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Clinical Investigation

Esophageal Dose Tolerance to Hypofractionated Stereotactic Body Radiation Therapy: Risk Factors for Late Toxicity

Kevin L. Stephans, MD,* Toufik Djemil, PhD,* Claudiu Diaconu, MD,† Chandana A. Reddy, MS,* Ping Xia, PhD,* Neil M. Woody, MD,* John Greskovich, MD,* Vinit Makkar, MD,‡ and Gregory M.M. Videtic, MD, CM, FRCPC*

**Department of Radiation Oncology, Cleveland Clinic, Taussig Cancer Center, Cleveland, Ohio; †Cleveland Clinic Learner College of Medicine, Cleveland, Ohio; and ‡Department of Medical Oncology, Cleveland Clinic, Taussig Cancer Center, Cleveland, Ohio*

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Summary

We retrospectively reviewed esophageal dosimetry in lung and liver stereotactic body radiation therapy (SBRT) patients for correlation with late grade ≥3 toxicity. Significant late toxicity was seen in select patients receiving point doses greater than 50 Gy, and 1-cc doses greater than 45 Gy, although other patients tolerated these doses without toxicity. Patients with toxicity were noted to have received both high esophageal radiation dose as well as adjuvant vaso-endothelial growth-factor (VEGF) modulating agents in close temporal proximity.

Purpose: To identify factors associated with grade ≥3 treatment related late esophageal toxicity after lung or liver stereotactic body radiation therapy (SBRT).

Methods and Materials: This was a retrospective review of 52 patients with a planning target volume within 2 cm of the esophagus from a prospective registry of 607 lung and liver SBRT patients treated between 2005 and 2011. Patients were treated using a risk-adapted dose regimen to a median dose of 50 Gy in 5 fractions (range, 37.5-60 Gy in 3-10 fractions). Normal structures were contoured using Radiation Therapy Oncology Group (RTOG) defined criteria.

Results: The median esophageal point dose and 1-cc dose were 32.3 Gy (range, 8.9-55.4 Gy) and 24.0 Gy (range, 7.8-50.9 Gy), respectively. Two patients had an esophageal fistula at a median of 8.4 months after SBRT, with maximum esophageal point doses of 51.5 and 52 Gy, and 1-cc doses of 48.1 and 50 Gy, respectively. These point and 1-cc doses were exceeded by 9 and 2 patients, respectively, without a fistula. The risk of a fistula for point doses exceeding 40, 45, and 50 Gy was 9.5% (n = 2/21), 10.5% (n = 2/19), and 12.5% (n = 2/16), respectively. The risk of fistula for 1-cc doses exceeding 40, 45, and 50 Gy was 25% (n = 2/9), 50% (n = 2/4), and 50% (n = 2/4), respectively. Eighteen patients received systemic therapy after SBRT (11 systemic chemotherapy, and 6 biologic agents, and 1 both). Both patients with fistulas had received adjuvant anti-angiogenic (vascular endothelial growth factor) agents within 2 months of completing SBRT. No patient had a fistula in the absence of adjuvant VEGF-modulating agents.

Conclusions: Esophageal fistula is a rare complication of SBRT. In this series, fistula was seen with esophageal point doses exceeding 51 Gy and 1-cc doses greater than 48 Gy.

Reprint requests to: Kevin L. Stephans, MD, Radiation Oncology, T28, 9500 Euclid Ave, Cleveland, OH 44195. Tel: (216) 445-8285; E-mail: stephak@ccf.org

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Notably, however, fistula was seen only in those patients who also received adjuvant VEGF-modulating agents after SBRT. The potential interaction of dose and adjuvant therapy should be considered when delivering SBRT near the esophagus.

Introduction

Stereotactic body radiation therapy (SBRT) provides excellent local control in the management of both lung and liver tumors (1-4). Even with the use of very high biologically equivalent treatment doses, lung and liver toxicity reported to date for these parallel target organs appears minimal. There are however serial structures in direct proximity to some tumors, potentially susceptible to toxicity from hypofractionated radiation, even when the volume of tissue exposed to high dose is carefully controlled.

Previous studies have identified a risk of toxicity to the airway, brachial plexus, ribs, and chest wall (5-9). After some early toxicities, the modern adoption of risk-adapted dosing strategies has demonstrated the safety of appropriate treatment strategies in higher-risk locations (10-14), and a nearly completed prospective multicenter dose-escalation trial, Radiation Therapy Oncology Group (RTOG) 0813, has provided some potential normal tissue constraints for consideration when treating tumors near sensitive central structures (5).

Toxicity in most central SBRT series has been mild, with most reports describing only occasional esophagitis; however, significant esophageal toxicity including fistula and perforation have been described in both spine and lung SBRT patients (14-16). Although the relationship of dose, volume, fractionation, and systemic therapy in regard to toxicity has been well defined for conventionally fractionated radiation (17-19), the interplay of these effects is still being defined for SBRT. This report examines our institutional experience with SBRT for tumors in proximity to the esophagus, with a goal of defining risk factors for significant toxicity such as fistula and perforation.

Methods and Materials

This is a retrospective review of an institutional review board–approved registry of 578 lung (499 primary and 78 oligometastasis) and 29 liver patients treated with SBRT between February 2005, and December 30, 2011. We limited our analysis to patients for whom the planning target volume (PTV) fell within 2 cm of any portion of the esophagus, leaving 48 lung tumors (46 primary and 2 oligometastatic) and 4 liver tumors (3 hepatocellular carcinoma and 1 oligometastatic lung cancer).

Lung cancer patients were treated on a Novalis platform (BrainLAB, Feldkirchen, Germany) using abdominal compression adjusted under fluoroscopy to limit tumor excursion. Radiation dose and fractionation followed a risk-adapted schedule at the discretion of the treating radiation oncologist. PTV was constructed from a 5-mm expansion of internal target volume (ITV) created by multiphase as well as 4-dimensional computed tomography in all cases, and radiation was delivered on consecutive days. Daily localization was performed by the combination of the ExacTrac stereotactic body system (BrainLAB) and orthogonal port films.

Liver patients were treated on either a Synergy S (Elekta, Stockholm, Sweden), or Novalis TX platform (Varian, Palo Alto, CA), using respiratory gated treatment delivery. Patients were simulated with Active Breathing Control (ABC, Elekta, Stockholm, Sweden) and CT scans acquired during gated native, arterial, and venous scan phases after IV administration of 100 cc contrast to reconstruct a tri-phasic CT under respiratory gated conditions. PTV was constructed as a 5- to 7-mm expansion of the ITV from the union of the 3 gated planning computed tomograms. Radiation dose and fractionation followed a risk-adapted schedule at the discretion of the treating radiation oncologist, with radiation typically delivered on consecutive days. Daily localization was performed by free-breathing cone beam computed tomography (CBCT) aligned with the spine, followed by respiratory gated orthogonal films through February 2011, and thereafter ExacTrac spine localization followed by respiratory gated CBCT with soft-tissue (liver and PTV) alignment.

All planning esophageal contours were reviewed retrospectively for accuracy. As defined by RTOG 0236, the esophagus was contoured from the lower border of the cricoid cartilage to the gastro-esophageal junction for lung patients, and from the highest available CT slice to the gastro-esophageal junction for liver patients.

Patients were followed 6 to 8 weeks after SBRT, then every 3 months thereafter with CT imaging and clinical assessment at each visit. Positron emission tomography scans were obtained when imaging or clinical findings suggested the possibility of recurrence. Esophageal toxicity was scored according to the Common Terminology Criteria for Adverse Events version 3.0, looking for any toxicity possibly related to treatment of the esophagus.

We assessed patient, tumor, and treatment factors for their potential relationship with esophageal toxicity in this series. Patient factors included age, gender, and performance status (KPS). Tumor factors included single dimension size of the tumor, gross target volume (GTV), PTV, and stage. Treatment factors included radiation dose, radiation fractionation, esophageal mean dose, esophageal point dose (D0.01 cc), 1-cc esophageal dose (D1cc), and 5-cc esophageal dose (D5cc), as well as administration of systemic therapy (conventional chemotherapy or biologically targeted therapy) either before or after SBRT.

The primary endpoint was development of late grade ≥ 3 esophageal toxicity. As the number of observed events was

Table 1 Patient characteristics (N=52)

Characteristic	All patients	Lung (n=48)	Liver (n=4)
Age, y, median (range)	73.5 (42-90)	74 (42-90)	54.5 (45-80)
KPS, median (range)	80 (60-90)	80 (60-90)	80 (70-90)
Gender, female	59.6%	60%	50%
Tumor size, cm, median (range)	3.0 (0.8-11.9)	3.0 (0.8-7.1)	6.7 (4.9-11.9)
Stage, n (%)			
Stage IA lung cancer	25 (48%)	25 (52%)	N/A
Stage IB lung cancer	20 (38%)	20 (42%)	N/A
Stage IIA lung cancer	1 (1.9%)	1 (2.1%)	N/A
Hepatocellular carcinoma	3 (5.8%)	N/A	3 (75%)
Oligometastasis	3 (5.8%)	2 (4.2%)	1 (25%)
Treatment schedule, n (%)			
37.5 Gy in 3 fractions	2 (3.8%)	N/A	2 (50%)
48 Gy in 4 fractions	2 (3.8%)	1 (2.1%)	1 (25%)
50 Gy in 5 fractions	30 (58%)	30 (63%)	N/A
50 Gy in 10 fractions	14 (27%)	13 (27%)	1 (25%)
60 Gy in 8 fractions	4 (7.7%)	4 (8.3%)	N/A

Abbreviations: KPS = Karnofsky Performance Status; N/A = not applicable.

small (n=2), formal statistical analysis of association was not believed to be appropriate; however, the relationship of potentially associated factors was plotted. Survival curves were created by Kaplan-Meier method.

Results

We identified 48 lung tumors and 4 liver tumors from a registry of 607 SBRT patients for which the treated PTV fell within 2 cm of the esophagus as the focus of this analysis. For lung tumor, histology was non-small cell lung cancer (NSCLC) in 34 patients, radiographic diagnosis only in 9, small cell in 2, oligometastasis in 2 (renal cell and colon cancer), and broncho-alveolar in 1 patient. For liver tumors, histology was hepatocellular carcinoma in 3 patients, and metastatic NSCLC in 1 patient. Of the patients, 31 (59.6%) were female; the median age was 74 years (range, 42-90 years), and the median Karnofsky Performance Status was (KPS) 80 (range, 60-90). Median tumor size was 3 cm overall, with the median size of lung tumors of 3 cm (range, 0.8-7.1 cm), and the median size of liver tumors 6.7 cm (range, 4.9 to 11.9 cm). Patient characteristics are summarized in Table 1.

The median SBRT dose was 50 Gy in 5 fractions, although a range of regimens were used; 50 Gy in 5 fractions (30 patients), 48 Gy in 4 fractions (2 patients), 37.5 Gy in 3 fractions (2 patients), 50 Gy in 10 fractions (14 patients), and 60 Gy in 8 fractions (4 patients).

The median values for esophageal D0.01 cc, D1 cc, and D5 cc were 32.3 Gy (range, 8.9-55.4 Gy), 24 Gy (range, 7.8-50.9 Gy), and 15.7 Gy (range, 1.3-38 Gy, with 3 patients exceeding the RTOG 0813 recommendation of keeping 5 cc below 27.5 Gy). The esophageal mean dose ranged from 2.02 to 15.93 Gy (mean, 5.53 Gy). Individual esophageal D0.01 cc (Fig. 1) and D1 cc (Fig. 2) are plotted.

Given previous reports of toxicity in combination with systemic agents, as well as note of adjuvant vascular endothelial growth factor (VEGF)–modulating agents in our 2 patients with significant late toxicity, we stratified these by patients receiving systemic chemotherapy and VEGF-modulating agents. Of the patients, 27 did not receive systemic therapy, whereas 25 did. Fifteen patients received chemotherapy before SBRT (11 within 12 months before SBRT), and 12 received adjuvant chemotherapy. Seven patients received VEGF-modulating agents (4 patients received Bevacizumab, 2 Sorafenib, and 1 Sunitinib). Five received VEGF-modulating agents before SBRT (4 within 12 months before SBRT), and 3 adjuvantly (1 Bevacizumab, 1 Sorafenib, 1 Sunitinib). Two additional patients received adjuvant Erlotinib, and 1 patient received an adjuvant poly-adenosine diphosphatase ribose polymerase (PARP) inhibitor. Individual esophageal D0.01 cc

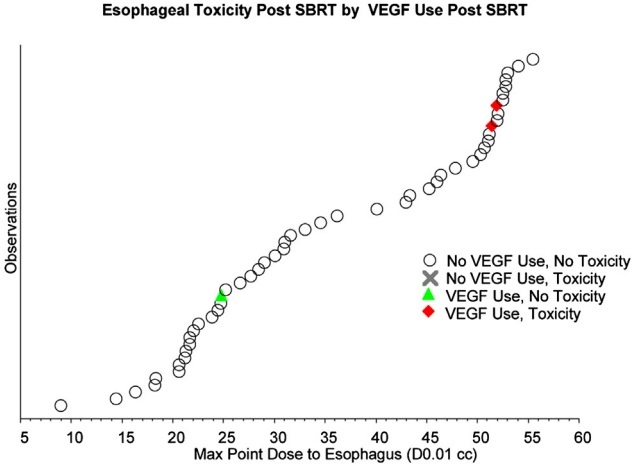

Fig. 1. Esophageal toxicity by maximum esophageal point dose and post–stereotactic body radiation therapy vascular endothelial growth factor use.

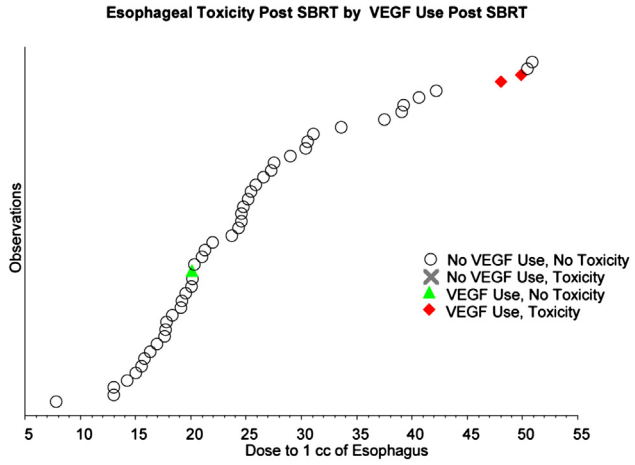

Fig. 2. Esophageal toxicity by dose to 1 cc of esophagus and post–stereotactic body radiation therapy vascular endothelial growth factor use.

(Fig. 3) and D1 cc (Fig. 4) are plotted stratified by systemic therapy use.

Median follow-up for living patients was 22.6 months (range, 5.1-54.5 months). Median overall survival was 20.7 months, and median progression-free survival 18.3 months. Six patients experienced local failure, 5 regional nodal failure, and 11 distant failure. In no case did local failure contribute to esophageal toxicity. Severe late esophageal toxicity was experienced by 2 patients (3.7%), at a median time of 8.4 months after SBRT. No additional late toxicities were noted.

Discussion

Overall, full-dose definitive intent SBRT to target volumes in proximity to the esophagus was well tolerated in this

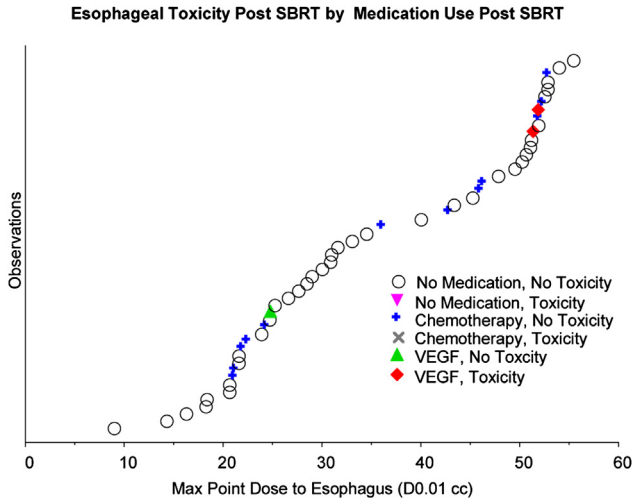

Fig. 3. Esophageal toxicity by maximum esophageal point dose and post–stereotactic body radiation therapy systemic therapy use.

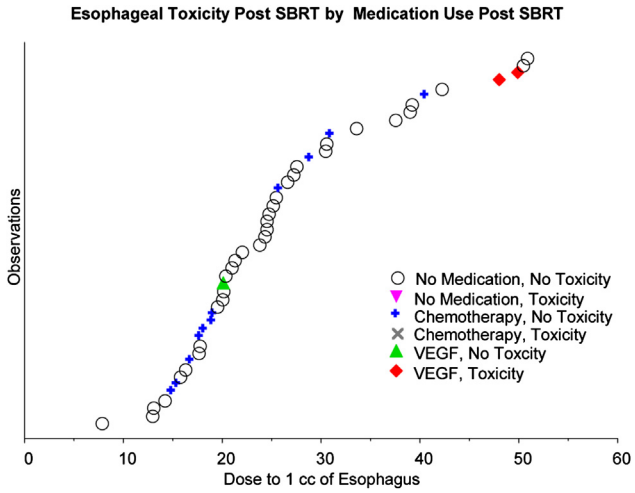

Fig. 4. Esophageal toxicity by dose to 1 cc of esophagus and post–stereotactic body radiation therapy systemic therapy use.

review, although in 2 cases significant toxicity were noted. Because of the limited number of events, no formal statistical analysis to identify cut-points could be done; however, some conclusions can be drawn from the descriptive data.

First, it is notable that no significant late esophageal toxicity occurred when the esophageal point dose was less than 50 Gy (37 patients) and the 1-cc dose was less than 45 Gy (48 patients). This correlates overall with RTOG 0813 constraints in which point dose was restricted to 105% of the prescription dose (5). It is possible that point dose should be restricted to 100% of the prescription dose rather than 105%, as we did see toxicity in 2 of 15 patients (13%) with maximum point doses beyond 100% of prescription dose, with toxicity occurring at D0.01 cc of 51.5 and 52 Gy (both below the RTOG constraint); however, it is also plausible that the combination of high esophageal dose and use of adjuvant VEGF-modulating agents led to toxicity in these 2 patients. If one restricts the analysis to patients receiving radiation with no adjuvant VEGF agents, no significant late toxicity developed in the entire series despite esophageal point dose exceeding 50, 52.5, and 55 Gy (100%, 105%, and 110% of prescription dose) in 13 patients, 6 patients, and 1 patient, respectively. A precedent for tolerability of high esophageal point-doses exists in high-dose rate (HDR) brachytherapy literature as well; for instance, a French report describes a median surface dose of 58.2 Gy over 6 weekly applications delivered to a median length of 8.3 cm of esophagus in 13 patients treated with HDR alone, and 62 to 65 Gy in 12 more patients treated with external beam radiation therapy (EBRT) HDR brachytherapy (20). Although 1 fistula was observed in the EBRT + HDR patients (in conjunction with local tumor progression), patients given HDR alone tolerated therapy well, despite median surface doses of greater than 58 Gy.

When looking at dose to 5 cc of esophagus, toxicity was seen in patients receiving 21.5 and 37.3 Gy, respectively.

On the other hand, 6 patients also received 5-cc doses greater than 21.5 Gy without toxicity (21.7, 23.2, 23.6, 30.0, 35.0, and 38.0 Gy), with toxicity developing in 1 of 4 patients above the RTOG 0813 5-cc dose limit of 27.5 Gy (5). It is interesting to note the development of toxicity both in a patient with a sharp dose gradient (D0.01 cc 52 Gy with D5 cc 21.5 Gy, both just below RTOG 0813 constraints), as well as a broader gradient (D0.01 cc 51.5 Gy with D5 cc 37.3 Gy, only the 5-cc dose violating RTOG 0813 constraints). It is unclear whether it is purely the effect of dose in these patients, or the interaction with VEGF-modulating agents that mediated toxicity.

Other published series investigating esophageal tolerance to SBRT include a Memorial Sloan Kettering (MSKCC) series of 204 patients with spinal metastasis abutting the esophagus receiving a median PTV dose of 24 Gy in a single fraction (16), as well as a Stanford report of 31 spine or lung tumors within 1 cm of the esophagus treated with a variety of SBRT dosing schedules (15). With regard to demonstration of a threshold for toxicity, this study is quite similar to the MSKCC and Stanford data. In the MSKCC series, grade $\geq$3 toxicity was extremely rare until the single fraction esophageal dose to 2.5 cc exceeded 15 Gy, at which point toxicity rose sharply with increasing dose. The Stanford series showed a similar threshold with the 2 high-grade events occurring at single fraction biological equivalents (by linear quadratic method) of 14.2 and 18.1 Gy to 2.0 cc of esophagus. Although the toxicity in the Stanford series was sometimes seen below previously reported thresholds, it was observed at doses at least very close to threshold. We used multiple fraction regimens; however, our data similarly demonstrated a threshold with no toxicity seen when the esophageal point dose was less than 50 Gy (37 patients) and the 1-cc dose was less than 45 Gy (48 patients).

Chemotherapy was notably cited as correlated with the development of high-grade esophageal toxicity in both the Stanford and MSKCC series. There was no evidence of such a relationship in our series, with only 1 of 21 patients who were receiving some form of chemotherapy experiencing significant late toxicity. That patient received both pre- and post-SBRT chemotherapy in combination with Bevacizumab and high-dose radiation with a broad gradient (D0.01 cc 51.5 Gy with D5 cc 37.3 Gy), and toxicity in this case is likely multifactorial. A potential explanation for the different effect of chemotherapy in these series is that the Stanford series particularly suggested risk for radiation recall—related agents such as doxorubicin and gemcitabine. None of our patients received these agents, instead being treated predominately with platinum doublets owing to the majority diagnosis of non-small cell lung cancer in our population. This may suggest the relative safety of platinum doublets without commenting on the risk of recall-related agents; however, the number of treated patients across all of the published series is still too small to draw a firm conclusion.

Although there is insufficient experience for a definitive conclusion, the high proportional rate of toxicity for patients receiving VEGF-modulating agents in our series demands attention despite the small numbers of patients involved. Many of these agents are associated with gastrointestinal fistula when given alone or in combination with fractionated radiation, and their combination with high-dose hypofractionated radiation should be carefully considered. A recent report from the Mayo Clinic noted serious bowel injuries in 7 of 20 patients (9%) receiving VEGF-modulating agents within 13 months of completing SBRT (5 of 7 within 3 months), compared to no bowel injuries in 63 patients not receiving VEGF active agents (21). With increasing use and indications for both hypofractionated stereotactic radiation therapy and an expanding array of VEGF-modulating agents, an increasing number of patients could potentially be affected by the combination of these therapies, and attention should be paid to potential interactions.

In conclusion, this retrospective review of hypofractionated SBRT to target volumes near the esophagus was found to be safe until esophageal doses approached the prescription dose. No significant late esophageal toxicity occurred when the esophageal point dose was less than 50 Gy (37 patients) and the 1-cc dose was less than 45 Gy (48 patients). Although our dose-fractionation schedule varied using a risk-adapted approach, both high-grade toxicities occurred in patients receiving 50 Gy in 10 fractions (5 Gy/fx), and we would expect that patients receiving higher dose-per-fraction regimens would be at equal or greater risk with similar dosimetry. High-grade late toxicity was seen in patients above these thresholds, although notably only in conjunction with the administration of VEGF-modulating agents in proximity to SBRT. In contrast to previous series, no clear association of cytotoxic chemotherapy with esophageal toxicity was seen, although, by virtue of patient populations, our series contained predominately platinum doublets compared to more classically recall-associated agents in other series. More data are needed to further establish safe esophageal dose thresholds, as well as the potential interaction of hypofractionated radiation with a range of conventional and targeted systemic agents.

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