

EDITORIAL

Stereotactic Body Radiation Therapy (SBRT) in Pancreatic Cancer: Is It Ready for Prime Time?

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Summary

Pancreatic cancer is a devastating disease with few effective treatment modalities. Stereotactic body radiation therapy is a novel technique that takes advantage of the technologic advancements in image guidance and radiation dose delivery to direct ablative doses to tumors with acceptable toxicity that was not previously achievable with conventional techniques. Recent literature contains reports of stereotactic body radiation therapy in patients with locally advanced pancreatic tumors. This paper presents a summary of the current data and highlights the limitations and the promise. Further clinical study in the form of multi-institutional trials is warranted to establish the role of stereotactic body radiation therapy as a comparable noninvasive alternative to surgery.

Introduction

The American Cancer Society estimates that 37,680 cases of pancreatic cancer will be diagnosed in the United States in 2008, with an estimated 34,290 deaths [1]. For patients with exocrine pancreatic cancer, the only curative treatment is complete surgical resection, but less than 20% are eligible for surgery at presentation. Another 40% present with localized tumors are unresectable due to involvement of the celiac axis, the superior mesenteric artery, or other major vascular

structures. For these patients with locally advanced disease, treatment typically consists of chemoradiation [2], or initial chemotherapy followed by chemoradiation [3] if there is no progression. Overall, the median survival is 8-12 months, and there are few long-term survivors. Likewise, patients with local recurrence or positive margins after definitive surgery have a poor prognosis and short expected survival.

Stereotactic body radiation therapy (SBRT) represents a relatively new development in the field of radiation therapy and is now beginning to deliver impressive results in the treatment of deeply situated tumors of various organ sites. This radiation therapy technique is being increasingly applied to pancreatic cancer, in part due to patient demand and marketing. In this article, we will review the principles underlying SBRT, examine the published evidence for its safety and efficacy, and discuss the role of SBRT in the management of pancreatic cancer.

SBRT Principles

In comparison to conventional radiotherapy, SBRT involves more accurate patient immobilization and greater attention to accurate replication of the simulation position for treatment delivery, allowing for sub-centimeter precision. Organ motion is taken into account, either through active suppression, tracking the moving target with the linear accelerator, or 'gating' the

accelerator to deliver treatment only when the target is in range. The target tumor and the normal tissue avoidance structures are stereotactically registered to the treatment machine. Multiple non-coplanar fixed beams or arc fields are used in order to minimize normal tissue exposure and provide rapid fall-off of the radiation dose outside of the target area. Finally, an ablative dose of ionizing radiation is delivered to the tumor, typically in one to five sessions (Figure 1). Many of the same principles are employed during stereotactic radiosurgery for brain lesions, but radiation oncologists are now adapting them to the treatment of extracranial tumors.

SBRT Results

The largest body of experience with SBRT relates to the treatment of medically inoperable, early-stage lung cancer. Timmerman *et al.* and McGarry *et al.* [4, 5] conducted a phase I trial of SBRT in medically inoperable non-small cell lung cancers (NSCLC). The radiation dose was escalated to 60 Gy in 3 fractions for T1 tumors and 66 Gy in 3 fractions for T2 tumors without reaching a maximum tolerated dose. A phase II study by the same group treated 70 patients with these doses and reported a 95% rate of local control. Severe toxicity was more likely to occur in patients with central tumors [6]. The RTOG 0236 phase II protocol for medically inoperable NSCLC enrolled 52 patients and used a dose of 60 Gy in 3 fractions. Tumors closer than 2 cm to the proximal bronchial tree were excluded. There has been no excess toxicity so far, and

preliminary estimates of local control are excellent [7]. High rates of local control and limited toxicity have been reported by groups in Europe and Japan [8, 9].

Both primary and metastatic liver tumors have been treated with SBRT. Herfarth *et al.* performed a phase I and II trial of single-fraction SBRT for limited liver metastases [10]. The 18-month freedom from local failure rate was 67%, and most failures occurred in the lower dose cohorts. The dose was safely escalated to 26 Gy, although further follow-up did reveal late local failures even at this dose level. Series by Wulf, Schefter, and Kavanaugh [11, 12, 13] utilized regimens of one to three fractions to treat a group of predominantly oligometastatic patients and showed high rates of local control (86-100% at 12 months) and little toxicity. Experience so far suggests that sparing an adequate amount of normal liver minimizes the risk of hepatitis, and that extreme caution should be employed when treating tumors in close proximity to small bowel and other tubular structures of the gastrointestinal tract.

Challenges and Promise of SBRT for Pancreatic Cancer

The pancreas presents unique difficulties with regard to performing SBRT. While it is not itself prone to damage from radiation, the pancreas is closely applied to the curve of the duodenum. Delivery of even moderate doses of radiation (more than 50 Gy in 1.8-2 Gy/day fractions) to small bowel is associated with a high risk of late stenosis, ulceration, bleeding and perforation. The risk of late bowel complications is substantially heightened by the use of large fraction sizes, as in SBRT. Tumors of the pancreas also move with respiration and with peristalsis, and are relatively difficult to visualize on the computed-tomography scans typically used for treatment planning. Nonetheless, SBRT has considerable theoretical appeal in pancreatic cancer. For patients who are unable to undergo curative surgery, it would seem to represent a relatively non-invasive tool to provide local control of the gross tumor. In

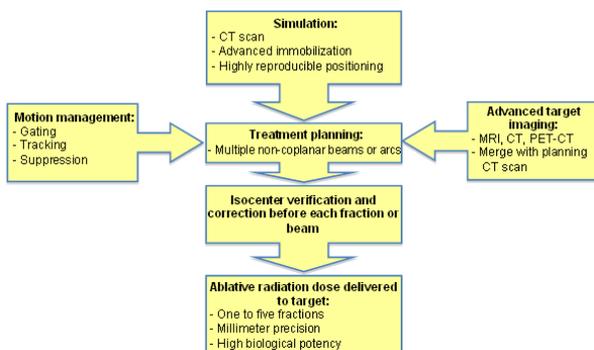


Figure 1. Treatment planning and delivery of stereotactic body radiation therapy (SBRT).

patients whose tumors recur locally, SBRT offers the ability to target a tumor nodule focally, without the toxicity of systemic therapy. Patients with positive margins after resection might benefit from delivery of high dose therapy to the margin, particularly if it were marked with surgical clips. But what evidence is available to support the use of SBRT in pancreatic cancer?

Results of SBRT for Pancreatic Cancer

The initial phase I study of SBRT in locally-advanced pancreatic cancer was performed by Koong *et al.* at Stanford University using Cyberknife[®] [14]. The Cyberknife[®] (Accuray Inc., Sunnyvale, CA, USA) system consists of a compact linear accelerator mounted on a robotic arm that permits rapid repositioning and delivery of radiation from almost any angle. X-ray cameras track metal fiducial markers implanted in the tumor to provide continuously updated targeting. Fifteen patients were enrolled and received doses of 15, 20, or 25 Gy to the primary tumor only. Twelve had not received prior radiation or chemotherapy. Treatment was planned using a contrast-enhanced thin-cut CT scan. The dose was prescribed to the isodose lines ranging from 64 to 85%, and the 50% isodose line was only allowed to cover the proximal duodenal wall. Acute toxicity consisted of grade 2 nausea, pain, or diarrhea in a total of 5 patients. The 6 patients who received 25 Gy were locally controlled, but all 6 succumbed to distant metastases. The median survival for the cohort was 11 months. The Stanford group then performed a phase II trial of chemoradiation with 5-fluorouracil and 45 Gy delivered in 1.8 Gy/day fractions to the tumor and regional lymph nodes, followed by a 25 Gy Cyberknife[®] boost to the gross tumor [15]. Fifteen out of 16 patients who completed treatment were locally controlled, but all patients developed distant disease, with a median freedom from progression of 17.5 weeks. The median survival was 33 weeks. Two patients experienced grade 3 acute toxicity - in the form of gastroparesis - that required parenteral support, and symptomatic

duodenal ulcers were reported to have developed 4-6 months after treatment. Recently, the Stanford group reported results of a trial of gemcitabine (1,000 mg/m² on days 1, 8, and 15) followed by 25 Gy SBRT on day 29. Two weeks or more after SBRT, gemcitabine was restarted at 1,000 mg/m² per week and continued until disease progression [16]. Sixteen patients were enrolled and all 16 completed treatment, with a median survival of 11.4 months and a 50% one-year survival. Thirteen of 16 patients were locally controlled, but these patients developed metastases. None of the patients had sufficient response to undergo resection. Acute toxicity was mild, but there were 5 late grade 2 duodenal ulcers, one grade 3 duodenal stenosis requiring stenting, and one grade 4 duodenal perforation requiring surgery. Hoyer *et al.* reported results of a Danish Phase II study of SBRT for locally advanced pancreatic cancer [17]. Treatment was delivered using a standard linear accelerator with abdominal compression to reduce respiratory motion and a stereotactic body frame for immobilization and planned using a contrast-enhanced CT scan. The target consisted of gross tumor and the surrounding edema and was enclosed by the 67% isodose, resulting in a delivered dose of 30 Gy in 3 fractions. Twenty-two patients were treated, and two achieved partial response. Six patients recurred locally; the mean time to progression was 4.8 months, with 6 patients receiving gemcitabine after relapse. Median survival was 5.7 months, and the one-year survival was 5%. Acute toxicity was substantial, and 4 patients had severe ulceration of the stomach or duodenum. One patient had a perforated gastric ulcer requiring surgery. Notably, although the gross tumor volumes were similar, the volumes treated to the prescription dose in the Danish study were much larger than those in the initial Stanford study, due to differences in target definition and margins. The poor local control seen in the Danish study could be a result of a biologically less potent dose, or to an aggressive biopsy policy during follow-up.

Results of a study by Mahadevan *et al.* of SBRT in pancreatic cancer were published in abstract form in 2007 [18]. Twenty-one locally advanced, 3 recurrent, and 8 positive margin patients were treated with Cyberknife®. Locally advanced patients and recurrent patients received 24-36 Gy in 3 fractions followed by gemcitabine, while positive margin patients were treated with a single 10 Gy fraction followed by 45-50.4 Gy radiation in conventional fractionation to the tumor bed with concurrent capecitabine. At a median follow-up of 8.8 months, all 8 post-operative patients were locally controlled, although two had failed distantly. Nineteen of the locally advanced patients were locally controlled at 8 months, and 10 had developed metastases. Toxicity included 25% grade 2 nausea, one grade 3 ulcer of the duodenum and one grade 3 thrombosis of the vena cava. A group at the University of Pittsburgh has presented early results of a series of 9 patients who had positive margins and received 16-24

Gy in a single fraction by Cyberknife® [19]. Two patients had had prior radiation. At a mean follow-up of 5 months, all were alive and locally controlled, although one patient had liver metastases. There was no acute toxicity; late toxicity was not reported due to short follow-up.

A retrospective series from Georgetown University included 20 patients with local recurrence after definitive chemoradiation and 8 with recurrence after surgery and adjuvant chemoradiation [20]. These patients had received a median prior radiation dose of 50.4 Gy with concurrent chemotherapy. Twenty to 30 Gy were delivered in 3-5 fractions using Cyberknife®. The median survival was 5.3 months, and only 25% lived 8 months after treatment. There was one bowel obstruction and one peri-pancreatic abscess, both occurring in patients receiving 3 fractions, and the authors now use a 5-fraction schedule. Only 14 patients had data on disease progression; 12 85.7% were locally controlled,

Table 1. Results of stereotactic body radiation therapy (SBRT) for pancreatic cancer.

Group	Patients	Previous RT?	SBRT dose	Local control	Distant control	Median survival (months)	1-year survival
Stanford phase I [14]	15 LA	2/15	15-25 Gy x 1	100% (25 Gy)	0% (25 Gy)	11	NR
Stanford Boost [15]	16 LA	16/16; 45 Gy with 5-FU	25 Gy x 1	94%	0%	8.3	15%
Stanford gemcitabine [16]	16 LA	No	25 Gy x 1	81%	0%	11.4	50%
Danish phase II [17]	19 LA; 3 LR	No	10 Gy x 3	57%; 2 PR	13%	5.7	5%
Beth Israel Deaconess [18]	21 LA 3 LR	No 3/3	8-12 Gy x 3 for LA, LR	79% at 8 months for LA, LR	55% at 8 months for LA, LR	NR	75% at 8 months for LA, LR
	8 PM	No	10 Gy x 1	100% at 8.8 months	75% at 8.8 months		75% at 8.8 months
University of Pittsburgh [19]	9 PM	2/9	16-24 Gy x 1	100% at 5 months	89% at 5 months	NR	NR
Georgetown University [20]	28 LR	28/28; median dose 50.4 Gy with chemo	20-30 Gy total; 3-5 fractions	86% (12/14)	43%	5.3	25% at 8 months

LA: locally advanced
 LR: locally recurrent
 PM: positive margin
 PR: partial response
 NR: not reported

with 8 (57.1%) developing metastases. Tables 1 and 2 summarize published series showing results and toxicity of SBRT for pancreatic cancer, respectively.

Discussion

Surgery remains the standard of care and the sole hope for cure in operable pancreatic cancer. In patients with local recurrence or positive margins, there is still too little data to judge whether SBRT confers a significant benefit over more conservative therapies. Caution should be exercised when SBRT is used in the setting of previous full-dose radiation. The initial published experiences with SBRT for locally advanced pancreatic cancer show considerable promise for local control, but many important questions have yet to be answered. SBRT appears to be well-tolerated acutely, but the optimal dose and fractionation to maximize local control while minimizing late toxicity have yet to be determined. After decades of work and tens of thousands of patients’ worth of experience, normal tissue tolerances to conventional fractionated radiation are relatively well-understood, but the tolerance of the duodenum and other abdominal viscera to the high-dose-per-fraction radiation used in SBRT remains largely unknown. Because toxicity occurs late, close attention should be

paid to the length and quality of follow-up in any SBRT series. A modest increase in the number of fractions could help to limit late toxicity.

Gemcitabine is the most active chemotherapy for pancreatic cancer, but it is also a potent radiosensitizer with a narrow therapeutic window. The recent Stanford study combining gemcitabine and SBRT resulted in significant late toxicity. Future studies of SBRT with non-gemcitabine regimens or altered sequencing of gemcitabine and SBRT are indicated. Finally, the overriding and ultimately fatal problem in all of the series cited above continues to be metastatic disease. Only when systemic agents are developed that can effectively eradicate occult micro-metastases will local therapies like SBRT take center stage in the management of pancreatic cancer. Still, the importance of local control should not be undervalued. Unchecked local disease can lead to significant problems with pain, gastric outlet obstruction, and biliary obstruction. SBRT certainly merits further investigation in depth, especially since outcomes for conventional therapies in pancreatic cancer are poor. Carefully designed prospective studies of SBRT in the setting of locally advanced disease, local recurrence, and positive margins should be strongly encouraged.

Table 2. Toxicity of stereotactic body radiation therapy (SBRT) for pancreatic cancer.

Group	Acute toxicity	Late toxicity	Notes
Stanford Phase I [14]	33% grade 1-2 GI	Not reported	-
Stanford Boost [15]	69% grade 1-2 GI 12.5% grade 3 GI	12.5% grade 2 duodenal ulcers	-
Stanford gemcitabine [16]	12.5% grade 2 GI 6.3% grade 3 GI	31.3% grade 2 GI 6.3% grade 3 GI 6.3% grade 4 GI	47% had late toxicities 4-10 months after SBRT
Danish phase II [17]	79% grade 2+ at 14 days	18% “severe” GI mucositis/ulceration; 4.5% grade 4 gastric perforation	Increased pain, nausea, and decreased performance status seen at 14 days vs. baseline
Beth Israel Deaconess [18]	25% grade 2 GI	4% grade 3 GI; 4% grade 3 vascular	Toxicities reported for locally advanced and local recurrence patients only
University of Pittsburgh [19]	0%	Not reported	Limited follow-up
Georgetown University [20]	Not reported	7% GI (1 abscess, 1 bowel obstruction)	-

Conclusions

SBRT is tolerable and shows excellent promise for local control of locally advanced, unresectable pancreatic cancers, although the development of metastatic disease remains problematic. Prospective, multi-institutional studies are required to confirm the long-term safety and efficacy of SBRT for locally advanced disease, and to further evaluate the role of SBRT in patients with positive margins and local recurrences.

Keywords gemcitabine; Pancreatic Neoplasms; Radiosurgery; Radiotherapy; Surgery

Abbreviations NSCLC: non-small cell lung cancers; SBRT: stereotactic body radiation therapy

Conflict of interest The authors have no potential conflicts of interest

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Document URL: <http://www.joplink.net/prev/200811/08.html>

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