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CLINICAL INVESTIGATION

GEMCITABINE CHEMOTHERAPY AND SINGLE-FRACTION STEREOTACTIC BODY RADIOTHERAPY FOR LOCALLY ADVANCED PANCREATIC CANCER

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Purpose: Fractionated radiotherapy and chemotherapy for locally advanced pancreatic cancer achieves only modest local control. This prospective trial evaluated the efficacy of a single fraction of 25 Gy stereotactic body radiotherapy (SBRT) delivered between Cycle 1 and 2 of gemcitabine chemotherapy.

Methods and Materials: A total of 16 patients with locally advanced, nonmetastatic, pancreatic adenocarcinoma received gemcitabine with SBRT delivered 2 weeks after completion of the first cycle. Gemcitabine was resumed 2 weeks after SBRT and was continued until progression or dose-limiting toxicity. The gross tumor volume, with a 2–3-mm margin, was treated in a single 25-Gy fraction by Cyberknife. Patients were evaluated at 4–6 weeks, 10–12 weeks, and every 3 months after SBRT.

Results: All 16 patients completed SBRT. A median of four cycles (range one to nine) of chemotherapy was delivered. Three patients (19%) developed local disease progression at 14, 16, and 21 months after SBRT. The median survival was 11.4 months, with 50% of patients alive at 1 year. Patients with normal carbohydrate antigen (CA)19-9 levels either at diagnosis or after Cyberknife SBRT had longer survival (p <0.01). Acute gastrointestinal toxicity was mild, with 2 cases of Grade 2 (13%) and 1 of Grade 3 (6%) toxicity. Late gastrointestinal toxicity was more common, with five ulcers (Grade 2), one duodenal stenosis (Grade 3), and one duodenal perforation (Grade 4). A trend toward increased duodenal volumes radiated was observed in those experiencing late effects (p = 0.13).

Conclusion: SBRT with gemcitabine resulted in comparable survival to conventional chemoradiotherapy and good local control. However, the rate of duodenal ulcer development was significant. © **2008 Elsevier Inc.**

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

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer deaths in the United States (1), and, despite intensive research efforts in chemotherapy and radiotherapy (RT), surgical resection in a small subpopulation of patients is the only modality associated with long-term survival. However, because most patients have unresectable or metastatic disease at presentation, the 5-year overall survival rate for pancreatic cancer remains <5% (2).

Approximately 40–50% of pancreatic cancer patients present with localized, yet nonoperable, disease. In this subgroup, the reported median survival has ranged broadly from 6 to 14 months. This range of survival outcomes likely depends on the intensity of the therapeutic regimen, patient selection factors, and the percentage of patients with marginally resectable disease included in each trial (3–12). Although the Gastrointestinal Tumor Study Group trials (13, 14) established combined modality therapy as the treatment of choice for locally advanced pancreatic cancer, the optimal scheduling of various treatment modalities remains unclear, particularly the integration of RT with gemcitabine chemotherapy. Most prospective randomized trials of locally advanced pancreatic cancer have reported local control rates of 38–55% (3–5, 11, 12, 15). These relatively low local control rates have persisted despite attempts to add concurrent chemotherapy, radiation doses >50 Gy, or hypofractionated radiation regimens

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(6, 7, 11). Local recurrence in this patient population is a significant cause of morbidity because of pain and gastric outlet obstruction.

Various dose escalation strategies have been studied to improve local control in patients with locally advanced disease. Intraoperative RT (IORT) has shown some promise, particularly with smaller tumors, resulting in a 5-year survival rate of 5–7% (16, 17). Intensity-modulated RT allows for a reduction of the radiation dose to surrounding normal tissues and is another promising approach for dose escalation (3). Radiation sensitization with gemcitabine is another strategy to increase treatment intensity, but it must be balanced against the toxicity profile of combined modality therapy. Previous trials used either reduced doses of gemcitabine with full-dose RT or reduced doses of radiation with full-dose gemcitabine to achieve a tolerable treatment regimen (8, 9, 18).

However, recent chemotherapy trials have also been largely unsuccessful in improving the disease outcomes. With the exception of adding erlotinib to gemcitabine, which resulted in a modest improvement in median survival, the addition of other systemic agents to gemcitabine chemotherapy have not demonstrated a clear benefit (19–22). Therefore, the state-of-the-art treatment of locally advanced pancreatic cancer remains unclear. An ongoing Phase III trial is comparing chemotherapy and chemoradiotherapy in an attempt to establish a clear role for RT for this disease (23), and a recent Cochrane meta-analysis concluded that the standard of care is single-agent gemcitabine (24).

We have previously demonstrated that a single fraction of stereotactic body RT (SBRT) is well tolerated and capable of producing local control rates >90% (25, 26). The present study aimed to integrate the administration of standard gemcitabine chemotherapy (to address the high propensity for distant metastases) with the delivery of a single fraction of 25 Gy by SBRT for local disease control, symptom palliation, and potential survival benefit.

METHODS AND MATERIALS

Patients

All patients signed a Stanford institutional review board–approved consent form and had pathologically confirmed adenocarcinoma of the pancreas. All were evaluated and underwent disease staging at the Stanford Gastrointestinal Multidisciplinary Tumor Board, as previously described (25). All patients underwent biphasic, pancreas-protocol computed tomography (CT) using 1.25-mm cuts with CT reconstruction to determine resectability. Patients were deemed to have locally advanced disease if they had no distant or regional disease and had >50% involvement of the superior mesenteric vein/superior mesenteric artery or any involvement of the celiac axis. Only patients with locally advanced disease were eligible for this study. Other inclusion criteria included age >18 years, Karnofsky performance score ≥70%, leukocytes >3,000/μL, absolute neutrophil count >1,500 μL, total bilirubin <1.5 times the institutional limits, aspartate aminotransferase/alanine aminotransferase <2.5 times the institutional limits, and creatinine within the institutional limits. Patients were excluded if they had undergone previous RT to the upper abdomen or liver.

Chemotherapy

Gemcitabine infusion chemotherapy was given at a dose of 1,000 mg/m^2 weekly on Days 1, 8, and 15. This was followed by 25 Gy of SBRT on Day 29. For logistical reasons, SBRT was allowed to be delayed for ≤1 week. At ≥2 weeks after SBRT, weekly gemcitabine (1,000 mg/m^2) in a 3-week-on, 1-week-off schedule was restarted and continued until disease progression or chemotherapy tolerance was reached. A minimal interval of 2 weeks was required after SBRT before gemcitabine chemotherapy was allowed. Chemotherapy dose reductions and delays were allowed at the discretion of the treating medical oncologist. Patients received other chemotherapeutic agents only after documented progression or poor tolerance to gemcitabine.

Stereotactic body RT

Gold fiducial seeds for tumor localization were implanted within and adjacent to the pancreas tumor percutaneously with CT guidance at least 5 days before each patient's RT planning session. The patients were placed in an alpha-cradle with their arms raised and underwent scanning using a GE positron emission tomography (PET)-CT scanner (GE Healthcare, Tampa, FL). Biphasic CT scans (1.5-mm slice thickness) were obtained at end-expiration. In addition, respiratory-gated CT scans (2.5-mm slice thickness) and fluorodeoxyglucose (FDG) PET-CT scans (3.275-mm slice thickness) were obtained for RT planning.

The scans were registered by manual overlay of the fiducial markers or by Digital Imaging and Communications in Medicine (DICM) co-ordinates in the case of the PET scan. The gross tumor volumes (GTVs) were contoured on the end-expiration arterial and venous CT scans. Furthermore, contouring of the GTV was performed on the CT scans at end-expiration, end-inspiration, and a mid-cycle phase. The fused PET scan was used to guide GTV contouring. To account for all respiratory-associated movement, as well as potential deformation of the tumor during the respiratory cycle, the final internal target volume represented the sum of all GTVs. An additional 2–3-mm circumferential expansion was used to create the planning target volume (PTV). Nodal regions were not targeted by SBRT. A typical PTV with associated isodose curves is shown in Fig. 1.

Although the radiation dose to the nearby normal structures, including the stomach, duodenum, bowel, liver, kidney, and spinal

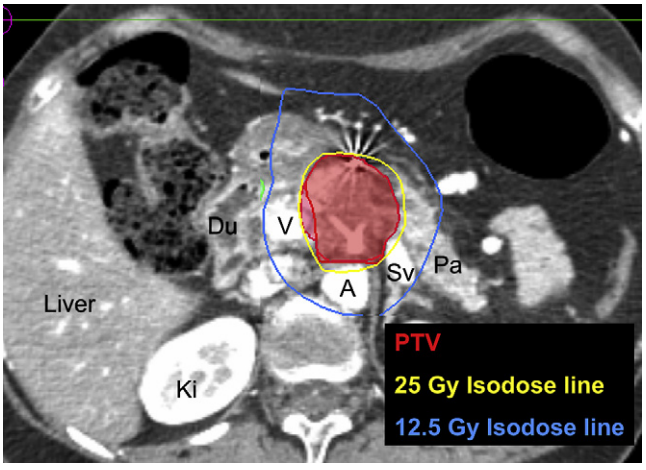

Fig. 1. Dose distribution of axial slice through celiac axis. Planning target volume (PTV) and isodose lines shown. A = aorta; Du = duodenum; Ki = kidney; Pa = pancreas tail; Sv = splenic vein; V = superior mesenteric vein.

Table 1. Patient parameters

Pt. no.	Age (y)	Gender	Location	PTV (cm^3)	Maximal dose (Gy)
1	69	Male	Head	84.2	38.46
2	80	Female	Head	31.5	38.46
3	72	Male	Head	52.7	38.46
4	62	Male	Head	41.4	39.07
5	83	Male	Head	56.5	32.89
6	75	Male	Body	72.0	39.06
7	68	Male	Head	51.5	38.48
8	63	Male	Head	43.6	34.24
9	53	Male	Head	64.6	38.46
10	82	Male	Head	36.8	35.71
11	55	Female	Head	32.6	39.60
12	80	Male	Head	60.6	40.32
13	39	Male	Head	59.7	32.47
14	59	Female	Head	37.7	37.88
15	87	Female	Head	25.0	38.46
16	49	Female	Body	21.5	36.76

Abbreviations: Pt. no. = patient number; PTV = planning target volume.

cord, was taken into account, the major dose constraint was prioritized for the duodenum. RT was planned using the Cyberknife planning system (Accuray, Sunnyvale, CA), and 25 Gy was prescribed to the isodose line, which completely surrounded the PTV; 6-MV beams were used, and the collimator size depended on the geometry of the treated tumor. During SBRT, tumor tracking was performed using the Synchrony system (Accuray), and RT was delivered throughout the respiratory cycle. The total treatment time was approximately 1–3 h, with most patients treated within 2 h.

Evaluation of response

Local control was evaluated with CT and FDG-PET-CT. Progressive local disease was defined by either growth in the tumor size of >20%, as defined by a CT body imaging radiologist (T.D.). Similarly, local progression on PET was scored by a nuclear medicine physician (A.Q.). Tumors that originally decreased in size or standardized uptake values only to enlarge in subsequent scans were scored as having progression even if they remained smaller than their pretreatment baseline measurements.

Follow-up

All follow-up visits consisted of history and physical examination, laboratory values, and a pancreas-protocol CT scan and PET scan. Follow-up visits occurred 4–6 weeks, 10–12 weeks, and every 3 months after SBRT until progression. Acute gastrointestinal (GI) toxicity (within the first 3 months after RT completion) and late GI toxicity (>3 months after) was scored according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0) (27).

Statistical analysis

The rates of freedom from local progression, time to progression, and overall survival were calculated by the Kaplan-Meier survival curve method. Student's t test was used to compare the average duodenal doses received in the group of patients that did and did not develop late complications.

RESULTS

Patients and treatment

Between August 2004 and February 2006, 16 patients were enrolled into this prospective Phase II study. The median follow-up after SBRT was 9.1 months for all patients, with a median follow-up of 22.3 months for living patients. At analysis, 13% of patients were alive. Table 1 lists the characteristics of all patients enrolled in this study. The patient age range was 39–87 years (median, 69 years). The SBRT volume range was 21.5–84.2 cm^3 (median, 48 cm^3), with a maximal dose of 32.2–40.3 Gy. All patients received the prescribed radiation dose. All patients received pre-SBRT chemotherapy (range 1–3 weeks of gemcitabine). The median number of consecutive chemotherapy cycles (defined as 3 weeks of gemcitabine) after SBRT was three (range, zero to eight). Inclusive of the single gemcitabine cycle before SBRT, 12 patients (75%) received at least four cycles of gemcitabine.

Toxicities

The acute toxicities from the treatment are listed in Table 2. The GI toxicity was considered acute if the symptoms occurred within 3 months after SBRT. The most common toxicities were pain and gastritis symptoms, experienced by 19% of patients (n = 3). Of these 3 patients, 2 required increased pain medication to treat their symptoms (Grade 2). The third patient required J-tube placement 6 weeks after Cyberknife treatment because of gastric outlet obstruction symptoms (Grade 3), which we attributed to the SBRT, even though some of these obstructive symptoms were present before SBRT.

Late toxicities were more common, occurring in 7 (47%) of the 15 patients with >4 months of survival after RT (Table 3). Five patients were treated medically for ulcer formation (Grade 2), one required a duodenal stent for a nonneoplastic stricture (Grade 3), and one required surgery after duodenal perforation (Grade 4). Late toxicities occurred 4–10 months after RT.

Because most of the late toxicities reported were duodenal ulcers/strictures, we hypothesized that the toxicity might correlate with the volume of duodenum irradiated. In the patients

Table 2. Acute complications

Pt. no.	Grade	Complication	Previous surgery	Therapy	Interval after treatment (wk)
13	2	Gastritis and pain	CDJ-GJ	None	<6
4	2	Gastritis and pain	Aborted Whipple	Medical	<6
1	3	Ulcer, gastritis, pain	CDJ-GJ	Medical and J-tube	6

Abbreviations: Pt. no. = patient number; CDJ = choledocojejunostomy; GJ = gastrojejunostomy.

Table 3. Late complications

Pt. no.	Grade	Age	Complication	Interval after Cyberknife (wk)	Previous bypass surgery	Treatment
1	2	69	Duodenojejunal ulcer	29	CDJ-GJ	Medical management
9	2	53	Duodenal ulcer	22	CDJ-GJ	Medical management
13	2	39	Duodenal ulcer	26	CDJ-GJ	Medical management
15	2	87	Gastric-duodenal ulcer	32	None	Medical management
6	2	75	Duodenal ulcer	20	None	Medical management
2	3	80	Duodenal stricture requiring stent	46	None	Duodenal Stent
8	4	63	Duodenal ulcer and perforation requiring surgery	34	CDJ-GJ	Surgery

Abbreviations as in Table 2.

with >12 weeks of follow-up after Cyberknife SBRT, we analyzed the volume of duodenum that had received ≥22.5 Gy (95% of the prescribed dose), ≥18.75 Gy (75% of the prescribed dose), and ≥12.5 Gy (50% of the prescribed dose; Table 4). Although the average duodenum volume irradiated to the ≥22.5, ≥18.75, and ≥12.5 Gy isodose lines was greater in the group of patients developing ulcers, significance was not reached for any of the three dose levels. The trend toward increased toxicity was greatest for the duodenal volume encompassed by the 12.5-Gy (50%) isodose line ($p = 0.13$). When analyzed by the percentage of duodenum receiving 22.5, 18.75, and 12.5 Gy, no significant differences were found between the ulcer and nonulcer groups (data not shown).

Local control

Local control was evaluated by both PET and CT and analyzed from the date of SBRT rather than the start of chemotherapy. One patient did not have follow-up scans after treatment because of rapid progression of systemic disease (malignant ascites and anorexia), and another patient was noncompliant with the follow-up protocol and had only one scan approximately 4 months after Cyberknife treatment. The median time from SBRT to the last radiographic evaluation for local control was 8.4 months. On the restaging studies, none of these patients had had a significant enough CT radiographic response to convert their tumors into resectable ones. Often, the borders of these pancreatic tumors developed an inflammatory response, which made it difficult to define the relationship of the tumor with the surrounding vasculature.

At last follow-up, 3 patients (19%) had experienced local recurrence at 14, 16, and 21 months after SBRT. Initially, all three local recurrences were only apparent on CT-PET imaging and were not apparent on contrast-enhanced CT scans. However, 1 patient subsequently demonstrated local tumor recurrence as determined by the CT criteria.

One of the 3 patients who had developed local recurrence also had simultaneous distant progression. The patient with local recurrence at 16 months was alive with no evidence of distant disease on CT or PET. The patient with recurrence at 21 months developed systemic progression 5 months after local recurrence was diagnosed and was still alive at their last follow-up visit. The patient with recurrence at 14 months was found to have concomitant distant and local disease and died 3 months thereafter.

Table 4. Duodenal dose comparison of those with and without late complications

	Duodenal volume (cm^3) receiving		
Late complication	≥22.5 Gy	≥18.75 Gy	≥12.5 Gy
Yes	6.02	16.26	36.48
No	5.24	14.09	29.96
p	0.39	0.31	0.13

Time to progression and overall survival

The time to progression is plotted in Fig. 2. Most patients had documented radiographic evidence of distant metastases (12 patients). Distant progression was also found in 3 other patients (2 with malignant ascites and 1 patient with both ascites and an increasing CA19-9). The median time to progression was 9 months. Overall, 13 of 16 patients had distant progression as the site of first progression, 2 patients had local progression only, and 1 patient had simultaneous local and distant progression.

A Kaplan-Meier curve of overall survival is plotted in Fig. 3. Two patients (13%) were alive at last follow-up. The median overall survival was 11.4 months, with a 1-year survival rate of 50% and a 2-year survival estimate of 18%.

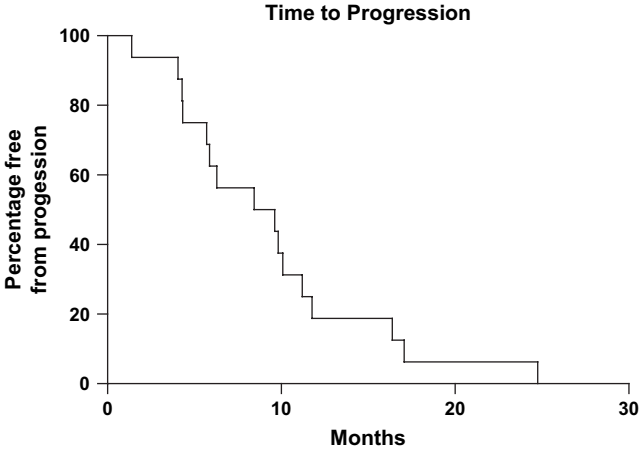

Fig. 2. Time to progression.

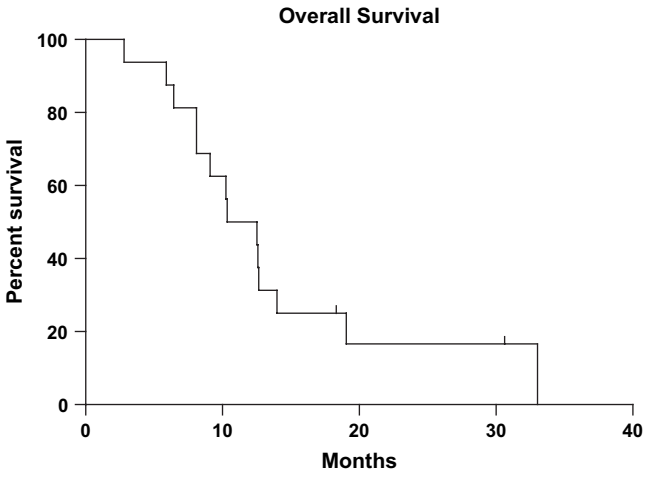

Fig. 3. Overall survival.

CA19-9 results

Only 9 of 16 patients had an elevated CA19-9 before treatment. In these 9 patients, the CA19-9 values were measured 6 weeks (range, 3–10) after SBRT. Three patients (33%) had a decrease in their CA19-9 into the normal range after SBRT, 4 (44%) had a CA19-9 decrease but not into the normal range, and 1 (11%) had an increasing CA19-9 level. One patient was not evaluated because of clinical disease progression.

Kaplan-Meier survival plots are compared in Fig. 4a for those with and without elevated CA19-9 at diagnosis. The median survival for those with normal CA19-9 levels was 12.7 months vs. 9.6 months for those with elevated CA19-9 levels ($p = 0.09$). Furthermore, the survival of those patients with a normal CA19-9 level, either at diagnosis or 6 weeks after SBRT, was significantly improved compared with those whose CA19-9 never returned to normal after treatment. The median survival for those achieving a normal CA19-9 level was 13.3 months compared with 7.3 months for those with constantly elevated CA19-9 levels ($p < 0.01$; Fig. 4b).

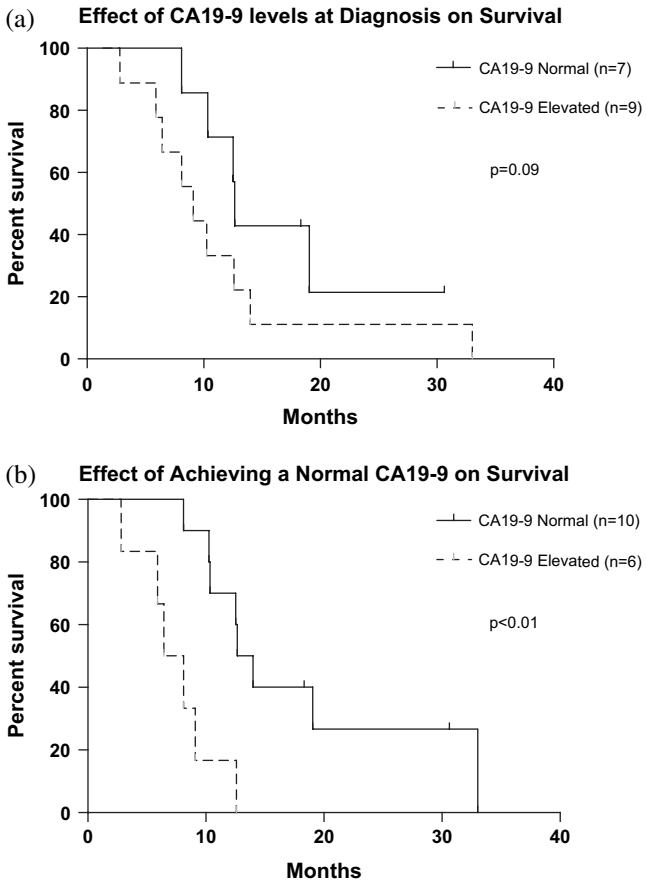

Fig. 4. (a) Effect of carbohydrate antigen (CA)19-9 levels at diagnosis on overall survival. (b) Effect of achieving normal CA19-9 level on overall survival.

DISCUSSION

Toxicity

Similar to our previous studies, the acute GI toxicity of SBRT reported in this trial was mild and therefore unlikely to affect patients' quality of life within the first few months after SBRT (25, 26). However, our acute toxicity data were divergent from the hypofractionated data reported by Hoyer *et al.* (6), who found that 100% of patients had Grade 2 or greater toxicity 2 weeks after treatment with 45 Gy given in three fractions. Several factors could account for the differences observed between the two studies. First, our standard margin expansion from the GTV to the PTV was 2–3 mm. The larger margin (≤10 mm) used in the study by Hoyer *et al.* (6) results in a significantly larger PTV and, because of the location of most pancreatic tumors, is more likely to result in a substantial portion of the duodenal mucosa being encompassed within the PTV. Also, their study used a multifield conformal plan (five to eight static fields), which could have resulted in a larger dose gradient outside the PTV. This would likely have also increased the dose to the adjacent normal tissues such as the duodenum, stomach, and liver. Finally, the larger total dose (45 Gy in three fractions vs. 25 Gy in one fraction) might have contributed to the increased damage to the mucosal and hepatic tissue. In our study, a typical Cyberknife plan used >100 ''nodes'' from which radiation was directed and corrected for respiratory-associated tumor movement in real time. This allowed smaller treatment margins, greater conformality, and larger dose gradients, which ultimately resulted in less normal tissue radiation. Although we treated comparable-size tumors, our median treated tumor volume (PTV) was 46.6 cm^3 (range, 21.5–84.2) and the study by Hoyer *et al.* (6) reported a median PTV of 136 cm^3 (range, 38–376 cm^3). Thus, the largest PTV we treated was smaller than the median tumor treated in their study. This factor is the most likely explanation for the decreased acute toxicity observed in our study.

The acute toxicity (within 90 days) of SBRT also appeared to be less severe than that after conventional external beam RT given within 5–6 weeks. In a trial by Shinchi *et al.* (11), 6% of patients could not complete a course of concurrent 5-fluorouracil and external beam RT to 50.4 Gy in 28 fractions. Concurrent gemcitabine was associated with even greater acute toxicity, with 22% of patients unable to finish the full course of 52.5 Gy in 30 fractions with low-dose

gemcitabine (40 mg/m^2 biweekly) in a recently published trial by Brade *et al.* (4). It is likely that greater doses of gemcitabine would further increase the toxicity. When 50.4 Gy was delivered with 250 mg/m^2 of weekly gemcitabine, 33% of patients required intravenous hyperalimentation and 21% had Grade 3 nausea (8). In contrast, when 50.4–61.2 Gy was delivered concomitant with gemcitabine (600 mg/m^2 weekly) 16 of 18 patients developed Grade 3, nonhematologic toxicity (7). However, reducing the PTV to exclude prophylactic nodal RT reduces the toxicity of concurrent gemcitabine, because Murphy *et al.* (28) reported that only 11% of patients developed Grade 3 or greater acute toxicity with full-dose gemcitabine (1,000 mg/m^2 on Days 1, 8, and 15) and 36 Gy of radiation in 15 fractions.

Although we did not observe significant acute GI toxicity (6% Grade 3); we did observe a significant risk of late GI toxicity, primarily the development of duodenal ulcers. Of the 15 patients alive ≥6 months after SBRT, 7 (47%) experienced Grade 2 or greater GI toxicity, with 2 (13%) of the 15 experiencing Grade 3 or greater GI toxicity. Our late toxicity results are similar to those of the SBRT trial by Hoyer *et al.* (6). Their trial used 45 Gy in three fractions, and of 12 patients evaluated at ≥3 months, 5 (42%) had severe mucositis, ulceration, or duodenal perforation (6). Similarly, when 24 Gy was delivered in three fractions (Days 1, 8, and 15) with gemcitabine (300 mg/m^2 weekly), the rate of ulceration in the stomach and duodenum was 37.5% (29). This toxicity profile appears similar to that with IORT. Willett *et al.* (17) reported a 15% risk of GI bleeding, duodenal obstruction, or abdominal wall dehiscence. Unlike the SBRT trials discussed in the preceding paragraphs, the IORT study did not report medically managed ulcers. However, given the reported toxicities of IORT, the incidence of ulcers was likely also substantial.

Although the SBRT late toxicity was similar to that after IORT, it appears elevated compared with that in conventional chemoradiotherapy studies (4, 8, 30–32). Late toxicities were not reported in the Gastrointestinal Tumor Study Group trials; however, both Okusaka *et al.* (8) (50.4 Gy and gemcitabine 250 mg/m^2 weekly) and Brade *et al.* (4) (52.5 Gy and gemcitabine 40 mg/m^2 biweekly) observed no late Grade 3 toxicity (13). Li *et al.* (7) reported an 11% risk of GI hemorrhage when ≤61.2 Gy was given concurrently with 600 mg/m^2 of weekly gemcitabine. However, hypofractionation does appear to increase the incidence of late toxicity. Symon *et al.* (33) reported a 4% incidence of Grade 3-4 GI toxicity in patients receiving a standard fractionated RT course with concurrent full-dose gemcitabine. In contrast, those treated with a hypofractionated regimen (2.4 Gy in 15 fractions) had a 19% incidence of Grade 3-4 GI complications (33). Similarly, Murphy *et al.* (28) (36 Gy in 15 fractions with full-dose gemcitabine) reported an 11% risk of Grade 3 or 4 late side effects. These moderate hypofractionation regimens resulted in late toxicities intermediate between those of conventionally fractionated RT and SBRT.

Our analysis of duodenal toxicity found a correlation that reached borderline significance between increased duodenum volumes irradiated and duodenal toxicity. The duodenal volume irradiated to ≥12.5 Gy (50% prescribed dose) was the most predictive of the development of toxicity. Although this trend did not reach statistical significance, we anticipate that with more patients and longer follow-up, the data will reach significance. To our knowledge, this is the first dosimetric report of the tolerance of the duodenum to single-fraction RT. On the basis of these results, we have routinely integrated an analysis of duodenal dose–volume histograms in our clinical SBRT practice. In addition, we prophylactically treat all our pancreatic cancer patients with proton-pump inhibitors for ≥6 months from the date of SBRT.

Local control

The results of this study have confirmed the excellent rate of local progression-free survival from our previous Phase I and II studies of SBRT for pancreatic cancer (25, 26). We obtained FDG-PET CT scans for all patients, in addition to the standard pancreas protocol CT scans. In the present study, 3 (19%) of 16 patients developed progressive local disease. All of these local recurrences developed >1 year after Cyberknife SBRT (freedom from local progression of 100% at 1 year). The disease of all patients with progression was originally scored according to increased FDG-PET activity. Distant progression was the site of first progression in 13 of 16 patients, with 1 patient having simultaneous local and distant progression and 2 patients having local disease as the first site of progression. These data suggest that if patients live long enough, local progression would be a more significant clinical problem. No patient developed progressive gastric/duodenal or biliary obstruction because of local tumor progression, although 7 (44%) of 16 had initially undergone gastrojejunostomy and/or choledochojejunostomy before any therapy, making it difficult to assess the effect of SBRT on potential biliary or duodenal obstruction.

Although we obtained excellent local control in this study, we did not observe substantial tumor regression away from surrounding vessels that would have allowed for surgical resection. We postulated that high-dose RT can result in peritumoral and peripancreatic inflammatory changes that tended to obscure the tumor borders. Although these lesions became PET negative on the follow-up scans, they generally did not regress significantly, as assessed by subsequent CT scans. We performed a volumetric analysis of the total metabolic tumor burden (standardized uptake value multiplied by tumor volume) and observed a trend toward increased survival in those patients with a lower total metabolic tumor burden after Cyberknife treatment. Similarly, we observed a trend toward increased survival in those patients with a lower maximal standardized uptake value (data not shown). Although these data are promising, we will need more patients and longer follow-up before any definitive conclusions can be drawn about the value of post-therapy FDG-PET restaging scans.

Because reviews of the published data have shown local progression rates of 40–60% with conventional fractionation (12, 34) and local progression rates in recent chemoradiotherapy trials have been as great as 60–65% (3, 11), local control

Table 5. Summary of treatment regimens, toxicities, local failure, and overall survival in recent phase II trials

Investigator	Patients (*n*)	RT dose (Gy)/ fraction	Concurrent gemcitabine dose (mg/m^2)	Nodal RT	Acute GI toxicity (≥G3) (%)	Late GI toxicity (≥G3) (%)	Local failure at 1 y (%)	Local failure (time not reported) (%)	Median overall survival (mo)
Brade *et al.* (4)	27	52.5/30	40 biweekly	Yes	48	0	48	—	13.9*
Magnino *et al.* (32)	23 (included 6 resected)	45/25	50–100 biweekly	Yes	10 events in 23 patients	—	—	33	12†
Blackstock *et al.* (30)	39	50.4/28	40 biweekly	Yes	41	—	—	15	7.9
Okusaka *et al.* (8)	38	50.4/28	250 weekly	Yes	≥33	0	— (site of 1st progression only)	6	9.5
Epelbaum *et al.* (31)	10	50.4/28	400 weekly	Yes	25	—	—	—	8
Li *et al.* (7)	18	50.4–61.2 Gy (1.8 Gy/ fraction)	600 weekly	Yes	100	11	—	33	14.5
Murphy *et al.* (28)	74	20–42 Gy (2.4 Gy/ fraction)	1,000 weekly	No	11	11	36	—	11.2
Hoyer *et al.* (6)		45/3	Nil	No	23	8	43	—	5.7
de Lange *et al.* (29)	24	24/3	300 weekly	Peripancreatic only	4	38	—	21	10
Present study	16	25/1	Nil	No	6	13	0	20	11.4
Willet *et al.* (17)	150	IORT	Nil	No	20 (postoperative complications)	15	—	—	13

Abbreviations: RT = radiotherapy; GI = gastrointestinal; G = grade; IORT = intraoperative RT.
* Reported as Phase I and II combined (n = 31).
† Unresected patients only.

in pancreatic cancer continues to be a significant clinical problem. The improvement in local progression-free rates in the present study was evident despite not treating the locoregional lymph nodes. The lack of nodal recurrences suggests that these areas do not need to be treated prophylactically. Reducing the volume treated with RT could significantly reduce normal tissue toxicities. Although gemcitabine might have some contribution in sterilizing microscopic disease in the regional lymph nodes, this effect was limited because most patients developed distant metastases (primarily liver) as the site of first progression.

The omission of prophylactic nodal RT in our study has been further supported by other recently reported studies. McGinn *et al.* (35) at the University of Michigan conducted a Phase I study in which full-dose gemcitabine was given concurrently with an increasing radiation dose during a 3-week period. In their study design, the radiation fields were limited to a 1-cm margin around the primary tumor, and no prophylactic RT was given to the regional lymph nodes (35). Murphy *et al.* (28) reported the patterns of failure and assessed the toxicities associated with this treatment. With a follow-up of 10.6 months, they reported a 1- and 2-year freedom from local progression rate of 64% and 38%, respectively. Despite the omission of prophylactic nodal RT, only 5% of patients had failure in the peripancreatic nodes (28). The differences between recent SBRT and conventionally fractionated RT trials, in terms of acute toxicity, late toxicity, local control, and field size are summarized in Table 5.

Time to progression and overall survival

The median time to progression was 9.7 months, and the median overall survival was 11.4 months. Because survival in this single-institution, Phase II study might have been influenced by selection bias, a direct comparison of the time to progression and overall survival data between trials was not practical. However, our survival rates are comparable with those in the experimental arms of recent fractionated chemoradiotherapy trials (as reviewed by Brade *et al.* [4] and Willett *et al.* [17]) and improved compared with the data reported in the SBRT trial by Hoyer *et al.* (12).

Previously, certain CA19-9 parameters were found to be predictive of survival in patients with operable and nonoperable pancreatic cancer (36, 37). Our small trial did not have sufficient numbers to stratify patients in the same manner as done in previous trials; however, when the patients were grouped according to normal CA19-9 levels at diagnosis vs. elevated values, a trend toward increased survival in those with normal CA19-9 levels was found. Furthermore, when our patients were grouped into those with normal CA19-9 levels at baseline or CA19-9 levels that decreased into the normal range after SBRT vs. those with elevated levels after SBRT, those who achieved a normal CA19-9 level had a statistically significant increased median survival compared with those with continually elevated CA19-9 values (median survival, 13.3 vs. 7.3 months, respectively). These data further support the use of CA19-9 as both a prognostic factor at diagnosis and a means to evaluate the response to treatment.

CONCLUSION

We acknowledge the significant differences between SBRT and standard chemoradiotherapy for pancreatic cancer and that additional clinical trials comparing both techniques are needed to improve the outcomes in patients with pancreatic cancer. The toxicity of conventionally fractioned RT is largely acute, especially when combined with concurrent chemotherapy. The lower biologic dose from conventionally fractionated RT leads to a greater local relapse rate but, likely, a lower risk of late complications. Furthermore, standard chemoradiotherapy is delivered within 5–6 weeks, which has a significant detrimental effect on the patients' quality of life. Also, some of the acute toxicities are certainly related to prophylactic regional nodal RT. Our current practice is to maximally spare the duodenum while still maintaining a tumoricidal radiation dose to achieve similar local progression-free survival rates and reduce the risk of long-term radiation toxicity. As more effective systemic therapies for pancreatic cancer become available, local control will become a more important clinical component of the treatment.

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