Editorial Commentary

Evolving treatment paradigms in recurrent and metastatic head and neck squamous cell carcinoma: the emergence of immunotherapy

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Introduction

Recurrent and metastatic (R/M) disease remains a major cause of morbidity and mortality among patients with head and neck squamous cell carcinoma (HNSCC). Recurrence rates after curative intent therapy range from 14–32% (1-3) and another 3–10% of patients present with distant metastasis at the time of diagnosis (4-6). The National Comprehensive Cancer Network (NCCN) Guidelines® outline several salvage therapeutic strategies for R/M HNSCC, including systemic, surgical, or radiation therapy (7). The U.S. Food and Drug Administration (FDA) approval of the immune checkpoint inhibitor (ICI) pembrolizumab as a first line agent in 2019 further broadened the landscape of therapeutic options in R/M HNSCC (8,9). However, median survival in R/M HNSCC remains less than one year (10,11). Studies have demonstrated significant survival advantage of surgical salvage for recurrent disease, but these studies are largely retrospective (12). With the introduction of ICI therapy, important and unanswered questions have arisen in defining optimal treatments for R/M HNSCC. Improving oncologic outcomes among patients with R/M HNSCC will hinge on knowledge gained from well-designed comparisons across established and emerging salvage therapies.

A retrospective comparison of oncologic outcomes in salvage surgery and immune checkpoint immunotherapy

In a first of its kind analysis, implementing a single-institution retrospective study design, Konuthula and colleagues compared oncologic outcomes of salvage surgery and ICI therapy as first line treatment in patients with recurrent HNSCC without distant metastasis who failed primary chemoradiotherapy (13). In their cohort, 2-year overall survival for patients who underwent salvage surgery was 69%, but only 25% in those who received ICI immunotherapy. In subgroup analyses combining patients with R/M HNSCC of the oral cavity and oropharynx, the authors noted a dramatic [167-fold, hazard ratio (HR) =0.006] survival benefit associated with salvage surgery compared to ICI-based immunotherapy and identified increased neutrophil-to-lymphocyte ratio (NLR) in the

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peripheral blood as a potential marker of poor survival in patients receiving immunotherapy.

This study aimed to answer a timely and important question: with the introduction of immunotherapy, what is the optimal treatment for R/M HNSCC? However, its findings should be considered in the context of the study's limitations. Notably, it appears that the authors' findings may in part be driven by selection bias related to institutional treatment patterns for patients with R/M HNSCC. Konuthula *et al.* identified 213 patients treated for locally recurrent HNSCC and categorized them into early (stage I/II) or advanced (stage III/IV) stage disease. The authors then excluded the 103 early-stage patients noting that most early-stage patients received ICI due to "extensive comorbidities", resulting in the exclusion of 48% of their locally recurrent HNSCC cohort. This is contrary to many clinical practices in which early-stage resectable disease would be treated with salvage surgery. Baseline characteristics for the early-stage patients were not reported.

The patients included in the analysis displayed treatment group imbalances in anatomic site, smoking history (14), and incomplete data on p16 status, a widely accepted surrogate for HPV-status (15). Each of these factors could contribute to reported survival differences and are not controlled for in a multivariate analysis given the limitation of small sample size. Anatomic site of HNSCC origin has a significant impact on prognosis. HPV-positive oropharyngeal carcinoma in non-smokers generally is associated with very favorable prognosis (16,17). Among HPV-negative HNSCC, tumors arising in the oral cavity confer the most favorable survival outcomes, followed by those in larynx, while oropharyngeal and hypopharyngeal carcinoma confer poor prognosis (18,19). In the context of R/M HNSCC, the site of recurrence—local, regional, or distant—is still associated with survival (20). HPV-positive tumor status confers a twofold better survival rate to recurrent oropharyngeal carcinoma treated with surgical salvage (21-23). Moreover, the inclusion of 7 cases of cutaneous squamous cell carcinoma, a disease entity distinct from HNSCC that may be more responsive to ICI (24), represents an unusual study decision. Considering these insights, imbalances in tumor site and smoking history by treatment group, incomplete data on p16 status, and lack of information on site of recurrence present significant challenges to interpreting the survival differences between salvage surgery and ICI groups.

Notably, in the advanced stage cohort nearly all patients who received ICI had extensive comorbidities, with 95% of patients who received ICI having a Charlson comorbidity index (CCI) ≥6. In comparison, only 20% of patients treated with surgical salvage had a CCI ≥6. These observations indicate CCI as a likely confounding factor. Since its first description in 1987, the CCI has been shown to predict long-term mortality in a variety of patient populations, including those with head and neck cancer and those undergoing surgery (25). Indeed, CCI is an extensively validated predictor of postoperative mortality, a useful metric to guide patient selection for surgical salvage, and a likely factor in patient selection for salvage therapy at the authors' institution (26,27). Given these findings, the authors performed a propensity score matched (PSM) analysis balancing CCI, age, and primary site across treatment groups. This analysis yielded a matched cohort of 15 patients in each group that demonstrated no difference in survival between patients treated with salvage surgery or immunotherapy. The lack of difference in survival after propensity matching underscores the significant confounding of comorbidities that may contribute to the apparent survival benefit of surgical salvage. While the PSM analysis is likely underpowered, this finding suggests again that survival differences between salvage surgery and immunotherapy observed in the full cohort are driven by selection bias in treatment groups. Furthermore, these results may suggest that within matched cohorts immunotherapy could have equivalent outcomes to salvage surgery.

Konuthula and colleagues should be congratulated for designing a study that aimed to answer an important and timely question. However important issues, including the single institution design, relatively small overall study size, selection bias, and the small size of the PSM cohort, limit this study's generalizability and render its findings inadequate to compare immunotherapy and surgical salvage in R/M HNSCC, and whether any patient or disease features are useful markers to guide treatment selection.

Study design considerations to evaluate optimal salvage strategies in R/M HNSCC

Careful study design incorporating translational scientific and clinical knowledge of therapies with appropriately powered, generalizable patient populations will be essential to gaining insight into contexts in which salvage surgery or ICI-based immunotherapy may be superior. A body of evidence spanning three decades, primarily in the form of prospective and retrospective cohort studies, supports the survival benefit of salvage surgery in R/M HNSCC (meta-analysis HR =0.25) compared to chemotherapy, radiotherapy, or chemoradiotherapy (12). ICI-based immunotherapy has demonstrated superiority compared to single-agent chemotherapeutic agents in multiple randomized controlled trials initially as second-line (28-31) and more recently as first line (8,32) treatment in R/M HNSCC. However, the study by Konuthula *et al*.—the only comparison of immunotherapy to surgical salvage in R/M HNSCC to date—underscores the challenge of comparing these treatment modalities.

Given the broad consensus supporting surgical salvage for resectable recurrent HSNCC, a randomized clinical trial would not be feasible due to lack of equipoise. However, in the subset of patients who respond to immunotherapy, these patients could potentially benefit from first line ICI therapy over salvage therapy. In other tumor types instances exist in which immunotherapy results in durable and complete clinical response. In cases where the promise of immunotherapy has borne fruit, there is first identification of biological processes that enhance tumor vulnerability to immune checkpoint inhibition. For example, mismatch repair (MMR) deficiency (33,34) was identified as a major biomarker in rectal cancer in which 12 of 12 patients harboring MMR deficiency demonstrated complete response to PD-1-based immune checkpoint inhibition therapy, and no patients underwent planned surgical resection. Deficiency of MMR, a physiologic DNA repair mechanism (35), in tumors is thought to represent an underlying mechanism leading to high tumor neoantigen burden, which renders a tumor more recognizable to the immune system and potentially more susceptible to immunotherapy (36). Another surrogate of high neoantigen burden is tumor mutational burden (TMB), which is also under intensive investigation as a predictive biomarker for response to ICI (37,38). Although these biomarkers are rarely present in HNSCC, they illustrate the critical importance of patient selection to the efficacy of immunotherapy.

PD-L1, an immune inhibitory signal expressed in the tumor microenvironment, forms the basis for PD-1-based ICI and represents a biomarker for ICI response in diverse tumor types (39). The combined positivity score (CPS), a surrogate of PD-L1 expression, has been shown to predict ICI response in R/M HNSCC (40). More recently, associations between copy number loss in chromosome 9p and an immune suppressive tumor microenvironment have been leveraged to identify copy number variation (CNV) in 9p24.1 as a marker of response to anti-PD1 ICI in HNSCC (41,42). Additionally, Konuthula and colleagues evaluated the potential of peripheral blood NLR as an easily measured predictive biomarker for immunotherapy response (43). Combining these insights, and others to come, with an incisive study design holds the potential to identify clinical and disease features to guide patient selection for immunotherapy.

We thus propose that a matched, multi-institutional case control study may constitute an ideal design to directly compare oncologic outcomes between immunotherapy and surgical salvage, and evaluate subgroups of patients that would more likely benefit from ICI or salvage surgery based on above mentioned biomarkers. In such a design, patient selection would center on patients eligible for surgical salvage, but who received either a standard ICI-based immunotherapy regimen (cases) or surgical salvage (controls). In an ideal study, data collected would include not only patient and tumor factors (age, sex, and CCI, recurrent stage, site, p16 status), but also potential predictive biomarkers such as tumor cell PD-L1 expression, NLR, CPS, TMB, and 9p24.1p CNV for all patients. Such a design holds the promise to yield not only valuable, controlled, and ethical comparison of immunotherapy and surgical salvage, but also the potential to understand the role of biomarkers for predicting response to immune checkpoint immunotherapy.

Despite the significant advances in head and neck cancer therapy, R/M disease continues to pose the most significant threat to survival for patients with HNSCC. Deepening our insight into the role of ICI therapy for R/M HNSCC will require a systematic approach incorporating principles of translational and clinical research to design a balanced and appropriately powered study. Moreover, we suggest that the continued discovery of biomarkers of immunotherapy response may enable the identification of patient subgroups in whom ICI could confer equivalent or better oncologic outcomes than salvage surgery.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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