Risk Factors for Hemorrhage After Chemoradiation for Oropharyngeal Squamous Cell Carcinoma

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**Importance:** Knowledge of the risk factors for oropharyngeal hemorrhage after chemoradiation therapy will guide clinicians in monitoring high-risk patients in order to prevent a life-threatening complication.

**Objective:** To determine risk factors for the development of oropharyngeal hemorrhage following chemoradiation therapy without surgery for oropharyngeal squamous cell carcinoma.

**Design:** Retrospective review of medical records of patients treated during the period January 2005 through December 2010.

**Setting:** University of Louisville Hospital.

**Participants:** The study population comprised 139 patients with a diagnosis of oropharyngeal squamous cell carcinoma who were treated with chemoradiation therapy without surgery. All patients received primary treatment from our institution. Those with recurrent tumors or prior oropharyngeal resections, with the exception of tonsillectomy, were excluded from the study. Patients were divided into 2 groups: those who did not hemorrhage following treatment (n=129) and those who developed oropharyngeal hemorrhage (n=10), defined as hemorrhage necessitating procedural intervention.

**Main Outcomes and Measures:** Four clinical variables were measured: T category, radiation therapy method, weight loss, and age.

**Results:** Results from logistic regression analysis showed that significant risk factors for hemorrhage were advanced T category (odds ratio [OR], 8.40 [95% CI, 2.44-26.61]; P<.001), radiation therapy method (OR, 7.94 [95% CI, 2.64-<999.90]; P=.008), weight loss (OR, 0.89 [95% CI, 0.79-0.98]; P=.01), and increased age (OR, 0.93 [95% CI, 0.86-0.99]; P=.03). After multiple logistic regression analyses, only advanced T category remained statistically significant (adjusted OR, 6.6 [95% CI, 1.2-∞]; P=.02). Results from Kaplan-Meier survival analysis on all patients showed that those who hemorrhaged had significantly shorter survival time than those who did not (P=.04). However, after multivariate analysis with a Cox proportional hazards regression model, hemorrhage no longer remained a significant factor (P=.13).

**Conclusions:** For patients with oropharyngeal squamous cell carcinoma treated with chemoradiation without surgery, advanced T category is the most important determinant of developing oropharyngeal hemorrhage; furthermore, hemorrhage occurs in the presence of either recurrent and/or persistent disease or radiation necrosis. Survival analysis indicates that development of hemorrhage is a poor prognostic marker for overall survival.


Oropharyngeal hemorrhage is a rare but life-threatening complication following treatment of oropharyngeal squamous cell carcinoma (OSCC). Squamous cell carcinomas are the most frequently occurring cancer in the oropharynx, making up 10% of all head and neck cancers. Half a million people receive a diagnosis of squamous cell carcinoma of the head and neck every year, and most present with advanced-stage (T3 or T4) tumors. Standard treatment of advanced oropharyngeal carcinomas includes a combination of chemotherapy and radiation therapy with or without surgery. For some patients, surgery is not an option because of advanced disease or patient preference. The use of combined chemoradiation and radiation therapy alone can cause secondary adverse effects, including erosion and ulceration of skin and mucosa, xerostomia, fibrosis of underlying soft tissue, and in some cases osteoradionecrosis. Additional sequelae are the secondary effects on surrounding vasculature, including premature atherosclerosis with stenosis and weakening of arterial walls due to adventitial fibrosis, fragmentation of elastic filaments, and destruction of the vasa vasorum. Following che-
moradiation therapy, spontaneous hemorrhage can result as a consequence of weakened arterial walls.\textsuperscript{7,8} In patients with head and neck cancer, previous radiation therapy increased the risk of vascular erosion 7.6-fold.\textsuperscript{8}

Vascular erosion leading to hemorrhage is common in patients with advanced-stage tumors, recurrent tumors, infection, and pharyngocutaneous fistula.\textsuperscript{9} More concerning, however, are cases of vascular erosions in patients after cancer treatment who show no histological evidence of tumor recurrence. In these situations, severe hemorrhage can be fatal (40% of cases).\textsuperscript{7} Hemorrhage may induce airway obstruction, cause aspiration of blood, and result in asphyxiation. Interventions for oropharyngeal hemorrhage are technically difficult to perform because of previous radiation-induced damage, hemostatic fluid imbalance, difficulty in localizing the hemorrhage, and decreased visualization leading to unsafe dissection.\textsuperscript{5,11} Even when intervention is successful, rates of neurological morbidity approach 60%, chiefly as a result of brain hypoxia.\textsuperscript{8,12} In this article, we analyze 139 patients with OSCC who underwent concomitant chemoradiation therapy without surgery to identify risk factors for life-threatening oropharyngeal hemorrhage.

### METHODS

Retrospective review of medical records identified patients who had undergone chemoradiation therapy without surgery for treatment of T1 through T4 OSCC during the period January 2005 through December 2010. Some patients were not candidates for surgery, and others chose nonsurgical modalities. All patients received primary treatment at our institution. Those with recurrent tumors or past oropharyngeal surgical procedures, with the exception of tonsillectomy, were excluded from the study.

A total of 139 patients met the criteria for the study. Patients were divided into 2 groups, those who developed acute, life-threatening, arterial hemorrhage (n=10) and those who did not hemorrhage (n=129). Hemorrhage was defined as blood loss requiring medical and/or surgical intervention, including endovascular treatment, as well as surgical exploration. Cases of hemorrhaging that was controlled by minor cautery or packing or that was observed to stop without intervention were excluded from the study. Seventy percent of patients with hemorrhage were admitted for a mean of 4.28 days following intervention. Of the 10 patients demonstrating hemorrhage, 7 had recurrence or persistent cancer and the remaining 3 had no evidence of disease.

Medical records were retrospectively reviewed for the variables age, sex, race, tumor stage, tumor location, radiation method (conventional radiotherapy vs intensity-modulated radiation therapy [IMRT]), weight loss, and outcome. Bivariate and multiple logistic regression, using the conditional exact test, assessed the relationship of these variables with vascular erosion. Overall comparisons of survival curves between patients who did and did not hemorrhage were calculated using Kaplan-Meier methods and log rank tests. Cox proportional hazards regression models were also used to assess survival rates between patients who did and did not hemorrhage.

### RESULTS

Of 139 patients, 10 (7.2%) hemorrhaged following concurrent chemoradiation therapy. Nine of the 10 patients who hemorrhaged had tumors of T category 3 or 4, whereas 68 of 129 patients who did not hemorrhage (53%) had tumors of T category 3 or 4. Patient demographics and TNM staging are presented in Table 1. The mean time from completion of treatment to hemorrhage was 69.1 days. Of the 10 patients who hemorrhaged, 7 were admitted to the hospital for treatment and 3 bled to death at home. Disease status for the patients who hemorrhaged was determined at the most recent follow-up appointment, which was within 2 months of hemorrhage for all 10 patients. At that follow-up appointment, 7 patients showed evidence of recurrent or persistent disease, whereas the other 3 demonstrated a persistent radiation soft-tissue ulcer without pathologic evidence of recurrent tumor. The most common presentation was acute hemorrhage (n=8) vs recurrent and/or persistent hemorrhage.

### Table 1. Demographic Characteristics of Patients With Oropharyngeal Squamous Cell Carcinoma Who Hemorrhaged

<table>
<thead>
<tr>
<th>Patient No./ Sex</th>
<th>Race</th>
<th>TNM Stage</th>
<th>Hospital Admission Diagnosis</th>
<th>Persistent vs Acute Hemorrhage</th>
<th>Intervention</th>
<th>Blood Transfusion</th>
<th>Disease Status</th>
<th>Posttreatment Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>African American</td>
<td>T4N2cM0</td>
<td>Oropharyngeal bleed</td>
<td>Acute</td>
<td>Tracheostomy and surgical cauterization</td>
<td>Yes</td>
<td>Persistent disease</td>
<td>Recurrent hemorrhage</td>
</tr>
<tr>
<td>2/M</td>
<td>White</td>
<td>T2N2cM0</td>
<td>Oropharyngeal bleed</td>
<td>Acute</td>
<td>Intubation and surgical cauterization</td>
<td>No</td>
<td>No evidence of disease</td>
<td></td>
</tr>
<tr>
<td>3/F</td>
<td>White</td>
<td>T4N2bM0</td>
<td>Weakness/fatigue</td>
<td>Acute</td>
<td>Intubation and surgical cauterization</td>
<td>Yes</td>
<td>Tumor recurrence</td>
<td></td>
</tr>
<tr>
<td>4/M</td>
<td>African American</td>
<td>T4N2M0</td>
<td>Oropharyngeal bleed</td>
<td>Acute</td>
<td>Embolization</td>
<td>Yes</td>
<td>Tumor recurrence</td>
<td></td>
</tr>
<tr>
<td>5/M</td>
<td>White</td>
<td>T4aN1M0</td>
<td>Oropharyngeal bleed</td>
<td>Persistent</td>
<td>Embolization</td>
<td>Yes</td>
<td>No evidence of disease</td>
<td>Tracheostomy</td>
</tr>
<tr>
<td>6/M</td>
<td>White</td>
<td>T4N1M0</td>
<td>Acute</td>
<td>None</td>
<td>...</td>
<td>...</td>
<td>Persistent disease</td>
<td></td>
</tr>
<tr>
<td>7/M</td>
<td>White</td>
<td>T4N0M0</td>
<td>Acute</td>
<td>None</td>
<td>...</td>
<td>...</td>
<td>No evidence of disease</td>
<td></td>
</tr>
<tr>
<td>8/M</td>
<td>White</td>
<td>T3N0M0</td>
<td>Acute</td>
<td>Embolization</td>
<td>No</td>
<td>No</td>
<td>Tumor recurrence</td>
<td></td>
</tr>
<tr>
<td>9/M</td>
<td>African American</td>
<td>T4N2bM0</td>
<td>Tongue mass</td>
<td>Acute</td>
<td>Embolization</td>
<td>Yes</td>
<td>Tumor recurrence</td>
<td></td>
</tr>
<tr>
<td>10/M</td>
<td>African American</td>
<td>T4bN2cM0</td>
<td>...</td>
<td>Acute</td>
<td>Cauterization</td>
<td>No</td>
<td>Persistent disease</td>
<td></td>
</tr>
</tbody>
</table>

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One patient was admitted for treatment of a tongue mass, and 1 patient was admitted for treatment of weakness and inanition. The intervention most commonly delivered was angiography with embolization performed by an interventional radiologist. Two patients required intubation with surgical cauterization. One patient underwent tracheostomy with surgical packing of a small ulcer. The 3 patients who bled to death at home received no intervention. Five of the 7 hemorrhaging patients (71%) who survived to reach the hospital required blood transfusion. Of the 7 surviving patients, 2 experienced additional complications that ultimately resulted in death, including recurrent hemorrhage and the need for tracheostomy.

The results of the hemorrhage vs nonhemorrhage analyses are given in Table 2. Results from the logistic regression analysis showed that significant risk factors for oropharyngeal hemorrhage were advanced T category (P < .001), radiation therapy method (P = .008), weight loss of at least 2.3 kg (P = .01), and increased age (P = .03). After multivariate logistic regression analysis, only advanced T category remained statistically significant (P = .02).

Kaplan-Meier survival analysis of data from all patients demonstrated that those who hemorrhaged had significantly shorter mean survival time than those who did not (13 vs 50 months; P = .04) (Figure). Of those who hemorrhaged, patients with evidence of recurrent or persistent disease had a mean survival time of 3.6 months after hemorrhage, whereas those with no evidence of disease had a mean survival time of 16.5 months after hemorrhage. However, after multivariate analysis with a Cox proportional hazards regression model, hemorrhage no longer remained a significant factor (P = .13). All other variables, when analyzed separately, were not significant.

**Table 2. Risk Factor Analysis**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No. of Patients</th>
<th>Mean (SD)</th>
<th>Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>10</td>
<td>3.7 (0.7)</td>
<td>8.40 (2.44-24.61)</td>
<td>6.63 (1.20-∞)</td>
<td>.02</td>
</tr>
<tr>
<td>No hemorrhage</td>
<td>129</td>
<td>2.6 (0.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss of ≥2.3 kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>7</td>
<td>8.8 (10.0)</td>
<td>0.89 (0.79-0.98)</td>
<td>0.92 (0.81-1.03)</td>
<td>.15</td>
</tr>
<tr>
<td>No hemorrhage</td>
<td>83</td>
<td>19.9 (14.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>10</td>
<td>51.6 (5.1)</td>
<td>0.93 (0.86-0.99)</td>
<td>0.91 (0.81-1.03)</td>
<td>.67</td>
</tr>
<tr>
<td>No hemorrhage</td>
<td>129</td>
<td>58.5 (10.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation therapy method</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No hemorrhage</td>
<td>60</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>7</td>
<td>NA</td>
<td>6.20 (0.76-287.13)</td>
<td>1.00 (0.16-∞)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>No hemorrhage</td>
<td>67</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2</td>
<td>NA</td>
<td>79.94 (2.64-&lt;999.90)</td>
<td>. . . . . .</td>
<td></td>
</tr>
<tr>
<td>No hemorrhage</td>
<td>1</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IMRT, intensity-modulated radiation therapy; NA, not applicable; ellipses, adjusted odds ratios could not be estimated.

a Odds ratio based on a weight loss increment of 5 pounds (2.3 kg).
b Odds ratio based on a 5-year increase in age.

Figure. Kaplan-Meier survival analysis of patients with oropharyngeal squamous cell carcinoma demonstrated that those who hemorrhaged had significantly shorter mean survival time than those who did not (13.0 vs 50.0 months; P = .04).

Oropharyngeal hemorrhage can be a life-threatening complication of OSCC treatment. Our results showed that overall survival (OS) of patients who hemorrhaged was significantly less (OS, 50%) than for those who did not hemorrhage (OS, 74%). Our study demonstrates that hemorrhaging patients survive a mean of 13 months, with those who hemorrhage because of recurrent and/or persistent disease surviving a mean of 3.6 months and those who hemorrhage with no evidence of disease surviving a mean of 16.5 months. Review of the literature shows that OS after oropharyngeal hemorrhage is typically less than 2 years.13 The incidence of oropharyngeal hemorrhage following treatment differs among studies, from less than 0.3%
to greater than 10% depending on treatment method and hemorrhage definition. Overall, the rate of posttreatment hemorrhage in our patient population was 7.2%.

Appropriate management of OSCC is controversial. A large meta-analysis conducted by Parsons et al reported similar survival rates for patients undergoing surgery alone or a combination of surgery and radiotherapy. Several studies have shown improved OS using concomitant chemotherapy and radiation therapy compared with radiation therapy alone. Individual patient history must be taken into account when designing a treatment protocol to maximize the cytotoxic effect on the patient’s cancer while minimizing treatment-related complications.

The presentation of oropharyngeal hemorrhage varies with the severity of the bleeding. In our series, 8 of 10 patients presented with acute hemorrhage, whereas only 2 presented with persistent hemorrhage, which manifested as recurrent hemoptysis that steadily increased in severity. Presentations from other institutions have included acute pharyngeal hemorrhage, as well as hemoptysis, melena, and epistaxis. Interestingly, in several case reports of acute oropharyngeal hemorrhage, it was found that blood collected in the hypopharynx and was swallowed by the patients to avoid aspiration. The aspirated blood caused irritation of the gastrointestinal tract, and as a result these patients were evaluated for gastrointestinal complications instead of oro-pharyngeal hemorrhage. With such a variety of presentations, it can be difficult to assess the cause of hemorrhage and, furthermore, to manage it.

Advanced T category significantly increases the risk of posttreatment hemorrhage following concomitant chemoradiation therapy for OSCC, and furthermore, hemorrhage occurred in the presence of recurrent and/or persistent disease (7 of 10 patients) or radiation-induced necrosis (3 of 10 patients). In our study, 9 of 10 patients who hemorrhaged had tumors of T category 3 or 4, compared with only 53% of patients who did not hemorrhage. The growth of advanced tumors is accompanied by progressive infiltration, invasion, and destruction of surrounding tissues. Rapidly dividing tumors recognize no anatomical barriers and can easily ulcerate into blood vessels and other normal tissue. Erosive and destructive growth in addition to the expanding pressure of a tumor can have devastating consequences on any anatomical structure that the tumor encounters. Even if hemorrhage caused by the tumor is managed, the risk of reoccurrence is high if antitumor therapy is not administered. The prognosis for advanced T category head and neck tumors is dismal, with a 5-year survival rate of less than 50%.

In addition to the poor surviviorship of advanced T category tumors, complications of management of these tumors include an increased risk of hemorrhage. Advanced tumors may necessitate additional rounds of cancer chemotherapy and a combination of chemotherapy agents. Erosion of the protective mucosa leaves underlying blood vessels susceptible to injury and infection. In addition, hematologic toxicities, including leukopenia and thrombocytopenia, increase the likelihood for infection and hemorrhage. Schrock et al demonstrated that infection increases incidence of posttreatment hemorrhage.

Advanced OSCC may also necessitate higher doses of radiation therapy and additional booster doses to the primary tumor site. This may compromise the integrity of the surrounding vasculature. The resultant radiation necrosis is likely the cause of hemorrhage for the 3 of 10 patients in this series who hemorrhaged with no evidence of disease. This reasoning is supported by the fact that none of these patients demonstrated pretreatment vessel involvement either clinically or radiologically on contrast computed tomography. Oropharyngeal cancers, especially tonsil cancers, bear a close anatomic relationship to the carotid arterial system, with the superior constrictor muscle, buccopharyngeal fascia, and carotid sheath forming a thin set of barriers between the tumor and carotid, even in cases in which there is not vascular abutment or encasement. Radiation therapy destroys the vasa vasorum of blood vessels, leading to disintegration of elastic filaments and fibrosis of vessel adventitia. The irradiated blood vessels become fragile and are more prone to rupture. In addition to direct toxic effects on cancer tissue, radiation therapy also compromises closely associated normal tissue. Patients who undergo repeated radiation treatments may receive cumulative radiation doses totaling over 200% of the tolerance of normal tissues. The consequences of additional radiation therapy include xerostomia, erosion and ulceration of skin and mucosa, and fibrosis of underlying soft tissue. As with chemotherapy, this leaves underlying vessels vulnerable to injury. Although higher doses of radiation come with substantial morbidity, investigators at the University of Chicago have reported that administration of an additional dose of radiation is correlated (P = .005) with survival. Because of this, use of radiation therapy as a treatment modality for OSCC must be evaluated on a case-by-case basis, weighing the potential for both efficacy and treatment-related complications including death.

Our analysis revealed that in a univariate model, radiation method (conventional vs IMRT) was a risk factor for hemorrhage, with IMRT being less likely to cause hemorrhage. Recent studies have had mixed results regarding use of IMRT for treatment of OSCC. Some studies have demonstrated IMRT’s ability to localize radiation to specific anatomical structures, thus causing fewer toxic effects to surrounding structures. Other investigators argue that this specificity, due to lack of homogenous dosing, can lead to subtherapeutic radiation levels to the tumor. Further evaluation of hemorrhage rates should be reported in large multicenter clinical trials to determine whether hemorrhage rates are reduced with IMRT or are sensitive to method, dose, and fractionation patterns of radiation therapy.

Although none of the patients in this study underwent surgical treatment for OSCC, this modality reportedly may increase the risk of acute hemorrhage postoperatively. Tumors form intimate anatomic relations with critical structures of the oropharynx, making dissection difficult. Distortions of the anatomy caused by advanced tumors can lead to insufficient visualization and unsafe dissection. In a study performed by Szudek and Taylor, it was reported that a major risk factor for hemorrhagic complications following pharyngeal wall surgery was advanced tumor stage. Other investigators have reported that dur-
ing surgical reconstruction of the oropharynx, advanced T category tumors are more likely to necessitate blood transfusions later. From this analysis, we can postulate that advanced T category may be a risk factor for posttreatment hemorrhage in both surgically and nonsurgically treated patients with oropharyngeal cancer.

One of the reasons for the high mortality associated with oropharyngeal hemorrhage is that safe management can be complex. Intervention methods for our patient population are demonstrated in Table 1. Massive bleeding necessitates immediate action, and interventions in previously irradiated necks are difficult to perform. Furthermore, interventions can become complicated by hemostatic imbalances, difficulty in localizing the hemorrhage, and decreased visualization leading to unsafe dissection. For acute stabilization of patients, first-line protocols include emergency stabilization of respiratory and cardiovascular function with tracheostomy or intubation. In our sample, 1 emergency tracheostomy was required and 2 patients required intubation before further management of their hemorrhage could be performed. Once patients are stabilized, hemostasis can be achieved by means of ligation of vessels, surgical cautery, local packing, or endovascular therapy. Techniques such as carotid bypass require more time than is available. Surgical ligation of major arteries is an effective method of hemostasis although rarely performed because of difficult transcutaneous access from fibrosed tissue or tumor mass obstructions. In addition, ligation has been associated with a high mortality rate (40%) due to backflow from collateral circulation and a higher incidence of neurological morbidities. Pharyngeal packing of the wound site can be traumatic for the patient, necessitating sedation, and there are complications associated with it. Increasingly, the preferred management option is endovascular therapy with stents and/or embolization performed by an interventional radiologist. The type of procedure (reconstructive vs deconstructive) depends on the cause of hemorrhage and/or disease status, which is not always known at admission. In cases of uncertainty or urgency, deconstructive procedures are recommended. Although balloon occlusion testing for neurologic deficits should be performed for patients with potential carotid hemorrhages, there is only a limited amount of time before exsanguination, so balloon testing may be contraindicated in this life-threatening scenario. When the balloon test cannot be performed, deconstructive occlusion of the carotid artery may be performed with glue embolization or coil embolization. A benefit of this method is that it may not necessitate anticoagulation therapy, thus reducing the risk of additional hemorrhage. In oropharyngeal hemorrhage as a result of radiation necrosis in patients with no evidence of disease, reconstructive procedures can be performed because there is no risk of tumor progression. This method, however, necessitates long-term anticoagulation therapy, predisposing patients to the possibility of recurrent bleeding. Overall, endovascular management has demonstrated improved safety and effectiveness over surgical management because of its ability to stop oropharyngeal hemorrhage or hemorrhage from tumor vasculature while better preserving the ves-

360
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reconstruction of the pharyngeal wall.28 These populations, however, are different. The implication is that nonsurgically treated patients with increased primary tumor volume have a greater propensity for bleeding.

In conclusion, vascular erosion following concomitant chemotheraphy and radiation therapy represents a rare yet potentially life-threatening complication of OSCC treatment. Our study found that for patients with OSCC treated with chemoradiation without surgery, advanced T category is the most important determinant of developing oropharyngeal hemorrhage. Furthermore, hemorrhage is more likely to occur in the context of recurrent and/or persistent disease or radiation necrosis. Results from survival analysis indicate that development of hemorrhage is a poor prognostic marker for OS.

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Author Contributions: Dr Potts had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bumpous. Acquisition of data: Self and Wilson. Analysis and interpretation of data: Ziegler and Potts. Drafting of the manuscript: Self, Bumpous, and Ziegler. Critical revision of the manuscript for important intellectual content: Wilson and Potts. Statistical analysis: Ziegler. Administrative, technical, and material support: Self and Wilson. Study supervision: Potts.

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REFERENCES