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Carotid arterial blowout after organ preserving chemoradiation therapy in hypopharyngeal cancer

Paula Francezca Padua, MD[a], Hsuan-Yeh Fang, MD[a,b], Chi-Kuan Young, MD[c], Chih-Hua Yeh, MD[d], Chia-Chen Lin, MD[a], Chun-Ta Liao, MD[a], Tung-Chieh Joseph Chang, MD[e], Chung-Kan Tsao, MD[f], Shiang-Fu Huang, MD, PhD[a,g,*]

Abstract

Laryngeal preserving concurrent chemoradiation has been advocated for hypopharyngeal cancers. The use of radiotherapy (RT) in the larynx could lead to increased rates of radionecrosis. In this study, we investigated a rare but disastrous complication, carotid blow-out syndrome (CBS), related with the persistent radionecrosis.

Retrospective cohort study.

This retrospective study enrolled hypopharyngeal cancer patients with biopsy-proven pharyngeal and laryngeal chondronecrosis (PLCRN), which was rated by the Chandler Grading System. From 2002 to 2018, a total of 346 hypopharygeal cancer patients received upfront radiation therapy, 13 PLCRN patients were identified in a rate of 3.8%. All PLRN patients received RT with a mean radiation dose of 70.81 ± 0.85 Gy. All patients had Chandler Grade IV at the time of presentation, which was a mean of 15.08 months (range: 5-109 months) from the time of cancer diagnosis to PLCRN diagnosis. In 5 of the 13 PLCRN patients developed CBS. Three of the CBS originated from superior thyroid artery, one from lingual artery and one from the carotid artery. Three (60%) of the 5 CBS patients expired due to loss of airway and hemodynamic instability. Two (40%) were rescued by emergent airway secure and emergent angiographic embolization.

Persistent PLCRN could lead to disastrous vascular complications. CBSs were demonstrated to be more frequently originated from the branches of carotid artery rather than carotid artery per se. Clinical alert with early airway protection could strive for time to do interventions and prevent mortalities.

Abbreviations: CT = chemotherapy, HypoSCC = hypopharyngeal squamous cell carcinoma, IGRT = Image-Guided Radiation Therapy, IMAT = Intensity-Modulated ARC Therapy, IMPT = Intensity-Modulated Proton Therapy, IMRT = Intensity-Modulated Radiation Therapy, PLCRN = pharyngeal and laryngeal chondronecrosis, RT = radiotherapy, TNM = tumor-node-metastasis staging (AJCC 6th ed., 2002), VMAT = Volumetric-Modulated ARC Therapy.

Keywords: carotid artery blow-out syndrome, chemoradiation therapy, hypopharyngeal cancer, radionecrosis

1. Introduction

The hypopharynx is subdivided into 3 anatomical subsites: the pyriform sinuses, the posterior pharyngeal wall, and the post-cricoid area. Malignancy commonly arises in the pyriform sinuses (65-85%), less on other sites at 10% to 20% for the posterior pharyngeal wall, and 5% to 15% for the post-cricoid area.[1,2] As is the case at other sites in the head and neck, the overwhelming majority (95%) of hypopharyngeal cancers are squamous cell carcinomas.[1] Hypopharyngeal squamous cell carcinoma (HypoSCC) is rare, representing only about 7% of all cancers of the upper aerodigestive tract.[3] It is a biologically aggressive cancer, with a suboptimal five-year survival at 30%, owing to late presentation of advanced

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[a] Department of Otolaryngology, Head and Neck Surgery, Chang Gung Memorial, Linkou Branch, Taoyuan, Taiwan, [b] Department of Otolaryngology, MacKay Memorial, Hsin-Chu, Taiwan, [c] Department of Otolaryngology, Head and Neck Surgery, Chang Gung Memorial, Keelung Branch, Keelung, Taiwan, [d] Department of Medical Imaging and Intervention, Chang Gung Memorial, Linkou Branch, Taoyuan, Taiwan, [e] Department of Radiation Oncology, Chang Gung Memorial, Linkou Branch, Taoyuan, Taiwan, [f] Department of Plastic Surgery, Chang Gung Memorial, Linkou Branch, Taoyuan, Taiwan, [g] Graduate Institute of Clinical Medical Sciences, Chang Gung University, Taoyuan, Taiwan.

**Correspondence: Shiang-Fu Huang, Department of Otolaryngology, Chang Gung Memorial Hospital, No. 5 Fu-Shin Street, Kwei-Shan, Taoyuan, Taiwan (e-mail: bigmac@adm.cgmh.org.tw).*

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disease, with approximately 80% of patients at stage III or IV on presentation.[1,4]

According to guidelines, early stage disease can be treated equally effectively with surgery or radiotherapy (RT), while advanced stage disease be treated with surgery and RT, with or without chemotherapy (CT).[1,5] However, due to its biologically aggressive behavior requiring a great extent of oncologic surgery, including the removal of the larynx, hypopharynx, and upper cervical esophagus with free-tissue transfer reconstruction, laryngeal preserving concurrent chemoradiation has been advocated.[3]

Conversely, higher rates of late toxicities are observed owing to the increased use of larynx preservation strategies. According to the Radiation Therapy Oncology Group late radiation morbidity scoring schema, grading of radiation therapy toxicity to the larynx was grouped into grade 0 to 5.[6] Results of a 10-year intergroup trial on the use of concomitant chemoradiation in the management of hypopharyngeal cancer by RTOG 91-11 showed a cumulative rate of grade 3 or 5 toxicity ranging from 30.6% to 38%.[7] In the study by Katsoulakis et al, out of 100 patients with HypoSCC who underwent curative RT at their institution, 5 patients developed grade 3 laryngeal stenosis and 1 developed grade 4 toxicity, specifically cartilage necrosis, requiring laryngectomy after completion of RT.[3]

Chondroradionecrosis (CRN) is a rare and late complication, with an incidence of less than 1%, presenting within a year after RT, or even several years after initial treatment.[2,8,9] It is one of the most serious complications of RT, secondary to an end-stage inflammatory reaction of the small vessels, leading to extensive arteritis and thrombosis, and ultimately hyaline cartilage degeneration and necrosis.[10] CRN leads to an unstable cartilaginous framework causing airway problems by altering the size, mobility, and structure.[8] The management of CRN was widely discussed before.[12]

In this study, we intended to analyze a rare but disastrous complication, carotid artery blow-out syndrome (CBS), subsequent to CRN after organ preservation therapy for HypoSCCs treated with RT and their outcomes. The findings of angiography, management in the occurrence of CBS and the outcome were analyzed.

2. Patients and methods

2.1. HypoSCC patients

This retrospective case series study enrolled patients diagnosed with primary HypoSCC with biopsy-proven pharyngeal and laryngeal chondronecrosis (PLCRN) between 2002 and 2018 at our institution. Basic demographic data such as age, gender, and tumor-related features were gathered. In addition, the preoperative physical examination, complete blood count, chest radiographs, routine blood chemistry, liver ultrasound, computed tomography or magnetic resonance imaging scans of the head and neck, and whole-body bone scan or positron emission tomography were also collected. Duration of follow-up was from the time of cancer diagnosis until December 2019 or death. The study was approved by the institution review board (IRB: 202001560B0).

2.2. Treatment of HypoSCC

The American Joint Committee on Cancer Staging Manual (2002 edition) was used to establish the tumor-node-metastasis staging (AJCC 6th ed., 2002) (TNM) classification.[13] All patients underwent RT using conventional fractionation, as well as CT. The CT in all of these patients was cisplatin-based regimen.

2.3. Radionecrosis diagnosis and management

All the patients received regular follow-up in the clinic after treatment. In the first year after therapy, the patients returned to clinic 1 to 2 monthly. Three monthly in the 2nd year, 4-monthly in the 3rd year, and longer follow-up after the 3rd year. In the clinic, fiberoscopic examinations were done to evaluate the tumor status and any signs of infection or necrosis. Imaging studies including CT or MRI follow-up were arranged in the 3rd month, 6th month after treatment and then annually. The presence of radionecrosis was determined using biopsy and imaging. For any necrosis or non-healing wound in the hypopharynx, laryngoscopic biopsy would be performed and further imaging studies such as CT or MRI would be arranged. For patients that were proved to be PLCRN, a grading would be given (Table 1). Treatment included debridement, hyperbaric oxygen therapy, salvage laryngectomy, or observation. The bleeding episode and management were recorded from the chart and imaging reports.

2.4. Statistical analysis

Statistical analyses were performed by SPSS 18.0 software (SPSS Inc., Chicago, IL), $P < .05$ was considered statistically significant.

3. Results

From 2002 to 2018, a total of 513 oropharyngeal, hypopharyngeal and laryngeal cancer patients were recruited. Three hundred and thirty-seven (65.7%) received concurrent chemo-radiation therapy and 9 (1.8%) received RT alone for organ preservation. In those received upfront radiation therapy (n = 346), 13 PLCRN patients managed at our institution were identified and given a rate of 3.8% to develop CRN (Table 1). All were men with a mean age of 51.31 years (range 35–64 years). Their clinical and treatment profiles are summarized in Table 1. Six patients underwent Intensity-Modulated ARC Therapy (IMAT) with Image-Guided Radiation Therapy (IGRT), 1 underwent Volumetric-Modulated ARC Therapy (VMAT) with IGRT, 1 had Intensity-Modulated Radiation Therapy (IMRT) only, 1 had simple RT with IMAT, 1 had IMAT only, 1 underwent Intensity-Modulated Proton Therapy (IMPT), and 2 were treated at a different hospital with unknown RT protocol. The mean total radiation dose received was 70.81 ± 0.85 Gy. All but one patient who was treated in a different institution underwent CT.

The mean duration of HypoSCC diagnosis to laryngeal CRN diagnosis was 15.08 months, the shortest being 5 months, and the longest at 109 months. Majority was found to have CRN at the pyriform sinus, while a few had thyroid cartilage, or posterior pharyngeal wall involvement (Fig. 1). One patient was found to have thyroid cartilage CRN on work-up for carotid artery blow-out. All had Chandler grade IV laryngeal CRN. Management of laryngeal CRN was done using debridement (n = 4), salvage total laryngectomy (n = 2), hyperbaric oxygen (HBO) (n = 1), and observation (n = 3). Ten out of 13 patients improved after CRN management.

In 5 of the patients diagnosed of PLCRN, CBS episodes occurred during their follow-up period (Fig. 2). All the patients returned to hospital from the emergency department due to persistent hemoptysis. Emergent intubation was performed in 3 patients and emergent trachestomy was done in the other 2 patients. All the patients received emergent angiography to detect the bleeding site. Two of which developed a month after biopsy, and 1 developed after debridement, 1 patient developed tumor recurrence a month after laryngeal CRN diagnosis on repeat biopsy and 1 patient developed 109 months after CCRT.

The sites of bleeding were from superior thyroid artery pseudoaneurysm (n = 2), superior thyroid artery bleeding (n = 1), lingual artery pseudoaneurysm (n = 1) and external carotid artery rupture (n = 1). In two patients, the bleedings were successfully embolized by coil. In the rest of 3 patients, the hemodynamic was unstable and not able to receive vascular embolic procedures and expired. The overall mortality rate for PLCRN related CBS was 60%.

Table 1

Summary of patients with chondroradionecrosis of the larynx.

No.	Age/Sex	HypoSCC TNM stage	RT type	Dose (Gy)	CT	Time[a]	CRN site	Grade[b]	CRN management	Outcome	Others
1	35/M	cT4aN0M0	US	US	US	6	Pyriform sinus	IV	Debridement	CBS, expired	Expired due to bleeding lingual artery pseudo-aneurysm
2	41/M	cT4aN0M0	US	72	Yes	6	Pyriform sinus and thyroid cartilage	IV	Debridement	Improved	
3	56/M	cT3N2bM0	IMAT + IGRT	72	Yes	5	US	IV	Salvage laryngectomy	Improved	Developed second primary oral cancer
4	41/M	cT4aN2bM0	IMAT + IGRT	72	Yes	109	Thyroid cartilage	IV	Salvage laryngectomy	CBS, improved	CBS prior to salvage laryngectomy; underwent coiling
5	46/M	cT4aN2bM0	VMAT + IGRT	72	Yes	8	Pyriform sinus	IV	HBO	Improved	
6	60/M	cT4aN2cM0	IMRT	72	Yes	8	Pyriform sinus	IV	Observation	Improved	Spine metastasis
7	58/M	cT4aN0M0	IMAT + IGRT	69.96	Yes	5	Pyriform sinus	IV	Debridement	Improved	
8	60/M	cT4aN2bM1	Simple RT + IMAT	69.96	Yes	7	Posterior pharyngeal wall and thyroid cartilage	IV	Observation	Improved	Developed recurrence
9	54/M	cT2N2bM0	IMAT + IGRT	69.96	Yes	9	Posterior pharyngeal wall	IV	Observation	CBS	Expired
10	55/M	cT4bN1M0	IMAT + IGRT	69.96	Yes	8	Pyriform sinus	IV	Observation	Improved	
11	64/M	cT3N2cM0	IMAT + IGRT	70	Yes	8	US	IV	Debridement	CBS	Embolization and improved
12	37/M	cT4bN2cM0	IMAT	69.96	Yes	10	US	IV	US	CBS	Expired
13	60/M	cT3N1M0	IMPT	69.96	Yes	7	Pyriform sinus	IV	Observation	Improved	

CT = chemotherapy, CBS = carotid blow-out syndrome, CRN = chondronecrosis, HBO = hyperbaric oxygen, HypoSCC = hypopharyngeal squamous cell carcinoma, IGRT = Image-Guided Radiation Therapy, IMAT = Intensity-Modulated ARC Therapy, IMPT = Intensity-Modulated Proton Therapy, IMRT = Intensity-Modulated Radiation Therapy, US = unspecified.

[a]Time (months) between HypoSCC diagnosis and CRN diagnosis.

[b]Chandler grading system for laryngeal radiation changes [11].

4. Discussion

In 1972, Lederman outlined four main post-irradiation complications of laryngeal cancer: laryngeal edema necessitating tracheostomy, skin damage, perichondritis, and cartilage necrosis.[14] Laryngeal CRN is an uncommon, but serious complication of RT. This is brought upon by alterations in the peri-laryngeal and laryngeal tissues, subsequently leading to tissue hypoxia, devascularization, inflammation, tissue fibrosis, and eventually, tissue necrosis.[15] Reported factors predisposing to laryngeal CRN are: dose and technique of RT; portals of RT; frequency of RT; pretreatment tumor invasion; trauma before or after RT including previous surgical interventions; and infection.[2,16] Furthermore, the incidence if this complication is probably related to the total dose, which is observed at total RT dose of 70 Gy or more, field size and duration of therapy.[8,11] Organ-preserving protocols are currently advocated in treating advanced hypopharyngeal cancer, and this confers to the increased utilization of combination RT and CT, with increased incidence of complications following therapy as a consequence.[8,11]

Patients may present with cutaneous erythema, weight loss, dysphagia, odynophagia, hoarseness, aspiration, airway obstruction, fetor, and fistula.[2] On CT, highly suggestive, but nonspecific clues to laryngeal CRN are sloughing of the arytenoid cartilage, fragmentation and collapse of the thyroid cartilage, and/or the presence of gas bubbles around the cartilage.[8,12] Post-radiation injury to the vascular and lymphatic channels may continue for months, even years after treatment.[2] This may explain the wide range of time for laryngeal ORN to develop in our series, which is 5 to 109 months following laryngeal CRN diagnosis.

Hyperbaric oxygen therapy improves tissue hypoxia by increasing oxygen partial pressure in radiation-induced obliterative endarteritis, stimulating fibroblast proliferation and capillary growth.[10,19] Therefore, this therapy has been suggested for late stage CRN, particularly grade IV patients, by most clinical studies as a means to avoid salvage laryngectomy.[2,18,19] In some cases, when frank necrosis has already compromised laryngeal function, a salvage total laryngectomy may be warranted, even in the absence of histologic proof of cancer.[2,11] The rationale for this decision is that a delay in diagnosis in a permanently crippled larynx portends a catastrophic outcome of further necrosis, infection, and in cases of true recurrence, further progression of malignancy,[11] as in the case of our 2 salvage total laryngectomy patients.

Radiation effects to larger vessels have also been reported. Progressive fibrosis, thrombosis and obliteration of the vasa-vasorum, and weakening of the arterial walls may be observed in histologic examinations of carotid arteries, placing them at risk for rupture from nearby cartilaginous or osseous fragments.[2,21] This predisposes laryngeal CRN patients to CBS, which was observed in 5 (38.5%) of our cases, and 3 (60%) patients expired. In a study by McCready et al, a total radiation dose of 40 Gy in 10 days may induce damage to the vasa-vasorum and may contribute to rupture of the great arteries in dogs.[22] The incidence of CBS in patients with head and neck cancers who underwent surgical procedures ranged from 2.9% to 4.3%, while for patients with recurrent head and neck cancers who received irradiation, it varied from 2.6% to 10%.[21] A systematic review done by McDonald et al revealed a CBS mortality rate as high as 76%, with no statistical difference between patients treated with or without concurrent CT, or between patients treated with or without salvage surgery before irradiation.[23]

Notably, in 5 patients with CBS in our study, angiography demonstrated the bleeding in 3 patients originated from superior thyroid artery and 1 from the lingual artery. Necrotic bony fragments in the laryngeal framework such as thyroid cartilage and hyoid bone were in proximity to the branches of external carotid artery. Superior thyroid artery and lingual artery rather than carotid artery were more vulnerable to the vascular injury in

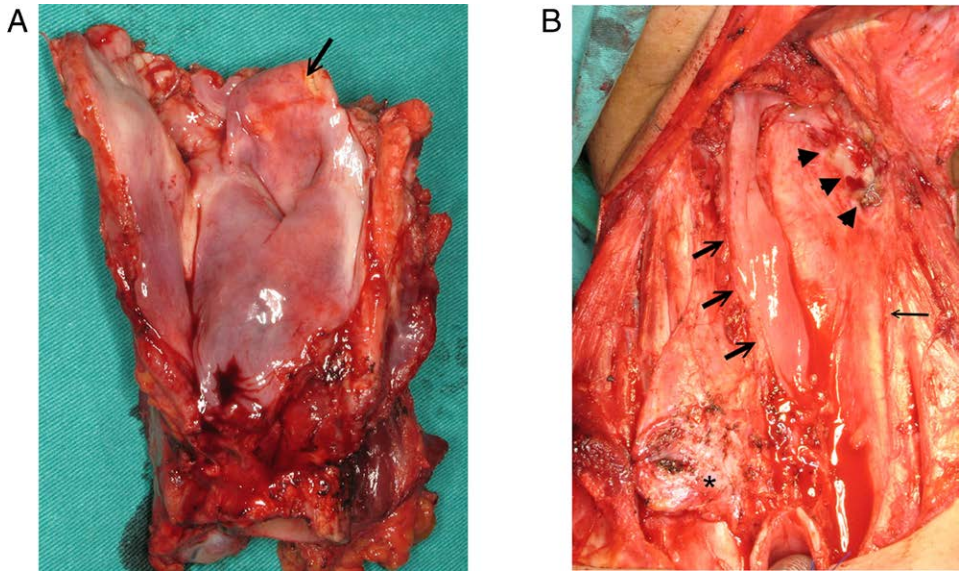

Figure 1. (A) Case #4, specimen after received salvage total laryngectomy. Arrow, epiglottis; white star, left later pharyngeal wall necrosis. (B) Surgical field after salvage total laryngectomy. Arrow, common carotid artery; arrows, posterior pharyngeal wall, arrowheads, necrotic external carotid artery with coil exposed; star, right thyroid gland.

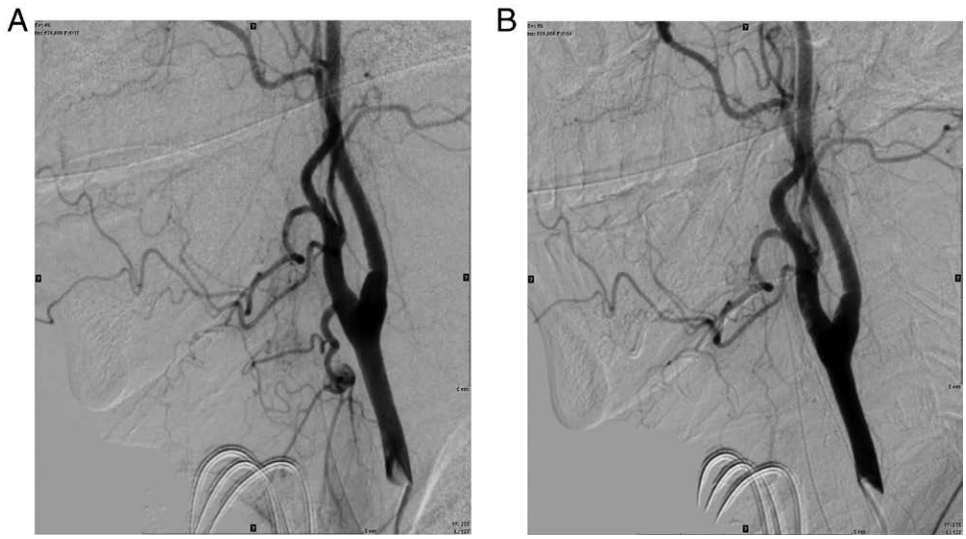

Figure 2. Angiography demonstrating pseudoaneurysm in right side superior thyroid artery with bleeding. (A) Before trans-arterial embolization (TAE). (B) After embolization (case #12).

patients with chondronecrosis. The chronic inflammation, infection and irritation of vessels would further weaken the vascular walls. They would result in the formation of pseudoaneurysm and subsequently cause bleeding. Once bleeding occurs, large amount of blood clots accumulated in the oropharynx or hypopharynx in a short period of time. Parapharyngeal soft tissue in CRN patients was necrotic and not able to provide any compression for the bleeding. Airway compromise developed rapidly and compromised patients' airway. From our experiences, when patients developed chrondronecrosis after CCRT, airway protection, tracheostomy, was strongly suggested. Angiography may be arranged and even selective embolization of branches of external artery could prevent the occurrence of disastrous event.

5. Conclusion

For hypopharyngeal cancers, primary CCRT was well adopted in the treatment for organ preservation. Radiation necrosis occasionally occurred after CCRT in a frequency of 3.8%. Persistently cartilaginous and nearby soft tissue necrosis could stimulate the formation of pseudoaneurysm in carotid artery and its branches and cause vascular rupture. CBS after the vascular rupture carries a 60% mortality rate. Repeated debridement and closely follow-up can identify high risk patients for CBS earlier. Tracheostomy for the protection of airway, and angiography with embolization could probably prevent the disastrous complication of CBS.

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Author contributions

PPF and FHY interpreted the patient data and drafted the manuscript. YCK analyzed patients' data. YCH, LCC, LCT and

CTCJ collected the data. All authors read and approved the final manuscript.

Conceptualization: Hsuan-Yeh Fang, Paula Francezca Padua, Shiang-Fu Huang.
Data curation: Chia-Chen Lin, Chih-Hua Yeh, Chun-Ta Liao, Chung-Kan Tsao, Hsuan-Yeh Fang, Paula Francezca Padua, Shiang-Fu Huang, Tung-Chieh Joseph Chang.
Formal analysis: Hsuan-Yeh Fang, Shiang-Fu Huang.
Funding acquisition: Shiang-Fu Huang.
Investigation: Chia-Chen Lin, Chi-Kuan Young, Chih-Hua Yeh, Chun-Ta Liao.
Methodology: Chi-Kuan Young, Chih-Hua Yeh, Hsuan-Yeh Fang, Tung-Chieh Joseph Chang.
Project administration: Shiang-Fu Huang.
Supervision: Shiang-Fu Huang.
Resources: Chun-Ta Liao, Chung-Kan Tsao.
Validation: Chi-Kuan Young, Chun-Ta Liao, Tung-Chieh Joseph Chang, Chung-Kan Tsao, Shiang-Fu Huang.
Visualization: Chih-Hua Yeh.
Writing – original draft: Hsuan-Yeh Fang, Paula Francezca Padua, Shiang-Fu Huang.
Writing – review & editing: Chia-Chen Lin, Chi-Kuan Young, Chih-Hua Yeh, Chun-Ta Liao, Chung-Kan Tsao, Tung-Chieh Joseph Chang, Shiang-Fu Huang.

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