Editorial

Challenges in addressing early stage laryngeal squamous cell carcinoma

Matthew E. Spector[1], Andrew J. Rosko[1], Andrew C. Birkeland[2]

[1]Department of Otolaryngology-Head and Neck Surgery, University of Michigan Health Center, Ann Arbor, Michigan, USA; [2]Department of Otolaryngology-Head and Neck Surgery, Stanford University, Stanford, California, USA

Correspondence to: Matthew E. Spector, MD, FACS. Department of Otolaryngology-Head and Neck Surgery, University of Michigan Health System, 1500 E Medical Center Dr., 1904 TC, SPC 5312, Ann Arbor, MI 48109-5312, USA. Email: mspector@med.umich.edu.

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Introduction

Laryngeal squamous cell carcinoma (LSCC) remains an important disease process worldwide, with over 150,000 cases diagnosed annually. Fortunately, most LSCCs overall are responsive to radiation (RT) and chemoradiation (CRT) therapies, which allows for preservation of the larynx structure and function. However, there remains room for improvement in RT/CRT protocols to achieve improved cure rates. As Sato *et al.* demonstrate in their manuscript in this issue, patients with early stage LSCC overall do reasonably well with their cohort 5-year overall survival of 91.4%. However, subsets of patients may have suboptimal results with RT alone. Thus, the addition of chemotherapy, particularly in certain groups of early stage LSCC (e.g., T2 or supraglottic disease), may improve outcomes and be of interest for further investigation.

Current treatment and survival in early stage LSCC

Currently, nonsurgical treatment of early stage LSCCs is defined as RT alone by national guidelines [National Comprehensive Cancer Network (NCCN)]. For glottic SCCs, RT dose recommendations range from 63–70 Gy, depending on the concern for high risk features and the risk of nodal metastasis. Recommendations for chemotherapy are limited in NCCN guidelines. For early stage supraglottic SCCs, nonsurgical treatment is generally recommended as RT alone, between 66–70 Gy (NCCN), with caution in using additional cytotoxic chemotherapy due to toxicity profiles (NCCN).

In early stage cancers, five-year local control rates for stage I glottic LSCC is 93–94%, while stage II glottic LSCC is 72–80% (1). For supraglottic cancers, five-year survival rates are worse, with 5-year survival rates just above 60% for early stage supraglottic LSCCs (2). These outcomes remain suboptimal, particularly in supraglottic and T2 tumors. T2 tumors, in particular, have been reported in great detail as to having worse outcomes than expected for their early clinical stage (3,4). Reasons for this lower survival for T2 LSCC are unclear, with potential explanations ranging from field misses, understaging of disease to other comorbidities or second primary cancers (3,4).

The benefits are significant in improving locoregional control for primary organ preservation therapy in LSCC. Patients with recurrent LSCC after RT/CRT have very poor outcomes, with 5-year overall survival rates under 50% (5). Generally, these patients undergo total laryngectomy as salvage surgery, with the inherent morbidities of surgery in radiated fields. Thus, modifications of standard protocols for early stage LSCC to further optimize disease free survival in this patient population, while allowing for laryngeal anatomic and functional preservation, may have significant benefit.

Chemoradiation for early stage larynx cancer

Although generally limited, there is literature suggesting a benefit to adding chemotherapy to RT in early stage LSCCs for laryngeal preservation rates in early phase clinical trial cohorts with acceptable toxicity profiles (6,7).

Notably these studies use a potentially more tolerable, less toxic regimen of chemotherapy. In this report, Sato *et al.* use S-1 (Taiho Pharmceutical Co. Ltd, Tokyo, Japan), which is a combination of tegafur (a prodrug form of 5-fluorouracil), gimeracil, and oteracil. This drug is utilized in Asia, particularly in gastric cancer, as well as head and neck cancer. It remains to be Food and Drug Administration (FDA) approved in the United States. Sato *et al.* in this study did not have any grade 4 adverse events from treatment, and very few grades 3 events, suggesting that their regimen is relatively tolerable. The authors demonstrate significant improvement in 5-year disease-free survival in stage II LSCC when given combination S-1 and RT, in comparison to RT alone or other regimens (94.0% *vs.* 75.6%), suggesting significant efficacy for this regimen. In considering future treatment regimens, continued long-term follow-up and close documentation of side effect and toxicity profiles of adding chemotherapy to RT will be critical in order to demonstrate a strong argument for concurrent regimens.

As the authors note, glottic LSCCs and supraglottic LSCCs behave very differently clinically. Glottic LSCCs have been reported throughout literature to have significantly better outcomes, which Sato *et al.* demonstrate in their cohort with 97.0% overall survival for glottis LSCC compared to 70.0% for other LSCC. Thus, when considering groups of early LSCC in which to trial chemotherapy, non-glottic, stage II LSCC patients would be most appropriate.

Advancing future therapy options for early stage LSCC

It will be critical to build on the work of Sato *et al.* and other studies in adjuvant therapies for early stage LSCC. Future considerations of concomitant therapies with RT may provide additional further options for improved disease-free survival while limiting effects on organ function. Considerations of timing of adjuvant chemotherapy in addition to RT will be important. Induction chemotherapy carries fewer toxic outcomes in comparison to concomitant chemoradiation in advanced LSCC cancer studies (8). Thus, in earlier stage tumors that normally do not receive chemotherapy, using an induction paradigm may provide the optimal balance of offering improved survival in comparison to RT alone, while avoiding the toxicities of concurrent chemoradiation. Notably, consideration of chemotherapy regimens less toxic than cisplatin (such as the authors' use of S-1, or potentially cetuximab) may also mitigate toxic side effects.

In the era of immunotherapeutics and new, targeted agents, developing novel regimens of RT in combination with these agents may prove to have exciting curative effects. Anti PD-1 agents (namely, nivolumab and pembrolizumab) appear to be much better tolerated than traditional chemotherapy (9,10), which may be crucial in considering the preservation of delicate laryngeal functions. As in traditional chemotherapeutics, alterations into the timing of adjuvant agents in relation to RT may identify an ideal sequence for optimizing disease control and toxicities/side effects. For instance, using an induction regimen of a nivolumab or pembrolizumab, which are being investigated currently in window of opportunity regimens, may have provide an ideal balance of curative effect and tolerable toxicity.

Stratification of patients into high and low risk groups will be important for future investigations to balance the benefits and toxicities of chemotherapy. As Sato *et al.* note, there are some clinical predictors of poorer outcomes in early LSCC, particularly non-glottic site and T2 disease. In the genomics era, further predictive biomarkers for survival will be valuable to dictate treatment stratification. Researchers have investigated *TP53* mutation types and the risk conferred on survival and response to cisplatin chemotherapy (11,12). Our group has identified CD4 and CD8 tumor infiltrating lymphocyte status as among the most significant predictors of survival in recurrent LSCC (13). Overall genomic signatures from The Cancer Genome Atlas (TCGA) and other studies are available (14); additional subset analysis of these cohorts as sequencing data becomes increasingly prevalent may shed insight into genomic or expression signatures that correlate with survival in early stage LSCC. In a similar fashion, analysis of the tumor immune microenvironment, particularly in respect to tumor infiltrating lymphocytes, may provide the greatest potential for altering prognosis, and thus treatment stratification. Further studies investigating their predictive role in early stage LSCC and potential responsiveness to chemotherapy and RT will be very important.

Conclusions

Laryngeal SCC remains an important disease process. As highlighted by Sato *et al.* in this issue, attempts to optimize clinical outcomes remain an important task. Particularly as T2 LSCCs have suboptimal outcomes across numerous studies and epidemiologic cohorts, there are opportunities to improve survival via alterations in treatment. Sato *et al.* have described their successful S-1 treatment regimen with encouraging results.

Further studies in this regimen, and others, for T2 LSCCs, with measurements of survival outcomes and toxicity profiles, will be important to establish an appropriate treatment protocol that balances survival and toxicity for these tumors.

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References

1. Mendenhall WM, Amdur RJ, Morris CG, et al. T1-T2N0 squamous cell carcinoma of the glottic larynx treated with radiation therapy. J Clin Oncol 2001;19:4029-36.
2. Cosetti M, Yu GP, Schantz SP. Five-year survival rates and time trends of laryngeal cancer in the US population. Arch Otolaryngol Head Neck Surg 2008;134:370-9.
3. Gainor DL, Marchiano E, Bellile E, et al. Survival Outcomes in Patients with T2N0M0 (Stage II) Squamous Cell Carcinoma of the Larynx. Otolaryngol Head Neck Surg 2017;157:625-30.
4. Chen JJ, Stessin A, Christos P, et al. Differences in survival outcome between stage I and stage II glottic cancer: A SEER-based analysis. Laryngoscope 2015;125:2093-8.
5. Birkeland AC, Beesley L, Bellile E, et al. Predictors of survival after total laryngectomy for recurrent/persistent laryngeal squamous cell carcinoma. Head Neck 2017;39:2512-8.
6. Nishimura G, Tsukuda M, Mikami Y, et al. Efficacy of concurrent chemoradiotherapy for T1 and T2 laryngeal squamous cell carcinoma regarding organ preservation. Anticancer Res 2009;29:661-6.
7. Taguchi T, Tsukuda M, Mikami Y, et al. Concurrent chemoradiotherapy with carboplatin and uracil-ftegafur in patients with stage two (T2 N0 M0) squamous cell carcinoma of the glottic larynx. J Laryngol Otol 2006;120:478-81.
8. Forastiere AA, Zhang Q, Weber RS, 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. J Clin Oncol 2013;31:845-52.
9. Mehra R, Seiwert TY, Gupta S, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. Br J Cancer 2018;119:153-9.
10. Harrington KJ, Ferris RL, Blumenschein G Jr, et al. Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): health-related quality-of-life results from a randomised, phase 3 trial. Lancet Oncol 2017;18:1104-15.
11. Osman AA, Neskey DM, Katsonis P, et al. Evolutionary Action Score of TP53 Coding Variants Is Predictive of Platinum Response in Head and Neck Cancer Patients. Cancer Res 2015;75:1205-15.
12. Neskey DM, Osman AA, Ow TJ, et al. Evolutionary Action Score of TP53 Identifies High-Risk Mutations Associated with Decreased Survival and Increased Distant Metastases in Head and Neck Cancer. Cancer Res 2015;75:1527-36.
13. Hoesli R, Birkeland AC, Rosko AJ, et al. Proportion of CD4 and CD8 tumor infiltrating lymphocytes predicts survival in persistent/recurrent laryngeal squamous cell carcinoma. Oral Oncol 2018;77:83-9.
14. Cancer Genome Atlas N. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature 2015;517:576-82.

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