International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Single- versus Multifraction Stereotactic Body Radiation Therapy for Pancreatic Adenocarcinoma: Outcomes and Toxicity

Erqi L. Pollom, MD,* Muthuraman Alagappan, BS,* Rie von Eyben, MS,* Pamela L. Kunz, MD,† George A. Fisher, MD,† James A. Ford, MD,† George A. Poultsides, MD,‡ Brendan C. Visser, MD,‡ Jeffrey A. Norton, MD,‡ Aya Kamaya, MD,§ Veronica L. Cox, MD,§ Laurie A. Columbo, RN,* Albert C. Koong, MD, PhD,* and Daniel T. Chang, MD*

Department of Radiation Oncology, Stanford University School of Medicine, Stanford, California; †Department of Medicine, Stanford University School of Medicine, Stanford, California; ‡Department of Surgery, Stanford University School of Medicine, Stanford, California; and §Department of Radiology, Stanford University School of Medicine, Stanford, California

Received May 17, 2014, and in revised form Jun 24, 2014. Accepted for publication Jun 25, 2014.

Summary

We reviewed our institutional stereotactic body radiation therapy (SBRT) experience with unresectable pancreatic adenocarcinoma. We found that multifraction SBRT reduces gastrointestinal toxicity significantly compared to single-fraction SBRT without compromising local control.

Purpose: We report updated outcomes of single- versus multifraction stereotactic body radiation therapy (SBRT) for unresectable pancreatic adenocarcinoma.

Methods and Materials: We included 167 patients with unresectable pancreatic adenocarcinoma treated at our institution from 2002 to 2013, with 1-fraction (45.5% of patient) or 5-fraction (54.5% of patients) SBRT. The majority of patients (87.5%) received chemotherapy.

Results: Median follow-up was 7.9 months (range: 0.1-63.6). The 6- and 12-month cumulative incidence rates (CIR) of local recurrence for patients treated with single-fraction SBRT were 5.3% (95% confidence interval [CI], 0.2%-10.4%) and 9.5% (95% CI, 2.7%-16.2%), respectively. The 6- and 12-month CIR with multifraction SBRT were 3.4% (95% CI, 0.0-7.2%) and 11.7% (95% CI, 4.8%-18.6%), respectively. Median survival from diagnosis for all patients was 13.6 months (95% CI, 12.2-15.0 months). The 6- and 12- month survival rates from SBRT for the single-fraction group were 67.0% (95% CI, 57.2%-78.5%) and 30.8% (95% CI, 21.9%-43.6%), respectively. The 6- and 12- month survival rates for the multifraction group were 75.7% (95% CI, 67.2%-85.3%) and 34.9% (95% CI, 26.1%-46.8%), respectively. There were no differences in CIR or survival rates between the single- and multifraction groups. The 6-

Reprint requests to: Daniel T. Chang, MD, Department of Radiation Oncology, Stanford University Medical Center, 875 Blake Wilbur Dr, Stanford, CA 94305-5847. Tel: (650) 724-3547; E-mail: dtchang@stanford.edu

This study was supported by Stanford Med Scholars (to M.A.) and My Blue Dots Foundation (to A.C.K.).

Conflicts of interest: Dr Koong has received speaker honoraria and grant support from Varian.

Int J Radiation Oncol Biol Phys, Vol. 90, No. 4, pp. 918–925, 2014
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2014.06.066

and 12-month cumulative incidence rates of gastrointestinal toxicity grade ≥3 were 8.1% (95% CI, 1.8%-14.4%) and 12.3% (95% CI, 4.7%-20.0%), respectively, in the single-fraction group, and both were 5.6% (95% CI, 0.8%-10.5%) in the multifraction group. There were significantly fewer instances of toxicity grade ≥2 with multifraction SBRT ($P = .005$). Local recurrence and toxicity grade ≥2 were independent predictors of worse survival.

Conclusions: Multifraction SBRT for pancreatic cancer significantly reduces gastrointestinal toxicity without compromising local control. © 2014 Elsevier Inc.

Introduction

Pancreatic cancer is a deadly malignancy with a 5-year survival rate of approximately 20% for operable patients (1) and <5% for inoperable patients (2). Most patients are inoperable at diagnosis. Treatment of these patients with borderline resectable or unresectable tumors has conventionally consisted of chemoradiation therapy with conventionally fractionated external beam radiation based on early data (3, 4). However, outcomes are poor with conventionally fractionated radiation, with local control rates of only 40% to 55% and median survival periods of 5 to 14 months (5-9).

Recent technological advances in image guidance and respiratory motion management have enabled stereotactic body radiation therapy (SBRT), which allows accurate and conformal delivery of much higher biologically effective doses (BED) and has shown excellent outcomes for extracranial sites including lung and liver (10-13). We previously published the first clinical report of SBRT in the treatment of pancreatic cancer in 2004, showing 100% local control with up to 25 Gy in a single fraction (14). Other groups have since reported their experiences using pancreatic SBRT with various fractionation schemes, also showing excellent local control compared to conventionally fractioned radiation therapy (15-23).

Further dose escalation has been limited by concern of damage to adjacent critical structures, namely the duodenum and stomach. Therefore, the optimal radiation treatment schedule has yet to be established for pancreas SBRT. A significant number of late gastrointestinal (GI) toxicity occurrences after SBRT were reported with single-fraction experiences (23-26). Although most of these toxicities were medically managed, in an attempt to lower GI toxicity, the fractionation schedule was altered to reduce the fraction size. Using the universal survival curve reported by Park et al (27), an equivalent BED of 25 Gy in a single fraction was estimated to be 33 Gy in 5 fractions. This dose fractionation has been used as our institutional standard since 2009 and has been the basis of a multi-institutional prospective trial. Preliminary results (JM Herman et al, 2014, unpublished results) show that this regimen appears to limit toxicity while still achieving good local control.

Here we report updated outcomes of our experience with pancreas SBRT at our single institution, with the objective of comparing local control and toxicity between our single- and multifraction treatments.

Methods and Materials

Patient population

After institutional review board approval, the records of all patients with newly diagnosed unresectable pancreatic adenocarcinoma treated with SBRT single fraction or with 5 fractions to a total dose of 25 Gy or greater at Stanford Cancer Institute between October 2002 and June 2013 were reviewed. Patients were excluded if they were treated to locally recurrent disease after resection or if they had received other abdominal radiation.

Treatment planning and technique

Specifics of treatment have been reported previously (23, 25). Briefly, all patients had 3 to 5 gold fiducial markers implanted within or adjacent to the pancreas tumor endoscopically, percutaneously, or surgically, prior to simulation. Simulation for all patients consisted of a biphasic CT scan (early arterial and portal venous phases) and, beginning in 2004, 4-dimensional (4D) computed tomography (CT) and ^{18}F-labeled fluorodeoxyglucose positron emission tomography (PET) and CT for most patients. All patients were immobilized in a supine position with arms up, using an Alpha Cradle (Smithers Medical Products, North Canton, OH).

The gross tumor volume (GTV) was contoured on axial slices of the contrast-enhanced CT with assistance of the 4DCT and PET-CT images. The 4DCT was used to assess the magnitude and direction of tumor motion during the respiratory cycle and allow for delineation of an internal tumor volume (ITV). The planning target volume (PTV) included the ITV plus a 2- to 3-mm isotropic expansion. Elective nodal regions were not included in the PTV. Dose was prescribed to the periphery of the tumor with 95% coverage of the PTV, although coverage could be reduced at the discretion of the treating physician in order to meet normal tissue dose constraints. Treatment planning was carried out using normal tissue constraints, which have been reported previously for single-fraction treatment (23). For multifraction treatment, the adjacent duodenum, stomach, and bowel structures were limited to a volume

receiving more than 33 Gy (V33) $\leq$ 1 cc, a V20 $\leq$ 3 cc, and a V15 $\leq$ 9 cc.

Treatment technique varied over the course of the study period. Patients were treated with either CyberKnife (Accuray, Inc, Sunnyvale, CA) using the Synchrony (Accuray) tracking method (28) or linear accelerator. Methods for tumor tracking and respiratory compensation have been previously described (29). The most current technique involves respiration-gated volumetric modulated arc therapy with RapidArc (Varian Medical Systems, Palo Alto, CA) on the TrueBeam unit (Varian) with single or double arcs. Treatment was delivered with 10-MV energy, using flattening filter−free mode. Fiducial position was verified prior to treatment start and during the treatment arc by using fluoroscopic imaging and then continuously during the treatment with kV imaging at each breathing cycle immediately prior to beam on.

Toxicity and clinical outcomes

Patients were followed every 3 months for the first 1 to 2 years with CT and/or PET CT to evaluate treatment response and monitor for toxicity. Time-to-event endpoints were calculated from the start date of SBRT, except for overall survival (OS), which was calculated from the date of diagnosis. Gastrointestinal toxicities were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Local recurrence was defined with CT according to the response evaluation criteria in solid tumors (RECIST) (30) and PET according to the PET response criteria in solid tumors (PERCIST) (31). Tumors were scored as progressive if they met either RECIST or PERCIST criteria for progression. Patients were usually evaluated with follow-up CT and/or PET scan every 3 months after treatment. A radiologist interpreted the imaging findings for this study.

Statistical methods

Kaplan-Meier method was used to calculate estimates of OS. Log-rank test was used to compare differences in Kaplan-Meier estimates between groups. Cox proportional hazard regression was used for univariate and multivariate analyses. Local control and toxicity were treated as time-dependent covariates in the univariate and multivariate analyses for survival.

As censoring patients at time of death with Kaplan-Meier method would lead to biased probability of recurrence and toxicity given the high rate of death in our patient population, time to local recurrence/toxicity was analyzed using competing risk analysis of Fine and Gray (32). Cumulative incidence of local recurrence (CIR) and cumulative incidence of GI toxicity (CIT) were analyzed with death without local recurrence and death without toxicity, respectively, as competing events. Patients were censored at the point of last follow-up if they were alive and without documented recurrence or toxicity. The Gray test (33) was used to compare cumulative incidence rates, and the Fine and Gray regression model was used to perform competing risk analysis.

Dose analyses were performed using the standard linear quadratic model for BED (34) in order to compare outcomes of various fractionation schemes. BED using α/β of 10 (BED10) and 3 (BED3) were defined.

All statistical tests were 2-sided, and a P value of $< .05$ was considered significant. Survival and competing risks analysis were performed with R software (version 3.0.1; R Development Core Team), using "cmprsk" and "survival" features, and SAS software (version 9.4; SAS, Inc, Cary, NC).

Results

Patient and treatment characteristics

There were 167 patients who met inclusion criteria for this study. Of these, 133 patients (79.6%) had unresectable disease, 11 patients (6.6%) had borderline resectable disease, 21 patients (12.6%) were medically inoperable, and 2 patients (1.2%) refused resection. Fourteen patients (8.4%) had distant metastases at the time of treatment that were either stable or had complete response after chemotherapy. The majority of patients (87.5%) received neoadjuvant and/or adjuvant chemotherapy, with 137 patients receiving gemcitabine alone or gemcitabine plus other chemotherapy agents. Other chemotherapy agents most commonly included protein-bound paclitaxel (Abraxane), cisplatin, and capecitabine. In total, 91 patients were treated with multifraction SBRT (median dose: 33 Gy; range: 25-45 Gy), and 76 patients were treated with a single fraction of 25 Gy. Patients in the multifraction group had a larger median PTV than those in the single-fraction group (56.7 cc vs 44.6 cc, respectively; $P = .004$). Additional patient, tumor, and treatment characteristics are listed in Table 1.

Clinical outcomes

The median follow-up for all patients was 7.9 months (range: 0.1-63.6 months) following SBRT and 12.9 months (range: 2.0-67.5 months) after diagnosis of pancreatic cancer. The median follow-up for patients alive at last follow-up visit was 6.8 months (range: 2.3-63.6 months). There were 23 total local failures, 10 (43.4%) among the patients who received single-fraction SBRT, and 13 (56.5%) among the patients who received multifraction SBRT. The 6- and 12-month CIR for all patients from end of SBRT were 4.2% (95% confidence interval [CI], 1.2%-7.4%) and 10.7% (95% CI, 5.9%-15.5%), respectively (Fig. 1).

The 6- and 12-month CIR for patients treated with single-fraction SBRT were 5.3% (95% CI, 0.2%-10.4%)

Table 1 Patient, tumor, and treatment characteristics

Characteristic	Total	Single fraction	Multifraction	*P*
Sex				.12
Male	84 (50.3%)	33 (19.8%)	51 (30.5%)	
Female	83 (49.7%)	43 (25.7%)	40 (24.0%)	
Median age, range	69.3, 30-93.1	66.6, 30.0-93.1	71.6, 38.3-92.3	.02
Location				.93
Body	38 (22.8%)	17 (10.2%)	21 (12.6%)	
Head	101 (60.5%)	45 (26.9%)	56 (33.5%)	
Uncinate	23 (13.8%)	11 (6.6%)	12 (7.2%)	
Tail	5 (3.0%)	3 (1.8%)	2 (1.2%)	
Chemotherapy				.02
None	21 (12.6%)	11 (6.5%)	10 (6.0%)	
Any neoadjuvant/adjuvant	146 (87.5%)	65 (38.9%)	81 (48.5%)	
Gemcitabine alone	76 (45.5%)	41 (24.6%)	35 (21.0%)	
Gemcitabine plus other	61 (36.5%)	24 (14.4%)	37 (22.2%)	
Folfirinox	9 (5.4%)	0 (0.0%)	9 (5.4%)	
Metastases at treatment				.14
None	153 (91.6%)	67 (40.2%)	86 (51.5%)	
Liver	9 (5.4%)	5 (3.0%)	4 (2.4%)	
Lung	3 (1.8%)	3 (1.8%)	0 (0.0%)	
Chest wall	1 (0.06%)	0 (0.0%)	1 (0.06%)	
Omentum	1 (0.06%)	1 (0.06%)	0 (0.0%)	
Median PTV (range)	50.4 cc (9.9-128.1)	44.6 cc (10.4-128.1)	56.7 cc (9.9-125.8)	.004
Median dose (range)	30.0 Gy (25.0-45.0)	25.0 Gy (25.0-25.0)	33.0 Gy (25.0-45.0)	
Median dose/fraction (range)	6.6 Gy (5.0-9.0)	25.0 Gy (25.0-25.0)	6.6 Gy (5.0-9.0 Gy)	
Median BED10 (range)	54.8 Gy (37.5-87.5)	87.5 Gy (87.5-87.5)	54.8 Gy (37.5-85.5)	
Median BED3 (range)	105.6 Gy (66.7-233.3)	233.3 Gy (233.3-233.3)	105.6 Gy (66.7-180.0)	

Abbreviations: BED = biologically effective dose ($\alpha/\beta = 3$; $\alpha/\beta = 10$); PTV = planning target volume.

and 9.5% (95% CI, 2.7%-16.2%), respectively. The 6- and 12-month CIR for patients treated with multifraction SBRT were 3.4% (95% CI, 0.0-7.2%) and 11.7% (95% CI, 4.8%-18.6%), respectively. There were no differences in CIR between the single- and multifraction groups ($P=.80$). Although more patients in the multifraction group received neoadjuvant/adjuvant chemotherapy, chemotherapy did not predict for CIR ($P=.58$). BED10 ($P=.55$), metastases at SBRT ($P=.38$), age ($P=.35$), PTV ($P=.98$), and tumor location ($P=.29$) also did not predict for CIR.

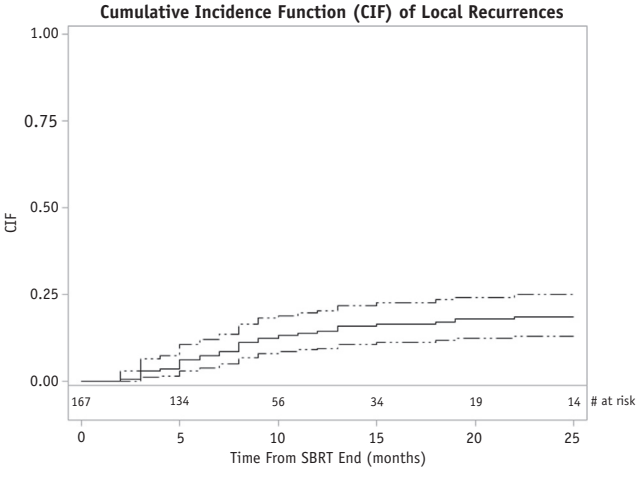

Fig. 1. Cumulative incidence of local recurrence for all patients.

Two patients who received single-fraction SBRT and 1 patient who received multifraction SBRT underwent R0 resection after SBRT. One of the 2 patients who received single-fraction SBRT and was clinically staged at T4N0 at the time of SBRT obtained a near pathologically complete response with focal tumor present on only 1 slide, whereas the other patient was clinically staged at T2N0 at the time of SBRT and was staged ypT3pN1 at resection. The third patient who received multifraction SBRT (33 Gy in 5 fractions) was clinically staged T3N0 at the time of SBRT and was staged ypT2pN0 at resection.

Median OS from diagnosis for all patients was 13.6 months (95% CI, 12.2-15.0 months). The 6- and 12-month OS rates from SBRT end for all patients were 71.7% (95% CI, 65.1%-79.0%) and 33.1% (95% CI, 26.4%-41.3%), respectively (Fig. 2). There were no differences in OS between the single- and multifraction groups ($P=.94$). The 6- and 12- month OS rates from end of SBRT for the single-fraction group were 67.0% (95% CI, 57.2%-78.5%) and 30.8% (95% CI, 21.9%-43.6%), respectively. The 6- and 12- month OS rates for the multifraction group were 75.7% (95% CI, 67.2%-85.3%) and 34.9% (95% CI, 26.1%-46.8%), respectively.

On multivariate analysis, local failure and development of GI toxicity $\geq$ grade 2 were each significant, independent

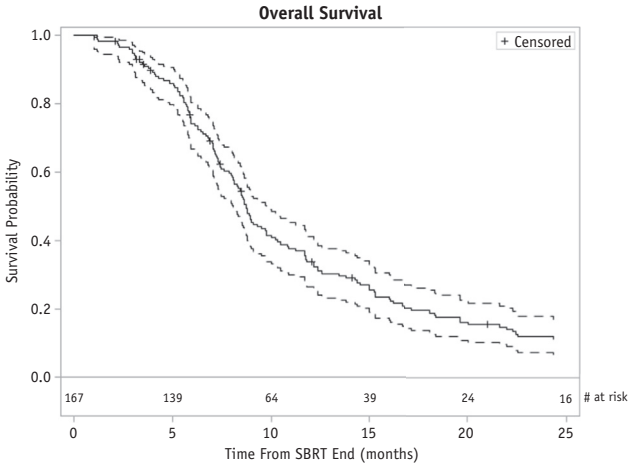

Fig. 2. Overall survival for all patients.

predictors for worse survival (Table 2). There was a trend toward improved OS with receipt of neoadjuvant/adjuvant chemotherapy and younger age. BED10 and tumor location did not predict for OS.

Gastrointestinal toxicity

There were 19 recorded instances of GI toxicities ≥ grade 2 after SBRT in the single-fraction group, and 8 in the multifraction group. The 6- and 12-month CIT ≥ grade 2 after single-fraction SBRT were 16.2% (95% CI, 7.7%-24.7%) and 26.1% (95% CI, 15.9%-36.4%), respectively. The 6- and 12-month CIT ≥ grade 2 after multifraction SBRT were both 7.8% (95% CI, 2.2%-13.5%). There were significantly more toxicities in the single-fraction SBRT group (hazard ratio [HR]: 3.01; 95% CI, 1.3-6.9; $P = .005$, Fig. 3). BED3, analyzed as a continuous variable, was a significant predictor for CIT ≥ grade 2 (HR 1.01; 95% CI, 1.00-1.02; $P = .006$). Larger PTV was associated with lower rates of toxicity (HR, 0.978; 95% CI, 0.96-0.99; $P = .022$). Tumor location ($P = .70$), receipt of neoadjuvant/adjuvant chemotherapy ($P = .97$), and age ($P = .46$) did not predict for toxicity.

For GI toxicity ≥ grade 3 (Table 3), the 6- and 12-month cumulative incidence of toxicity were 8.1% (95% CI, 1.8%-14.4%) and 12.3% (95% CI, 4.7%-20.0%), respectively, in the single-fraction group, and both 5.6% (95% CI, 0.8%-10.5%), respectively, in the multifraction group. There were no significant differences in CIT ≥ grade 3 between the single and multifraction groups ($P = .26$).

Discussion

Here we report updated outcomes of our single-institution experience with treating unresectable pancreatic cancer with SBRT over the past decade, which to our knowledge, is the largest reported series to date. We found significantly fewer occurrences of GI toxicity ≥ grade 2 with multifraction SBRT than with single-fraction SBRT, with continued excellent local control rates with SBRT. Additionally, we found that local failure and the development of grade 2 or higher toxicity are each independent and significant predictors of worse survival, which suggests that these improvements ultimately impact survival for patients

Table 2 Univariate and multivariate analysis of predictive factors for OS

	Overall survival					
	Univariate			Multivariate		
Predictive factors	HR	95% CI	*P*	HR	95% CI	*P*
Single fraction vs multifraction	1.01	0.73-1.40	.94	-	-	-
BED10 (continuous)	1.00	0.99-1.01	.96	-	-	-
Any chemotherapy vs none	0.63	0.37-1.07	.09	0.67	0.43-1.06	.08
Chemotherapy by category	-	-	.39	-	-	-
Gemcitabine alone*	0.63	0.37-1.10	.10	-	-	-
Gemcitabine plus other*	0.64	0.37-1.12	.12	-	-	-
Folfirinox*	0.57	0.24-1.35	.20	-	-	-
GI toxicity ≥ grade 2	2.40	1.61-3.58	<.0001	2.67	1.79-3.97	<.0001
Local failure	2.20	1.61-3.58	.0003	2.29	1.53-3.44	<.0001
Tumor location	-	-	.78	-	-	-
Head†	1.15	0.78-1.70	.48	-	-	-
Uncinate†	1.07	0.60-1.89	.82	-	-	-
Tail†	1.63	0.57-4.60	.36	-	-	-
Presence of metastases	1.53	0.84-2.78	.16	1.70	1.02-2.84	.04
Age (continuous)	1.01	1.00-1.02	.23	1.01	1.00-1.02	.08
PTV	1.00	1.00-1.01	.25	-	-	-

Abbreviations: BED = biologically effective dose ($\alpha/\beta = 10$); CI = confidence interval; HR = hazard ratio; PTV = planning target volume
* Versus no chemotherapy.
† Versus body location.

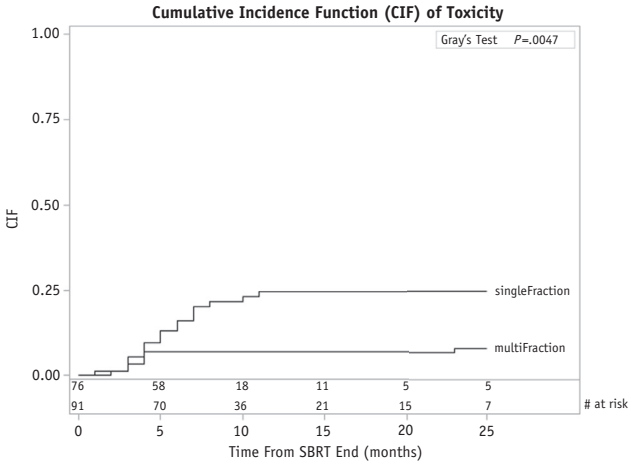

Fig. 3. Cumulative incidence of gastrointestinal toxicities grade ≥2 for single versus multifraction SBRT groups. SBRT = stereotactic body radiation therapy.

with unresectable pancreatic cancer treated with multifraction SBRT.

We previously reported 6- and 12- month rates of grades 2 to 4 GI toxicity of 17% and 28%, respectively, with single-fraction SBRT (23). In order to reduce late toxicities, we implemented a multifraction dose schedule with modified dose constraints. Recognizing that the standard linear quadratic model does not apply to large doses per fraction, we used the universal survival curve formula derived by Park et al (27) to convert 25 Gy in 1 fraction to a BED of 33 Gy in 5 fractions (R. Timmerman, personal communication). This fractionation schedule was then used as the basis for a prospective multi-institutional protocol, with preliminary results (JM Herman 2014 Herman et al, unpublished data) showing similarly low rates of GI toxicity. Fifteen patients in the unpublished study by Herman et al were also included in this study.

Other series have also reported increased GI toxicity after SBRT (15, 19-21). Hoyer et al (21) reported that after SBRT with 45 Gy in 3 fractions, 64% of patients had toxicity > grade 2, including nausea and pain, and 23% of patients developed severe mucositis or ulceration of the stomach or duodenum, including 1 patient who needed an operation for perforation. Their high rates of toxicity could be explained by larger treatment volumes as they added 5 mm transversely and 10 mm longitudinally to define the PTV.

We used a PTV expansion of only 2 to 3 mm in our series, and median PTV for all tumors was 50.4 cc. Tumors treated with multifraction SBRT actually had significantly larger PTVs than those treated with single-fraction SBRT (Table 1), which strengthens our findings that the multifraction schedule significantly reduced toxicity without compromising local control despite larger tumors.

Additionally, the BED3 in the study by Hoyer et al (21) was 270 Gy. We found in our series that BED3 was a significant predictor of GI toxicity. Of the 79 patients who received BED3 of 180 Gy or higher, 20 patients developed toxicity ≥ grade 2, 10 of whom had toxicity ≥ grade 3. Of the 88 of 180 patients who received less than BED3, only 7 patients developed toxicity ≥ grade 2 toxicity, and 5 of whom had toxicity ≥ grade 3.

On the other hand, Chuong et al (18) reported a toxicity rate ≥ grade 2 of only 5.3% in their series. They similarly used a 5-fraction regimen to decrease the risk of late normal tissue injury, treating to a total dose of 35 to 50 Gy, with mean BED3 125 Gy. Polistina et al (22) also found no toxicity ≥ grade 2 with 30 Gy in 3 fractions.

The wide range of toxicity rates among different series highlights the importance of further optimization of fractionation and treatment delivery technique, as well as improved understanding of dosimetric constraints of bowel structures. Phase 1 and 2 studies of SBRT for liver tumors have suggested that the duodenal maximal point dose be

Table 3 Gastrointestinal toxicities (grade ≥3)

Patient	Dose × no. of fractions	BED3 (Gy)	Time to toxicity (months)	Toxicity	Grade
1	25 Gy × 1	233.3	7.7	Duodenal perforation	4
2	25 Gy × 1	233.3	5.4	Duodenal perforation	4
3	6.6 Gy × 5	105.6	3.4	Duodenal perforation	4
4	25 Gy × 1	233.3	5.3	Biliary sclerosis	3
5	25 Gy × 1	233.3	4.2	Gastric ulcer	3
6	25 Gy × 1	233.3	3.2	Gastric ulcer	3
7	25 Gy × 1	233.3	1.6	Duodenal ulcer/upper GI bleed	3
8	25 Gy × 1	233.3	4.8	Duodenal stricture	3
9	25 Gy × 1	233.3	7.3	Gastric ulcer	3
10	25 Gy × 1	233.3	11	Duodenal stricture	3
11	9 Gy × 5	180.0	2.2	Gastric ulcer	3
12	6 Gy × 5	90.0	23.0	Gastric ulcer	3
13	6 Gy × 5	90.0	3.7	Upper GI bleed (source unknown)	3
14	6.6 Gy × 5	105.6	3.1	Duodenal ulcer	3
15	6.6 Gy × 5	105.6	4.2	Duodenal ulcer	3

Abbreviations: BED = biologically effective dose ($\alpha/\beta = 3$); GI = gastrointestinal.

kept to less than the equivalent of 30 Gy in 3 fractions (35, 36). Dosimetric analysis of our single-fraction SBRT series found the maximum dose to 1 cc of the duodenum $\geq$ 23 Gy to be associated with increased rates of duodenal toxicity (37). Bae et al (38, 39) found for 3-fraction SBRT, V25 $>$ 20 cc and maximum point dose of 35 Gy and 38 Gy predicted for severe gastroduodenal toxicity. Further clarification of the dosimetric determinants of duodenal toxicity is needed for multifraction SBRT, although this may be challenging given our low event rate (only 3 patients treated with multifraction SBRT had duodenal toxicity $\geq$ grade 3).

More importantly, we found that fractionation of SBRT does not compromise local control. Both Chuong et al (18) and Polistina et al (22) reported excellent local control rates of >80% with their fractionated SBRT regimens. In contrast, Gurka et al (40) reported no grade 3 toxicities with 25 Gy in 5 fractions (BED10 = 37.5 Gy) but had low 1-year local control (40%). Although BED10 has been associated with local control at other sites (10, 12), we found no relationship between BED10 and local control. This may be due to our low local recurrence rates and the fact that most of our patients were treated with BED10 $\geq$ 48 Gy.

There are limitations to this retrospective study. First, definition of local control varies across SBRT series, with some groups calling local progression based on size, metabolic activity, or clinical presentation or a combination of all three. We chose to define local control radiographically, using PERCIST or RECIST. Fulfillment of either PERCIST or RECIST criteria was counted as local progression, as there were instances when a patient progressed by PERCIST criteria but not by RECIST criteria and vice versa. We acknowledge that our failures may miss cases in which tumor may fulfill neither PERCIST nor RECIST but have other radiographic features that suggest progression, such as increased infiltration. Additionally, our failure rates do not include patients who had stable imaging findings but clinical symptoms suspicious for local progression. However, we thought that using PERCIST/RECIST would be the least subjective and most consistent way to retrospectively review our outcomes for this analysis. If we included those patients with radiographically stable disease but clinical symptoms of local progression, our 1-year CIR would be 13.9% (95% CI, 8.9-19.0). Regardless, more work is needed in the evaluation of tumor response after SBRT as consensus on the best approach is lacking.

Second, toxicity data collection was limited because patients with GI toxicity were often diagnosed with endoscopy after presenting with pain. Toxicities may be different if all patients underwent routine pre- and post-treatment endoscopy. In some cases, it was challenging to distinguish between tumor progression and treatment-related ulceration. Biopsies were obtained when possible to differentiate between the 2. Third, reporting of local control and toxicity endpoints is challenged by the high mortality rates and short follow-up of our patient population. We attempted to account for this by using competing risk analysis, accounting for death as a competing risk, by using the Kaplan-Meier method and censoring patients at death without event would overestimate local recurrence and toxicity. Finally, although BED analysis using the standard linear-quadratic model is not reliable for large doses over a few fractions (27), it is a useful estimate that allows comparison of a variety of fractionation schedules.

The role of radiation therapy for locally advanced pancreatic cancer, already controversial, has been made more so in light of the recent results from the LAP07 trial (41). This randomized trial showed that conventionally fractionated radiation therapy and concurrent 5-fluorouracil (5-FU)-based chemotherapy did not improve survival over gemcitabine-based chemotherapy alone for patients who did not progress after 4 cycles of chemotherapy. One explanation for these findings is that concurrent 5-FU-based chemoradiation may interrupt optimal chemotherapy, leading to poorer systemic control of disease. If so, SBRT may have a distinct advantage over concurrent chemoradiation in that SBRT is able to deliver highly effective radiation within 1 week between chemotherapy cycles, thereby optimizing local control while minimally interrupting chemotherapy. In addition, because SBRT is well-tolerated, delays in continuing chemotherapy afterwards due to acute toxicity are rare.

Conclusions

In conclusion, multifraction SBRT for pancreatic cancer significantly reduces GI toxicity without compromising local control. With reduced toxicity, the role of SBRT for unresectable pancreatic adenocarcinoma should continue to be investigated.

References

1. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. *Ann Surg* 1995; 221:721-733. discussion 731−733.
2. Sener SF, Fremgen A, Menck HR, et al. Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the National Cancer Database. *J Am Coll Surg* 1999; 189:1-7.
3. Gastrointestinal Tumor Study Group. Treatment of locally unresectable carcinoma of the pancreas: Comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. *J Natl Cancer Inst* 1988;80:751-755.
4. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: A randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. *Cancer* 1981;48:1705-1710.
5. Small W Jr., Berlin J, Freedman GM, et al. Full-dose gemcitabine with concurrent radiation therapy in patients with nonmetastatic pancreatic cancer: A multicenter phase II trial. *J Clin Oncol* 2008;26:942-947.
6. Murphy JD, Adusumilli S, Griffith KA, et al. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2007;68:801-808.
7. Shinchi H, Takao S, Noma H, et al. Length and quality of survival after external-beam radiotherapy with concurrent continuous 5-

fluorouracil infusion for locally unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2002;53:146-150.
8. Ko AH, Quivey JM, Venook AP, et al. A phase II study of fixed-dose rate gemcitabine plus low-dose cisplatin followed by consolidative chemoradiation for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2007;68:809-816.
9. Haddock MG, Swaminathan R, Foster NR, et al. Gemcitabine, cisplatin, and radiotherapy for patients with locally advanced pancreatic adenocarcinoma: Results of the North Central Cancer Treatment Group Phase II study N9942. *J Clin Oncol* 2007;25:2567-2572.
10. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: A pooled analysis. *Cancer* 2011;117:4060-4069.
11. Liu E, Stenmark MH, Schipper MJ, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors. *Transl Oncol* 2013;6:442-446.
12. Onishi H, Kuriyama K, Komiyama T, et al. Clinical outcomes of stereotactic radiotherapy for stage I non-small cell lung cancer using a novel irradiation technique: Patient self-controlled breath-hold and beam switching using a combination of linear accelerator and CT scanner. *Lung Cancer* 2004;45:45-55.
13. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070-1076.
14. Koong AC, Le QT, Ho A, et al. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 58:1017-1021.
15. Didolkar MS, Coleman CW, Brenner MJ, et al. Image-guided stereotactic radiosurgery for locally advanced pancreatic adenocarcinoma results of first 85 patients. *J Gastrointest Surg* 2010;14:1547-1559.
16. 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.
17. Mahadevan A, Miksad R, Goldstein M, et al. Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer. *Int J Radiat Oncol Biol Phys* 2011;81:e615-e622.
18. Chuong MD, Springett GM, Freilich 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.
19. Rwigema JC, 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.
20. Goyal K, Einstein D, Ibarra RA, et al. Stereotactic body radiation therapy for nonresectable tumors of the pancreas. *J Surg Res* 2012;174:319-325.
21. Hoyer M, Roed H, Sengelov L, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. *Radiother Oncol* 2005l;76:48-53.
22. Polistina F, Costantin G, Casamassima F, et al. Unresectable locally advanced pancreatic cancer: A multimodal treatment using neoadjuvant chemoradiotherapy (gemcitabine plus stereotactic radiosurgery) and subsequent surgical exploration. *Ann Surg Oncol* 2010;17:2092-2101.
23. Chang DT, Schellenberg D, Shen J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer* 115:665−672.
24. Koong AC, Christofferson E, Le QT, et al. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2005;63:320-323.
25. Schellenberg D, Kim J, Christman-Skieller C, et al. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 81:181−188.
26. Schellenberg D, Goodman KA, Lee F, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2008;72:678-686.
27. Park C, Papiez L, Zhang S, Story M, Timmerman RD. Universal survival curve and single fraction equivalent dose: Useful tools in understanding potency of ablative radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;70:847-852.
28. Schweikard A, Shiomi H, Adler J. Respiration tracking in radiosurgery. Med Phys 31:2738-2741.
29. Minn AY, Koong AC, Chang DT. Stereotactic body radiation therapy for gastrointestinal malignancies. *Front Radiat Ther Oncol* 2011;43:412-427.
30. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205-216.
31. Wahl RL, Jacene H, Kasamon Y, et al. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med* 2009;50(suppl 1):122S-150S.
32. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of competing risk. *J Am Stat Assoc* 1999;94:496-509.
33. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;16:1141-1154.
34. Yaes RJ, Patel P, Maruyama Y. On using the linear-quadratic model in daily clinical practice. *Int J Radiat Oncol Biol Phys* 1991;20:1353-1362.
35. Kavanagh BD, Schefter TE, Cardenes HR, et al. Interim analysis of a prospective phase I/II trial of SBRT for liver metastases. *Acta Oncol* 2006;45:848-855.
36. Schefter TE, Kavanagh BD, Timmerman RD, et al. A phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases. *Int J Radiat Oncol Biol Phys* 2005;62:1371-1378.
37. Murphy JD, Christman-Skieller C, Kim J, Dieterich S, Chang DT, Koong AC. A dosimetric model of duodenal toxicity after stereotactic body radiotherapy for pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2010;78:1420-1426.
38. Bae SH, Kim MS, Cho CK, et al. Predictor of severe gastroduodenal toxicity after stereotactic body radiotherapy for abdominopelvic malignancies. *Int J Radiat Oncol Biol Phys* 2012;84:e469-474.
39. Bae SH, Kim MS, Kim SY, et al. Severe intestinal toxicity after stereotactic ablative radiotherapy for abdominopelvic malignancies. *Int J Colorectal Dis* 2013;28:1707-1713.
40. Gurka MK, Collins SP, Slack R, et al. Stereotactic body radiation therapy with concurrent full-dose gemcitabine for locally advanced pancreatic cancer: A pilot trial demonstrating safety. *Radiat Oncol* 2013;8:44.
41. Hammel P, Huguet F, Van Laethem J-L, et al. Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. *J Clin Oncol* 2013;31(suppl; abstr #LBA4003).