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Esophageal Dose Tolerance in Patients Treated With Stereotactic Body Radiation Therapy

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Mediastinal critical structures such as trachea, bronchus, esophagus, and heart are among the dose-limiting factors for stereotactic body radiation therapy (SBRT) to central lung lesions. The purpose of this study was to characterize the risk of esophagitis for patients treated with SBRT and to develop a statistical dose-response model to assess the equivalent uniform dose, $D_{10\%}$, $D_{5\ cc}$, $D_{1\ cc}$, and D_{max}, to the esophagus and the risk of toxicity. Toxicity outcomes of a dose-escalation study of 56 patients who had taken CyberKnife treatment from 45-60 Gy in 3-7 fractions at the Erasmus MC-Daniel den Hoed Cancer Center were utilized to create the dose-response model for esophagus. A total of 5 grade 2 esophageal complications were reported (Common Terminology Criteria for Adverse Events version 3.0); 4 complications were early effects and 1 complication was a late effect. All analyses were performed in terms of 5-fraction equivalent dosing. According to our study, $D_{1\ cc}$ at a dose of 32.9 Gy and D_{max} dose of 43.4 Gy corresponded to a complication probability of 50% for grade 2 toxicity. In this series of 58 CyberKnife mediastinal lung cases, no grade 3 or higher esophageal toxicity occurred. Our estimates of esophageal toxicity are compared with the data in the literature. Further research needs to be performed to establish more reliable dose limits as longer follow-up and toxicity outcomes are reported in patients treated with SBRT for central lung lesions.
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Stereotactic body radiotherapy (SBRT) targets and delivers high, ablative doses of radiation to sites within the body while applying methods to reduce the effects of tumour motion to help assure accuracy and precision. However, caution must be taken if the tumor is close to organs at risk (OAR) of injury such as trachea, mainstem bronchus, esophagus, or heart. Serious complications, including death following bacterial pneumonia, pericardial effusion, radiation pneumonitis, or massive hemoptysis, have been reported.[1,2] Therefore, these tumors are classified into 2 groups—peripheral tumors and central tumors. Although there are several definitions, central tumors are tumors located <2 cm from the trachea, mainstem bronchus, main bronchi, or esophagus, but also are tumors located close to the heart and tumors located in the mediastinum. The tumour-ablative effects of high-dose SBRT for lung cancer can be safely extended to lesions in the central chest if treatment is adapted to reduce the risk to OAR of injury. Several studies have shown that delivering lower doses in 4-10 fractions can reduce toxicity of SBRT in the central chest[3-8] compared with single dose treatment, as doses that are often used in treating peripheral lung lesions can result in serious toxicity and death when delivered to central lesions,[1,2,9,10] or can result in at least a higher rate of toxicity than for peripheral lesions.[11]

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In the treatment of central tumors, one of the important OARs is the esophagus. Several authors have published data on the toxicity to the esophagus with stereotactic treatment,[12-14] however, quantitative estimates of the risk are still unclear. We developed a statistical dose-response model to characterize the risk of esophagitis for stereotactic radiotherapy and we applied the model to several published dose constraints of the esophagus. In this article, we examine and discuss the dose-response models for $D_{5\ cc}$, $D_{1\ cc}$, and D_{max} to the esophagus and we reviewed the literature on the toxicity to the esophagus after SBRT.

Modeling a Clinical Dataset

Central lung tumors in 56 predominantly inoperable patients were treated with the CyberKnife at the Erasmus MC Cancer Institute from July 2006 until September 2009. The dose-escalation study was previously published[15] and 4 acute grade 2 esophageal complications were reported (Common Terminology Criteria for Adverse Events version 3.0), but the dose-response analysis was beyond the scope of the initial publication. Subsequently, an additional grade 2 late effect has occurred in the cohort, bringing the total esophageal complications to 5. No grade 3 or higher esophageal events have been reported in this series.

Dose escalation began with 5 fractions of 9 Gy ($n = 6$), followed by 5 fractions of 10 Gy ($n = 15$) and later to 5 fractions of 12 Gy ($n = 21$). For 14 tumors near the esophagus, 6 fractions of 8 Gy were prescribed. Additionally, a patient received 7 fractions of 8 Gy, and another patient received 3 fractions of 20 Gy. The median number of fractions is 5, so the linear-quadratic model with $\alpha/\beta = 3$ Gy was used to convert each bin of every dose-volume histogram (DVH) to 5-fraction equivalent doses before modeling the dose response.

Among treatment plans for 58 tumors in 56 patients, 46 cases were close enough to the esophagus to warrant delineating the structure, and the corresponding 46 DVHs were analyzed. The modeling was performed in the DVH Evaluator (DiversiLabs, LLC, Huntingdon Valley, PA) software by reducing each DVH into a scalar dose descriptor that is a function of dose and volume, such as the equivalent uniform dose (EUD) given by[16]

$$\mathrm{EUD} = \left(\sum_i D_i^{1/n} \frac{V_i}{V_{\mathrm{tot}}}\right)^n \quad (1)$$

where D_i and V_i are the 5-fraction equivalent dose and volume corresponding to the ith differential DVH bin, V_{tot} is the total volume of the contoured anatomical critical structure, and n is the volume parameter that was fitted to the data. From this, the normal tissue complication probability was estimated using the Lyman-Kutcher-Burman dose-response model by[17,18]

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-x^2/2} dx \quad (2)$$

where $t = (D_V - \mathrm{TD}_{50}(V))/(m \times \mathrm{TD}_{50}(V))$, m is the slope parameter, and D_V is the dose descriptor. The slope m, the volume parameter n, and the tolerance dose $\mathrm{TD}_{50}(V)$ were fitted using maximum likelihood techniques.[19] The slope parameter m can be readily connected to the normalized slope at the 50% response level $\gamma_{50} = D_{50}\partial P/\partial D = (m\sqrt{(2\pi)})^{-1}$.

Other quantities were also investigated as dose descriptors in the same probit model. An extensive literature review found 500 published SBRT dose-tolerance limits,[20] and among these were 29 limits for the esophagus in 1-6 fractions. The most commonly reported limits for esophagus were in terms of $D_{5\ cc}$, $D_{1\ cc}$, and D_{max}, so these 3 quantities were also chosen as dose descriptors D_V for the analysis. To consider relative volume, the $D_{10\%}$ was also included. In summary, the maximum likelihood parameter fitting was used 5 times, on each of the 5 dose descriptors separately, D_V = (EUD, $D_{10\%}$, $D_{5\ cc}$, $D_{1\ cc}$, and D_{max}). The dose-tolerance limits and the normal tissue complication probability estimates from the clinical data were arranged in a DVH Risk Map,[21] which is a graphical and numerical comparison of constraints and risk of complications as a function of dose, volume, and fractionation. The profile likelihood method was used to estimate confidence intervals.[22]

The dose-tolerance limits from the literature review[20] were partitioned into high-risk and low-risk categories. For each dose descriptor, a trendline of the highest available limits was used as the high-risk limits, and a more conservative trendline of the next highest limits in the review were used as the low-risk limits. The actual risk of each selected limit was quantitatively estimated from the dose-response model.

A total of 2 other clinical datasets with esophagus dose-volume data and outcomes from SBRT lung treatments have been published,[23,24] and a similar methodology was used to analyze and compare those results. Wu et al[24] included logistic models for $D_{5\ cc}$ and D_{max}, as well as a DVH atlas, for 125 SBRT cases from Memorial Sloan Kettering Cancer Center. Stephans et al[23] provided $D_{1\ cc}$ and D_{max} data for 52 SBRT cases with targets within 2 cm of the esophagus. No dose-response model was included, but the 2 cases with grade 3 or higher complications were indicated in Figures 1-4 of the article of Stephans et al, so from this information we constructed a logistic model. Pertinent details of the 3 studies are compared in Table 1.

Results

Modeled outcomes for grade 2 esophageal symptoms are displayed in Figure 1, and the fitted parameters are shown in Table 2, all in terms of 5-fraction equivalent doses. Each subplot of the figure corresponds to one of the dose descriptors $D_V = \{D_{10\%}, D_{5\ cc}, D_{1\ cc}, D_{max}\}$, and each of them was modeled independently of the rest. The risk level of any dose-tolerance limit for these dose descriptors can be estimated by using the linear-quadratic model to convert the limit to the desired fractionation and then by interpolating from the analytical modeled curves in Figure 1 and Table 2.

The DVH Risk Map in Figure 2 was created by applying this conversion and interpolation technique to all of the selected dose-tolerance limits from the literature review.[20] For example, Figure 1(B) shows that in the 5-cc model a dose of 19.5 Gy in 5 fractions corresponds to 12.5% risk of grade 2 complications,