



Small Bowel Dose Tolerance for Stereotactic Body Radiation Therapy

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Inconsistencies permeate the literature regarding small bowel dose tolerance limits for stereotactic body radiation therapy (SBRT) treatments. In this review, we organized these diverse published limits with MD Anderson at Cooper data into a unified framework, constructing the dose-volume histogram (DVH) Risk Map, demonstrating low-risk and high-risk SBRT dose tolerance limits for small bowel. Statistical models of clinical data from 2 institutions were used to assess the safety spectrum of doses used in the exposure of the gastrointestinal tract in SBRT; 30% of the analyzed cases had vascular endothelial growth factor inhibitors (VEGFI) or other biological agents within 2 years before or after SBRT. For every dose tolerance limit in the DVH Risk Map, the probit dose-response model was used to estimate the risk level from our clinical data. Using the current literature, 21 Gy to 5 cc of small bowel in 3 fractions has low toxicity and is reasonably safe, with 6.5% estimated risk of grade 3 or higher complications, per Common Terminology Criteria for Adverse Events version 4.0. In the same fractionation for the same volume, if lower risk is required, 16.2 Gy has an estimated risk of only 2.5%. Other volumes and fractionations are also reviewed; for all analyzed high-risk small bowel limits, the risk is 8.2% or less, and the low-risk limits have 4% or lower estimated risk. The results support current clinical practice, with some possibility for dose escalation. *Semin Radiat Oncol* 26:157-164 © 2016 Elsevier Inc. All rights reserved.

The use of stereotactic body radiation therapy (SBRT) continues to increase as more therapy machines are able to administer SBRT and the available literature expands regarding efficacy. Usage of SBRT within the upper abdomen has expanded, including but not limited to primary hepatocellular carcinoma, metastatic liver lesions, spine metastasis, pancreatic malignancies, and retroperitoneal tumors. With more SBRT upper abdomen treatments, the potential for SBRT-induced gastrointestinal side effects becomes increasingly relevant. Heeding published dose tolerance limits can avoid excessive toxicity, but the wide variation of reporting standards and parameter values makes this challenging.

Our definition of dose tolerance limit is, “a specified radiation dose, fractionation and volume, with an associated estimated risk of developing a complication of the specified end point within a specified follow-up time.”¹ The SBRT literature frequently addresses many of these

properties except for the estimate of the degree of risk of each limit. How can we obtain this risk estimate? Sufficient information does not currently exist in the literature for many of the organs. Analysis of our patient data provides an answer by combining (1) planning constraints from the literature,²⁻⁵ (2) the statistical method of dose-response modeling,⁶⁻⁹ and (3) a relatively new entity called the dose-volume histogram (DVH) Risk Map.^{1,10}

Dose-response modeling such as the probit model^{11,9} is the statistical method that can estimate the risk based on clinical outcomes data. Modeling is better than a simple average, because it provides an equation that has risk as a function of dose. After the parameters of the equation have been fitted to the clinical dataset, the estimates of risk for any dose tolerance limit can be calculated from the model.

The DVH Risk Map compares the dose tolerance limits graphically for each specified volume as a function of the number of fractions. By plotting the dose tolerance limits, it becomes immediately apparent that some have higher risk than others do. The dose-response models provide quantitative estimates of the risk of each limit, and these are shown in the table at the bottom of the DVH Risk Map.

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Table 1 Historical Summary of Small Bowel Toxicity

Study	Number of Patients	Dose (Gy)	Number of Fractions	Volume (cc or %)	Small Bowel D_{max}	Adverse Events > Grade	Number of Patients With Adverse Events	Comments
Koong et al ¹²		25	1	$V_{50\%}$ 14.5 Gy $V_{5\%}$ 22.5 Gy		None		
Hoyer et al ¹³	22	45	3	Median target volume $\geq$ 30 Gy = 136 cc	30 Gy to small part of stomach or duodenum	$\geq$ G2 = 18%	4	Severe mucositis of duodenum and nonfatal perforation
Hoyer et al ¹⁴	64	45	3		30 Gy to minimal volume	$\geq$ G2 = 48% $\geq$ G3 = 3%	$\geq$ G2 = 29 $\geq$ G3 = 2	G3 = duodenal ulceration
Chang et al ¹⁵	77 (61 SBRT + 16 SBRT + EBRT)	25	1	$V_{22.5\text{ Gy}} < 5\%$ $V_{12.5\text{ Gy}} < 50\%$ 50% IDL < nonadjacent wall		Acute $\geq$ G2 late G2 late G3	4 (5%) 3 (4%) 7 (9%)	1 Of 4 acute and 3 of 10 late $\geq$ G2 toxicity received EBRT and SBRT
Kopeck et al ¹⁶	27	45	3	$V_{21\text{ Gy}} \leq 1\text{ cc}$		$\geq$ G3 ulceration 22% $\geq$ G3 stenosis 11%	6 and 4	$D_{1\text{ cc}} = 37.4\text{ Gy}$ in patients with ulceration
Mahadevan ¹⁷	36	24-36	3		$D_{max} < 30\text{ Gy}$	G3	Acute 3 (8%) late 2 (6%)	Prescription dose determined by GTV duodenal proximity and volume
Murphy et al ¹⁸	73	25	1	$V_{22.5\text{ Gy}} < 5\%$ $V_{12.5\text{ Gy}} < 50\%$	$D_{max} < 23\text{ Gy}$ reduced toxicity from 49%-12%	G2-4 $V_{15} < 9.1\text{ cc}$ and $V_{20} < 3.3\text{ cc}$ reduced risk from 52%-11%	12	86% Of patients received gemcitabine
Rwigema et al ¹⁹	71	18-25 (median 24 Gy)	1		$D_{max} \leq 15.1\text{ Gy}$ (median). D_{max} ranged from 7.7-21.6 Gy	G3	3 (4.2%)	1 Nausea, 1 abdominal pain, 1 gastroparesis, but no ulceration
Schellenberg et al ²⁰	20	25	1	$V_{22.5} < 5\%$ $V_{12.5} < 50\%$			1 (5%)	G4 duodenal ulceration gemcitabine chemotherapy
Barney 2012 ²¹	47	50	5	$V_{38} \leq 5\text{ cc}$ $V_{32.5} \leq 15\text{ cc}$ $V_{20} \leq 30\text{ cc}$	$D_{max} \leq 42\text{ Gy}$	$\geq$ G3 late	5	1 Stenosis, 2 perforations both had bevacizumab
Barney et al ²²	76				$D_{max} \text{ BED}_3 \leq 125\text{ Gy}$	$\geq$ G3	7 (9%)	If VEGF1 delivered within 3 months of SBRT COT rate 38%
Dholakia et al ²³	49	33	5	$V_{33} \leq 1\text{ cc}$ $V_{20} \leq 3\text{ cc}$ $V_{15} \leq 9\text{ cc}$		$> \text{G2 acute}$ $> \text{G2 late}$	16.3% 5 (11%)	3 Cases G3 ulcer, 1 case G4 fistula
Bae et al ²⁴	202	33-60 (median 45 Gy)	3	$V_{20} < 14\text{ cc}$ $V_{25} < 7\text{ cc}$ $V_{30} < 5\text{ cc}$ $V_{35} < 1\text{ cc}$ $D_{max} < 45\text{ Gy}$	$D_{max} < 45\text{ Gy}$	$\geq \text{G3} = 4 \geq \text{G4} = 2$	6 (15%)	Best predictor of toxicity $V_{25\text{ Gy}} > 20\text{ cc}$ and D_{max} of 35-38 Gy with 5%-10% severe toxicity
Wild et al ²⁵	15	25	5	$V_{15} < 9\text{ cc}$ $V_{20} < 3\text{ cc}$ $V_{33} < 1\text{ cc}$		G3	No acute 1 (6%) late	Reirradiation with varied chemo

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