



Dose-Volume Histogram Analysis of Stereotactic Body Radiotherapy Treatment of Pancreatic Cancer: A Focus on Duodenal Dose Constraints

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Pancreatic carcinoma is an aggressive disease and radiotherapy treatment delivery to the primary tumor is constrained by the anatomical close location of the duodenum, stomach, and small bowel. Duodenal dose tolerance for radiosurgery in 2-5 fractions has been largely unknown. The literature was surveyed for quantitative models of risk in 1-5 fractions and we analyzed our own patient population of 44 patients with unresectable pancreatic tumors who received 3 or 5 fractions of stereotactic body radiotherapy (SBRT) between March 2009 and March 2013. A logistic model was constructed in the dose-volume histogram (DVH) Evaluator software for the duodenal $D_{50\%}$, $D_{30\text{ cc}}$, $D_{5\text{ cc}}$, $D_{1\text{ cc}}$, and maximum point dose $D_{0.035\text{ cc}}$. Dose tolerance limits from the literature were overlaid onto the clinical duodenal data in the form of a DVH Risk Map, with risk levels of the published limits estimated from the model of clinical data. In 3 fractions, Kopek 2010 found a statistically significant difference in $D_{1\text{ cc}}$ of patients with no common terminology criteria for adverse events (CTCAE) v3 grade 2 or higher duodenal complications (mean $D_{1\text{ cc}} = 25.3\text{ Gy}$) as compared with patients with grade 2 or higher toxicity (mean $D_{1\text{ cc}} = 37.4\text{ Gy}$). From the logistic model of our duodenal data in 3 fractions, $D_{1\text{ cc}} = 25.3\text{ Gy}$ had 4.7% risk of grade 3-4 hemorrhage or stricture and $D_{1\text{ cc}} = 37.4\text{ Gy}$ had 20% risk. The 10% risk level was $D_{1\text{ cc}} = 31.4\text{ Gy}$ and we were able to keep duodenum dose for all our patients later this level.

Semin Radiat Oncol 26:149-156 © 2016 Elsevier Inc. All rights reserved.

Locally advanced unresectable pancreatic cancer is often treated with chemotherapy as pancreatic cancer tends to metastasize early, and patients often have occult metastases.¹ However, radiotherapy is also frequently used to control the primary disease and has been shown to increase progression free survival and provide effective pain relief. The short duration of stereotactic body radiotherapy (SBRT) (compared with

conventionally fractionated radiotherapy) is an attractive feature for patients who may benefit from a shorter period of interruption of chemotherapy^{2,3} to control micrometastatic disease, provide quicker pain relief, and allow the potential for dose escalation with reduced side effects. For soft tissue targets such as pancreatic tumors, SBRT delivery is typically guided by either cone beam computed tomography (CT) or by implanted gold fiducials as a surrogate for the tumor target.

The duodenum is invariably the dose-limiting organ-at-risk (OAR) when delivering radiotherapy to a pancreatic target. To limit toxicity, some treating centers determine the prescribed dose to tumor according to the relationship between tumor location and duodenum.⁴ There is scope to improve local control rates following SBRT (84%-85% at 12-21 months follow-up),⁴⁻⁵ either by dose escalation to tumor, or by reduced compromise of tumor coverage adjacent to duodenum.

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This research was funded in part by Accuray, Inc.

Conflict of Interest: None.

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However, these strategies to improve local control need to be guided by robust, evidence-based, dose tolerance limits for duodenum to avoid excessive toxicity.

A separate article in this issue of Seminars in Radiation Oncology studies dose-volume histogram (DVH) analysis of small bowel tolerance in general (to include duodenum, jejunum, and ileum) for any adjacent treatment site. The DVH Risk Map in their article applied data from the literature as well as estimates of risk from a dose response model from patients treated with SBRT at their center.⁶ Of the patients studied, 15% received SBRT for pancreatic cancer. The authors performed a subanalysis on the toxicity of vascular endothelial growth factor inhibition with SBRT.

The aim of this article is to report on DVH analysis of duodenal tolerance following SBRT in the treatment of pancreatic cancer. The DVH Risk Map was constructed incorporating planning constraints from the literature, dose-response modeling, and importantly, the published dose tolerance limits in the DVH Risk Map were validated with outcome data from patients treated with SBRT for pancreatic cancer at The Harley Street Clinic, London. The first author had explored aspects of fiducial tracking accuracy, and dose delivery in SBRT for her Research MD thesis. A subanalysis was therefore performed to investigate the effect of the number of fiducials implanted on duodenal toxicity.

Duodenal Toxicity From Pancreatic SBRT: Literature Review

A Pubmed search of the keywords (pancreas or pancreatic) and stereotactic returned 153 citations in 2015 November, but quantitative guidance on duodenal tolerance is limited. Dose tolerance limits from published series are stored in the DVH Evaluator software (DiversiLabs LLC, Huntingdon Valley, PA) to obtain an overview of the world literature. To assess the validity of such an approach this tool has then been tested against our own data by performing duodenum DVH analysis, and linking to toxicity outcome data.

The first dose response model for duodenum in SBRT was from a series of 73 patients at Stanford with locally advanced unresectable pancreatic adenocarcinoma who received 25 Gy in 1 session⁷ (biological effective dose [BED] 87.5 Gy₁₀ using $\alpha/\beta = 10$ Gy for tumor control) from October 2002 to December 2007. Of the 73 patients studied, 53 (73%) were treated with the CyberKnife treatment platform (Accuray Inc., Sunnyvale, CA) using the Synchrony tracking system, and the remaining 20 patients (27%) were treated with a Trilogy linear accelerator (Varian Medical Systems, Palo Alto, CA). A Lyman model⁸⁻¹⁰ was fitted to the data, providing an estimate of toxicity risk as a function of duodenal dose in 1 fraction. The BED formula could be used to predict the likely toxicity of a multisession treatment based on the observed toxicity from this single-fraction regime. However, there is a caveat to this approach; the BED model tends to overestimate the radiation effects of larger fraction sizes.⁷ Careful assessment of toxicity

outcomes, linked to delivered dose to duodenum, in a patient cohort receiving multisession SBRT would provide more reliable risk data for multisession SBRT.

The study of Bae et al¹¹ from Korea Institute of Radiological and Medical Sciences retrospectively examined 40 eligible patients with various abdominopelvic malignancies, treated with SBRT from 2002-2011, providing a probit dose response model for the gastrointestinal maximum point dose ($D_{\max}$). The patients were treated in 3 fractions with either CyberKnife or RapidArc and the analysis included not only duodenal complications, but also those which occurred in other areas of the bowel. In all, 3 patients (7.5%) experienced Grade 3+ duodenal toxicity following $D_{\max}$ doses to the duodenum of 42, 54, and 58 Gy (BED3 = 238, 378, and 432 Gy). A subsequent publication from the same group reported an additional duodenal complication with $D_{\max}$ to duodenum 47 Gy in 3 fractions (BED3 292 Gy).¹² Volume effects were not analyzed, and these 2 studies did not specifically address duodenal tolerance for pancreatic SBRT (as the patients had various abdominopelvic malignancies), however, they provide an important point of reference.

The Medical College of Wisconsin published pooled analysis of duodenal tolerance from the literature for both conventional fractionation and SBRT, with emphasis on pancreatic carcinoma but also inclusion of other disease sites near the duodenum.¹³ A modified linear quadratic (LQ) model was used to generate a Lyman-Kutcher-Burman⁸⁻¹⁰ model in 2 Gy equivalent doses.

A recent systematic literature search used the LQ model with $\alpha/\beta = 3$ Gy to convert the prescription dose of 13 studies into a surrogate for duodenal dose.¹⁴ Regression analysis and Lyman-Kutcher-Burman modeling⁸⁻¹⁰ were used to formulate benefit or risk tradeoffs of expected local control vs duodenal toxicity. Overall, 1 of the studies included in the review employed selective integrated boosting of the portion of tumor surrounding the superior mesenteric vein or superior mesenteric artery.¹⁵ This strategy has potential to further improve the benefit or risk tradeoff by delivering a higher dose to the core of the tumor whereas still sparing the abutting critical structures.^{16,17} Strategies to dose-escalate to the tumor, while still sparing adjacent OAR, offers the opportunity to optimize patient outcomes. However, it would be critical to analyze delivered doses to the duodenum, linked with toxicity outcomes.

Duodenal Toxicity From Pancreatic SBRT: Dataset With Outcomes

At The Harley Street Clinic, London, 44 patients with unresectable pancreatic tumors¹⁸ received SBRT using CyberKnife between March 2009 and March 2013. This dataset was used for validating dose tolerance limits from the published literature. Overall, 41 patients were prescribed 18-36 Gy in 3 fractions, with corresponding BED ranging from 24.5-79.2 Gy₁₀, using the LQ model¹⁹⁻²¹ with $\alpha/\beta = 10$ Gy for tumor control. In all, 3 patients were prescribed 22.5-25 Gy

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