

Chapter 10

Stereotactic Body Radiotherapy (SBRT) for Pancreatic Cancer

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Abstract Pancreatic cancer is the tenth most common cancer and is the fourth leading cause of cancer mortality. While surgery remains the current potentially curative treatment of choice, few cancers are resectable at presentation. Chemotherapy and radiation play a vital role in locally advanced non-metastatic pancreatic cancer. Systemic therapy is vital in these patients and often, when they remain non-metastatic after induction therapy radiation improves local control. Conventional chemoradiation is delivered in 5–6 weeks. Stereotactic body radiotherapy (SBRT) has been used in patients with locally advanced pancreas cancer, in fewer treatments, without significantly affecting systemic therapy, thereby maximizing systemic and local control. SBRT has also been used to boost positive margins, local recurrences after prior radiation, and in oligometastatic pancreatic cancer.

Keywords Locally advanced pancreatic cancer • Induction chemotherapy • Gemcitabine

10.1 Introduction

With an estimated 45,220 new cases, resulting in 38,460 deaths, in the United States in 2013, pancreatic cancer is the fourth-leading cause of cancer-related deaths [1]. Despite many new treatment approaches, pancreatic cancer survival has not improved in the past 25 years [2]. Surgical resection remains the only treatment approach with the potential for providing long-term survival for patients without metastatic disease at presentation, but between 40 and 50 % of patients have locally advanced

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inoperable cancer at presentation or at surgical exploration [3]. The 5-year overall survival rate for patients with inoperable pancreatic cancer is less than 5 % [4–6].

Radiation therapy and chemotherapy, used either alone or in combination, are the only treatment options available for patients with locally advanced unresectable disease [6, 7]. However these treatments only marginally improve the median survival time to between 8 and 14 months [8–15]. Conventional radiation therapy requires approximately 6 weeks of daily treatments, which thus may take a significant fraction of the patient's limited life expectancy. In addition, side effects from radiation therapy can be substantial. Studies using chemotherapy alone have suggested outcomes equivalent to those of chemoradiation, raising further doubts about the value of a long course of conventional radiation therapy given the additional toxicity [16–23].

Stereotactic body radiotherapy (SBRT) is a minimally invasive treatment option that has been shown in prospective Phase I and Phase II studies and single institution studies to be a safe, quick and feasible approach for the treatment of locally advanced pancreatic cancer [24–36].

10.2 Patient Selection

Patients with biopsy proven non-metastatic locally advanced unresectable pancreatic cancer who are referred for conventional chemoradiation are also ideal potential candidates for SBRT. Patients with gastric or duodenal obstruction are generally excluded. Patients with borderline resectable disease can also be considered for this hypofractionated approach. A radiologist and experienced pancreatic surgeon should review a pancreas-specific multiphase CT angiogram, to determine inoperability using standard CT criteria [37]. Patients who appear potentially resectable by axial imaging and considered for surgery and those found unresectable at the time of surgery would also be candidates. EUS (Endoscopic Ultrasound) has further increased diagnostic yield to identify patients with unresectable pancreas cancer and use the opportunity to obtain histological diagnosis and placement of fiducials [38].

Most patients eventually succumb to metastatic disease. This fact and randomized trials which did not show the benefit of addition of radiation therapy to systemic treatment [9] emphasizes the role of systemic therapy. As with conventional chemoradiation [12], it is now acceptable practice to use systemic therapy as induction therapy prior to SBRT for pancreas cancer. Single institution prospective studies have indeed validated this approach [31].

10.3 Patient Work-Up

In addition to the history and clinical examination, Carbohydrate antigen 19–9 (CA19–9) measurements, complete blood counts, and a biochemistry panel including liver function tests are performed in all patients prior to treatment and at

follow-up. As mentioned above a multiphasic CT scan of the abdomen with oral and IV contrast is mandatory in the evaluation of these patients.

10.4 Treatment Planning

For image guidance, three to five fiducial seeds are commonly placed in and around the tumor percutaneously using CT guidance, at laparotomy, or (more commonly) under endoscopic ultrasound guidance. CT planning images with oral and IV contrast are obtained at least 1 week after fiducial placement, to allow for potential fiducial migration. Patients were imaged and treated in the supine position, with their arms down, lying in memory foam placed over a customized Vac-Lok™ (CIVCO Medical Solutions, Orange City, IA) immobilization cradle to ensure a comfortable and reproducible position. The CT images are transferred to a SBRT planning workstation and the target volume (visible gross disease) and critical structures, including the stomach, duodenum, kidneys, liver and spinal cord, are contoured. The clinical target volume is generally defined as the gross disease. No expansion margin is used where the tumor was in contact with the bowel (stomach or duodenum); otherwise, a 5 mm or smaller expansion margin (extending up to the outer bowel wall) is usually included to determine the planning target volume (PTV) [31].

10.5 Stereotactic Body Radiotherapy Dose Prescription

The SBRT dose is commonly prescribed to a conformal isodose line generally covering at least 95 % of the target volume (usually 70–80 %). While some institutions use a single fixed dose prescription [25–27, 29, 30, 34, 39], others use a radiation dose based on the relationship between the tumor location and the gastro-duodenal loop, in order to limit toxicity (Fig. 10.1) [32]. However, when patients have had a palliative gastro-duodenal bypass, such duodenal constraints may have a lesser significance. The suggested maximal point tolerance dose of the duodenum is three fractions of 10 Gy each [40, 41]. In one institutional scheme [32], if the tumor approximated one-third or more of the circumference of the duodenum or stomach, then a dose of 24 Gy (three fractions of 8 Gy each) is used. If the tumor abutted the bowel in only one area and/or the space between the tumor and the bowel wall was less than 3 mm, then a dose of 30 Gy (three fractions of 10 Gy each) is prescribed. Finally, if the gap between the tumor and the duodenum was 3 mm or wider, a dose of 36 Gy (three fractions of 12 Gy each) is used. A representative treatment plan is shown in Fig. 10.2.

Normal tissue constraints are respected during treatment planning. When treating in three fractions, the volumes of liver receiving 21 Gy (V_{21}) or more and 15 Gy (V_{15}) or more are kept below 30 and 50 %, respectively. The corresponding doses to these volumes in single fraction would be V_{12} and V_7 [42]. The volume of each

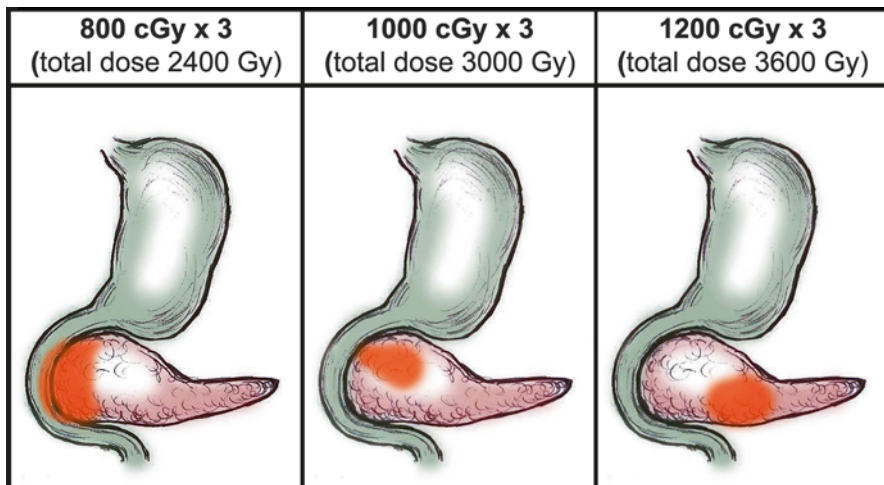


Fig. 10.1 Adaptive tolerance based stereotactic body radiotherapy dose prescription, showing a graphical depiction of the relationship between the duodenum and pancreatic tumor (red) that is used to determine each of the three prescribed doses

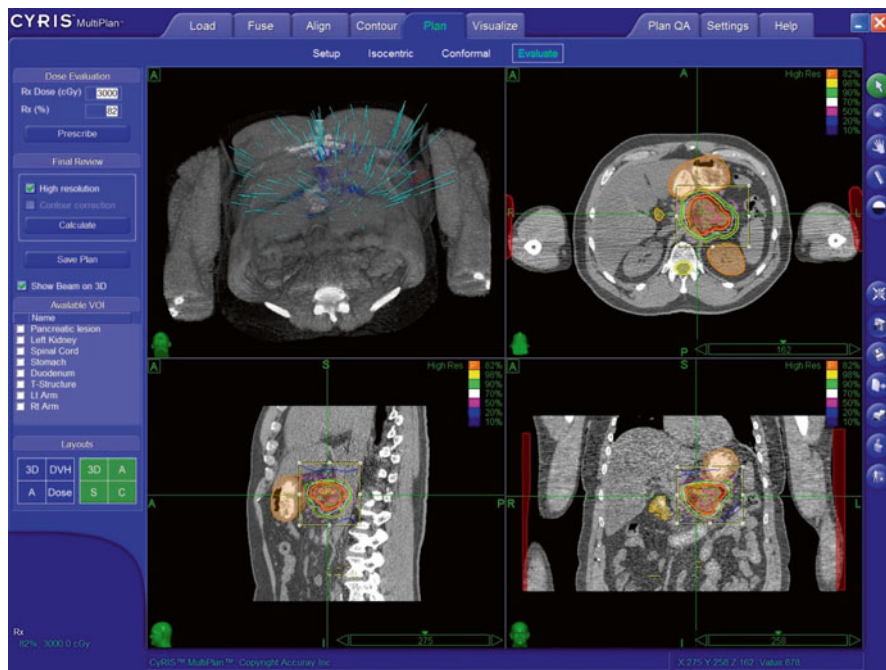


Fig. 10.2 Representative treatment plan

kidney receiving 12 Gy or more will be maintained below 25 %. The total maximal spinal cord limit is usually 12 Gy and the maximum point dose to the bowel is less 10 Gy per fraction.

10.6 Treatment Delivery

The CyberKnife Robotic Radiosurgery system (Accuray Incorporated, Sunnyvale, CA) with Synchrony motion tracking has been commonly used as a SBRT system to treat locally advanced pancreas cancer. Other SBRT modalities with image guidance and respiratory gating or dampening (E.g. Novalis, TrueBeam) can be equally applicable to treat these patients. Patients are generally premedicated with H₂ receptor blockers or proton pump inhibitors, and antiemetics.

10.7 Systemic Chemotherapy

Patients with unresectable, locally advanced pancreatic cancer often progress with metastatic disease as they harbor micrometastasis at presentation. Hence systemic therapy plays a vital role in the management of these patients. By utilizing a strategy of delivering upfront systemic chemotherapy it is possible to select those patients who are more likely to benefit from local therapy [12, 31]. Intensified chemotherapy regimens with proven improved response rates in the metastatic setting, like FOLFIRINOX, or Gemcitabine and nab-Paclitaxel is now being routinely used in patients with locally advanced pancreas cancer.

The use of single- and multiple-fraction SBRT has been shown to be feasible and safe for patients with locally advanced pancreatic cancer. The results of published data on the use of SBRT in locally advanced pancreas cancer is presented in Table 10.1 [25–27, 29–36, 39, 43]. In contrast to 5–6 weeks of conventional chemoradiation, SBRT can be performed in only 1–3 days, resulting in only a minimal delay in initiating systemic therapy. When SBRT is selectively used for patients who have been treated with systemic therapy, it appears to benefit them most without immediate overt development of metastasis when used upfront [31, 44].

Initial experience with single fraction SBRT with or without external beam radiation has been fraught with acute and chronic toxicity [25, 27, 29, 30]. Similarly high fixed doses of SBRT without accounting for respiratory motion has been associated with significant toxicity [27]. More recently tolerance based moderate doses of hypo fractionated radiation, with respiratory motion tracking and in the setting of systemic therapy has proven to be an acceptable regime [31]. Assuming an α/β ratio of 10 for pancreatic tumor response, Chang et al. calculated their scheme to be equivalent to 74 Gy delivered in 1.8-Gy fractions of conventional radiation. The Hoyer et al. study gave a dose equivalent to 95 Gy. In the study from Mahadevan et al., the equivalent dose was 51–76 Gy, comparable to a conventional radiation

Table 10.1 Clinical outcomes in published literature for SBRT for locally advanced pancreas cancer

Study (author)	Treatment	Number of patients	Progression-free survival (months)	Overall survival (months)
Koong et al. Phase I [29]	SRS 15–25 Gy	15	2	11 ^a
Koong et al. Phase II [30]	RT 45 Gy + SRS 25 Gy	19	4.5	8 ^a
Schellenberg et al. [26]	GEM + SRS 25 Gy + GEM	16	9	11.4 ^a
Chang et al. (includes all of above patients) [25]	SRS 25 Gy ± GEM EBRT	77	–	11.4 ^a
Hoyer et al. [27]	SBRT 45 Gy	22	4.8	5.7 ^a
Mahadevan et al. [32]	SBRT 24–36 Gy + GEM	36	CA 19–9: 7.9 CT: 9.6	14.3 ^b
Polistina et al. [33]	GEM + SBRT 30 Gy	33	NR	10.6 ^a
Didolkar et al. [43]	SBRT 15–30 Gy + GEM	85 ^c	NR	18.6 ^a 8.6 ^b
Rwigema et al. [34]	SRS 18–25 Gy	71 ^d	NR	10.3 ^b
Mahadevan et al. [31]	GEM- SBRT-GEM	39	15	20 ^a
Goyal et al. [39]	SRS 20–25, SBRT 24–30 (3#) ± Chemo	20	NR	14.4
Chuong et al. [36]	GEM/GTX (borderline)-SBRT 35/25 Gy (5#)	64 (57 borderline)	9.7	15 (16.4 borderline)
Tozzi et al. [35]	SBRT 36 Gy (6#)	30 (9 Recc.)	8	11

Abbreviations: *EBRT* external beam radiation therapy, *GEM* gemcitabine, *GTX* gemcitabine, taxotere, xeloda, *NR* not reported, *RT* radiation therapy, *SBRT* stereotactic body radiation therapy, *SRS* stereotactic radiosurgery, *Recc* recurrent cancer

^aFrom diagnosis

^bFrom start of treatment

^cIncludes recurrent patients

^dIncludes recurrent and positive margin patients some of which received post-SRS chemotherapy

dose. While this may potentially appear to decrease the likelihood of local control it likely provides a better therapeutic ratio. The RBE (Relative Biological Effectiveness) and the equivalent doses for tumor control, acute and late toxicity in these series are presented in Table 10.2 [25, 27, 32].

10.8 Toxicity

Most patients experience fatigue and some nausea and temporary loss of appetite. Flare pain at the tumour site can also sometime occur and is usually self-limiting. Given the high doses of radiation per fraction, and the close association of the gasw-Phase I and Phase II SBRT toxicity data for liver tumors suggest that the maximum

Table 10.2 Relative radiation dose, local control and toxicity in three commonly used prescriptions for stereotactic radiosurgery or stereotactic body radiotherapy

Study	Fractionation	Conventional radiation equivalent dose (Gy) $Eq_{1.8}$	Tumor control biological equivalent dose (Gy) BED_{10}	Long term toxicity equivalent dose (Gy) BED_3	Median follow-up (months)	Local control (%)	Grade 3 or higher toxicity	
							Acute (%)	Long term (%)
Hoyer et al. [27]	15 Gy \times 3	95	112.5	270	6	57	78	33
Chang et al. [25]	25 Gy \times 1	74	87.4	23.3	12	84	1	9
Mahadevan et al. [32]	8–12 Gy \times 3	51–76	43–54	88–180	24	78	8	6

Abbreviations: $Eq_{1.8}$ equivalent dose to conventional radiation in 1.8 Gy per daily fraction, BED_{10} biologically equivalent dose assuming α/β of 10 for tumor control and acute toxicity, BED_3 biologically equivalent dose assuming α/β of 3 for long term toxicity

point dose to the duodenum should be kept below the equivalent of three fractions each of 10 Gy (equivalent to 130 Gy in 1.8-Gy fractions, assuming an α/β ratio of 3) [40]. Other Dose Volume constraints have been proposed [45, 46]. The acute and long-term toxicity of the Hoyer study was higher than either the Stanford or the Boston groups. Assuming an α/β ratio of 3, the Chang et al., Hoyer et al. and Mahadevan et al. treatment schemes are equivalent to 233 Gy, 270 Gy, and 88–180 Gy in 1.8-Gy fractions, respectively. While this may explain the toxicity, a tolerance based (gastrointestinal tolerance) approach could decrease toxicity. This strategy has been used to reduce toxicity in other cancers treated with SBRT [47, 48].

10.9 Review of Literature

The treatment of patients with non-metastatic locally advanced pancreatic cancer continues to evolve. While the data is conflicting, the general standard of care appears to be concurrent chemoradiation in addition to systemic chemotherapy [49]. However, the effectiveness of the addition of chemoradiation to a chemotherapy treatment plan has been questioned. In addition there are significant side effects associated with 5–6 weeks of upper abdominal radiation, which are particularly problematic for these patients with short life expectancies. Nevertheless, randomized trials have shown a survival benefit to giving radiation therapy to such patients, as in other gastrointestinal cancers, and radiotherapy may be particularly helpful in local control and palliating local symptoms [50–52].

The use of single- and multiple-fraction SBRT has been shown to be feasible and safe for patients with locally advanced pancreatic cancer in several series. In contrast to 5–6 weeks of conventional chemoradiation, SBRT can be performed in only 1–3 days, resulting in only a minimal delay in initiating systemic therapy. Table 10.1 summarizes the outcomes for published studies of SRS and SBRT. Initial experience with single fraction SBRT with or without external beam radiation has been fraught with acute and chronic toxicity. Similarly high fixed doses of SBRT without accounting for respiratory motion has been associated with significant toxicity. More recently tolerance based moderate doses of hypo fractionated radiation, with respiratory motion tracking and in the setting of systemic therapy has proven to be an acceptable regime. While fractionation may decrease the likelihood of local control it potentially provides a better therapeutic ratio. The RBE (Relative Biological Effectiveness) and the equivalent doses for tumor control, acute and late toxicity in these series are presented in Table 10.2. Assuming an α/β ratio of 10 for pancreatic tumor response, 25 Gy single fraction is equivalent to 74 Gy delivered in 1.8-Gy fractions of conventional radiation. Similarly 45 Gy in three fractions delivers a dose equivalent to 95 Gy and the 24–36 Gy equivalent doses are 51–76 Gy, comparable to a conventional radiation dose. This along with consideration of equivalent doses for long-term toxicity as described above may explain the differences in outcomes.

10.10 Other Potential Roles of SBRT in Pancreas Cancer

Local failure is a significant problem in resected cancers even after an R0 resection. It is particularly relevant in patients with positive margins. A stereotactic boost to areas of known positive margins in addition to standard adjuvant therapy may provide additional local control and even a survival benefit [53]. In Boston fiducial seeds are routinely placed during pancreaticoduodenectomy at the uncinate, retroperitoneal, superior mesenteric and pancreatic margins, and pathology guided stereotactic boost of 10 Gy is delivered in addition to standard 50 Gy of postoperative chemoradiation for R1 resections.

Young patients with good performance status and isolated oligo metastasis (e.g. liver metastasis) presenting synchronously or metachronously, may also benefit from local control with SBRT in addition to systemic therapy. Yet another rare indication would include re-irradiation for local failure after prior radiation therapy in the absence of controlled metastatic disease.

10.11 Conclusion

SBRT can be delivered safely and quickly to potentially benefit patients with locally advanced unresectable pancreatic cancer. The toxicity and outcomes appear comparable or more favorable than those of conventional chemoradiation. A randomized trial will be required to answer whether SBRT plus chemotherapy will improve progression-free survival, overall survival, and patients' quality of life compared to chemotherapy with or without conventional chemoradiation. SBRT may have a role in patients with positive margins, oligometastasis and local recurrence after prior radiation.

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