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Analysis of pneumonitis and esophageal injury after stereotactic body radiation therapy for ultra-central lung tumors

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Abstract

Objectives: SBRT has been associated with serious toxicity in ultra-central lung tumors, but little is known about the incidence and dosimetric correlates of pulmonary and esophageal complications in this setting.

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Conflict of Interest Statement

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Materials and Methods: We retrospectively reviewed SBRT patients whose lung tumor abutted proximal airways, or whose planning target volume overlapped esophagus. All patients received 5 to 15 fractions of high-dose, image-guided radiation. The primary endpoint was SBRT-related toxicity, with local control and survival as secondary endpoints.

Results: We included 88 patients. Nineteen patients (22%) experienced grade ≥3 (G3+) toxicity, including 6 cases of G3+ radiation pneumonitis and 4 cases of G3+ esophageal injury. Two patients developed trachea-esophageal fistula. Overall incidence of radiation pneumonitis was 23%. Ten patients (11.4%) succumbed to SBRT-related complications. Multiple dosimetric parameters for lung (including mean lung dose and $V20_{Gy}$) and esophagus (including maximum point dose) correlated with radiation pneumonitis and esophageal toxicity, respectively. No impact of fractionation on toxicity was seen.

Conclusion: This analysis indicates that high rate and multiple manifestations of pulmonary and esophageal toxicity after SBRT for ultra-central tumors. In particular, severe radiation pneumonitis and tracheoesophageal fistula are possible. Dosimetric parameters such as mean lung dose and maximum esophageal dose are significantly correlated with toxicity. Further study is needed to optimize the safe delivery of SBRT in these patients.

Keywords

non-small cell lung cancer; SBRT; SABR; ultracentral; toxicity

1. Introduction

Stereotactic body radiation therapy (SBRT) is widely used for early-stage non-small cell lung cancer (NSCLC) or lung metastases, with 2-year local control ranging from 80% to 97%[1, 2]. However, an early trial indicated that patients with centrally located lung tumors, within 2cm of the proximal bronchial tree (PBT), had increased risk for severe pulmonary toxicity [3]. A very wide range of toxicity rates after SBRT for central tumors has been reported, but studies often utilize different definitions of “central,” as well as different fractionations[4-6].

Patients with tumors directly abutting PBT, known as “ultra-central,” are now widely suspected to be at especially high complication risk, and we recently reported that antiangiogenic agents may potentiate fatal pulmonary hemorrhage in this group[7, 8]. A recent multi-center trial suggests the maximum tolerated SBRT dose for central tumors is 12Gy x 5, but this study did not include many ultra-central patients[9].

Besides pulmonary hemorrhage, there also exists concern for other significant complications such as radiation pneumonitis, esophagitis, and tracheoesophageal fistula in these patients. Here we report toxicity and tumor control outcomes, with a focus on pneumonitis and esophageal injury, in a large cohort of ultra-central SBRT patients.

2. Material and methods

2.1 Patient and Treatment Characteristics

The Institutional Review and Privacy Boards approved this study, and patient confidentiality was maintained as required by the Health Insurance Portability and Accountability Act. An institutional, prospectively maintained database was queried to identify patients with NSCLC or lung metastases between 2008 and 2017. We defined “ultra-central” as gross tumor volume (GTV) abutting the PBT, or planning tumor volume (PTV) overlapping the esophagus. All patients received 5-15 fractions of image-guided radiotherapy with biologically effective dose $(BED)_{10}$ ≥84 Gy. Patients were followed with chest CT every 3 months for the first 2 years, and every 6 to 12 months thereafter.

Our SBRT technique has been previously described, and utilizes custom immobilization with 4-dimensional CT for motion management [5]. Target volumes were created with a 2-3mm CTV margin and an additional 5mm PTV margin. Patients were treated with intensity-modulated RT (IMRT) or volumetric arc therapy (VMAT) using 6MV photons and cone-beam image verification at each fraction. To ensure consistency of dosimetric analysis, all plans were recalculated using the Eclipse AAA algorithm. PTV underdosage was allowed to avoid exceeding organ at risk (OAR) constraints. Normal tissue constraints for different fractionations are detailed in Supplementary Table 1.

2.2 Toxicity and dosimetry analysis

Pulmonary, esophageal, cardiac, and chest wall toxicities were scored using Common Terminology Criteria for Adverse Events (CTCAE), version 4. Local failure was defined as progression or recurrence in the originally radiated lesion as defined by CT, PET-CT, or biopsy. We extracted maximum point doses (Dmax), minimum doses received by 2.5cc and 5cc ($D_{2.5cc}$ and D_{5cc}) of PBT and esophagus, mean lung dose, and lung volume receiving 20 Gy or more (V_{20Gy}).

Wilcoxon Rank Sum tests were used to compare dosimetric parameters by toxicity status for G2+ radiation pneumonitis and G2+ esophageal toxicity. Kaplan-Meier method was used to assess G3+ toxicity-free survival and overall survival. A univariate Cox model was built to assess factors associated with G3+ toxicity-free survival including RT fractionation (5 vs. 8 vs. 15 fractions). Local failure was evaluated by cumulative incidence with competing risk of death. A competing risk regression model was constructed to determine factors associated with local failure. All analysis was done using RStudio 3.4.0.

3. Results

3.1 Patient characteristics

88 patients were included in the analysis; 76 patients had GTV abutting PBT and 23 had PTV overlapping esophagus. Median follow-up time was 19.5 months. Forty-six patients had primary NSCLC, 7 had locally recurrent NSCLC and 35 had lung metastases of non-lung origin. Their median age was 74 years (range 25-91) and 44% were male. One-third (n=29) had baseline COPD. 42 (48%) patients received a prescription BED_{10} ≥ 100Gy.

Patients were treated with 9-10Gy × 5 (n=54), 7.5Gy × 8 (n=13) or 4Gy × 15 (n=21). Median GTV size was 25cc and median PTV size was 103cc.

3.2 Toxicity

Nineteen patients (21.6%) experienced G3+ toxicity, one had G4 toxicity and 10 had G5 toxicity. One-year G3+ toxicity-free survival was 79.2% (95%CI 70.6-89.0%). Age, gender and RT fractionation were not significantly associated with G3+ toxicity-free survival. Patients treated with antiangiogenic agents had a trend toward lower G3+ toxicity-free survival (hazard ratio (HR) 2.1, P=.19). Table 1 describes G3+ toxicity in detail.

10 patients (11%) had likely (n=6) or possible (n=4) RT-related death (see Supplementary Table 2). Four deaths were attributed to likely (n=1) or possible (n=3) radiation pneumonitis, ranging from 2.4 to 8.2 months after RT. All four patients had chronic obstructive pulmonary disease (COPD). The patient with likely fatal radiation pneumonitis had baseline interstitial lung disease. The bilateral lung V_{20} in these patients ranged from 8.8 to 11.8%, well within our institutional limits. Six patients were considered as having likely (n=5) or possible (n=1) fatal pulmonary hemorrhage (range: 7.2 to 13.0 months after RT). Maximum BED_3 doses to PBT ranged from 160 to 257 Gy.

One patient developed G4 dyspnea 11.3 months after radiation, associated with necrosis and stenosis of the distal trachea that required mechanical ventilation. Five patients experienced G3 radiation pneumonitis (RP) 1.3 to 7.6 months after RT for which hospitalization was required. Only one had pre-existing COPD. Two patients developed G3 dyspnea; one was attributed to main bronchus occlusion and lung atelectasis. The other was attributed to tracheobronchial perforation and pneumomediastinum; this patient had antiangiogenic treatment before and after RT. G2+ RP occurred in 23 (27%) patients.

One patient whose GTV abutted esophagus developed acute G3 esophagitis, and one patient developed a bleeding esophageal ulcer requiring endoscopic intervention; this patient's PTV did not overlap with esophagus and the maximum esophageal dose was 16.5Gy over 5 fractions. Two patients developed tracheoesophageal fistula (TEF) 13.8 and 11.3 months after treatment; both patients' GTV abutted trachea and PTV overlapped esophagus. One of these patients received bevacizumab before and after SBRT until the toxicity occurred. Among the 23 patients with PTV overlapping esophagus, 9 (39%) developed G2+ esophageal toxicity, including 3 (13%) patients with G3 esophageal toxicity.

3.3 Dosimetric analysis

Multiple metrics of lung dose were significantly higher in patients with radiation pneumonitis (Table 2). In particular, ipsilateral lung V_{20Gy}; ipsilateral, contralateral, and total mean lung dose; and total lung V_{20Gy} were significantly higher in patients who developed G2+ RP compared to those who did not. For example, median ipsilateral lung V20 was 24.6% in RP patients compared to 18.6% in non-RP patients (p=0.001). Dose to PBT (Dmax, D2.5cc and D5cc) was not significantly different between patients with and without G5 pulmonary hemorrhage.

Multiple metrics of esophageal dose were found to be significantly higher in patients with esophageal toxicity. Patients with G2+ esophageal toxicity received higher esophageal $D_{max\text{-}BED3}$, $D_{2.5cc\text{-}BED3}$ and $D_{5cc\text{-}BED3}$ (Supplementary Table 3) than those without esophageal toxicity. The median esophageal $D_{max\text{-}BED3}$ in patients with G2+ esophageal injury was 146.3 vs. 78.4 in patients without esophageal injury (p=0.015).

3.4 Local control and survival

Median follow-up for living patients was 19.6 months. The 1 and 2-year rates of local failure were 12.2% (95%CI, 5.1-19.4%) and 19.0% (95%CI, 9.7-28.3%), respectively. At last follow-up, fifteen patients experienced local failure. On univariate analysis, age, gender, smoking history, histology, stage, GTV volume, prescription BED (<100Gy vs. ≥100Gy) were not significantly associated with local control (Supplementary Table 4). For patients with primary and locally recurrent NSCLC, median survival was 38.6 months (95% CI, 28.7-not reached); their 1, 2 and 3- year OS rates were 78.6%, 64.5% and 53.1%, respectively.

4. Discussion

This is one of the largest reported series of patients who received SBRT for ultra-central lung tumors, defined as tumors directly abutting the PBT. We recently reported an excessive risk of fatal hemorrhage when these patients were also exposed to antiangiogenic agents, and we note that one case of tracheoesophageal fistula described here was also associated with antiangiogenic exposure. This fuller analysis demonstrates that other significant toxicities, including fatal ones, also occur at a significant rate, likely due to the extreme proximity of the PBT and esophagus.[7, 10] In contrast, other previous studies of ultra-central patients did not uniformly describe excessive toxicity, though this may be partly due to more permissive definitions of “ultra-central” and to the use of lower-BED regimens.

The high incidence of pneumonitis (27%), including 5% fatal cases, is the most striking new finding of this analysis. This suggests that ultra-central tumor location entails additional pulmonary risks in addition to airway hemorrhage. Notably, the four fatal pneumonitis cases were not associated with unusually high lung doses, but one patient had baseline interstitial lung disease and all four had COPD. This suggests a need for caution when treating patients with significant pulmonary comorbidity.

Esophageal toxicity is another pertinent risk in this anatomic location. The risk of grade≥3 esophageal toxicity was 13% in patients whose PTVs overlapped the esophagus, and two cases of tracheoesophageal fistula occurred. Further study and dosimetric analysis in more patients are warranted to identify and validate predictors for severe pneumonitis and esophageal toxicity in these patients.

Our cohort is unique for including a variety of fractionation schemes, including two schemes (7.5Gy x 8 and 4Gy x 15) which have been employed specifically as risk-adapted prescriptions for higher-risk central NSCLC. Yet we did not identify any significant correlation of fractionation with toxicity in our cohort. However, the limited numbers and

non-randomized nature of our study preclude definitive conclusions about whether altering fractionation may have a protective effect in these patients.

Though these results call for caution and further study when considering SBRT for ultra-central lung tumors, the clinical context is important to remember. Radiation is often employed in ultra-central locations because no other local modality is feasible. Lowering radiation doses, while possibly safer, also would be less likely to achieve durable local control in these situations where tumor progression itself often leads to severe morbidity or even mortality.

Other limitations of our study should be taken into account. The retrospective scoring of toxicity and treatment-related death has inherent drawbacks, as not all SBRT-related toxicity may be captured in the medical record. The attribution of specific toxicities to SBRT is also often unclear, particularly respiratory symptoms which often can be caused by coexisting pulmonary comorbidities.

5. Conclusions

To our knowledge, this series contains the largest number of SBRT patients whose tumors directly abutted the proximal bronchial tree, and the high incidence of severe toxicity suggests that direct abutment of PBT, not merely close proximity, is the most pertinent criterion to define “ultra-central” as a high-risk group. Severe pneumonitis, in addition to pulmonary hemorrhage, should be considered a potential grave complication of SBRT in this setting. Extreme caution is also warranted when treating tumors very near the esophagus, as tracheoesophageal fistula is possible.

Overall, we conclude that use of high-dose SBRT in such patients should be undertaken with the utmost discretion, while also acknowledging that local progression in these locations may be highly morbid and unlikely to be controlled by any other local modality. Further study is needed to establish SBRT techniques that achieve the optimal therapeutic ratio in these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- SBRT for ultra-central lung tumors can lead to severe pulmonary and esophageal toxicity
- There was a 24% rate of radiation pneumonitis, and a 5% rate of fatal pneumonitis
- Severe esophageal toxicity including tracheo-esophageal fistula was observed
- Multiplew metrics of lung and esophageal dose correlate with pulmonary and esophageal complications, respectively

Table 1.

Details of grade 3 or higher toxicity

Grade	Toxicity	No. Patient (%)	Time after RT (months)
Grade≥ 3	In total	19 (22)	
Grade 3	Pulmonary		
	Radiation pneumonitis	5 (6)	1.3-7.6
	Main bronchi occlusion	1 (1)	7.1
	Tracheobronchial perforation	1 (1)	12.4
	Esophageal/ Trachea		
	Esophagitis	1 (1)	0.7
	Esophageal bleeding	1 (1)	0.3
	Tracheo-esophageal fistula	2 (2)	11.3, 13.8
	Fatigue	1 (1)	1
	Chest wall pain	1 (1)	2.33
Grade 4	Tracheal necrosis	1 (1)	11.3
Grade 5	Hemoptysis	6 (7)	7.2-13.0
	Radiation pneumonitis	1 (1)	2.4
	Respiratory failure	3 (3)	6.9-8.2

Table 2.

Dosimetric comparison between patients with and without G2+ radiation pneumonitis (mean values)

Factor	Overall (N=88)	No (N=64)	Yes (N=24)	p-value
Ipsilateral lung V20 (%)	20.1 (4.3, 64.0)	18.6 (4.3, 52.6)	24.6 (11.9, 64.0)	0.001
Ipsilateral lung mean dose (cGy)	1055 (314, 3428)	958 (314, 2524)	1304.5 (715, 3428)	0.001
Contra lung V20 (%)	0 (0, 30.2)	0 (0, 4.73)	0 (0, 30.2)	0.445
Contra lung mean dose (cGy)	250 (49, 1443)	215.5 (49, 580)	317 (133, 1443)	0.028
Overall lung V20 (%)	9.9 (2.3, 29.1)	9.1 (2.3, 27.4)	12.93 (6.6, 29.1)	<.001
Overall lung mean dose (cGy)	655 (203, 1599)	561.5 (203, 1555)	807 (475, 1599)	<.001