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EDITORIAL – HEAD AND NECK ONCOLOGY

Treatment Deintensification for Human Papillomavirus-Associated Oropharyngeal Cancer

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The oropharyngeal (OPSCC) subtype of head and neck squamous cell cancer (HNSCC) has a rapidly rising incidence in the US.[1] Declines in tobacco and alcohol use have reduced the incidence of OPSCC related to substance use by 50%, with similar decreases throughout the developed world. However, this decline has been more than offset by OPSCC caused by human papillomavirus (HPV), which has increased in incidence by 225% between 1988 and 2004.[1]

HPV-OPSCC is associated with sexual behavior, and confers a markedly improved survival compared with patients with non-HPV-related HNSCC.[2] The rise of a clinically distinct form of HNSCC has occurred simultaneously with important shifts in therapy. Several trials demonstrated the efficacy of concurrent chemoradiotherapy for OPSCC compared with radiation alone. These trials include the 94-01 GORTEC trial,[3] an Italian phase III trial showing improved but non-significant survival with chemoradiotherapy,[4] as well as a meta-analysis demonstrating better survival with concurrent chemoradiation versus radiation alone for HNSCC.[5]

During this shift to more intense concurrent chemoradiation, advances in surgery allowed transoral resection of primary HNSCC, with better functional outcomes compared with open surgery.[6] While transoral excision of early-stage OPSCC in accessible sites such as the tonsil and soft palate has been performed for decades,[7] it took the emergence of improved surgical microscopes and lasers for transoral surgery (TOS) to be applied to advanced cancers in less accessible areas such as the base of tongue.[8] However, transoral laser microsurgery (TLMS) is technically challenging, with access and visualization being highly dependent on tumor size and location, requiring each operation to be tailored to the specific patient.[9] Transoral robotic surgery (TORS), another significant advance, dramatically improved access and visualization, decreasing the spatial complexity of surgery, allowing operations to become more standardized when compared with TLMS.[9] Studies of TOS for OPSCC with both TORS and TLMS have demonstrated excellent and comparable oncologic and functional swallowing outcomes, even in advanced primary OPSCC.[8,10,11]

The epidemiologic changes in OPSCC and improvements in therapy have led to efforts to better match disease and treatment. For HNSCC, the addition of chemotherapy to radiation improves survival outcomes but at the cost of sharply higher treatment-related side effects.[12] Similarly, functional and patient-reported outcomes following TOS are affected by the intensity of adjuvant therapy.[13,14] A critical question is whether de-escalation of therapy to reduce treatment-related side effects is possible for HPV-OPSCC since it has a better overall prognosis.

An early trial to address this question, NRG 1016, is testing the hypothesis that radiotherapy plus cetuximab is non-inferior to standard cisplatin plus radiotherapy in HPV-OPSCC. Another deintensification trial, E1308, was a phase II trial of induction chemotherapy (IC) followed by reduced-dose radiation and weekly cetuximab for complete clinical responders to IC.[15] It showed reduced-dose radiation with concurrent cetuximab following IC, resulting in progression-free and overall survival of 80 and 94%, respectively, at 2 years.[15]

Related to these non-surgical efforts to de-escalate therapy, in this issue of Annals of Surgical Oncology,

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Jackson and colleagues perform a retrospective case-matched cohort analysis at two institutions on patients with advanced-stage HPV-OPSCC who were either treated with TOS and neck dissection alone or with adjuvant therapy. TOS consisted of either TORS or TLMS for the primary tumor, with selective neck dissection of the involved high-risk nodal basins. While adjuvant therapy significantly improved disease-free survival and was associated with a lower risk of local and regional recurrence, there was no difference in disease-specific survival or overall survival. They conclude that adjuvant therapy could potentially be spared in a select subset of patients and reserved for instances of recurrence. Other retrospective studies have suggested similar results, raising the question of whether radiation and chemotherapy are necessary postoperatively in the setting of advanced-stage HPV-OPSCC.[16,17]

Two clinical trials, RTOG 9501 and EORTC 22931, underpin the rationale for postoperative adjuvant therapy in advanced HNSCC.[18,19] While postoperative radiotherapy has been standard of care for patients at high risk for locoregional failure after surgery for HNSCC,[20–22] these two trials showed the addition of chemotherapy improves survival when high-risk features (HRFs) are present.[23] However, the two trials did not test patients for HPV status and included subsites outside of the oropharynx, thus including a large proportion of patients with non-HPV-related HNSCC with a worse prognosis. It is probable that HPV-OPSCC patients with HRFs would derive less benefit from the addition of adjuvant chemotherapy to postoperative radiation.[24] The ongoing ADEPT trial randomized HPV-OPSCC patients with HRFs following TOS and neck dissection to standard-of-care adjuvant chemoradiotherapy versus radiotherapy alone to test whether adjuvant chemotherapy can be avoided.

ECOG 3311, an ongoing, randomized, prospective, phase II clinical trial for patients with advanced-stage HPV-OPSCC who undergo TOS and neck dissection, extends this idea even further. Patients with HRFs receive standard-of-care adjuvant chemoradiotherapy, but intermediate-risk patients with close but clear margins and greater than N1 disease regionally are randomized between standard- and reduced-dose radiation. Low-risk patients with N1 disease receive no adjuvant treatment. The 2-year rate of locoregional recurrence and progression-free survival are primary outcomes and the study will collect data on functional outcomes with respect to swallowing. SiRS (NCT02072148) and PATHOS (NCT02215265) are two other ongoing clinical trials focused on this concept of adjuvant therapy de-escalation following TOS. It is in this contemporary context that Jackson et al. provide data to support the approach ECOG 3311 pursues, and suggests that even further de-escalation of adjuvant therapy after TOS may be possible.

As new technologies such as image-guided surgery become increasingly common,[25,26] we can continue to anticipate improvements in oncologic and functional outcomes for HNSCC patients. Just as significant is the larger ongoing effort to better match treatment intensity to a disease that is now epidemiologically better defined. Therapy for HPV-OPSCC is undergoing significant changes. With newly available genomic information,[27] treatment for other subsites of HNSCC will also undergo similar and exciting changes in the coming years.

DISCLOSURE Baran D. Sumer is a co-founder, consultant, and co-inventor at OncoNano Medicine Inc.

REFERENCES

1. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011;29(32):4294-4301.
2. 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.
3. 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.
4. Fallai C, Bolner A, Signor M, et al. Long-term results of conventional radiotherapy versus accelerated hyperfractionated radiotherapy versus concomitant radiotherapy and chemotherapy in locoregionally advanced carcinoma of the oropharynx. *Tumori.* 2006;92(1):41-54.
5. Pignon JP, le Maitre A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol.* 2009;92(1):4-14.
6. Williams CE, Kinshuck AJ, Derbyshire SG, et al. Transoral laser resection versus lip-split mandibulotomy in the management of oropharyngeal squamous cell carcinoma (OPSCC): a case match study. *Eur Arch Otorhinolaryngol.* 2014;271(2):367-372.
7. Laccourreye O, Hans S, Menard M, Garcia D, Brasnu D, Holsinger FC. Transoral lateral oropharyngectomy for squamous cell carcinoma of the tonsillar region: II. An analysis of the incidence, related variables, and consequences of local recurrence. *Arch Otolaryngol Head Neck Surg.* 2005;131(7):592-599.
8. Steiner W, Fierek O, Ambrosch P, Hommerich CP, Kron M. Transoral laser microsurgery for squamous cell carcinoma of the base of the tongue. *Arch Otolaryngol Head Neck Surg.* 2003;129(1):36-43.
9. Sumer BD, Goyal V, Truelson JM, Myers LL. Transoral robotic surgery and transoral laser microsurgery for oropharyngeal squamous cell cancer. *J Robot Surg.* 2013;7(4):377-383.
10. Haughey BH, Hinni ML, Salassa JR, et al. Transoral laser microsurgery as primary treatment for advanced-stage oropharyngeal cancer: a United States multicenter study. *Head Neck.* 2011;33(12):1683-1694.
11. Weinstein GS, O'Malley BW, Jr., Cohen MA, Quon H. Transoral robotic surgery for advanced oropharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg.* 2010;136(11):1079-1085.
12. Bentzen SM, Trotti A. Evaluation of early and late toxicities in chemoradiation trials. *J Clin Oncol.* 2007;25(26):4096-4103.

13. Hutcheson KA, Holsinger FC, Kupferman ME, Lewin JS. Functional outcomes after TORS for oropharyngeal cancer: a systematic review. *Eur Arch Otorhinolaryngol.* 2015;272(2):463-471.
14. Ling DC, Chapman BV, Kim J, et al. Oncologic outcomes and patient-reported quality of life in patients with oropharyngeal squamous cell carcinoma treated with definitive transoral robotic surgery versus definitive chemoradiation. *Oral Oncol.* 2016;61: 41-46.
15. Marur S, Li S, Cmelak AJ, et al. E1308: phase II trial of induction chemotherapy followed by reduced-dose radiation and weekly cetuximab in patients with hpv-associated resectable squamous cell carcinoma of the oropharynx- ECOG-ACRIN Cancer Research Group. *J Clin Oncol.* 2016; 35:490-497
16. Weinstein GS, Quon H, Newman HJ, et al. Transoral robotic surgery alone for oropharyngeal cancer: an analysis of local control. *Arch Otolaryngol Head Neck Surg.* 2012;138(7):628-634.
17. Moore EJ, Henstrom DK, Olsen KD, Kasperbauer JL, McGree ME. Transoral resection of tonsillar squamous cell carcinoma. *Laryngoscope.* 2009;119(3):508-515.
18. 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.
19. 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.
20. 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.
21. 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.
22. Kramer S, Gelber RD, Snow JB, et al. Combined radiation therapy and surgery in the management of advanced head and neck cancer: final report of study 73-03 of the Radiation Therapy Oncology Group. *Head Neck Surg.* 1987;10(1):19-30.
23. Cooper JS, Zhang Q, Pajak TF, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys.* 2012;84(5):1198-1205.
24. Cooper JS, Fortpied C, Gregoire V, et al. The role of postoperative chemoradiation for oropharynx carcinoma: a critical appraisal revisited. *Cancer.* 2017;123(1):12-16.
25. Rosenthal EL, Warram JM, de Boer E, et al. Successful translation of fluorescence navigation during oncologic surgery: a consensus report. *J Nucl Med.* 2016;57(1):144-150.
26. Zhao T, Huang G, Li Y, et al. A transistor-like pH nanoprobe for tumour detection and image-guided surgery. *Nature Biomedical Engineering.* 2016; 1:0006
27. Cancer Genome Atlas N. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature.* 2015;517(7536):576-582.