

# Stereotactic Body Radiotherapy in the Treatment of Pancreatic Cancer

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**Most patients diagnosed with pancreatic cancer are unable to have a curative surgical resection. Chemoradiation is a standard of care treatment for patients with locally advanced unresectable disease, but local failure rates are high with conventionally fractionated radiotherapy. However, stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy offers an alternative type of radiation therapy, which allows for the delivery of high-dose, conformal radiation. The high doses and shorter overall treatment time with SBRT may provide advantages in local control, disease outcomes, quality of life, and cost-effectiveness, and further investigation is currently underway. Here, we review the technology behind SBRT for pancreatic malignancy and its future direction in the overall management of pancreatic cancer. Semin Radiat Oncol 24:140-147 © 2014 Elsevier Inc. All rights reserved.**

Pancreatic cancer is an aggressive malignancy with high mortality rates. Nearly 44,000 cases of pancreatic cancer were reported in the United States in 2012, making it the tenth most common solid cancer diagnosis and the fourth highest cause of cancer death.<sup>1</sup> The mortality rate in the same year was more than 37,000, and mortality rates have changed very little over the past 20 years.<sup>2</sup>

The only curative treatment for pancreatic cancer is surgery, most commonly by pancreatoduodenectomy or distal pancreatectomy (for pancreatic tail tumors). Less than 20%-25% of pancreatic tumors are amenable to resection at the time of diagnosis.<sup>3</sup> The treatment of patients with borderline resectable or unresectable tumors, commonly termed “locally advanced” disease, has traditionally consisted of conventionally fractionated external beam radiation (EBRT) with chemotherapy (chemoradiation [CRT]). The value of CRT is controversial but is used based on studies conducted in the 1980s by the Gastrointestinal Tumor Study Group (GITSG) and, more recently, by the Eastern Cooperative Oncology Group (ECOG).<sup>4,5</sup> Outcomes for these patients are quite poor, with median survival of 9-12 months. More importantly, local control of the primary tumor

using conventional CRT is suboptimal, as 50% of patients experience local progression of disease, often causing pain or obstructive symptoms that negatively affect quality of life (QoL).<sup>6</sup> In an autopsy series from Hopkins, up to 30% of patients died of locally destructive disease with few or no distant metastases.<sup>7</sup> These data suggest that a significant population of patients with pancreatic cancer may have prolonged survival if the primary tumor can be sterilized and that local control is a clinically relevant end point for optimal QoL.

The poor overall survival (OS) rates in pancreatic cancer are mainly owing to its propensity to early metastasis and the lack of effective systemic treatments. Recent chemotherapy clinical trials have focused on the use of targeted agents and novel immunogenic treatment in an attempt to improve outcomes, with limited success.<sup>8</sup> At the same time, radiotherapy techniques have evolved and improved, allowing more accurate target delineation, treatment delivery, and dose escalation.<sup>9</sup> Stereotactic body radiotherapy (SBRT), also referred to as stereotactic ablative radiotherapy or SABR, is a form of radiotherapy that makes use of many of the technological advances in radiotherapy delivery and image-guidance developed over the past 2 decades and allows the delivery of high doses of radiation conformally and accurately. SBRT has been extremely successful in the treatment of thoracic tumors and is currently the accepted standard of care treatment for medically inoperable patients with early-stage non-small-cell lung cancer.<sup>10</sup> At the same time, SBRT has also been used for intra-abdominal sites, including the pancreas, with very promising early results. This review focuses on the technical aspects and reported clinical experience in the use of SBRT in the treatment of pancreatic cancer.

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## Technical Aspects of Pancreatic SBRT

Stereotactic radiosurgery was first developed in the 1950s, where it was used in the treatment of intracranial tumors. Radiosurgery outside the central nervous system was pioneered at the Karolinska Institute in the 1990s<sup>11</sup> and has been continually refined ever since. Body radiosurgery is challenging because tumors in the upper abdomen move with respiration, and rigid immobilization, which was easily achieved by fixation of a rigid frame to the skull but is not possible in the body. Instead, techniques have been developed to visualize, track, and increase the accuracy and rapidity of targeting radiation to moving tumors.<sup>12,13</sup>

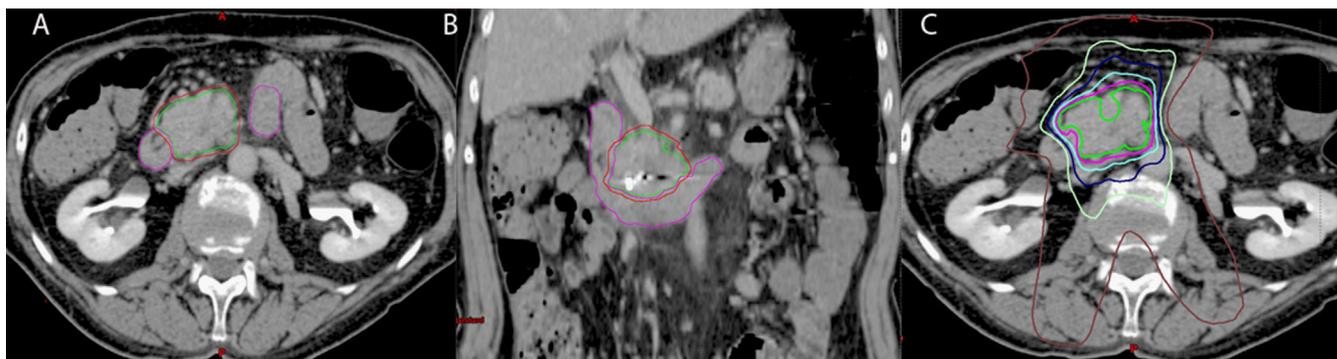
Accurate target delineation is of critical importance in SBRT. High-quality treatment planning scans with contrast enhancement, in both the arterial and venous phases, can greatly assist in the identification and delineation of pancreatic tumors. Tumors are usually best seen in the early venous phase and appear as a hypodense lesion in comparison with the enhancing normal pancreatic parenchyma. However, approximately 10% of lesions appear isodense relative to the normal pancreas, making target delineation very difficult. The arterial phase is helpful in determining the exact extent of involvement by the tumor to the superior mesenteric artery and celiac axis. Fluorodeoxyglucose–positron emission tomography may be used for target delineation as well to help distinguish tumor from adjacent normal organs.<sup>14</sup> The degree of positron emission tomography avidity may hold prognostic value.<sup>15,16</sup>

Pancreatic tumors, like other upper abdominal and intrathoracic tumors, are subject to respiratory motion. The magnitude of motion for pancreatic tumors, though variable, has been estimated to be as much as 2–3 cm.<sup>17</sup> Four-dimensional (4D) computed tomography (CT) should be used to assess the magnitude and direction of tumor motion during the respiratory cycle and allow for delineation of an internal tumor volume. Respiratory gating may be used to limit treatment to specific phases of the respiratory cycle, or tracking can be used based on the position of implanted fiducial markers.<sup>18</sup> Other mechanical techniques, such as abdominal

compression and active breathing control, can also be used to limit tumor motion, reducing the internal tumor volume expansion required.<sup>19</sup>

It is also important to have some means of verification of tumor movement at the time of treatment, as 4D CT may underestimate the degree of tumor motion that can occur during treatment delivery.<sup>20</sup> On-board kilovoltage (kV) imaging and cone-beam CT (CBCT) may be used, but provide poor soft tissue resolution, which is of greater importance in the treatment of pancreatic tumors in comparison with tumors located in the lung. Furthermore, unless these images are obtained as a 4D CBCT, there is additional image degradation due to respiratory motion. Implantation of peritumoral or intratumoral fiducial markers is therefore essential to visualize the position of the tumor and, in the authors' opinion, is an essential part of the SBRT.<sup>21</sup> Implantation can be performed via endoscopic ultrasound or percutaneously with low complication rates.<sup>22,23</sup> Because tumors cannot be visualized with kV imaging and CBCT, the implanted fiducial markers allow for fluoroscopic verification of tumor motion during the respiratory cycle. It is also possible to use fiducial markers for real-time tracking of motion during treatment delivery.<sup>24</sup> The CyberKnife robotic radiosurgery system and Synchrony (Accuray, Inc, Sunnyvale, CA) allows for respiratory tracking by using periodic kV imaging and correlating the position of the fiducial markers with respiration, which is tracked by light-emitting diodes placed on the patient's abdomen. The robot-mounted gantry then adjusts in real time as the patient breathes.

Typically, a further expansion of 2–5 mm is added for planning treatment volume (PTV) margin to account for setup uncertainty. At Stanford University, dose is prescribed to the periphery of the tumor with 95% coverage of the PTV. Dose heterogeneity may exceed 15%–20%, given the strict dose constraints imposed while ensuring a high degree of conformality (Fig.). SBRT may be delivered using nonisocentric technique, intensity-modulated radiotherapy (IMRT), or volumetric-modulated arc therapy. However, no matter which mode of radiation dose delivery is selected, strategies for compensating for respiratory-associated tumor motion should



**Figure** Representative pancreatic SBRT plan: (A) axial view showing pancreatic tumor (GTV: green), a typical PTV (red), and the duodenum (magenta); (B) coronal view demonstrating tumor relationship with the duodenum; and (C) dose distribution for a plan treating to 33 Gy in 5 fractions. Isodose lines: green = 45 Gy; magenta = 40 Gy; cyan = 33 Gy; blue = 30 Gy; light green = 20 Gy; and brown = 10 Gy. Abbreviation: GTV, gross tumor volume. (Color version of figure is available online.)

be used to reduce the margin expansion. Flattening filter-free mode, where the flattening filter is removed during treatment, further increases the dose rate and reduces the time of treatment, making treatments not only more convenient and allowing higher throughput but also reducing the risk of patient movement during treatment because of discomfort or inattention.<sup>25</sup>

## Clinical Results for SBRT in the Treatment of Pancreatic Cancer

The first clinical report on SBRT in the treatment of pancreatic cancer was published in 2004 from the Stanford University. Using the CyberKnife system, 15 patients with locally advanced pancreatic tumors were treated to doses of 15, 20, or 25 Gy in a single fraction. Local control was 100%, but all patients ultimately succumbed to metastatic disease, and median survival was 11 months.<sup>26</sup> In an attempt to improve outcomes, the Stanford group conducted a phase II study incorporating a 25 Gy SBRT boost to the primary tumor after a course of IMRT-based CRT, using 45 Gy EBRT to the tumor and regional lymph nodes with concurrent 5-fluorouracil.<sup>27</sup> Local control rates were also very high in this study (94%), but median survival was only 8.3 months. Also noted was an increased rate (12.5%) of grade 3 gastrointestinal (GI) toxicity. In the next protocols, SBRT was incorporated with induction chemotherapy using gemcitabine, which allows for earlier treatment of micrometastatic disease. In these phase II studies, patients received one course of induction gemcitabine (1000 mg/m<sup>2</sup>), followed by SBRT, again using 25 Gy in a single fraction, the first with CyberKnife<sup>28</sup> and more recently with linac-based<sup>29</sup> SBRT. Local control was, once again, excellent (100% and 94% freedom from local progression at 1 year), but OS was only modestly improved (median survival of approximately 11 months). Additionally, toxicity was somewhat increased in these studies, especially late (4-10 months after XRT) bowel toxicity, with 1 patient from each study experiencing a grade 4 bowel perforation requiring surgery. The volume of duodenum receiving radiation was correlated with increasing risk of late toxicity.<sup>28</sup>

Because of the late GI toxicity observed in these studies, the Stanford group investigated a hypofractionated course integrated with gemcitabine chemotherapy, delivering 33 Gy in 5 fractions. Along with Johns Hopkins University and Memorial Sloan Kettering Cancer Center, they conducted a multi-institutional prospective trial using this dose and fractionation with pre-SBRT gemcitabine (up to 1 cycle). Preliminary results from this trial indicate that the treatment was well tolerated, with a median survival of 13.9 (95% CI: 10.2-17.9) months and 61% of patients surviving 1 year, and 18% surviving 2 years (Herman et al, manuscript submitted). The local control rate at 1 year was 83%. The only acute toxicity was grade 1 fatigue and nausea. Late grade 2+ duodenal toxicity was seen in 8% of patients, supporting the fractionated approach as a means of reducing toxicity. In addition, standardized QoL was unchanged before or after treatment, and patients reported significant improvements in pancreatic pain and body image.

Other groups have reported encouraging results for SBRT in pancreatic cancer. Investigators from Beth Israel described a series of 36 patients treated with 24-36 Gy in 3 fractions using an adaptive dosing scheme based on tumor location relative to the duodenum and the stomach, followed by 6 months of adjuvant gemcitabine. The local control rate was 78% with low toxicity (14% grade 3). Median survival was 14.3 months.<sup>30</sup> A subsequent study adopted the neoadjuvant chemotherapy approach, delivering 2 cycles of gemcitabine before restaging and SBRT. Using the same risk-adapted dosing scheme, local control rates of 85% were achieved, with an excellent median survival of 20 months. There were no acute toxicities above grade 3, and 3 cases had late grade 3 toxicity.<sup>31</sup>

An Italian study used a similar approach, treating 23 patients with locally advanced disease with 6 weeks of gemcitabine preceding radiation and indefinitely after treatment. A standard dose of 30 Gy in 3 fractions was used. Local control was 50% at 1 year, and OS was 10.6 months. No toxicity greater than grade 2 was recorded.<sup>32</sup> A smaller study (10 patients) from Georgetown University attempted to integrate SBRT seamlessly in a gemcitabine chemotherapy regimen. Full-dose (1000 mg/m<sup>2</sup>) gemcitabine was given for 3 weeks, then 5 fractions of 5 Gy SBRT was delivered during the fourth week without chemotherapy. Chemotherapy was then resumed the following week, which differs from the Stanford regimen that required 1 week off chemotherapy before and after SBRT. This approach did not increase toxicity, with no grade 3 or higher toxicity reported. Local control was quite poor, however, with 6 the 10 patients experiencing local failure. This study suggests that there is no need to delay SBRT in the neoadjuvant setting.<sup>33</sup>

Other institutions in the United States and Europe have reported their experiences using pancreatic SBRT. Hoyer et al from Denmark delivered 3 fractions of 15 Gy and reported local control rates of 57%, median survival of 5.4 months, and high rates of GI toxicity (79%). Treatment volumes in this study were significantly larger than those used in similar studies. The median volume treated by Hoyer et al<sup>34</sup> was 136 cc, whereas the median PTV treated by the Stanford group in their most recent report was 41 cc.<sup>29</sup> Larger treatment volumes by Hoyer et al were the result of larger margin expansions and coverage of both the tumor as well as peritumoral edema. Furthermore, dose was prescribed to a reference point with the PTV covered by the 67% isodose line. These technical differences likely explain the discrepancy in the clinical results observed in this study and highlight the importance of consistency in reporting how dose is prescribed and in treatment techniques in SBRT studies.<sup>34</sup>

Didolkar et al reported on a retrospective study of 85 patients with mixed stages of pancreatic cancer receiving 15-30 Gy in 3 fractions. Local control rates were high (91.7%), and median survival was 18 months.<sup>35</sup> The University of Pittsburgh published their experience using a variety of hypofractionated regimens, including single-fraction treatments in a wide variety of patients, encompassing those with locally recurrent disease and those who had undergone surgical resection with positive margins. Local control was 48% at 1 year, and median survival was 10.3 months.<sup>36</sup> Case

Western Reserve University reported their experience with pancreatic SBRT, with 19 patients with unresectable tumors treated with 20-25 Gy in a single fraction or 24-30 Gy in 3 fractions, prescribed to the 70% isodose line. Local control at 1 year was 65% and median survival was 14.4 months, with 16% grade 3 toxicity. This study measured tumor response to treatment using a grading system based on tumor volume as measured by treatment planning software. By this method, 32% of patients had a greater than 50% reduction in tumor volume after treatment.<sup>37</sup>

The high doses achievable with SBRT and the excellent conformality make SBRT an appealing option for 2 distinct groups of patients at opposite ends of the “locally advanced” disease spectrum: patients with so-called “borderline” resectable disease and those with locally recurrent disease after conventional CRT. Patients with “borderline” resectable disease have locally confined disease, but involvement of critical vascular structures significantly reduces the probability of a negative resection margin (R0) resection. If the area of vascular involvement can be regressed or sterilized, it may be possible to achieve an R0 resection in these patients.

A report from Moffitt Cancer Center in Tampa examined a cohort of 73 patients treated with SBRT, 56 of whom had borderline resectable disease. These patients were treated using a dose-painting technique, where the area of tumor in contact with blood vessel was treated to a higher dose (35-50 Gy) than the remainder of the tumor (25-30 Gy) in 5 fractions after a course of 3 cycles of neoadjuvant chemotherapy with gemcitabine, taxotere, and xeloda. Restaging imaging was obtained 4 weeks after treatment, and patients with significant regression away from the blood vessel in question underwent exploratory surgery and tumor resection if possible. For the subset of patients with borderline resectable tumors, 77% of patients had a treatment response and underwent an exploratory laparotomy with 56% ultimately having a surgical resection. There was a high rate (97%) of R0 resection, with a complete pathologic response rate of 9%. Patients who underwent surgical resection had significantly improved survival compared with those who did not (19.3 vs 12.3 months,  $P = 0.03$ ). Toxicity was acceptable, with only 5% of patients experiencing grade 3 GI toxicity.<sup>38</sup> These results provide support for further exploring SBRT as a means of allowing curative resection in patients with borderline resectable disease.

Another subset that may derive benefit from SBRT includes patients with locally recurrent disease after conventional EBRT. As mentioned previously, although distant failure is much more prevalent, there is a distinct patient population that presents with isolated local recurrence following chemotherapy. Reirradiation typically carries a risk of increased normal tissue toxicity, dependent on the dose and volume of normal tissue irradiated during each course. The high conformality of SBRT minimizes dose to structures outside the treated volume, making it an ideal technique for reirradiation, which has been shown to be safe and effective in lung cancer.<sup>39</sup>

There is a report focusing on patients receiving SBRT in the setting of prior radiation. Lominska et al identified 28 patients at Georgetown University Medical Center treated with SBRT

who had received prior irradiation. Of these patients, 11 were treated with a planned SBRT boost after treatment with CRT, similar to the Stanford study described previously.<sup>27</sup> The remaining 17 patients were treated with salvage SBRT after a local recurrence. The median prior radiation dose was 50.4 Gy, and the SBRT dose was 20-30 Gy in 3-5 fractions. Although the median survival was only 5.9 months, this is not unexpected given the poor prognosis associated with recurrent disease. SBRT did provide local control (86% freedom from local progression), and more importantly, there were only 2 cases of grade 3 or higher late toxicity, 1 bowel obstruction, and 1 gastric perforation.<sup>40</sup> This study and data from the Stanford boost trial provide evidence that reirradiation of patients who had received prior external beam XRT is feasible but must be carefully weighed against the risk of toxicity.

The published data regarding SBRT in the treatment of pancreatic cancer are summarized in the Table. Despite the variability in dosing and patient selection, a few conclusions can be drawn. Local control rates with SBRT appear, in general, to be superior compared with conventionally fractionated EBRT for locally advanced pancreatic cancer. Rates of both acute and chronic toxicities can be kept at acceptable levels with fractionated SBRT regimens. Mortality rates remain high, owing to the high rate of distant metastasis, highlighting the need for more effective systemic therapies. However, there is a population of patients who are not surgical candidates with favorable biology who may benefit from aggressive local therapy. Future studies may better elucidate whether there is an optimum biologically effective dose needed for control of pancreatic tumors, leading to more standardized dosing, risk-adapted dosing or volume-adapted dosing or both, such as is currently done in the setting of early stage lung cancer.<sup>41-43</sup> It has been hypothesized that a population of hypoxic cells in tumors targeted by SBRT may be relatively resistant to hypofractionated radiation,<sup>44</sup> and further investigations may examine the feasibility of combining cell sensitizers with SBRT. However, the published clinical data across a variety of tumors demonstrate relatively high rates of local control, suggesting that tumor hypoxia may not be a significant clinical problem in patients treated with SBRT.

## Treatment-Related Toxicity

The organs at greatest risk of toxicity in pancreatic SBRT are the stomach and small bowel (particularly duodenum) because of their proximity to the tumor. Early and late bowel toxicities have been reported in SBRT, including nausea, stricture, obstruction, ulceration, bleeding, and perforation, which can be life threatening. Early studies showed a correlation between the volume of duodenum irradiated and toxicity.<sup>28</sup> Investigators at Stanford performed a dose-volume analysis of duodenal toxicity in a cohort of 73 previously unirradiated patients treated with 25 Gy in 1 fraction using the Lyman-Kutcher-Burman model.<sup>45</sup> In this cohort, the 12-month risk of duodenal toxicity was 29%, with the most common toxicity being ulceration. Several dosimetric parameters, including  $V_{15}$  (volume receiving 15 Gy or greater)  $>9.1$  cc,  $V_{20} > 3.3$  cc,

**Table** Outcomes in Reported Studies of Pancreatic SBRT

References	Patients	Dose	Local Control (1 y Unless Specified)	Median Survival (mo)	Toxicity	Chemo
Koong et al <sup>26</sup>	15 LA or LR	15-25 Gy × 1	100%	11	33% Grades 1 and 2 0% ≥ Grade 3	None
Koong et al <sup>27</sup>	16 LA	25 Gy × 1 (boost)	94%	8.3	69% Grades 1 and 2 12.5% ≥ Grade 3	5-FU with EBRT prior to boost
Hoyer et al <sup>34</sup>	22 LA	15 Gy × 3	57%	5.4	79% ≥ Grade 2 4.5% Grade 4	
Schellenberg et al <sup>28</sup>	16 LA	25 Gy × 1	100%	11.4	19% Acute 47% Late	1 Cycle induction GEM + post-SBRT GEM
Didolkar et al <sup>35</sup>	85 LA or LR	5-10 Gy × 3	92%	18.6	22.3% ≥ Grade 3	Post-SBRT GEM
Mahadevan et al <sup>30</sup>	36 LA	8-12 Gy × 3	78%	14.3	33% Grades 1 and 2 8% Grade 3	Post-SBRT GEM
Polistina, et al <sup>32</sup>	23 LA	10 Gy × 3	82% 6 mo 50% 1 y	10.6	20% Grade 1 0% ≥ Grade 2	6 wk induction GEM
Mahadevan et al <sup>31</sup>	39 LA	8-12 Gy × 3	85%	20	41% Grades 1 and 2 0% ≥ Grade 3 (acute) 9% Grade 3 (late)	2 Cycles induction GEM
Rwigema et al <sup>36</sup>	71 LA, LR, RPM, and MD	24 Gy (med) × 1 (94%) 8-10 Gy × 2-3 (6%)	71.7% 6 mo 48.5% 1 y	10.3	39.5% Grades 1 and 2 4.2% Grade 3	90% Received chemo (various regimens)
Schellenberg et al <sup>29</sup>	20 LA	25 Gy × 1	94%	11.8	15% Grades 1 and 2 5% ≥ Grade 3	1 Cycle induction GEM + post-SBRT GEM
Goyal et al <sup>37</sup>	19 LA or LR	20-25 Gy × 1 8-10 Gy × 3	81%	14.4	11% Grades 1 and 2 16% Grade 3	68% Received chemo (5-FU or GEM based)
Lominska et al <sup>40</sup>	28 LA or LR	4-8 Gy × 3-5	86%	5.9	7% Grade 3 (late)	5-FU or GEM prior to SBRT
Gurka et al <sup>33</sup>	10 LA	5 Gy × 5	40%	12.2	0% ≥ Grade 3	1 cycle GEM prior, 6 cycles GEM total
Chuong et al <sup>38</sup>	73 BR or LA	5-10 Gy × 5	81%	16.4 BR 15 LA	5% Grade 3 (late)	3 cycles GTX

Abbreviations: BR, borderline resectable; 5-FU, 5-fluorouracil; GEM, gemcitabine; GTX, gemcitabine, taxotere, and xeloda; LA, locally advanced; LR, locally recurrent; MD, metastatic disease; RPM, resected positive margins; SBRT, stereotactic body radiotherapy.

and  $D_{\max}$  (maximum dose received) correlated with increased toxicity. As these patients were treated in a single fraction, these data may be less applicable with multifraction regimens, and additional studies are needed to further elucidate the tolerance of bowel structures with hypofractionation.

Investigators from South Korea examined dosimetric parameters that correlated with intestinal toxicity after 3-fraction SBRT in patients treated for abdominal malignancies.<sup>46,47</sup> They found that a  $D_{\max}$  of 35 Gy and 38 Gy correlated with a 5% and 10% rate of grade 3+ gastroduodenal toxicity, respectively. They also found that  $V_{25} > 20$  cc correlated with a 50% rate of intestinal toxicity compared with 4% for  $V_{25} \leq 20$  cc. In addition, they reported that patients treated over consecutive days had a higher rate of toxicity compared with those treated over 4-8 days (0% vs 18%,  $P = 0.037$ ), suggesting that increasing the interfraction interval to greater than 24 hours may reduce the risk of toxicity.

The treatment delivery technique may have an effect on the dose to these critical structures. Tumors, which usually arise in the pancreatic head region, are often in contact with the duodenum (Fig.). The amount of contact may vary during the respiratory phase as the diaphragm moves inferiorly during inspiration, causing possible compression of the upper abdominal organs. Taniguchi et al investigated the effect of respiratory motion and gating on duodenal dose and found that overlap between the PTV of pancreatic head tumors and the duodenum was reduced in the end-expiratory phase of the respiratory cycle compared with the end-inspiratory phase. In addition, better sparing of the duodenum was achieved when planning on the expiratory phases compared with the inspiratory phases. These data indicate that respiratory gating during end expiration may have the potential to reduce duodenal toxicity.<sup>48</sup>

## Cost-Effectiveness and QoL

There are other appealing aspects of SBRT in addition to the possibility of better tumor control. An entire course of SBRT is usually 3-5 days, in contrast to 5-6 weeks for a course of conventionally fractionated CRT. Many patients with locally advanced pancreatic cancer have significant pain and obstructive symptoms, which can often, but not always, be palliated through endoscopic stenting and celiac nerve blockade. The rapid delivery of higher biologically effective dose radiation with SBRT may provide earlier and more durable palliation. Additionally, given the poor prognosis of patients with pancreatic cancer, life expectancy is short, and one would like to minimize patient time spent undergoing treatment and procedures. There have been a few attempts to quantify the effects of pancreatic SBRT on pain control and QoL. The previously mentioned study from Italy included pain control and QoL measures. Overall, there was no significant decrease in pain as measured by a visual analog scale, but patients who responded to treatment without developing metastatic disease reported significantly less pain at 3 months. Objectively, a reduction in analgesic consumption was also noted. Similarly, a general QoL questionnaire only showed a significant

improvement at 3 months in patients who had a good response to treatment.<sup>32</sup> Another previously cited paper in this study included a QoL questionnaire and found no difference between pretreatment and 3 months after treatment.<sup>33</sup> Pain and QoL are notoriously difficult parameters to measure objectively, but given the dearth of data on these outcomes, it is hoped that more studies will collect and report these data in the future.

Another area in which SBRT may provide some advantage over EBRT is cost-effectiveness. One study investigating cost-effectiveness in the treatment of pancreatic cancer compared gemcitabine chemotherapy alone with 3D conformal radiotherapy, IMRT, and SBRT in combination with gemcitabine. Using a Markov decision model, Murphy et al<sup>49</sup> found that SBRT provided the greatest probability of increased cost-effectiveness in terms of quality-adjusted life-years. SBRT has been shown to have similar rates of high overall cost-effectiveness compared with conventionally fractionated EBRT in the treatment of other malignancies.<sup>50</sup>

## Conclusions and Future Directions

SBRT is a recently developed technique that is becoming increasingly adopted in a wide range of malignancies. For the treatment of pancreatic cancer, SBRT has shown promising outcomes in increased rates of local tumor control when compared with conventional EBRT. Although there is the potential for increased late toxicity, improved understanding of normal organ tolerance and further refinements in treatment planning and delivery will continue to minimize this risk. Moreover, SBRT was originally investigated for locally advanced disease, but it may have applicability toward both borderline resectable disease and locally recurrent disease. In addition, there is currently an ongoing trial investigating the role of preoperative SBRT in patients with resectable disease.<sup>51</sup>

Distant metastasis still remains the most common site of treatment failure, and improvements in systemic disease control are crucial to maximize the clinical utility of SBRT. Although most previous studies have combined SBRT with gemcitabine, FOLFIRINOX has been shown to have superior outcome compared with gemcitabine for patients with metastatic disease,<sup>52</sup> and future studies should investigate whether this chemotherapy regimen (or a modified FOLFIRINOX regimen) combined with SBRT may improve OS. In addition, future trials should incorporate molecular profiling to determine the risk of disease progression in individual patients and allow for tailoring therapy based on the site at highest risk of disease failure. For instance, investigators showed in an autopsy series that tumors with loss of expression of the tumor suppressor gene DPC4 had a higher rate of metastatic disease whereas those with intact DPC4 had a higher proportion of isolated locally destructive disease ( $P = 0.007$ ).<sup>7</sup> These results suggest that it may be possible to predict the pattern of failure in patients with pancreatic cancer. If so, SBRT could be further reserved for those with a higher risk of local failure compared with those with a risk of metastatic disease progression.

Finally, the recent LAP-07 trial further calls into the question the role of conventional CRT in the role of locally advanced pancreas.<sup>53</sup> In this trial, patients were randomized to 4 cycles of either gemcitabine or gemcitabine and erlotinib. Patients who did not have disease progression were further randomized to concurrent CRT or 2 additional cycles of chemotherapy. Among those who underwent the second randomization, OS did not differ between those who had CRT vs those who continued with chemotherapy (15.2 months vs 16.4 months, respectively;  $P = 0.83$ ). The lack of benefit in the CRT arm is likely owing to the high risk of systemic progression. SBRT, therefore, may have a potentially important role in this disease given the ability to deliver a highly effective dose in a short time frame and minimizing interruptions of chemotherapy.

With so many questions unanswered, pancreatic SBRT remains an exciting field for further investigation. As more clinical evidence becomes available, its efficacy and safety will be further improved. The next generation of studies should focus on organ tolerance, combining with improved systemic therapy, testing with biological modifiers and sensitizers, and using molecular profiling to select patients. QoL metrics should be incorporated into future protocols to determine the benefit that patients experience with this treatment approach. Finally, there will likely be an increased emphasis on cost efficacy in the future, given the growing attention on health care reform, and further research should be devoted to determining the true benefit of SBRT relative to its costs when compared with other treatment modalities.

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