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# Chemoradiation and local recurrence of head and neck squamous cell carcinoma and the risk of carotid artery blowout

**Christian Jacobi MD[1] | Constanze Gahleitner MD[1] | Henning Bier MD[1] | Andreas Knopf MD[1,2]**

[1]Department of Otorhinolaryngology/Head and Neck Surgery, Klinikum rechts der s Isar Technische Universität München, München, Germany

[2]Department of Otorhinolaryngology/Head and Neck Surgery, Universitätsklinikum Freiburg, Freiburg, Germany

**Correspondence**
Andreas Knopf, Department of Otorhinolaryngology/Head and Neck Surgery, Universitätsklinikum Freiburg, Killianstr. 5, 79106 Freiburg, Germany.
Email: knopf.ent@gmail.com

**Abstract**

**Background:** Carotid blowout syndrome (CBS) is a rare but life-threatening complication of head and neck squamous cell carcinoma (HNSCC). Chemoradiation (CRT) may make CBS more likely, but so far no longitudinal analysis of different treatment strategies has been conducted.

**Methods:** In the present study, 1072 patients with HNSCC were divided into groups depending on whether they had experienced CBS. Disease-related data were analyzed using chi-square test, Fisher exact test, and Student's *t* test. Survival rates were calculated using Kaplan-Meier test, log-rank test, and the Cox regression analysis for forward selection.

**Results:** Thirty-six patients suffering from CBS demonstrated significantly advanced T status ($P = .001$) and UICC stage ($P = .004$) when compared with unaltered counterparts. After adjustment for UICC stage, OS was comparable in both groups, whereas the mean recurrence-free survival (RFS) rate was better in unaltered patients (67 vs 24 months; $P < .0001$). Cox regression for forward selection revealed local recurrence (hazard ratio [HR], 1.9; $P < .0001$), T status (HR, 1.9; $P = .03$), and CRT (HR, 2.0; $P < .0001$) as independent risk factors for mortality related to CBS.

**Conclusion:** CBS is a rare event in patients with HNSCC demonstrating reduced OS/RFS. Advanced T status, C/RT, and the recurrence of local tumors increase the risk of CBS-associated death.

**KEYWORDS**

carotid artery blow out, chemoradiation, head and neck squamous cell carcinoma, outcome, risk factor, therapy

## 1 | INTRODUCTION

Carotid blowout syndrome (CBS), defined as a rupture of the carotid artery or its extracranial branches, is a rare but life-threatening complication that occurs in up to 4.3% of patients with head and neck cancer (HNSCC).[1] Sudden and severe bleeding from the oral cavity and/or the exposed neck are predictive symptoms of a blowout. Immediate clinical assessment including digital subtraction angiography is required for diagnosing CBS.[2] Multidisciplinary and standardized treatment paths are crucial for mastering the quick selection of the appropriate treatment strategy, which must be patient-specific.[3,4] Radiological interventions, such as angiographic embolization or stenting, are first-line treatments for CBS. Recent advances have created a noninvasive, lifesaving alternative to the challenging procedure of open surgical ligation of the carotid arteria.[5,6] The management of CBS by endovascular carotid occlusion has significantly

  

improved patient outcome after carotid rupture. The cumulative mortality and (neurologic) morbidity of untreated CBS are 40% and 60%, respectively.[6-10] Despite the possibility for preinterventional balloon occlusion tests, postprocedural stroke rates remain as much as 10% after embolization and 3% after stent grafting.[11] Several predisposing factors, including chemoradiation (CRT), tumor recurrence, fistulas in the neck, cachexia, diabetes mellitus, and long-term corticosteroid intake have been discussed as potentially increasing the risk of metachronous CBS.[12-14] Although prior or repeated CRT seem to be the most frequent preconditions in patients with CBS, longitudinal data analysis for predicting the contributions of different risk factors is still lacking.[3,15-17]

In the present study, a total of 36 patients with CBS within a comprehensive, large sample-size HNSCC cohort were evaluated for the predictive parameters that lead to CBS and survival rates with respect to different treatment regimes.

## 2 | PATIENTS AND METHODS

### 2.1 | Patient selection

All patients treated for HNSCC in the ENT Department of the University Hospital Rechts der Isar, Munich, between January 2001 and December 2011 were included in the current study. Dysplasia, carcinoma in situ, and other histologic subtypes were excluded. Two or more experienced pathologists histologically reviewed tumor samples. Clinicopathological parameters and survival data were collected retrospectively: age, sex, TNM classification (7th edition), grading, treatment modalities, recurrence, and death after treatment. Patients with incomplete data or incomplete staging, as well as patients who refused or did not finish surgical and/or conservative treatment were excluded from the survival analysis. The overall cohort was divided into groups based on the occurrence of CBS. CBS is defined as the acute and life-threatening bleeding of the internal or external carotid artery vessel supply, which requires surgical treatment and/or interventional radiological measures.

### 2.2 | Statistical analysis

Differences between the groups were analyzed using the chi-square test and Fisher exact categorical test, and the unpaired Student's *t* test for continuous variables. The overall survival (OS), recurrence-free survival (RFS), and CBS-free survival rates were assessed by measuring the time from treatment to death from any cause, recurrence, and CBS onset. Survival rates and curves were calculated and illustrated with the Kaplan-Meier method and were further analyzed with the log-rank test. Variables that revealed prognostic or effect-modifying potentials on the outcome were subsequently evaluated with the proportional Cox regression for forward selection. *P*-values <.05 were considered statistically significant. All statistical analysis was performed in SPSS (SPSS Inc, Chicago, Illinois).

## 3 | RESULTS

### 3.1 | Description of the HNSCC cohort

A total of 36 patients (3%) suffered from CBS. Patients with CBS demonstrated significantly advanced tumor (T) status ($P = .001$) and Union Internationale Contre le Cancer (UICC) stage ($P = .004$) as compared with unaltered counterparts (n = 1036). Striking differences in therapeutic strategies undertaken with these two groups were apparent ($P = .002$; Table 1). The majority of patients with CBS (61%) underwent primary C/RT, whereas the second largest group of 11 patients underwent surgery and adjuvant C/RT (31%). Surgery without adjuvant therapy was applied to only three patients (8%). In the control group, 18% of patients underwent surgery alone, whereas another 498 patients (48%) underwent surgery and adjuvant C/RT, and a further 352 patients (34%) received only primary C/RT. We observed no differences either in the age and sex distribution or in the nodal (N−), metastatic (M−), or resection (R−) status (Table 1). We did observe a tendency toward a higher incidence of CBS in oropharyngeal HNSCC when compared with unaltered counterparts (53% vs 39%; $P = .06$; Table 1). However, comparing CBS onset in the entire cohort with respect to different tumor localization, we found no differences in the primary tumor site ($P = .41$; data not shown).

### 3.2 | CBS-related data

The median and mean age at CBS onset was 63 years (Table 2). The median and mean time between therapy and CBS was 14 months and 19 ± 21 months, respectively. The majority of patients (94%) were seen with manifest carcinoma at the time of diagnosis (Table 2). Only two patients became symptomatic with acute bleeding presenting simultaneously with primary HNSCC. All other patients presented with recurrence at the primary tumor site. Eight patients experienced further lymph node recurrence, three patients presented distant metastases, and one patient presented lymph node recurrence along with distant metastases (Table 2). None of our patients were seen with lymph node recurrence or distant metastases without simultaneous recurrence at the primary tumor site (Table 2). Three patients (8%) were diagnosed with two affected vessels. The external carotid artery and its branches accounted for the most affected vessels (75%), followed by the common carotid artery (17%).

**TABLE 1** Description of the entire HNSCC cohort subdivided into patients with CBS (CBS+) and unaltered controls (CBS−)

| | CBS+ | CBS− | *P*-value |
|---|---|---|---|
| No. of patients with HNSCC by CBS, n (%) | 36 (3) | 1036 (97) | |
| Age at diagnosis (y) | | | .29 |
| Mean ± SD | 62 ± 11 | 60 ± 10 | |
| Median | 61 | 60 | |
| Sex, n (%) | | | .27 |
| Male | 26 (72) | 826 (80) | |
| Female | 10 (28) | 210 (20) | |
| Primary location, n (%) | | | .06 |
| Nasopharynx | 1 (3) | 20 (2) | |
| Oropharynx | 19 (53) | 407 (39) | |
| Hypopharynx | 9 (25) | 212 (21) | |
| Larynx | 5 (14) | 204 (20) | |
| Oral cavity | 2 (6) | 153 (15) | |
| Sinonasal | 0 | 35 (3) | |
| CUP | 0 | 5 (1) | |
| T status, n (%) | | | .001 |
| T1 | 4 (11) | 272 (26) | |
| T2 | 6 (17) | 310 (30) | |
| T3 | 11 (31) | 218 (21) | |
| T4 | 15 (42) | 231 (22) | |
| N status, n (%) | | | .29 |
| N0 | 11 (31) | 411 (40) | |
| N1 | 4 (11) | 127 (12) | |
| N2a,b | 12 (36) | 300 (29) | |
| N2c | 7 (19) | 165 (16) | |
| N3 | 1 (3) | 33 (3) | |
| M status, n (%) | | | .53 |
| M0 | 35 (97) | 995 (96) | |
| M1 | 1 (3) | 41 (4) | |
| UICC stage, n (%) | | | |
| I | 1 (3) | 159 (15) | .004 |
| II | 3 (8) | 132 (13) | |
| III | 4 (11) | 176 (17) | |
| IV | 28 (78) | 564 (54) | |
| Grading, n (%) | | | .66 |
| G1 | 2 (6) | 35 (4) | |
| G2 | 21 (58) | 497 (48) | |
| G3 | 13 (36) | 466 (45) | |
| Therapy | | | .002 |
| Surgery | 3 (8) | 186 (18) | |
| Surgery + aC/RT | 11 (31) | 498 (48) | |
| pC/RT | 22 (61) | 352 (34) | |

Abbreviations: A/pC/RT, adjuvant/primary chemoradiation; CBS, carotid blowout syndrome; CUP, Cancer of unknwon primary; HNSCC, head and neck squamous cell carcinoma.

### 3.3 | CBS risk stratification and outcome

In the entire HNSCC cohort, the mean CBS-free survival time was 130 months. Cox regression for forward selection analyzing the T status, UICC stage, tumor localization, therapeutic regimen, and recurrence at the primary tumor site showed that the therapeutic regimen (hazard ratio [HR], 2.8; 95% CI, 1.6-5.6; $P = .001$) and recurrence at the primary tumor site (HR, 7.6; 95% CI, 3.0–14.7; $P < .0001$) are associated with an increased risk for developing CBS. Patients with CBS demonstrated significantly reduced median and mean OS (29/39 months) when compared with unaltered counterparts (86/75 months; $P = .03$; Figure 1A). Again, the Cox regression for forward selection was performed to analyze the parameters that affect survival. These parameters included the presentation of oropharyngeal carcinoma (HR, 1.2; 95% CI, 1.0-1.3; $P < .0001$), increased T status (HR, 1.1; 95% CI, 1.0-1.2; $P = .04$), and UICC stage (HR, 1.4; 95% CI, 1.3-1.6; $P < .0001$), patients with primary C/RT (HR, 2.0; 95% CI, 1.7-2.4; $P < .0001$), and patients with recurrence at the primary tumor site (HR, 2.4; 95% CI, 1.9-2.9; $P < .0001$) (Table 3). According to the OS, the mean RFS was significantly better in unaltered patients (86 months) when compared with patients with CBS (22 months; $P < .0001$; Figure 1B).

### 3.4 | CBS risk stratification and outcome after adjustment to UICC IV

After adjustment for the UICC stage IV mean, CBS-free survival was reduced to 108 months. Again, the Cox regression for forward selection was used to identify risk factors for CBS: the therapeutic regimen (HR, 2.9; 95% CI, 1.2-7.3; $P = .02$) and recurrence at the primary tumor site (HR, 5.3; 95% CI, 1.9-12.7; $P < .0001$) were again associated with an increased risk for CBS. Median and mean OS were comparable in both groups (CBS+: 30/41 vs CBS−: 31/52; $P = .96$; Figure 1C).

In a further analysis of survival rates, the Cox regression for forward selection showed that increased T status (HR, 1.9; 95% CI, 1.8-2.4; $P = .03$), patients with primary C/RT (HR, 2.0; 95% CI, 1.6-2.6; $P < .0001$), and patients with recurrence at the primary tumor site (HR, 1.9; 95% CI, 1.6-2.7; $P < .0001$) were at an increased risk of death associated with CBS (Table 4). Subsequently, the median and mean RFS were significantly better in unaltered patients (61/67 months) when compared with patients with CBS (14/24 months; $P < .0001$; Figure 1D).

## 4 | DISCUSSION

CBS is a devastating complication of head and neck therapy. CBS is rare, presenting in 2.6% to 4.3% of cases of head and neck treatment, with higher rates in patients who undergo

**TABLE 2** Parameters associated with carotid blowout syndrome

| | |
|---|---|
| No. of all patients with HNSCC with CBS | 36 |
| Age at bleeding (y) | |
| Mean ± SD | 63 ± 14 |
| Median | 63 |
| Time initial diagnosis to bleeding (mo) | |
| Mean ± SD | 19 ± 21 |
| Median | 14 |
| Manifest carcinoma, n (%) | 34 (94) |
| Progression | 9 (25) |
| Recurrence | 25 (69) |
| Local | 13 (36) |
| Regional | 0 |
| Distant | 0 |
| Locoregional | 8 (22) |
| Multiple sites | 4 (11) |
| Initial diagnosis at the time of bleeding | 2 (6) |
| Affected vessel, n (%) | |
| Common carotid artery | 6 (17) |
| Internal carotid artery | 3 (8) |
| External carotid artery | 27 (75) |
| Branches of the external carotid artery | 12 (33) |

Abbreviations: CBS, carotid blowout syndrome; HNSCC, head and neck squamous cell carcinoma.

radical neck dissection.[1,12,16] In our comprehensive cohort, we pooled all treatment modalities together, and the overall CBS rate was 3%, which was in agreement with the incidence rate reported in the literature. CBS is subdivided into three clinical subtypes depending on the severity of the bleeding: threatened, impending, and acute.[18,19] For this reason, it is of crucial importance to stratify high-risk patients quickly to decrease peri-interventional and postinterventional mortality and morbidity following CBS. As data that enable detailed risk stratification in clinical settings is lacking in the literature, we performed a longitudinal data analysis to identify predictive clinical risk factors.

Our data revealed the T status and UICC stage as significantly increased in patients with CBS, but there were no significant differences in age, nodal, or resection status. Primary (chemo)radiation was most common in the patients' history with CBS (61%), whereas only 34% of unaltered patients without CBS were treated with this therapy modality. Only 8% (n = 3) of patients treated by surgery without adjuvant therapy developed metachronous CBS, suggesting that CRT is a predominant but not obligate precondition for CBS. At the median CBS onset after 14 months, the vast majority of patients (94%) were seen with manifest locoregional tumors either as progression (25%) or recurrence (75%) concurrent with a history of either primary or adjuvant (chemo)radiation (92%). As these variables are typically strongly correlated, further multivariate analysis is needed to reveal independent and clinically relevant predictors leading to CBS. Therefore, we included all parameters that were significantly associated with the occurrence of CBS in the Cox regression model. Local recurrence at the primary tumor site was determined as the strongest, most significant predictor with a HR of 7.6, followed by the therapeutic regime; CRT had a HR of 2.8. In terms of OS, these parameters are most significant, among other significant risk factors such as T status, UICC, and the specific localization of oropharyngeal subsite. According to the OS data, the mean RFS was significantly better in unaltered patients (86 months) when compared with patients with CBS (22 months). To avoid the selection bias, patients were analyzed separately only for UICC stage IV, confirming that the therapeutic regimen (HR, 2.9; $P = .02$) and recurrence at the primary tumor site (HR, 5.3; $P < .0001$) were associated with an increased risk of CBS. Overall, our results revealed that the risk factor of local recurrence predicts the incidence of CBS better than CRT.

Previous studies have suggested radical neck dissection and radiation as major etiological factors in the development of CBS, because they can cause distinct long-term alteration of vessels.[12,16,20,21] CRT can cause the obliteration of the carotid's vasa vasorum, which leads to fibrosis of the adventitia and subsequent weakening of the arterial wall.[5,22] In today's treatment regimes, radical neck dissection might be neglected when considering CBS risks, because this treatment has been mostly replaced by selective neck approaches. None of the patients in our cohort had undergone radical neck dissection.

The risk for developing CBS was estimated to be increased sevenfold after radiation in a descriptive analysis.[16] After re-irradiation, the risk is increased another four times, although this increased risk was not associated with chemotherapy and/or salvage surgery.[12,13] Only one controlled study with 62 patients (31 with CBS) with nasopharyngeal cancer after curative radiotherapy has been published, which revealed both local (but not neck) recurrence and re-irradiation as significant risk factors in an univariate analysis.[13] McDonald et al. performed a meta-analysis of a total of 1554 patients from 27 studies who were re-irradiated to treat recurrent head and neck cancer. The incidence rate of CBS was 2.6% with a median time to CBS of 7.5 months (range 0-54 months); the results of the analysis showed that 76% of these cases had a fatal outcome. Until now, no comparable data about multivariate risk stratification has been published that could further distinguish between the toxicity of radiation and local recurrence as predictors of CBS. Both factors frequently co-occur with the median CBS onset at 14 months. This concurrence may result in interdependency and could bias the multivariate

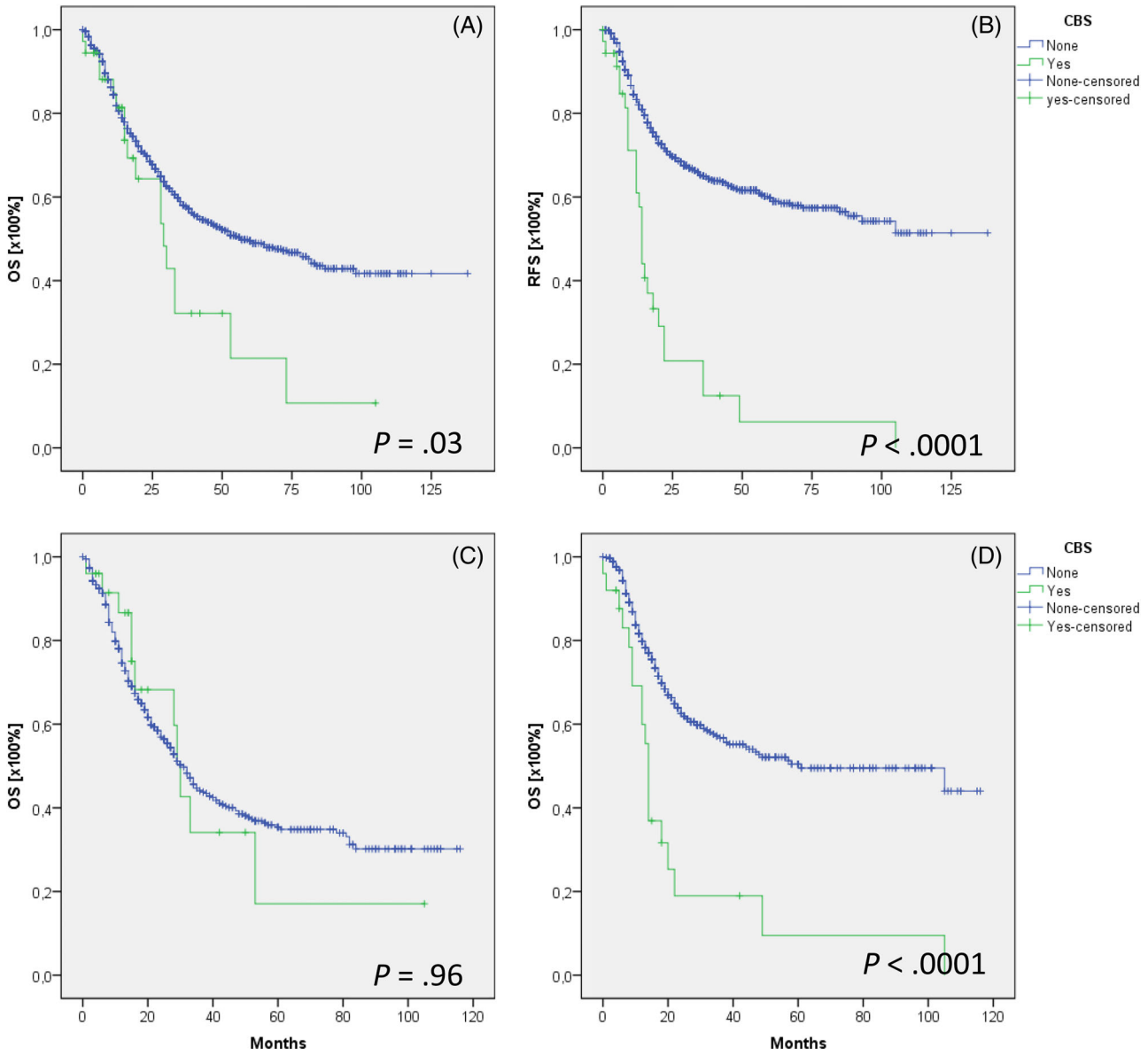


**FIGURE 1** Overall survival (OS) and recurrence-free survival (RFS) in patients with and without CBS (A and B) along with data adjusted for Union Internationale Contre le Cancer IV occurrence (C and D) [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 3** Cox regression for forward selection analyzing T status, tumor localization, therapeutic regimen, and recurrence at the primary tumor site as OS-modifying parameters

| | HR | 95% CI | *P*-value |
|---|---|---|---|
| Primary tumor localization | 1.2 | 1.0-1.3 | <.0001 |
| T status | 1.1 | 1.0-1.2 | .04 |
| UICC stage | 1.4 | 1.3-1.6 | <.0001 |
| Therapeutic regimen | 2.0 | 1.7-2.4 | <.0001 |
| Recurrence at the primary tumor site | 2.4 | 1.9-2.9 | <.0001 |

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; UICC, Union Internationale Contre le Cancer.

**TABLE 4** Cox regression for forward selection analyzing T status, tumor localization, therapeutic regimen, and recurrence at the primary tumor site as OS-modifying parameters after UICC IV adjustment

| | HR | 95% CI | *P*-value |
|---|---|---|---|
| T status | 1.9 | 1.8-2.4 | .03 |
| CRT | 2.0 | 1.6-2.6 | <.0001 |
| Local recurrence | 1.9 | 1.6-2.7 | <.0001 |

Abbreviations: CI, confidence interval; CRT, Chemoradiation; HR, hazard ratio; OS, overall survival; UICC, Union Internationale Contre le Cancer.

analysis. Yamazaki et al. presented multivariate data about a small cohort treated by re-irradiation for recurrent HNSCC and found that the area of lymph node irradiation and the presence of ulceration were significant risk factors for CBS.[21] However, these findings cannot address the question of whether tumor recurrence alone or tumor recurrence concurrent with re-irradiation increases the risk of CBS.

Nonetheless, with recent increases in HPV-induced oropharyngeal cancer and targeted therapy regimes, both long-term survival after multimodal therapy, particularly comprising CRT, and the rates of late locoregional recurrence can be expected to increase.[23,24] This emphasizes the necessity for early assessment of a patient´s individual risk profile for CBS to help guide the application of preventive endovascular procedures such as carotid stenting. This procedure can reinforce vessel walls to prevent the complication of acute CBS. The findings presented above may therefore contribute to the development of a targeted risk stratification method for patients at risk of CBS.

## 5 | CONCLUSION

As long-term survival rates after multimodal therapy increase over time in patients with head and neck cancer, and the incidence rates of HPV-induced carcinogenesis are rising (with subsequently higher rates of CRT), the prevalence of CBS is becoming more important to clinicians. High-risk patients for CBS might be effectively stratified by the rates of locoregional tumor recurrence and previous CRT treatment.

## CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

## ORCID

*Andreas Knopf* https://orcid.org/0000-0001-5196-1803

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