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Validity of Current Stereotactic Body Radiation Therapy Dose Constraints for Aorta and Major Vessels

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Understanding dose constraints for critical structures in stereotactic body radiation therapy (SBRT) is essential to generate a plan for optimal efficacy and safety. Published dose constraints are derived by a variety of methods, including crude statistics, actuarial analysis, modeling, and simple biologically effective dose (BED) conversion. Many dose constraints reported in the literature are not consistent with each other, secondary to differences in clinical and dosimetric parameters. Application of a dose constraint without discriminating the variation of all the factors involved may result in suboptimal treatment. This issue of Seminars in Radiation Oncology validates dose tolerance limits for 10 critical anatomic structures based on dose response modeling of clinical outcomes data to include detailed dose-volume metrics. This article presents a logistic dose-response model for aorta and major vessels based on 238 cases from the literature in addition to 387 cases from MD Anderson Cancer Center at Cooper University Hospital, for a total of 625 cases. The Radiation Therapy Oncology Group (RTOG) 0813 dose-tolerance limit of $D_{max} = 52.5$ Gy in 5 fractions was found to have a 1.2% risk of grade 3-5 toxicity, and the Timmerman 2008 limit of $D_{max} = 45$ Gy in 3 fractions had 2.3% risk. From the model, the 1% and 2% risk levels for $D_{4\ cc}$, $D_{1\ cc}$, and $D_{0.5\ cc}$ are also provided in 1-5 fractions, in the form of a dose-volume histogram (DVH) Risk Map.
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The aorta is among the most critical of all anatomical structures, but complication data for the structure is particularly sparse. In most protocols, the constraints placed on the aorta are well below the expected tolerance levels. Owing to the critical nature of this structure, these constraints typically take precedence over tumor control. Although the dose tolerance is seemingly quite high, the uncertainty of its true value makes it a dose-limiting factor for many cases.

Aorta and Major Vessel Toxicity

Grade 5 events from doses relevant to stereotactic body radiation therapy (SBRT) occurring before 2008 have been reported in the literature after several years of follow-up.[1] Among 35 patients in an MD Anderson retrospective study[1] received 2 courses of radiation therapy for thoracic tumors, with fraction size ranging from 1.2-3.0 Gy per day. In this series, 2 complications occurred and in both cases the composite aortic $D_{1\ cc}$ exceeded an equivalent dose of 90 Gy in 1.8 Gy fractions, accounting for time to repair sublethal damage among the 2 courses of treatment. Although these are conventionally fractionated cases, the composite $D_{1\ cc}$ had an equivalent dose of 40 Gy in 5 fractions using the linear quadratic (LQ) model with $\alpha/\beta = 3$ Gy. This may provide some insight into useful constraints for SBRT.

The Accuray STARS protocol[2,3] used a $D_{1\ cc} = 40$ Gy aorta limit for 4-fraction treatments, that has a 10% higher effective dose than in 5 fractions, but may have been influenced by the 2 complications that occurred before 2008. Timmerman[4] allowed a substantially higher dose of $D_{10\ cc} = 39$ Gy to the aorta in 3 fractions. No studies at that time had reported aortic toxicity for any actual SBRT cases. Thus $D_{1\ cc} = 40$ Gy as a 5-fraction limit is probably overly cautious, and using it for a 4-fraction limit seems to have been a good compromise.

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Dose-tolerance limits of most critical structures in the Accuray STARS protocol were higher than most other protocols of the time period, except for the aorta constraints, which still remain lower than any other SBRT protocol aortic dose constraints.

The large-volume effects cannot be overlooked. For hyperfractionation and mildly hypofractionated treatments, the tumor margins are often larger and a greater volume of normal tissue is typically exposed to radiation. For example, Radiation Therapy Oncology Group (RTOG) 0617[5] and RTOG 1106[6] have prescriptions of 74 Gy or higher, but no aorta constraints. The RTOG 1106 eligibility criteria excludes cases with "radiographic evidence of invasion of a large pulmonary artery and tumor causing significant narrowing of that artery," but many cases with tumor in close proximity to the aorta would still meet the criteria, leading to large volumes of the aorta receiving the prescription dose. The 74 Gy dose in conventional fractionation corresponds to 36 Gy in 5 fractions so this could be used as a large-volume aorta constraint for SBRT. Until the interaction of large-volume and small-volume doses are better understood[7-9]; however, it may be prudent to start with $D_{50\%}$ doses in a more conservative range, like an equivalent dose of 25 Gy in 5 fractions, when possible.

Another reirradiation study from Wake Forest School of Medicine with 33 patients had a single grade 5 event with an aorta-esophageal fistula after receiving an estimated aortic 2 Gy equivalent (EQD2) composite maximum dose of 200 Gy.[10] The patient exsanguinated 6 months after the central lung retreatment. The article explained that the aorta received 100% of the prescription in both the 74 Gy in 37 fraction initial course and the 54 Gy in 3-fraction SBRT reirradiation, for a total physical composite dose of 128 Gy, corresponding to EQD2 = 200 Gy, using $\alpha/\beta = 10$ Gy for early effects. If an $\alpha/\beta = 3$ Gy, for late effects had been used instead the EQD2 would have been closer to 300 Gy. The article also provided the time interval among courses, which was 1 year; together all of these details would be very useful in determining more accurate models of reirradiation tolerance when more data emerges.

Maximum point doses as high as 19.7 Gy × 3 fractions to the aorta were reported in a series of 20 patients,[11] treated from 2000-2005 at Tuen Mun Hospital in Hong Kong. Overall, 1 patient received this dose to the aorta and in another case the aortic maximum dose exceeded 10 Gy × 4 fractions. Another patient had a maximum aorta dose more than 8 Gy per fraction and 2 more patients had aorta doses exceeding 6 Gy per fraction; these 3 patients all received 3 fractions. After a median follow-up of 21 months, no aortic toxicity was observed in any of the patients. Although this was a small study with relatively short follow-up, it is commendable that the authors gave such detail of the critical structure doses.

The most comprehensive report to date of major vessel dose distributions involving toxicity from SBRT is the study by Nishimura et al.[12] A cohort of 381 patients received 40-60 Gy in 5 fractions, for centrally located lung tumors, with a median follow-up of 33 months (range: 3-87). The entire dose-volume histogram (DVH) >25 Gy, for 238 major vessels with at least some part exceeding 5 Gy × 5 fractions in 133 patients were plotted, including aorta ($n = 72$), vena cava ($n = 33$), pulmonary artery ($n = 73$), and pulmonary vein ($n = 60$). The pulmonary artery was implicated in 1 grade 3 and 2 grade 5 adverse events, and those 3 DVHs were identified in the article. In both cases, the grade 5 hemoptysis occurred more than a year after the SBRT at the pulmonary artery and bronchus, near the pulmonary hilum. The Nishimura 2014 article provided a detailed table summarizing the median doses and ranges, for each of the major vessels for the cases with and without complications. The 2 patients with grade 5 hemoptysis received high doses at the pulmonary artery (59.2 Gy and 61.3 Gy, respectively).

Clinical Dataset

From July 2008-February 2015, 387 cases with aorta or major vessel contours were treated in 1-5 fractions on CyberKnife (Accuray, Inc., Palo Alto, CA) at MD Anderson Cancer Center at Cooper University Hospital, and loaded into the DVH Evaluator software (DiversiLabs, LLC, Huntingdon Valley, PA) for analysis. Grade 3 or higher complications to major vessels were not observed in any of the cases. Dose calculations for all cases were from the MultiPlan treatment planning system; 363 of the cases used Monte Carlo and 24 of them used Ray Tracing.

The major vessel contours included any involved aorta, vena cava, pulmonary artery, or pulmonary vein, but they were not routinely differentiated, often simply called "major vessels." Therefore, in the aggregate analysis of our data with the Nishimura 2014 data, all of the various major vessels were analyzed together as one. All of the Nishimura 2014 treatments were delivered in 5 fractions, whereas our cases used 3 fractions for 139 cases, 4 fractions for 79 cases, and 5 fractions for 164 cases. The median number of fractions in the aggregate dataset was 5, so all doses were converted to 5 fraction equivalent dose using the LQ model with $\alpha/\beta = 3$ Gy before dose-response modeling.

The most common volumes for aorta constraints in Supplementary Table A1 are 0 (D_{max}), 1 and 10 cc. However, the 3 complications in Nishimura 2014 all occurred with a $V_{25\ Gy}$ less than 10 cc, so a smaller volume than 10 cc had to be used in our analysis; the largest feasible volume for this dataset is 4 cc. Nishimura 2014 also provided data for $V_{25\ Gy}$ and $D_{0.5\ cc}$, so we also extracted those dose-volume descriptors from our own data for the aggregate model. In total, 5 dose-volume descriptors were analyzed: $V_{25\ Gy}$, $D_{4\ cc}$, $D_{1\ cc}$, $D_{0.5\ cc}$, and D_{max}. Equivalent uniform dose was not studied in this analysis, but for other anatomical structures in this issue of Seminars in Radiation Oncology that had clinical data and outcomes (such as esophagus), equivalent uniform dose was also analyzed.

The exponential form of the logistic model[13,14] was chosen because of its stability in a wide variety of circumstances:

$$NTCP = \frac{e^{\left(4g_{50\ v}\left(\frac{D_v}{TD_{50\ v}}-1\right)\right)}}{\left(1+e^{\left(4g_{50\ v}\left(\frac{D_v}{TD_{50\ v}}-1\right)\right)}\right)} \quad (1)$$

where D_V is the dose to a particular dose descriptor, $TD_{50\ v}$ is the corresponding 50% tolerance dose (ie, risk level), and $g_{50\ v}$ is the slope parameter. The minimum $D_{0.5\ cc}$ and $D_{1\ cc}$