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Outcomes utilizing intensity-modulated radiotherapy in oropharyngeal cancers: Tonsils versus base of tongue

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Abstract

Background: The purpose of this study was to present the outcomes of oropharyngeal cancers treated with intensity-modulated radiotherapy (IMRT) especially the differences between tonsillar and base of tongue (BOT) primaries.

Methods: Retrospective analysis of 124 patients with biopsy proven squamous cell carcinomas of the oropharynx, treated with IMRT.

Results: Human papillomavirus (HPV) association correlated with improvement in survivals in both tonsillar and BOT primaries. At the 2-year median follow-up, the cumulative incidences of locoregional recurrences were 8% in both the tonsil and BOT groups ($P = .76$) but the distant metastases were 8% in the tonsil group versus 26% in the BOT group ($P = .009$). Thirty percent of tonsil primaries has $\geq$N2c neck disease as compared to 54% of BOT. Incidence of distant metastases increases with advanced nodal classification, especially >N2c.

Conclusion: Even though the locoregional controls are excellent with IMRT and chemotherapy, these patients continue to fail distantly, particularly significant for the BOT group and for nodal stage >N2c.

KEYWORDS
concurrent chemoradiation, human papillomavirus (HPV), intensity-modulated radiotherapy, oropharyngeal cancer, tonsil versus base of tongue

1 | INTRODUCTION

Historically, squamous cell carcinomas of the oropharynx, especially of the tonsil and base of tongue (BOT) were managed with surgical resection, which dependent upon pathological findings, was then followed by either postoperative radiotherapy and/or chemotherapy.[1–4] Surgery often resulted in functional disability to the patients. This led to several phase III trials examining organ preservation approaches using radiotherapy and concurrent chemotherapy.[5,6] The results of these trials demonstrated the feasibility of managing advanced squamous cell carcinomas of the tonsil and BOT with these approaches. Most of the data in the literature published utilizing 3D radiotherapy; however, intensity-modulated radiotherapy (IMRT) has now become the standard of care in the treatment of these malignancies. Further improvement of IMRT is the volumetric-modulated arc therapy, which allows for precise targeting of the tumor while sparing critical normal tissues, such as the parotid gland.[7–9] Additionally, recent discoveries demonstrated that human papillomavirus (HPV) infections are associated with a large number of oropharyngeal cancers, especially those arising in the tonsils. These HPV-

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associated malignancies have a better prognosis than HPV-negative squamous cell carcinomas.[10–12] We reviewed our experience of IMRT for the management of locally advanced squamous cell carcinomas of the oropharynx, in particularly differences between the tonsils versus the BOT.

2 | MATERIALS AND METHODS

A retrospective analysis was performed on 124 patients with oropharyngeal cancer treated in our department between the years 2008 and 2015. We obtained approval from our institutional review board for this study. Consent was waived, as this was a retrospective, observational study, all patients finished their treatments, and the study results had no impact on patient care. Patient identifiable information was removed after data collection and was stored in the password-protected computers.

All the patients underwent biopsy proven squamous cell carcinoma on histology. Staging workup included CT scan of the neck and chest with contrast and the majority of the patients additionally had a positron emission tomography (PET) scan. They were treated with definitive concurrent chemoradiotherapy. Chemotherapy included weekly cisplatin 40 mg/m^2. The CT simulation was performed with the patients fitted with a head and neck shoulder mask and bite block in the mouth for immobilization. Gross tumor volume was defined on simulation CT with contrast fused with PET scan, endoscopic and clinical findings, and PET and endoscopy findings. The gross tumor volume was expanded by 1 cm, which adjusted it to the natural pathways of tumor spread and surrounding normal tissues to generate the clinical target volume. The clinical target volume was expanded by 3 mm to create the planning target volume. The total radiation dose delivered was 70 Gy at 200 cGy per fraction to the gross tumor and 56 Gy at 160 cGy per fraction to the subclinical microscopic disease using the simultaneous integrated boost technique. We utilized IMRT/volumetric-modulated arc therapy for delivery of radiotherapy because it improved the therapeutic ratio by decreasing the radiation doses to the normal structures. Daily cone-beam CT scans were done for setup verification. All patients received the full prescribed dose of radiotherapy and the chemotherapy.

After completion of the planned treatment, follow-up consisted of a history and physical examination performed every 2 months for the first year, every 4 months during the second year, and every 6 months from 3 to 5 years. Posttreatment included baseline imaging. A CT of the neck with contrast was obtained at 8 weeks and as clinically indicated afterward.

We studied the difference in the initial stage at presentation based on the primary site of disease the tonsils versus the BOT. We also evaluated the outcomes of treatment, including locoregional failure, distant metastases, disease-free survival (DFS), and overall survival (OS).

TABLE 1 Characteristics and staging in the tonsils versus base of tongue cancer

	Tonsils	BOT
No. of patients	76	48
Age, years	54.3 ± 8.2	58.4 ± 9.7
Sex		
Male:female	6.0:1	2.7:1
Race		
Whites:blacks	1.2:1	1.2:1
TNM classification		
T1-2	49 (64.47%)	20 (41.66%)
T3-4	27 (35.53%)	28 (58.33%)
N0, N1, and N2a	25/76 (32.89%)	9/48 (18.75%)
N2b	28/76 (36.84%)	13/48 (27.08%)
≥N2c	23/76 (30.26%)	26/48 (54.16%)
AJCC stage 7th edition		
I and II	8/76 (10.3%)	2/48 (4.17%)
III and IV	68/76 (89.5%)	46/48 (95.8%)
HPV		
HPV status known	49/76 (64.47%)	18/48 (37.5%)
HPV-positive	23/49 (46.93%)	6/18 (33%)
Smoking		
Tobacco	62/76 (81.58%)	37/48 (77.1%)
Median follow-up	23.5 mo	17.8 mo

Abbreviations: AJCC, American Joint Committee on Cancer; BOT, base of tongue; HPV, human papillomavirus.

We analyzed the cumulative incidence of events between the groups using Gray's test. Survivals were analyzed using the log-rank test.

3 | RESULTS

There were 124 patients in our study with 76 having a tonsillar primary carcinoma and 48 with BOT carcinomas. The median age at diagnosis for tonsillar primaries was 54 years compared to 58 years for the BOT. The median follow-up was 24 months.

Tonsillar primaries had early-stage T1 and T2 disease (64.5%), compared to only 41.6% in the BOT tumors. Similarly, only 30% of tonsillar primaries had ≥N2c neck disease as compared to 54% of BOT. Overall, 89.4% of the patients with tonsillar cancer presented with stages III and IV disease, and it was 95% for the BOT group. Therefore, the majority of patients were treated with concurrent chemoradiotherapy (Table 1).

TABLE 2 Cumulative incidence of recurrences of cancer in the tonsils versus the base of the tongue

Recurrences	Tonsil	BOT
Locoregional	8%	8% ($P = .76$)
Distant	8%	26% ($P = .009$)
Overall	16%	34%

Abbreviation: BOT, base of tongue.

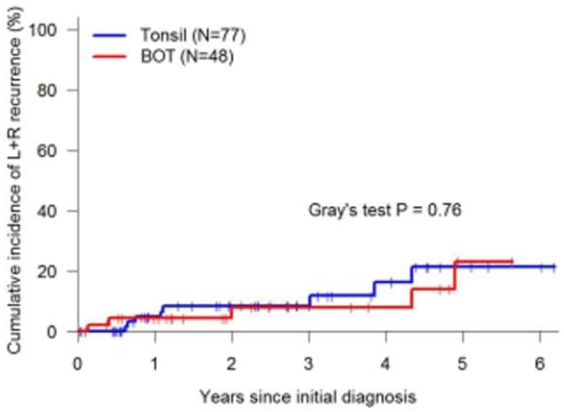

FIGURE 1 Cumulative incidence of locoregional recurrences of cancer in the tonsils versus the base of the tongue (BOT) [Color figure can be viewed at wileyonlinelibrary.com]

In the patients with tonsillar primary carcinoma, 49 had known HPV status. Among the 49 patients, 23 were HPV-positive and 26 were HPV-negative. The overall locoregional control for the whole group with known HPV status was 84.7%; for those with HPV-positive disease it was 93%, and HPV-negative was 77.7%. At 2 years, the OS was 77%. It was 82% for patients with HPV-positive disease and 58.9% for HPV-negative disease.

In the patients with BOT primary cancer, 18 had known HPV status. Among the 18 patients, 6 were HPV-positive and 12 were HPV-negative. The overall locoregional control

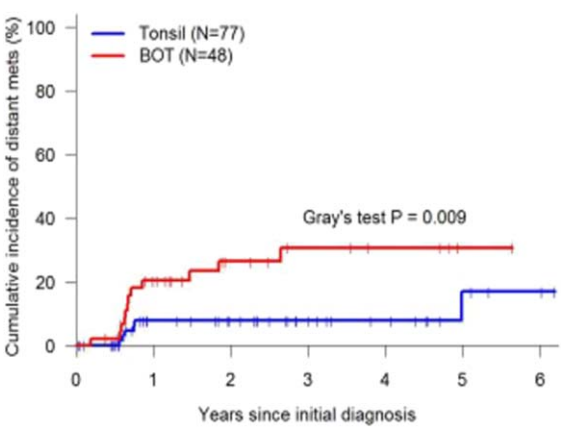

FIGURE 2 Cumulative incidence of distant metastases (mets) of cancer in the tonsils versus the base of the tongue (BOT) [Color figure can be viewed at wileyonlinelibrary.com]

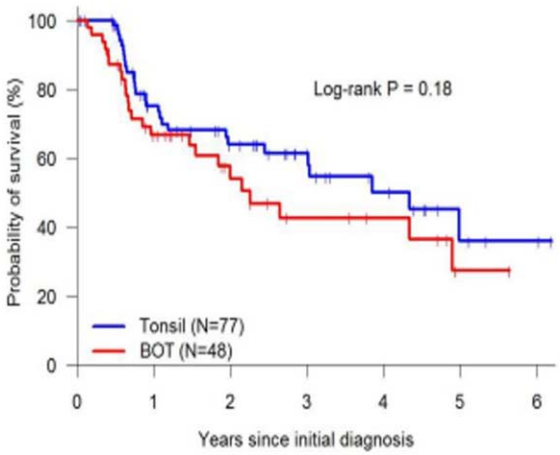

FIGURE 3 Disease-free survival rates of cancer in the tonsils versus the base of the tongue (BOT) [Color figure can be viewed at wileyonlinelibrary.com]

for the whole group with known HPV status was 91.7%; and patients with HPV-positive disease was 100%, and HPV-negative disease was 85.7%. At 2 years, the OS was 75.2%. It was 100% for HPV-positive disease and 62.5% for HPV-negative disease.

In both the tonsillar and BOT groups, the overall locoregional control for the whole group at 2 years was 92% (Table 2, Figure 1). The incidence of distant metastasis for the whole group was 34%. However, the cumulative incidence of distant metastases at 2 years was 26%, as compared to 8% in the tonsillar site group, which is statistically significant with a P value of .009 (Table 2, Figure 2). At 2 years, the DFS was 54% and the OS was 75% with no difference between the tonsil group and the BOT group (Figures 3 and 4).

The incidence of distant metastases was also higher in patients with ≥N2c nodal disease 54.1% in the BOT group as compared to 21.7% in the tonsil group. The local recurrences and distant metastases based on nodal classification in both the tonsil and BOT groups are summarized in Table 3.

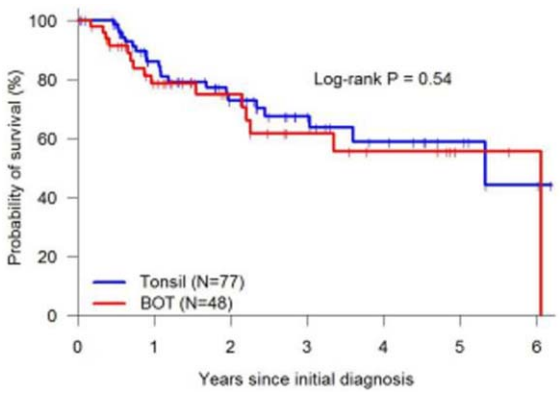

FIGURE 4 Overall survival rates of cancer in the tonsils versus the base of the tongue (BOT) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Recurrences based on nodal groups of tonsillar versus base of tongue cancers

Nodal Stage, Outcomes	Tonsil	BOT
N0, N1, and N2a	25/76 (32.89%)	9/48 (18.75%)
Locoregional	4/25 (16%)	5/9 (55.5%)
Distant metastasis	0	1/9 (11.1%)
N2b	28/76 (36.84%)	13/48 (27.08%)
Locoregional	2/28 (7.14%)	1/13 (7.69%)
Distant metastasis	1/28 (3.57%)	2/13 (15.38%)
N2c + N3	23/76 (30.26%)	26/48 (54.16%)
Locoregional	4/23 (17.39%)	4/26 (15.38%)
Distant metastasis	5/23 (21.73%)	8/26 (30.76%)

Abbreviation: BOT, base of tongue.

4 | DISCUSSION

Patients with oropharyngeal cancer can be treated with surgery or radiotherapy. If they are treated with surgery, radiotherapy is added for those at a high risk for local failure.[13] Radiotherapy-only schedules have been used primarily in the past. These were mainly standard fraction treatments given at 2 Gy per fraction once a day. Better understanding of radiobiology led to the development of altered fraction trials in which multiple fractions per day were used.[14,15] These altered fractionation regimens varied the overall treatment time to exploit radiobiological factors, such as reoxygenation, repair, redistribution in the cell cycle, and repopulation. In a meta-analysis of 15 phase III trials with >6000 patients, these fraction schemes resulted in a 3.4% absolute benefit overall in survival at 5 years, as compared to the standard once a day fractionation.[16] In addition, there have been technological improvements in radiation delivery, such as the IMRT. The modulation of radiation fields allows sparing of normal structures, such as the parotid glands and the spinal cord. This results in lower normal tissue toxicity. In the United Kingdom, the parotid-sparing intensity-modulated versus conventional radiotherapy (PARSPORT) trial grade II xerostomia was significantly reduced at 12 and 24 months in the IMRT arm compared to standard fractionation,[17] mainly due to protection of the parotids by IMRT. In the Surveillance, Epidemiology, and End Results (SEER)-based study by Beadle et al,[18] IMRT in patients with head and neck cancers has shown to improve survival rates.

For stages III and IV oropharyngeal cancers, concurrent chemoradiotherapy improved DFS and OS in 2 randomized trials.[5,6] As summarized in Table 4,[19–24] the 3-year OS of patients with oropharyngeal cancers treated with IMRT and concurrent chemotherapy ranged from 67%-87%. Malone et al[25] reported a 2-year distant metastases rate of 7.5% and OS of 74.7% in patients with resectable squamous cell carcinoma of the BOT treated with multimodality therapy.

In recent years, there has been a rise in the number of patients with oropharyngeal cancers. This increase is believed to be due to an increase in HPV infections and associated cancers. Several studies have reported the OS rates are better in patients with HPV-positive tumors. Further, Grisar et al[26] reported that the HPV association occurs more with

TABLE 4 Summary of studies reporting outcomes of oropharyngeal cancer

Study	Treatment	Patient Characteristics	Outcomes	Percentage (%)
Guy's St. Thomas UK 2016[19]	IMRT + chemotherapy	177 patients with oropharyngeal SCC stages II and II = 23stages III and IV = 154	3-y OS	77%
UCSF 2008[20]	IMRT + chemotherapy	71 patients with oropharyngeal SCC stages III and IV	3-y OS 3-y local control	83% 90%
MSKCC 2012[21]	IMRT + chemotherapy (91%)	442 patients with oropharyngeal SCC stage I = 2%stage II = 4% stage III = 21%stage IV = 73%	3-y OS	85%
SWOG 9451[22]	Induction >50% tumor reduction >CRT	37 patients with BOT, 22 with hypopharyngeal All stages III and IV	3-y OS 3-y organ preservation	64% 52%
Emory 2007[23]	IMRT + chemotherapy	34 patients with BOT cancer	2-y actuarial OS 2-y local control	90% 92%
Moffitt[24]	IMRT ± chemotherapy	170 patients 85 tonsillar cancer 76 BOT cancer 9 others	3-y local control 3-y OS	92% 87%

Abbreviations: BOT, base of tongue; CRT, chemoradiotherapy; IMRT, intensity-modulated radiotherapy; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; SCC, squamous cell carcinoma; SWOG, Southwest Oncology Group; UCSF, University of California - San Francisco.

the tonsillar sublocalization. Therefore, the OS rates were better in tonsillar carcinomas due to higher HPV association compared to the BOT.

In our series, the patients with BOT carcinomas had advanced nodal stage disease (>N2c) at presentation 54% compared to the patients with tonsillar cancers of 30%. In spite of this, they had good local control with chemotherapy and radiotherapy. This local control and survivals are comparable to advanced BOT tumors reported in literature.[23,25] However, in spite of achieving excellent locoregional control, the patients with BOT tumors had a significantly increased rate of distant metastasis as compared to similar stage tonsillar tumors. This also correlated with the advanced nodal stage at presentation in BOT tumors.

Squamous cell carcinomas that are HPV-positive are biologically distinct and have a better prognosis. In our series, 49 patients with tonsillar tumors had known HPV status. Of these tumors, 23 tonsillar and 6 BOT tumors were HPV-positive. The local control and survivals were superior in HPV-positive tumors compared with HPV-negative tumors. This is in keeping with other reports in literature in which the local control ranged from 85%-90% and survival ranged from 80%-85%.[27–29]

This led to design of the deescalation studies in HPV-positive tumors. The Eastern Cooperative Oncology Group (ECOG) 1308 trial randomized patients with resectable oropharyngeal cancer classifications T1 to 3 and N0 to 2b, with <10-year smoking history to 54 Gy in 27 fractions versus 69.3 Gy in 33 fractions after neoadjuvant chemotherapy with cetuximab, paclitaxel, and cisplatin. There was no difference in outcomes between the arms, supporting radiation dose deescalation in these patients.[30] The ongoing NRG HN-002 trial compares reduced dose radiotherapy with or without chemotherapy (cisplatin weekly 40 mg/m^2) in HPV-positive, nonsmokers/light smokers (≤10 pack-years) with stage III or IV disease but no distant metastases.[31]

In conclusion, patients with advanced squamous cell carcinomas of the oropharynx can be effectively treated with chemotherapy and radiotherapy reserving surgery for salvage. This will result in organ preservation for most patients. The HPV positivity is an important determinant as it will result in a change in treatment with possible dose reduction protocols. On the other hand, HPV-negative tonsillar tumors and BOT tumors need to be aggressively treated with combined radiotherapy and chemotherapy. Patients with advanced nodal disease, especially those with N2c neck disease and BOT primaries are at increased risk for distant metastasis. These patients should be considered for neoadjuvant chemotherapy trials.

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REFERENCES

[1] Peters LJ, Goepfert H, Ang KK, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. *Int J Radiat Oncol Biol Phys*. 1993;26(1):3-11.

[2] Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2004;350(19): 1937-1944.

[3] Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004;350(19): 1945-1952.

[4] Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). *Head Neck*. 2005;27 (10):843-850.

[5] Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol*. 2004;22(1):69-76.

[6] Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol*. 2003;21(1):92-98.

[7] Masoud Rahbari R, Winkley L, Hill J, et al. Definitive intensity-modulated radiotherapy concurrent with systemic therapy for oropharyngeal squamous cell carcinoma: outcomes from an integrated regional Australian cancer centre. *J Med Imaging Radiat Oncol*. 2016;60(3):414-419.

[8] de Arruda FF, Puri DR, Zhung J, et al. Intensity-modulated radiation therapy for the treatment of oropharyngeal carcinoma: the Memorial Sloan-Kettering Cancer Center experience. *Int J Radiat Oncol Biol Phys*. 2006;64(2):363-373.

[9] Chao KS, Ozyigit G, Blanco AI, et al. Intensity-modulated radiation therapy for oropharyngeal carcinoma: impact of tumor volume. *Int J Radiat Oncol Biol Phys*. 2004;59(1):43-50.

[10] Kim L, King T, Agulnik M. Head and neck cancer: changing epidemiology and public health implications. *Oncology (Williston Park)*. 2010;24(10) 915-919.

[11] Vokes EE, Agrawal N, Seiwert TY. HPV-associated head and neck cancer. *J Natl Cancer Inst*. 2015;107(12):djv344.

[12] Mallen-St Clair J, Alani M, Wang MB, Srivatsan ES. Human papillomavirus in oropharyngeal cancer. The changing face of a disease. *Biochim Biophys Acta*. 2016;1866(2):141-150.

[13] Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2001;51(3):571-578.

[14] Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck

squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys*. 2000;48(1):7-16.

[15] Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. *Lancet*. 2003;362(9388):933-940.

[16] Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet*. 2006;368(9538):843-854.

[17] Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol*. 2011;12(2):127-136.

[18] Beadle BM, Liao KP, Elting LS, et al. Improved survival using intensity-modulated radiation therapy in head and neck cancers: a SEER-Medicare analysis. *Cancer*. 2014;120(5):702-710.

[19] Bird T, De Felice F, Michaelidou A, et al. Outcomes of intensity-modulated radiotherapy as primary treatment for oropharyngeal squamous cell carcinoma - a European single institution analysis. *Clin Otolaryngol*. 2016;42(1):115-122.

[20] Huang K, Xia P, Chuang C, et al. Intensity-modulated chemoradiation for treatment of stage III and IV oropharyngeal carcinoma: the University of California-San Francisco experience. *Cancer*. 2008;113(3):497-507.

[21] Setton J, Caria N, Romanyshyn J, et al. Intensity-modulated radiotherapy in the treatment of oropharyngeal cancer: an update of the Memorial Sloan-Kettering Cancer Center experience. *Int J Radiat Oncol Biol Phys*. 2010;82(1):291-298.

[22] Urba SG, Moon J, Giri PG, et al. Organ preservation for advanced resectable cancer of the base of tongue and hypopharynx: a Southwest Oncology Group Trial. *J Clin Oncol*. 2005;23(1):88-95.

[23] Lawson JD, Otto K, Chen A, Shin DM, Davis L, Johnstone PA. Concurrent platinum-based chemotherapy and simultaneous modulated accelerated radiation therapy for locally advanced squamous cell carcinoma of the tongue base. *Head Neck*. 2008;30(3):327-335.

[24] May JT, Rao N, Sabater RD, et al. Intensity-modulated radiation therapy as primary treatment for oropharyngeal squamous cell carcinoma. *Head Neck*. 2013;35(12):1796-1800.

[25] Malone JP, Stephens JA, Grecula JC, Rhoades CA, Ghaheri BA, Schuller DE. Disease control, survival, and functional outcome after multimodal treatment for advanced-stage tongue base cancer. *Head Neck*. 2004;26(7):561-572.

[26] Grisar K, Dok R, Schoenaers J, et al. Differences in human papillomavirus-positive and -negative head and neck cancers in Belgium: an 8-year retrospective, comparative study. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2016;121(5):456-460.

[27] Goodman MT, Saraiya M, Thompson TD, et al. Human papillomavirus genotype and oropharynx cancer survival in the United States of America. *Eur J Cancer*. 2015;51(18):2759-2767.

[28] Guo T, Rettig E, Fakhry C. Understanding the impact of survival and human papilloma virus tumor status on timing of recurrence in oropharyngeal squamous cell carcinoma. *Oral Oncol*. 2016;52:97-103.

[29] Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35.

[30] Marur S, Lee J-W, Cmelak A, et al. ECOG 1308: A phase II trial of induction chemotherapy followed by cetuximab with low dose versus standard dose IMRT in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx (OP). *J Clin Oncol*. 2012;30 (suppl; abstract 5566).

[31] NRG Oncology. Reduced-dose intensity-modulated radiation therapy with or without cisplatin in treating patients with advanced oropharyngeal cancer. www.clinicaltrials.gov/ct2/show/NCT02254278. Accessed January 3, 2017.

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