Published in final edited form as:

Curr Opin Oncol. 2014 May ; 26(3): 252–258. doi:10.1097/CCO.0000000000000072.

OROPHARYNGEAL SQUAMOUS CELL CARCINOMA TREATMENT: CURRENT STANDARDS AND FUTURE DIRECTIONS

Shanthi Marur, MD¹ and Barbara Burtneess, MD²

¹Johns Hopkins University, School of Medicine, Baltimore, Maryland ²Fox Chase Cancer Center, Philadelphia, Pennsylvania

Abstract

Purpose of review—To discuss the changing landscape and significant developments in diagnosis and management of oropharyngeal squamous cell carcinoma (OPSCC).

Recent findings—High-risk human papilloma viruses have been recognized as important causative factors for oropharyngeal cancer. The diagnosis is established with type specific and broad-spectrum in-situ hybridization (ISH) probes and/or p 16 immunohistochemistry (IHC) assays on fresh frozen paraffin embedded (FFPE) tissue blocks. HPV associated tumors have superior response and outcomes compared to HPV unrelated tumors. Retrospective studies have been able to stratify OPSCC based on HPV status, tumor stage, nodal stage and smoking history into risk groups with differing risks of death or distant disease. Selected patients, non-smokers with less advanced nodal stage, may be over-treated with current treatment paradigms, and de-intensification of curative therapy is a current research focus for these patients. Smokers, patients with advanced nodal or tumor stage, and HPV-unrelated cancers have a less favorable prognosis and the search for novel targets in particularly important for these patients.

Summary—This review will highlight the current standards and the future direction of novel therapies in both HPV-associated and HPV-unrelated cancers.

Keywords

Oropharynx cancer; HPV; Smoking; Chemoradiation; De-escalation; Novel targets in HNSCC

Introduction

Worldwide, the incidence of pharyngeal carcinoma is approximately 136 000, with OPSCC on the rise in developed countries.^(1, 2) The proportion of all head and neck squamous cell cancers (HNSCC) arising in the oropharynx has risen from 20% in the 1980's to 70% in the United States at present.^(3, 4) This increase has been linked to a rise in HPV-associated cancers.^(5, 6) Epidemiologic studies indicate oral HPV infection is predominantly sexually

acquired.⁽⁷⁾ A generational change in sexual behavior may have contributed to the surge in HPV-associated OPSCC.^(8, 9)

The scope of this review is to highlight the standards of care for managing oropharyngeal cancer, and how these are forecast to change for HPV-associated and non-associated OPSCC, given a current generation of studies exploring treatment deintensification for favorable prognosis cancers, and testing novel targeted therapies in intermediate and unfavorable prognosis cancers.

The distinct clinical phenotypes, molecular biology and testing of oropharyngeal cancer

Patients with HPV-associated cancer have a younger median age, and lower lifetime exposure to tobacco and alcohol, than patients with HPV-unrelated cancers. [Table 1] (3, 9, 10) In contrast HPV-negative OPSCC is more common in men in the seventh decade, heavy smokers and in those with a history of alcohol dependence.^(7, 9, 10) The two phenotypes are very distinct and Table 1 outlines the differences.

The molecular differences between the HPV-associated and HPV-negative OPSCC suggest distinct pathogenesis.^(9, 11) Following viral integration, HPV E6/E7 oncoproteins promote cell cycle progression in keratinocytes by inactivating two important tumor suppressor genes, the tumor protein p53 and Rb. Rapid degradation of p53 results in low levels of intact wild type p53, while Rb inactivation induces the cyclin dependent kinase inhibitor p16.^{(9) (11)} The inactivation of p53 can foster activation of the Wnt signaling pathway⁽¹²⁾ and specific mutations in PIK3Ca have been described in HPV-associated OPSCC.⁽¹³⁾ In contrast, HPV-negative OPSCC are characterized by high mutational burden, with p53 mutation and activation of the PI3K pathway via mutation or PTEN loss the most common abnormalities.^(14–16) The enhanced sensitivity to radiation and chemotherapy of HPV associated cancers is not fully explained.^(17, 18) Gene expression differences between these two cancers include frequent p53 mutation in HPV-negative cancers, differential expression of other genes associated with treatment resistance such as TYMS, STMN1, CCND1, and RBBP4; and enhanced immune clearance of virally infected cells following radiation injury.⁽¹⁹⁾⁽²⁰⁾

HPV DNA is detected by several methods, including type-specific and broad spectrum in situ hybridization (ISH), PCR-based amplification assays, real time PCR to quantify viral load, and IHC for p16, upregulated following oncoprotein E7-induced Rb degradation.^(21, 22) p16 IHC is a reliable surrogate marker (sensitivity, 96.8%; specificity, 83.8%) comparable to ISH (sensitivity, 88.0%; specificity, 94.7%)^{(21–23).}⁽²⁴⁾ The discordance between p16 IHC and HPV ISH for HPV16, the type of HPV most commonly associated with OPSCC, is about 25%. p16-positive /HPV 16 negative cases may be associated with a different HPV genotype. A liquid phase assay used in cervical cancer is being tested with HNSCC.^(21, 25)

Risk stratification and identification of favorable oropharyngeal cancer

Prospective and retrospective studies have helped us understand the impact of smoking on oropharyngeal cancer prognosis.

Ang et al retrospectively evaluated a subgroup of 433 patients with oropharyngeal cancer treated on RTOG 0129, a randomized trial comparing accelerated fraction chemoradiation (CRT) to standard fraction RT.⁽²⁶⁾ Tissue was available for HPV testing in 63.8%. The three year overall survival and progression-free survival were significantly better in the HPV-positive than the HPV-negative patients. (HR 0.42 (95% CI 0.27-0.66) $p < 0.001$). A recursive partition analysis (RPA) explored smoking history of ≤ 10 years vs > 10 years, nodal stage and tumor stage, yielding 3 putative risk categories: favorable risk HPV-associated cancer in non-smokers, intermediate risk consisting of HPV-associated cancers with tobacco exposure and high nodal stage, or HPV-negative cancers with intermediate tumor stage, and high risk consisting of HPV-negative cancers with high tumor stage. Table 2 illustrates the differences in outcomes in the various risk for death groups.

O'Sullivan et al conducted a similar RPA in a retrospective study with over 800 oropharyngeal cancer patients treated with radiation or concurrent CRT at a single institution between 2001 and 2009.⁽²⁷⁾ HPV status was determined in 56%. HPV-association was demonstrated in 382 patients. RPA stratified patients on HPV status, T stage and nodal stage (Table 2). Smoking status was not identified as a significant risk factor for distant metastases. Conversely, the risk of developing a second primary was significantly higher in patients with > 10 pack year smoking history (11% vs 4%, $p = 0.009$). HPV-associated disease manifested a more indolent natural history, with development of distant metastases occurring until 5 years of follow up, in contrast to most distant failures occurring in the first 2 years in HPV-negative cases.

General principles in the treatment of oropharyngeal cancer

Upfront surgery or radiation alone, for early stage (T1-T2 N0) oropharyngeal cancer are equally effective in loco-regional control and overall survival.⁽²⁸⁾ For patients with early nodal involvement (T1N1, T2N1), resection of the primary with neck dissection or adjuvant radiation is effective. Radiation Therapy Oncology Group (RTOG) study R0920 [NCT00956007] examines whether the addition of cetuximab to radiation in intermediate risk patients without classic indications for chemoradiation improves outcome in the adjuvant setting.

For patients with more advanced T stage and nodal stage (Stage III, IV a and IV b), concurrent high dose cisplatin with radiation has been considered optimal treatment since the publication of the Intergroup trial.⁽²⁹⁾ These findings are also supported by metaanalysis.⁽³⁰⁾ Chemoradiation emerged as the preferred treatment because of the morbidity of conventional surgical approaches to oropharyngeal cancers, which required morbid exposures and generally involved total glossectomy. The advent of transoral surgical approaches for T1 and T2 oropharyngeal cancers has reopened the question of when resection belongs in standard management. Sequential therapy with multiagent induction

chemotherapy (IC) followed by standard CRT has been explored as an approach to improve outcome, but randomized trials have failed to demonstrate a benefit in unselected patients. (31, 32)

While organ preservation with concurrent high dose cisplatin with 70Gy radiation is standard of care for locally advanced OPSCC, these patients are at risk for developing long-term toxicities secondary to damage to pharyngeal constrictor muscles, salivary glands, skin and thyroid gland. The risk of dysphagia increases above 55Gy radiation dose to superior and middle pharyngeal constrictors; (33) feeding tube dependence increases when more than 30% of the pharyngeal constrictors receive 70Gy; (34) stricture and aspiration are more common if 50% the pharyngeal constrictors receive 70Gy (33); Additionally, xerostomia, (35) radiation dermatitis, (36) chronic cosmetic changes (36) and hypothyroidism (37) are also associated with higher radiation dose and volume. Long-term follow-up of patients treated curatively for larynx cancer with high dose radiation and high dose cisplatin also raises the possibility that CRT increases non-cancer mortality. (38)

Future directions in the treatment of oropharyngeal cancer

The HPV-associated oropharyngeal cancer patients are relatively younger individuals, with a lower burden of co-morbidity and excellent prognosis. E2399 treated patients with oropharynx and larynx cancer with induction chemotherapy followed by 70Gy with concurrent paclitaxel, an early attempt at reducing treatment morbidity in unselected patients. (18) Prospective subset analysis demonstrated that for HPV-positive compared to HPV-negative patients, objective response (81.6 % vs 55.2%, $p=0.01$) and 2-year progression-free survival were markedly superior (84.2 % vs 56.9%, $p=0.06$)

Tissue samples from oropharyngeal cancer patients enrolled on Phase III trials RTOG0129 (discussed above), (26) TROG 02.02, (39) TAX 324, (40) DAHANCA (17) all reported that for 3 and/or 5 year survival, HPV positive/p16 positive patients had a significant advantage. (Table 3).

I: HPV associated disease: De-escalation clinical trials in progress

Given the difference in etiology, molecular profile, natural history and treatment responsiveness, investigators have concluded that HPV-associated and HPV-unrelated oropharyngeal cancer are two different diseases, and that different research questions arise in the two diseases. For HPV-positive cancer, it will be important to develop reliable tests – whether based on clinical criteria or on validated biomarker panels – to select patients with a very high chance of cure, and to find treatments for these patients which are less arduous, and which are associated with the least possible risk of long term toxicity and of non-cancer mortality. For HPV-associated cancer with a greater risk of recurrence, defining the causes of failure and adapting treatments to address these causes will be important. For the HPV-negative locally advanced patient, who currently appears to have only a 35% chance of cure, identification of novel targets, and incorporation of new agents, will be critical to improved outcomes.

Several strategies have been explored.

1. De-escalating treatment with upfront induction chemotherapy followed by response adapted radiation (low vs standard) with an alternative radiosensitizer

E1308[NCT01084083], a prospective Phase II trial designed specifically for HPV16 ISH or p16 positive, stage III, IVa oropharyngeal cancer patients, completed accrual in 2011. (ASCO 2013, Abstract 6005) Treatment included IC with three cycles of cetuximab/paclitaxel/cisplatin to identify the most treatment responsive patients, who then received 54 rather than 69 Gy radiation with concurrent cetuximab. With a median follow up of 16.2 months, the one-year PFS in low dose arm in patients with 10 pack year smoking history patients was 97% (95% CI: 0.83 to 0.99). Follow on studies planned within ECOG include a trial to examine whether the dose to next echelon nodes can be reduced, what the least toxic induction regimen to identify the 70% of patients who are eligible for radiation de-escalation is, and whether cisplatin or cetuximab is the preferable radiosensitizer. These developmental studies are anticipated to lead to an optimal low toxicity approach to deintensification which will be appropriate for phase III testing against conventional full dose CRT with high dose cisplatin. RTOG proposes to test treatment deintensification from 70 to 60Gy with no radiation sensitizer in a comparable population.

2. Deescalating treatment by optimizing the type of radiosensitizer with standard dose radiation

RTOG 1016 [NCT01302834], a Phase III trial comparing weekly cetuximab with accelerated RT 70Gy/6 weeks to cisplatin 100mg/m² d1 and 22 with accelerated RT 70Gy/6 weeks in patients with p16 positive, T1-2, N2a-N3 and T3/4 any N, oropharyngeal cancer reached its initial accrual goal in mid-2013, but proved to have a lower event rate than projected. It has recently reopened with an increased sample size of 1000. This study is the first trial to compare cisplatin with cetuximab as a radiosensitizer in a homogenous population.

3. Deescalating treatment using upfront surgery with minimally invasive techniques followed by reduced dose radiation in the adjuvant setting

Previously surgery for oropharyngeal cancer required transcervical neck exposure and resulted in significant morbidity. Minimally invasive techniques for transoral have emerged. (28) To date, the experience with these techniques, specifically on tonsillar and base of tongue T1 and T2 OPSCC have reported excellent long term swallowing outcomes. ECOG 3311 [NCT01898494] is a Phase II trial in p16 positive resectable Stage III, IV a and b oropharyngeal cancer. All patients will undergo transoral resection and neck dissection, followed by risk adapted adjuvant therapy. Patients with pathological Stage I and II, are considered low risk for recurrence and will enter the observation arm. Patients with <1mm extracapsular extension (ECE), 2–4 positive lymph nodes or close margins, will be considered intermediate risk. These patients will be randomized to 50Gy vs 60Gy radiation. The high-risk group are those with positive margins, with >1mm ECE, or at least 5 positive lymph nodes. These patients will receive 66 Gy with weekly cisplatin. This study hopes to demonstrate that transoral resection followed by reduced dose adjuvant radiation can maintain a 2 year PFS in the intermediate risk group of 85% or better.

II: HPV Negative Disease: Treatment intensification with novel targeted therapy

As noted above, decades of trials examining longer duration and intensity of therapy,^(31, 41) accelerated fractionation in chemoradiation, and the addition of novel agents to CRT,^(26, 42) have failed to advance survival for patients with HPV-negative cancer. Data from a randomized phase II trial suggest the possibility that the dual EGFR/HER2 inhibitor lapatinib added to CRT improves disease control and survival in HPV-negative HNSCC, and has led to the design of an RTOG Foundation study of lapatinib and CRT in p16-negative HNSCC [NCT00490061].⁽⁴³⁾ Another dual EGFR-HER2 targeted agent is the irreversible inhibitor afatinib. This tolerable and orally administered agent is active in HNSCC and opened up the opportunity for long term adjuvant therapy in patients who have no evidence of disease following CRT, but are at high risk of recurrence by virtue of tobacco history or stage and subsite. These patients are eligible for 2:1 randomization between afatinib and placebo on a trial powered for disease-free and overall survival [NCT01427478]. Additional novel targets of interest in this population are Aurora A kinase [NCT01540682];⁽⁴⁴⁾ tubulin;⁽⁴⁵⁾ EGFR⁽⁴⁶⁾ and the PI3K pathway, now recognized to be the most commonly deranged pathway in these cancers [NCT01111058; NCT01602315; NCT01737450]. [Table 4]

An important new direction in anticancer therapy has been the ability to target T cell exhaustion. Both in HPV-associated and HPV-unrelated HNSCC, it seems likely that a subset of PD-1 expressing cancers will benefit from this approach, with phase I trials ongoing and trials through phase III currently under development.

Conclusions

The oropharyngeal cancer landscape is swiftly changing and the number of HPV associated oropharyngeal cancers are expected to surpass the number of cervical cancers by 2020.⁽⁴⁾ Investigators now hope to devise different treatment paradigms for optimal management of OPSCC based on HPV status, tumor stage, nodal stage and smoking history. Important research questions will be the most accurate means of identifying highly curable patients, the least toxic treatment approaches which do not sacrifice cure in favorable risk patients, and identification of new agents and paradigms for patients who currently do not have a high expectation of cure.

Acknowledgments

Conflicts of Interest:

Shanthi Marur: Research Funding: Bristol Myers Squibb

Barbara Burtness: Research funding: Genentech, Boehringer Ingelheim

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA: a cancer journal for clinicians. 2013; 63(1):11–30. [PubMed: 23335087]

2. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, et al. Worldwide Trends in Incidence Rates for Oral Cavity and Oropharyngeal Cancers. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013
3. Jemal A, Simard EP, Dorell C, Noone AM, Markowitz LE, Kohler B, et al. Annual Report to the Nation on the Status of Cancer, 1975–2009, featuring the burden and trends in human papillomavirus(HPV)-associated cancers and HPV vaccination coverage levels. *Journal of the National Cancer Institute*. 2013; 105(3):175–201. [PubMed: 23297039]
4. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011; 29(32):4294–301. [PubMed: 21969503]
5. Kurdgelashvili G, Dores GM, Srouf SA, Chaturvedi AK, Huycke MM, Devesa SS. Incidence of potentially human papillomavirus-related neoplasms in the United States, 1978 to 2007. *Cancer*. 2013; 119(12):2291–9. [PubMed: 23580435]
6. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2008; 26(4): 612–9. [PubMed: 18235120]
7. Joseph AW, D'Souza G. Epidemiology of human papillomavirus-related head and neck cancer. *Otolaryngologic clinics of North America*. 2012; 45(4):739–64. [PubMed: 22793850]
8. Heck JE, Berthiller J, Vaccarella S, Winn DM, Smith EM, Shan'gina O, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. *International journal of epidemiology*. 2010; 39(1):166–81. [PubMed: 20022926]
9. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. *The lancet oncology*. 2010; 11(8):781–9. [PubMed: 20451455]
10. Benson E, Li R, Eisele D, Fakhry C. The clinical impact of HPV tumor status upon head and neck squamous cell carcinomas. *Oral oncology*. 2013
11. Rampias T, Sasaki C, Psyrri A. Molecular mechanisms of HPV induced carcinogenesis in head and neck. *Oral oncology*. 2013
12. Smeets SJ, van der Plas M, Schaaij-Visser TB, van Veen EA, van Meerloo J, Braakhuis BJ, et al. Immortalization of oral keratinocytes by functional inactivation of the p53 and pRb pathways. *International journal of cancer Journal international du cancer*. 2011; 128(7):1596–605. [PubMed: 20499310]
13. Lui VW, Hedberg ML, Li H, Vangara BS, Pendleton K, Zeng Y, et al. Frequent mutation of the PI3K pathway in head and neck cancer defines predictive biomarkers. *Cancer discovery*. 2013; 3(7):761–9. [PubMed: 23619167]
14. Klussmann JP, Mooren JJ, Lehn M, Claessen SM, Stenner M, Huebbers CU, et al. Genetic signatures of HPV-related and unrelated oropharyngeal carcinoma and their prognostic implications. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2009; 15(5):1779–86. [PubMed: 19223504]
15. Sturgis EM, Ang KK. The epidemic of HPV-associated oropharyngeal cancer is here: is it time to change our treatment paradigms? *Journal of the National Comprehensive Cancer Network : JNCCN*. 2011; 9(6):665–73. [PubMed: 21636538]
16. Lin BM, Wang H, D'Souza G, Zhang Z, Fakhry C, Joseph AW, et al. Long-term prognosis and risk factors among patients with HPV-associated oropharyngeal squamous cell carcinoma. *Cancer*. 2013; 119(19):3462–71. [PubMed: 23861037]
17. Lassen P, Eriksen JG, Krogdahl A, Therkildsen MH, Ulhøi BP, Overgaard M, et al. The influence of HPV-associated p16-expression on accelerated fractionated radiotherapy in head and neck cancer: evaluation of the randomised DAHANCA 6&7 trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2011; 100(1):49–55. [PubMed: 21429609]

18. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *Journal of the National Cancer Institute*. 2008; 100(4):261–9. [PubMed: 18270337]
19. Lohavanichbutr P, Houck J, Fan W, Yueh B, Mendez E, Futran N, et al. Genomewide gene expression profiles of HPV-positive and HPV-negative oropharyngeal cancer: potential implications for treatment choices. *Archives of otolaryngology–head & neck surgery*. 2009; 135(2):180–8. [PubMed: 19221247]
20. Vermeer DW, Spanos WC, Vermeer PD, Bruns AM, Lee KM, Lee JH. Radiation-induced loss of cell surface CD47 enhances immune-mediated clearance of human papillomavirus-positive cancer. *International journal of cancer Journal international du cancer*. 2013; 133(1):120–9. [PubMed: 23292955]
21. Holmes BJ, Westra WH. The expanding role of cytopathology in the diagnosis of HPV-related squamous cell carcinoma of the head and neck. *Diagnostic cytopathology*. 2013
22. Schache AG, Liloglou T, Risk JM, Filia A, Jones TM, Sheard J, et al. Evaluation of human papilloma virus diagnostic testing in oropharyngeal squamous cell carcinoma: sensitivity, specificity, and prognostic discrimination. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2011; 17(19):6262–71. [PubMed: 21969383]
23. Walline HM, Komarck C, McHugh JB, Byrd SA, Spector ME, Hauff SJ, et al. High-Risk Human Papillomavirus Detection in Oropharyngeal, Nasopharyngeal, and Oral Cavity Cancers: Comparison of Multiple Methods. *JAMA otolaryngology– head & neck surgery*. 2013
24. Jordan RC, Lingen MW, Perez-Ordóñez B, He X, Pickard R, Koluder M, et al. Validation of methods for oropharyngeal cancer HPV status determination in US cooperative group trials. *The American journal of surgical pathology*. 2012; 36(7):945–54. [PubMed: 22743284]
25. Bishop JA, Maleki Z, Valsamakis A, Ogawa T, Chang X, Pai SI, et al. Application of the hybrid capture 2 assay to squamous cell carcinomas of the head and neck: a convenient liquid-phase approach for the reliable determination of human papillomavirus status. *Cancer cytopathology*. 2012; 120(1):18–25. [PubMed: 21751428]
26. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *The New England journal of medicine*. 2010; 363(1):24–35. [PubMed: 20530316]
27. O’Sullivan B, Huang SH, Siu LL, Waldron J, Zhao H, Perez-Ordóñez B, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013; 31(5):543–50. [PubMed: 23295795]
28. Adelstein DJ, Ridge JA, Brizel DM, Holsinger FC, Haughey BH, O’Sullivan B, et al. Transoral resection of pharyngeal cancer: summary of a National Cancer Institute Head and Neck Cancer Steering Committee Clinical Trials Planning Meeting, November 6–7, 2011, Arlington, Virginia. *Head & neck*. 2012; 34(12):1681–703. [PubMed: 23015475]
29. Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2003; 21(1):92–8. [PubMed: 12506176]
30. Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2011; 100(1):33–40. [PubMed: 21684027]
31. Haddad R, O’Neill A, Rabinowits G, Tishler R, Khuri F, Adkins D, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. *The lancet oncology*. 2013; 14(3):257–64. [PubMed: 23414589]
32. Hitt R, Grau JJ, Lopez-Pousa A, Berrocal A, Garcia-Giron C, Irigoyen A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2013

33. Paleri V, Roe JW, Strojan P, Corry J, Gregoire V, Hamoir M, et al. Strategies to reduce long-term postchemoradiation dysphagia in patients with head and neck cancer: An evidence-based review. *Head & neck*. 2013
34. Eisbruch A, Schwartz M, Rasch C, Vineberg K, Damen E, Van As CJ, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? *International journal of radiation oncology, biology, physics*. 2004; 60(5):1425–39.
35. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *The lancet oncology*. 2011; 12(2):127–36. [PubMed: 21236730]
36. Dean NR, Sweeny L, Harari PM, Bonner JA, Jones V, Clemons L, et al. Wound healing following combined radiation and cetuximab therapy in head and neck cancer patients. *Journal of wound care*. 2011; 20(4):166–70. [PubMed: 21537303]
37. Diaz R, Jaboin JJ, Morales-Paliza M, Koehler E, Phillips JG, Stinson S, et al. Hypothyroidism as a consequence of intensity-modulated radiotherapy with concurrent taxane-based chemotherapy for locally advanced head-and-neck cancer. *International journal of radiation oncology, biology, physics*. 2010; 77(2):468–76.
38. Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, et al. Long-term results of RTOG 91–11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013; 31(7):845–52. [PubMed: 23182993]
39. Rischin D, Young RJ, Fisher R, Fox SB, Le QT, Peters LJ, et al. Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010; 28(27):4142–8. [PubMed: 20697079]
40. Posner MR, Lorch JH, Goloubeva O, Tan M, Schumaker LM, Sarlis NJ, et al. Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2011; 22(5):1071–7.
41. Salama JK, Haraf DJ, Stenson KM, Blair EA, Witt ME, Williams R, et al. A randomized phase II study of 5-fluorouracil, hydroxyurea, and twice-daily radiotherapy compared with bevacizumab plus 5-fluorouracil, hydroxyurea, and twice-daily radiotherapy for intermediate-stage and T4N0–1 head and neck cancers. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2011; 22(10):2304–9.
42. Martins RG, Parvathaneni U, Bauman JE, Sharma AK, Raez LE, Papagikos MA, et al. Cisplatin and radiotherapy with or without erlotinib in locally advanced squamous cell carcinoma of the head and neck: a randomized phase II trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013; 31(11):1415–21. [PubMed: 23460709]
43. Harrington K, Berrier A, Robinson M, Remenar E, Housset M, de Mendoza FH, et al. Randomised Phase II study of oral lapatinib combined with chemoradiotherapy in patients with advanced squamous cell carcinoma of the head and neck: rationale for future randomised trials in human papilloma virus-negative disease. *European journal of cancer*. 2013; 49(7):1609–18. [PubMed: 23265705]
44. Mehra R, Serebriiskii IG, Burtness B, Astsaturov I, Golemis EA. Aurora kinases in head and neck cancer. *The lancet oncology*. 2013; 14(10):e425–35. [PubMed: 23993387]
45. Burtness BA, Manola J, Axelrod R, Argiris A, Forastiere AA, Eastern Cooperative Oncology G. A randomized phase II study of ixabepilone (BMS-247550) given daily x 5 days every 3 weeks or weekly in patients with metastatic or recurrent squamous cell cancer of the head and neck: an Eastern Cooperative Oncology Group study. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2008; 19(5):977–83.
46. Argiris A, Ghebremichael M, Gilbert J, Lee JW, Sachidanandam K, Kolesar JM, et al. Phase III randomized, placebo-controlled trial of docetaxel with or without gefitinib in recurrent or metastatic head and neck cancer: an eastern cooperative oncology group trial. *Journal of clinical*

oncology : official journal of the American Society of Clinical Oncology. 2013; 31(11):1405–14.
[PubMed: 23460714]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

KEY POINTS

1. Oropharyngeal carcinoma is on the rise in developed countries.
2. High risk human papilloma viruses (HPV) have been recognized as important causative factors for oropharyngeal cancer.
3. HPV associated OPSCC has a distinct clinical and molecular biology compared to HPV negative OPSCC.
4. Treatment response and survival outcomes in HPV associated OPSCC are superior compared to HPV negative OPSCC.
5. Clinical trials focus on de-escalation of treatment in select group of HPV associated OPSCC, and intensification of treatment with addition of novel targeted agents to standard treatment in HPV negative OPSCC.

Table 1The two distinct subtypes of OPSCC^{9,10}

	HPV associated OPSCC	HPV negative OPSCC
EPIDEMIOLOGY/RISK FACTORS		
1. Race 2. Age 3. Sex 4. Socioeconomic status 5. Smoking /Alcohol History 6. Marijuana use 7. Early sexual debut 8. Multiple lifetime sexual partners	White >Black Between 4 th to 6 th decade M:F 8:1 Middle to Higher Never or minimal exposure Strong association Strong association Strong association	White > Black Usually 7 th decade M: F 3:1 Lower to middle Significant exposure Not known Not known Not known
CLINICAL FEATURES		
9. Tumor (T) stage 10. Nodal (N) stage	Early tumor stage More advanced nodal stage	More advanced tumor stage Early nodal stage
OUTCOMES IN STAGE III /IV a,b		
11. Distant metastasis risk 12. Second primary (SP) risk 13. Overall response to treatment 14. 2 year OS	Distant control rate : 70–90% Rate of SP :11% >80% respond 95% [95% CI, 87–100]	Distant control rate : 70–90% Rate of SP: 4.6% >50% respond 62% [95% CI, 49–74]

Illustrates the two distinct subtypes that differ by epidemiology, risk factors, clinical features and outcomes. Abbreviations: M: F Male : Female, DC: Distant Control, SP: Second Primary, OS: Overall Survival

Table 2

Illustrates the OPSCC risk groups from RPA analysis of two retrospective studies and the outcomes.^(26, 27)

STUDY	RISK GROUP	VARIABLES	n	3yr OUTCOME (95% CI)
Ang et al. RTOG 0129 (n= 266) ²⁵	Low risk for death (n=114)	HPV +, <10py HPV +, >10 py N0-N2a	83 26	OS: 93% (88.3to 97.7)
	Intermediate risk for death (n=79)	HPV +, >10py, N2b-N3 HPV -, <10py, T2-T3	64 15	OS: 70.8% (60.7 to 80.8)
	High risk for death (n= 23)	HPV – >10py, all T4	23	OS 46.2% (34.7 to 57.7)
O’Sullivan et al (n= 505) ²⁶	HPV positive low risk for DM	T1–3, N0-N2c	286	DC 93%(89 to 95) LRC 95% (91 to 97)
	HPV positive high risk for DM	T4 N3	63 33	DC 78% (65 to 84) LRC 82% (72 to 89)
	HPV negative low risk	T1-T2, N0-N2c	56	DC 93%(79 to 98) LRC 76% (62 to 86)
	HPV negative high risk	T3–4, N3	67	DC 72% (56 to 82) LRC 62% (46 to 74)

Abbreviations. RPA: Recursive Partition Analysis, py: pack year, n: Number, HPV : Human Papilloma Virus, OS: Overall Survival, DC: Distant Control, LRC: Locoregional control, T: Tumor, N: Nodal

Table 3

Selected studies with HPV associated oropharyngeal cancer, completed and in progress.

Study	Number	Phase	Treatment	Follow-up (years)	PFS HR (95% CI)	OS HR (95% CI)
ECOG 2399 ¹⁷	96	II	IC + CRT with paclitaxel/70Gy	2	0.27 (0.10 to 0.75)	0.36 (0.15–0.85)
RTOG 0129 ²⁵	323	III	Accelerated RT/Cisplatin vs Standard RT/Cisplatin	5	0.49 (0.33 to 0.74)	0.42 (0.27–0.66)
TROG 02.02 ³⁸	185	III	Cisplatin RT+/- Tirapazamine	2	0.39(0.20–0.74)	0.36 (0.17–0.74)
DHANCA 6 and 7 ¹⁶	794	III	Accelerated RT vs Conventional RT	5	DSS 0.47 (0.33–0.67)	0.54 (0.42–0.68)
ECOG 1308	90	II	IC f/b 54 or 69 Gy RT/Cetuximab	1	N/A	N/A
ECOG 3311	377	II	Surgery f/b risk adapted adjuvant therapy	Active	N/A	N/A
RTOG 1016	1000	III	Cisplatin/RT vs Cetuximab/RT	Active	N/A	N/A

Abbreviations: PFS: Progression free Survival, DSS : Disease Free Survival, OS : Overall Survival, HR : hazard ratio, CI :confidence interval

Table 4

Selected studies in progress with targeted therapies in HNSCC

Study	Number	Phase	Treatment	Targets
NCT00490061	60	II	Lapatinib+RT	EGFR and Her-2/neu expressions
NCT01427478	315	III	Afatinib vs Placebo after CRT	EGFR and Her-2/neu expressions
NCT01540682	9-18	I	MLN8237 + Cetuximab + RT	Aurora A and EGFR expression
NCT01111058	160	II	Everolimus vs Placebo after CRT	PI3K pathway
NCT01602315	186	Ib/II	BYL719 and Cetuximab in metastatic/refractory	PI3K pathway
NCT01737450	70	II	BKM120 in metastatic/refractory	PI3K pathway

Abbreviations: RT: Radiation therapy, CRT: Chemoradiation therapy