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Dose-Response Model for Chest Wall Tolerance of Stereotactic Body Radiation Therapy

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Many recent studies have described rib fractures and chest wall pain following stereotactic body radiation therapy (SBRT). Although these toxicities generally are not life-threatening, the chest wall and ribs are considered dose-limiting tissues because of the potential effect on patients' quality of life. Few studies have reported dose-response models that can provide quantitative estimates of risk as a function of dose and volume. Notably, Memorial Sloan Kettering Cancer Center (Mutter et al[8]) analyzed grade 2 or higher chest wall toxicity in a cohort of 126 patients treated with linear accelerator–based SBRT; the authors provided detailed dose-volume histogram (DVH) data to allow for pooled analyses. We pooled these 126 patients with an additional 44 patients treated with CyberKnife at the Erlanger Medical Center to create an updated dose-response model for chest wall tolerance. In the aggregate analysis, the 10% risk level for grade 2 or higher complications for $D_{70\ cc}$ was 16.2 Gy in 4 fractions, and the 50% risk level was $D_{70\ cc} = 65.1$ Gy in 4 fractions. For $D_{2\ cc}$, the 10% and 50% risk levels in 4 fractions were 43.0 Gy and 87.9 Gy, respectively. These dose-tolerance limits may help quantify chest wall toxicity risks. Further research continues to determine more accurate estimates of grade 3 risk levels.
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Chest wall toxicity after radiation therapy includes rib fracture with or without pain, as well as pain in the absence of fracture that is likely attributable to radiation-induced neuropathy of the intercostal nerves or nerve branches or both. Hairline rib fractures, not readily apparent on imaging, may also cause pain.[1] The risk of rib fracture after conventionally fractionated radiotherapy have been recognized for decades,[2,3] whereas postradiotherapy neuropathic pain had not been as well characterized until recently. Although stereotactic body radiotherapy (SBRT) has been utilized since 2000 and increasingly adopted in more recent years,[4] chest wall toxicity following SBRT was not well described until 2009,[5] after which 2 landmark articles described dosimetric measures predictive of toxicity.[6,7]

In a retrospective study by Dunlap et al[7] of 60 patients from the University of Virginia, 17 patients developed Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 grade 3 chest wall toxicity after SBRT for primary or metastatic lesions; the volume of chest wall receiving ≥ 30 Gy ($V_{30\ Gy}$) best predicted toxicity risks. The authors reported a 30% toxicity risk with a chest wall $V_{30\ Gy}$ of 35 cc. In a study by Pettersson et al[6] of 68 patients treated at Sahlgrenska University for Stage I non–small cell lung cancer, 13 fractures developed in 7 patients; the dose to a smaller volume of just 2 cc ($D_{2\ cc}$) of rib best predicted fracture risk. Volumes as large as $V_{30\ Gy}$ =

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70 cc have been found to be the most robust predictor in the Memorial Sloan Kettering Cancer Center (MSKCC) Mutter et al[8]study, so the ideal dose-volume metric is still an area of active research.

Many more recent publications have also analyzed dosimetric parameters predictive of rib fracture or chest wall toxicity or both,[1,8-24] although with varying endpoints and definitions of the chest wall organ-at-risk (OAR) and toxicity outcomes.[25] For example in some studies [7-10,14,17,21,24] (including Dunlap et al[7]), chest wall was defined as a 2-3 cm volumetric lung or liver expansion subtracted from non–chest wall normal tissue (ie, liver, lung, spine, and mediastinum) with nonintercostal skeletal muscles subtracted in a study[10]; some studies[12,18,20] defined chest wall as the body contour or hemibody subtracted from lungs, another[15] study defined it as an arc of tissue outside the lung and another[22] study did not define a chest wall structure. In other studies,[6,9,13,16,23] (including Pettersson et al[6]) chest wall was defined as individual ribs, whereas a rib volume was not defined in some studies[1,11] that correlated rib fracture risk with maximum doses. In some studies, a range of volume-based chest wall parameters (ie, V_{30} through V_{60}) were predictive of toxicity,[14,15] whereas in a study, no dosimetric measures were significantly correlated with toxicity risk.[24]

After conventional fractionation Emami et al[2] estimated, for rib fractures, the 5% and 50% tolerance doses to be 50 Gy and 65 Gy, respectively, to one-third of the structure. Overgaard[26] analyzed rib fracture risk among 231 patients with breast cancer treated from 1978-1981 with postmastectomy radiation using electrons in 22 or 12 fractions. As this was before the era of 3-dimensional treatment planning, the rib dose was estimated at a reference point based on depth dose curves and the ultrasound measurements of chest wall thickness. Despite the technical limitations of this approach, the estimated 5% and 50% tolerance doses of 50.5 Gy and 60.4 Gy from the 22-fraction curve are remarkably comparable to the Emami results. With 12 fractions, the 5% and 50% risk levels were 41.0 Gy and 51.9 Gy, respectively. Their data set is reproduced in Figure 1.

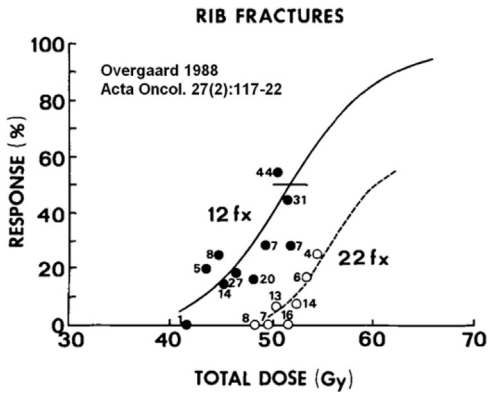

Figure 1 Rib fracture risk from postmastectomy chest wall electron irradiation (Reprinted with permission from Overgaard[26]). A logistic model was fitted for both the 12-fraction and 22-fraction data, based on the reference point dose of each rib. The number of patients in each rib dose group is shown next to each response data point.

Currently, the optimal dosimetric measures to predict chest wall toxicity for SBRT are not well established,[25] and certainly depend on how the chest wall OAR is defined, what outcome measure is being assessed, and the frequency and rigor of toxicity assessment. For example, robust dosimetric predictors of toxicity risks may be different for endpoints of any rib fracture, painful rib fracture, any chest wall pain or grade 2+ chest wall pain. Rib fracture is often not associated with pain, although the extent to which this occurs is inconsistent in published studies. Among those who develop fracture after SBRT, the published rate of painless fracture ranges from none[7] to some (20%-50%)[13,16] to most (66%-100%)[6,9-11,19,21,23] study patients, further muddying the understanding of chest wall toxicity risks after SBRT. In one study, the severity of pain was correlated with the severity of rib fracture,[18] although in another study such a correlation was not observed.[19]

In the current study, we sought to analyze dosimetric predictors of CTCAE version 3 grade 2+ chest wall pain after SBRT for lung tumors. We hypothesized that $D_{70\ cc}$, $D_{30\ cc}$, $D_{2\ cc}$, and D_{max} would be significant predictors of toxicity outcomes. We also sought to compare our normal tissue complication probability (NTCP) modeling of grade 2+ chest wall pain after SBRT with the historic postmastectomy radiotherapy rib fracture data from Overgaard[26]

Dose-Volume Histogram Atlas

Jackson et al[27] designed the atlas of complication incidence and QUANTEC authors recommended[28] that tools such as this be used to improve the quality of reporting for outcomes analysis. The Mutter et al[8] article included the dose-volume histogram (DVH) atlas for chest wall tolerance, without which the present analysis would not be possible. Their actuarial DVH atlas reported the full dose-volume data separately for 2 cm thick chest wall contours and for 3 cm thick chest wall contours, as well as separated by the number of fractions 3, 4, and 5, for a total of 6 spreadsheets. Within each spreadsheet, the dose-volume data shows the number of complications and noncomplications as a function of follow-up time.

Patient Population

Overall, 275 SBRT cases treated from April 2011-September 2013, at Erlanger Medical Center have been reviewed in the DVH Evaluator, treated with the CyberKnife, and the follow-up is stored prospectively in the RSSearch Registry. From this database, 44 lung cases with chest wall contours and Ray Tracing dose calculations have been identified. The 126 linear accelerator (LINAC)–based cases from the MSKCC DVH atlas (Mutter et al[8]) were also imported into the DVH Evaluator. The MSKCC authors provided detailed DVH data in the supplemental online materials to allow for pooled analyses. The MSKCC patients were followed 1 month after treatment and then every 3 months, at which times pain was assessed using CTCAE version 3.0 criteria. Median follow-up in the Erlanger data set was 15 months (range: 1-35 months) so the 15-month timepoint was extracted from the published MSKCC DVH