Staged transoral resection of primary tumors in synchronous HPV-mediated oropharynx cancer (HPV OPSCCa).

Samih J. Nassif, MD[1]; Erin Longstreth, PA-C[2]; Gregory S. Weinstein, MD[3]; Shravan Kandula, MD[2]; Bruce H. Haughey, MD[2]
Department of Otolaryngology, Huntsville Hospital and North Alabama ENT Associates P.C.
Department of Otolaryngology and Head and Neck Surgery, AdventHealth Celebration
Department of Otorhinolaryngology – Head and Neck Surgery, University of Pennsylvania

Abstract

Background: The reported incidence of synchronous human papilloma virus (HPV) related oropharyngeal squamous cell carcinoma (OPSSCa) is 1-3%.[1-4] Treatment strategies for these have focused on non-surgical intervention, due to unacceptable side effect profile. We propose primary surgical resection in a staged fashion as an acceptable strategy with excellent oncologic control and improved functional outcomes.
Methods: A retrospective review of four cases of synchronous HPV+ OPSCCa treated by the senior authors and colleagues was performed. Demographic information, surgical approach, and post-operative oncologic/functional outcomes were tabulated with Microsoft Excel.
Results: Four patients presented with synchronous tumors from 2017 to 2020. Patients 1 and 2 were heavy smokers, but the other two patients smoked less than 10 pack years. All patients underwent sequential transoral resection with selective neck dissections. Timing of surgical interval ranged from 7 days to 10 weeks. All but one patient required adjuvant radiation therapy, while patient 3 also required chemotherapy secondary to extranodal extension on final pathology. At 18 mo to 84 mo follow up, no patients displayed recurrence and were swallowing well, despite dysphagia and mild VPI in patients 1 and 2, respectively.
Conclusion: Staged transoral resection of synchronous HPV+ OPSCCa shows excellent oncologic outcomes at mature follow up. Use of de-escalated doses of radiation in the adjuvant setting may contribute to the acceptable swallowing outcomes that were observed in our cases.

Introduction

Human papilloma virus (HPV) driven oropharyngeal squamous cell carcinoma (OPSCCa) has an incidence of about 50,000 cases per year.[1] These mostly present as early stage, unilateral primary tumors of the palatine or lingual tonsils with clinically detectable, often radiologically "cystic" lymphadenopathy in the ipsilateral neck. Bilateral adenopathy is understandably common in tongue base tumors, especially if they involve or approach the midline. However, most tumors present unilaterally[7].

Synchronous primary tumors are diagnosed at or within six months of the index tumor and the reported incidence in HPV-OPSCCa is 1-3%.[1-4,8,9] Most studies report the contralateral tonsil as the most likely site for synchronous primaries.[8] Treatment strategies for these have focused on non-surgical intervention, with one report of *simultaneous* surgical excision of bilateral tonsil primaries leading to severe dysphagia.[2,5]

There is an active effort to increasingly employ transoral resection approaches to mitigate overtreatment of these patients especially from chemoradiation using traditional head and neck cancer doses.[6]

With this in mind, we propose staged primary surgical resection +/- risk-based adjuvant therapy as an acceptable strategy with excellent oncologic control and maintenance of functional outcomes.

Table 1: Patient and tumor characteristics

Patient number	Patient 1	Patient 2	Patient 3	Patient 4
Age	79 years	66 years	63 years	44 years
Sex	Female	Male	Male	Male
Smoking status	23 pack years	30 pack years	Never smoker	2 pack years
Alcohol use	Heavy drinker	Occasional drinker	Occasional drinker	Occasional drinker
First Primary Site	Left base of tongue	Left glossotonsillar sulcus	Left base of tongue	Left base of tongue
Second Primary Site	Left tonsil	Right lateral pharyngeal wall	Right tonsil	Right glossotonsillar sulcus and base of tongue

Methods and Materials

A retrospective review of four surgically managed cases of synchronous HPV+ OPSCCa by the two senior authors (BHH, GSW) and colleagues at tertiary /quaternary head and neck centers. Demographic information, surgical approach, and post-operative oncologic/functional outcomes were tabulated with Microsoft Excel. Identifiable patient data was removed once all the above measures were tabulated.

Surgical methods/considerations:

Three of the patients received transoral laser microsurgical (TLM) resection of their tumors, in staged fashion, and each to a negative margin. In two of the three cases, the index TLM defect had reached full mucosal healing before the second defect was created. In the other staged TLM case the second primary was addressed seven days after the index resection using the Haughey hybrid approach, prior to complete index site healing.[10] The fourth case was managed by TLM for the index base of tongue primary and a secondary TORS resection with immediate radial forearm free flap (RFF) reconstruction. Overall, selection of TLM vs. TORS was by surgeon preference. In the patient who had a different resection modality on each of his tumors, selection of TLM for the first resection was an attempt to achieve rapid healing from the CO2 laser wound and maintain a mucosal bridge

Table 2: Surgical treatment and staging

Patient number	Patient 1	Patient 2	Patient 3	Patient 4
Date of Operation #1	11/29/16	6/18/19	8/6/19	12/11/20
Operation #1	TLM left partial glossectomy with selective left neck dissection	Left TLM left glossotonsillar sulcus and partial glossectomy with left neck dissection	Left TLM partial glossectomy and limited pharyngectomy with selective neck dissection	Left TLM partial glossectomy and limited pharyngectomy with bilateral neck dissection
Margin status	negative, 5 mm (deep)	negative, 1 mm (posteromedial)	negative, 1 mm (deep)	negative, 7 mm (deep)
Date of Operation #2	2/14/17	6/25/19	8/19/19	1/22/21
Operation#2	TLM left limited pharyngectomy	Right TLM limited pharyngectomy, soft palate resection and partial glossectomy, right neck dissection, digastric flap and Alloderm placement	Right TORS limited pharyngectomy with right neck dissection, free flap and tracheostomy (Dr. Weinstein)	Right TLM limited pharyngectomy, glossotonsillar sulcus and base of tongue excision
Margin status	negative, <1 mm (deep)	negative, not recorded	negative, <1 mm (deep)	negative, 3 mm (deep)
Final Pathology Site 1	T2N1	T2N1	T2N0	T1N0
Final Pathology Site 2	T1N0	T2N1	T3N0	T1N2

TLM: Transoral laser microsurgery; TORS: Transoral robotic surgery

Table 3: Adjuvant treatment and functional outcomes

Patient number	Patient 1	Patient 2	Patient 3	Patient 4
Adjuvant RT	No	Yes, only 5 weeks (due to toxicity)	Yes	Yes
Site and quantity of RT	N/A	48 Gy, to right tongue base and bilateral necks	63 Gy to right tonsil bed and right neck	Right neck level II/III 60 Gy, rest of right neck 54 Gy and right base of tongue/GT sulcus 54 Gy
Adjuvant Chemo	No	Yes, 4 doses of 90 mg cisplatin	No	No
Date of completion of treatment	2/14/17	10/1/19	12/3/19	3/17/21
Last follow up	9/7/23	7/11/22	8/10/2022 at HUP	11/18/22
Trach Dependent	No	No	No	No
G tube Dependent	No	No	No	No
VPI and severity	Mild dysphagia, no VPI	Mild, nasal regurgitation to liquids	No comment	None

GT: Glossotonsillar sulcus; HUP: Hospital of the University of Pennsylvania; VPI: velopharyngeal insufficiency

Results

Patient details are seen in Table 1 and they presented with synchronous tumors. Patients 1 and 2 were heavy smokers, but the other two patients smoked less than 10 pack years. All patients underwent sequential transoral resection with selective neck dissections. Timing of surgical interval ranged from 7 days to 10 weeks. Oropharynx reconstruction was performed via radial forearm free flap for the right tonsil defect of patient 3 and right digastric flap with Alloderm placement for patient 2, all other 6 defects healed via secondary intention. (Table 2)

Each of the eight primary tumor margins was reported negative on the patient's pathology results, the range of closest margins being from less than 1 mm to about 7 mm. One of the specimen reports did not contain a numerical margin but was read as negative. (Table 2)

All but one patient received adjuvant radiation therapy, while one patient also received chemotherapy secondary to extranodal extension on final pathology. At 18 mo to 84 mo follow up, no patients displayed recurrence and were swallowing well, although patient 1 had mild dysphagia and patient 2 had mild VPI (table 3).

Discussion

This is the first study to show that sequential surgical resections with or without adjuvant treatment can result in oncologically sound treatment of synchronous HPV+ OPSCCa. Our four patients are still alive to this day, with no evidence of recurrence. Their functional outcomes are excellent and compare remarkably well with reported outcomes from primary chemoradiation. Of note, we did not experience oropharyngeal stenosis or prolonged dysphagia as reported in previous case reports, further solidifying this algorithm as an appropriate strategy.[2] Our patients received a maximum of 63 Gy radiation dose, with lower doses in the oropharynx for patient 2. Compared with 70 Gy of radiation, 63 Gy has been shown to have less long-term dysphagia and trismus.[11] Patient 2 in our series required adjuvant chemotherapy as well. Worse swallowing and velopharyngeal insufficiency were seen in patient 1 and 2. In review of our data it is possible that their smoking history contributed to the aggressive nature of these tumors, as well as suboptimal wound healing.

Our study has some limitations. It is a case report of 4 patients; this is inherent given the rarity of synchronous HPV tumors reported the literature. There was no direct comparison between the radiation doses and fields between AdventHealth and the Hospital for the University of Pennsylvania, making standardization impossible to perform. Patient 2 did not complete adjuvant chemoradiation due to mucositis after 48 Gy and 4 doses of chemotherapy; it is possible his long-term functional outcomes might have been worse should he have completed full dose adjuvant chemoradiation.

Conclusions

Staged transoral resection of synchronous HPV+ OPSCCa in this case series shows excellent oncologic outcomes at 2-5 year follow up. Use of de-escalated doses of radiation in the adjuvant setting may contribute to the acceptable swallowing outcomes that were observed in our cases.

Contact

Samih J. Nassif Abudinen, MD
North Alabama ENT Associates P.C.
1963 Memorial Parkway Suite 5 and 9
Huntsville, Alabama
35801
nassifsamih@gmail.com
305-542-5626

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