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REVIEW

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The promise of immunotherapy in the treatment of young adults with oral tongue cancer

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Abstract

Historically considered a disease of the older male resulting from cumulative tobacco and alcohol use, more recently we have witnessed a rise in the global incidence of oral tongue squamous cell carcinoma in younger adults, particularly those without any identifiable risk factor exposure. These patients appear to be at higher overall risk for locoregional treatment failure and often experience a more heterogeneous clinical course, with some afflicted with particularly aggressive, rapidly progressive disease. Recent research efforts have supported the idea that although this disease may be genomically similar in these groups, and molecular differences in the tumor immune microenvironment may account for biological differences between young and older patients, as well as patients with and without exposure to alcohol or tobacco. In this review, we seek to summarize current knowledge regarding pathogenesis of oral tongue carcinoma in the young adult patient and examine the potential role of the immune response in disease progression and as a target for novel immunotherapies.

KEYWORDS

immunotherapy, oral cavity squamous cell carcinoma, tongue cancer, young adult

1 | INTRODUCTION

Squamous cell carcinoma of the oral cavity has historically been considered a disease more common in males in their sixth to seventh decade related to cumulative exposure to tobacco and alcohol. It was not until 1975 that oral tongue squamous cell carcinoma (SCCA) in young adults began to be described as a unique clinical entity in the head and neck literature.[1,2] Over the ensuing decades, we have witnessed a global rise in the incidence of oral tongue SCCA in younger adults below the age of 45, with most epidemiological estimates in the range of 4% to 7% of all oral tongue cancers, though some single institutions have reported incidence as high as 13%.[2-7] The initiation and progression of oral tongue carcinomas in young adults has been the subject of significant debate and controversy owing to a lack of association with tobacco or alcohol consumption, HPV infection, and increasing incidence of young, white, female patients without history of risk factor exposure. This article provides a review of current literature on oral tongue carcinoma in young adults with special attention to the impact of the immune system in tumor development and prognosis, with implications for the potential role of immunotherapy.

2 | CHARACTERISTICS OF ORAL TONGUE SCCA IN YOUNG ADULTS

There has been significant debate concerning the etiological factors and prognosis of oral cavity squamous cell carcinoma in younger patients. Retrospective data published by a number of authors have supported the notion that younger patients are more likely to experience a more aggressive clinical course and worse overall prognosis,

thus making the case for a more aggressive initial therapeutic approach.[5,6,8-10] In a review of the experience at their institution, Myers et al reported significantly improved survival (81% vs 72% 5-year survival) in patients (<40 years) whose primary treatment involved neck dissection, advocating for it to be included as part of the treatment plan for any surgical patient.[2]

Other studies have found no differences in overall survival between younger and older patients.[2,3,11-15] In their series of patients, Friedlander et al found that although age of the patient at time of presentation did not impact overall survival, younger patients (<40 years) did experience higher rates of locoregional failure.[10] In a stage-matched comparative analysis, Park et al found that young patients (<45 years) with advanced-stage tongue cancer did worse than older subjects, most commonly as a result of higher likelihood of regional recurrence.[16] Despite similar disease-specific outcomes between younger and older patients, Popovtzer found that the clinical course in their younger patients (<45 years) tended to be more heterogeneous—it followed either a more indolent clinical course with long term freedom from disease or a highly aggressive pattern with 40% mortality in 2 years (vs 10.7% in the older group).[17] Similar to other subsites of the head and neck, younger patients with oral tongue SCCA without related history of alcohol and tobacco exposure tend to do poorer overall, with worse control free survival.[12,18] At our institution, we have experienced a rising incidence of younger patients presenting with oral tongue carcinoma and do have the general sense that some patients experience an extremely aggressive clinical course, particularly those patients without history of alcohol or tobacco exposure.

3 | PATHOGENESIS OF ORAL TONGUE SCCA IN YOUNGER PATIENTS

The pathogenesis of squamous cell carcinoma affecting young patients remains controversial and is an area of intense active research given the pressing need to offer treatment options with greater efficacy and potential for less long-term morbidity. As the usual suspects for development of oral cancer-tobacco and alcohol are believed to be less of a factor when considering conflicting data on their rates of relative use in younger vs older patients, but truly understanding the impact of age alone on the clinical course is inherently difficult. Schantz et al[19] described significantly higher use of tobacco products in older patients, with some indication that tobacco use did influence cancer progression.[20,21] When independently stratifying for age and tobacco use, similar findings were noted in young vs old patients with regard to subsite at risk for cancer development, decreased risk of developing a second primary malignancy, and lack of accuracy of AJC staging parameters in predicting overall disease course. The challenge of discerning the contribution of age vs tobacco exposure to disease biology is inherently difficult when considering that both age and duration of exposure to tobacco are both important yet intrinsically linked variables. Interestingly, recent work from Campbell et al was the first to report that patients with early age disease onset (<50 years) had greater exposure to chewing tobacco (snuff) than older patients,[22] and international reports from areas with high incidence of chewing tobacco such as India, Pakistan, and Yemen do support a similar link between chewing tobacco exposure and early age disease onset.[23-25]

Although there is considerable speculation that the molecular basis of SCCA is likely to be different between young and old patients, few studies have demonstrated differences in the genetic profiles of these two groups (though often with discordant results).[26,27] For example, mutation of the TP53 tumor suppressor gene, which is known to be an important driver pathway in oral cavity SCCA, has been shown to be common in young patients in some studies, rare in others, but overall less common in frequency than found in older patients.[3,28-30] Although tobacco and alcohol are known to increase the frequency of TP53 mutations in head and neck cancers, Lingen et al identified a high proportion of p53 immunoexpression in younger patients with no history of tobacco use. When comparing DNA isolated from tongue tumors of young, nonsmokers and older patients with a smoking history, they found no differences in gene-specific mutation and copy-number alteration frequencies or the types of base changes seen between the two groups.[31] In a whole exome sequencing study of a large Asian cohort of patients with oral tongue SCCA, Vettore et al did not identify any mutations unique to either younger patients or nonsmokers.[32] Patients with Fanconi anemia, an inherited heterogeneous disease characterized by bone marrow failure and genomic instability due to diminished capacity for DNA repair, have been found to be at significantly elevated risk of developing oral cavity squamous cell carcinoma relative to the general population, with average disease onset occurring around 33 years of age.[33-35] Chandrasekharappa et al examined germline DNA from head and neck squamous cell carcinoma (HNSCC) patients younger than 50 years of age and found that up to 26% of patients had a rare Fanconi anemia gene variant that would be predicted to be damaging.[36]

Molecular markers for proteins involved in cell cycle progression, cell proliferation, local invasion, and lymphatic growth have been compared demonstrating differential expression in young and older patients, although few clinically meaningful associations have been clearly delineated. In one recent study by Costa et al, EGFR amplification was demonstrated to be higher in younger patients (≤40 years). Epidermal growth factor receptor (EGFR) amplification was also more prevalent in advanced stage tumors irrespective of age, and overexpression was associated with worse disease-free and overall survival.[37] Studies investigating differences in epigenetic alterations of gene expression in young vs old patients have been sparse. Su et al observed higher frequency of methylation of the p16 promoter gene in younger patients, though no analysis of gene expression was performed.[26,38]

Although now well established as a critical factor in the development of oropharyngeal SCCA, with its own distinct clinical manifestations and prognosis, the role of the human papillomavirus in the etiology of oral cavity SCCA is a subject of significant controversy, specifically when considering the development of disease in the young never-smoker, never-drinker. A number of studies have reported ranging contradictory data supporting differences in both the frequency of

HPV positivity[28,39-41] and p16 expression levels,[26,39,42-44] in younger and older groups of patients. However, it is critical to note that no association between the presence of HPV DNA and outcome in oral cavity SCCA has borne out in the literature.[45] More recent multi-institutional efforts have further strengthened the belief that HPV does not seem to be playing a significant role in the development of oral tongue SCCA.[44] Attempts to identify other potentially oncogenic viruses in the oral cavity have been unrevealing.[46]

4 | ROLE OF IMMUNE EVASION IN TUMOR DEVELOPMENT AND PROGRESSION

With the advent of immunotherapy and early positive results from clinical trials involving patients with recurrent/metastatic disease, research efforts have increasingly shifted to focus on immune-characterization of oral cavity SCCA. Oral tongue carcinoma is one of the most immunogenic tumors of the head and neck.[47,48] Development of effective and durable immunotherapies requires an understanding of the mechanisms used by malignant cells to evade the host immune response. Cancer cells can be thought to evade the immune system via two mechanisms: (a) inhibiting initiation of the host antitumor immune response and (b) suppression of an activated antitumor response.[49-51] Inhibition of tumor antigen presentation appears to be an important mechanism used to prevent an initial antitumor immune response and can occur by downregulating expression of human leukocyte antigen class I molecules as well as decreased expression of proteins involved in the antigen processing machinery. Dendritic cells are considered the most potent antigen-presenting cells and perhaps the only cells capable of initiating the adaptive immune response.[52] Goldman et al examined the inflammatory infiltrate of oral tongue tumors following surgical resection and found that presence of a higher number of CD1a-positive (surface antigen mediating T-cell interactions) dendritic cells adjacent to the tumor was associated with improved patient overall survival and decreased rates of recurrence.[52] A similar study by Jardim et al showed that depletion of peritumoral CD1a-positive cells was associated with presence of lymph node metastasis, whereas depletion of peritumoral CD83 cells was correlated with smoking history, lymph node metastasis, and extracapsular spread. Higher levels of peritumoral CD1a-positive cells correlated with lower rates of recurrence and better overall survival.[53] Decreased signaling from pattern recognition receptors (ie, toll-like receptor) is also thought to result in a reduced initial immune response to a developing tumor.[49]

The immunosuppressive composition of the tumor microenvironment (TME) is thought to have a number of interrelated effects on immune evasion—by both decreasing initiation of the host antitumor response and suppressing an activated response. T-lymphocyte proliferation and cytolytic function are reduced in an overall sense due to a high concentration of immunosuppressive cytokines, including TGF-β, IL-6, and IL-10 among others.[54,55] Increased IL-6 has been shown to inhibit maturation of dendritic cells, and decrease activation of macrophages, NK, and T cells.[56] IL-10 has been associated with major histocompatibility complex (MHC) downregulation.[57] TGF-β is associated with suppressed T and NK cell activation as well as stimulating differentiation of immunosuppressive Treg cells.[51] In contrast to immunosuppressive Treg cells, CD8 cytotoxic T lymphocytes are considered to be the critical immune cell involved in mounting a successful host antitumor response, and considerable data support the notion that higher infiltration of CD8 T cells into the TME are associated with improved locoregional control and overall survival in patients with head and neck cancer across multiple subsites.[49,58-61]

Recent studies investigating the TME of patients with oral tongue SCCA have provided support for the idea that the density, type, and location of tumor infiltrating lymphocytes do have significant prognostic implications.[62] Gannot et al examined differences in the composition of infiltrating immune mononuclear cells in tongue tissue specimens and correlated this with the degree of transformation of the epithelium, finding that the progression toward malignancy correlated with a distinct shift in the lymphocyte profile.[63] Malignancy was found to be associated with an increase in the total amount of infiltrating lymphocytes and a transition from T to B cells. Chen et al similarly examined the prognostic implications of the composition of tumor infiltrating lymphocytes based on subtype and found that tongue tumors with higher overall CD4 infiltration and higher ratios of CD4 cells compared to CD3 (pan-T cells), CD8, and FOXP3 (Treg cells) were associated with absence of lymphovascular invasion, pointing to a potential role for CD4 tumor infiltrating lymphocytes in the prevention of early metastatic disease.[64] Patients with advanced stage tumors also had higher proportions of CD3 cells compared to CD4 or CD8 T cells, suggesting that progression of their disease correlated with a shift toward a more suppressive TME. Of critical importance, this study demonstrated that patients with a low ratio of CD8 and CD4 cells to Treg cells ultimately had a lower overall survival, regional recurrence-free survival, and distant metastasis-free survival.[64] These findings correlate with previous studies showing that patients with nuclear localization of Treg's and overall high levels of Treg cells in both stroma and cancer nests were associated with increased risk of tumor recurrence and worse disease-free survival, respectively.[65-67] In a recent large meta-analysis of studies reporting survival data and immunohistochemical information from oral cavity squamous cell tumors, Hadler-Olsen et al found that a high count of tumor infiltrating CD163 M2 macrophages was significantly associated with decreased overall survival. In contrast to the classically activated M1 macrophages which are induced by factors such as interferon gamma and tumor necrosis factor, stimulating a Th1 immune response which is considered to be tumor suppressive, M2 macrophages are induced by interleukins (4, 10, 13) and are associated with angiogenesis and immunosuppression.[68]

Oral lichen planus (OLP) is a chronic inflammatory disorder of the oral mucosa characterized by immune cell-mediated tissue destruction, and debate remains regarding its true malignant potential.[69] Review of the literature does not demonstrate a link between OLP and formation of oral tongue SCCA in the young adult. In a large study of 722 patients, Eisen et al identified six patients (0.8%) who went on to develop SCCA at a site previously known to have erosive or

erythematous OLP, two of which developed tongue tumors (at 44 and 49 years of age).[69] In a population-based retrospective study of 303 patients with OLP in Minnesota over a 25 year period, Laniosz et al found that patients with OLP were 4.8 times more likely to develop SCCA than their matched referents (seven patients developed SCCA with an average age at diagnosis of 65.8 years).[70] A recent meta-analysis of 33 studies with a total of 12 838 OLP patients reported a malignant transformation rate of only 0.44%, suggesting that previously reported rates may be exaggerated to some degree.

5 | IMPLICATIONS FOR IMMUNOTHERAPY

The various immune cells within the TME exert differential effects on tumor formation via surface immune checkpoint receptors to induce tolerance to HNSCC tumor specific antigens.[71,72] Cell surface expression of inhibitory immune checkpoint receptors CTLA-4 and PD-1 has been found to be higher on intratumoral effector T cells and Treg cells than in peripheral blood.[73,74] PD-1 expression on both CD4 and CD8 T- lymphocytes in patients with HNSCC has been demonstrated to be significantly higher when compared to healthy controls.[75] PD-L1 has been found to be highly expressed on primary tumor cells in oral SCCA, and appears to be negatively correlated to quantity of tumor infiltrating lymphocytes.[76] Agents targeting the downregulation of the PD-1/PD-L1 immune checkpoint signaling pathway have shown promising results and safety profiles in the treatment of patients with platinum refractory HNSCC, as well as neoadjuvant therapy for patients with surgically resectable disease.

Keynote-012 was a multicohort phase1b trial using the PD-1 receptor antagonist pembrolizumab that included a cohort of 192 patients with recurrent/metastatic HNSCC and reported an overall response rate of 17.7%, with a median overall survival of 8.5 months. Approximately 20% of patients experienced grade 3-4 adverse events including elevated liver enzymes and hyponatremia.[77-80] Based on the results of the Keynote-012 trial, the FDA approved the use of Pembrolizumab for the treatment of recurrent/metastatic HNSCC refractory to chemotherapy in 2016. Ferris et al recently reported preliminary results from CheckMate 358—an open-label phase I/II study that is one of two recent trials investigating the neoadjuvant use of nivolumab in previously untreated, HPV^+ or HPV^-, SCCA from multiple sites in the head and neck. Patients are administered doses of Nivolumab on days 1 and 15 and undergo surgical resection on day 29 ± 7. Grade 3-4 drug related adverse events occurred in 4 of the 29 patients reported to date (glossodynia, increases in lipase), but did not result in a delay in surgery. The reported preliminary results are quite encouraging-based on CT scan measurements, 48% of patients had some reduction in tumor size, with three patients experiencing tumor reduction of over 40% and one patient having tumor reduction of 75%.[81]

Excitement over recent advances in immunotherapy in the recurrent/metastatic setting should encourage us to consider the implications on treatment of the young, immune competent patient with oral tongue SCCA. In a study involving examination of surgical specimens from young adults (<45 years old) with HNSCC, Ryu et al found that PD-L1 tumor cell expression and costimulatory inducible T cell costimulator (ICOS) tumor infiltrating lymphocyte expression were both higher in younger patients. Perineural invasion, PD-L1 positivity, and a higher ratio of CD163 M2 tumor infiltrating macrophages to CD8 T cells were all determined to be independent factors for poor progression-free survival as well.[82] Foy et al compared protein expression profiles and genomic alterations of tumors from oral SCCA tumors of never-smokers/ never-drinkers and smokers/drinkers and found that disease in the two groups were molecularly distinct—a difference mainly characterized by differences in the immune microenvironments. A significant enrichment for interferon gamma and PD1 pathways was observed in patients without any history of alcohol and tobacco exposure, in addition to overexpression of PD-L1 and IDO1 (an enzyme involved in tryptophan catabolism resulting in an immunosuppressive local environment), and increased CD8 T-cell tumor infiltration.[83] Overexpression of IDO1 is considered one mechanism of cancer cell immune evasion and thus its inhibition may enhance the host antitumor immune response. Melanoma patients overexpressing IDO1 have been noted to respond favorably to PD-L1 inhibitors.[83-87] Overexpression of PD-L1, IDO1, higher rates of tumor infiltrating CD8 T lymphocytes, and enrichment of interferon gamma gene signatures have all been shown to be correlated with better response to PD1/PD-L1 pathway inhibition.[80,88]

6 | DISCUSSION

The global incidence of oral tongue squamous cell carcinoma is increasing in young adults, particularly females without any history of alcohol or tobacco exposure. In contrast to older patients, the clinical course in young adults is quite heterogeneous with some patients experiencing a particularly aggressive, devastating progression of disease. Overall, younger patients are also more likely to experience locoregional treatment failure.[16] Recent research efforts have suggested that although squamous cell carcinoma of the oral tongue may be genomically similar in young and older patients, the principle biological difference between younger patients without a history of tobacco or alcohol exposure appears to be lie in the TME with younger patients demonstrating higher levels of PDL-1 expression on the surfaces of tumor cells and higher intratumoral cytotoxic CD8 lymphocyte infiltration. The full biological role of PD-1/PD-L1 signaling in the formation and progression of oral squamous cell carcinomas remains to be elucidated, but there is evidence that increased expression is correlated with higher rates of cervical lymph node metastasis and worse prognosis.[89]

There is an urgent need to identify both prognostic markers to better detect young oral tongue SCCA patients that are likely to experience locoregional failure with standard therapy, and to develop new therapies that result in lower morbidity and more durable responses. To this end, we have seen modestly successful results reported from attempts to use neoadjuvant chemotherapy prior to surgical intervention in these patients. In a retrospective study of young patients with

oral tongue caner, Sturgis et al identified 15 patients who received neoadjuvant taxane-based chemotherapy prior to undergoing glossectomy and neck dissection. When compared with an age-matched cohort of patients who did not receive the neoadjuvant treatment, there was equal overall and disease-specific survival despite patients in the neoadjuvant group having higher T classifications, increased incidence of nodal metastatic disease, and presenting with a more advanced stage of disease.[90] A subsequent prospective study at the same institution found that 39% of patients receiving neoadjuvant chemotherapy had evidence of a major histologic response at the tongue primary site and this was associated with improved prognosis. In another recent retrospective study of oral tongue SCCA patients treated with neoadjuvant chemotherapy prior to surgery, Naruse et al discovered that patients who received neoadjuvant treatment and had higher expression of PD-1/PD-L1 immune checkpoint molecules demonstrated higher rates of local recurrence than patients who did not receive chemotherapy, implying another complex treatment consideration exists with regard to how manipulating the local immune response with other therapeutic modalities may have unintended effects on disease progression.[91]

Blockade of the PD-1/PD-L1 axis enhances the immune response, and early positive results from landmark clinical trials have been reported in the treatment of patients with recurrent/metastatic disease as well as in the neoadjuvant setting.[80,92-95] Although younger patients with oral tongue cancers have been included, results from these clinical trials have not been stratified based on age or tumor subsite. Results from the use of immune checkpoint inhibitors specifically for treatment of young adults with oral tongue SCCA have not yet been reported. Given our developing understanding of the immunologic differences between older and younger patients, there is substantial reason to be optimistic that the advent of immunotherapy in the treatment of head and neck cancer has the potential to fundamentally impact the treatment paradigm for younger patients. This could offer a means to improve functional outcomes by enabling more conservative extirpative surgery and sparing adjuvant radiotherapy without sacrificing disease control and overall prognosis.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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