Jour. of Radiosurgery and SBRT, Vol. 6, pp. 83-89
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Clinical Investigation

Dose-response modeling the risk of carotid bleeding events after stereotactic body radiation therapy for previously irradiated head and neck cancer

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(Received: November 24, 2018; Accepted: January 15, 2019)

ABSTRACT

Given the lack of clear dose constraints for the carotid artery, we created dose-response models to better quantify the risk of carotid bleeding events following re-irradiation stereotactic body radiation therapy (SBRT) for head and neck cancer (HNC). We performed a retrospective analysis on 75 patients treated with SBRT for recurrent, previously irradiated HNC. Logistic dose-response models were created to predict the risk of a carotid bleeding event, defined as any mucosal bleeding event or bleeding resulting from rupture of the carotid artery or its major branches in the setting of controlled disease. According to the models, the risk of a carotid bleeding event with a cumulative $D_{0.1cc}$ of 20 Gy from SBRT is 0.8% (95% CI 0.1%-3.9%), and rises to 5.0% with a $D_{0.1cc}$ of 50 Gy. No patient experienced a carotid bleeding event with $D_{0.1cc}$ < 39.4 Gy, and none experienced carotid blowout syndrome with a cumulative $D_{0.1cc}$ < 47.6 Gy.

Keywords: SBRT, re-irradiation, head and neck cancer, dose-response, carotid blowout syndrome

BACKGROUND

Stereotactic body radiation therapy (SBRT) has been increasingly used as a treatment option for recurrent, previously irradiated head and neck cancer. Early retrospective reports suggested higher rates of carotid blowout syndrome (CBOS) after SBRT compared with conventional re-irradiation techniques (1-3), although factors which significantly reduce the risk of CBOS after SBRT have since been identified, such as prolonging the treatment delivery schedule to every-other-day as opposed to daily fractions, and avoiding SBRT in patients with skin invasion or ulceration (4-6). Other factors that have been reported to potentially increase risk of CBOS include >180° carotid involvement and carotid artery dose >100% of prescription dose (2, 3),

although adoption of these criteria to exclude patients for SBRT has been variable across institutions. Currently, no validated dose constraints for the carotid artery exist to guide treatment planning. Due to the increasing interest in SBRT for previously irradiated head and neck cancer, a better understanding of the dose tolerance of the carotid artery in this setting is warranted. We previously reported on carotid dosimetry for a cohort of patients treated at our institution (7), but were unable to identify a significant association between carotid dose and CBOS using time-dependent Kaplan Meier analysis. Given the lack of clear dose constraints for the carotid artery, we sought to create more detailed dose-response models to better quantify the risk of any-grade carotid bleeding events following re-irradiation SBRT.

METHODS AND MATERIALS

We retrospectively reviewed 186 patients with recurrent, previously irradiated head and neck cancer of any histology treated between January 2008 and March 2013. Of these, 75 patients with 150 carotid arteries had complete dosimetry data available and were included for analysis. Patients treated early in our experience with incomplete dosimetry data or treated with <5 fractions to doses <40 Gy were excluded. Patients were treated with conventional linear accelerator-based SBRT to a median dose of 44 Gy (range: 40-50 Gy) in 5 fractions delivered every other day. The majority (87.3%, n = 62) of patients with squamous cell carcinoma received concurrent cetuximab (administered at a loading dose of 400 mg/m2 on day −7, followed by 250 mg/m2 on days 0 and +8) with SBRT. Our treatment planning and delivery process has been previously described (7). At our institution, no specific dosimetric constraints for the carotid artery were used in treatment planning. Patients were not excluded for SBRT based on extent of carotid involvement.

The bilateral common, internal, and external carotid arteries 2 cm above and below the PTV were contoured retrospectively for each patient. Dose-response models were created based on the 75 cases with complete dosimetry data using the DVH Evaluator software (DiversiLabs, LLC, Huntingdon Valley, Pa) (8). The following logistic model was utilized:

$$NTCP = \frac{1}{1+(TD50v\,/\,Dv)^{k}}$$

where TD50v is the 50% risk level for dose-descriptor Dv, and the slope at Dv = TD50v is k/(4*TD50v). In this study, the Dv parameters were dose corresponding to 0.1 cc of carotid artery ($D_{0.1cc}$), 1cc (D_{1cc}) and 2cc (D_{2cc}), as well as mean carotid dose (D_{mean}) from re-irradiation SBRT. For patients who received more than one course of re-irradiation SBRT, the cumulative carotid doses from fused summary plans of all SBRT treatments were recorded. Due to inconsistent availability of prior records over a variable and often long re-irradiation interval, dose from prior external beam radiation was not included. The outcome analyzed was carotid bleeding events, defined as any mucosal bleeding event or CBOS. CBOS was defined as rupture and hemorrhage from the carotid artery or its major branches after re-irradiation in the absence of residual or progressive local disease.

RESULTS

The median follow-up was 8 months for all 75 patients included for analysis, and 37 months for surviving patients (range: 31-91 months). The median re-irradiation interval was 20 months (range: 3-423 months), and the median prior external beam radiation dose was 70 Gy (range: 52.5-140 Gy). Eight patients (10.7%) received more than one course of SBRT. More detailed patient and treatment characteristics for this cohort of patients have been previously published (7). Of the 75 patients, a total of 4 (5.3%) patients experienced carotid bleeding events, including 2 with CBOS events which were both fatal. One patient was treated to a midline stoma recurrence, and subsequently presented with bleeding from his stoma site resulting in hemoptysis, which was stabilized with embolization. He had received a $D_{0.1cc}$ of 39.4 Gy to the right carotid artery and 48.6 Gy to the left carotid artery. For the purposes of logistic modeling, this patient was conservatively coded as experiencing a carotid bleeding event bilaterally; therefore, the models have 5 scored complications in 4 patients. One patient developed buccal mucosa bleeding after his second course of SBRT requiring embolization; he had received a cumulative $D_{0.1cc}$ of 75 Gy to the carotid artery on the affected side. The remaining two patients, who both experienced CBOS, had received a $D_{0.1cc}$ of 47.6 Gy and 48.4 Gy, respectively. **Table 1** shows the treatment characteristics and event details for the 4 patients who had a carotid bleeding event.

Figure 1A, B, C, and D display the logistic models for $D_{0.1cc}$, D_{01cc}, D_{2cc}, and D_{mean}, respectively. According to the logistic models, the risk of a carotid bleeding event with a $D_{0.1cc}$ of 20Gy is 0.8% (95% CI 0.1%-3.9%), whereas the risk is 2.7% (95% CI 0.8%-6.5%) with a D_{1cc} of 20 Gy, and 4.0% (95% CI 1.5%-8.2%) with a D_{2cc} of 20 Gy. The risk is reduced to 0.2% with a

Table 1. Disease and treatment characteristics of patients with carotid bleeding events

Patient	Original Primary Site	Original Dose	Number of SBRT Courses	Re-irradiation interval (months)	Site of Recurrence	SBRT dose	Time from SBRT to Bleed (months)	Type of Carotid Bleed	Management	Carotid D0.01cc	Carotid D1cc	Carotid D2cc	Carotid Dmean
8	Oral cavity	64 Gy	3	EBRT to 1st SBRT: 33.1 1st to 2nd SBRT: 8.2 2nd to 3rd SBRT: 3.2	1st: Oral cavity (left buccal mucosa) 2nd: Submental neck and left parapharyngeal space 3rd: Left infratemporal fossa	1st course: 44 Gy 2nd course: 44 Gy 3rd course: 44 Gy	12.7 (time from 1st SBRT)	Mucosal bleeding (left buccal mucosa)	Embolization of carotid artery branches	75 Gy*	28.3 Gy*	10.1 Gy*	12.6 Gy*
179	Larynx	70.5 Gy	1	37.5	Stoma	44 Gy	11.4	Stoma bleeding	Embolization of carotid artery branches	Left: 48.6 Gy Right: 39.4 Gy	Left: 37.5 Gy Right: 28.9	Left: 10.5 Gy Right: 11.8 Gy	Left: 18.2 Gy Right: 13.0 Gy
18	Paranasal Sinus	70.2 Gy	1	44.3	Right neck	44 Gy	10.9	Carotid blowout	Embolization of right common carotid artery	47.6 Gy	42.5 Gy	22.1 Gy	18.4 Gy
165	Larynx	70.5 Gy	1	18.6	Larynx	44 Gy	4.5	Carotid blowout	Resuscitation then made CMO after anoxic brain injury	48.4 Gy	45.4 Gy	41.0 Gy	26.6 Gy

SBRT = stereotactic body radiation therapy. EBRT = external beam radiation therapy. CMO = comfort measures only. *Cumulative carotid dose across all SBRT treatments.

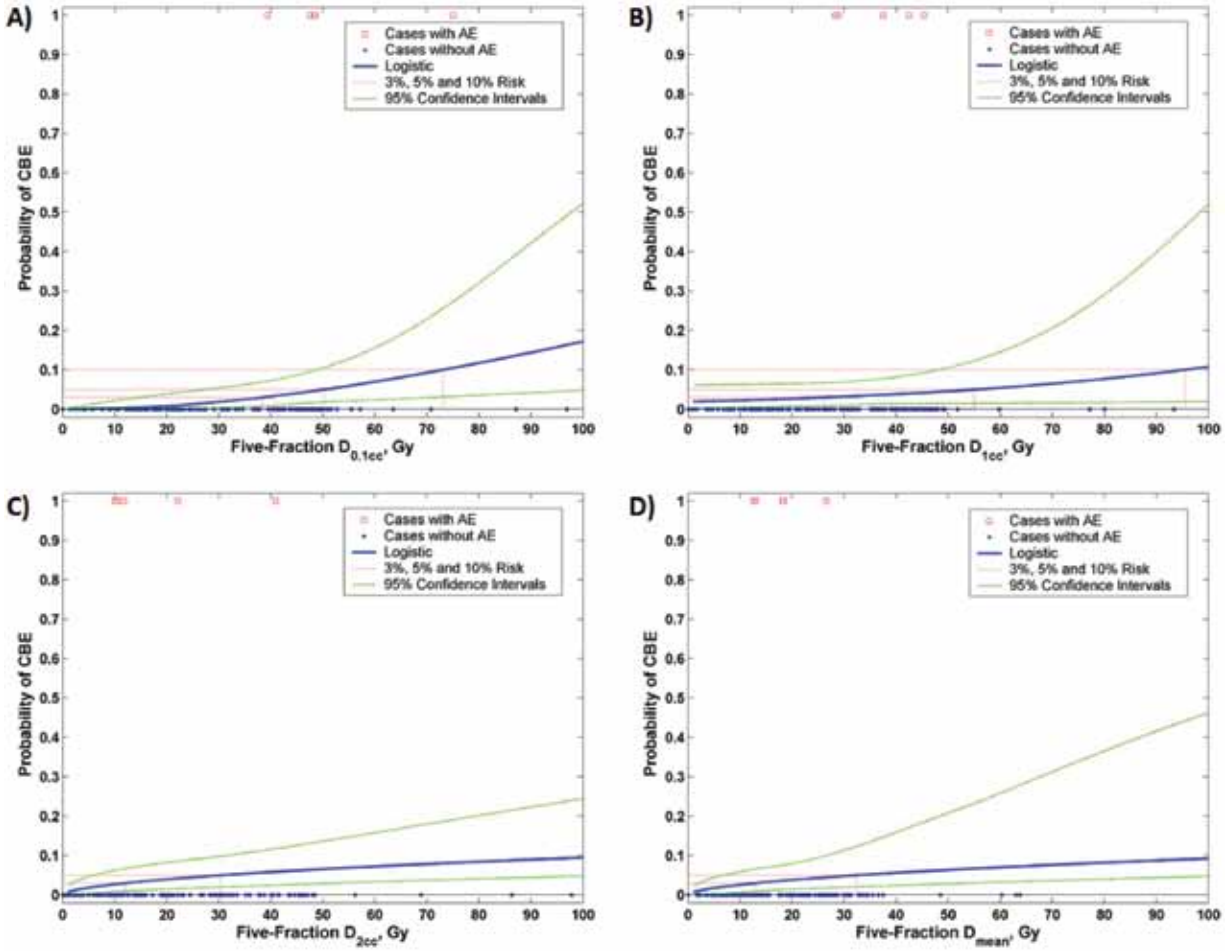

Figure 1. Logistic models of carotid artery dose-tolerance: (A) $D_{0.1cc}$, (B) D_{1cc}, (C) D_{2cc}, (D) D_{mean}. CBE = carotid bleeding event. AE = adverse event.

$D_{0.1cc}$ of 10 Gy, but rises to 5.0% with a $D_{0.1cc}$ of 50 Gy, a value that may be reached when a patient receives more than 1 course of SBRT. Similarly, the risk of a bleeding event is reduced to 1.8% with a D_{2cc} of 5 Gy, but rises to 5.0% with a D_{2cc} of 30 Gy. No patient experienced a carotid bleeding event with a cumulative $D_{0.1cc}$ < 39.4 Gy, D_{1cc} < 28.3 Gy, or D_{2cc} < 10.1 Gy. No patient experienced CBOS with a cumulative $D_{0.1cc}$ < 47.6 Gy. **Table 2** shows the risk of a carotid bleeding event according to $D_{0.1cc}$, D_{1cc}, and D_{2cc} based on the logistic model.

DISCUSSION

Carotid blowout syndrome is a rare but usually fatal complication of re-irradiation SBRT for recurrent HNC. Herein, we have used logistic modeling techniques to quantify the relationship between carotid artery dose and risk of a carotid bleeding event following re-irradiation SBRT for recurrent head and neck cancer. We had previously identified a trend toward greater risk of bleeding events with increasing $D_{0.1cc}$, but were unable to identify a specific cut-off (7). A recently published study from Turkey using logistic modeling techniques similar to ours found that a maximum dose to the internal carotid of <34 Gy appears to significantly reduce the risk for CBOS (9). However, the patients in that study were treated with 5-fraction SBRT to a median dose of 30 Gy. In contrast, the patients in our study were treated with much higher SBRT doses of 40 to 45 Gy over 5 fractions, and thus our study offers valuable insight into carotid artery tolerance within this higher dose range. This is important because doses below 35 Gy may be suboptimal for disease control. We have previously reported a dose-volume response relationship with local control that became prominent above 35 Gy (10). The HyTEC working group subsequently

Table 2. Estimated risk of carotid bleeding event as a function of cumulative SBRT dose and volume in 5 fractions

Dose (Gy)	Volume (cc)	Risk (%)
10	0.1	0.2%
10	1	2.2%
10	2	2.7%
20	0.1	0.8%
20	1	2.7%
20	2	4.0%
50	0.1	5.0%
55	1	5.0%
30	2	5.0%

published a Probit model highlighting the steep dose relationship across 35 to 45 Gy in 5-fraction equivalents (11), and a recently published AAPM working group report confirmed superior local control and possibly overall survival with doses of 35 to 45 Gy in 5 fractions compared with <30 Gy, and recommended doses of 40 to 50 Gy for re-irradiation SBRT (12). In addition, there was a confounding variable of an admixture of daily vs. every-other-day fractionation schedules used in the Turkish study, whereas our patients were all treated on an every-other-day schedule with the intent to minimize the risk of CBOS. Our modeling results, based on our experience with re-irradiation SBRT spanning 5 years with long-term median follow-up of 37 months among surviving patients, are an important contribution to ongoing efforts to better understand the dose tolerance and formulate consistent dose constraints for the carotid artery to guide SBRT treatment planning. This is highly relevant given the increasing interest in utilizing re-irradiation SBRT in the cooperative group setting, as reflected in the upcoming NRG KEYSTROKE trial examining SBRT plus pembrolizumab for locally recurrent HNC.

Of the four dose-volume descriptors analyzed, we identified $D_{0.1cc}$ as the strongest predictor of a carotid bleeding event. As can be seen in Figure 1A, $D_{0.1cc}$ is associated with the most prominent slope curve. According to the logistic model, the absolute risk remains extremely low at less than 1% if the cumulative $D_{0.1cc}$ from SBRT is limited to 20 Gy, which represents roughly the 50% isodose line. Unfortunately, a subset of patients fail locally multiple times and may require multiple courses of re-irradiation SBRT. We found that the risk of carotid bleeding rises to 5.0% with a $D_{0.1cc}$ of 50 Gy, a value that may be reached when a patient receives more than 1 course of SBRT. Indeed, one patient who experienced carotid blowout had received a cumulative $D_{0.1cc}$ of 75 Gy after 3 courses of SBRT. By contrast, the curves for D_{2cc} and D_{mean} are nearly flat, while the slope for D_{1cc} was not as large as for $D_{0.1cc}$. This suggests that D_{1cc}, D_{2cc}, and D_{mean} are not efficient predictors for carotid bleeding and that rather, it is the maximum point dose to a small volume that matters most in increasing the risk of CBOS, congruent with the fact that the carotid artery is a series organ.

No patient experienced any grade carotid bleeding event with a cumulative $D_{0.1cc} < 39.4$ Gy, although a significant portion of patients received a dose higher than this, as the median $D_{0.1cc}$ was 40.8 Gy. This suggests that while limiting the $D_{0.1cc}$ to below 40 Gy resulted in minimal to no risk of bleeding events, we were still able to safely dose escalate far beyond this dose level in the majority of patients, which is important to keep in mind as in certain clinical situations it may be impossible to keep the $D_{0.1cc}$ to below 40 Gy based on tumor location or if the patient has already received multiple prior courses of re-irradiation. Of note, no patients experienced CBOS with a $D_{0.1cc} < 47.6$ Gy.

A potentially important factor is that at our institution, SBRT is delivered on an every-other-day basis as opposed to in daily fractions. Early retrospective reports on re-irradiation SBRT from institutions utilizing a daily fractionation scheme found CBOS rates of 8.4 to 17.3% (2, 3). Later studies have shown lower rates of CBOS within the range of 1 to 4% (13, 1), which may be due in part to a shift toward every-other-day treatment delivery, which appears to be much safer (6, 14). For instance, in one study, increasing the fractionation interval from daily to every-other-day significantly increased the freedom from carotid blowout survival from 9 to 23 months (6). While the risk of CBOS appears to be lower with every-other-day treatments, concern over this potentially fatal complication of re-irradiation SBRT remains a limiting factor in widespread acceptance of this technique. Our logistic model should offer some assurance that when treatment is delivered on alternating days, the risk of CBOS is extremely low especially if the carotid artery $D_{0.1cc}$ is kept below specific parameters.

Avoiding re-irradiation of recurrent tumors encasing more than 1/3 of the carotid artery or tumors with skin infiltration have been suggested as additional ways to minimize the risk of CBOS (6, 15). However, these are commonly factors that preclude patients from definitive surgery, and thus re-irradiation may be such patients' only potentially curative treatment option. At our institution, we do not exclude patients for consideration of re-irradiation SBRT based on either of these factors. Our data suggest that even so, the overall risk of any grade carotid bleeding is low at 5.3%, and can be further reduced when limiting the $D_{0.1cc}$.

As with any dose-response model, our models are limited by the complexity of clinical and dosimetric factors which may contribute to the risk of an adverse outcome, such as delivery technique, dose distribution, and patient factors which may not be captured in the analysis. Due to the rarity of CBOS especially with a modern every-other-day treatment delivery schema, the number of events is low, and thus the model may have a large margin of error. Nevertheless, given the extremely limited data on dose tolerance of the carotid artery in this setting, these models and their associated risk estimates are an important contribution to the ongoing efforts to delineate clearer dose constraints for the carotid artery in the setting of re-irradiation SBRT for HNC, for a patient population with oftentimes few if any alternative treatment options for their recurrent disease.

CONCLUSION

Based on our logistic dose-response models, the risk of any carotid bleeding event following SBRT for recurrent, previously irradiated head and neck cancer is less than 1% with a cumulative $D_{0.1cc}$ of 20 Gy from SBRT. No patient experienced any-grade carotid bleeding event with a cumulative $D_{0.1cc} < 39.4$ Gy, and none experienced CBOS with a cumulative $D_{0.1cc} < 47.6$ Gy. Dose-response models can be used to quantify the relationship between carotid bleeding events and carotid artery dose, even in the context of multiple courses of re-irradiation SBRT.

ACKNOWLEDGEMENTS

Source of Financial Support/Funding: No funding was provided for this project.

Authors' disclosure of potential conflicts of interest

John A. Vargo receives speaking honoraria from BrainLab, outside the submitted work. Other authors have nothing to disclose.

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