

Review

The Evolving Field of Stereotactic Body Radiation Therapy in Pancreatic Cancer

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ABSTRACT

Pancreatic cancer remains a devastating disease with dismal outcomes despite the development of novel chemotherapeutic regimens and radiation techniques. Stereotactic body radiation therapy (SBRT) offers an advantage both in image guidance and radiation dose delivery to direct ablative doses to tumors with acceptable toxicity compared to conventional techniques. Recent literature is clustered with data pertaining to SBRT in patients with resectable, borderline resectable and locally advanced pancreatic tumors. We here present a summary of the current data and highlight the limitations and potential for future growth. Further clinical study in the form of multi-institutional trials is warranted to establish the role of SBRT in combination with new chemotherapeutic agents as well as a non-invasive alternative to surgery.

Keywords

Pancreatic neoplasms; Pancreas cancer; Radiosurgery; Stereotactic; Stereotactic body radiation therapy (SBRT); Radiation; Radiotherapy.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with limited effective therapeutic options and exceedingly high mortality. Currently, a cure may be achieved through resection; recent evidence suggests that neoadjuvant therapy can increase R0 (pathologically negative margin) resection rates with effective local control.¹ Stereotactic body radiation therapy (SBRT) has garnered significant interest for pancreatic cancer patients as it is completed quickly over 1-5 fractions, requires less time away from full doses of chemotherapy, and is generally much better tolerated than conventional radiographic testing (RT) as a result of more limited target volumes. Favorable results of SBRT for locally advanced pancreatic cancer (LAPC) patients are now leading to the exploration of SBRT for other pancreatic cancer patients.²

SBRT FOR LOCALLY ADVANCED PANCREAS

The utility of pancreatic SBRT was established in the locally advanced patient population. With the advent of gemcitabine-based (GEM) chemotherapy, the role of RT for LAPC has become more

precarious.³ The European Fédération Francophone de Cancérologie Digestive (FFCD)/The Société Francophone de Radiothérapie Oncologique (SFRO) Phase III trial compared GEM alone *versus* induction 5 Fluorouracil (FU) and cisplatin chemoradiation (CRT), followed by maintenance gem.⁴ Overall survival (OS) was shortened in the CRT arm from 13 to 8.6-months. Higher grade 3 toxicities with CRT were observed during both induction (36% *vs.* 22%) and maintenance (32% *vs.* 18%) phases. Notably, the trial utilized a higher than normal conventionally fractionated 60 Gy dose. The recent success of more aggressive, but increasingly toxic, chemotherapy regimens such as FOLFIRINOX and gem plus nab-paclitaxel have spurred re-examination of local therapy.^{5,6} With improved systemic control, local progression may become a more serious issue for survival and quality of life. However, local control rates from standard external beam radiotherapy (EBRT) have been disappointing with 1-year local progression rates of around 50%.⁷ Furthermore, with two-thirds of patients failing distantly within 1 year, a shorter course approach with minimal interruption to systemic therapy is desirable.⁷ These factors paved the way for the use of SBRT in pancreatic cancer patients, and initially those with LAPC.

The inception of SBRT for pancreatic cancers began at Stanford with a phase I dose escalation study in a LAPC cohort.⁸ The trial was stopped at a dose of 25 Gy since all patients achieved local control with distant metastasis as the first site of failure. The median survival for all patients was 11-months, with 100% local control. However, despite smaller margins and less acute toxicity, patients treated on the Stanford single-fraction SBRT protocol experienced a high degree of late toxicities (25% grade ≥ 2).⁹ Hypofractionated studies showed reduced 1-year grade 2 toxicity to 7.8%. This reduction came without a compromise in disease control. The 1-year local control was 91.5% *vs.* 88.3% ($p=0.8$) for single *vs.* 5-fraction SBRT with median OS of 13.6-months for all patients. More contemporary SBRT series have also largely employed a fractionated approach.¹⁰⁻¹⁴ These institutional studies reveal a median survival of 14-15-months, 1-year local control rates of about 80%, and grade 3 toxicities below 10%.¹⁵

Very recently, a few groups have reported that LAPC patients may have an increased likelihood of undergoing resection after aggressive induction chemotherapy regimens. Recently, the group from Hopkins reported on 88 patients treated from 2010-14 with SBRT using gem-based or FOLFIRINOX regimens.¹⁶ SBRT doses ranged from 25-33 Gy in 5 fractions. The 1-year local control rate was 61%, but with a median OS of 18.4-months for LAPC patients. Notably, 20% of LAPC patients underwent surgery. Resected patients had a median OS of 20.2-months, compared to 12.3-months for unresected cases. Grade 3 toxicity was below 6%. Similar to the study from Hopkins, SBRT data from Moffitt also shows the possibility of downstaging for surgery.¹⁴ They reported a 24% surgical conversion rate for LAPC patients receiving FOLFIRINOX chemotherapy. All converted patients achieved an R0 (microscopic negative margin) resection. Any grade 3 or higher toxicity was 7%. Median OS was 34.2-months for patients who underwent resection, and 11.3-months for those who did not. See Table 1 for a list of SBRT studies for LAPC.

SBRT FOR BORDERLINE RESECTABLE PANCREAS

While pancreatic SBRT has been most extensively evaluated in LAPC patients, there is emerging data that SBRT may also benefit patients with borderline resectable pancreas (BRPC) (Table 2). The SBRT literature for BRPC largely comes from the Moffitt Cancer Center. Chuong et al reported on a larger series of 73 patients (57 BRPC, 16 LAPC) who received induction gem, docetaxel, and capecitabine (GTX) followed by SBRT.¹² SBRT was delivered using 5 consecutive daily fractions targeting the primary tumor with a median dose of 30 Gy (range, 25-30 Gy), the region of vascularity involvement was prescribed a median dose of 35 Gy (range, 35-50 Gy) using a simultaneous integrated boost (SIB) to further increase the likelihood of tumor regression and R0 resection. After restaging, 56.1% of the BRPC patients underwent surgical resection with all except for one (96.9%) having negative margins. Resected patients had significantly improved median OS (19.3 *vs.* 12.3 months; $p=0.03$) and median progression-free survival (PFS) (12.7 *vs.* 5-months; $p<0.0001$). No acute grade 3 toxicities were reported and the most common acute toxicities were grade 1-2 fatigue and nausea. Their subsequent study of 159 patients (110 BRPC, 49 LAPC), surgical resection was performed on 51% of the BRPC patients and R0 resection was achieved in 96%. Portal vein (PV) or superior mesenteric vein (SMV) resection and reconstruction was performed in 34% of BRPC patients. Median OS was significantly higher among patients who had surgery compared to those who did not (34.2 *vs.* 14.0-months; $p<0.001$). Finally, while the prescription doses generally increased compared to the previous publication (primary tumor: median 30 *vs.* 35 Gy; tumor-vessel interface: median 35 *vs.* 40 Gy), the incidence of late grade 3 radiation-related toxicity remained consistently low (~5%).¹⁴

The feasibility of using SBRT for BRPC is also supported by other studies with more limited numbers of BRPC patients. A study from Johns Hopkins included 88 patients (74 LAPC, 14

Table 1. SBRT for Locally Advanced Pancreatic Cancer

Study	n	Dose Fractionation	Chemo	Local control	Survival	Toxicity
Koong et al ⁸	6	25Gy in 1fx (73 Gy2)	None	100% @ 1 year	Median 8 mo	33% acute G3+
Chang et al ⁹	77	25Gy in 1fx (73 Gy2)	Gemcitabine	84% @ 1 year	Median 12 mo	25% G2+ @ 1yr
Mahadevan et al ¹¹	39	24-36Gy in 5fx (30-50 Gy2)	Gemcitabine	85% crude	Median 20 mo	9% late G3+
Herman et al ¹³	49	33Gy in 5fx (46 Gy2)	Gemcitabine	78% @ 1 year	Median 13.9 mo	12% acute G3+ 11% late G2+
Moningi et al ¹⁷	88	25-33Gy in 5fx (31-46 Gy2)	Gemcitabine or FOLFIRINOX	61% @ 1 year	Median 18.4 mo	3% acute G3+ 6% late G2+

Table 2. SBRT for Borderline Resectable Pancreatic Cancer

Study	n	Dose Fractionation	Chemo	Survival	Conversion rate	R0	pCR	Toxicity
Chuong et al ¹²	73 (78% BRPC)	25-50Gy in 5fx (31-83 Gy2)	GTX	Median 16.4m 72% @ 1 year	56%	97%	Not reported	0% acute G3+ 5% late G3+
Mellon et al ¹⁴	159 (69% BRPC)	30-40 Gy in 5fx (40-60 Gy2)	GTX	Median 19.2 m	51%	96%	7%	7% acute & late G3+
Rajagopalan et al ¹⁸	12 (58% BRPC)	36 Gy in 3fx (66 Gy2) 24 Gy in 1fx (68 Gy2)	Gemcitabine-Capecitabine	Median 47.2 m 92% @ 1 year	100%	92%	25%	0% acute G3+

BRPC) who received 5-fraction SBRT and reported favorable surgical and SBRT-related toxicity outcomes.¹⁷

Investigators from the University of Pittsburgh published their experience of 12 patients (7 BRPC, 5 LAPC) who received chemotherapy followed by SBRT prescribed to 36 Gy in 3 fractions (n=7) or 24 Gy in a single fraction (n=5) and then had surgery.¹⁸ A high rate of R0 resection was achieved (92%) with minimal toxicity. Pathologic complete response (pCR) was achieved in 25%, which is higher than would be expected with standard EBRT and perhaps signaling that SBRT may have unique histopathologic effects. It is plausible that a higher rate of pCR may be achieved using dose fractionation schedules with a higher biologically effective dose. He et al compared surgical outcomes among BRPC/LAPC patients who received SBRT (n=29), CRT (n=82), or chemotherapy alone (n=26) and reported R0 resection rates of 90%, 84% and 62%, respectively ($p=0.02$).¹⁹ The PCR rate was notably higher among patients who received SBRT (21% vs. 4% vs. 0%; $p<0.001$).

In conclusion, while various neoadjuvant treatment regimens are commonly used for BRPC including standard fractionation CRT, increasing consideration should be given to SBRT based on its clear advantage in increasing R0 resectability with higher PCR rates, and providing improved OS in these patients.

SBRT FOR RESECTABLE PANCREAS

The significance of microscopic margin involvement on survival is a controversial topic, with some studies claiming an impact on survival and others finding no such correlation.²⁰ Recent studies based on rigorous pathological examination protocols report R1 rates of well over 70%.²¹⁻²⁵ Several studies have shown that residual cancer cells are frequently present in the resection bed even in appropriately staged patients after surgery that is properly performed,²⁶ where even with R0 resections nearly 80% of patients were found to have evidence of microscopic cells left *in situ* at the surgical site.²⁷ In a recent phase III adjuvant chemotherapy trial in patients with resected pancreatic cancer in which many patients had positive margins (0-60%) and nodal involvement (63-80%), local recurrence rates were 18-41%, suggesting the presence of residual disease may benefit from local therapy in addition to systemic therapy.²⁸ Early data from MD Anderson Cancer Center included 86 patients who received gemcitabine-based X-ray telescope (XRT) radiation (30 Gy); 75% of patients were resected, 95% had R0 resections and the median OS for those who completed all therapy was 34-months.²⁹ Their subsequent study of cisplatin and gemcitabine followed by gemcitabine-based chemoradiation in 90 patients with remote procedure call (RPC) revealed an R0 resection rate of 96% and median OS of 31-months.³⁰ Cloyd et al published a unique retrospective study utilizing propensity score weighted methodologies. The authors queried MD Anderson database to identify all patients who received pre-operative chemotherapy or CRT before pancreatotomy for anatomically resectable PDAC between 1999 and 2014. They concluded that the receipt of pre-operative CRT alone was associated with a higher rate of margin-negative resection (91% vs. 79%, $p<0.01$), lower rate of positive lymph nodes

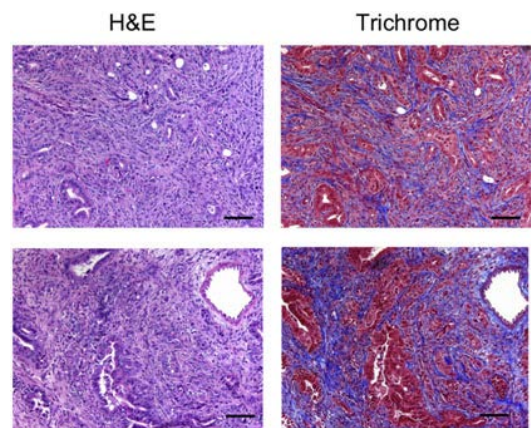
(53% vs. 23%, $p<0.01$), greater treatment effect, reduced incidence of locoregional recurrence (LR) (LR; 16% vs. 33%, $p<0.01$) but similar median overall survival (OS; 33.6 vs. 26.4-months, $p=0.09$) compared with systemic chemotherapy alone.³¹ Katz et al, reported wider special memorandum account (SMA) margin distance on histological examination on patients who receive pre-operative CRT.³² This suggests that the local effect of CRT may occur primarily through sterilization of the retroperitoneum.

THE IMPACT OF SBRT ON THE TUMOR MICROENVIRONMENT

Both SBRT and SRS have been used effectively for the treatment of lung, liver, brain, prostate, and recurrent head and neck cancers, among others.³³⁻³⁷ Damage to tumor cell deoxyribonucleic acid (DNA) is thought to account for only part of the efficacy of hypofractionated regimens.³⁸ Many studies indicate that in addition to the direct impact on DNA, the effects of high-dose radiation on the tumor microenvironment (TME) may play a role in tumor control by SBRT and stereotactic radiosurgery (SRS).³⁸⁻⁴¹ Many studies indicate the effect of a single fraction or hypofractionated radiation therapy in the treatment of pancreatic tumor xenografts.

In the stroma of human carcinomas, cancer-associated fibroblasts (CAFs) are the most abundant cell types and play a significant role in tumor cell growth, angiogenesis, and invasiveness (Figure 1).⁴²⁻⁴⁶ CAFs are also responsible for the deposition of key extracellular matrix (ECM) proteins (e.g., collagen, fibronectin, and laminin) as well as secreting ECM-degrading enzymes (e.g., matrix metalloproteinases),^{42,43} which promotes migration of CAFs and degradation of the ECM, allowing the invasion of tumor cells.⁴⁷

Figure 1. The Paradoxical Web of Pancreatic Cancer Tumor Microenvironment



Hematoxylin and eosin (H&E) and trichrome staining of pancreatic tumors arising in two KPC mice recapitulating the dense collagen-rich stroma seen in human pancreatic adenocarcinoma tumors. Scale bars Z 100 mm.

In vitro studies have shown that fibroblasts develop an irreversible senescent phenotype when exposed to a dose >10 Gy of radiation, whereas low doses of radiation induce reversible DNA damage without growth arrest. Senescent fibroblasts release proteolytic enzymes, cytokines, growth factors, and reactive oxygen

species, creating a protumorigenic environment.⁴⁸ Radiation doses higher than 10 Gy per fraction are associated with severe vascular damage leading to the deterioration of the TME.^{39,49} Although endothelial cell damage has been shown to be a major factor in the biological mechanism of SBRT and SRS, this phenomenon is sometimes transient and may lead to neovasculogenesis *via* hypoxia-inducible factor (HIF)-1 induction.⁴⁹ Baird et al reported pancreatic tumor regression through activation of type 1 interferon-dependent responses with a single dose of 10 Gy and co-treatment with *cGAMP* or *STING* (simulator of interferon genes) agonists that amplify the radiation-induced antitumor immune response.^{50,51} Type 1 interferons (interferon (IFN)- α and IFN- β) are important for activation of both innate and adaptive immune responses and are well-known for their role in viral immunity.⁵²

Treatment of pancreatic tumor xenografts with radiation given as 4 Gy in 2 fractions resulted in a switch in tumor-infiltrating macrophages from a protumorigenic M2 phenotype to an antitumorigenic M1 phenotype.⁵³ Likewise, increased infiltration of T-cells into tumors and tumor killing mediated by iNOS+M1 macrophages through the expression of Type 1 T helper (TH1) cytokines have been reported in murine models of pancreatic cancer and melanoma after low-dose radiation treatment.^{53,54} Moreover, many studies have demonstrated M2 polarization after treatment with single high-dose and hypofractionated radiation regimens.⁵⁵⁻⁵⁷ Several clinical trials are underway to determine the effects of combination therapy with radiation and immune checkpoint inhibitors (Table 3).⁵⁸⁻⁶⁰

Table 3. Ongoing Pancreatic Trials	
Unresectable pancreatic cancer	NCT01926197
Borderline resectable pancreatic cancer	NCT01992705, NCT02308722, NCT01446458
Resectable pancreatic cancer	NCT03704662, NCT02347618, NCT02318095, NCT02208024, NCT01446458

CONCLUSION

SBRT has been shown to be safe and effective in pancreatic cancer patients. It offers several advantages over standard EBRT including increased patient convenience, reduced toxicities, and the ability to minimize delays in modern multi-agent chemotherapy. The ability of SBRT to convert patients with borderline and locally advanced tumors to resectable disease with higher percentage of negative resection margins may improve survival. Favorable SBRT outcomes for LAPC patients have paved the way for exploration of SBRT for resectable pancreatic cancer patients, with promising early results. The immunotherapeutic approach has very limited clinical activity to date in pancreatic cancer, it is still unclear how to optimally combine ablative radiation and immunotherapy, including optimal sequencing, radiation dose to effectively overcome the immunosuppressive pancreatic tumor microenvironment.

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