

INDUCTION GEMCITABINE AND STEREOTACTIC BODY RADIOTHERAPY FOR LOCALLY ADVANCED NONMETASTATIC PANCREAS CANCER

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Purpose: Stereotactic body radiotherapy (SBRT) has been used successfully to treat patients with locally advanced pancreas cancer. However, many patients develop metastatic disease soon after diagnosis and may receive little benefit from such therapy. We therefore retrospectively analyzed a planned strategy of initial chemotherapy with restaging and then treatment for those patients with no evidence of metastatic progression with SBRT.

Methods and Materials: Forty-seven patients received gemcitabine (1,000 mg/m² per week for 3 weeks then 1 week off) until tolerance, at least six cycles, or progression. Patients without metastases after two cycles were treated with SBRT (tolerance-based dose of 24–36 Gy in 3 fractions) between the third and fourth cycles without interrupting the chemotherapy cycles.

Results: Eight of the 47 patients (17%) were found to have metastatic disease after two cycles of gemcitabine; the remaining 39 patients received SBRT. The median follow-up for survivors was 21 months (range, 6–36 months). The median overall survival for all patients who received SBRT was 20 months, and the median progression-free survival was 15 months. The local control rate was 85% (33 of 39 patients); and 54% of patients (21 of 39) developed metastases. Late Grade III toxicities such as GI bleeding and obstruction were observed in 9% (3/39) of patients.

Conclusion: For patients with locally advanced pancreas cancer, this strategy uses local therapy for those who are most likely to benefit from it and spares those patients with early metastatic progression from treatment. SBRT delivers such local therapy safely with minimal interruption to systemic chemotherapy, thereby potentially improving the outcome in these patients. © 2011 Elsevier Inc.

Chemotherapy, Gemcitabine, Locally advanced pancreatic cancer, Stereotactic body radiotherapy.

INTRODUCTION

Pancreas cancer is the fifth most common cancer in men and women and the fifth most common cause of cancer mortality (1). Forty to fifty percent of pancreatic cancer patients present with inoperable, locally advanced pancreatic cancer without apparent distant metastasis (2). Despite efforts to aggressively treat these patients with chemotherapy, radiation therapy, or various combinations thereof, the 5-year overall survival rate is less than 5% (3), and the median survival time is between 8 and 14 months (4–11). The optimal treatment for these patients is uncertain. A phase III trial found gemcitabine therapy alone was less toxic and more effective than chemoradiotherapy followed by gemcitabine therapy (12). However, other, phase II and III studies found

that chemotherapy followed by chemoradiation improved survival compared to that for those patients who received chemotherapy alone (13).

Stereotactic body radiotherapy (SBRT) is a minimally invasive treatment option that can be delivered in 1 to 3 days compared to approximately 6 weeks of daily treatments for conventional radiotherapy for patients with locally advanced pancreas cancer. Prospective phase I and phase II studies (14–17) and retrospective studies (18, 19) have shown SBRT to be a safe and effective approach for treating these patients. In addition, we recently demonstrated that hypofractionated SBRT can be delivered effectively with acceptable side effects and minimal interference to gemcitabine chemotherapy (20). However,

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Conflict of interest: Anand Mahadevan has received honoraria from Accuray, Inc., for educational presentations and CME activities regarding the use of the CyberKnife device.

Received Jan 13, 2011, and in revised form April 8, 2011. Accepted for publication April 19, 2011.

as in other studies, we observed a high rate (78%) of distant metastasis. Moreover, 4 patients (11%) developed distant failure soon after SBRT. Other studies have found that about 30% of patients given induction chemotherapy develop metastatic disease prior to beginning chemoradiation (8, 13). We hypothesized that a strategy of giving initial chemotherapy treatment with two cycles of gemcitabine followed by restaging, to ensure the absence of rapid development of overt metastases, would avoid SBRT for those unlikely to benefit from it. We also wished to determine if chemotherapy could be delivered uninterrupted by SBRT, thereby, potentially improving outcomes in these patients.

METHODS AND MATERIALS

Patients and eligibility

This was a retrospective analysis of 47 consecutive patients seen at Beth Israel Deaconess Medical Center from October 2007 to February 2010 with biopsy proven, locally advanced, unresectable nonmetastatic pancreatic cancer, whose initial treatment plans were to receive sequential gemcitabine and hypofractionated SBRT. Patients were prospectively entered into an institutional review board-approved database. Patients with gastric or duodenal obstruction were excluded. All patients were surgically staged using computed tomography (CT) criteria. Patients were deemed inoperable after review of a pancreas-specific multiphasic CT angiogram by a radiologist and experienced pancreatic surgeon, using standard CT criteria (21). These patients had three to five gold fiducials (0.8×5 mm) placed under endoscopic ultrasound guidance after induction gemcitabine chemotherapy, if they remained nonmetastatic. Patients who appeared potentially resectable by imaging but were found to be unresectable at the time of surgery were also included in this analysis. These patients had fiducials placed directly at laparotomy. Carbohydrate antigen 19-9 (CA19-9) measurements, complete blood counts, and a biochemistry panel were performed in all patients prior to treatment and at follow-up.

Systemic chemotherapy

Patients began treatment with two initial cycles of gemcitabine chemotherapy. Each chemotherapy cycle consisted of 1,000 mg/m² of gemcitabine given once per week for 3 of 4 weeks per cycle. Patients were restaged with CT after the second cycle. Patients without metastasis received a third cycle of gemcitabine, during which time fiducial placement, if necessary, and SBRT treatment planning were undertaken. SBRT was delivered during the week off between the third and fourth cycles of chemotherapy. Following SBRT, patients continued to receive gemcitabine until tolerance, disease progression, or at least completion of six cycles at the discretion of the treating medical oncologist. Chemotherapy treatment was managed by the patient's oncologist, using standard-of-care guidelines for dosing, adverse event monitoring and treatment, and evaluation for progression and treatment discontinuation. Figure 1 details the patient treatment approach flow chart.

SBRT

SBRT was performed as previously described (20). Briefly, a CyberKnife robotic radiosurgery system (Accuray Inc., Sunnyvale, CA) with Synchrony motion tracking was used for all patients. CT planning images with oral and intravenous contrast were obtained for treatment planning. For endoscopic ultrasound-placed fiducials located close to the bowel-tumor interface, scatter can

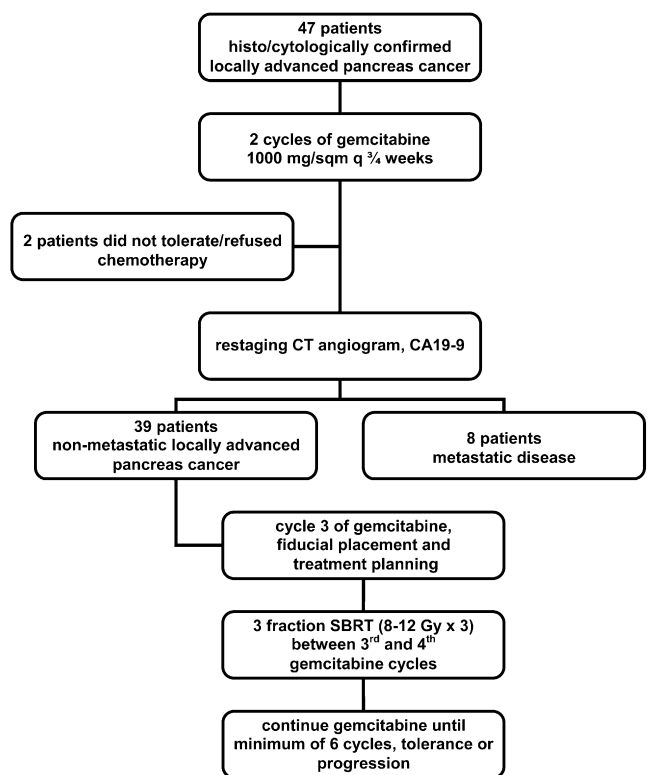


Fig. 1. The flow chart shows patient treatment from initial staging to initial gemcitabine treatment, restaging, SBRT, and remaining gemcitabine treatment.

make target volume and organ-at-risk delineation difficult. In those cases, the volumes were extrapolated from prefiducial images, often with CT-CT fusion. Normal tissue dose constraints were used to select the prescription dose in order to limit toxicity; if the tumor approximated one-third or more of the duodenum or stomach circumference, then a dose of 24 Gy (3 fractions of 8 Gy each) was used. If the tumor abutted the bowel in only one area, as determined by the relationship of the tumor to the duodenum in axial, coronal and sagittal planes in CT scans with oral contrast and/or the space between the tumor and the bowel wall was less than 3 mm, then a dose of 30 Gy (3 fractions of 10 Gy each) was prescribed. Finally, if the gap between the tumor and the duodenum was 3 mm or larger, a dose of 36 Gy (3 fractions of 12 Gy each) was used. The dose was prescribed to the isodose line covering at least 95% of the planning target volume, which was defined as coincident with gross disease where the tumor was in contact with the bowel (stomach or duodenum); a 5-mm or smaller expansion margin (extending up to the outer bowel wall) was included to determine the planning target volume. The stomach and duodenum surrounding the tumor were contoured in all patients, and dose-volume histograms were generated for all treatment plans as this was our dose-determining and -limiting structure. Target volumes and treatment plans were reviewed by the radiation oncologist and the surgeon.

Other normal tissue constraints were also used during treatment planning. The volumes of liver receiving 21 Gy or more and 15 Gy or more were kept below 30% and 50%, respectively. The volume of each kidney receiving 12 Gy or more was kept below 25%. The total maximal spinal cord limit was 12 Gy, and the maximum point dose to the bowel was below 10 Gy per fraction.

Patients were treated on three consecutive working days in the same position used for treatment planning. Prophylactic prochlorperazine (used during pretreatment and as required posttreatment)

and H2 receptor antagonists (used during pretreatment and for 2 weeks posttreatment) were given. All but 3 patients received at least six cycles of gemcitabine after SBRT. One patient had progression, 1 patient had intolerance, and the other patient refused continuation of chemotherapy.

Follow-up and statistical analysis

Patients were followed for 1 month after SBRT and then every 4 months thereafter by the treating radiation oncologist for the duration of this study. Patients were also frequently seen by the medical oncologist during chemotherapy. At each follow-up visit, a clinical examination was performed, with measurement of CA19-9 and a contrast-enhanced CT. Local control was defined by stable, decreasing, or normalized CA 19-9 values and nonprogression in the CT scan. Acute toxicity was defined as adverse events occurring less than 3 months after SBRT, and long-term toxicity was defined as events occurring after 3 months, using Common Terminology Criteria for Adverse Events version 3.

Local and distant progression rates and the lengths of overall survival were calculated from the date of diagnosis to the date of progression or death. The Kaplan-Meier method was used for calculating actuarial rates, using GraphPad Prism version 5.00 software for Windows (GraphPad Software, San Diego, CA; Windows; Microsoft, Seattle, WA).

RESULTS

Patients and treatment characteristics

Table 1 summarizes patient and treatment characteristics. Eight of the 47 patients progressed with metastatic disease after two cycles of gemcitabine. The remaining 39 patients received SBRT. This group contained 23 males and 16 females with a median age of 67 years old (range, 44–88 years old). Twenty-eight patients received 24 Gy (8 Gy \times 3), 11 patients received 30 Gy (10 Gy \times 3), and no patient/tumor was eligible to receive 36 Gy (12 Gy \times 3). The overall mean prescription dose was 24.92 Gy (range, 24–30 Gy), the mean minimum dose was 21.26 Gy (range, 14.81–24.98 Gy), and the mean maximum dose was 32.96 Gy (range, 29.27–38.96 Gy). The mean prescription isodose

Table 1. Patient and treatment characteristics

Characteristic	Value(s)
Mean/median age (range) (years)	67/67(44–88)
Gender:	
Male	23
Female	16
Mean tumor volume (range)	64.23 cc (21–175 cc)
Tumor location (number of patients):	
Head	35
Body	4
Tail	0
Proximity to duodenum (number of patients):	
Involving duodenum (8 Gy \times 3)	28
Abutting duodenum (10 Gy \times 3)	11
Away from duodenum (12 Gy \times 3)	0
Mean total dose (range)	24.92 Gy (24–30 Gy)
Mean prescription isodose (range)	77.6% (72%–86%)
Mean Dmax (range)	32.96 Gy (29.3–38.9 Gy)
Conformality index (mean)	1.21
Homogeneity index (mean)	1.29

was 77.6%. The mean volume within the prescription isodose was 64.23 cc with an average conformality index of 1.21 and a homogeneity index of 1.29. A representative treatment plan is shown in Figure 2.

One patient did not tolerate the initial two cycles of systemic therapy, and 1 patient refused to take additional cycles; all other patients received the planned systemic therapy. Patients were managed until disease progression, unacceptable toxicity, or completion of at least 6 monthly gemcitabine cycles at the discretion of their primary oncologists, who were not necessarily part of the study team or institution.

Clinical outcomes

At a median follow-up of 21 months, in all patients who received SBRT (range, 6–33 months), the local control rate was 85%, the median overall survival duration was 20 months, and the median duration of survival free from either local or distant progression was 15 months (Fig. 3). Twenty-one patients (54%) developed distant metastases. Twelve patients (31%) were free from progression at last follow-up as determined by having normalized tumor markers with stable CT. The two patients who refused or did not tolerate additional systemic therapy developed metastatic disease and died soon after SBRT. No differences in outcome were found between the two different dose groups, but the statistical power to detect differences was limited by the number of patients.

Toxicity

Twenty-two patients (56%) were fatigued in the first 4 weeks after SBRT but did not require any additional intervention (Grade 1). Sixteen patients (41%) reported nausea soon after treatment; 9 (23%) of these patients required additional antiemetics, typically ondansetron (Grade 2). Two of these patients had persistent nausea at 1 month. There were no acute Grade 3 toxicities.

Late Grade III toxicity (3 months or more after SBRT) occurred in 3 patients. Two patients developed gastrointestinal bleeding requiring endoscopic intervention and transfusion. The bleeding occurred from the duodenum adjacent/infiltrated by the pancreatic tumor. One of these patients had local tumor progression, and it was therefore unclear if the bleeding was really treatment related or from tumor progression. One patient developed gastric outlet obstruction, although it was again unclear if this was from local progression or treatment related. All three Grade III side effects occurred in patients receiving 24 Gy (8 Gy \times 3).

DISCUSSION

Patients with unresectable, locally advanced pancreatic cancer often progress to metastatic disease as they harbor micrometastasis at presentation. We have shown that by using a strategy of delivering systemic chemotherapy, it is possible to select those patients who are more likely to benefit from local therapy. In this study, SBRT was used as a quick and effective local control modality, without interrupting

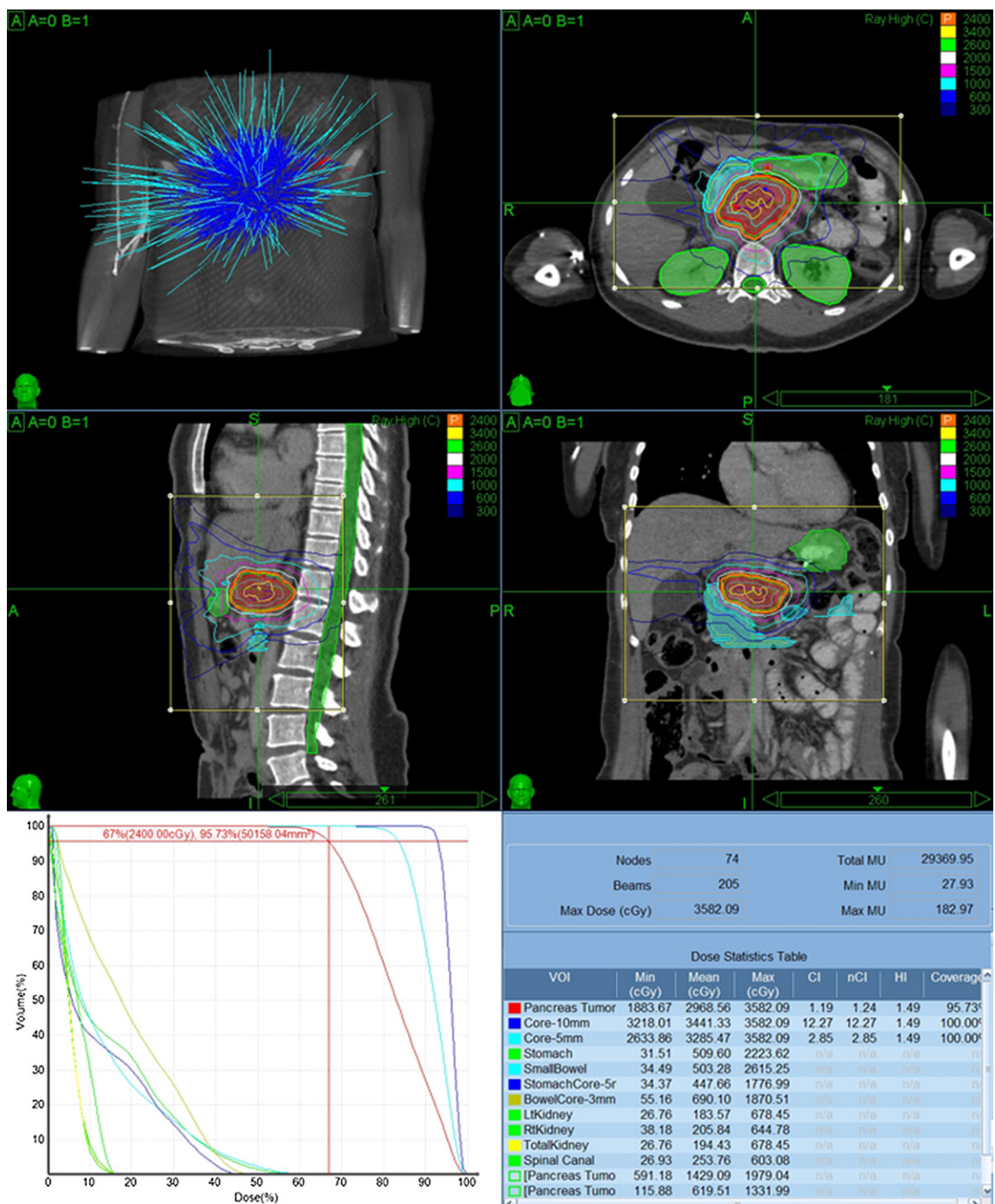


Fig. 2. A representative treatment plan is shown. (Top left) Nonisocentric beam profile; (middle left) sagittal isodose plan; (top right) axial isodose plan; (middle right) coronal isodose plan; (bottom left) dose-volume histogram; and (bottom right) dose statistics.

systemic therapy in patients who remained nonmetastatic after an initial course of gemcitabine (Table 2).

While chemoradiation has long been used for management of unresectable locally advanced pancreas cancer (22), its efficacy is limited and its routine use is currently controversial (23–25). The value of chemotherapy alone in this setting is difficult to assess as patients with localized disease are often included in clinical trials that include predominantly patients with overt metastatic disease, without always

reporting outcomes in subgroups (Table 3). For the subset of patients with localized disease, median survival times of 9.1 to 9.9 months have been reported with chemotherapy alone (26, 27). These outcomes compare favorably with traditional chemoradiation schemas (22, 28), although results with more recent chemoradiation trials have reported slightly better outcomes (10, 29, 30).

Two modern phase III trials have compared chemoradiation and additional systemic therapy to chemotherapy alone

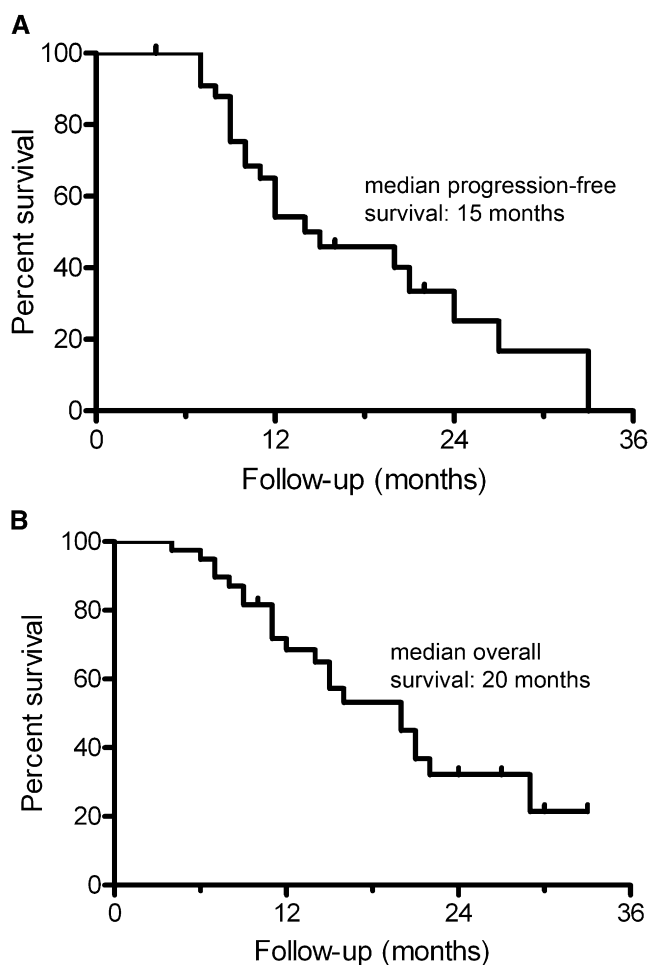


Fig. 3. Actuarial clinical outcomes (A) progression-free survival and (B) overall survival are shown.

for locally advanced nonmetastatic disease patients with contradictory results. In the France Foundation of Digestive Oncology and the French Society of Radiation Oncology (FFCD-SFRO) trial, gemcitabine therapy alone was compared to an experimental chemoradiation arm followed by gemcitabine therapy (12). The median overall survival in the gemcitabine-alone arm was an unusually high 14.3 months compared to the 9.1 to 9.9 months for comparable trials of the same era (26, 27), and the survival for the chemoradiation patients was comparably poorer (median overall survival, 8.4 months) than recent chemoradiation trials (10, 29, 30). Patients in the chemoradiation arm received a nonstandard experimental concurrent chemotherapy with *cis*-platinum and 5-fluorouracil (5-FU), which caused substantial toxicity leading to poor compliance, decreased performance status, and an overall decrease in the amount of systemic therapy received. Better outcomes in this trial were associated with more use of systemic therapy. This is not inconceivable as most patients eventually die of systemic failure.

The Eastern Cooperative Oncology Group trial (ECOG4201) study compared gemcitabine therapy alone to gemcitabine followed by chemoradiotherapy, using concurrent 5-FU followed by additional gemcitabine (31, 36).

Despite premature closure of this trial due to poor accrual, there was a statistically significant increase in the duration of median survival for patients receiving chemoradiation compared to that with chemotherapy alone (11.0 vs. 9.2 months). The modest prolongation of survival came at the cost of significant gastrointestinal toxicity (Grade 4, 5.7% vs. 41.2%). These results are comparable with contemporaneous chemoradiation studies. Therefore, while the role of systemic therapy seems logical, the role of radiation therapy cannot be ignored.

Based on contemporary chemoradiation trials, it is conventional practice to administer chemoradiation followed by systemic therapy for locally advanced pancreas cancer (22, 28, 34–36). One reason for the apparent lack of benefit of conventional radiation therapy is that many patients develop overt distant metastasis during the first few months following diagnosis and beginning of treatment. Patients who develop early metastatic disease have a limited life span, and an arduous 6-week course of radiation is questionable. For example, studies show that after undergoing neoadjuvant systemic therapy for apparently localized disease, 30% to 35% of patients present with metastatic disease (13, 37) prior to planned local therapy. Emerging data suggest that giving systemic therapy followed by consolidation chemoradiation in patients who do not demonstrate progression may be preferable to initial chemoradiation (8, 13, 25, 30, 37). In a study by Huguet *et al.* (13), 29.3% of patients progressed with metastatic disease after three cycles of chemotherapy. The remaining patients continued with chemotherapy or had chemoradiation at the discretion of the treating physician. The median progression-free and overall survival lengths were 10.8 months and 15.3 months, respectively. These outcomes compared favorably to those for patients receiving initial chemoradiation. Similarly, in a trial from Wake Forest University, Mishra *et al.* (8) gave all patients two cycles of gemcitabine and CPT11 and then treated the 65% of patients who did not progress with consolidation chemoradiation. The median overall survival was 9.6 months. A large retrospective analysis from the M. D. Anderson Cancer Center found that patients receiving chemotherapy followed by consolidation chemoradiation had a longer median survival (11.9 months) than those receiving initial chemoradiation therapy (8.4 months) (5). Another study from the University of California at San Francisco further validated this sequencing and treatment selection, demonstrating a median overall survival of 17 months (38).

An attempt to minimize the duration of radiation in these patients with limited lifespans while minimizing toxicity and interruptions to systemic therapy has been made with SBRT. The use of SBRT has been shown to be feasible in treating locally advanced pancreas cancer (14–19, 32, 33). However, no gain (33), little gain (17, 19, 32), or modest gain (18, 20) has been noted in clinical outcomes. Our initial experience showed that SBRT and gemcitabine can be effectively and safely delivered for locally advanced pancreatic cancer (20). However, similar

Table 2. Clinical outcomes after SBRT for locally advanced pancreas cancer

Author, study (ref.)	Treatment	Number of patients	Progression-free survival (months)	Overall survival (months)
Koong <i>et al.</i> , Phase I (15)	SRS 15–25 Gy	15	2	11*
Koong <i>et al.</i> , Phase II (14)	RT 45 Gy plus SRS 25 Gy	19	4.5	8*
Schellenberg <i>et al.</i> (16)	GEM plus SRS 25 Gy plus GEM	16	9	11.4*
Chang <i>et al.</i> (includes all of above patients) (32)	SRS 25 Gy with or without GEM	77	–	11.4*
Hoyer <i>et al.</i> (33)	SBRT 45 Gy	22	4.8	5.7*
Mahadevan <i>et al.</i> (20)	SBRT 24–36 Gy plus GEM	36	CA 19-9: 7.9 CT: 9.6	14.3 [†]
Polistina <i>et al.</i> (17)	GEM plus SBRT 30 Gy	33	NR	10.6*
Didolkar <i>et al.</i> , (18)	SBRT 15–30 Gy plus GEM	85 [‡]	NR	18.6* 8.6 [†]
Rwigema <i>et al.</i> , (19)	SRS 18–25 Gy	71 [§]	NR	10.3 [†]
Present series	GEM-SBRT-GEM	39	15	20*

Abbreviations: EBRT = external beam radiation therapy; GEM = gemcitabine; NR = not reported; RT = radiation therapy; SBRT = stereotactic body radiation therapy; SRS = stereotactic radiosurgery.

* From diagnosis.

[†] From start of treatment.

[‡] Includes recurrent patients.

[§] Includes recurrent and positive margin patients, some of whom received post-SRS chemotherapy.

to the chemoradiation trials mentioned above (8, 13), a substantial proportion of patients diagnosed with metastasis soon after SBRT not only render such local treatment unnecessary but also leave micrometastatic disease untreated longer.

Our strategy of giving two cycles of gemcitabine followed by restaging spared nearly one-fifth of the patients from undergoing unnecessary SBRT while achieving excellent local control in the remaining patients. We observed systemic disease progression in 18% of patients. Clearly, these patients

Table 3. Results of chemotherapy and chemoradiation treatment for patients with locally advanced pancreas cancer*

Author, study, year (ref.)	Treatment	No. of patients	Median survival (months)
Chemotherapy alone modern phase III			
CALGB 80303 (34, 39)	GEM with or without bevacizumab	93	9.9
ECOG 6201 (22, 35, 40)	GEM with or without oxaliplatin	100	9.1
ECOG 4201 (31, 36)	GEM	22	9.2
Chemoradiation classic trials: pre-CT era			
Moertel <i>et al.</i> (34)	35–40 Gy plus 5-FU	32	10.4
GITSG, 1981 (22, 35)	60/4 Gy plus 5-FU	11	11.4
ECOG (36)	40 Gy plus 5-FU	47	8.3
GITSG, 1988 (28)	54 Gy plus 5-FU plus streptozotocin	22	9.7
Phase II cooperative group			
RTOG 9812 (10)	50.4 Gy plus paclitaxel	122	11.3
RTOG PA-0020 (29)	50.4 Gy plus paclitaxel/GEM	154	11.7
RTOG PA-0411 (30)	50.4 Gy plus capecitabine plus bevacizumab	94	11.9
Modern phase III			
FFCD-SSRO (12)	60 Gy plus 5-FU plus cisplatin	59	8.6
ECOG 4201 (31)	50.4 Gy plus GEM	34	11.0
Single institution			
University of Texas M.D. Anderson Cancer Center, 2006 (5)	50.4 Gy/28fx plus capecitabine plus bevacizumab	47	14.4
University of California at San Francisco (38)	50.4 Gy/28fx plus capecitabine	17	17.0
Memorial Sloan-Kettering Cancer Center (41)	50.4 Gy/28fx plus erlotinib plus GEM	20	18.7
University of Michigan (42)	50-6-Gy/25fx plus GEM	27	23.1
University of Texas M.D. Anderson Cancer Center, 2010 (43)	50.4/28fx plus capecitabine plus cetuximab	69	18.8

Abbreviations: GITSG = Gastro-Intestinal Study Group; ECOG = Eastern Cooperative Oncology Group; FFCD-SSRO = France Foundation of Digestive Oncology and the French Society of Radiation Oncology; CALGB = Cancer and Leukemia Group B; RTOG = Radiation Therapy Oncology Group; EBRT = external beam radiation therapy; 5-FU = 5-fluorouracil; GEM = gemcitabine.

* Adapted from ref. 25.

would not have had a survival benefit from local therapy. Among the remaining nonmetastatic patients who went on to have SBRT and further gemcitabine chemotherapy, the median overall survival was 20 months. While the local control rate remained high, patients still developed metastatic disease later, underscoring the need for effective systemic therapy. A similar strategy was studied by the group at Stanford University (16), where 16 patients had one cycle of gemcitabine (1,000 mg/m² given on 3 of 4 weeks), a single fraction of 25 Gy stereotactic radiosurgery (SRS) on day 29, and then 2 weeks later received further cycles of chemotherapy. After a median follow-up of 9.1 months, the local control rate was 81%, and the median overall survival was 11.4 months. Three patients (19%) developed acute complications, and 7 patients (47%) developed significant late toxicity. That study differs from ours in two important ways, namely, following the schedule of systemic therapy patients were neither restaged nor selected for SBRT. In contrast, we administered two full cycles of systemic therapy, and after restaging, nonmetastatic patients received another cycle of gemcitabine, prior to administration of SBRT. Based on our previous experience (20), we felt that a fractionated, tolerance-based approach would result in being able to treat tumors of different size, shape, and locations in relation to sensitive dose-limiting structures more effectively with less toxicity. The biologically equivalent dose for our regimen (24–36 Gy in 3 fractions compared to 25 Gy in one fraction) is closer to conventionally fractionated external beam radiation, both for tumor and normal tissue toxicity. However, our clinical outcome with a median survival of 20 months appears better. While the differences in the patient population make it difficult to assess why our approach is truly more effective, our toxicity was also markedly less.

It is conceivable that the better survival with little toxicity in our study is due to the quick and effective delivery of safe radiation, comparable to a prolonged course of standard ra-

diation, while at the same time allowing delivery of uninterrupted maximal systemic therapy. Although local control remains high, patients still developed metastatic disease underscoring the need for effective systemic therapy. This is particularly relevant if the basis of the current chemoradiation controversy stems from interruption of the beneficial effects of systemic therapy. Nevertheless, the role of local therapy cannot be discounted. Our strategy capitalizes on the benefits of local therapy without interrupting systemic therapy. This may be particularly beneficial if this approach is applied to patients selected after initial control of systemic disease with chemotherapy as used in this study.

This study was a retrospective analysis of patients treated with a particular strategy in partnership with community oncologists. The inherent drawback is rigorous follow-up, which in this study, involved missing tumor marker (CA 19-9) values in some patients. Another aspect of this study was the use of conventional contrast-enhanced CT scans for diagnosis, staging, target delineation, and follow-up. It remains to be studied if the addition of magnetic resonance imaging would improve the accuracy of target delineation and whether the use of positron emission tomography scans would enhance the accuracy of either locoregional staging or assessment of response.

CONCLUSIONS

Patients with locally advanced, unresectable pancreas cancer who do not have overt metastasis at presentation often progress to metastatic disease. In this study, we have shown that by first delivering systemic chemotherapy, it is possible to select the patients most likely to benefit from local therapy with SBRT. We have also demonstrated that a brief course of SBRT provides effective local control without interrupting essential systemic therapy.

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