Scientific Article

Risk of carotid blowout after reirradiation with particle therapy

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Abstract

Purpose: Carotid blowout (CB) is a serious complication in retreatment of neoplasms in the head and neck (H&N) region. Rates seem to increase in hypofractionated or accelerated hyper-fractionated regimens. In this study, we investigate the CB rate and the cumulative doses received by the carotid artery (CA) in a cohort of patients who were reirradiated at CNAO with particle therapy in the H&N region.

Methods and materials: The dosimetric information, medical records, and tumor characteristics of 96 patients were analyzed. For 49 of these patients, the quality of dosimetric information was sufficient to calculate the cumulative doses to the CA. The corresponding biological equivalent dose in 2 Gy fractions (EQD2) was calculated with an α/β-ratio of 3.

Results: In the final reirradiation at CNAO, 17 patients (18%) had been treated with protons and 79 (82%) with carbon ions. Two patients experienced profuse oronasal bleeding, of which one case was confirmed to be caused by CB. If attributing both cases to CB, we found an actuarial CB rate of 2.7%. Interestingly, there were no CB cases in the carbon ion group even though this was the large majority of patients and they generally were treated more aggressively in terms of larger fraction doses and higher cumulative EQD2.

Conclusions: The current practice of particle reirradiation at CNAO for recurrent neoplasms in the H&N region results in acceptable rates of CB.

Introduction

Carotid blowout (CB), defined as a sudden rupture of the carotid artery (CA) or one of its main branches, is a feared complication in the treatment of neoplasms in the head and neck (H&N) region. CB results from pathologic alterations in or loss of the soft tissues surrounding the CA and from alterations in the vessel wall itself. Risk factors include ulceration, radiation to lymph nodes, dose to the neck >70 Gy, reirradiation, radical neck surgery, nutritional status (body mass index <22.5 kg/m^2), osteonecrosis, and the degree to which the CA is involved in the tumor.[1-4]

The properties of radiation therapy (RT) also seem to affect the risk of CB because rates as high as 8.4% to 15% are observed in reirradiation with hypofractionated stereotactic body RT (SBRT)[4-6] in contrast to >4% with more conventional fractionated photon regimens.[2,7]

Particle therapy, because of its physical advantages in dose distribution, is a suitable treatment modality for recurrent neoplasms in the H&N region. For carbon ion RT (CIRT) in particular, there are even biological advantages that could be harnessed through the use of hypofractionated schedules.[8,9] In a report on CIRT reirradiation of 52 patients with recurrent adenoid cystic carcinoma, 2 patients (3.8%) developed CB after nasopharyngeal necrosis.[10] The patients received reirradiation doses of 36 Gy (relative biological effectiveness [RBE]) to 74 Gy (RBE) in a moderately hypofractionated regimen of 3 Gy (RBE) per fraction.

At the National Center of Oncological Hadrontherapy (CNAO) in Pavia, Italy, patients with recurrent neoplasms in the H&N region are treated under protocols for reirradiation using protons or carbon ions with fraction doses ranging from 2 Gy (RBE) to 5 Gy (RBE). This prompted us to investigate the outcome of these patients with regard to CB with a special focus on the cumulative doses received by the CA.

Methods and materials

Reirradiation at CNAO

All patients were treated under prospective protocols that were approved by the regional ethics committee. A signed consent was required for participation. Proton RT was used as a first option, with conventional fractionation of 2 Gy (RBE) per fraction. A fixed RBE value of 1.1 was employed. CIRT was used for histologies with a poor response to low linear energy transfer (LET) radiation (eg, sarcoma, melanoma, and salivary gland tumors), in cases of early in-field recurrence after photon RT (assuming selection of a radio-resistant clone), or in cases in which the sharper lateral penumbra of CIRT resulted in significantly better sparing of organs at risk (OARs). Dose per fraction ranged from 2 Gy (RBE) to 5 Gy (RBE). RBE

was calculated with the local effect model version 1[11] using the *syngo* RT Planning (Siemens Healthcare, Erlangen, Germany) treatment planning system (TPS).

To avoid long-term toxicity to OARs that were previously irradiated, an estimate of the cumulative biological equivalent dose (EQD2) from the prior and planned reirradiation was performed using a conservative α/β-ratio of 2 Gy for all OARs. When using an active scanning technique, it is feasible to selectively restrain the dose to the CA while retaining a high dose to most of the target (Fig 1b). The current practice at CNAO is to avoid cumulative EQD2 to the CA that exceeds 120 Gy (RBE) by using this method.

Patient population

A total of 128 patients were reirradiated at CNAO with either protons or carbon ions from September 2012 to March 2016. Four patients were excluded from the study because there were no records on the doses given in the previous RT, and 27 patients were excluded because they did not receive doses to their CA in the primary RT or the reirradiation or because these doses did not overlap in their CA. One patient, a foreign citizen, never appeared for follow-up and was also excluded.

A total of 96 patients were available for analysis with regard to the rate of CB (Fig 2; pink boxes). General details on past and present RT, patient and disease characteristics, and prior surgery were collected. In addition, the following information was also gathered:

1) tumor involvement grade: *(a)* no involvement, *(b)* <1/3 of CA circumference, *(c)* 1/3 to 2/3 of CA circumference, or *(d)* >2/3 of CA circumference
2) segment of CA that received the highest dose: *(a)* neck, *(b)* skull base, *(c)* sinus cavernosus, or *(d)* intracranial
3) whether surgery had been performed in the immediate vicinity of the high-dose segment of the CA, thus potentially making the CA more vulnerable.

Because tumor involvement grade and surgery near the CA have been suggested as factors that decrease the integrity of the CA wall and thereby increase the risk of CB,[1,2,7] we defined 2 potential high-risk features to assess their impact on CB rate in our material:

1) tumor involvement grade that is >2/3 of the CA circumference
2) prior surgery in the immediate vicinity of the segment of the CA that received the highest cumulative dose

### Calculation of cumulative dose statistics to carotid arteries

For 49 of the 96 patients, there was sufficient documentation on prior RT to calculate cumulative doses to
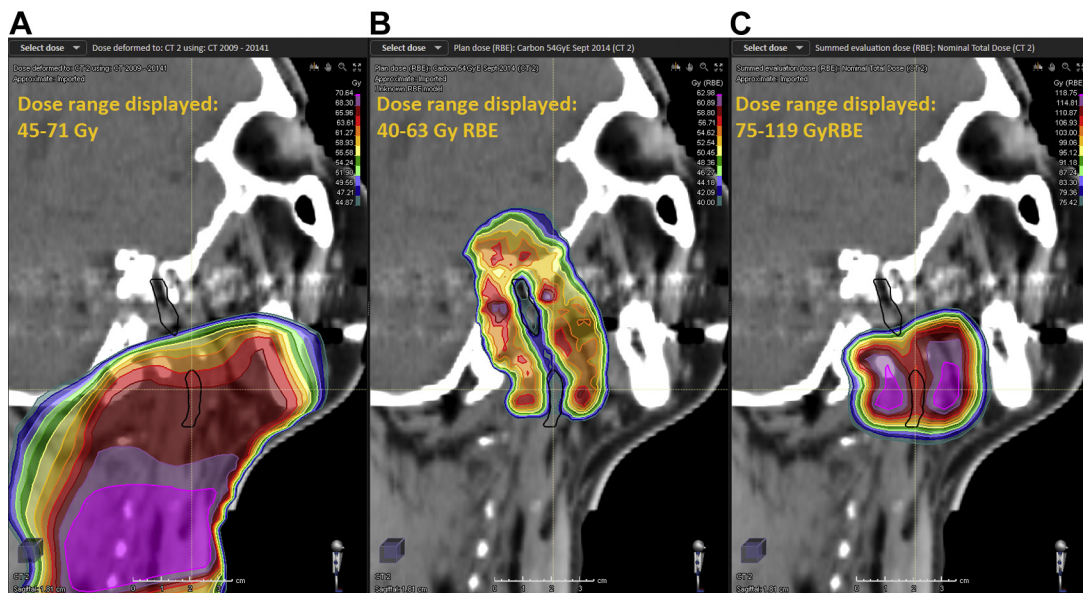
Figure 1 Dose distribution from (A) first photon treatment (70 Gy), (B) reirradiation at CNAO with carbon ions (54 Gy [RBE]) and (C) cumulative nominal dose. The carotid artery is outlined in black and demonstrates the selective sparing of the carotid artery in (B).

the CA. In 25 patients, both CAs had been reirradiated, giving a total of 74 CAs to be analyzed. For 32 of these patients (49 CAs), Digital Imaging and Communications in Medicine (DICOM) files of their previous RT was available. For the remaining 17 patients (25 CAs), dose data of previous RT could be extracted from printed computed tomography (CT) images with isodose curves (Fig 2; blue boxes).

For the group of patients with DICOM files, the CT images, structure set files, and dose files from both the primary and subsequent RT courses were imported to a workstation with the RayStation version 5.0 TPS (Ray-Search Laboratories AB, Stockholm, Sweden). For the treatment course at CNAO, magnetic resonance imaging (MRI) scans in the treatment position were also imported and co-registered with the planning CT and used to
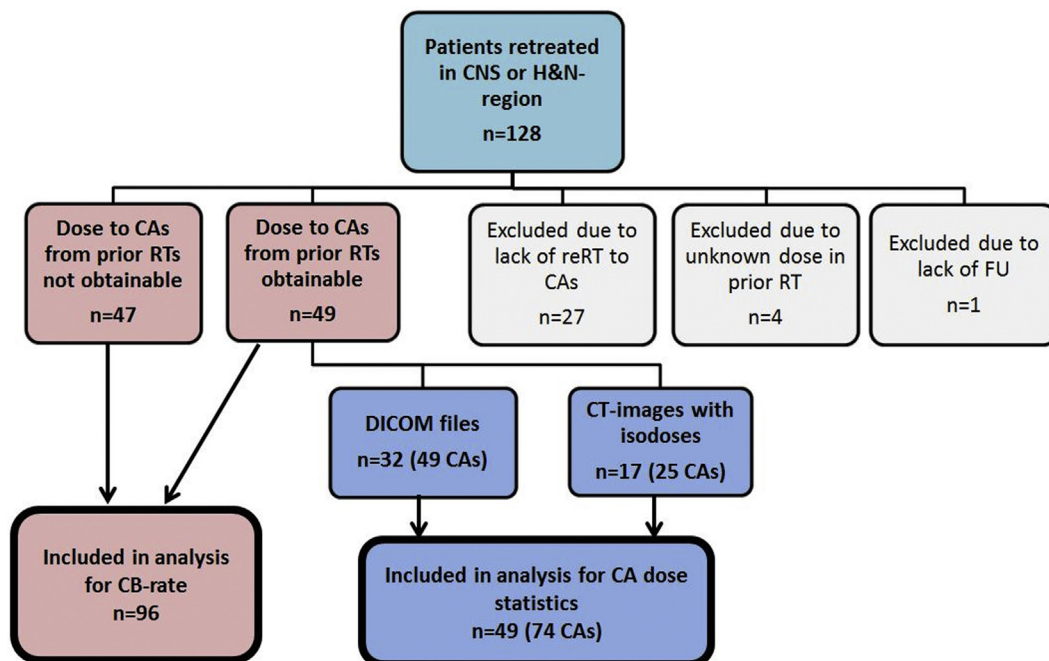
Figure 2 Patient selection.

support the contouring of the CAs on the CNAO planning CT. For the purpose of this study, the CA was defined as the common CA and internal CA, with a distal limit at the origin of the medial cerebral artery. Thus, we excluded smaller branches and the external CA because these arteries would be impossible to contour in many of the patients and because the current practice at CNAO is to delineate only the common CA and internal CA. All contouring was done by the same radiation oncologist, and only the segment of the CAs that was reirradiated was contoured.

To obtain the cumulative dose to the CA, the doses from patients' previous RT courses were deformed to the planning CT of the final RT course (CNAO CT) as follows: A rigid registration was made between the patients' different planning CTs, with a focus on achieving the best possible match in the area of the reirradiated CAs. We then performed a deformable registration between the planning CTs with the CNAO CT defined as the reference CT.

A cumulative nominal dose distribution was then created with the RayStation TPS by summing the deformed doses with the dose from the final RT on the CNAO CT (Fig 1). Cumulative nominal maximum dose ($CumDmax_{nom}$) to the CA and nominal dose to 1% of the CA volume ($CumD1_{nom}$) then were collected from the TPS. To provide an indication of the concentration of the highest dose, we calculated the volume of the CAs that received ≥90% of the $CumD1_{nom}$ ($V90\%_{CumD1nom}$).

Because many of the treatments were given with fraction doses well above 2 Gy/Gy (RBE), we also calculated a cumulative maximal EQD2 to the CA ($CumDmax_{EQD2}$) with the following equation:

$$CumDmax_{EQD2} = \frac{D_{1st}\left(\frac{D_{1st}}{Fx_{1st}} + \frac{\alpha}{\beta}\right)}{\left(2 + \frac{\alpha}{\beta}\right)} + \frac{D_{2nd}\left(\frac{D_{2nd}}{Fx_{2nd}} + \frac{\alpha}{\beta}\right)}{\left(2 + \frac{\alpha}{\beta}\right)} + \frac{D_{3}\left(\frac{D_{3rd}}{Fx_{3rd}} + \frac{\alpha}{\beta}\right)}{\left(2 + \frac{\alpha}{\beta}\right)}$$

where D_{1st} was the dose from the first RT course contributing to the $CumDmax_{nom}$ and Fx_{1st} was the fraction number of the same course. The second term of the equation was used for patients who had more than one previous RT, and the third term represented the final reirradiation at CNAO. Due to the lack of published data on the α/β-ratio of the CA, an α/β-ratio of 3 Gy was chosen, acknowledging that the α/β-ratio of 2 Gy, which has been employed at CNAO, probably is too conservative compared with what would be used at most other institutions. This is also in agreement with other publications on the toxicity to arteries induced by radiation.[12,13]

For the 17 patients for whom the dose distribution was obtainable from printed CT slices, the dose statistics were collected as follows: We identified the segment of the CA

in which the highest $CumDmax_{nom}$ would be located by visually comparing the dose plan from the particle therapy course at CNAO with the printed CT slices from the previous RT courses. The doses (D_{1st}, D_{2nd},...) that contributed to the $CumDmax_{nom}$ were then collected from the prints for the respective segment of the CA. If, for example, the CA in the first RT course was situated between the 50 Gy and 60 Gy isodose curves, an approximation of the D_{1st} was set to 55 Gy. Thereafter, the dose given to the same segment in the particle therapy course at CNAO (D_{3rd}) was derived directly from the *syngo* TPS that is installed at CNAO. In this way, an approximation of the $CumDmax_{nom}$ was collected for these 17 patients. A $CumDmax_{EQD2}$ was also calculated using the previously mentioned equation.

Follow-up

Patients were followed at CNAO with a clinical examination and an MRI scan every 3 months after completion of the reirradiation.

Statistics

The data were analyzed with the IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). Differences in frequencies between groups were compared using the χ^2 or Fischer's exact test. Nonparametrical distributions were compared with the Mann-Whitney U-test, and normally distributed data were compared with the independent samples t test. Bivariate correlations between skewed data were analyzed with Spearman's rho. All P-values were obtained from two-sided tests. Survival estimates were generated with the Kaplan-Meier method.

Results

The median follow-up was 13.4 months (range, 0.8-49.2 months), and the median time from the first RT to the final reirradiation was 3.4 years (range, 0.3-50 years). Eleven patients (11.5%) had previously undergone 2 courses of RT. Two of these patients had been treated with photons primarily, followed by a second and third course of CIRT at CNAO due to 2 consecutive relapses. One patient had been treated at CNAO with CIRT for all

Table 1   Patient and disease characteristics

	Quality of Final Re-RT			P value
	All (n = 96)	Proton RT (n = 17)	CIRT (n = 79)	
Median age (range), y	61 (24-88)	55 (24-75)	63 (24-88)	
Sex, male:female	56:40	8:9	48:31	NS
Comorbidity, n (%)				
Hypertension	26 (27.0)	2 (11.8)	24 (30.4)	NS
Diabetes mellitus	6 (6.3)	2 (11.8)	4 (5.1)	NS
Cardiovascular disease	5 (5.2)	3 (17.6)	2 (2.5)	.037
Histology, n (%)				
Adenoid cystic carcinoma	28 (29.2)	0 (0.0)	28 (35.4)	.003
Squamous cell carcinoma	27 (28.1)	13 (76.5)	14 (17.7)	
Sarcoma	11 (11.5)	0 (0.0)	11 (13.9)	
Mucoepidermoid carcinoma	5 (5.2)	0 (0.0)	5 (6.3)	
Undifferentiated carcinoma	5 (5.2)	1 (5.9)	4 (5.1)	
Pleomorphic adenoma	5 (5.2)	0 (0.0)	5 (6.3)	
Adenocarcinoma	3 (3.1)	0 (0.0)	3 (3.8)	
Myoepithelial carcinoma	3 (3.1)	0 (0.0)	3 (3.8)	
Meningioma	3 (3.1)	1 (5.9)	2 (2.5)	
High grade glioma	2 (2.1)	2 (11.8)	0 (0.0)	
Other[a]	4 (4.2)	0 (0.0)	6 (7.8)	
Site of Primary Tumor, n (%)				
Parotid gland	18 (18.8)	0 (0.0)	18 (22.8)	.003
Paranasal sinuses	17 (17.7)	0 (0.0)	17 (21.5)	
Rhinopharynx	15 (15.6)	6 (35.3)	9 (11.4)	
Oropharynx	10 (10.4)	3 (17.6)	7 (8.9)	
Oral cavity	7 (7.3)	2 (11.8)	5 (6.3)	
Brain/meninges	5 (5.2)	3 (17.6)	2 (2,5)	
Nasal cavity	5 (5.2)	1 (5.9)	4 (5.1)	
Skull base	5 (5.2)	0 (0.0)	5 (6.3)	
Skin of scalp or face	4 (4.2)	1 (5.9)	3 (3.8)	
Submandibular gland	3 (3.1)	0 (0.0)	3 (3.8)	
Larynx	2 (2.1)	1 (5.9)	1 (1.3)	
Lacrimal gland	2 (2.1)	0 (0.0)	2 (2.5)	
Other[b]	3 (3.1)	0 (0.0)	3 (3.8)	
Site of Highest Dose to CA, n (%)				
Neck	50 (52.1)	9 (52.9)	41 (51.9)	NS
Skull base	34 (35.4)	4 (23.5)	30 (38.0)	
Sinus cavernosus	10 (10.4)	3 (17.6)	7 (8.9)	
Intracranial	2 (2.1)	1 (5.9)	1 (1.3)	
Tumor Involvement Grade, n (%)				
No involvement	24 (25.0)	6 (35.3)	18 (22.8)	NS
<1/3 of CA circumference	14 (14.6)	2 (11.8)	12 (15.2)	
≥1/3 < 2/3 of CA circumference	9 (9.4)	2 (11.8)	7 (8.9)	
≥2/3 of CA circumference	49 (51.1)	7 (41.2)	42 (53.2)	
Surgery, n (%)				
Any surgery	80 (83.3)	10 (58.8)	70 (88.6)	.007
Neck dissection	26 (27.1)	6 (35.3)	20 (25.3)	NS
In vicinity of highest dose to CA	46 (47.9)	5 (29.4)	41 (51.9)	NS
High-Risk Features[c], n (%)				
0 risk factors	28 (29.2)	8 (47.1)	20 (25.3)	NS
1 risk factor	41 (42.7)	6 (35.3)	35 (44.3)	
2 risk factors	27 (28.1)	3 (17.6)	24 (30.4)	

CA, carotid artery; CIRT, carbon ion radiation therapy; NS, not significant; RT, radiation therapy.

[a] Esthesioneuroblastoma, sinonasal carcinoma, carcinoma ex pleomorphic adenoma, oncocytoma.
[b] Mandible, hyoid bone, lymph node metastasis neck.
[c] Risk factors: Tumor involvement grade ≥2/3 and surgery in high-dose areas.

Table 2 Radiation therapy and dose statistics

	Quality of Final Re-RT			P value
	All (n = 96)	Proton (n = 17)	CIRT (n = 79)	
Previous RT Courses	107 courses	17 courses	90 courses	
Nom. prescribed dose, median (range)				
Gy/Gy (RBE)	60 (8-79.2)	66 (32-70)	60 (8-79.2)	.036
Fraction dose, median (range)				
Gy/Gy (RBE)	2 (1-6)	2 (1.8-4)	2 (1-6)	NS
Fraction dose, n (%)				
≤2 Gy/Gy (RBE)	75 (70.1)	11 (64.7)	65 (72.2)	NS
>2 to ≤3 Gy/Gy (RBE)	19 (17.8)	5 (29.4)	14 (15.6)	
>3 Gy/Gy (RBE)	10 (9.3)	1 (5.9)	9 (1.0)	
Unknown	3 (2.8)		2 (2.2)	
Radiation quality, n (%)				
Cobalt-60	4 (3.7)		4 (4.4)	NS
Photon	96 (89.7)	17 (100)	79 (87.8)	
Photon+Proton boost	1 (1.0)		1 (1.1)	
Photon+Carbon boost	1 (1.0)		1 (1.1)	
Proton	1 (1.0)		1 (1.1)	
Carbon	4 (3.7)		4 (4.4)	
Radiation technique, n (%)				
Conventional	83 (77.6)	17 (100)	66 (73.3)	NS
SBRT/SRS	10 (9.3)		10 (11.1)	
Conv.+particle boost	2 (1.9)		2 (2.2)	
Particle scanning technique	4 (3.7)		4 (4.4)	
Particle passive technique	1 (1.0)		1 (1.1)	
unknown	7 (6.5)		7 (7.8)	
Chemotherapy, n (%)				
Yes	31 (29.0)	10 (58.8)	21 (26.6)	.007
No	76 (71.0)	7 (41.2)	69 (73.4)	
Final Re-RT Course				
Nom. prescribed dose, median (range)				
Gy (RBE)	56 (12-76.8)	54 (30-70)	60 (12-76.8)	NS
Fraction dose, median (range)				
Gy (RBE)	3 (2-5)	2 (2-3)	3 (2-5)	<.005
Fraction dose, n (%)				
2 Gy (RBE)	17 (17.7)	15 (88.2)	2 (2.5)	
≥3 to <4 Gy (RBE)	59 (61.5)	2 (11.8)	57 (72.2)	
≥4 Gy (RBE)	20 (20.8)		20 (25.3)	
Prescribed Cumulative Lifetime Doses				
Nominal, median (range)				
Gy (RBE)	120 (32-197)	120 (62-138)	119 (32-197)	NS
EQD2, α/β = 3 Gy, median (range)				
Gy (RBE)	132 (46-296)[a]	122 (67-140)[a]	132 (46-296)[a]	<.005
median (range)				
CumDmax, median (range)				
nominal, Gy (RBE)	103 (27-129)[b]	107 (40-129)[b]	101 (27-128)[b]	NS
EQD2 (α/β = 3), Gy (RBE)	109 (25-167)[b]	107 (33-131)[b]	109 (25-167)[b]	NS
CumD1, median (range)				
nominal, Gy (RBE)	107 (35-128)[c]	107 (40-128)[c]	107 (35-127)[c]	NS
V90%CumD1, median (range)				
cm³	0.18 (0.01-3.44)[c]	0.18 (0.01-3.44)[c]	0.18 (0.01-1.19)[c]	NS

CA, carotid artery; CIRT, carbon ion radiation therapy; CumD1, dose to 1% of the CA volume; CumDmax, cumulative maximum dose; NS, not significant; RBE, relative biological effectiveness; RT, radiation therapy; SBRT, stereotactic body radiation therapy; SRS, stereotactic radiosurgery; V90%CumD1, volume of the CAs that received ≥90% of the CumD1.

[a] Based on 94 patients because data on fraction size were missing for 2 patients.
[b] Based on 74 CAs of the 49 patients with dose data available.
[c] Based on the 49 CAs of the 32 patients with Digital Imaging and Communications in Medicine files.
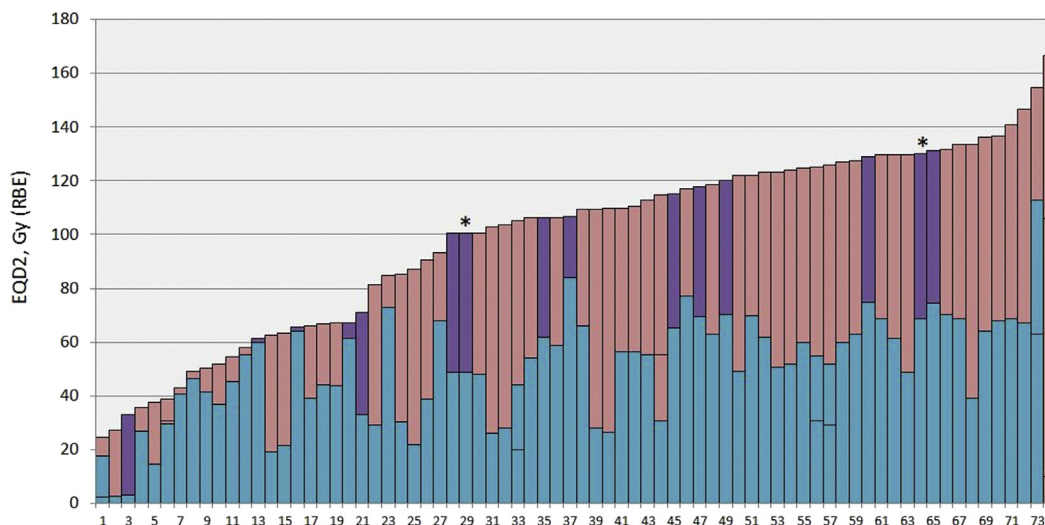
Figure 3 $CumDmax_{EQD2}$ for all 74 carotid arteries, displaying the contribution from photon radiation therapy (RT) (blue), carbon RT (pink), and proton RT (purple). * Carotid arteries of the 2 patients who developed oronasal hemorrhage.

3 courses, and another had undergone 2 Cobalt-60 treatments 50 years before reirradiation at CNAO. The remaining 7 patients had a first and second course of photon RT before the final reirradiation at CNAO. In the final reirradiation at CNAO, 17 patients (18%) were treated with protons versus 79 (82%) with carbon ions. Tables 1 and 2 present details on patient and disease characteristics, prior surgery, and previous and final RT courses for all patients and their distribution among the patients who received either proton RT or CIRT in the final reirradiation at CNAO.

A significantly larger proportion of patients had received chemotherapy in the proton group compared with the carbon group (55.6% vs 27.8%; $P = .026$), and the prescribed cumulative lifetime EQD2 was significantly higher in the carbon ion group, which was a result of higher fraction doses because the prescribed cumulative nominal lifetime doses were similar. There was a significant difference ($P < .005$) in the distribution of histologic entities between the two groups, with a dominans of salivary gland tumors and sarcomas in the CIRT group (69.5% total) while the proton RT group was dominated by squamous cell carcinomas (SCCs) (76.5%).

Dose statistics to carotid arteries

For the group of 49 patients with detailed dosimetric data, a total of 74 CAs had been reirradiated. When only analyzing the CA that received the highest cumulative dose in each patient, the difference between the prescribed cumulative nominal lifetime dose and the $CumDmax_{nom}$ ranged from -12 Gy (RBE) to 89 Gy (RBE) with a median of 6 Gy (RBE). In addition, the correlation between these 2 parameters was poor, with a Spearman's rho correlation coefficient of 0.363 ($P = .010$).

Median $CumDmax_{EQD2}$ for all 74 CAs was 109 Gy (RBE) (range, 25-167 Gy [RBE]). The contributions from each RT course to each individual CA are presented in Figure 3. The median $CumD1_{nom}$ was 107 Gy (RBE) (range, 35-128 Gy [RBE]). In most cases only small volumes of the CA recieved the highest dose, demonstrated by the median $V90\%_{CumD1nom}$ of 0.18 cm^3 (range, 0.01-3.44 cm^3), which corresponds to the volume of a cylinder 0.92 cm long with a diameter of 5 mm.

Cases of carotid blowout

Two of the 96 patients experienced an acute oronasal hemorrhage. The first patient had been treated for an SCC of the nasopharynx with chemotherapy and photon RT (66 Gy/33 fractions) in the primary setting. Eighteen months later, the patient was reirradiated with protons (60 Gy [RBE]/30 fractions) because of a recurrent tumor that completely surrounded his CAs at the skull base. Both CAs received a $CumDmax_{nom}$ of 107 Gy (RBE), which corresponds to a $CumDmax_{EQD2}$ of 100 Gy (RBE). Before the acute hemorrhage, which occurred 6 months after the reirradiation, the patient had a second relapse in the reirradiated site of the nasopharynx. The hemorrhage was fatal and an autopsy was refused, so whether the bleeding was caused by the recurrent tumor or by a rupture of one of the CAs is uncertain.

The second patient, also with an SCC of the nasopharynx, was initially treated with chemoradiation with photons (70 Gy/35 fractions). Twenty months later, the patient underwent total parotidectomy due to metastases. Because of a recurrent tumor in the cranial part of the surgical bed, which completely encased the CA, the patient received reirradiation with protons (56 Gy [RBE]/28 fractions) 72 months after the primary RT. This CA
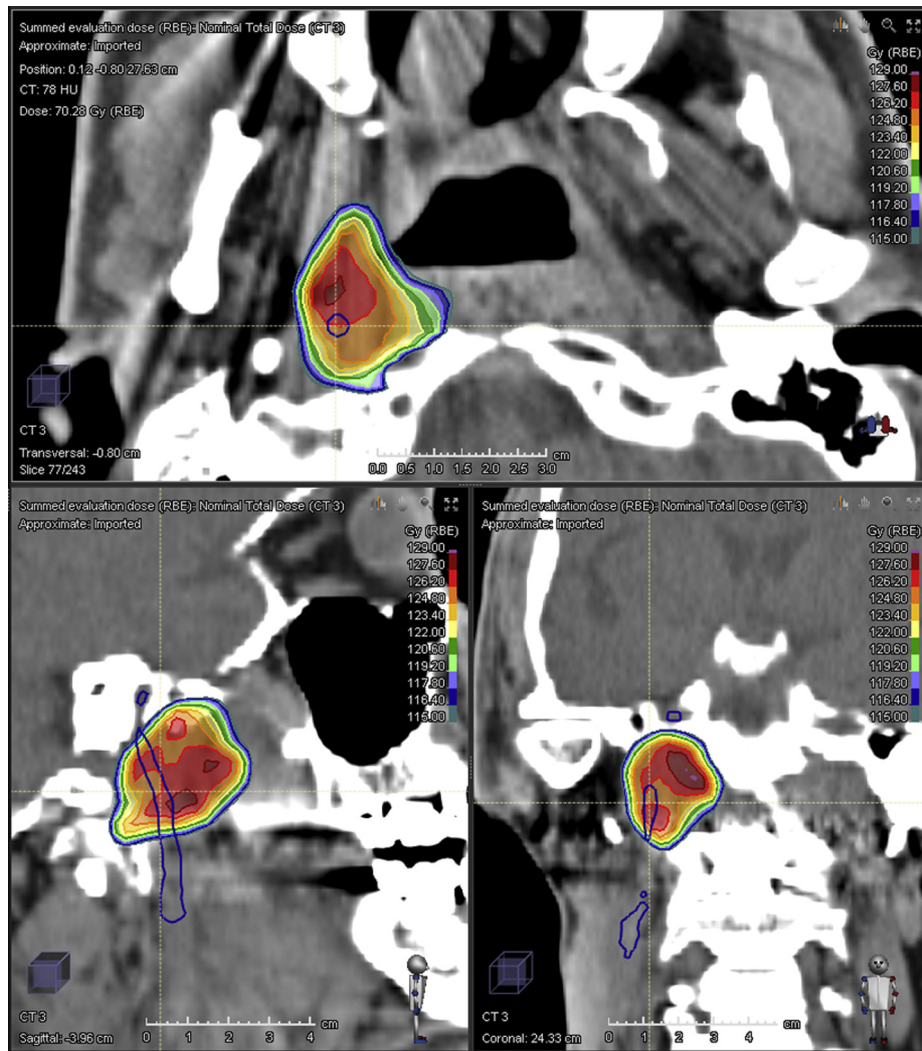
Figure 4   Dose corresponding to ≥90% of CumD1nom (115-129 Gy [RBE]). V90%$_{CumD1}$ for this patient was 0.28 cm^3.

received a $CumDmax_{nom}$ of 129 Gy (RBE), which corresponds to a $CumDmax_{EQD2}$ of 130 Gy (RBE). The cumulative dose distribution is presented in Fig 4. Eight months later, the patient was admitted to his local hospital with profuse oronasal bleeding that required intubation. A CT angiography revealed a pseudoaneurysm on the CA in the high-dose area. No intervention was performed. The next night, the patient experienced another profuse bleed and died.

When attributing both cases to CB, we found a gross CB rate of 2.1% (95% confidence interval, 0.01-7.3%) in our series. The actuarial 1-year CB rate and overall survival probability were 2.7% and 81.5%, respectively. Figure 5 presents the Kaplan-Meier plot for the CB rate.

Discussion

In this study, we examined the rate of CB in a cohort of patients who underwent particle reirradiation for recurrent neoplasms of the head and neck. The patient population was diverse with regard to histology and site, in contrast to most other publications on CB, due to the current indications and referral practices for particle therapy.

Interestingly, both cases of probable CB were reirradiated with protons in 2 Gy (RBE) fractions, although we initially were more concerned about the high-LET, hypofractionated carbon ion reirradiation. This apparent difference in CB rate likely is caused by chance or by other confounding factors. For example, reirradiation for mucosal carcinomas of the upper pharynx may be more susceptible to CB than other combinations of histology and site because these tumors will always receive high doses to the tissues separating the CA from the pharynx lumen. Indeed, the highest CB rates published were in patient populations that were dominated by SCC and oro-/nasopharyngeal locations reirradiated by SBRT.[4,5] On the other hand, if this were true, we should have encountered CB in the CIRT group as well; the CIRT group had at least as many patients in terms of absolute numbers who
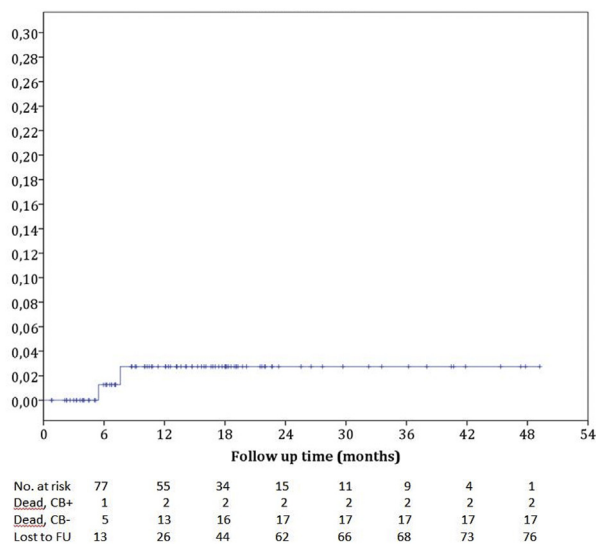
Figure 5 Cumulative carotid blowout (CB) rate. The table displays the absolute number of patients who were at risk of CB, death due to CB, death due to cause other than CB, and loss to follow-up at the end of each 6-month interval.

had similar site and histology and in whom treatments generally were more aggressive in dose and fractionation.

Another possible explanation for this apparent higher risk of proton RT versus CIRT could be that hypofractionation using high-LET radiation theoretically widens the therapeutic window between normal tissue complications and tumor control so that an equivalent CIRT dose generally would lead to fewer complications.[8,9]

In a report by Jensen et al[10] on outcome and toxicity after reirradiation with CIRT for recurrent adenoid cystic carcinoma, CB occurred in 2 of 52 patients (3.8%). In our study, there was no CB among the 77 patients who received CIRT, even though the prescribed total dose and fractionation at CNAO were more aggressive and the cumulative biological equivalent lifetime doses were comparable between the series. The apparent difference may be explained by the small study populations, differences in histology and site, or the possible benefit of more aggressive hypofractionation when using high-LET radiation. Most likely, the difference can be explained by CNAO's current practice of selectively sparing the CAs, thus resulting in the cumulative doses to the CAs probably being lower in our study. If this is the case, this strategy would be reasonable to pursue in the future as long as it does not affect tumor control probability. This will be a topic for upcoming publications.

To the best of our knowledge, there are no other studies on the CA as an OAR in which the cumulative doses to CAs have been reproduced in this detailed manner. Among the 74 CAs analyzed, our confirmed CB case had received among the highest nominal cumulative doses to the CA, and only a few patients had received

significantly higher $CumDmax_{EQD2}$ (Fig 3). These few patients were all in the CIRT group, and it is questionable whether the conversion of nominal dose to EQD2 is valid for CIRT.

From the experience of our analysis, in which we found a substantial difference and poor correlation between the prescribed cumulative lifetime dose and the $CumDmax$ to the CA, we conclude that a simple summation of a patient's prescribed doses is an unsuitable surrogate for this organ, especially with highly conformal RT techniques. We propose considering the CA to be an OAR, especially in the reirradiation setting, and use CA sparing when using proton or carbon ion RT. Other authors also suggest this in the setting of SBRT reirradiation.[14] More publications on cumulative doses to this organ are needed. Only by pooling data from different institutions can we hopefully shed more light on the impact of dose, volume, and fractionation with regard to the life threatening complication of CB.

Conclusions

The current practice of particle reirradiation at CNAO for recurrent neoplasms in the H&N region results in acceptable rates of CB that are better than the published results of photon SBRT and comparable to rates achieved with non-hypofractionated photon reirradiation. Applying specific dose constraints to the CA in re-RT with CIRT using the carotid sparing technique may explain the apparent favorable rate of CB compared with those from other institutions.

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