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RAPID COMMUNICATION

PHASE I STUDY OF STEREOTACTIC RADIOSURGERY IN PATIENTS WITH LOCALLY ADVANCED PANCREATIC CANCER

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Purpose: To determine the feasibility and toxicity of delivering stereotactic radiosurgery to patients with locally advanced pancreatic cancer.

Methods and Materials: Patients with Eastern Cooperative Oncology Group performance status ≤2 and locally advanced pancreatic cancer were enrolled on this Phase I dose escalation study. Patients received a single fraction of radiosurgery consisting of either 15 Gy, 20 Gy, or 25 Gy to the primary tumor. Acute gastrointestinal toxicity was scored according to the Radiation Therapy Oncology Group criteria. Response to treatment was determined by serial high-resolution computed tomography scanning.

Results: Fifteen patients were treated at 3 dose levels (3 patients received 15 Gy, 5 patients received 20 Gy, and 7 patients received 25 Gy). At these doses, no Grade 3 or higher acute gastrointestinal toxicity was observed. This trial was stopped before any dose-limiting toxicity was reached, because the clinical objective of local control was achieved in all 6 evaluable patients treated at 25 Gy.

Conclusions: It is feasible to deliver stereotactic radiosurgery to patients with locally advanced pancreatic cancer. The recommended dose to achieve local control without significant acute gastrointestinal toxicity is 25 Gy.

Radiosurgery, Pancreatic cancer, Unresectable, Phase I.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related deaths for men and women in the United States. In 2003, pancreatic cancer will result in approximately 30,000 deaths (1). The natural history of this disease is characterized by a propensity for early nodal and liver metastases, even in patients with relatively small primary tumors. Overall, the 5-year survival is less than 5%, and surgical resection offers the best chance for long-term survival.

Clinical outcome and prognosis are determined by the extent of disease and performance status at presentation. Most often, patients with pancreatic cancer are classified into those with localized, locally advanced, or metastatic disease. The median survivals for patients in these groups range from 11–18 months, 10–12 months, and 5–7 months, respectively (2).

The role of chemoradiotherapy for patients with unresectable pancreatic cancer was defined by the Gastrointestinal Tumor Study Group in a landmark study demonstrating that treatment with 5-fluorouracil (5-FU) and concurrent radiotherapy resulted in superior survival compared to radiotherapy alone. Although this study is criticized for using split-course radiotherapy and for having small numbers, it nevertheless established a role for combined modality therapy in the management of locally advanced pancreatic cancer (3). A follow-up Gastrointestinal Tumor Study Group study comparing 5-FU/continuous radiotherapy with chemotherapy alone (streptozocin, mitomycin, and 5-FU) also demonstrated a survival benefit in the combined modality arm (4).

We hypothesized that stereotactic radiosurgery may also

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provide a similar benefit in pancreatic cancer with the advantage of compressing the entire treatment into a single day. Recent technologic advances have made extracranial radiosurgery possible by coupling the delivery of highly conformal radiotherapy with real-time imaging. Although overall survival in pancreatic cancer is impacted most by the progression of systemic disease, local control is an important clinical end point that affects quality of life and may prevent tumor seeding to distant sites.

To address the feasibility and impact of radiosurgical treatment in patients with locally advanced pancreatic cancer, we conducted a Phase I dose escalation single-fraction radiosurgery study in these patients. Although no dose-limiting toxicity (DLT) was observed even at the highest dose level (25 Gy), all evaluable patients who received 25 Gy had control of their primary pancreatic tumor and developed distant metastases as the site of first progression. The study was therefore stopped at 25 Gy, because we achieved our primary clinical objective of local control at this dose.

METHODS AND MATERIALS

We enrolled 15 patients with locally advanced pancreatic cancer on this institutional review board–approved dose escalation protocol. All patients signed an informed consent, also approved by the institutional review board. To be eligible for this study, patients must have had an Eastern Cooperative Oncology Group performance status of ≤ 2 and pathologically confirmed pancreatic adenocarcinomas. Three patients received 15 Gy, 5 patients received 20 Gy, and 7 patients received 25 Gy. All patients received a single fraction of stereotactic radiosurgery. At least 3 patients completed the treatment and were assessed for acute toxicity in the 12-week follow-up period before we escalated to the next dose level. Maximum tolerated dose was defined as $>50\%$ of patients experiencing Grade 3 or higher acute toxicity. These study parameters were based upon the recommendations of our institutional biostatisticians and are consistent with our institutional guidelines for Phase I studies.

Patients underwent standard pretreatment staging studies, including history and physical examination, complete blood count, chemistry panel, CEA, CA19-9, chest radiograph, and pancreas protocol computed tomography (CT) scan (high-speed abdominal CT scan with dual-phase contrast, thin cuts, and 3D reconstruction). Selection criteria for patients included those with pancreatic tumors less than 7.5 cm in greatest dimension in a single plane. Prior therapy was allowed if it had been administered more than 1 month before radiosurgery. All patients were evaluated and determined to have unresectable tumors at the Stanford Gastrointestinal Combined Modality Tumor Board.

All patients had 3–5 gold fiducials implanted into the tumor for targeting purposes, via a laparoscopic procedure in 1 patient, an open laparotomy in 2 patients, and with the help of CT guidance in 12 patients. The method of placement was left to the discretion of the attending physician. All except the 2 patients with an open laparotomy had the fiducials placed while they were outpatients.

An Alpha Cradle (Smithers Medical Products, North Canton, OH) immobilization device was custom made for each patient 7–14 days after fiducial placement. Next, a pancreatic protocol CT scan was performed with the patient in the treatment position. These images were then processed for radiosurgery with an algorithm specifically developed for the CyberKnife (Accuray Inc., Sunnyvale, CA).

The attending surgeon and attending radiation oncologist delineated the pancreatic tumor volume on cross-sectional images from the planning CT scan. A body imaging radiologist was also asked to confirm the location and extent of each pancreatic tumor. A radiosurgical treatment plan was then generated based on tumor geometry and location. All patients were treated within 2 weeks of their planning CT scan and within 4 weeks of enrollment on the protocol.

All radiosurgery treatments were administered as single fractions, using a breath hold technique. Patients were trained to hold their breath in mid–late cycle for 15–20 s. The fiducials were tracked by orthogonal X-ray to ensure reproducibility. Previous studies from our institution revealed that pancreas positioning was reproducible within 2.5 mm on average (5). Because the small bowel is the most radiosensitive structure in the vicinity of these pancreatic tumors, all patients had the 50% isodose line covering only the duodenal wall closest to the tumor. Overall, the treatment time ranged from 3 to 6 h with the majority of patients treated in less than 4 h.

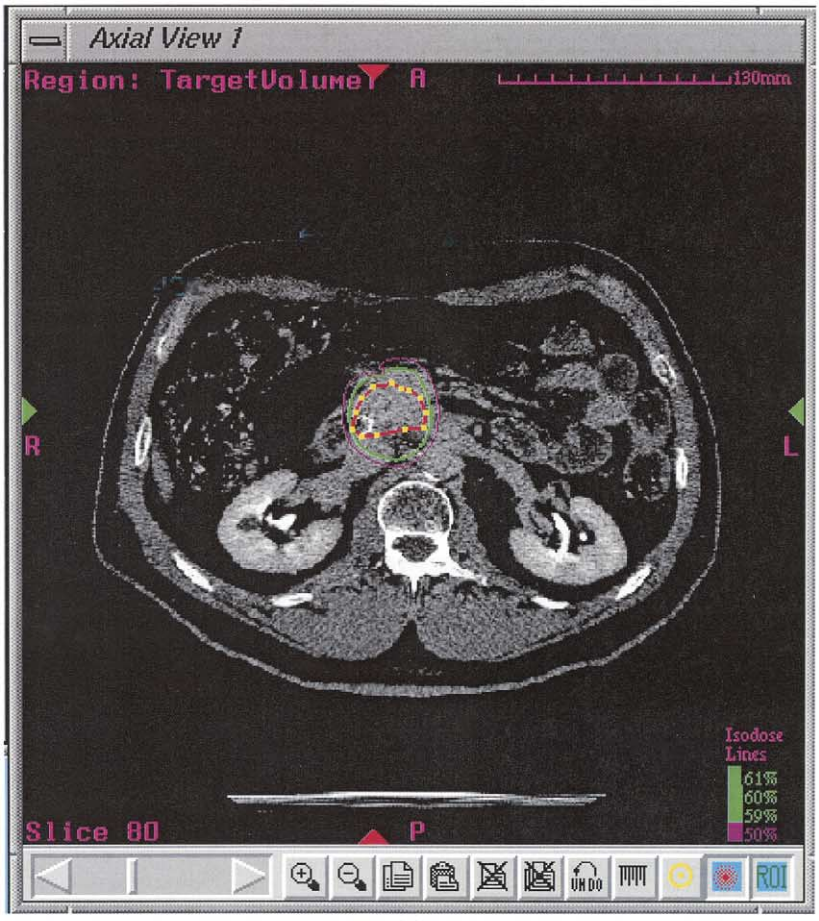
Patients were evaluated at follow-up intervals of 4 to 6 and 10 to 12 weeks. At each follow-up visit, standard evaluation consisted of history and physical examination, tumor marker assessment, and pancreatic protocol CT scans. Gastrointestinal toxicities were scored according to the Radiation Therapy Oncology Group acute radiation morbidity criteria (http://rtog.org/members/toxicity/acute.html). Patients could receive chemotherapy after this 12-week period or earlier if there was evidence of progression.

RESULTS

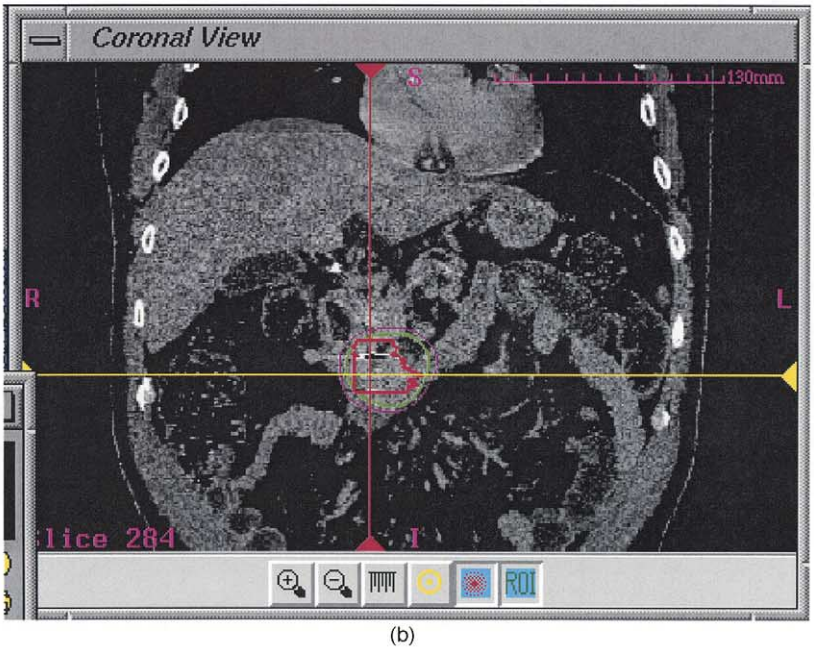
Figures 1a and 1b show axial and coronal views of a radiosurgical treatment plan for one of the patients treated on this study. The structure outlined in red is the tumor volume. The green line represents the 60% isodose line, and the purple line represents the 50% isodose line. The high degree of conformality and rapid dose drop-off minimize the dose to the surrounding normal structures.

Table 1 lists the characteristics of the patients enrolled in this study. Of the 3 patients who had prior treatment, 2 received conventional 5-FU–based chemoradiotherapy to a dose of 50 Gy, and 1 received chemotherapy alone. All of these patients had local progression of their pancreatic tumor before radiosurgery, and none had any treatment in the 4 weeks before radiosurgery.

Table 2 lists the radiosurgery treatment parameters, toxicity data, and site of first progression for the patients treated



(a)



(b)

Fig. 1. (a) Axial and (b) coronal views of radiosurgical treatment plan for a patient treated with 25 Gy. The tumor located in the head of the pancreas is outlined in red. The green line represents the 60% isodose line, and the purple line represents the 50% isodose line.

Table 1. Patient characteristics

Patient	Age	Location	Previous treatment
1	65	Body	None
2	81	Head	None
3	57	Body	None
4	68	Body	None
5	62	Body	None
6	80	Head	None
7	64	Head	None
8	81	Head	None
9	50	Head	None
10	82	Head	Gemcitabine, taxotere
11	43	Tail	5-FU/XRT, gemcitabine
12	51	Head	None
13	60	Head	Gastrojejunostomy
14	55	Head	5-FU/XRT
15	61	Head	Gastrojejunostomy

on this study. The radiosurgery dose (*Dmin*) was prescribed to the isodose line that completely surrounded the tumor. The *Dmax* was the isocenter dose. The gross tumor volume treated ranged from 19.2 to 71.9 cc (mean: 32.9 cc, median: 29.0 cc). All evaluable patients treated at the highest dose level (25 Gy) developed distant metastases as the site of first progression after radiosurgery. This observation was determined by direct comparisons of pretreatment pancreatic protocol CT scans and those taken at 4 to 6 weeks and 10 to 12 weeks after radiosurgery.

Within the 12-week follow-up period after radiosurgery, we observed no significant gastrointestinal acute toxicity. Table 2 summarizes the toxicity data obtained at each dose level during this period. The Grade 1 toxicity reported by 2 patients consisted of mild nausea lasting less than 24 h. With regard to Grade 2 toxicity, 1 patient experienced diarrhea requiring i.v. hydration, another experienced moderate abdominal pain immediately after radiosurgery requiring analgesics, and another experienced moderate abdominal pain requiring increased analgesics at 10 weeks after radiosurgery. In both of the patients with increased abdominal pain, the symptoms resolved within 24 h, and no further workup was indicated. Overall, we did not observe any significant changes in follow-up blood tests, including CBC and liver function tests.

During the course of this study, 2 patients did not receive follow-up CT scans to assess response. Patient 8 developed a deep vein thrombosis, experienced complications related to anticoagulation therapy, and refused to come for further follow-up evaluation. Patient 10 also refused further follow-up care and was placed into a hospice program, even though the patient had a clinical improvement after radiosurgery. Of the remaining 13 patients, 6 were placed into hospice care after the 4–6-week follow-up CT scan demonstrated radiographic evidence of metastatic disease. The remaining 7 patients were imaged at 4 to 6 weeks and 10 to 12 weeks after radiosurgery. Additional follow-up data were obtained on all patients until death.

For all patients, the median overall survival was 11 months with a median follow-up time of 5 months. Among the evaluable patients, the median time to progression was 2 months. Changes in CA19-9 levels after radiosurgery were difficult to interpret because of the rapid development of metastatic disease in this patient population.

In the 6 evaluable patients treated at the highest dose level (25 Gy), the median overall survival was 8 months with a median follow-up time of 4.5 months. All of these patients had local control of their pancreatic tumors until death or at last follow-up (2 patients were still alive with local tumor control at 7 months after radiosurgery) and progressed systemically as the site of first progression. Because we achieved our primary objective of local control at this dose, we elected to stop the dose escalation portion of this trial before reaching any DLT.

Table 3 summarizes the radiosurgery doses to the normal tissues in the vicinity of the pancreatic tumors. These values represent the mean dose to 50% or 5% of nearby abdominal

Table 2. Radiosurgery parameters, toxicity, and site of first progression

Patient	*Dmin* (Gy)	*Dmax* (Gy)	Tumor volume (cc)	Acute gastrointestinal toxicity	Site of first progression
1	14.8	17.40	26.8	2 (diarrhea)	Distant
2	15.0	23.00	28.9	0	Local
3	15.0	20.00	22.7	0	Distant
4	20.0	23.50	39.8	0	Distant
5	20.0	25.00	71.9	0	Local
6	20.0	25.64	29.1	0	Local
7	20.0	25.18	36.7	0	Distant
8	20.0	25.32	36.7	0	Not evaluable
9	25.0	31.25	27.2	0	Distant
10	25.0	31.25	28.1	0	Not evaluable
11	25.0	29.75	21.5	1 (nausea)	Distant
12	25.0	37.87	54.6	0	Distant
13	25.0	41.66	20.0	2 (abdominal pain)	Distant
14	25.0	33.33	19.2	2 (abdominal pain)	Distant
15	25.0	33.78	51.0	1 (nausea)	Distant

Table 3. Mean dose to abdominal organs in the cohort of patients treated at the highest dose (25 Gy)

Structure	Mean dose to 50%	Mean dose to 5%
Duodenum	14.5 Gy	22.5 Gy
Bowel	1.1 Gy	12.3 Gy
Liver	0.7 Gy	7.0 Gy
Left kidney	1.5 Gy	5.0 Gy
Right kidney	2.0 Gy	5.8 Gy

organs in all 6 evaluable patients treated at the highest dose level (25 Gy). Because 2 of these patients had received previous external beam radiotherapy, the actual dose to these structures is somewhat higher.

DISCUSSION

This is the first study to demonstrate the feasibility of using stereotactic radiosurgery for the treatment of locally advanced pancreatic adenocarcinomas. In this cohort of 15 patients, we achieved our primary clinical end point of local control at 25 Gy and therefore stopped the trial before reaching any DLT.

Longer follow-up and treatment of more patients with radiosurgery are necessary to determine the full scope of any treatment-related toxicity. However, the majority of these patients will succumb to their disease before manifesting any symptoms related to long-term morbidity.

As expected, an analysis of mean doses to surrounding normal tissues reveals that the duodenum received the highest dose. The duodenum is in closest proximity to the majority of the pancreatic tumors treated, and it was impossible to avoid treating this structure to a relatively high dose. These data suggest that it is possible to irradiate a small volume of duodenum to a dose of 22.5 Gy with acceptable toxicity.

Because all evaluable patients treated at 25 Gy had local control of their disease and progressed systemically as the site of first progression, effective chemotherapy needs to be integrated into this treatment before we will substantially improve survival. Although there was a trend toward more Grades 1 and 2 toxicity in the patients treated at the highest dose, these toxicities were transient and managed conservatively on an outpatient basis.

We chose to target only the primary pancreatic tumor with radiosurgery and not the regional lymph nodes, in an attempt to minimize the volume treated. In a prospective study from Johns Hopkins randomizing 299 patients to a standard pancreaticoduodenectomy or a pancreaticoduodenectomy with an extended lymph node dissection, there was an increased overall complication rate in the radical surgery group without a corresponding survival benefit (6). However, the treatment of regional lymph nodes with conventional radiotherapy may influence treatment outcome, because lymph nodes are a common site of metastatic spread. Furthermore, standard pancreaticoduodenectomy includes en bloc resection of some peripancreatic lymph nodes.

Radiosurgery for locally advanced pancreatic cancer is a promising treatment strategy, and the future challenge is to determine how best to integrate this treatment with other innovative therapeutic approaches (7, 8). Because a single dose of 25 Gy seems to be well tolerated and effective in controlling local disease, our next trial will incorporate a radiosurgical dose of 25 Gy as a boost treatment after conventional chemoradiotherapy for patients with locally advanced pancreatic cancer.

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