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SBRT of lung cancer

Dosimetric predictors of esophageal toxicity after stereotactic body radiotherapy for central lung tumors

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ABSTRACT

Background and purpose: Stereotactic body radiotherapy (SBRT) to central lung tumors can cause esophageal toxicity, but little is known about the incidence or risk factors. We reviewed central lung SBRT patients to identify dosimetric factors predictive of esophageal toxicity.

Materials and methods: We assessed esophageal toxicity in 125 SBRT patients. Using biological equivalent doses with $\alpha/\beta = 10$ Gy (BED_{10}), dose–volume histogram variables for the esophagus (D_v and V_d) were assessed for correlation with grade $\geqslant 2$ acute toxicity.

Results: Incidence of grade $\geqslant 2$ acute toxicity was 12% ($n = 15$). Highly significant logistic models were generated for D_{5cc} and D_{max} ($p < 0.001$). To keep the complication rate <20%, the model requires that $D_{5cc} \leqslant 26.3$ BED_{10}. At 2 years, the probability of complication with BED_{10} $D_{5cc} > 14.4$ Gy was 24%, compared to 1.6% if $\leqslant 14.4$ Gy.

Conclusions: This novel analysis provides guidelines to predict acute esophageal toxicity in lung SBRT. Dose to the hottest 5cc and D_{max} of the esophagus were the best predictors of toxicity. Converting the BED_{10} limits to physical doses, D_{5cc} to the esophagus should be kept less than 16.8, 18.1 and 19.0 Gy for 3, 4, and 5 fractions, respectively, to keep the acute toxicity rate <20%.

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Stereotactic body radiotherapy (SBRT) has revolutionized the non-operative management of early-stage non-small cell lung cancer (NSCLC) due to its excellent local control, particularly compared to conventionally fractionated radiation therapy [1]. Lung SBRT has been associated with relatively modest rates of significant toxicity [1]. However, seminal work by Timmerman et al. revealed disproportionately and unacceptably high rates of severe pulmonary toxicity when delivering high-dose-per-fraction SBRT to tumors near the proximal bronchial tree [2]. As a result, subsequent trials of lung SBRT have generally excluded tumors in this location.

A multicenter, phase I/II dose-escalation trial of SBRT for central lung tumors has recently completed accrual, but results are not yet available [3]. Until then, many centers including ours have opted to treat carefully selected patients with central lung tumors using more conservative fractionation schemes, with fraction sizes on the order of 6–12 Gy instead of 18–20 Gy. Retrospective reports have indicated acceptably low rates of severe pulmonary toxicity with such risk-adapted schemes [4–8]. However, SBRT in this anatomic region often also results in high dose to other critical structures besides the lungs, notably the heart and the esophagus.

Esophageal toxicity, including esophagitis, stricture or perforation, is a well-known complication of radiotherapy involving the mediastinum, such as for NSCLC or esophageal cancer. Dose guidelines to predict and minimize the risk of esophageal toxicity are available for conventional RT [9]. However, these guidelines cannot be readily extrapolated to SBRT, because the relationship between fraction size and esophageal toxicity is largely unknown. Furthermore, whereas mean dose to the whole esophagus is commonly used to evaluate risk of toxicity in conventional RT, SBRT is associated with much smaller target and esophageal volumes and therefore it is less likely that a mean dose constraint would be clinically robust. Although ongoing SBRT trials stipulate dosimetric guidelines for esophageal dose [3], firm data to justify these guidelines do not yet exist.

Our institution has extensive experience treating lung tumors in the central lung zone with SBRT. We therefore reviewed our experience with the aim of characterizing the nature and incidence of esophageal toxicity. In addition, we undertook a quantitative dosimetric analysis with the specific aim of identifying dosimetric parameters that may predict esophageal toxicity.

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Materials and methods

Patient selection

Institutional review and privacy boards approved this study, and patient confidentiality was maintained as required by the Health Insurance Portability and Accountability Act. Institutional databases were queried to identify all patients receiving SBRT to tumors within the lung, including metastases as well as primary NSCLC. SBRT was defined as fraction size of 600 cGy or greater and delivered in five fractions or fewer, using linear accelerators with on-board CT guidance. Patients who had received prior radiotherapy to the thorax were excluded, as were patients receiving synchronous RT to two or more lesions within the lung. Radiation treatment plans were reviewed to identify patients with central lung tumors, as defined by one of the following two criteria: (1) tumor within 2 cm of the proximal bronchial tree (the definition utilized in the RTOG 0236 trial, also known as the "no-fly-zone"), or (2) planning target volume (PTV) intersecting mediastinal structures (the definition used in the RTOG 0813 trial).

Radiation technique

Our SBRT technique has been previously described [10]. Typically, patients underwent simulation with custom immobilization using an Alpha Cradle (Smithers Medical Products, North Canton, OH). A 2 mm reconstructed CT slice thickness was used, as well as a four-dimensional CT (4DCT) scan to characterize the degree of respiratory motion. The tumor was contoured on all respiratory phases to generate an internal target volume (ITV). This was then expanded by 2–3 mm to account for subclinical spread and generate a clinical target volume (CTV). The CTV was uniformly expanded by 5 mm in all directions to generate a PTV. An IMRT plan was generated using custom in-house treatment planning software, and dose was prescribed to the 100% isodose line (IDL). PTV coverage was kept as homogeneous as possible, with tolerance of a hotspot up to 110% of the prescription dose. Per our institutional guidelines, the maximum point dose to the esophagus was to be kept $\leqslant$30 Gy, unless the PTV overlapped with esophagus, in which case up to 45 Gy in 5 fractions was allowed. Four to 7 co-planar 6 MV beams were typically used to deliver an IMRT plan prescribed to the 100% IDL covering the PTV. Cone-beam CT guidance was used at each fraction to ensure accurate patient setup. Patients were treated every other weekday. Patients were followed up 1 month after completion of SBRT, then every 3 months for the first 2 years and every 6–12 months thereafter.

A wide variety of fractionation schemes were prescribed, at the discretion of the treating physician (see Table 1). Most commonly, patients who had been identified by the treating physician as having high-risk tumors due to central location were treated in five fractions of 9 or 10 Gy each, which is our current institutional practice. In other cases, higher doses per fraction and 3 or 4-fraction schemes were utilized, typically because the tumor was not considered "central" by the treating physician. Less aggressive fractionation schemes (e.g. 3000 cGy in 5 fractions) were also sometimes employed based on the clinical scenario, or in some cases because treatment was delivered at a time when institutional guidelines for SBRT dose had not yet been implemented.

Dosimetric analysis

The primary endpoint was grade 2 or greater esophageal toxicity (E2), as defined by the Common Terminology Criteria for Adverse Events, version 4.0. We included all events occurring during RT or within 120 days of its completion. Only one instance of E2 occurred outside of this timeframe and was significantly later (371 days after RT), therefore we limited our dosimetric analysis to acute and subacute events only ($E2_a$). Esophageal contours were reviewed in all patients and where necessary, revised to ensure that the outer wall of the entire organ was contoured, starting from the cricoid cartilage and extending to the gastroesophageal junction. The proximal bronchial tree and no-fly-zone (NFZ) were also contoured according to RTOG 0236 guidelines in all patients, and treatment plans reviewed to identify all patients with lung tumors inside the NFZ. As noted above, tumors outside the NFZ, but with the PTV abutting mediastinal structures, were included in the analysis.

Table 1
Patient and treatment characteristics ($N = 125$).

Characteristic	No. of patients
Disease	
Primary NSCLC	91
Recurrent NSCLC	12
Lung metastasis	22
Median age at diagnosis, years (range)	76 (32–95)
Sex	
Male	62
Female	63
Dose	
60 Gy in 3 fx ($BED_{10} = 180$)	4
54 Gy in 3 fx ($BED_{10} = 151.2$)	9
48 Gy in 4 fx ($BED_{10} = 105.6$)	21
36 Gy in 2 fx ($BED_{10} = 100.8$)	1
50 Gy in 5 fx ($BED_{10} = 100$)	14
44 Gy in 4 fx ($BED_{10} = 92.4$)	1
45 Gy in 5 fx ($BED_{10} = 85.5$)	56
40 Gy in 4 fx ($BED_{10} = 80$)	2
36 Gy in 3 fx ($BED_{10} = 79.2$)	1
40 Gy in 5 fx ($BED_{10} = 72$)	6
30 Gy in 5 fx ($BED_{10} = 48$)	7
Other	3
Median PTV size, cm^3 (range)	63.0 (17.3–401.7)
Median GTV size, cm^3 (range)	13.1 (0.6–195.4)

Abbreviations: BED_{10}, biologically equivalent dose for $\alpha/\beta = 10$; PTV, planning treatment volume; GTV, gross tumor volume; Gy, gray; fx, fraction.

Due to the wide range of fractionation schemes used, doses were converted into biological equivalent doses, using $\alpha/\beta = 10$ Gy (BED_{10}) since the analyzed esophageal events were acute. However, to validate this choice of α/β and to check the dependence of α/β in our results, the analysis was repeated for α/β values between 0.1 and 30 Gy, in steps of 0.1 Gy.

Two primary dose–volume variables were assessed for their correlation to the primary endpoint: D_v, in which D is the minimum dose to the hottest absolute esophageal volume v; and V_d, in which V is the absolute esophageal volume exposed to at least the dose d. These variables were calculated from each patient DVH, and correlation with toxicity was assessed using logistic regression and Cox proportional hazards modeling. Models were constructed for D_v with $0 < v < 180$ cc in steps of 1 cc, and for V_d with $0 < d < 75$ BED_{10}. Based on the variables that were determined to be significant, log-rank tests were then performed using the median splits for each variable.

In view of the controversy in applicability of the linear-quadratic (LQ) model to treatment regimens using doses per fraction >10 Gy, we also examined Cox models based on D_v using physical dose, and multivariate Cox models based on D_v (physical dose) and fraction number. These were compared with the models based on D_v (BED_{10}) using the Akaike Information Criterion (AIC).

For the purposes of future data synthesis [11,12], dose–volume atlases of the incidence of $E2_a$ [13,14], based on physical dose to the esophagus, are provided in a Microsoft Excel file in electronic Appendix A1 for each number of fractions separately. The format of this file is described in electronic Appendix A2.