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ORIGINAL RESEARCH

Stereotactic body radiation for pancreatic cancer: results of an international survey of practice patterns

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Abstract
Objective Stereotactic body radiotherapy (SBRT) is an emerging treatment option for borderline resectable and locally advanced, unresectable pancreatic cancer (PCA). However, no standardized guidelines for treatment exist and patterns of SBRT use for PCA are unclear.
Methods Radiation oncologists known to use SBRT in the setting of PCA were invited to complete a 26-item Web-based survey on practice patterns.
Results Thirty of the 36 (83 %) invited radiation oncologists completed the survey. Of the responders, 86 % treat with 6–8 Gy ×5 fractions. The majority (93 %) of responders use four-dimensional computed tomography (4D-CT) for simulation, with 50 % using gating for breathing motion. Two thirds of radiation oncologists use fiducials for tumor localization. Most (79 %) responders noted an improvement in patient-reported pain after SBRT. Approximately, 59 % report difficulty obtaining insurance clearance for pancreas SBRT in the absence of a clinical trial. The largest variations in practice were related to gross tumor volume (GTV) to planning target volume (PTV) expansions and management of respiratory motion.
Conclusions SBRT is increasingly used for PCA. The data presented here indicate that the majority of radiation oncologists treat with 6–8 Gy ×5 fractions and use fiducials with 4D-CT simulation for localization and planning. Although the majority of the surveyed physicians prefer SBRT to standard radiation, it may be underutilized due to the difficulty of obtaining insurance approval outside of a clinical trial. Our investigation documents current pancreas SBRT practice patterns and highlights the need for prospective clinical trials as a means to develop consensus guidelines for this emerging treatment.

Keywords Pancreatic adenocarcinoma · SBRT · Practice pattern · Survey

Introduction

Pancreatic cancer (PCA) remains one of the leading causes of cancer-specific mortality in the USA, with the Surveillance, Epidemiology, and End Results (SEER) reporting 39,590 related deaths in 2014 [1]. Although surgical resection is the only potentially curative therapy, only 15–20 % of patients with PCA are deemed surgical candidates at presentation [2]. While most patients die of metastatic disease, nearly 30 % of PCA patients will die from isolated local disease progression [3]. These findings reinforce the importance of local therapy, especially as advances in systemic agents will likely lead to better systemic control.

Since the 2011 publication of the Gastrointestinal Tumor Study Group, chemoradiation (CRT) has been the core of treatment recommendations for locally advanced pancreatic cancer (LAPC) [4]. Overall survival, however, remains dismal with most reports publishing a median of 9–12 months [4–6].

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These suboptimal outcomes have called the role of CRT into question and subsequently led to increasing interest in dose escalation for the primary pancreatic tumor. Stereotactic body radiation therapy (SBRT), which allows for delivery of much higher doses of radiation in a more conformal and accurate manner, has been shown in early clinical reports to yield excellent local control rates with limited acute toxicity [7–9]. With promising preliminary data as well as the increasing use of pancreas SBRT by radiation oncologists worldwide, we sought to survey physicians familiar with this technique on their varied practice methods.

Methods

A 26-question Web-based survey was developed. Questions focused on practice patterns of SBRT for PCA, including treatment planning, target volume delineation, dose fractionation schedules, insurance approval, and symptomatic outcomes. The survey was distributed to 36 gastrointestinal radiation oncologists at large academic institutions in the USA and Europe (31 USA, 5 from Europe) who treat PCA. Individuals were selected based on known familiarity with pancreas SBRT, as our goal was to assess for variances in practice patterns across major academic institutions.

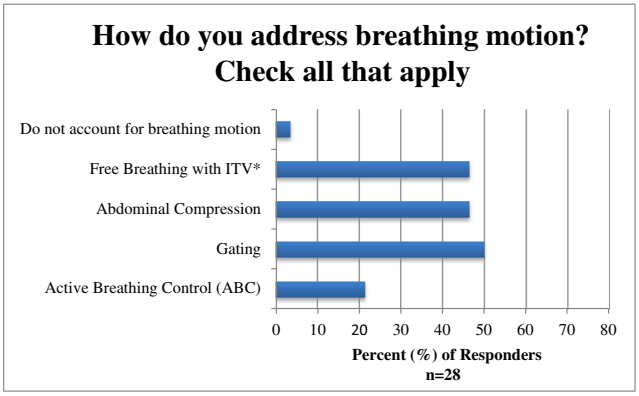
The data were collected and analyzed anonymously. Survey results were generally presented as percentages of evaluable responses.

Results

A total of 30 of the 36 invited radiation oncologists completed the survey, for a response rate of 83 %. Of the responders, one-third (33 %) reported treating more than 20 cases of pancreas SBRT each year. Given the choice of treating PCA with conventional fractionation versus SBRT, 83 % preferred treating with SBRT. Despite this, 59 % of the surveyed participants reported difficulty in getting SBRT for PCA approved by insurance companies outside of protocol use.

Treatment planning

Overall, 87 % of respondents reported using intravenous (IV) contrast-enhanced computed tomography CT simulation for planning, with 57 and 30 % also using positron emission tomography (PET) and magnetic resonance imaging (MRI) for target volume delineation, respectively. The majority (93 %) reported using four-dimensional CT (4D-CT) simulation to assess tumor motion during simulation. As shown in Fig. 1, methods to address breathing motion varied across the group. Among those clinicians who added additional comments to this question ($n = 9$), two (22 %) reported using CyberKnife® Synchrony® motion tracking. All respondents reported using additional tumor localization, with the majority (69 %) using gold fiducials, 14 % using stents, and 17 % using both.



*ITV: Internal target volume

Fig. 1 Management of respiratory motion

With respect to the contraindications to treatment with SBRT, 80 % of radiation oncologists state that they do not treat with SBRT if there is evidence of direct tumor involvement of the stomach or duodenum. Among those who commented ($n = 6$), five (83 %) physicians stated they would reduce dose per SBRT fraction or use standard CRT when there is evidence of critical organ involvement. One commented that patients with biopsy-proven (in addition to radiographic) invasion of critical organs are excluded from pancreas SBRT.

For delineation of normal organs at risk (OARs), most respondents (63 %) reported that they do not utilize an internal target volume (ITV) for normal structures such as the bowel or stomach. If institutional dose constraints could not be achieved, 70 % of the respondents preferred to still treat with SBRT but use lower doses per fraction while 30 % reported treating with standard CRT instead.

When asked about the method of gross tumor volume (GTV) to clinical target volume (CTV)/planning target volume (PTV) expansion, results varied. Only 27 % of the respondents reported using a uniform expansion, 23 % described using a non-uniform expansion, and the remaining 50 % state that although a uniform expansion is used from GTV to PTV, it is subsequently modified to avoid overlap of OARs.

Prescription and delivery

The majority (86 %) of the respondents report treating with 6–8 Gy ×5 fractions, with a smaller group (14 %) treating 10–15 Gy ×3 fractions. Most (70 %) also prescribe a minimum dose to cover the entire PTV but allow heterogeneity within the PTV. The survey allowed comments regarding degree of heterogeneity accepted; among those who added comments ($n = 13$), the average allowed heterogeneity within the PTV was 27 % (range 10–50 %).

Nearly all (97 %) responding radiation oncologists reported using linear accelerator (LINAC)-based machines for treatment delivery, with 14 % reporting also using CyberKnife®. Similarly, nearly all (93 %) noted that they utilize volumetric arc therapy (VMAT) or arc therapy when delivering SBRT. During treatment, 76 % of respondents prophylactically prescribe proton pump inhibitors (PPIs).

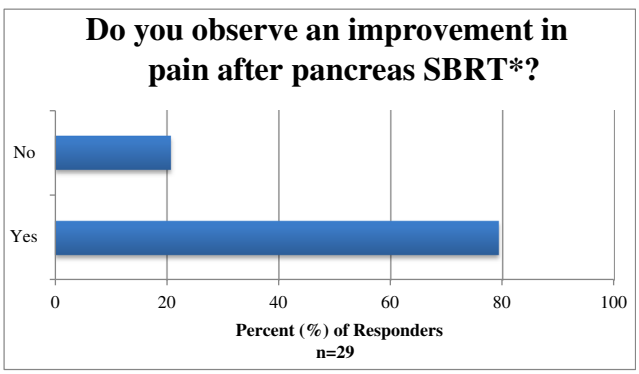
Role of chemotherapy and surgery

Survey participants were also polled on practices related to chemotherapy administration and use of surgery along with SBRT. As expected, 90 % of the responders denied combining SBRT concurrently with chemotherapy or targeted agents. All participating physicians, however, recommend an average of 3 months (range 1–12 months) of chemotherapy prior to SBRT delivery.

Only 3/25 (12 %) participants state that SBRT is never used preoperatively. The remainder ($n = 22$) report waiting an average of 5.5 weeks (range 2–12 weeks) after SBRT prior to attempting surgery in patients deemed to be resectable. Regardless of whether surgery is performed, 79 % of the respondents (Fig. 2) observe an improvement in pain after pancreas SBRT.

Discussion

The use of SBRT in PCA is emerging, yet dose delivery and treatment techniques vary. Interest and adoption of SBRT has increased in recent years, largely due to the appeal of shorter treatment times compared to conventional CRT, and rapid resumption of systemic therapy and/or surgery. More timely resumption of systemic therapy is critical in this aggressive disease with high propensity for distant dissemination. Prior to incorporating SBRT into cooperative group trials, there is a need to develop a standardized approach to pancreas SBRT. Therefore, we sought to assess practice patterns in the USA and Europe regarding the use of SBRT in patients with PCA among academic radiation oncologists known to be familiar with this technique.



*SBRT: Stereotactic body radiotherapy

Fig. 2 Outcomes of pain after pancreas SBRT

While the optimal dose and fractionation of SBRT for PCA remain unclear, our survey results indicate that the majority of physicians favor a five-fraction regimen. Compared with single-fraction SBRT, five-fraction regimens have demonstrated decreased short- and long-term gastrointestinal toxicity [10–13].

Data from Brunner et al. investigating optimal biologically equivalent dose (BED) indicate that dose escalation beyond a BED of 75 Gy does not prolong survival and confers worse toxicity [14]. At our institutions, we use 6.6–8.0 Gy ×5 fractions; however, the dose may be lowered in increments of 0.1 Gy in order to safely achieve established dose constraints. Most respondents similarly utilize a five-fraction regimen, while a minority opts for a three-fraction approach for a total dose of 30–45 Gy. In review of the literature (Table 1), there is no clear difference in local control and/or toxicity between these two fractionation regimens; therefore, both appear acceptable [8,12,15–23]. In circumstances involving adjacent organs in close proximity to the stomach or bowel, a five-fraction regimen may be optimal. In contrast, a three-fraction regimen may be preferred for body lesions or when surgery following SBRT is planned such as in borderline resectable PCA.

In the past decade, pancreas SBRT has evolved as a local technique used in patients with varying stages of disease. SBRT has historically been evaluated in patients with locally advanced disease (Table 1), with our recent multicenter study reporting favorable local control and acceptable gastrointestinal toxicity with gemcitabine and SBRT [12]. With the hopes of further improving outcomes in locally advanced PCA, an ongoing randomized trial in North America is currently investigating outcomes of SBRT in combination with the more aggressive FOLFIRINOX (NCT01926197). The role of pancreas SBRT in the adjuvant setting for those with high-risk pathologic features, or the salvage setting for patients who experience a local recurrence, is less well known. Available data, albeit small series, suggest that SBRT holds a promising role in these cases, with local control rates ranging from 60 to 90 % at 1 year with minimal associated toxicity [21–23]. We await the results of several clinical trials (NCT01781728, NCT01595321, NCT01357525, NCT02461836) that explore SBRT for PCA in both the adjuvant and salvage setting.

Yet another novel application is neoadjuvant pancreas SBRT. In this case, SBRT is given approximately 4–8 weeks prior to surgery in an attempt to increase the likelihood of a margin-negative resection and/or prevent local recurrence. Our survey results demonstrate that pancreas SBRT is increasingly used to help bridge patients with borderline resectable and locally advanced disease prior to surgery, yet the ideal timing between SBRT and surgery remains a subject of discussion. If the goal is to prevent a local recurrence in a patient that is resectable, then 1 week following SBRT is reasonable [24, 25]. However, if the goal is to downstage and/or improve

Table 1 Key studies: stereotactic body radiation therapy

Study	Regimen	Number	FFLP, 1 year (%)	Median OS (months)	Toxicity, Acute/Gr ≥ 3	Toxicity, Late/Gr ≥ 2	Dose constraints for organs at risk
Definitive setting (LAPC)							
Koong et al. (2004) [15]	25 Gy SBRT, 1 fraction	6	100 %	8.0	33 %	–	Duodenal wall (50 % isodose line)
Mahadevan et al. (2010) [16]	24 Gy–36 Gy SBRT, 3 fractions → GEM	36	78 %	14.3	41 %	6 %	Liver (<30 % ≥21 Gy; <50 % ≥15 Gy), kidney (<25 % ≥12 Gy), spinal cord (12 Gy max), bowel (<10 Gy/fx max)
Polistina et al. (2010) [17]	GEM → 30 Gy SBRT, 3 fractions	23	50 %	10.6	0	0	Mean dose to 50 %: duodenum (14.5 Gy), bowel (1.1 Gy), liver (0.7 Gy), left kidney (1.5 Gy), right kidney (2.0 Gy)
Schellenberg et al. (2011) [18]	GEM → 25 Gy SBRT, 1 fraction→ GEM	20	94 %	11.8	15 %	20 %	Duodenum (≤5 % ≥22.5 Gy, ≤50 % ≥12.5 Gy), spinal cord (<6 Gy max), liver (50 % <5 Gy), kidney (75 % <5 Gy)
Tozzi et al. 2013 [19]	GEM → 45 Gy SBRT, 6 fractions	30	86 %	11.0	20 %	0	Duodenum (1 mL <36 Gy), stomach and small bowels (3 mL <36 Gy), kidney (<35 % 15 Gy), liver (total spread volume > 700 mL), spinal cord (1 mL <18 Gy)
Chuong et al. (2013) [8]	GTX → 25 Gy–50 Gy SBRT, 5 fractions	16	81 %	15.0	0 %	5.3 %	Kidney (<10 Gy), duodenum/small bowel/stomach (35 Gy max, 5 mL <30 Gy, 1 mL <35 Gy), liver (10 % 30 Gy), spinal cord (20 Gy max)
Gurka et al. (2014) [20]	25–30 Gy SBRT, 3 fractions → GEM	38	79 % (7.2 mo)	14.3	7.9 %	15.8 %	Stomach, duodenum, bowel (V100 % < 1 ml, V80 % < 40 %, V50 % < 90 %)
Herman et al. (2015) [12]	GEM → 33 Gy SBRT, 5 fractions → GEM	49	83 %	13.9	12.2 %	10.6 %	Proximal duodenum and stomach (9 mL <15 Gy; 3 mL <20 Gy; 1 mL <33 Gy), liver (50 % <12 Gy), combined kidneys (75 % <12 Gy), spinal cord (1 mL >8 Gy)
Salvage and reirradiation (Postoperative or locally recurrent)							
Lominska et al. (2012) [21]	50.4 Gy IMRT → Median 22.5 Gy SBRT, 3 fractions	28	86 %	5.9	0 %	7 %	Duodenum and stomach: max point dose ≤ prescription dose
Wild et al. (2013) [22]	50.4 Gy IMRT → Median 25 Gy SBRT, 5 fractions	18	62 %	8.8	0 %	6 %	Duodenum (V 15 Gy < 9 cm^3,V33Gy < 1 cm^3), liver (50 % < 12 Gy), stomach (50 % <12 Gy), spinal cord (V 8 Gy < 1 cm^3)
Dagoglu et al. (2016) [23]	Median 25 Gy SBRT, 5 fractions	30	78 %	14.0	11 %	7 %	Max point dose to stomach and duodenum ≤ prescription dose

the likelihood of a margin-negative resection in a borderline resectable or unresectable patient, a prolonged delay between SBRT and surgery is recommended (4–8 weeks). While the optimal delay between SBRT and surgery is unknown, we typically recommend approximately 6 weeks. If the delay is greater than 12 weeks, the development of treatment-related fibrosis can make resection more difficult.

The majority (90 %) of survey responders does not recommend delivery of concurrent chemotherapy with pancreas SBRT; however, this strategy is a subject of investigation. A currently active protocol at Massachusetts General Hospital (MGH) is investigating the use of concurrent hydroxychlororoquine and capecitabine with a five-fraction proton or photon therapy for resectable PCA (NCT01494155). Similarly, the University of Nebraska reported early results of SBRT and concurrent nelfinavir for LAPC [26]. Integration of such therapeutics with SBRT remains a novel treatment paradigm for PCA and we await mature results. We typically recommend holding chemotherapy for 1 week prior, during, and 1 week after SBRT in order to limit treatment-related toxicity; however, whether this precaution is necessary is unknown. Integrating SBRT during the week off from chemotherapy was described by some of the respondents.

Our report highlights the rapidly growing interest in treating PCA with SBRT, with the majority of those surveyed reporting preference for this approach over conventional techniques. However, our results importantly also demonstrate the considerable variability in methods of use, including volumetric expansions, management of respiratory motion, and imaging used for target volume delineation. Despite preferring SBRT over conventional CRT, the majority of responders also report difficulty obtaining insurance approval for SBRT. This stresses the importance of standardization of SBRT through prospective trials such as the upcoming Alliance A021501 protocol for borderline resectable PCA. Given the data

supporting its effectiveness at pain control and decreased cost compared to conventionally fractionated therapy, pancreas SBRT has been formally adopted in the recent clinical practice guidelines published by the National Comprehensive Cancer Action Network (NCCN) and American Society of Clinical Oncology (ASCO) [27, 28].

Conclusions

Our survey highlights the interest and preference for fractionated SBRT in the treatment of PCA and demonstrates similarities in tumor localization and image guidance. Prospective cooperative trial evaluation is warranted to further standardize treatment delivery and provide guidelines for radiation oncologists.

Compliance with ethical standards

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Conflict of interest A. Parekh declares that she has no conflict of interest. L. M. Rosati declares that she has no conflict of interest. D. T. Chang declares that he has no conflict of interest. K. A. Goodman, MD declares that she has no conflict of interest. T.M. Pawlik declares that he has no conflict of interest. A. C. Koong declares that he has no conflict of interest. J. M. Herman declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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