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ORIGINAL ARTICLE

Stereotactic body radiation vs. intensity-modulated radiation for unresectable pancreatic cancer

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ABSTRACT

Background: Stereotactic body radiation therapy (SBRT) is an emerging treatment option for unresectable pancreatic cancer, and is postulated to be more effective and less toxic than conventionally fractionated intensity modulated radiation therapy (IMRT).

Material and methods: We retrospectively reviewed unresectable stage I–III pancreatic adenocarcinoma treated from 2008 to 2016 at our institution with SBRT (five fractions, 30–33 Gy) or IMRT (25–28 fractions, 45–56 Gy with concurrent chemotherapy). Groups were compared with respect to overall survival (OS), local and distant failure, and toxicity. Log-rank test and Cox proportional hazards regression model, and competing risks methods were used for univariate and multivariate analysis.

Results: SBRT patients ($n = 44$) were older than IMRT ($n = 226$) patients; otherwise there was no significant difference in baseline characteristics. There was no significant difference in OS or local or distant failure. There was no significant difference in rates of subsequent resection (IMRT =17%, SBRT =7%, $p = .11$). IMRT was associated with more acute grade 2+ gastrointestinal toxicity, grade 2+ fatigue, and grade 3+ hematologic toxicity ($p = .008$, $p < .0001$, $p = .001$, respectively).

Conclusions: In this analysis, SBRT achieves similar disease control outcomes as IMRT, with less acute toxicity. This suggests SBRT is an attractive technique for pancreatic radiotherapy because of improved convenience and tolerability with equivalent efficacy. However, the lack of observed advantages in disease control with this moderate-dose SBRT regimen may suggest a role for increasing SBRT dose, if this can be accomplished without significant increase in toxicity.

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Introduction

Pancreatic adenocarcinoma remains a devastating disease with an extremely poor prognosis, and it is the third leading cause of cancer death in the United States [1]. The five-year overall survival (OS) rate is around 7%, and prognoses vary depending on whether the cancer is localized (27% five-year OS), regional (11% five-year OS), or distant (2% five-year OS) [1]. Improving local control and preventing tumor dissemination may improve prognosis. Surgical resection remains the only established curative option, but is limited to patients with resectable or borderline resectable tumors [2]. Locally advanced or unresectable pancreatic cancer is the most common stage at presentation and when treated with radiation, conventionally fractionated courses with concurrent radiosensitizing chemotherapy are typically used [3]. To minimize potential for toxicity to adjacent abdominal viscera, intensity modulated radiation therapy (IMRT) is now commonly used. A typical course of IMRT involves 5–6 weeks of daily treatment, and the potential toxicity and inconvenience of such treatment is not insignificant given the limited prognosis of these patients. Furthermore, the recently published LAP07 trial failed to demonstrate a survival impact using standard doses of radiotherapy, though IMRT was not employed [4].

Stereotactic body radiation therapy (SBRT) is an emerging alternative to standard RT for pancreas cancer. It can be delivered using just 3–5 fractions, making it logistically appealing to patients and clinicians [5]. In other settings, SBRT has proven to yield superior local control with relatively low toxicity due to its high effective dose and limited target volumes [6].

Initial experiences with single-dose pancreatic SBRT demonstrated promising local control but unacceptable rates of significant gastrointestinal toxicity [3]. A recent multi-institutional prospective study used a five-fraction regimen in an effort to balance efficacy and toxicity, and reported improved pain scores and quality of life with acceptable toxicity [7]. There has been increased interest in pancreatic SBRT, but data directly comparing the effectiveness of pancreas SBRT with standard chemoradiation is lacking. We therefore aimed to compare outcomes of unresectable pancreatic cancer patients treated with SBRT vs. IMRT plus concurrent chemotherapy at our institution.

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Material and methods

Patients and radiation treatment

The institutional review board approved this study. Patient confidentiality was maintained in accordance with the Health Insurance Portability and Accountability Act. We retrospectively reviewed all patients with the following criteria: (1) diagnosis of pancreatic adenocarcinoma confirmed by central pathologic review. (2) No distant metastases at baseline or after induction chemotherapy. (3) Unresectable disease based on assessment by a surgeon with expertise in pancreatic malignancies, who considered them unresectable either due to tumor extent or medical comorbidies. (4) Treated with SBRT (five fractions, total dose 30–33 Gy) or IMRT (25–28 fractions, total dose 45–56 Gy with concurrent chemotherapy) between 2008 and 2016 at our institution. Patients treated for locally recurrent disease after prior surgery or radiation, were excluded. As per our usual institutional practice, patients were generally first treated with a period of induction chemotherapy prior to being considered for IMRT or SBRT. The decision to treat with IMRT or SBRT was at the discretion of the treating radiation oncologist. There was no institutional guideline in place governing patient selection for SBRT, though there was a bias to use SBRT for older patients.

All patients underwent CT simulation with intravenous and oral contrast (unless contraindicated), with supine positioning and arms above the head in a customized foam cradle. Radiation therapy was delivered using 5–7 co-planar, intensity-modulated beams. For SBRT, patients were treated using abdominal compression, with adequacy of compression ($\leq$3–5mm superior–inferior motion) verified with fluoroscopic visualization of fiducial motion. Each SBRT fraction was delivered using cone-beam imaging and matching on implanted fiducial markers. PTV was defined using a 3–5 mm expansion from GTV, without CTV expansion or elective nodal irradiation. GTV was defined based on contrast-enhanced simulation CT. Most patients also had diagnostic pancreatic CT angiograms which were used to assist in defining the GTV, and where available, PET-CT and MRI images were also used as references. For SBRT, the following normal tissue constraints were used for both the duodenum and stomach (treating each organ separately): V33 Gy $\leq$ 1cc, V20 Gy $\leq$ 3cc, and V15 Gy $\leq$ 9cc.

Intensity modulated radiation therapy patients were either treated using respiratory gating if fiducial markers or a metal stent had been placed, or with an ITV approach if no fiducial markers were available or the patient was otherwise not a candidate for respiratory gating. CTV was generated using an approximately 1 cm expansion from GTV (or ITV), and then was further modified to ensure coverage of the vascular margin and nodal regions around the superior mesenteric artery and celiac axis. The PTV was then generated using a 0.5 cm expansion on CTV. For both IMRT and SBRT patients, dose was prescribed to the 100% isodose line encompassing the PTV, and dose within the PTV was kept as homogeneous as possible. For IMRT, the duodenum maximum point dose was limited to 58 Gy, and the mean dose to the stomach was limited to 30 Gy. The following small bowel constraints were used: V45 Gy $\leq$ 100 cc and V50 Gy $\leq$ 10 cc.

We recorded baseline patient characteristics including age at diagnosis, gender, and Karnofsky performance status (KPS). Tumor and treatment characteristics included TNM stage (using AJCC seventh edition criteria), tumor location (head vs. body/tail/uncinate process), maximum axial tumor dimension on staging CT scans, duration of induction chemotherapy (ICT) prior to RT, and radiographic response to ICT. These patient and treatment characteristics are summarized in Table 1.

Toxicity and clinical outcomes

Patients receiving either form of RT were monitored weekly during radiation therapy for acute toxicity, and again

Table 1. Comparison of patient characteristics between patients treated with SBRT vs. IMRT using Fisher's exact test ($N = 270$).

Characteristics	IMRT ($n = 226$)	SBRT ($n = 44$)	p Value
Age at diagnosis (years), median (range)	65.0 (36.7–88.5)	68.3 (45.1–90.1)	
$\leq$70	160 (71)	24 (55)	.05
>70	66 (29)	20 (45)	
Gender *n* (%)			.87
Male	120 (53)	24 (55)	
Female	106 (47)	20 (45)	
Karnofsky performance status, *n* (%)			.42
<80	22 (10)	6 (14)	
$\geq$80	204 (90)	38 (86)	
Clinical stage, *n* (%)			1.00
I/II	72 (32)	14 (32)	
III	154 (68)	30 (68)	
Tumor location			.61
Head	142 (63)	30 (68)	
Body/tail/uncinate process	84 (37)	14 (32)	
Maximum tumor dimension (cm)' median (range)	3.4 (1.2–8.9)	3.2 (1.2–6.1)	
<3.4	108 (48)	23 (52)	.62
$\geq$3.4	117 (52)	21 (48)	
Duration of induction chemotherapy, (months), median (range)	3.4 (0.2–15.9)	4.1 (0.5–11.7)	
<3.6	117 (52)	18 (43)	.32
$\geq$3.6	108 (48)	24 (57)	
Radiographic response to ICT, *n* (%)			.47
No	150 (67)	31 (74)	
Yes	75 (33)	11 (26)	

IMRT: intensity-modulated radiation therapy; SBRT: stereotactic body radiation therapy; ICT: induction chemotherapy.

4–8 weeks after RT completion. Clinical assessment and imaging then took place every three months thereafter, with the radiation and/or medical oncologist. Toxicity assessments are collected and documented prospectively, using the common terminology criteria for adverse events (CTCAE v4.0) as part of our routine institutional practice. These assessments were then retrospectively reviewed for this analysis. Acute toxicity was defined as occurring within 90 days of the end of RT. Documented acute toxicities included: diarrhea, nausea, fatigue, vomiting, mucositis, dysphagia, heartburn, and dermatitis. Patients were assessed for anemia, neutropenia and thrombocytopenia with weekly blood counts. Instances of radiation-induced sequelae leading to clinically appreciable late toxicities were also recorded by reviewing documentation from post-radiation clinical assessments with oncologists. The assessed categories of late toxicities included: gastric ulcer/gastritis, duodenal/jejunal ulcer, enteritis, colitis, GI bleed, compression fracture, bowel perforation/stenosis, limb edema, and cellulitis.

Response to induction chemotherapy or to RT was assessed using contrast-enhanced abdominal CT. Local failure was defined as radiographic disease progression of the originally radiated pancreatic lesion or involved adjacent nodes. Distant failure was defined as clinical evidence of malignancy beyond the pancreas and regional nodes. If no post-RT imaging was available for review, that patient was included in the analysis of OS and toxicity, but excluded from the analysis of failure patterns.

Statistical analysis

All survival outcome endpoints were calculated from RT end date. For local failure (LF), distant failure (DF), and any failure (LF/DF), death without an event was treated as a competing risk. Gray and Fine–Gray competing risks methods were used for univariate (UVA) and multivariate analysis (MVA), respectively. The Kaplan–Meier method was used to estimate OS. Log-rank test was used for UVA, and Cox proportional hazards regression model was used for MVA for OS. Fisher's exact test was performed to compare patient and clinical characteristics, proportion of patients undergoing post-RT resection, and incidence of acute toxicities between the SBRT and IMRT groups. A $p < 0.05$ was considered significant. The SAS 9.4 (SAS institute Inc., Cary, NC, USA) and R version 3.0.1 package 'cmprsk' were used for statistical analysis.

Results

Patient and treatment characteristics

There were 44 SBRT and 226 IMRT patients who met the inclusion criteria. The SBRT group had a marginally greater proportion of elderly patients (45% > 70 years old) compared to the IMRT group (29%> 70 years old, $p = .05$). Otherwise, the SBRT and IMRT group had comparable gender ratio, KPS, stage, tumor location, maximum tumor dimension, duration of ICT, and response to ICT (Table 1). In the SBRT group, 47.7% received gemcitabine-based ICT, 43.2% received FOLFIRINOX, 4.5% received FOLFOX, and 4.5% had no ICT. In the IMRT group, 52.7% received gemcitabine-based ICT, 44.7% received FOLFIRINOX, 2.2% received FOLFOX, and 0.4% had no ICT. Concurrent chemotherapy for IMRT patients consisted of gemcitabine (51.8%), capecitabine (29.6%), or infusional 5-fluourouracil (14.6%). A single IMRT patient (0.4%) received concurrent flavopiridol and eight IMRT patients (3.5%) did not receive concurrent chemotherapy.

Clinical outcomes

The median follow-up for surviving patients was 12.9 months (1.7–107.6 months). The median OS was 15.7 months (95% CI, 12.8–17.8 months). There was no significant difference in OS between SBRT and IMRT ($p = .75$) (Figure 1). One and two-year OS was 56.2% and 25.7% for SBRT patients vs. 59.6% and 27.2% for IMRT patients. Multivariate analysis showed that response to ICT was independently associated with improved OS ($p = .03$) (Table 2).

The one-and two-year cumulative incidence of LF was 34.4% and 48.7% for the SBRT group vs. 30.2% and 45.5% for the IMRT group (Figure 2). There was no significant difference in LF between groups on univariate or multivariate analysis (Tables 2 and 3).

The one-year cumulative incidence of DF was 61.7% for the SBRT group and 52.4% for the IMRT group. There was no significant difference in DF between groups on UVA or MVA (Figure 3). None of the baseline factors was significantly associated with DF.

The one-year cumulative incidence of any failure (distant or local failure) was 71.5% for the SBRT group and 63.5% for the IMRT group. There was no significant difference in any failure between groups on UVA or MVA (Figure 4). There was no significant difference in the proportion of patients who underwent post-RT resection (IMRT =17% and SBRT 7%; $p = .11$).

Toxicity

Intensity modulated radiation therapy patients were significantly more likely to experience acute Grade 2+ GI toxicity (24% vs. 7%, $p = .008$), Grade 2+ fatigue (42% vs. 7%, $p < .0001$), and Grade 3+ hematologic toxicity (26% vs. 5%, $p = .001$) compared to SBRT (Table 4). About 15.9% of SBRT patients experienced documented late RT-associated toxicity, with the most common being GI bleed (9.1%); while 13.7% of IMRT patients experienced a late toxicity, with the most common toxicity being gastric ulcer/gastritis (3.1%) or GI bleed (3.1%).

Discussion

To our knowledge, this is the first reported comparison of clinical outcomes between SBRT and conventionally fractionated chemoradiation for unresectable pancreas cancer. For other sites such as lung and liver, SBRT is being increasingly utilized and preferred over conventional RT due to its high rates of local control and shorter treatment courses. SBRT has also generated increasing interest and adoption in

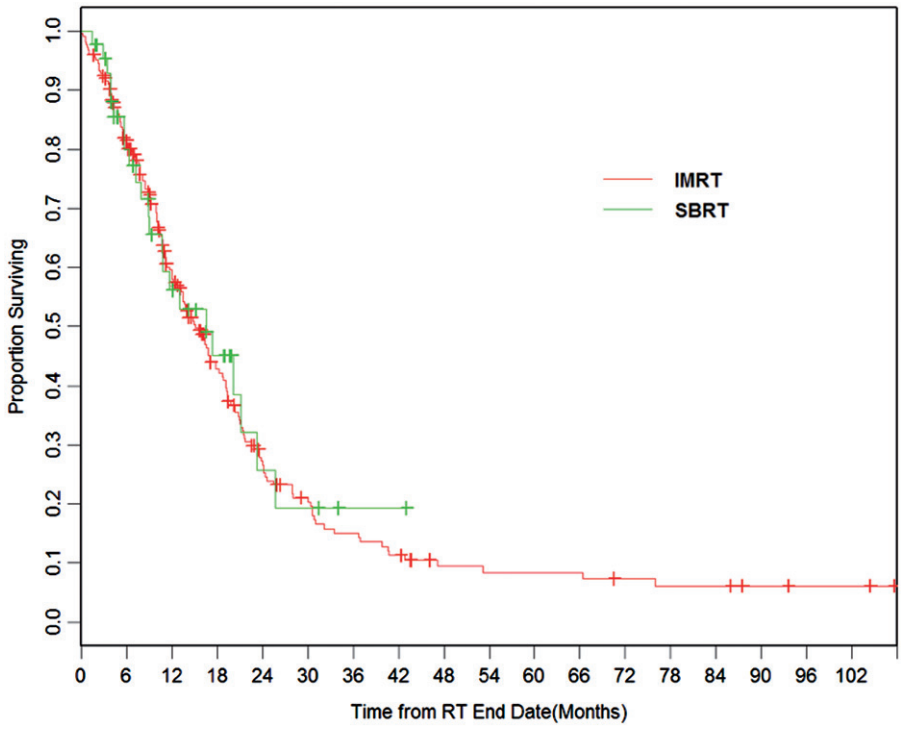

Figure 1. Kaplan–Meier overall survival curves stratified by type of RT. There was no significant difference in overall survival between patients treated with SBRT and IMRT ($p = .75$ by log-rank test). IMRT: intensity-modulated radiation therapy; SBRT: stereotactic body radiation therapy.

Table 2. Analysis of relationship between patient characteristics and overall survival using log-rank test for UVA and cox proportional hazards regression model for MVA ($N = 270$, 190 died, 80 alive).

		Multivariate analysis	
Characteristics	Univariate analysis *p* value	HR (95% CI)	*p* value
Age at diagnosis	.32		.28
≤70		1.00	
>70		0.84 (0.61–1.15)	
Gender	.21		.29
Male		1.00	
Female		0.85 (0.63–1.15)	
Karnofsky performance status	.09		.12
<80		1.00	
≥80		0.68 (0.42–1.10)	
Stage	.43		.67
I/II		1.00	
III		0.93 (0.68–1.29)	
Tumor location	.33		.64
Head		1.00	
Body/tail/uncinate process		0.93 (0.68–1.27)	
Maximum tumor dimension (cm)	.97		.65
<3.4		1.00	
≥3.4		1.07 (0.79–1.45)	
Duration of induction chemotherapy, (months)	.66		.46
<3.6		1.00	
≥3.6		1.12 (0.83–1.50)	
Partial response to ICT, *n* (%)	.01		.03
No		1.00	
Yes		0.69 (0.49–0.96)	
Type of radiation therapy	.75		.73
IMRT		1.00	
SBRT		0.92 (0.59–1.46)	

IMRT: intensity-modulated radiation therapy; SBRT: stereotactic body radiation therapy; ICT: induction chemotherapy; MVA: multivariate analysis; UVA: univariate analysis; HR: hazard ratio.

unresectable pancreatic cancer, due in large part to disappointing results with conventional chemoradiation, which appears to provide little if any survival benefit compared to chemotherapy alone [4], is relatively inconvenient for the patient, and causes significant acute toxicity due to larger radiated volumes and the use of concurrent chemotherapy.

Some of the first reports of SBRT for unresectable pancreatic cancer utilized high-dose single-fraction treatment,

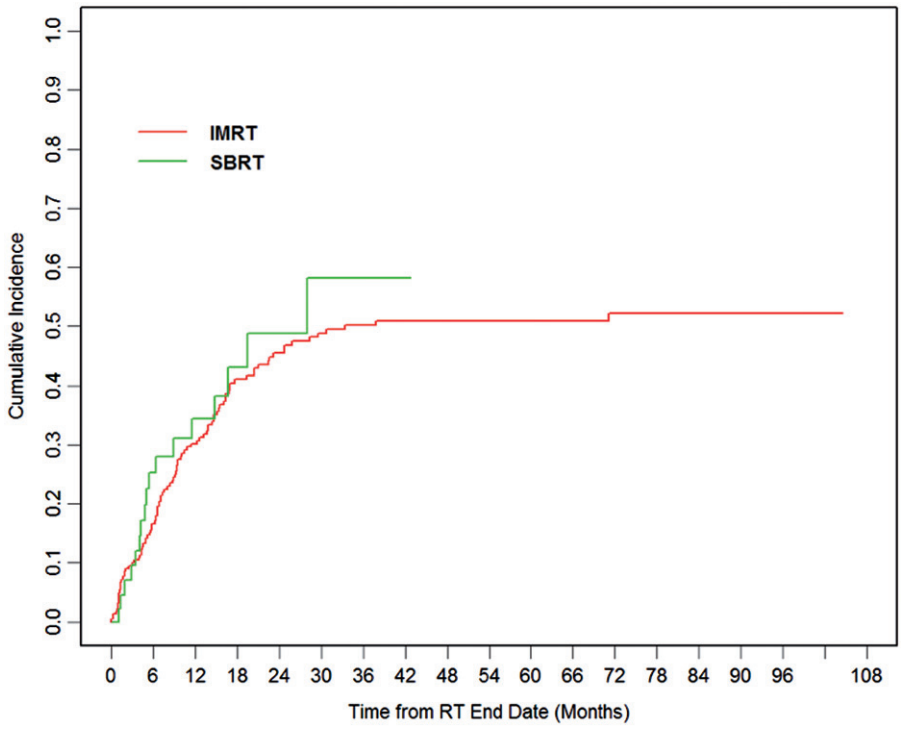

Figure 2. Cumulative incidence of local failure stratified by type of RT. There was no significant difference in local failure between patients treated with SBRT and IMRT on univariate analysis ($p = .51$ by Gray's method). IMRT: intensity-modulated radiation therapy;. SBRT: stereotactic body radiation therapy.

Table 3. Analysis of relationship between patient characteristics and local failure ($N = 265$, 115 LF, 91 died without LF, 59 censored) using Gray's competing risks method for UVA and fine and Gray's method for MVA.

		Multivariate analysis	
Characteristics	Univariate analysis p value	HR (95% CI)	p value
Age at diagnosis	.81		.94
≤70		1.00	
>70		1.01 (0.68–1.51)	
Gender	.88		.69
Male		1.00	
Female		1.08 (0.74–1.58)	
KPS	.44		.22
<80		1.00	
≥80		1.48 (0.79–2.78)	
Stage	.14		.10
I/II		1.00	
III		1.45 (0.94–2.25)	
Tumor location	.40		.37
Head		1.00	
Body/tail/uncinate process		1.19 (0.82–1.72)	
Maximum tumor dimension (cm)	.08		.09
<3.4		1.00	
≥3.4		0.73 (0.51–1.05)	
Duration of induction chemotherapy (months)	.67		.68
<3.6		1.00	
≥3.6		1.08 (0.74–1.58)	
Partial response to ICT, n (%)	.08		.06
No		1.00	
Yes		0.67 (0.44–1.02)	
Type of radiation therapy	.51		.81
IMRT		1.00	
SBRT		1.07 (0.63–1.81)	

IMRT: intensity-modulated radiation therapy; SBRT: stereotactic body radiation therapy; ICT: induction chemotherapy; MVA: multivariate analysis; UVA: univariate analysis; HR: hazard ratio.

sometimes as a boost after conventionally fractionated radiation. However, significant rates of late GI toxicity called into question the safety of such an aggressive approach [8]. Subsequent reports suggested that a multifraction SBRT regimen may achieve a better therapeutic ratio by reducing late toxicity while maintaining local control [9]. This led to a multi-institutional phase 2 trial of multi-fraction SBRT with the primary endpoint of reducing late GI toxicity

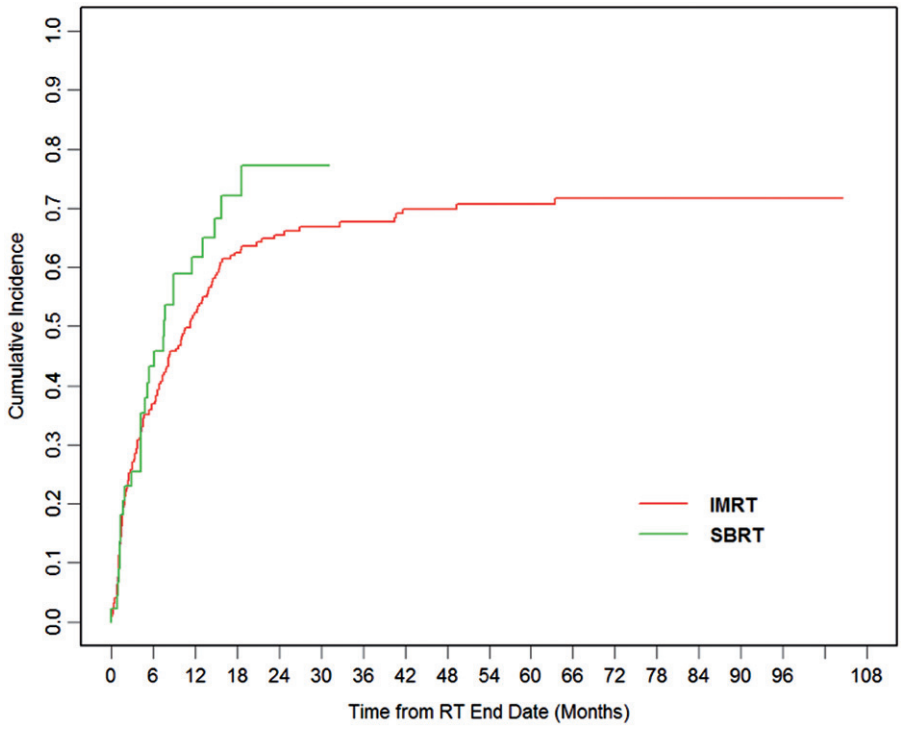

Figure 3. Cumulative incidence of distant metastasis stratified by type of RT. There was no significant difference in distant failure between patients treated with SBRT and IMRT on univariate analysis ($p = 0.25$ by Gray's method). IMRT: intensity-modulated radiation therapy; SBRT: stereotactic body radiation therapy.

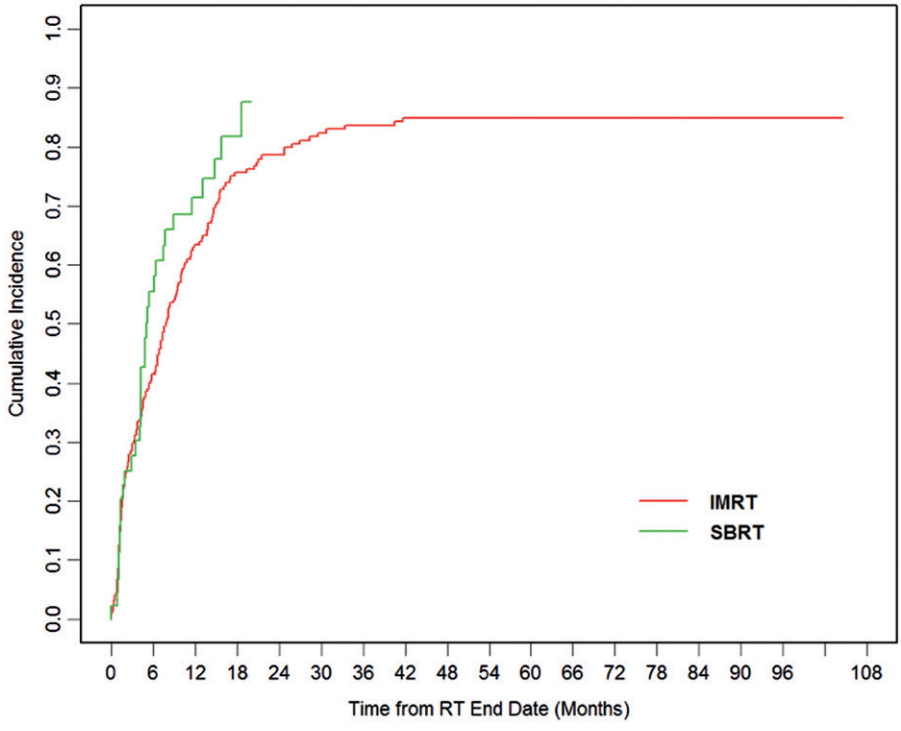

Figure 4. Cumulative incidence of any failure stratified by type of RT. There was no significant difference in any failure between patients treated with SBRT and IMRT on univariate analysis ($p = 0.18$ by Gray's method). IMRT: intensity-modulated radiation therapy; SBRT: stereotactic body radiation therapy.

compared with the prior single-fraction experience. This trial indicated that a regimen of 33 Gy in five fractions after induction gemcitabine chemotherapy yields acceptably low rates of late GI toxicity [7]. This SBRT regimen has a similar biologically effective dose as the standard 50.4 Gy in 28 fractions (BED_{10} of 54.8 vs. 59.5 for standard regimen). This SBRT regimen also has a significantly lower late BED than 25 Gy in a single fraction (BED_3 of 105.6, vs. 233.1 for 25 Gy), and only modestly higher than that of 50.4 Gy in 28 fractions ($BED_3 = 80.6$). Patient-reported outcomes indicate that this SBRT regimen is well-tolerated and can be readily incorporated into a multimodality

Table 4. Comparison of acute toxicity between SBRT and IMRT groups using Fisher's exact test.

Acute toxicity	IMRT ($n = 227$)	SBRT ($n = 44$)	p Value
Grade 2+ GI			0.008
No	171 (76%)	41 (93%)	
Yes	55 (24%)	3 (7%)	
Grade 3+ GI			1.00
No	221 (98%)	44 (100%)	
Yes	5 (2%)	0 (0%)	
Grade 2+ fatigue			<0.0001
No	130 (58%)	41 (93%)	
Yes	96 (42%)	3 (7%)	
Grade 3+ hematologic			0.001
No	167 (74%)	42 (95%)	
Yes	59 (26%)	2 (5%)	

IMRT: intensity-modulated radiation therapy; SBRT: stereotactic body radiation therapy.

treatment regimen for locally advanced pancreatic cancer [10].

Pancreas SBRT at our institution has been delivered in a similar way to this trial, and has been offered to patients based primarily on the preference and clinical judgment of the individual radiation oncologist. Otherwise, conventionally fractionated chemoradiation using IMRT has remained the standard radiation technique at our institution. It remains unclear whether SBRT is more effective, or even as effective, as conventionally fractionated chemoradiation. We therefore undertook this analysis to determine if SBRT using a safe five-fraction regimen is associated with better outcomes compared to standard IMRT.

Though this was a retrospective analysis, the IMRT and SBRT groups were well-balanced in terms of stage and nearly all other baseline factors. Because the use of SBRT vs. IMRT was nonrandom, the greatest potential weakness of this study is that patient selection biases would render comparison invalid. However, we found that in nearly all assessed covariables, particularly stage, performance status, and use of induction chemotherapy, there was no significant difference between the groups. The exception was a borderline-significant predominance of older patients in the SBRT group. We found no significant differences in survival or any disease control outcome between the two groups. The lack of a survival difference may not be surprising, given that chemotherapy rather than radiation efficacy may be the primary determinant of prognosis in this disease. More telling is that the local control was also very similar, which suggests that the two radiation techniques and regimens compared here are equivalent in tumor-directed efficacy.

Acute toxicity, by contrast, was found to be significantly decreased when using SBRT. This result is perhaps intuitive, given the much shorter duration of SBRT, its smaller radiated volumes, and absence of concurrent chemotherapy. In particular, we did not utilize any CTV expansion or elective nodal irradiation in our SBRT patients. The larger irradiated volume in the IMRT patients may explain part of the observed difference in toxicity, as could the use of concurrent chemotherapy. Since patients are evaluated weekly, IMRT patients would also have had more opportunities to report toxicity to clinicians as well. However, at the time of post-treatment follow-up all SBRT patients are asked about the highest-grade toxicity they experienced, even if it has resolved, so it is unlikely that our toxicity analysis is biased by the omission of unreported SBRT-induced toxicity. Nevertheless, we conclude that SBRT is significantly better tolerated than IMRT, which is clinically meaningful particularly given the limited prognosis of patients with unresectable pancreatic cancer.

There are significant limitations, as would be inherent in any retrospective study. Most notably, the selection of IMRT vs. SBRT was nonrandom and subject to selection bias. However, we did not have any institutional policy that would systematically skew certain patients towards SBRT or IMRT, and we attempted to measure and adjust for relevant covariates. The number of SBRT patients is also relatively small compared to IMRT patients, which limited our ability to draw firm conclusions about less common endpoints such as late toxicity or subsequent surgical resection.

Achieving significant improvements in efficacy with SBRT may require higher effective doses than this conservative five-fraction regimen. Experience from other sites, notably lung, indicates that a more ablative effect can be achieved by increasing the biologically equivalent dose above a certain threshold [11]. The use of large fraction sizes poses a difficulty in pancreas cancer, given the proximity of duodenum and other radiosensitive viscera, and the prior experience indicating significant toxicity with high-dose single-fraction treatment. An alternative approach for safe dose escalation is increasing the number of fractions, and tailoring the radiation dose to increase the dose to the tumor center while decreasing dose to the overlap region with GI luminal organs [12].

More broadly, the negative results of the LAP07 trial with respect to survival benefit raise the question of whether radiotherapy, in any form, has a meaningful role in the routine management of unresectable pancreatic cancer. As noted above, the equivalent survival of the SBRT and IMRT groups could be interpreted to mean that radiotherapy is equally ineffective in either form. However, the LAP07 trial did demonstrate a significant decrease in the rate of local progression, which is still clinically meaningful given the potential for pancreatic tumors to cause significant symptoms and complications. Radiotherapy also retains a potentially useful role in allowing patients to pause their systemic therapy, or in promoting future surgical resectability. For these reasons, the improved toxicity profile of SBRT and its equivalent local control still argue in favor of a meaningful, if somewhat limited, role for radiotherapy in this disease. It is also notable that our SBRT patients achieved a comparable local control as the IMRT patients despite the absence of CTV expansion or elective nodal irradiation, which is in line with recent guidelines suggesting that elective nodal coverage is not routinely needed for locally advanced pancreatic cancer [13].

Overall, we found that SBRT using a moderate-dose regimen was associated with similar outcomes as IMRT with respect to OS, local control, and distant metastasis. Though this suggests that moderate-dose SBRT may not be the breakthrough that some had hoped, it is also reassuring that its efficacy did not prove to be inferior in any measurable way. Given its improved toxicity profile, this data affirms the

emerging role of SBRT as a suitable alternative to standard chemoradiation in eligible patients.

Disclosure statement

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