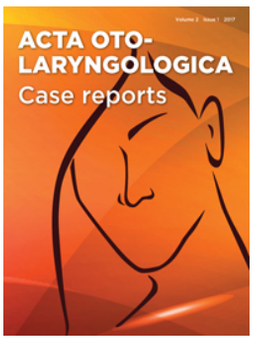

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CASE REPORT

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De-escalation of radiotherapy for the treatment of HPV-associated head and neck cancer: A case report and a word of caution

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ABSTRACT

Background: It has been noted that HPV associated head and neck cancers have an increased responsiveness to radiotherapy. For this reason, strategies at de-escalation are currently being prospectively evaluated.

Methods: We report a case of a 58-year-old male who presented with a right neck mass and was diagnosed with HPV associated, p16 positive, cT2N2bM0 tonsillar squamous cell carcinoma. The patient unintentionally received reduced doses of radiation and systemic therapy due to inability to tolerate treatment.

Results: The patient was found to have no evidence of disease on 4-month follow-up PET scan and clinical exam. However, several months later, he developed disease recurrence and ultimately required surgical salvage.

Conclusions: Until mature results from prospective phase 3 clinical trials are available, we recommend caution in the de-intensification of therapy particularly as current therapy achieves high rates of long term disease control.

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HPV; oropharyngeal carcinoma; radiotherapy; de-escalation; head and neck cancer

Introduction

Over the past 30 years, we have witnessed a dramatic rise in the incidence of human papilloma virus (HPV)-associated oropharyngeal carcinoma of the head and neck [1,2]. It is estimated that HPV related oropharyngeal carcinoma has an annual incidence of 2.6 per 100,000 people in the United States [2]. HPV associated oropharyngeal cancer can be detected via viral assessment with polymerase chain reaction or with immuno-histochemical staining of a surrogate marker, p16 [3]. Interestingly, HPV related cancers appear to possess a unique biology and have a better overall prognosis compared with HPV negative carcinomas [4]. It has also been noted that HPV associated head and neck cancers have an increased responsiveness to radiotherapy [5]. For this reason, strategies at de-escalation are currently being prospectively evaluated. Herein we report a case of HPV-related oropharyngeal carcinoma treated at our institution with multidisciplinary management. He was initially treated with reduced doses of radiation and systemic therapy due to inability to tolerate therapy and had a clinical complete response. Ultimately, however, the patient required tri-modality therapy including surgical management in order to attempt to control his cancer.

Case presentation

The patient was a 58-year-old male who presented with a right neck mass in August 2014 at an outside facility. His past medical history was significant for chronic hepatitis C with cirrhosis, daily alcohol use, esophageal varices, a 40-year history of tobacco use, and he was currently smoking 1 pack per day. He also had a history of stage 3 chronic kidney disease, secondary to outlet obstruction due to prostate enlargement. His initial workup in October 2014 consisted of a CT scan of the neck (non-contrast secondary to chronic kidney disease) and a PET scan, revealing right cervical lymphadenopathy and uptake in the right tonsil. He then underwent an FNA of the neck mass, revealing squamous cell carcinoma. At that

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time, he had cT2N2bM0 disease. He did not receive treatment immediately following his diagnosis and presented to our facility for evaluation in March 2015 after he moved to Florida.

Physical exam in March 2015 revealed a right tonsillar mass extending toward the soft palate and pharyngeal wall on direct inspection. There was also progression of the right upper neck mass measuring up to approximately 5 cm in greatest diameter. A direct laryngoscopy with biopsy was initially performed, revealing a bulky neoplasm of the right tonsil, which extended onto the posterior pharyngeal wall behind the posterior tonsillar pillar and also involved the soft palate, approaching the uvula. The neoplasm also extended down the lateral wall of the oropharynx, with some irregular tissue extending into the vallecula. Biopsies of the right tonsil and right vallecula in March 2015 revealed moderately differentiated non-keratinizing invasive squamous cell carcinoma (Figure 1). Immunohistochemical staining for p16 performed on the right vallecula biopsy was strongly and diffusely positive for p16 immunoreactivity in the tumor cells, suggesting this was an HPV related neoplasm (Figure 1). A repeat PET scan performed in April 2015 (Figure 2(A)) revealed a metabolically active mass on the right side of the pharynx and uptake in the right neck.

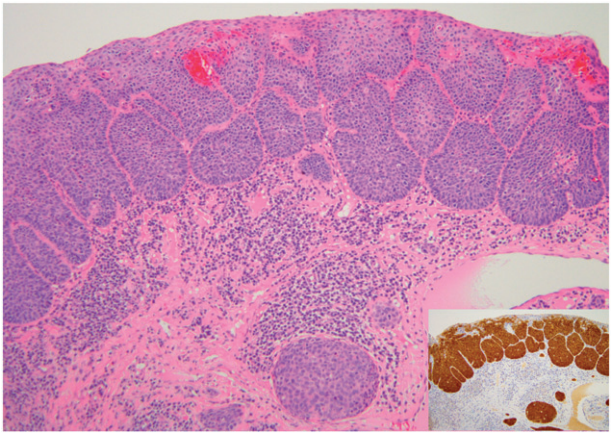

Figure 1. Tumor histopathology (pre-treatment) of right vallecula biopsy revealing moderately differentiated non-keratinizing invasive squamous cell carcinoma (H&E stain, 100× magnification), alongside p16 immunohistochemical stain revealing positivity (inset).

The patient's case was presented at head and neck tumor board and primary chemoradiotherapy was recommended as definitive treatment. Given his poor renal function, he was started on systemic treatment with cetuximab and a course of external beam radiation therapy in June 2015. He was initially prescribed a dose of 7000 cGy to the gross tumor volume and 5600 cGy to the elective regions of the neck in 35 fractions with intensity modulated radiation therapy. However, one month after beginning treatment, he was hospitalized with drug rash involving the face, neck, and lower extremities, difficulty swallowing and acute on chronic renal insufficiency secondary to volume depletion. At this point, he had only received a total dose of 3600 cGy in 18 fractions in early July 2016. During his 2-week hospital stay, he also developed *Staphylococcus aureus* bacteremia and an upper

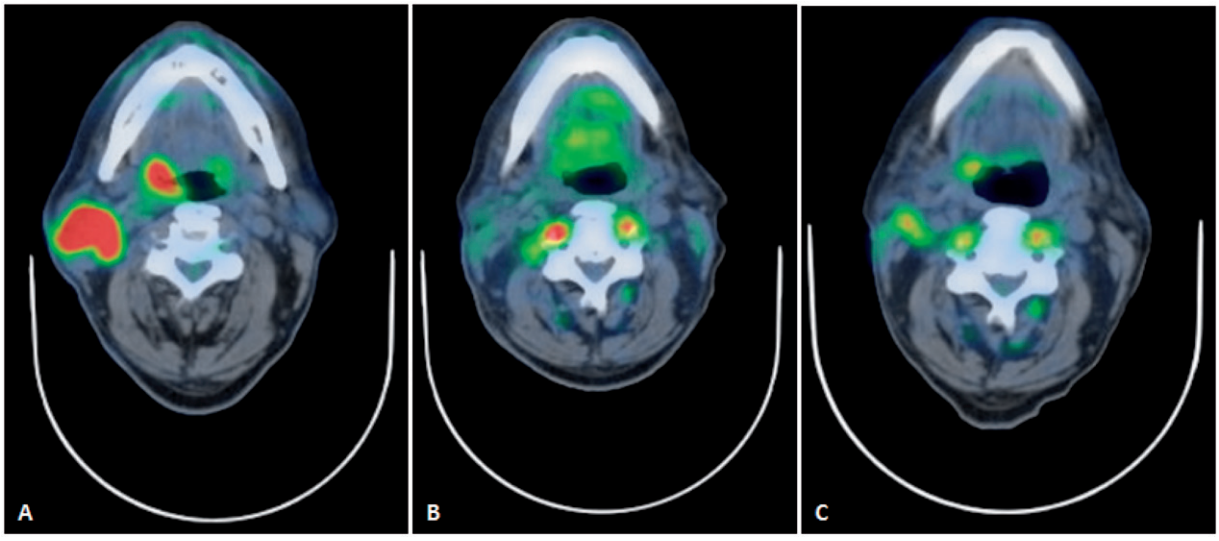

Figure 2. Pre- and post-treatment positron emission tomography-computed tomography axial images. (A) Pre-treatment axial image revealing metabolically active mass of the right tonsil and uptake in the right neck (April 2015). (B) Post-treatment image revealing interval resolution of FDG uptake in the oropharynx and neck (October 2015). (*Note*: physiological activity in the scalene muscles and oral cavity). (C) Post-treatment image revealing interval increase in FDG activity of right neck and right oropharynx (March 2016).

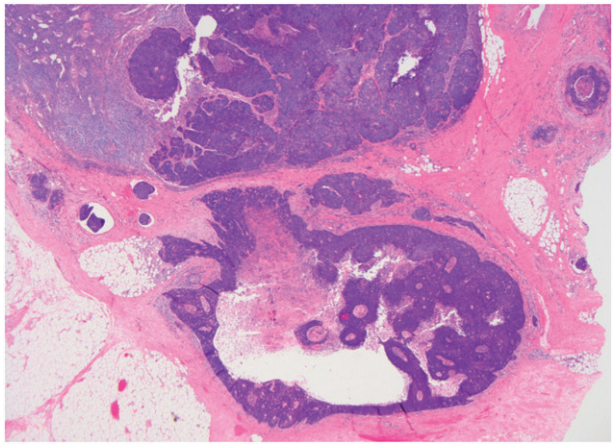

Figure 3. Tumor histopathology (post-treatment) of right neck lymph node revealing squamous cell carcinoma with extracapsular spread (H&E stain, 20× magnification).

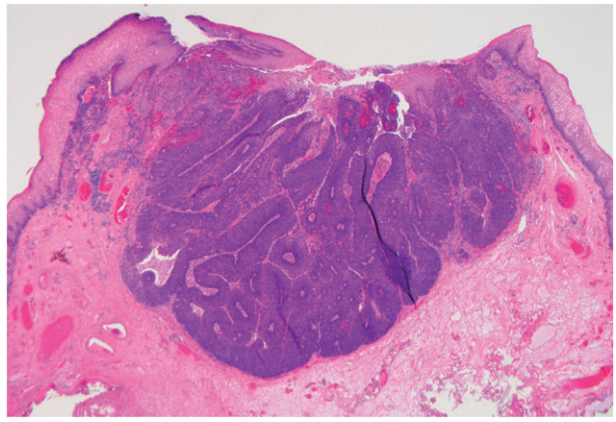

Figure 4. Tumor histopathology (post-treatment) of epiglottis focus revealing invasive non-keratinizing squamous cell carcinoma, with negative surgical margins (H&E stain, 20× magnification).

extremity DVT. His dysphagia and renal function improved and he was discharged on IV antibiotics. Chemotherapy and radiation therapy were not resumed following discharge given patient preference at that time.

On follow-up visit in August 2015, there was regression of disease, with the right tonsillar tumor no longer visible on physical examination of the oropharynx. A follow-up PET/CT scan in October 2015 (Figure 2(B)), 3 months after incomplete prescribed doses of radiation and cetuximab were completed, revealed interval resolution of FDG uptake in the right side of the oropharynx and tonsillar region as well as the right upper neck lymphadenopathy. Fiber optic exam performed at a follow-up visit in November 2015 did not reveal any evidence of gross tumor involving the pharyngeal wall, base of tongue, or tonsil. The patient also no longer reported difficulty swallowing and was regaining weight.

In November 2015, the patient's case was presented again at tumor board and surveillance was recommended with a 4-month follow-up PET/CT. Unfortunately, follow-up PET/CT March 2016 (Figure 2(C)) revealed an interval increase in size and FDG activity of lymphadenopathy and salvage surgery was recommended.

In April 2016, he underwent right modified neck dissection and biopsy of the tumor from the oropharynx. The right tonsil biopsy revealed invasive moderately differentiated non-keratinizing squamous cell carcinoma. The neck dissection revealed nine of 12 lymph nodes containing metastatic squamous cell carcinoma. The largest was 2.5 cm in diameter with extranodal extension (Figure 3). Subsequently a week later he underwent transoral robotic surgery with limited pharyngectomy with final pathology revealing a 2.5 cm tumor within the right palatine tonsil. The surgical margins were free other than the inferior margin which was multifocally positive for cauterized tumor for maximal length of 2 mm. Additionally, there was no treatment effect identified within the tumor but there was surrounding non-neoplastic tissue showing changes consistent with prior radiation. He was noted to have nodularity of the epiglottis and right hypopharynx. He therefore underwent resection of both areas in early June, revealing squamous cell carcinoma with negative margins. The epiglottis focus was 5 mm in diameter and the hypopharynx focus was 5 mm in diameter (Figure 4). At this time, post-surgical radiotherapy has been recommended.

Discussion

In this case report, we described a patient with HPV related oropharyngeal carcinoma who obtained a complete response as noted on examination and PET/CT at 3 months after receiving reduced-dose radiation with cetuximab due to inability to tolerate treatment. Subsequently he developed recurrent disease and required salvage surgical therapy.

A previous report in the literature described a durable complete response to chemoradiation after a patient with HPV associated oropharyngeal carcinoma had received 46 gray and then subsequently discontinued therapy [6]. These results have been promising particularly in the current area where we are attempting to de-escalate therapy for our HPV related head and neck cancer population [6].

There has been a recent report of excellent pathologic complete response rates noted with reduced dose chemotherapy and reduced dose radiotherapy using combined modality weekly cisplatin and radiotherapy

Table 1. Open clinical trials examining de-escalation of therapy in HPV-positive head and neck cancer.

Phase II Study of De-intensification of Radiation and Chemotherapy for Low-Risk HPV-related Oropharyngeal Squamous Cell Carcinoma (NCT01530997)
Phase II Trial Of Induction Chemotherapy Followed By Attenuated Chemoradiotherapy For Locally Advanced Head And Neck Squamous Cell Carcinoma Associated With Human Papillomavirus (HPV) (NCT01716195)
Reduced-intensity Therapy for Advanced Oropharyngeal Cancer in Non-smoking Human Papilloma Virus (HPV)-16 Positive Patients (NCT01663259)
A Phase II Study on Treatment De-Intensification in Favorable Squamous Cell Carcinoma of the Oropharynx (NCT01088802)
ECOG 3311: Phase II Randomized Trial of Transoral Surgical Resection Followed by Low-Dose or Standard-Dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer (NCT01898494)
NRG-HN002: A Randomized Phase II Trial for Patients With p16 Positive, Non-smoking Associated, Locoregionally Advanced Oropharyngeal Cancer (NCT02254278)
Adjuvant De-escalation, Extracapsular Spread, P16+, Transoral (ADEPT) Trial for Oropharynx Malignancy (NCT01687413)
The Quarterback Trial: A Randomized Phase III Clinical Trial Comparing Reduced and Standard Radiation Therapy Doses for Locally Advanced HPV Positive Oropharynx Cancer (NCT01706939)

given to a total dose of 60 gray [7]. These patients subsequently had planned surgical therapy. Additionally, strategies have looked at using up front systemic therapy in the management of these cancers with response subsequently directing radiotherapy dose [8].

Current clinical trial strategies for de-escalation of therapy (Table 1) include the use of primary surgical management in the treatment of HPV related oropharyngeal carcinoma as per ECOG 3311. In this trial, there is a risk stratification after surgery with low risk patient receiving no further therapy, intermediate risk patients being randomized to 50 gray versus 60 gray of radiation and high risk patients receiving combined modality chemoradiation. In addition, an ongoing prospective study by the NRG is evaluating 60 gray radiotherapy for HPV related oropharyngeal carcinoma versus 60 gray radiotherapy with cisplatin as definitive management [9].

The case report demonstrates the potential for recurrence of head and neck cancer after a complete response and negative PET CT scan after the use of reduced dose radiotherapy and systemic therapy. Current literature has shown a 94.5% negative predictive value with a negative PET CT scan after combined modality radiotherapy, with greater diagnostic accuracy if the scan was performed $\geq$12 weeks after completion of therapy [10,11]. The predictive value of a negative PET CT scan may be less useful in this setting of reduced dose radiotherapy or chemoradiotherapy administration and needs further study.

Our case also illustrates the complex biological interaction between the HPV associated oropharyngeal carcinoma with smoking and possibly with other patient co-morbidities. Multiple studies have previously shown worse outcomes for patients who have HPV related cancer and who are smokers [12–14]. It thus appears that we will need to exercise additional caution as we develop dose de-intensification strategies for our HPV related smoking population and may learn that other comorbidities affect prognosis [15,16].

It is becoming apparent that the future of HPV related oropharyngeal carcinoma will require multidisciplinary care with skilled surgeons, medical oncologists and radiation oncologists. We strongly suggest that patients are treated as per current NCCN guidelines [17]. A curative strategy encompassing chemoradiation or bio-radiation with EGFR-inhibition is highly intensive, and there is a need for a robust monitoring plan during treatment with possible tube-feeding and admission during treatment for these patients. This is especially true for the socioeconomically disadvantaged patients and patients with significant comorbidities, regardless of the HPV-status. This management strategy is necessary for all patients receiving intensive systemic therapy and radiation for head and neck cancer and is of utmost importance to ensure the patient has the best chance to complete all prescribed treatment and to have the best possible outcome. In the future, we are confident that we will discover the optimal treatment intensity required to optimize disease control and minimize morbidity with the use of surgery, radiation and/or chemotherapy in this cancer population. However, until mature results from prospective phase 3 clinical trials are available we recommend caution in the de-intensification of therapy particularly as current therapy achieves high rates of long term disease control.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References

[1] Pytynia KB, Dahlstrom KR, Sturgis EM. Epidemiology of HPV-associated oropharyngeal cancer. Oral Oncol. 2014;50:380–386.

[2] Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29:4294–4301.

[3] Duncan LD, Winkler M, Carlson ER, et al. p16 immunohistochemistry can be used to detect human papillomavirus in oral cavity squamous cell carcinoma. J Oral Maxillofac Surg. 2013;71:1367–1375.
[4] Klozar J, Tachezy R. What are the implications of human papillomavirus status in oropharyngeal tumors for clinical practice? Curr Opin Otolaryngol Head Neck Surg. 2014;22:90–94.
[5] Mirghani H, Amen F, Tao Y, et al. Increased radiosensitivity of HPV-positive head and neck cancers: molecular basis and therapeutic perspectives. Cancer Treat Rev. 2015;41:844–852.
[6] Wu CC, Horowitz DP, Deutsch I, et al. De-escalation of radiation dose for human papillomavirus-positive oropharyngeal head and neck squamous cell carcinoma: a case report and preclinical and clinical literature review. Oncol Lett. 2016;11:141–149.
[7] Chera BS, Amdur RJ, Tepper J, et al. Phase 2 trial of de-intensified chemoradiation therapy for favorable-risk human papillomavirus-associated oropharyngeal squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2015;93:976–985.
[8] Cmelak A, Li S, Marur S, et al. E1308: reduced-dose IMRT in human papilloma virus (HPV)-associated resectable oropharyngeal squamous carcinomas (OPSCC) after clinical complete response (cCR) to induction chemotherapy (IC). ASCO Annual Meeting; 2014.
[9] Masterson L, Moualed D, Liu ZW, et al. De-escalation treatment protocols for human papillomavirus-associated oropharyngeal squamous cell carcinoma: a systematic review and meta-analysis of current clinical trials. Eur J Cancer. 2014;50:2636–2648.
[10] Mak D, Corry J, Lau E, et al. Role of FDG-PET/CT in staging and follow-up of head and neck squamous cell carcinoma. Q J Nucl Med Mol Imaging. 2011;55:487–499.
[11] Gupta T, Master Z, Kannan S, et al. Diagnostic performance of post-treatment FDG PET or FDG PET/CT imaging in head and neck cancer: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2011;38:2083–2095.
[12] May JT, Rao N, Sabater RD, et al. Intensity-modulated radiation therapy as primary treatment for oropharyngeal squamous cell carcinoma. Head Neck. 2013;35:1796–1800.
[13] Liskamp CP, Janssens GO, Bussink J, et al. Adverse effect of smoking on prognosis in human papillomavirus-associated oropharyngeal carcinoma. Head Neck. 2016;38:1780–1787.
[14] Platek AJ, Jayaprakash V, Merzianu M, et al. Smoking cessation is associated with improved survival in oropharynx cancer treated by chemoradiation. Laryngoscope. 2016;126:2733–2738.
[15] Mahale P, Sturgis EM, Tweardy DJ, et al. Association between hepatitis C virus and head and neck cancers. JNCI J Natl Cancer Inst. 2016;108:djw035.
[16] Hess CB, Rash DL, Daly ME, et al. Competing causes of death and medical comorbidities among patients with human papillomavirus-positive vs human papillomavirus-negative oropharyngeal carcinoma and impact on adherence to radiotherapy. JAMA Otolaryngol Head Neck Surg. 2014;140:312–316.
[17] Pfister DG, Spencer S, Brizel DM, et al. Head and neck cancers, Version 1.2015. J Natl Compr Canc Netw. 2015;13:847–855; quiz 856.