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SINGLE-FRACTION STEREOTACTIC BODY RADIATION THERAPY AND SEQUENTIAL GEMCITABINE FOR THE TREATMENT OF LOCALLY ADVANCED PANCREATIC CANCER

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Purpose: This Phase II trial evaluated the toxicity, local control, and overall survival in patients treated with sequential gemcitabine and linear accelerator–based single-fraction stereotactic body radiotherapy (SBRT).

Methods and Materials: Twenty patients with locally advanced, nonmetastatic pancreatic adenocarcinoma were enrolled on this prospective single-institution, institutional review board-approved study. Gemcitabine was administered on Days 1, 8, and 15, and SBRT on Day 29. Gemcitabine was restarted on Day 43 and continued for 3–5 cycles. SBRT of 25 Gy in a single fraction was delivered to the internal target volume with a 2- 3-mm margin using a nine-field intensity-modulated radiotherapy technique. Respiratory gating was used to account for breathing motion. Follow-up evaluations occurred at 4–6 weeks, 10-12 weeks, and every 3 months after SBRT.

Results: All patients completed SBRT and a median of five cycles of chemotherapy. Follow-up for the 2 remaining alive patients was 25.1 and 36.4 months. No acute Grade 3 or greater nonhematologic toxicity was observed. Late Grade 3 or greater toxicities occurred in 1 patient (5%) and consisted of a duodenal perforation (G4). Three patients (15%) developed ulcers (G2) that were medically managed. Overall, median survival was 11.8 months, with 1-year survival of 50% and 2-year survival of 20%. Using serial computed tomography, the freedom from local progression was 94% at 1 year.

Conclusion: Linear accelerator–delivered SBRT with sequential gemcitabine resulted in excellent local control of locally advanced pancreatic cancer. Future studies will address strategies for reducing long-term duodenal toxicity associated with SBRT.

Pancreatic cancer, Stereotactic body radiotherapy, Image-guided radiotherapy, Gemcitabine.

INTRODUCTION

Pancreas cancer is the fourth leading cause of cancer death in the United States, with an overall 5-year survival rate of only 5% (1). Long-term survival may be achieved in surgically resectable patients. However, patients presenting with nonmetastatic yet nonoperable disease are considered to be incurable, with a median survival ranging from 6 to 14 months (2–11). Although the Gastrointestinal Tumor Study Group (12, 13) established combined modality therapy as the treatment of choice for locally advanced pancreatic cancer, advances in both chemotherapy and radiation have resulted in ongoing modifications of many aspects of treatment in the search for a more effective therapy.

Recent chemotherapy trials have examined the use of gemcitabine in combination with other agents. However, except for a very modest survival benefit seen with erlotinib, combination chemotherapy has not substantially improved survival (14–18). Recent radiation trials have altered the chemoradiation scheduling, delivering both different daily doses and total doses of radiation concurrently with varying amounts of gemcitabine (2, 8, 19). Furthermore, the radiation therapy techniques have varied across trials,

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making interpretation and comparison of these results difficult (2, 6, 8, 19, 20). Currently, there is no widely accepted consensus on the radiation fractionation scheme, the radiation field volume, the timing of radiation, or the dose of concurrent gemcitabine or 5-fluorouracil. Unfortunately, despite the use of different conventional radiation fractionation schedules with varying doses of concurrent chemotherapy, local control rates remains relatively low, ranging from 38% to 55% (2, 6, 8, 12, 19, 20).

Hypofractionation has resulted in increased local control in other tumor locations, such as lung and liver, and previous pancreas trials have examined the delivery of high radiation doses in 1–3 fractions (5, 21–23). Although toxicities have been reported to be associated with hypofractionated treatment (especially with the use of larger fields and less conformal techniques), local control rates have ranged from 57% to 94% (21–23). The local control achieved by SBRT is similar to that reported for intraoperative radiation therapy (24, 25).

Unfortunately, the use of high-dose radiation for pancreas cancer has, until recently, been largely confined to the operating room or Cyberknife treatment facilities. This study examined the feasibility, tolerability, and outcomes of standard-dose gemcitabine chemotherapy administered sequentially with single-fraction SBRT dose of 25 Gy delivered via a linear accelerator for pancreatic adenocarcinomas.

METHODS AND MATERIALS

Patients

All patients were enrolled on this prospective, single-institution study, which was approved by the Institutional Review Board. Eligible patients had pathologically confirmed adenocarcinoma of the pancreas. All patients were evaluated and staged at the Stanford Gastrointestinal Multidisciplinary Tumor Board as previously described (22, 23). Briefly, patients underwent biphasic pancreas-protocol computed tomography (CT) scans using 1.25 mm cut thickness with CT reconstruction to determine resectability. Patients were eligible if they were medically inoperable or had locally advanced disease, as defined by the absence of distant or regional disease and any of the following criteria: (*1*) >180° involvement of superior mesenteric artery/vein or any involvement of the celiac axis, (*2*) portal vein occlusion, or (*3*) aorta or inferior vena cava invasion. Other inclusion criteria included age >18 years, Karnofsky Performance Status ≥70%, leukocytes >3,000/uL, Absolute neutrophil count >1,500 uL, total bilirubin <1.5 × institutional limits, aspartate aminotransferase and alanine aminotransferase <2.5 × institutional limits, and creatinine within institutional limits. Patients were excluded if they had prior radiotherapy to the upper abdomen or liver. There was no upper age or carbohydrate antigen 19-9 (CA19-9) limit. The study enrolled patients from April 2006 to October 2007.

Chemotherapy

Gemcitabine chemotherapy was administered at a dose of 1,000 mg/m^2 weekly on Days 1, 8, and 15. This was followed by 25 Gy single-fraction SBRT on Day 29. For logistic reasons, SBRT was allowed to be delayed for up to 1 week. There was a mandated interval of 2 weeks or more after SBRT before weekly gemcitabine (1,000 mg/m^2) was restarted on a 3-week-on, 1-week-off schedule. Three to five cycles of additional gemcitabine were recommended after SBRT. Chemotherapy dose reductions and delays were allowed at the discretion of the treating medical oncologist.

Stereotactic body radiotherapy

Three to five gold fiducial seeds for tumor localization were implanted within and adjacent to the pancreas tumor by upper endoscopy under ultrasound guidance (26). There were at least 5 days between fiducial implantation and radiation planning to ensure the stability of the placed fiducials. Patients were immobilized in the supine position with the arms above the head, using a custom-formed binary foam mold (Alpha Cradle, Smither Products Inc., North Canton, OH). Fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) scans were performed on a GE Discovery PET-CT scanner (GE Medical Systems, Milwaukee, WI). Each patient fasted for at least 8 hours before imaging. After ensuring that blood glucose was <180 mg/dL, patients were injected with 12–18 mCi of FDG. After a tracer uptake time of 45–60 minutes, patients underwent PET/CT imaging. Initially, frontal and lateral x-ray projection images were acquired to act as localizers. Using these images, a whole body scan volume was defined, and CT data were collected in helical acquisition mode. Using the same scan locations, generally spanning three bed positions, PET data were acquired in two-dimensional mode for 3–5 minutes of acquisition time per bed position. The PET data were reconstructed with an ordered set expectation maximization algorithm, using the CT images for attenuation correction. A biphasic expiration breath hold scan was obtained (1.25-mm slice thickness). Oral contrast medium was given to delineate the stomach, duodenum, and small bowel. Subsequently, four-dimensional (4D) CT scans were acquired on the same PET-CT scanner that was equipped with the Real-Time Position Management system (RPM, Varian Medical Systems, Palo Alto, CA) for monitoring the patients' breathing, using previously describe acquisition techniques (27). Slice thickness was 2.5 mm. Ten reconstructed phase bins were used, yielding 10 full-field volumetric image datasets per respiratory cycle for each patient. Image processing was performed on an Advantage Workstation 4.1 with Advantage 4D CT software (GE Medical Systems, Waukesha, WI). Tumor motion was evaluated by measuring the displacement of the three to five implanted gold seeds, using the measurement tool feature of the Advantage Workstation 4.1. After selecting the optimal gating window, the respective phase(s) (mainly end-exhale, 50%, and the two gating boundaries 30% and 70%) were exported into our treatment planning software (Eclipse 7.3, Varian Medical Systems).

The biphasic CT scans, the selected 4D CT datasets, and the PET/CT images were all coregistered by either Digital Imaging and Communications in Medicine (DICOM) co-ordinates (for PET/CT matching) or fused according to fiducials (for CT/CT matching). The gross tumor volume was contoured on the arterial CT scans with the aid of the 4D CT and of the PET images. The gross tumor volume was adjusted on each of the selected 4D CT phases to account for tumor motion and deformation to define the internal target volume. An additional 2- to 3-mm expansion was used to create the planning target volume (PTV). Nodal regions were not included in the PTV. For image guidance purposes, the fiducial markers were contoured, and these images were projected onto the fluoroscopic images during treatment to ensure proper targeting.

The dose guidelines for the duodenum were as follows: (*1*) ≤5% of the duodenum was to receive ≥22.5 Gy, (*2*) ≤50% of the duodenum at the PTV (defined as duodenum only on the same axial images and within 1 cm superior/inferior to the PTV) was to receive ≥12.5 Gy. The maximum cord dose was limited to <6 Gy. Fifty percent of the liver was limited to <5 Gy. Seventy-five percent of each

kidney was limited to <5 Gy. Radiation was planned using the Eclipse 7.3 planning system. The prescription dose was 25 Gy, with the PTV covered by the 95% isodose line. Intensity-modulated radiotherapy was planned using nine equally spaced non-opposed beams. Beam energies of either 6 MV or 15 MV were used. A typical PTV with associated isodose curves is shown in Fig. 1.

All patients were treated using a Varian trilogy 21EX Linear Accelerator with fluoroscopy mode enabled. At the time of treatment, the contours of the expanded fiducial markers and biliary stent (if present) were projected onto the planning digitally reconstructed radiograph (DRR) and kV electronic portal image. Based on orthogonal kilovoltage imaging, patients were first aligned according to bony anatomy. Then, using orthogonal fluoroscopic imaging, the patients were aligned according to the fiducial position at end expiration as determined by the RPM system. Once aligned, the respiratory gating parameters were manually modified to ensure that the radiation beam was on only when the fiducials were within the margin of projected fiducial contours. This process was repeated for each beam angle.

Evaluation of response

Local control was evaluated clinically, by CT, and by PET-CT imaging for all patients. Progressive local disease was defined clinically by symptoms (such as tumor bleeding or gastric obstruction) and by imaging criteria (Response Evaluation Criteria In Solid Tumors- RECIST). The CT progression was determined by increase in the pancreatic tumor size of >20% in the longest diameter, as determined by a CT body imaging radiologist (T.D.). Similarly, local progression on PET imaging was scored by a nuclear medicine physician (A.Q.). Tumors that originally decreased in size/standardized uptake value but subsequently increased in standardized uptake value on follow-up imaging were scored as progressive even if they remained lower than their pretreatment baseline measurements.

Follow-up

All follow-up visits consisted of a history and physical examination, determination of laboratory values, pancreas-protocol CT scan, and a PET-CT scan. Follow-up visits occurred at 4–6 weeks, 10–12 weeks, and every 3 months after SBRT until progression. Acute gastrointestinal toxicity (within the first 3 months after completion of radiation) and late gastrointestinal toxicity (after 3 months) was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v3.0) (28).

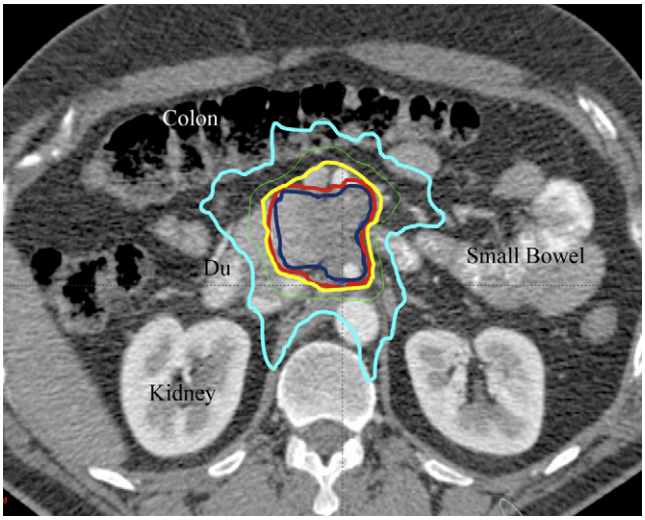

Fig. 1. Axial slice of stereotactic body radiotherapy radiation plan. The 50% isodose line is in light blue, the 75% isodose line is in green, and the 95% isodose line is in yellow. The planning target volume is contoured in red, and the internal target volume is in dark blue. Normal structures are labeled. Du = Duodenum.

Statistics

Our previous Cyberknife studies demonstrated a local control of approximately 95% at 1 year (22, 23). This study of 20 patients has an 80% power to detect a difference in freedom from local progression (FFLP) from 95% to 80%. The null hypothesis is therefore that 1-year local control would be nonsignificantly different from our previous published results and would be rejected only if FFLP were <80% at 1 year. Rates of FFLP, progression-free survival, and overall survival were calculated by the Kaplan-Meier survival curve method. Toxicity correlations were analyzed by one-sided *t* tests with the hypothesis that the larger the volume radiated the greater the chance of developing toxicity.

RESULTS

Patients and treatment

Of the 20 patients enrolled, 18 patients were followed up until death, with 2 patients alive at the time of most recent analysis. The follow-up time for these 2 alive patients was 25.1 and 36.4 months. Table 1 lists the characteristics of all patients enrolled onto this study. Patients ranged in age from 45 to 85 years (median, 63). The PTV volumes ranged from 12.1 to 84.3 cc (median, 40.8 cc). All patients received the prescribed radiation.

All patients received pre-SBRT chemotherapy. The median number of weekly gemcitabine doses before SBRT was three (range, one to five). One patient received 4 weeks and 1

Table 1. Patient characteristics.

Patient	Age	Sex	Tumor stage	Gemcitabine cycles	PTV size (cc)
1	72	M	T4N1	2	47.7
2	63	M	T4N1	4	45.3
3	59	F	T4N0	6	62.1
4	57	F	T4N1	4	27.0
5	62	M	T4N1	5	37.4
6	59	F	T4N0	4	17.3
7	65	M	T4N0	4	54.9
8	45	F	T4N0	6	19.1
9	79	F	T4N0	4	27.3
10	53	F	T4N0	6	22.1
11	60	F	T4N0	6	41.1
12	85	F	T3N0	3	23.9
13	54	F	T4N0	4	12.1
14	77	M	T4N0	6	40.5
15	51	M	T4N0	5	38.3
16	67	M	T4N0	6	50.9
17	52	M	T4N0	13	45.0
18	73	F	T4N0	5	54.2
19	79	M	T4N0	7	84.3
20	69	F	T4N0	7	42.5
Median	63	9 M, 11 F		5	41

Abbreviations: cc = cubic centimeters; PTV = planning target volume.

patient received 5 weeks of gemcitabine before SBRT secondary to a delay in starting SBRT. The median number of gemcitabine cycles (defined as 3 weeks of gemcitabine) given after SBRT (before documented disease progression) was four (range, two to twelve), with a median number of total gemcitabine cycles (before and after SBRT) being five.

Nonhematologic toxicities

Acute gastrointestinal toxicity was scored if these symptoms occurred within 3 months after SBRT. Only 3 patients experienced a Grade 2 acute toxicity. Patient 1 reported an increase in pain, and Patients 18 and 20 experienced transient nausea (Table 2).

Late grade 3 or greater late toxicities occurred in a single patient (5%) who needed surgery for a duodenal perforation. Three patients had medically treated ulcers (Grade 2 2 gastric, 1 duodenal) and made full recoveries. The two gastric ulcers occurred at 4.2 and 5.6 months after SBRT treatment, respectively. The single duodenal ulcer was asymptomatic and was found incidentally on endoscopy 11.8 months after SBRT. The single duodenal perforation occurred 5.4 months after SBRT. Actuarial freedom from late toxicity is shown in Fig. 2. We analyzed the radiation dose and duodenal toxicities as part of another analysis that will be reported separately (29). When the toxicities from this study were analyzed alone, there were too few events to enable a statistically significant correlation between volume of normal tissue irradiated and the development of toxicity.

Freedom from local progression

The FFLP was evaluated with biphasic CT and CT-PET imaging after SBRT. All patients were compliant with follow-up diagnostic imaging. Local progression occurred as the site of first progression in 2 (10%) patients. Both of these local progressions were observed only as an increase in FDG-PET activity. Neither patient had local progression by CT scan (RECIST criteria). These local progressions occurred at 16.1 and 24.1 months, respectively.

Patients completed follow-up scans to evaluate local control even after they had documented distant progression. To date, a total of 5 patients have experienced local progression either before or after distant progression. Four of the five local progressions have been documented only by PET scan with a rise in standardized uptake value and no corresponding tumor growth by CT scan (RECIST criteria). For the entire

Table 2. Acute and late toxicities

Acute toxicity (≤3 months after SBRT)			Late toxicity (>3 months after SBRT)		
Severity	%	Reaction	Severity	%	Reaction
Grade 2	15	Pain (n = 1) Vomiting (n = 2)	Grade 2	15	Ulcer (n = 3)
Grade 3	0	—	Grade 3	0	—
Grade 4	0	—	Grade 4	5	Perforation (n = 1)

Abbreviation: SBRT = stereotactic body radiotherapy.

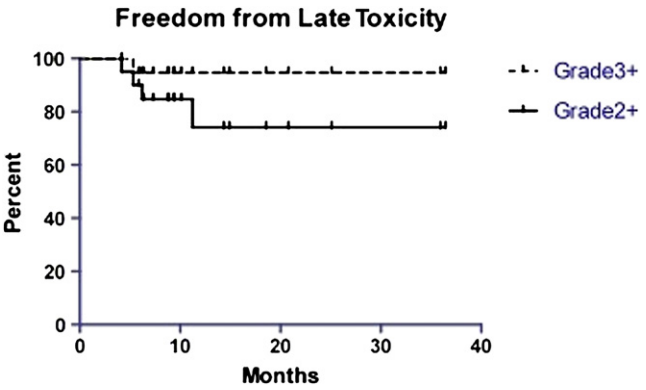

Fig. 2. Freedom from late toxicity.

study population, the actuarial 1-year freedom from local progression rates was 94% using CT criteria and 88% using PET criteria. Figure 3 delineates FFLP when CT criteria alone or CT-PET criteria are used.

Progression-free survival

Time to progression is shown in Fig. 4. Progression has occurred in 19 patients, with the site of first progression being distant in 17 of 19. The median time to progression was 9.2 months. The single patient alive without progression has been followed up for 25.1 months.

Overall survival

A Kaplan-Meier curve of overall survival is shown in Fig. 5. Median survival was 11.8 months, with 2 patients alive at last follow-up. The 1-year survival was 50%, the 2-year survival was 20%, and the 3-year survival was 7%.

DISCUSSION

Toxicity

This study remains consistent with our previous trials investigating the role of SBRT in pancreatic cancer (22, 23, 30). The change from a Cyberknife to a Trilogy linear accelerator did not alter acute toxicity, with only 3 patients experiencing acute Grade 2 toxicity and no patient experiencing nonhematologic acute Grade 3 or greater toxicity. Furthermore, the Grade 2 toxicity (nausea) observed in patient 20 was likely due to noncompliance

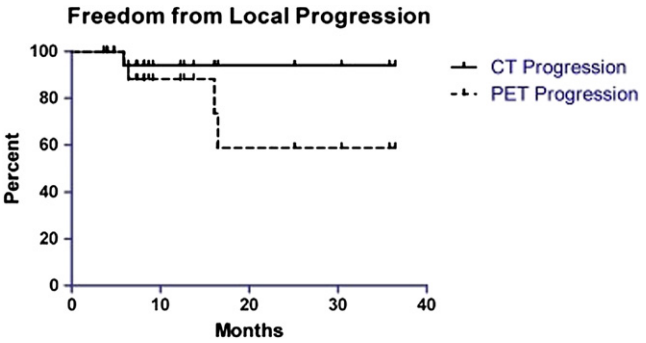

Fig. 3. Freedom from local progression.

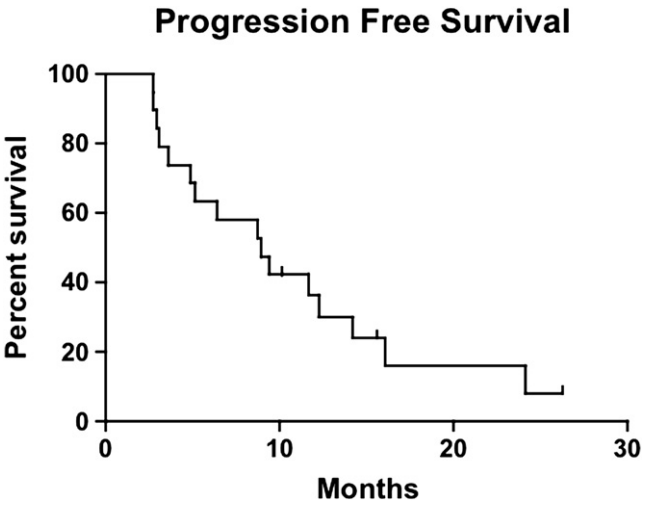

Fig. 4. Progression-free survival.

with prophylactic ondansetron dosing. Previously, Hoyer *et al*. (21) reported significant acute toxicity associated with SBRT for pancreatic cancer. Although the fractionation scheme was somewhat different from what was used in this trial, the most likely explanation for the higher acute gastrointestinal toxicity is that larger treatment volumes were used in the study by Hoyer *et al*. This would correspondingly lead to an increased radiation dose to adjacent bowel. Although we treated pancreatic tumors of similar size, we allowed only a minimal margin expansion to keep the treatment volumes small.

Although direct comparisons between trials are difficult, the acute toxicity from SBRT seems less substantial than that from conventionally fractionated radiation therapy. With conventional radiation (from 50.4 to 61.2 Gy) and concurrent 5-florouracil chemotherapy, recent studies have reported varying nonhematologic Grade 3 toxicity. One of 16 patients (6%) had Grade 3 toxicity in a study by Shinchi *et al*. (20), whereas 14 Grade 3 toxicities were reported in 18 patients in a study by Li *et al*. (6). Conventionally fractionated radiation with concurrent low-dose gemcitabine has also resulted in substantial nonhematologic acute toxicity rates. Brade *et al*. (2) reported a 48% rate of Grade 3 or greater nonhematologic toxicity, and Okusaka *et al*. (9) reported a 57% rate of Grade 3 or greater anorexia and a 21% rate of Grade 3 nausea. Furthermore, trials using full-dose gemcitabine with radiation to 36 Gy, and a reduced PTV (to exclude prophylactic nodal radiation) have shown divergent toxicity results, with Murphy *et al*. (8) reporting only 11% of patients having Grade 3 or greater acute toxicity and Small *et al*. (19) reporting 49% nonhematologic acute toxicity (of which 26% were determined to be directly related to treatment). Interestingly, although this study was not designed formally to assess the hematologic toxicity of SBRT, we did not observe significant acute hematologic toxicity, which may at least partially be related to the smaller volumes irradiated and potentially less bone marrow toxicity.

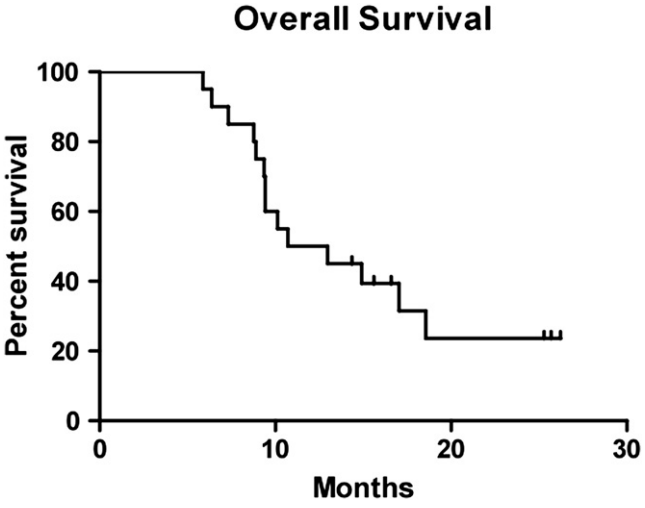

Fig. 5. Overall survival.

Although we have observed a low rate of acute gastrointestinal toxicity from SBRT, the late risk of ulcers continues to be significant and similar to our previous Cyberknife data (31). Three patients (15%) developed Grade 2 ulcers within 4 to 12 months from SBRT. All ulcers were managed medically and resolved with proton pump inhibitor therapy. More significantly, 1 patient (5%) developed a duodenal perforation requiring surgical repair. Similar to Cyberknife data in which ulcerative toxicities occurred 20–46 weeks after treatment (23), in this trial, toxicities occurred 18–49 weeks after treatment. In our institution we have not observed any toxicities occurring more than 1 year after SBRT, and actuarial freedom from Grade 2 or higher toxicity in this trial was 74% at both 1 and 2 years from treatment, with an actuarial freedom from Grade 3 or higher toxicity of 94% at 2 years (Fig. 2).

In attempts to reduce late toxicities, radiation techniques and dose constraints have changed through the course of SBRT trials. In this particular trial we prioritized the duodenal dose constraints above all other critical structures. We aimed to keep at least 50% of the duodenum near the PTV to under the 50% dose (12.5 Gy). Furthermore, we aimed to limit 5% of the duodenum near the PTV to receive 95% of the dose (22.5 Gy). We also encouraged the use of proton pump inhibitors from the time of radiation for 3–6 months after treatment, (although we have no direct evidence that this reduces long-term toxicity). The dose constraints necessary to reduce duodenal toxicity are evolving and will be the subject of a future article that reviews all pancreatic SBRT patients treated at our institution. Given that we did not observe late toxicities to any other critical structures, attempting to further reduce duodenal dose by escalating dose to other normal structures may be possible in future trials. However, because the duodenum is often directly adjacent to the tumor, it is frequently within the PTV, and therefore the only way to reduce toxicity may be to fractionate treatment.

At present, the late complication rate of SBRT appears similar to the rate seen in recent pancreas cancer trials using 2.4 Gy per fraction (to 36 Gy) and concurrent gemcitabine. In

these studies, the Grade 3 late gastrointestinal toxicity rates were 11–19% (8, 32). It is also similar to the toxicity profile of intraoperative radiation therapy, where Willett *et al*. (33) have reported a 15% risk of gastrointestinal bleeding, duodenal obstruction, or abdominal wall dehiscence.

Local control

Local progression rates of 40–65% have been reported with conventionally fractionated radiation (20, 33–35). Local progression is a significant clinical problem because it can lead to increased pain, obstruction, and bleeding. This study confirms that the excellent freedom from local progression previously observed with Cyberknife SBRT treatment of the pancreas (22, 23) can also be achieved using a conventional linear accelerator. In the current study, all patients were followed with biphasic pancreas-protocol CT scans and PET imaging, whereas CT scanning alone was used in the comparative studies. Overall, local progression occurred in 5 patients, with 2 patients experiencing local progression as the site of first progression. Few studies have used PET to evaluate local control, and most have not routinely imaged patients after systemic progression to report the ultimate rates of local control. The most comparable studies in terms of rigorous evaluation of local control were conducted by Murphy *et al*. (8) and Brade *et al*. (2). Using 36 Gy in 15 fractions concurrently with 1,000 mg/m^2 gemcitabine, Murphy *et al*. (8) reported that 1-year and 2-year FFLP were 64% and 38%, respectively. Brade *et al*. (2) reported FFLP of approximately 60% at 1 year and 10% at 2 years using 52.5 Gy concurrently with twice-weekly low-dose gemcitabine. In the current study, using CT RECIST criteria, the FFLP at 1 and 2 years were both 94%. However, according to PET scanning, the FFLP at 1 and 2 years was 88% and 59%, suggesting that PET scanning may be a more sensitive than CT scanning in determining disease activity. Nevertheless, the 1-year and 2-year FFLP rates achieved in this SBRT trial suggest that SBRT may enhance local control in comparison with conventionally fractionated radiotherapy.

Furthermore, the improvement in local control by SBRT was achieved despite the omission of elective radiation to the regional lymph nodes. The reduction in volume treated significantly reduces the toxicity of radiation and does not seem to substantially influence regional recurrence rates. The omission of prophylactic nodal radiation is a developing trend and is supported by other radiation studies, which also did not show significant rates of nodal recurrences (8, 19, 36).

After distant progression, the majority of patients experienced rapid deterioration, and we were not able to obtain follow-up imaging studies to confirm the duration of freedom from local progression. However, in a subset of patients (n = 9), we did obtain follow-up CT scans after distant progression. In this analysis, no patient experienced local progression after systemic progression, with a median follow-up scan time of 4.3 months (mean, 5.5 months; range, 66–677 days). These data suggest that in the interval in which patients remain alive after distant progression, the primary site remains free from local progression. However, one must be cautious in generalizing from these data, because the period of observation was relatively short, and this was a highly selected group of patients.

As was observed in previous SBRT trials, although local control was excellent, there was not enough of a radiographic response to justify surgical exploration and attempt a resection. By RECIST criteria there were no complete responses and no partial responses. After high-dose radiation, inflammatory changes in the pancreas are frequently seen, which can prevent accurate delineation of the tumor borders.

This trial did not enroll potentially operable patients; therefore, future studies using SBRT on a different subset of patients would be necessary to enable direct conclusions to be drawn. However, based on recent data, we cannot recommend SBRT as a method to downstage potentially resectable patients.

Distant progression and survival

Consistent with our previous studies, distant progression was the most common form of progression. Of the 19 patients who experienced progression, 17 experienced distant progression as the first site of recurrence. The median time to progression of 9.2 months was comparable to that in other locally advanced pancreas trials (2, 6, 8, 23). The median overall survival of 11.8 months and the 1-year survival of 50% were also similar to the outcomes reported in other radiotherapy studies for locally advanced pancreatic cancer (2, 6, 8, 20, 22, 23). A recently reported Eastern Cooperative Oncology Group study that randomized patients with locally advanced pancreatic cancer to gemcitabine alone or gemcitabine and radiotherapy was reported in abstract form (37). Despite early closure due to slow accrual, these investigators found an improvement in overall survival with the addition of radiotherapy. These data support an important role of radiotherapy in the management of locally advanced pancreatic cancer. Despite improved local control with SBRT, patients did not show improved disease-free survival or overall survival in this small trial. The lack of benefit is likely attributable to patients having undetected distant micrometastases at time of diagnosis/treatment. Given the limited efficacy of systemic chemotherapy to control metastatic disease, optimizing local control may have limited efficacy on overall survival. However, freedom from local progression is an important clinical endpoint because the progression of pancreatic tumors can cause pain or obstructive symptoms. As systemic chemotherapy improves, the control of the local disease becomes much more important and more likely to be associated with an overall survival benefit. The aim of SBRT is to deliver local therapy expediently to allow patients to reduce delays in the delivery of systemic chemotherapy. Future studies are needed to address the optimal sequencing of chemotherapy, SBRT, and surgery.

To our knowledge, this is the first clinical study reporting the results of SBRT integrated with gemcitabine chemotherapy for pancreas cancer using a conventional linear accelerator, respiratory gating, and fiducial localization. The techniques used in this study are applicable to any linear

accelerator with image-guided radiotherapy capabilities. Furthermore, these techniques are commonly used by many centers worldwide for the treatment of lung and liver tumors. The clinical results achieved in this study using a conventional linear accelerator approach were comparable to the clinical results obtained in our previous studies using Cyberknife SBRT, despite differences in how dose is prescribed. In our previous studies using CyberKnife, 25 Gy was prescribed to the maximum isodose line that covered the PTV, which was typically ~80%, which meant that the maximum point dose to the PTV was >31 Gy. In the current study, the plans were optimized such that the 95% isodose covered the PTV and the maximum point dose was ~26 Gy. Modeling studies have suggested that dose heterogeneity within the tumor can enhance tumor control (38, 39), potentially favoring outcome with the Cyberknife. However, comparison between our studies does not seem to suggest any differences. Further investigation is needed to decide the optimal hypofractionation schedule and whether selective boosting of tumor subvolumes can achieve similar control rates while reducing normal tissue doses. As it stands, we did not observe an obvious detriment in local control when dose homogeneity was improved.

Although there is a risk of late duodenal perforation (5% in this study), continued refinement of SBRT and identification of adjacent normal tissues dose limitations will result in decreased long-term toxicity. Furthermore, adopting a hypofractionated SBRT approach and prophylactic use of proton pump inhibitors may further decrease this risk. We are currently testing this concept in a multicenter Phase II setting.

In conclusion, to our knowledge this is the first prospective Phase II study to demonstrate that a high rate of local control can be achieved using a conventional linear accelerator to deliver SBRT for locally advanced pancreatic cancer. Inasmuch as Murphy *et al.* (8) have shown that local failure was a significant predictor of overall survival, we anticipate that the high local control rate associated with SBRT will eventually translate into improved overall survival as better systemic chemotherapy becomes available. An SBRT or hypofractionated radiotherapy approach for pancreatic cancer is a promising treatment strategy because it allows for integration with more dose-intensive systemic chemotherapy. Future studies will elucidate the optimal sequencing of local and systemic therapies for pancreatic cancer.

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