Original Article

Stereotactic Radiotherapy for Unresectable Adenocarcinoma of the Pancreas

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BACKGROUND: The authors report on the local control and toxicity of stereotactic body radiotherapy (SBRT) for patients with unresectable pancreatic adenocarcinoma. **METHODS:** Seventy-seven patients with unresectable adenocarcinoma of the pancreas received 25 gray (Gy) in 1 fraction. Forty-five patients (58%) had locally advanced disease, 11 patients (14%) had medically inoperable disease, 15 patients (19%) had metastatic disease, and 6 patients (8%) had locally recurrent disease. Nine patients (12%) had received prior chemoradiotherapy. Sixteen patients (21%) received between 45 to 54 Gy of fractionated radiotherapy and SBRT. Various gemcitabine-based chemotherapy regimens were received by 74 patients (96%), but 3 patients (4%) did not receive chemotherapy until they had distant failure. **RESULTS:** The median follow-up was 6 months (range, 3-31 months) and, among surviving patients, it was 12 months (range, 3-31 months). The overall rates of freedom from local progression (FFLP) at 6 months and 12 months were 91% and 84%, respectively. The 6- and 12-month isolated local recurrence rates were 5% and 5%, respectively. There was no difference in the 12-month FFLP rate based on tumor location (head/uncinate, 91% vs body/tail, 86%; $P = .52$). The progression-free survival (PFS) rates at 6 months and 12 months were 26% and 9%, respectively. The PFS rate at 6 months was superior for patients who had nonmetastatic disease versus patients who had metastatic disease (28% vs 15%; $P = .05$). The overall survival (OS) rates at 6 months and 12 months from SBRT were 56% and 21%, respectively. Four patients (5%) experienced grade $\geq$2 acute toxicity. Three patients (4%) experienced grade 2 late toxicity, and 7 patients (9%) experienced grade $\geq$3 late toxicity. At 6 months and 12 months, the rates of grade $\geq$2 late toxicity were 11% and 25%, respectively. **CONCLUSIONS:** SBRT for pancreatic adenocarcinoma was effective for local control with associated risk of toxicity and should be used with rigorous attention to quality assurance. Efforts to reduce complications are warranted. Distant metastases account for the vast majority of disease-related mortality. (See editorial on pages 468–472, this issue.) **Cancer 2009;115:665–72. © 2008 American Cancer Society.**

KEY WORDS: local control, pancreatic cancer, locally advanced, stereotactic body radiotherapy.

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Pancreatic cancer is the fourth leading cause of cancer death in the United States.[1] Surgery with complete resection (R0) is the only treatment option associated with any substantive chance of cure, with a 5-year survival rate of approximately 20%.[2] However, only a minority of patients are able to undergo surgical resection and, among these patients,[3] many still will have a microscopic positive margin after surgery.[2]

Locally advanced or unresectable disease is the most common presentation of pancreatic cancer, and studies have demonstrated that combined-modality therapy with chemotherapy and radiation therapy (RT) are superior to single-modality therapy. The Gastrointestinal Tumor Study Group (GITSG) study demonstrated that chemoradiotherapy (chemo-RT) improved overall survival (OS) compared with RT alone.[4] Another study demonstrated that chemotherapy combined with RT resulted in improved survival compared with chemotherapy alone.[5] Even in those studies, despite the poor survival, local failure still was a major component of disease progression (30%-50%),[6] which often can lead to symptoms of pain, obstruction, and other morbidities that decrease quality of life. Therefore, intensified local therapy has been investigated.[7,8]

Previously, our institution published trials using stereotactic body RT (SBRT).[9-11] Those trials established our institutional standard of care for the treatment of locally advanced pancreatic cancer as 25 gray (Gy) in a single fraction in combination with systemic therapy. The objective of the current study was to report local control and toxicity using SBRT in this manner on the largest group of patients reported to date.

MATERIALS AND METHODS

This study was a retrospective study examining all patients who were treated at Stanford University for unresected pancreatic adenocarcinoma and received 25 Gy in a single fraction using SBRT. Between October 2002 and October 2007, 77 patients met the inclusion criteria for this study, which were: 1) confirmed histologic evidence of adenocarcinoma of the pancreas, 2) treated in a single fraction of 25 Gy, 3) had not undergone a previous Whipple procedure or other resection, and 4) had unresectable disease. Reasons for unresectability included the presence of metastatic disease; radiographic findings of major vessel involvement, as determined by the surgeon and/or radiologist; and comorbid illnesses that made the patient high risk for undergoing surgical resection. In addition, patients with tumors that measured >7.5 cm in any 1 dimension were considered too large for single-fraction SBRT. Forty patients who were included in this analysis were part of 3 other completed prospective trials.[9-11] Patients with metastatic disease who were treated with SBRT had low-volume, distant disease that either 1) responded well to initial chemotherapy if their prognosis was favorable enough that local disease potentially could lead to death or significant morbidity or 2) the local tumor was causing symptoms of pain or obstruction. Table 1 shows the patient characteristics. There were 8 patients with resectable primary tumors, including 4 patients who were identified as metastatic at the time of attempted resection, and 4 patients who were medically inoperable. Two additional patients had disease that was marginally resectable and were treated with preoperative intent, but

Table 1. Patient and Treatment Characteristics

Characteristic	No. of Patients (%)
Overall stage	
Locally unresectable	56 (73)
Medically inoperable	4 (5)
Marginally resectable	2 (3)
Metastatic	15 (19)
Initial diagnosis	69 (90)
Recurrent disease	8 (10)
Regional lymph node disease	
Involved	15 (19)
Uninvolved	62 (81)
Nonmetastatic disease	62 (81)
Metastatic disease	15 (19)
Sex	
Men	49 (64)
Women	28 (36)
Median age [range], y	64 [39 to >90]
Prior RT	
Yes	9 (12)
No	68 (88)
SBRT alone	61 (79)
SBRT with fEBRT	16 (21)
Chemotherapy	
Prior treatment	15 (19)
Current treatment	59 (77)
None	3 (4)

RT indicates radiotherapy; SBRT, stereotactic body radiotherapy; fEBRT, fractionated external beam radiotherapy.

did not undergo underwent surgery because their tumors did not become resectable on post-treatment imaging. An additional 4 patients underwent aborted Whipple procedures after determining that the extent of tumor made the disease unresectable.

Patients underwent standard pretreatment staging studies, including history and physical examination, complete blood count, chemistry panel, carcinoembryonic antigen, carbohydrate antigen 19-9 (CA19-9), chest radiograph, and pancreas-protocol computed tomography (CT) scan (high-speed, biphasic abdominal CT scan; 1.25 mm cuts, 3-dimensional reconstruction).

All patients had 3 to 5 gold fiducials implanted into the tumor for targeting purposes through open laparotomy (8 patients), endoscopy (4 patients), or CT-guided percutaneous needle (65 patients). Patients who had an open laparotomy placement did so at the time of an abandoned resection with the anticipation of SBRT because of unresectable disease. Otherwise, the method of placement was left to the discretion of the attending physician. With the exception of the open laparotomy method, all fiducial placements were completed on an outpatient basis, and there were no complications related to the placement of these fiducials.

Patients underwent radiation planning scans 7 to 14 days after fiducial implantation to reduce the possibility of fiducial migration between radiation planning and radiation delivery. An Alpha Cradle (Smithers Medical Products, North Canton, Ohio) immobilization device was custom made for each patient. Planning was done using a biphasic CT scan; and, beginning in 2004, 4-dimensional (4-D) CT scans and positron emission tomography (PET) scans were incorporated into the treatment planning process.

The gross tumor volume (GTV) was delineated on the biphasic scan with the aide of the PET scan when it became available. After 4-D CT imaging and respiratory tracking became available, the biphasic CT images were coregistered with the end-expiration and end-inspiration phases from the 4-D CT scan using the fiducial seeds as registration points, and adjustments were made to include variations in the GTV geometry to account for tumor deformation caused by motion of the pancreas during respiration.[12] The planning target volume (PTV) for SBRT was defined as the GTV only plus 2 or 3 mm for setup error. The regional lymph nodes were not included in the target volume. For patients who were treated on protocol with intensity-modulated RT (IMRT) (45 Gy in 1.8 Gy fractions) in addition to SBRT, the IMRT portion included the primary tumor and regional lymph nodes (peripancreatic, celiac, superior mesenteric, porta hepatic, and retroperitoneal) before the delivery of SBRT to the primary tumor only.

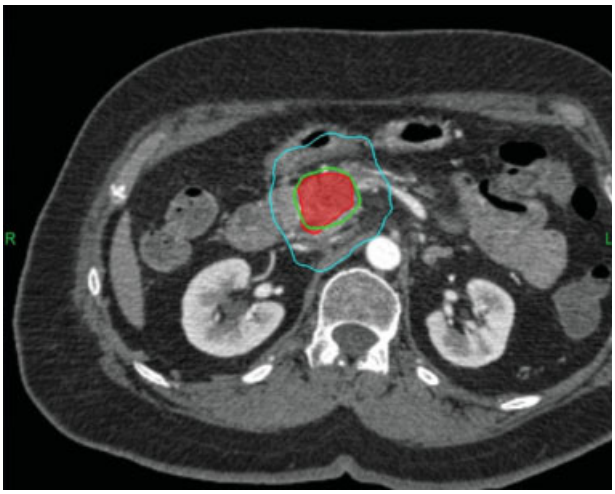

FIGURE 1. Typical isodose distribution for patients receiving stereotactic body radiotherapy. Twenty-five grays (Gy) are prescribed to the line that completely encompasses the planning target volume. The 12.5-Gy line is kept away from the distal wall of the duodenum and stomach.

Next, a radiosurgical treatment plan was generated. The dose was 25 Gy prescribed to the isodose line that completely covered 95% of the PTV (Fig. 1). Normal tissue constraints for treatment planning are shown in Table 1. SBRT was delivered for all patients using CyberKnife (Accuray, Sunnyvale, Calif) with the Synchrony (Accuray Inc.) respiratory tracking system.

The CyberKnife is a frameless, image-guided RT system that has a 6-megavolt linear accelerator mounted on a robotic arm with 6 degrees of freedom. The imaging system is composed of 2 diagnostic orthogonal x-ray sources on the ceiling paired with amorphous silicon detectors that capture digital radiographic images of the patient in real time. The Synchrony respiratory tracking system is composed of light-emitting diodes (LEDs) placed on the patient's chest wall. The motion of the LEDs with the respiratory cycle is registered by a camera array. The Synchrony system identifies a correspondence model between the movement of the fiducials and the LEDs, representing

internal and external motion, respectively. This model enables the linear accelerator to track the motion of the markers continuously through the motion of the LEDs, thereby adjusting the position of the beam automatically relative to the moving target. This correspondence model is updated continuously throughout the treatment.

A variety of gemcitabine-based chemotherapy regimens were used. Eight patients had received prior chemoRT as part of initial treatment and were treated with the CyberKnife because of progressive or persistent local disease. In addition, 7 patients had received prior chemotherapy alone. No chemotherapy was given 2 weeks before SBRT and 2 weeks after SBRT.

To determine response, follow-up pancreatic-protocol CT scans and PET/CT scans were obtained at 4 to 12 weeks after SBRT and every 2 to 4 months thereafter until disease progression. CA19-9 levels also were obtained at each of these intervals. Acute toxicity was defined as toxicity that occurred within 3 months of SBRT, and late toxicity was defined as toxicity that occurred >3 months after SBRT.

Statistics

Local progression and disease progression were defined from the date of SBRT to the time of the documented first site of progression, either radiographically or clinically. Often, on the CT scans, tumor growth or progression was not always obvious because of peritumoral fibrosis and inflammation. Therefore, to minimize bias toward the efficacy of treatment, patients who developed gastric outlet obstruction with uncertain growth observed on a CT scan were categorized with local progression. Local control was evaluated only in patients who had at least 1 follow-up CT, magnetic resonance imaging, or PET scan. OS was calculated from 2 different time points: 1) from the date of SBRT until death or last follow-up and 2) from the date of diagnosis to the date of death or last follow-up.

The SAS and JMP software packages were used for statistical computation (SAS Institute, Cary, NC). The Kaplan-Meier product-limit method was used to calculate estimates of survival, local failure, and disease progression.[13] Stratifications of these endpoints by selected prognostic factors were assessed for statistical significance by using the log-rank test statistic.

Table 2. Normal Tissue Constraints Used for Treatment Planning

Organ	Constraint
Prescription dose	25 Gy to the isodose line covering >95% of PTV
Tissue	
Liver	50% Of volume <5 Gy
	70% <2.5 Gy
Kidney	75% Of volume of each kidney <5 Gy
Spinal cord	Maximum dose <5 Gy
Stomach	<4% of volume <22.5 Gy
	The 50% isodose line should not reach the distal (nonadjacent) wall of the lumen
Duodenum	<5% Of volume <22.5 Gy
	<50% Of volume <12.5 Gy
	The 50% isodose line should not reach the distal (nonadjacent) wall of the lumen
Other bowel	Maximum dose <21 Gy
	<5% Of volume <20 Gy

Gy indicates grays.

RESULTS

The overall median follow-up was 6 months (range, 3-31 months); and, among the patients who were alive at last follow-up, it was 12 months (range, 3-31 months). Patient and treatment characteristics for all 77 patients are shown in Table 2. Ten patients had local progression as a component of initial failure (13%), but only 4 patients had isolated local failures (5%). Nine patients (12%) progressed initially in the regional lymph nodes, but all 9 occurred in the setting of either local progression (1 patient), distant failure (7 patients), or both (1 patient). Sixty-five patients had distant metastasis as a first site of failure (84%). Nine of those patients (14%) had metastatic disease at the time of SBRT and progressed at the known metastatic site.

No patients achieved a radiographic complete response. One patient was able to undergo surgical resection after a partial response to SBRT allowed for a surgical resection. The surgical specimen in that patient had a negative margin with a near-complete pathologic response observed on pathology review. For the entire group, the rates of freedom from local progression (FFLP) at 6 months and 12 months were 91% and 84%, respectively (Fig. 2, top). The 6- and 12-month isolated local recurrence rates were both 5% (Fig. 2, bottom). There was no difference in the 12-month FFLP rate based on tumor location (head/uncinate [91%] vs body/tail [86%]; $P = .52$).

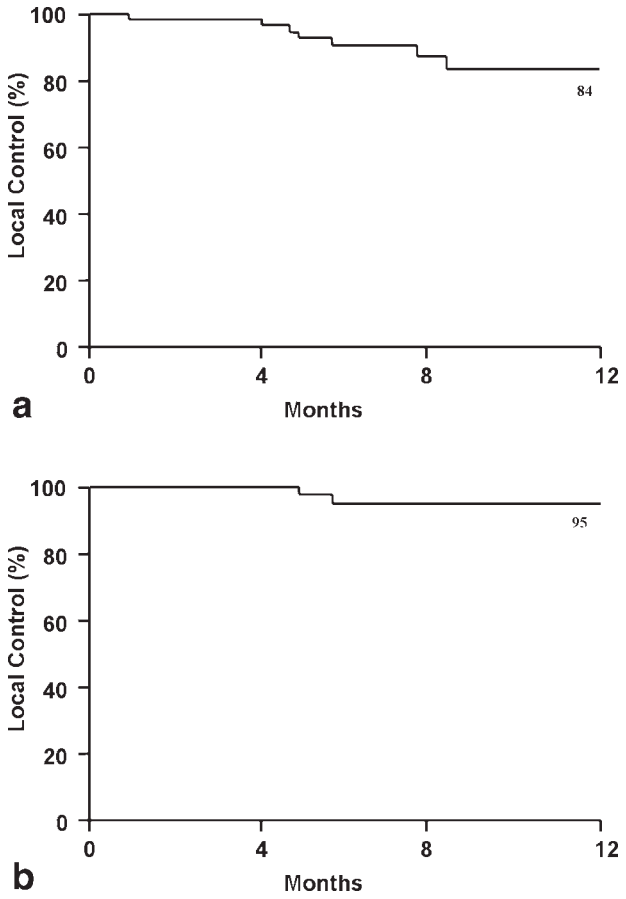

FIGURE 2. Actuarial curves of freedom from local progression (top) and freedom from local progression without other sites of failure (bottom).

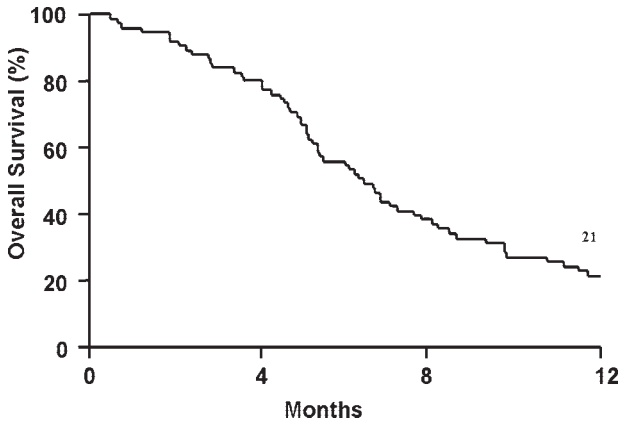

FIGURE 3. Actuarial curve of overall survival calculated from date of stereotactic body radiotherapy.

Table 3. Associated Toxicities

	No. of Patients (%)			
Toxicity	Grade 2	Grade 3	Grade 4	Total
Acute				
Small bowel ulcer	2	0	0	2 (3)
Gastric ulcer	0	1	0	1 (1)
Pain	1	0	0	1 (1)
Late				
Small bowel ulcer	3	0	0	3 (4)
Gastric ulcer	0	3	0	3 (4)
Duodenal stricture	0	1	0	1 (1)
Biliary stricture	0	2	0	2 (3)
Small bowel perforation	0	0	1	1 (1)
Total	6 (8)	7 (9)	1 (1)	14 (18)

The progression-free survival (PFS) rates at 6 months and 12 months were 26% and 9%, respectively. The OS rates at 6 months and 12 months were 56% and 21%, respectively (Fig. 3). The median survival durations calculated from the time of SBRT for the entire group, the locally advanced group, and the metastatic group were 6.4 months, 6.7 months, and 4.7 months, respectively. The median survival durations for the entire group calculated from the time of diagnosis, the locally advanced group, and the metastatic group were 11.9 months, 11.5 months, and 10.5 months, respectively.

Univariate analysis indicated that tumor location (head vs body/tail), initial CA19-9 level (normal vs elevated), percent drop in CA19-9 (from initial to nadir), and metastatic versus nonmetastatic disease had no influence on OS or FFLP. The PFS rate at 6 months was superior for patients with nonmetastatic disease versus patients with metastatic disease (28% vs 15%; $P = .05$).

Toxicity

Toxicities in the absence of progressive disease are listed in Table 3. Four patients (5%) experienced grade $\geq$2 acute toxicity. One patient with a grade 2 small bowel ulcer received IMRT to 45 Gy with SBRT. Three patients (4%) experienced grade 2 late toxicity, and 7 patients (9%) had grade $\geq$3 late toxicity. One of the patients with a grade 2 small bowel ulcer and 1 of the patients with a grade 3 gastric ulcer had received a previous course of RT to the tumor site to 50.4 Gy. Another patient with a grade 2 ulcer received IMRT to 45 Gy along with SBRT. In total, 1 of 4 acute toxicities and 3 of 10 late grade $\geq$2

toxicities occurred in patients who had received external-beam RT to the pancreas in addition to SBRT.

The 3-month actuarial grade $\geq$2 acute toxicity rate was 5%. The 6-month and 12-month grade >2 late toxicity rates were 11% and 25%, respectively. Overall, the grade $\geq$2 acute and late toxicity rates at 6 months and 12 months were 17% and 28%, respectively. The median OS duration from the date of SBRT for patients who developed a grade $\geq$2 complication was 11.7 months.

DISCUSSION

Our institution previously reported on the results of SBRT for patients with locally advanced pancreatic cancer. Koong et al conducted a phase 1 study that escalated the single-fraction SBRT dose to 25 Gy.[10] At a median follow-up of 4.5 months in 6 evaluable patients who were treated at the 25-Gy dose, the local control rate was 100%. The median OS for that group was 8 months. A subsequent phase 2 study investigated SBRT at 25 Gy after fractionated IMRT to 45 Gy at 1.8 Gy per fraction to the tumor and regional lymph nodes.[9] At a median follow-up of 23 weeks, 15 of the 16 patients who completed all therapy had achieved local control. The median OS for that group was 33 weeks. Schellenberg et al reported the outcomes of a phase 2 study in which 16 patients received 25-Gy SBRT integrated with standard-dose gemcitabine chemotherapy. In that study, 3 of 16 patients had local progression (19%), and the median survival duration was 11.4 months.[11]

To our knowledge, this study represents the largest reported series to date on SBRT for patients with locally advanced pancreatic cancer. Our results further support the use of SBRT. The major advantages of this approach compared with conventional fractionated RT are 1) more intensified treatment to the primary tumor, 2) increased patient convenience, and 3) minimal interference with the delivery of maximal systemic chemotherapy. The overall local control rates at 6 months and 12 months were 91% and 84%, respectively; however, perhaps even more compelling was the isolated local failure rate, which was only 5% at 6 months and 12 months, indicating that only 5% of patients died because of uncontrolled local disease rather than systemic failure.

It is worth noting that we calculated survival from the time of SBRT to death, which provides the most accurate indication of the fate of these patients while minimizing bias. Because several patients had received courses of chemotherapy or had failed treatment with chemo-RT before SBRT, the median OS duration from the date of diagnosis was 11.9 months. Although the OS in our series was poor, it was consistent with historic series of patients with locally advanced disease.[4,14] The vast majority of deaths were from distant metastases.

Hoyer et al performed a phase 2 study using SBRT to a dose of 45 Gy given in 3 fractions for locally advanced pancreas.[15] Of 22 patients in that study, 6 patients (27%) developed local progression as a component of progression, and only 1 patient (5%) had isolated local tumor progression. Those investigators reported significant gastrointestinal toxicity, including 5 patients (22%) with severe mucositis, ulceration, or perforation, as well as worse pain, nausea, and performance status after treatment. Although their population was small, 1 possible reason for their observed morbidity probably was because of the irradiation volume. Although the actual tumor sizes probably were comparable in these series, they added 5 mm transversely and 10 mm longitudinally to define the PTV. This approach likely contributed to a higher risk of toxicity.

The effectiveness of SBRT as a local therapy in controlling local tumor growth is evident, because it allows for the delivery of a high radiobiologically effective (RBE) radiation dose. Limitations of applying the linear quadratic equation to single large fractions of radiation currently exist[16]; however, according to the standard equation, 25 Gy in a single fraction has an RBE of approximately 87.5 Gy (assuming an a/b ratio of 10 for rapidly proliferating tumor cells and an a/b ratio of 3 for normal tissues), which is equivalent to delivering 74 Gy at 1.8 Gy per fraction. In contrast, conventionally fractionated RT using standard beam arrangements typically delivers only 50 to 54 Gy because of concerns regarding toxicity to surrounding normal tissue (eg. small bowel, kidneys, and liver) and is inadequate treatment with high local failure.[6] Although survival is determined primarily by systemic control, local control is an important factor contributing to quality of life (eg, pain control, prevention of gastric outlet obstruction).

Dose escalation using fractionated RT has not provided improvement in disease outcome or local control. The early GITSG study compared 40 Gy with 60 Gy

combined with chemotherapy but did not report an improvement in OS or in local control between the 2 RT arms.[17] Ceha et al reported a phase 2 study investigating dose escalation for locally advanced pancreatic carcinoma in 44 patients using fractionated RT at doses from 70 Gy to 72 Gy at 2 Gy per fraction.[7] They reported an ultimate local disease progression rate of 44%, which is inferior to the local control reported in the current study. Although their study cannot be compared directly with the current study, there may be other factors that could contribute to local control with SBRT, such as endothelial cell apoptosis. Preclinical studies have suggested that endothelial cell apoptosis is an important component of tumor control when single-fraction doses of radiation exceed 11 Gy.[18] Thus, endothelial cell kill after SBRT (25 Gy in a single fraction) could be a significant contributor to radiation response and local tumor control. In addition, tumor hypoxia likely plays a role in radioresistance, because it has been demonstrated that pancreatic cancer is extremely hypoxic.[19] Further studies are needed to support these hypotheses, because they suggest a rationale for further investigation using hypofractionated treatments with large doses per fraction.

Unfortunately, SBRT did not produce a significant radiographic response, which is consistent with observations from other studies. Ceha et al did not report any complete or partial responses, even after dose escalation to 70 to 72 Gy.[7] In our study, there were no radiographic complete responses. It is noteworthy that 1 patient (1%) proceeded to surgery after follow-up imaging indicated that a radiographic response had rendered the tumor resectable. This patient had a near pathologic complete response and remained alive and disease free 12 months after SBRT. Overall, SBRT does not seem to be effective in converting locally advanced disease to resectable disease by radiographic criteria.

The main concern of toxicity is with small bowel and stomach complications because of their close proximity to the tumor. For tumors in the head of the pancreas, the duodenum and tumor are associated intimately with each other, making exclusion of the former impossible without under dosing the target volume. Hoyer et al reported that 4 of 22 patients (18%) had severe mucositis or ulceration of the stomach or duodenum, including 1 episode of a nonfatal perforation.[15] In the prior phase 1 study by Koong et al, as discussed above, there were no episodes of grade $\geq$3 toxicity when patients received SBRT alone.[10] The same investigators reported a higher rate of grade 3 gastrointestinal toxicity (2 of 19 patients) in patients who received combined fractionated external-beam RT to 45 Gy and SBRT to 25 Gy.[9] In the current study, our patients had a 5% rate of grade $\geq$2 acute toxicity and a 13% rate of grade $\geq$2 late toxicity. There was only a 10% rate of grade 3 or 4 toxicity, there were no treatment-related deaths, and the majority of these episodes occurred >6 months after SBRT. Most notably, 1 patient did have a small bowel perforation that required surgery. The 6- and 12-month actuarial rates of late grade $\geq$2 toxicity were 11% and 25%, respectively. These risks certainly are nontrivial and need to be balanced with regard to the benefit of local tumor control, because local failure likely also would produce symptoms of obstruction, perforation, and erosion. The median OS of patients who developed toxicity calculated from the time of SBRT was 11.7 months. We believe that these results are encouraging, because toxicity did not appear to hasten death and, in fact, patients who developed toxicity had better survival. An obvious explanation for this finding is that the patients who lived longer were at higher risk of developing treatment morbidity, which, again, speaks to the need of striking a balance between intensifying treatment and limiting toxicity. Because of concerns regarding toxicity, we are planning future studies using fractionated SBRT with smaller doses per fraction in an attempt to reduce the risk of complications while maintaining excellent local control.

Patients with locally advanced disease often have significant pain, and RT can provide palliation in 50% to 85% of patients.[3,7,20] Although pain reduction was not a primary endpoint of our study, we did observe significant improvement in pain in most patients who received SBRT. Current and future studies will address this question specifically. We hypothesize that more intensive local therapy should result in improved and more durable pain relief.

Elective regional lymphatics deliberately were excluded from the target volume in our study to meet normal tissue constraints and to minimize toxicity. The results demonstrate that locoregional control was not compromised by this approach. Nine patients developed regional lymph node recurrences, all in the setting of either local failure (1 patient), distant failure (7 patients), or both (1 patient), indicating that regional lymph node

disease is not a significant mode of disease mortality but, rather, is an indicator of disease aggressiveness and systemic progression. Another contributing factor to locoregional control may be related to the effects of gemcitabine, because most patients in the current analysis received systemic gemcitabine-based chemotherapy. Only 2 of the 9 regional recurrences occurred in patients who initially had lymph node disease, and both of those patients had received 45 Gy of fractionated RT to the regional lymph nodes as part of treatment.

In conclusion, SBRT with 25 Gy delivered in a single fraction provides excellent local control for patients with locally advanced pancreatic cancer but has an associated risk of complications, mainly with ulcer formation and duodenal stricture. SBRT should be used carefully and with attention to the details of treatment planning and delivery. Maximum effort should be made to define the optimal target volumes and ensure setup accuracy to minimize morbidity. In addition, efforts to investigate fractionated schedules with smaller fraction sizes are warranted. Nevertheless, the survival of patients in this series appears to be consistent with historic results, mainly because distant progression is the primary cause of mortality. Further improvements in systemic chemotherapy are needed before local control can have a meaningfully impact on OS.

Conflict of Interest Disclosures

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