0.98-1.05)   | .414    | 1.01 (0.98-1.04)            | .414    |
| PTV volume (cc)                               | 1.01 (0.98-1.04)   | .414    | 1.01 (0.97-1.05)            | .565    |
| PTV V100% (%)                                 | 1.00 (0.96-1.06)   | .760    | 1.00 (0.96-1.06)            | .760    |
| BED10                                         | 1.01 (0.95-1.07)   | .760    | 1.01 (0.95-1.07)            | .760    |
| EQD210                                        | .818               |         |                            |         |

Abbreviations: BED10 = biologically effective dose using an alpha/beta ratio of 10; CI = confidence interval; CTV = clinical target volume; EQD210 = equivalent dose in 2 Gray per fraction using an alpha/beta ratio of 10; HR = hazard ratio; LF = local failure; NR = not reportable; PTV = planning target volume; PTV V100% = percent of PTV that received 100% of the prescription dose.
with volume and not dose, and thus expanding treatment volumes to include all portions of the pancreas/pancreatic bed and abutting vasculature may be warranted. Because RTOG consensus volumes encompassed most LFs as well as RFs in this study, adopting a similar philosophy with SBRT treatment volumes may be warranted if feasible.

We note several limitations of this study, including its retrospective nature, relatively small sample size, and the subjective nature of mapping LFs and RFs to PTV volumes and RTOG consensus volumes. The latter issue was mitigated by systematically noting the location and distance of failures relative to abdominal vasculature, which allowed for more precise mapping.

**Conclusions**

In patients with resectable or borderline resectable adenocarcinoma of the pancreas who received adjuvant SBRT for close or positive margins, the majority of LFs occurred outside the PTV. Future trials involving adjuvant SBRT or hypofractionated RT should consider expansion of treatment volumes if feasible.

**References**

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.
2. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. Lancet. 2004;363:1049-1057.
3. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med. 2014;371:1039-1049.
4. Konstantinidis IT, Warshaw AL, Allen JN, et al. Pancreatic ductal adenocarcinoma. Ann Surg. 2013;257:731-736.
5. 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.
6. Delpero JR, Bacheller P, Regenet N, et al. Pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: A French multicentre prospective evaluation of resection margins in 150 evaluable specimens. HPB. 2014;16:20-33.
7. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capcitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): A multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389:1011-1024.
8. Stocken DD, Bù Chler MW, Dervenis C, et al. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. Br J Cancer. 2005;92:1372-1381.
9. 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.
10. Parikh AA, Maiga A, Bentrem D, et al. Adjuvant therapy in pancreatic cancer: Does it influence patterns of recurrence? J Am Coll Surg. 2016;222:448-456.
11. Ghaneh P, Kleeff J, Halloran CM, et al. The impact of positive resection margins on survival and recurrence following resection and adjuvant chemotherapy for pancreatic ductal adenocarcinoma. Ann Surg. 2019;269:520-529.
12. Morganti AG, Falconi M, Van Stiphout RGPM, et al. Multi-institutional pooled analysis on adjuvant chemoradiation in pancreatic cancer. Int J Radiat Oncol Biol Phys. 2014;90:911-917.
13. Smeenk HG, Van Eijck CHJ, Hop WC, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: Long-term results of EORTC trial 40891. Ann Surg. 2007;246:734-740.
14. Kaiser MH, Ellenberg SS. Pancreatic cancer: Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg. 1985;120:899-903.
15. 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.
16. Tesfaye AA, Philip PA. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Gastrointestinal Tumor Study Group. Cancer. 1987;59:2006-2010.
17. Van Laethem JL, Hammel P, Momex F, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: A randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. J Clin Oncol. 2010;28:4450-4456.
18. Schmidt J, Abel U, Debus J, et al. Open-label, multicenter, randomized phase III trial of adjuvant chemoradiation plus interferon-alfa-2b versus fluorouracil and folinic acid for patients with resected pancreatic adenocarcinoma. J Clin Oncol. 2012;30:4077-4083.
19. Kooby DA, Gillespie TW, Liu Y, et al. Impact of adjuvant radiotherapy on survival after pancreatic cancer resection: An appraisal of data from the national cancer data base. Ann Surg Oncol. 2013;20:3634-3642.
20. Shinde A, Verma V, Li R, et al. The role of sequential radiation following adjuvant chemotherapy in resected pancreatic cancer. J Gastrointest Oncol. 2019;10:462-473.
21. Gemcitabine hydrochloride with or without erlotinib hydrochloride followed by the same chemotherapy regimen with or without radiation therapy and capecitabine or fluorouracil in treating patients with pancreatic cancer that has been removed by surgery. Available at: https://clinicaltrials.gov/ct2/show/NCT01013649. Accessed January 9, 2020.
22. Chuong MD, Springett GM, Frellich JM, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. Int J Radiat Oncol Biol Phys. 2013;86:516-522.
23. Mahadevan A, Jain S, Goldstein M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2010;78:735-742.
24. Herman JM, Chang DT, Goodman KA, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiation therapy after resection of pancreatic adenocarcinoma. Cancer. 2015;121:1128-1137.
25. Bernard ME, Sutera PA, Iarrobino NA, et al. Initial results of a prospective study of adjuvant pancreatic stereotactic body radiation therapy for close or positive margins. Adv Radiat Oncol. 2019;4:294-301.
26. Rwigema J-CM, Parikh SD, Heron DE, et al. Stereotactic body radiotherapy in the treatment of advanced adenocarcinoma of the pancreas. Am J Clin Oncol. 2011;34:63-69.
27. Rwigema JCM, Heron DE, Parikh SD, et al. Adjuvant stereotactic body radiotherapy for resected pancreatic adenocarcinoma with close or positive margins. J Gastro Cancer. 2012;43:70-76.
28. Goodman KA, Regine WF, Dawson LA, et al. Radiation Therapy Oncology Group consensus panel guidelines for the delineation of the clinical target volume in the postoperative treatment of pancreatic head cancer. Int J Radiat Oncol. 2012;83:901-908.
29. Zhu X, Ju X, Cao Y, et al. Patterns of local failure after stereotactic body radiation therapy and sequential chemotherapy as initial
treatment for pancreatic cancer: Implications of target volume design. *Int J Radiat Oncol Biol Phys* 2019;104:101-110.

30. Kharofa J, Mierzwa ML, Olowokure OO, et al. Pattern of marginal local failure in a phase II trial of neoadjuvant chemotherapy and stereotactic body radiation therapy for resectable and borderline resectable pancreas cancer. *Am J Clin Oncol* 2019;42:247-252, 482-482.

31. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016;133:601-609.

32. Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: An easy guide for clinicians. *Bone Marrow Transplant* 2007;40:381-387.

33. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res* 2007;13:559-565.

34. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2019.

35. Baine MJ, Sleightholm R, Lin C. Incidence and patterns of locoregional failure after stereotactic body radiation therapy for pancreatic adenocarcinoma. *Pract Radiat Oncol* 2019;9:e29-e37.

36. Dholakia AS, Kumar R, Raman SP, et al. Mapping patterns of local recurrence after pancreaticoduodenectomy for pancreatic adenocarcinoma: A new approach to adjuvant radiation field design. *Int J Radiat Oncol Biol Phys* 2013;87:1007-1015.