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## Carotid Dosimetry and the Risk of Carotid Blowout Syndrome After Reirradiation With Head and Neck Stereotactic Body Radiation Therapy

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### Abstract

**Purpose**—To correlate carotid dose and risk of carotid blowout syndrome (CBOS) after stereotactic body radiation therapy (SBRT), hypothesizing that carotid dose does not correlate with CBOS.

**Methods and Materials**—We retrospectively reviewed 186 patients with recurrent, previously irradiated head and neck cancer treated between January 2008 and March 2013. Patients treated early in our experience with incomplete dosimetry were excluded from analysis (n = 111). A total of 75 patients were identified, providing 150 carotid arteries for analysis. Median follow-up was 8 months (range, 1–91 months) for all patients, and 37 months for surviving patients (range, 31–91 months). Patients were treated with linear accelerator-based SBRT to a median dose up to 44 Gy (range, 40–50 Gy) in 5 fractions delivered on a twice-weekly basis. Concurrent cetuximab was used in 63 patients (84%). The bilateral common, internal, and external carotid arteries were delineated 2 cm above and below the planning target volume. The maximum dose to 0.1 cm<sup>3</sup> (D<sub>0.1cc</sub>), 1 cm<sup>3</sup> (D<sub>1cc</sub>), and 2 cm<sup>3</sup> (D<sub>2cc</sub>) of the carotid and the mean carotid dose from SBRT were recorded and analyzed for association with carotid bleeding events, using binary logistic regression.

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**Results**—Median reirradiation interval was 20 months (range, 3–423 months), and median prior radiation dose was 70 Gy (range, 52.5–140 Gy). Sixteen patients (21.3%) received more than 1 course of SBRT, and the cumulative carotid doses from fused summary plans were recorded. The overall median  $D_{0.1cc}$ ,  $D_{1cc}$ ,  $D_{2cc}$ , and mean carotid doses were 40.8 Gy (interquartile range [IQR], 21.6–47.6 Gy), 26.8 Gy (IQR, 14.1–42.1 Gy), 15.4 Gy (IQR, 8.4–32.7 Gy), and 15.0 Gy (IQR, 8.9–23.3 Gy), respectively. There were a total of 4 bleeding events (5.3%): 2 patients (2.7%) had mucosal bleeds that resolved after embolization of carotid branches, and 2 patients (2.7%) died from complications of CBOS. In the 2 patients with CBOS the  $D_{0.1cc}$  was 48.4 Gy and 47.6 Gy, respectively. There was no significant association between bleeding events and  $D_{1cc}$  ( $P = .280$ ),  $D_{2cc}$  ( $P = .571$ ), or mean dose ( $P = .568$ ). There was a trend toward increased risk of bleeding and  $D_{0.1cc}$  ( $P = .080$ ).

**Conclusions**—These results demonstrate a low risk of bleeding after reirradiation with SBRT when 5 fractions are delivered on nonconsecutive days, even when tumor is completely encasing the carotid artery. Although limited by the low number of events, no significant association was found between dose-volume parameters and the risk of carotid bleeding. No CBOS was noted when  $D_{0.1cc}$  was  $<47.6$  Gy.

## Introduction

Stereotactic body radiation therapy (SBRT) has emerged as a viable treatment modality for patients with unresectable, locally recurrent, previously irradiated head and neck cancer (rHNC) (1). Compared with other modern reirradiation techniques, SBRT offers comparable disease outcomes with shorter treatment time and decreased acute toxicity (2). Limiting the widespread use of SBRT are concerns of carotid blowout syndrome (CBOS), an often fatal complication of head and neck cancer in which the carotid artery or one of its major branches rupture(s) (3). A number of early reports suggested comparatively higher rates of CBOS after SBRT than had been previously reported with conventional reirradiation techniques (3–5). However, with continued study, both tumor- and treatment-related factors have been identified to reduce the risk of CBOS after SBRT, including increasing the length of the treatment delivery period from daily to every other day and avoiding SBRT in patients with skin invasion or tumor-related ulceration (6–8).

Some of the earlier series also noted that the risk of CBOS may be higher in patients with  $>180^\circ$  carotid involvement or carotid artery dose  $>100\%$  of prescription (4, 5). This has prompted some practitioners to exclude patients with carotid encasement from SBRT or aggressively spare the carotid when using SBRT in such patients. Others, including our institutional practice, have not excluded patients from SBRT on the basis of extent of carotid involvement or carotid dose. As the potential outreach of SBRT is expanded into the cooperative group setting, such as the NRG KEYSTROKE trial examining SBRT plus pembrolizumab, consistent factors for patient selection and validated dose constraints to guide treatment planning are needed. Thus, we aimed to correlate carotid dose and risk of CBOS after SBRT, hypothesizing that carotid dose does not correlate with CBOS.

## Methods and Materials

Following appropriate institutional review board approval, we retrospectively reviewed 186 patients with rHNC treated between January 2008 and March 2013 as a part of our prospectively maintained institutional radiosurgery registry. Patients treated early in our experience with incomplete dosimetry or treated with <5 fractions to doses <40 Gy were excluded from analysis, as were patients treated with primary SBRT without prior irradiation. Patients were treated with linear accelerator-based SBRT using Varian Trilogy or TrueBeam treatment platforms (Varian Medical Systems, Palo Alto, CA) to 40 to 50 Gy in 5 fractions delivered on an alternating-day basis (maximum of 3 fractions per week). Patients treated with <40 Gy were excluded, given the importance of doses >35 to 40 Gy noted in prior publications (2, 9). Patients with squamous cell histology also received concurrent cetuximab with SBRT, administered at 400 mg/m<sup>2</sup> on day -7 (loading dose) then 250 mg/m<sup>2</sup> days 0 and +8. Radiation dose selection was based on gross tumor volume (GTV): those >25 cm<sup>3</sup> received 44–50 Gy, and those <25 cm<sup>3</sup> received 40 Gy in 5 fractions (9). Positron emission tomography/computed tomography (CT) or magnetic resonance imaging was used along with contrast-enhanced CT simulation with 1.25-mm slice thickness to define the GTV; the GTV to planning target volume (PTV) expansion included 0 to 5 mm, with no expansion for clinical target volume and no elective nodal irradiation (10). We initially used no margin early in our experience, but review of patients with recurrences after SBRT demonstrated that the addition of a small margin up to 5 mm may reduce the risk of failure, though this can be reduced if there is concern for toxicity to critical structures, such as the spinal cord or carotids (10). Treatment localization included at minimum daily image guidance with cone beam CT imaging, with Brainlab ExacTrack (Brainlab, Munich, Germany) also commonly used daily, especially in patients with lesions close to the base of skull. Patients treated in our previously reported phase 2 study examining SBRT and cetuximab were included in this analysis (11).

Our institutional practices, including our institutional protocols, inclusion criteria, and treatment planning parameters, have not excluded patients on the basis of the extent of carotid involvement, and no specific dosimetric goals were used in treatment planning for the carotid artery. Thus, we retrospectively delineated the bilateral common, internal, and external carotid arteries 2 cm above and below the PTV. The maximum dose to 0.1 cm<sup>3</sup> (D<sub>0.1cc</sub>), 1 cm<sup>3</sup> (D<sub>1cc</sub>), and 2 cm<sup>3</sup> (D<sub>2cc</sub>) of the carotid and the mean carotid dose from SBRT were recorded. Because of the wide capture of our SBRT program and inconsistent recording/changes in treatment planning systems over the often long reirradiation interval, prior radiation therapy dose from external beam radiation was not included in this analysis. However, if patients were treated with multiple courses of SBRT after prior external beam irradiation, the cumulative doses to the carotids from SBRT courses were summated and included for this analysis.

Carotid blowout syndrome was defined as rupture and hemorrhage from the carotid artery or its major branches after reirradiation in the absence of residual or progressive local disease. Other previously established risk factors for CBOS were collected, including contact angle of the tumor with the carotid artery (0°, <180°, 180°, 360°), skin invasion, diagnosis of infection/necrosis (according to imaging), treatment site (mucosal vs neck), presence of

ulceration, and PTV size (5, 6). The carotid dosimetric parameters and other risk factors were analyzed for association with carotid bleeding events using the Kaplan-Meier method and log-rank test for significance for categorical variables and Cox regression for continuous variables. The low number of events limited formation of valid multivariable analysis. Statistical analyses were completed using IBM SPSS, version 23 (IBM, Armonk, NY).

## Results

Of the initial 186 patients identified, a total of 75 patients with complete dosimetric data available were identified, providing 150 carotid arteries for analysis. Median follow-up was 8 months (range, 1–91 months) for all patients and 37 months for surviving patients (range, 31–91 months). Median reirradiation interval was 20 months (range, 3–423 months), and median prior radiation dose was 70 Gy (range, 52.5–140 Gy). Eight patients (10.7%) received more than 1 course of SBRT, and the cumulative carotid doses from fused summary plans were recorded. The median SBRT prescription dose was 44 Gy (range, 40–50 Gy). Complete patient and treatment characteristics are included in Table 1.

The overall median  $D_{0.1cc}$ ,  $D_{1cc}$ ,  $D_{2cc}$ , and mean carotid doses were 40.8 Gy (interquartile range [IQR], 21.6–47.6 Gy), 26.8 Gy (IQR, 14.1–42.1 Gy), 15.4 Gy (IQR, 8.4–32.7 Gy), and 15.0 Gy (IQR, 8.9–23.3 Gy), respectively (Table 2). There were a total of 4 bleeding events (5.3%): 2 patients (2.7%) had mucosal bleeds that resolved after embolization of carotid branches, and 2 patients (2.7%) died from complications of CBOS (Fig. 1). The median time to carotid bleeding events was 12 months (range, 5–13 months). In the 2 patients with CBOS, the  $D_{0.1cc}$  was 48.4 Gy and 47.6 Gy, respectively. There was no significant association between bleeding events and PTV size ( $P = .685$ ),  $D_{1cc}$  ( $P = .280$ ),  $D_{2cc}$  ( $P = .571$ ), or mean dose ( $P = .658$ ). There was a trend toward greater likelihood of carotid bleeding with increasing  $D_{0.1cc}$  (odds ratio 1.03, 95% confidence interval 0.996–1.067,  $P = .080$ ). Additionally, no significant association was found between bleeding events and other baseline risk factors, including male versus female gender ( $P = .286$ ), neck versus mucosal site of recurrent disease ( $P = .624$ ), skin involvement ( $P = .167$ ), diagnosis of necrosis/infection ( $P = .318$ ), presence of ulceration ( $P = .315$ ), or contact angle of tumor with the carotid artery ( $P = .868$ ). Table 1 includes the number of patients with each risk factor experiencing carotid bleeding and the association between bleeding events and risk factors on univariate analyses.

## Discussion

Locoregional recurrence remains the predominant pattern of failure for locally advanced head and neck cancers treated with definitive radiation therapy (12, 13). Although the preferred treatment of rHNC is salvage surgery, the majority of patients are not candidates owing to either extent of local invasion or the presence of comorbidities, and survival rates remain poor (14). Reirradiation with conventional radiation therapy techniques has been shown to provide prolonged survival in some patients, though it is associated with severe acute and late toxicity rates of up to 78% and 37%, respectively (15–17). Modern reirradiation techniques, including intensity modulated radiation therapy and SBRT, have been used in an attempt to improve tumor control and reduce toxicity. Although no

prospective comparisons of these techniques exist, a recent multi-institutional retrospective study demonstrated decreased acute grade 4 toxicity with SBRT and no difference in late effects (2). Although patients in this study with recursive partitioning analysis class II demonstrated improved survival with IMRT, survival was comparable when 35 Gy was delivered with SBRT (18).

Our institutional policy has been to treat patients with unresectable rHNC with SBRT delivered in 5 fractions over 2 weeks with concurrent cetuximab, with demonstrated 1-year locoregional progression-free survival and overall survival rates of 37% and 40%, respectively (11). Other institutions have also demonstrated the efficacy and feasibility of this treatment technique in prospective settings (19, 20). Prior analyses have shown a benefit to dose escalation to at least 40 Gy, on the basis of the volume of recurrence tumor, and this reirradiation technique is the subject of the upcoming NRG KEYSTROKE trial (9).

One of the primary concerns with SBRT for treatment of rHNC has been the possibility of significant late toxicities, which can include dysphagia, osteonecrosis, laryngeal edema/stenosis, and trachea-esophageal fistula (21). Carotid blowout syndrome is a rare but often fatal complication of reirradiation of rHNC that has been reported in 1% to 4% of patients undergoing conventional reirradiation with daily or twice-daily fractionation (3). Early reports of reirradiation with SBRT demonstrated CBOS rates ranging from 8% to 17%, raising serious concerns with the feasibility of this modality (4, 5). Some previously identified risk factors have included carotid encasement  $>180^\circ$  by tumor, skin invasion, presence of ulceration, diagnosis of infection/necrosis, treatment of neck recurrences, and increased PTV size (5–7). A later analysis, however, demonstrated that CBOS rates can be reduced substantially by delivering 5 fractions in an every-other-day course, which may allow for increased sublethal damage repair of normal tissues compared with daily irradiation (8).

In the present study we demonstrate an overall 5.3% risk of carotid bleeding events, including patients with bleeds of minor branches of the carotid that resolved after embolization. Only 2 patients (2.6%) in our cohort experienced true CBOS, a figure that is comparable to reported CBOS rates with conventional reirradiation (3). We sought to examine the potential association of dosimetric parameters on carotid bleeding, as well other previously established risk factors. A total of 75 patients were investigated, providing 150 carotid arteries for analysis, and no significant association was found between bleeding risk and any of the established baseline risk factors as well as the  $D_{0.1}$ ,  $D_{1cc}$ ,  $D_{2cc}$ , or mean carotid dose. It should be noted, however, that in the 2 patients with CBOS the  $D_{0.1}$  values were 48.4 Gy and 47.6 Gy, which does exceed the typical marginal prescription dose. This suggests that although it is not necessary to avoid treating patients with complete carotid encasement provided an every-other-day fractionation scheme is used, it may be reasonable to avoid a hot spot within the carotid artery because no CBOS was noted when  $D_{0.1cc}$  was  $<47.6$  Gy. Carotid artery  $D_{0.1cc} < 47.6$  Gy represents a potential constraint to guide application of SBRT for future clinical trial design.

Some limitations of this study include its retrospective nature and unavoidable problems with patient selection bias. Additional toxicities may have been underreported in patients

who were eventually lost to follow-up, though our minimum follow-up time of 31 months among living patients exceeds the normal interval at which CBOS occurs (3). Summary plans were created in patients who underwent multiple courses of SBRT, though registration errors are inevitable when fusing head and neck plans with significant time intervals between treatment courses. The fact that we were not able to confirm previously identified risk factors for CBOS could be due to the overall low number of events, which also limited multivariable analysis. Notwithstanding these limitations, our extensive experience does corroborate these results indicating a low risk of bleeding after reirradiation with SBRT when 5 fractions are delivered on nonconsecutive days, even when tumor is completely encasing the carotid artery. Though no significant associations with bleeding risk and dose parameters were found, both patients suffering CBOS received a carotid  $D_{0.1cc}$  of at least 47.6 Gy. We would caution against allowing an excessive hot spot within the carotid artery, as a note of precaution. As the utilization of SBRT for reirradiation of rHNC continues to expand and future cooperative group protocols are planned, these data can help to guide future patient selection and dose constraints.

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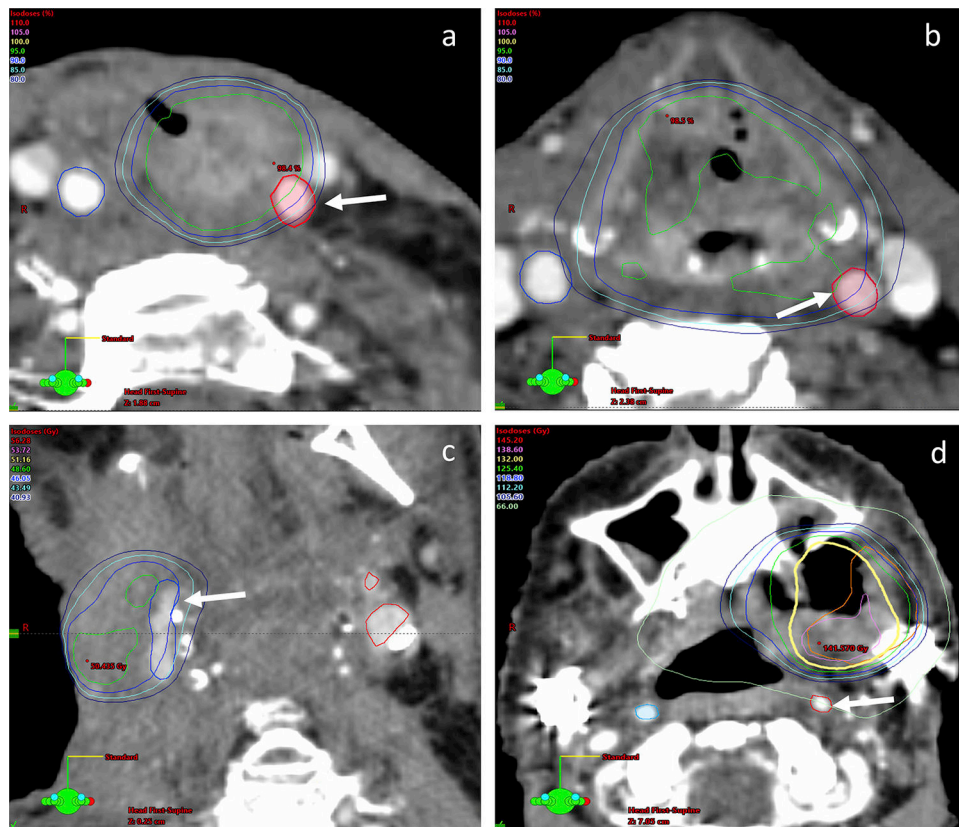
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### Summary

Stereotactic body radiation therapy has emerged as a viable treatment option for recurrent head and neck cancers after prior irradiation, though carotid dose constraints are not defined. The maximum dose to 0.1 cm<sup>3</sup>, 1 cm<sup>3</sup>, and 2 cm<sup>3</sup> of the carotid and the mean dose were analyzed for association with bleeding. No significant association was found between dose-volume parameters and risk of carotid bleeding, and no CBOS was noted when D<sub>0.1cc</sub> was <47.6 Gy.





**Fig. 1.** Axial view of treatment plans in patients with carotid bleeding events, with solid white arrows indicating carotid artery. (a) Stereotactic body radiation therapy (SBRT) plan of a 59-year-old man treated with a single course of SBRT (44 Gy in 5 fractions), who developed a mucosal bleed that stabilized after embolization. (b) Plan of a 64-year-old man treated with a single course of SBRT (44 Gy in 5 fractions), who developed rupture of the right carotid. (c) Plan of a 67-year-old man treated with a single course of SBRT (44 Gy in 5 fractions), who died after right carotid rupture. (d) Summary plan of a 70-year-old woman treated with 3 courses of SBRT (44 Gy in 5 fractions each), who developed bleeding that stabilized after embolization.

Table 1

## Patient and treatment characteristics

Factor	Number	Percentage	Carotid bleed, n (%)	Association of factor with carotid bleeding (P)
Age (y), median (IQR)	65 (57–72)	-	-	.978
Sex				.286
Male	46	61.3	3 (6.5)	
Female	29	38.7	1 (3.4)	
Prior surgery				.235
Yes	50	66.7	0 (0)	
No	25	33.3	4 (8)	
Concurrent cetuximab				.430
Yes	63	84.0	4 (6.4)	
No	12	16.0	0 (0)	
Interval from EBRT to SBRT (mo), median (IQR)	20 (8.6–56.25)	-	-	.477
Courses of SBRT				.352
1	67	89.3	3 (4.5)	
2	5	6.7	0 (0)	
3	3	4.0	1 (33.3)	
Site of recurrence				.624
Mucosal	46	61.3	2 (4.3)	
Neck	29	38.7	2 (6.9)	
Carotid encasement with tumor				.868
0°	59	78.7	1 (1.7)	
>0°, 180°	4	5.3	3 (50.0)	
>180°, <360°	5	6.7	1 (20.0)	
360°	7	9.3	0 (0)	
Skin invasion				.167
Yes	4	5.3	1 (25)	
No	71	94.7	3 (4.2)	
Necrosis/infection				.318
Yes	19	25.3	0 (0)	

Factor	Number	Percentage	Carotid bleed, n (%)	Association of factor with carotid bleeding (P)
No	56	74.7	4 (7.1)	.315
Ulceration				
Yes	7	9.3	1 (14.3)	
No	68	90.3	3 (4.4)	

Abbreviations: EBRT = external beam radiation therapy; IQR = interquartile range; SBRT = stereotactic body radiation therapy.

**Table 2**

Carotid dosimetry and association with bleeding events

Parameter	Median	IQR	OR (95% CI)	P
D <sub>0,lec</sub>	40.8 Gy	21.6–47.6 Gy	1.031 (0.996–1.067)	.080
D <sub>1,lec</sub>	26.8 Gy	14.1–42.1 Gy	1.022 (0.982–1.064)	.280
D <sub>2,cc</sub>	15.4 Gy	8.4–32.7 Gy	1.013 (0.968–1.061)	.571
Mean dose	15.0 Gy	8.9–23.3 Gy	1.017 (0.943–1.098)	.658
PTV size	39.3 cm <sup>3</sup>	17.2–76.6 cm <sup>3</sup>	0.992 (0.952–1.033)	.685

Abbreviations: CI = confidence interval; IQR = interquartile range; OR = odds ratio; PTV = planning target volume.