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The Last Word

Stereotactic Body Radiation Therapy: A New Standard Option for Pancreatic Cancer?

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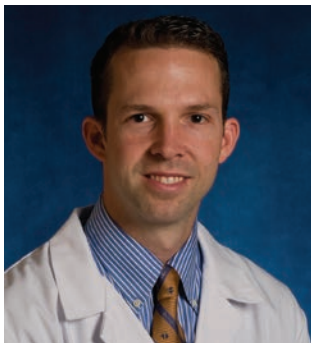
For many patients, a pancreatic cancer diagnosis involves a dismal (<6%) chance of survival beyond 5 years, and little progress has been made in terms of prevention and early detection of this disease. As a result, most patients present with advanced disease and a poor performance status that often precludes them from receiving aggressive therapy or surgery.

Advances in imaging technology, such as multidetector CT, high-field MRI, and PET, have improved staging for patients with pancreatic cancer. In addition, multiagent chemotherapy regimens such as FOLFIRINOX (leucovorin, 5-FU, irinotecan, and oxaliplatin) and gemcitabine with nab-paclitaxel have resulted in significant improvements in survival when compared to gemcitabine monotherapy. Nonetheless, these multiagent regimens can cause more toxicity than single-agent chemotherapy, including nausea, vomiting, infection, and severe neuropathy. These toxicities can be debilitating, particularly with chronic administration. Efforts to include targeted therapies have not been very effective and, unfortunately, often increase rates of treatment-related toxicity.

Radiation therapy has been shown to improve local control, stability of disease progression, and pain control in many stages of pancreatic cancer. However, these clinical benefits have historically been limited by (1) the relatively long courses of therapy, which often exceed 5 to 6 weeks; (2) the associated toxicity resulting from a lack of dose conformality; and (3) the fact that concurrent chemoradiation often decreases the ability to give patients full-dose systemic therapy. Recently, however, advances in radiation therapy techniques, including image guidance, target delineation (ie, fiducial markers, dose constraints), and motion management (ie, active breathing control, respiratory gating, respiratory tracking) now allow for very precise irradiation of pancreatic tumors, with an accuracy of 1 mm.

This form of therapy, otherwise known as *stereotactic body radiation therapy* (SBRT) or *stereotactic ablative radiation therapy* (SABR), has now been used in several malignancies, including those of the lung, liver, brain, spine, and prostate. However, its integration into the treatment paradigm of pancreatic cancer has been limited thus far. This slow integration primarily stems from the requirement for increased physical support and findings of several early studies in which SBRT resulted in increased rates of late gastrointestinal toxicity (ie, ulcers, gastrointestinal bleeding).[1–3] More recently, however, single-institution studies and a multi-institution prospective study with SBRT[4–7] have shown acceptable levels of late toxicity with minimal acute toxicity when treatment is delivered over 3 to 5 days as opposed to 1 day. Additionally, SBRT is typically delivered without the need for concurrent chemotherapy, resulting in improved quality of life, less delay in the administration of full-dose systemic therapy, and enhanced integration with other cancer treatment modalities. To date, more than 600 patients with pancreatic cancer have been treated with SBRT, and reports suggest an improvement in pain scores and quality of life. Furthermore, the efficacy and toxicity data compare favorably with those on conventional chemoradiotherapy.

Nonetheless, evaluation of SBRT in a prospective randomized trial is necessary to define its role in the management of pancreatic cancer and to ensure its safe implementation for treating patients. Precise delivery of SBRT is particularly important because errors involving any dimension of the planning and treatment process (ie, contouring, target delineation, breathing motion) can significantly increase the risk of toxicity due to the close proximity of adjacent radiosensitive organs (ie, bowel and stomach).



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SBRT has most often been studied in the setting of locally advanced, unresectable cancer. Although early studies evaluating single-fraction (25 Gy x 1 fraction) SBRT showed excellent local control (>90%), high rates of late grade 2 to 4 gastrointestinal toxicity were reported.[1–3] Limiting toxicity in this patient population is especially important because this group of patients may not recover from any gastrointestinal toxicity that requires an invasive intervention. However, when appropriate strict dose constraints are met,[8] significant gastrointestinal toxicity from SBRT can be avoided. Furthermore, when compared with single-fraction SBRT, 5-fraction SBRT also results in decreased long-term gastrointestinal toxicity (J.M.H. et al, unpublished data, 2014).[4] These data indicate that SBRT is an ideal option to complement any systemic regimen with the goal of maximizing local control, preserving quality of life, and potentially enhancing overall survival.

Patients with resectable or borderline resectable pancreatic cancer are more likely than those with locally advanced cancer to undergo successful surgical resection. Therefore, this clinical scenario provides an ideal opportunity to use SBRT to treat the pancreas tumor and the interface adjacent to or involving blood vessels, with the ultimate goal of achieving a margin-negative (R0) resection. SBRT has been studied in the neoadjuvant and borderline settings.[9,10] One study evaluated neoadjuvant capecitabine and SBRT with protons (5 Gy x 5) in patients with resectable pancreatic cancer. The regimen was tolerable (grade ≥3 toxicity, 4.1%); however, local recurrences still occurred (16.2%). The relatively high rate of local recurrence may be attributed to insufficient radiation dose to sterilize all microscopic disease. Another study reported the combination of gemcitabine, docetaxel, and capecitabine (GTX) and SBRT in 57 patients with borderline resectable pancreatic cancer.[11] Of these patients, 32 (56.1%) underwent successful surgical resection, with a 96.9% rate of R0 resection, a 9.4% rate of pathologic complete response, and a median overall survival (OS) of 19.3 months. Median OS for all patients with borderline resectable disease who received GTX and SBRT was 16.4 months.

Although the data are limited, SBRT can also offer potential advantages in the adjuvant setting. In a study by Rwigema et al,[12] 12 patients underwent adjuvant SBRT after resection with a close (0.5–1.5 mm) or positive margin after surgery. Rates of freedom from local progression and OS at 1 year were 70.7% and 81.8%, respectively, whereas the mean OS was reported to be 20.6 months. The same group also published a follow-up study of 24 patients with close (1.0–2.5 mm) or positive margins who received adjuvant SBRT.[13] Freedom from local progression at 1 year was 66%, and 1-year OS was 80.4%, with a median OS of 26.7 months. The small sample size of these cohorts merits further investigation. SBRT targeting of the tumor bed outlined by surgical clips is being explored in a prospective single-arm trial in combination with a pancreatic tumor cell vaccine (GVAX) and FOLFIRINOX in the adjuvant setting (ClinicalTrials.gov identifier: NCT01595321, Table 1).[14]

SBRT may also offer significant clinical benefit in patients with pancreatic cancer with a poor performance status, advanced age, or existing comorbidities. Approximately 20% to 30% of patients diagnosed with pancreatic cancer never receive any therapy because of these precluding factors.[15] Data suggest that these patients are not optimal surgical candidates,[16] and standard or multiagent systemic therapy or long-course chemoradiation (5–6 weeks) is often not well tolerated. Recently, Von Hoff et al[17] showed that the addition of nab-paclitaxel to gemcitabine monotherapy provided a survival benefit in patients with metastatic pancreatic cancer with a poor performance status. Because the median survival of this population is typically about 6 months, adding SBRT (3–5 fractions) to chemotherapy may minimize local progression, decrease pain, and possibly prolong survival.

Given the current health care environment characterized by limited resources and cost containment, another potential benefit of SBRT is the reduced costs

Table 1 Ongoing Clinical Trials Exploring the Role of Fractionated SBRT in Pancreatic Cancer

ClinicalTrials.gov Identifier	Phase	Regimen	Setting	Primary Location	Date Opened
NCT01595321	NA	GVAX vaccine → SBRT (6.6 Gy x 5) + FOLFIRINOX	Adjuvant	Johns Hopkins University	August 2012
NCT01992705	0	FOLFIRINOX → SBRT (6 Gy x 5)	BRPC	University of Maryland	March 2014
NCT02153450	NA	Metformin → SRS (25 fx) + metformin	BRPC, LAPC	Case Cancer Center	August 2014
NCT01342354	I	SBRT (3 fx)	Unresected	University of Chicago	April 2009
NCT01446458	I	FOLFIRINOX → SBRT (12 Gy x 3)	Neoadjuvant (resectable, BRPC)	Emory University	November 2011
NCT01918644	I	Cap + SBRT (5 fx)	Neoadjuvant (resectable)	University of Wisconsin, Madison	August 2013
NCT02208024	I	SBRT (6.6 Gy x 5)	Neoadjuvant (resectable)	University of Cincinnati	August 2014
NCT01360593	II	Gem/Cap → SBRT (12 Gy x 3)	LAPC	University of Pittsburgh	July 2011
NCT01357525	II	SBRT (12 Gy x 3)	Resected with close or positive margins	University of Pittsburgh	July 2011
NCT01781728	II	SBRT (6.6 Gy x 5)	Unresectable recurrent or residual	Johns Hopkins University	January 2013
NCT01754623	II	GTX → SBRT	BRPC	Moffitt Cancer Center	February 2013
NCT01898741	II	SBRT (8 Gy x 3)	LAPC	UMC Utrecht	July 2013
NCT01959672	II	Gem + LV +/- oregovomab → SBRT (5 fx) + nelfinavir mesylate	LAPC	University of Nebraska	September 2013
NCT01926197	III	mFOLFIRINOX +/- SBRT (8 Gy x 5)	LAPC	Stanford University	August 2013
NCT02128100	II	FOLFIRINOX → SBRT (6.5 Gy x 5)	LAPC	James Graham Brown Cancer Center	May 2014

Abbreviations: BRPC, borderline resectable pancreatic cancer; Cap, capecitabine; FOLFIRINOX, 5-FU, leucovorin, irinotecan, and oxaliplatin; fx, fractionated; Gem, gemcitabine; GTX, gemcitabine, docetaxel, and capecitabine LAPC, locally advanced pancreatic cancer; LV, leucovorin; mFOLFIRINOX, dose-modified FOLFIRINOX; NA, not applicable; SBRT, stereotactic body radiation therapy; SRS, stereotactic radiosurgery.

when compared with standard chemoradiation.[18] In general, SBRT treatment is approximately half the cost of a standard pancreas regimen of 28 fractions with intensity-modulated radiation therapy. Furthermore, fewer routine laboratory tests and clinic visits are necessary to monitor symptoms, thereby decreasing the costs and burden for the patient and family.[18]

At the 2014 ASCO Annual Meeting, a preliminary report of the LAP 07 trial reported no significant improvement in survival of patients with locally advanced pancreatic cancer who received standard chemoradiation after induction chemotherapy.[19] However, chemoradiation did result in improved local control (65% vs 34%; $P<.0001$). Since patients with unresectable disease have an expected survival of approximately 1 year after diagnosis, undergoing conventional chemoradiation essentially commits patients to spending a significant portion of their remaining life receiving and recovering from radiation treatment. If SBRT can be shown to be equivalent to or better than with regard to local control and tumor response, it seems reasonable that it should be evaluated as a possible standard option for these patients.

Current trials evaluating fractionated SBRT in pancreatic cancer are outlined in Table 1. Given the potential benefits described previously and the number of trials evaluating SBRT, why has SBRT not been more widely accepted? The most likely reason is that linear accelerators capable of SBRT have only recently become widely available. Further, early publications suggested that significant toxicity may be encountered if technical considerations related to dose and gating are not met.[1–3,8,20] However, since the early SBRT studies, dose constraints have been defined, and 3 to 5-fraction SBRT regimens have been shown to result in less toxicity than single-fraction SBRT. As the technology and physician education regarding SBRT become more widespread, radiation oncologists will become more adept at using this method of radiation delivery. This will inevitably lead to higher-quality SBRT and well-defined indications for its use in pancreatic cancer.

Future SBRT studies in localized (resectable, borderline resectable, and locally advanced) pancreatic cancer should determine the optimal dose needed to maximize tumor response while limiting associated toxicity. Subsequent steps include integration of novel radiosensitizers (eg, poly[ADP-ribose] polymerase inhibitors) and radioprotectors (to enhance recovery of duodenum/stomach after radiation). Finally, unpublished data on patients with pancreatic cancer receiving radiotherapy at Johns Hopkins demonstrate that patients who received SBRT tended to have less immunosuppression, as indicated by lymphopenia levels 2 months after radiation therapy, than patients who underwent conventional chemoradiation therapy. This suggests that SBRT may be better integrated with immunotherapy than conventional approaches. In summary, we believe that SBRT shows considerable potential as a standard option in the treatment paradigm of pancreatic cancer. However, additional prospective studies with well-selected clinical end points are needed to advance this modality into the standard of care.

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