Commentary

Salvage Surgery for Squamous Cell Carcinoma of the Head and Neck in the Era of Immunotherapy: Is It Time to Clarify Our Guidelines?

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Treatment for recurrent squamous cell carcinoma of the head and neck (SCCHN) remains a challenge, and the disease carries a significant burden for patients and their families. Although the overall survival of patients with locally advanced SCCHN has improved with the addition of platinum-based chemotherapy to definitive radiation,[1] significant numbers of patients continue to have recurrent disease.[2,3] It is estimated that 30% to 40% of patients treated with definitive therapy will experience recurrence, with the majority of recurrences occurring locoregionally.[4,5] Patients with recurrent disease are faced with few curative options and are desperate for modalities that will prolong their life expectancy while preserving key functions and quality of life.

Although salvage surgery (SS) has been advocated as the modality of choice to achieve these goals, its indications remain poorly defined, with a significant risk of complications of up to 67%.[2,6,7] It is clear that although patients may benefit from SS, the outcomes for a number of those who are offered this modality remain poor.[7] Even though age and performance status are important predictors of patient outcomes,[8,9] clear guidelines determining eligibility are lacking.[7] SS has not been compared directly with re-irradiation because of the obvious challenges in implementing such a trial and because of the difficulty in interpreting nonrandomized data on account of the lack of uniformity and inherent selection biases.

In the locally recurrent and metastatic setting, we witnessed improvements with the addition of cetuximab to the platinum backbone, and this led to the adoption of the EXTREME (platinum, 5FU and Cetuximab) regimen as a new standard of care a decade or so ago[10]; however, despite these advances, practices and recommendations for SS continued to be untested. In that respect, it is noteworthy that patients are enrolled into systemic therapy trials often based on the exclusion of SS, and this introduces an inherent bias that renders retrospective comparisons impossible to perform.

Because immunotherapy has recently evolved in a relatively short time into a new standard for patients with advanced, incurable, heavily pretreated SCCHN, with 2 immune checkpoint inhibitors (ICPIs) approved in 2016,[11,12] we believe that it is time to look at our long-held practices in a new light.[13] Historically, although induction chemotherapy has failed to produce significant improvements in patient survival, preoperative single doses of ICPIs have produced impressive responses with little toxicity in different tumor types, including SCCHN.[14] Chemoresponders consistently show improved survival and increased responses to subsequent radiation. It is also significant that bioselection with induction chemotherapy has achieved impressive cure rates for laryngeal cancers.[15] Although the picture remains unclear as far as the best way to use ICPIs in the definitive setting, there is every reason to believe that the standard of care for locally advanced SCCHN will soon change. Because a single-agent ICPI can result in long-term progression-free and overall survival for some heavily pretreated patients, it is legitimate to ask whether combination ICPI approaches could result in this much desired outcome for at least a percentage of patients currently offered SS who continue to fare poorly despite aggressive surgery. A plausible innovative strategy here would be induction immunotherapy for bioselection and

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a subsequent decision regarding the need for SS versus continued systemic therapy. It is worth noting that current trials are already exploring the impact of induction immunotherapy in locally advanced settings and could inform similar designs of future SS trials. It is also important that the human papillomavirus status appears to influence the rate of pathologic remissions noted with SS, and this points to the fact that future trials or guidelines will need to account for human papillomavirus.[3] In addition, the effects that center volume and expertise have on the outcomes of patients treated in such trials need to be accounted for.[16]

Two difficult questions still need to be asked. First, is SS a 1-size-fits-all approach? Second and more importantly, in the era of immuno-oncology, what are the criteria according to which SS should be the uncontested modality of choice? Getting closer to clarity will require taking courageous steps. The first step would be to consider clinical trial designs targeting patients for whom clear indications for SS have not been established. Getting there will require a meeting of the leading experts in the various therapeutic disciplines. Lessons from the not too distant past are worth remembering: they include but are not limited to the lack of improvement in laryngeal cancer mortality despite the increase in the nonsurgical management of this disease. Needless to say, factors such as side effects expected from immunotherapy, the rare but concerning phenomenon of hyperprogression, the cost of ICPIs, and surgical and center expertise, need to be taken into consideration when we are evaluating ICPIs in the context of SS and must be factored into the outcome measure designs of such studies.

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REFERENCES

1. 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;92:4-14.
2. Tan HK, Giger R, Auperin A, Bourhis J, Janot F, Temam S. Salvage surgery after concomitant chemoradiation in head and neck squamous cell carcinomas—stratification for postsalvage survival. *Head Neck*. 2010;32:139-147.
3. Galloway TJ, Zhang QE, Nguyen-Tan PF, et al. Prognostic value of p16 status on the development of a complete response in involved oropharynx cancer neck nodes after cisplatin-based chemoradiation: a secondary analysis of NRG Oncology RTOG 0129. *Int J Radiat Oncol Biol Phys*. 2016;96:362-371.
4. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363:24-35.
5. Ang MK, Patel MR, Yin XY, et al. High XRCC1 protein expression is associated with poorer survival in patients with head and neck squamous cell carcinoma. *Clin Cancer Res*. 2011;17:6542-6552.
6. Esteller E, Vega MC, Lopez M, Quer M, Leon X. Salvage surgery after locoregional failure in head and neck carcinoma patients treated with chemoradiotherapy. *Eur Arch Otorhinolaryngol*. 2011;268:295-301.
7. Hamoir M, Holvoet E, Ambroise J, Lengele B, Schmitz S. Salvage surgery in recurrent head and neck squamous cell carcinoma: oncologic outcome and predictors of disease free survival. *Oral Oncol*. 2017;67:1-9.
8. Ho AS, Kraus DH, Ganly I, Lee NY, Shah JP, Morris LG. Decision making in the management of recurrent head and neck cancer. *Head Neck*. 2014;36:144-151.
9. Kim J, Kim S, Albergotti WG, et al. Selection of ideal candidates for surgical salvage of head and neck squamous cell carcinoma: effect of the Charlson-Age Comorbidity Index and oncologic characteristics on 1-year survival and hospital course. *JAMA Otolaryngol Head Neck Surg*. 2015;141:1059-1065.
10. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*. 2008;359:1116-1127.
11. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375:1856-1867.
12. Bauml J, Seiwert TY, Pfister DG, et al. Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: results from a single-arm, phase II study. *J Clin Oncol*. 2017;35:1542-1549.
13. 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;18:1104-1115.
14. Uppaluri R, Zolkind P, Lin T, et al. Neoadjuvant pembrolizumab in surgically resectable, locally advanced HPV negative head and neck squamous cell carcinoma (HNSCC). *J Clin Oncol*. 2017;35(15 suppl):6012-6012.
15. Wolf GT, Bellile E, Eisbruch A, et al. Survival rates using individualized bioselection treatment methods in patients with advanced laryngeal cancer. *JAMA Otolaryngol Head Neck Surg*. 2017;143:355-366.
16. Wuthrick EJ, Zhang Q, Machtay M, et al. Institutional clinical trial accrual volume and survival of patients with head and neck cancer. *J Clin Oncol*. 2015;33:156-164.