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Short Communication

Tumor Hyperprogression in Squamous Cell Carcinomas of Head and Neck after Immunotherapy: Our Perspective

Aravind Viswanathan[1], Samir Jambhekar[2], Archith Rajan[1], Alexander Lin[3], Laurie A Loevner[1] and Sanjeev Chawla[1]*

[1]*Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA*

[2]*Drexel University College of Medicine, Philadelphia, USA*

[3]*Radiation Oncology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA*

Abstract

Head and Neck Squamous Cell Carcinoma (HNSCC) is the sixth most common cancer worldwide. Although there have been some advances in multimodality therapy, the overall 5-year survival rate remains poor approximately at 40%-50%. Currently, Immune Checkpoint Inhibitor (ICI) based Immunotherapies are being evaluated as an alternate treatment modality for recurrent/metastatic HNSCCs in clinical trials. These immunotherapeutic approaches harness the patient's immune response to fight and eliminate cancer cells. However, an undesirable side effect of tumor Hyperprogression (HPD) has emerged in HNSCCs and other cancers after the administration of ICIs. Given this unfavorable tumor response pattern, therefore, there is an unmet need for the development of a Clinical Decision Support (CDS) tools for risk stratification and individualized decision-making. While the "low-risk" patients could benefit from ICIs, the "high-risk" patients could be excluded from ICI options and instead could be offered alternative therapies for improving their survival outcomes and quality of life measures. Standard MR imaging is not adequate for predicting response assessment to immunotherapies in HNSCC patients even after using refined response assessment criteria secondary to amplified immune response at the tumor beds. To this end, some groups have reported the potential of diffusion and perfusion MR imaging and amino acid-based positron emission tomography techniques in the prediction and evaluation of treatment response to various treatment modalities including immunotherapeutic regimens in HNSSCs. The main goal of these techniques is to provide definitive metrics of treatment response at earlier time points for making informed decisions on future therapeutic interventions. Additionally, some studies have demonstrated the utility of "liquid biopsy" (blood plasma derived DNA contents) in predicting and monitoring treatment response in HNSCCs. This review provides an overview of available physiologic MR imaging techniques to understand the tumor microenvironment and biology of HNSCCs and their clinical potentials in decision making in these patients. We will also describe the existing challenges associated with these imaging modalities and potential solutions to avoid them. We believe that machine learning based CDS tool comprising of multiparametric quantitative MRI parameters and liquid biopsy-based biomarkers will allow more accurate assessment and aid in identification of suitable candidates for receiving ICIs in HNSCCs.

***Corresponding author:** Sanjeev Chawla, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA, Tel: +1 2156151662; Email: Sanjeev.Chawla@pennmedicine.upenn.edu

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Introduction

Head and neck squamous cell carcinomas (HNSCCs) are among the most common neoplasms of upper aerodigestive tract and can occur in several anatomical sites including oral cavity, nasopharynx, oropharynx, hypopharynx and larynx [1]. The standard of care treatment for advanced-stage nonsurgical HNSCCs includes concurrent cisplatin (with a weekly dose of 40mg/m^2) and radiation therapy (with a total dose of 70Gy over a period of 7 weeks) [2]. Recurrent or metastatic (R/M) HNSCCs are primarily treated via a well-established multimodal treatment plan including platinum-based chemotherapy, 5-Fluorouracil (5-FU), and cetuximab-an IgG1 subclass antibody that targets epidermal growth factor receptor (EGFR). However, these interventions are mainly associated with partial response and variable degrees of success and survival benefits. Thus, there is a pressing need for the development of novel and more effective therapeutic strategies for HNSCCs.

In the quest for an effective treatment, Immune Checkpoint Inhibitor (ICI)-based immunotherapeutic approaches have been introduced for the treatment of several cancers including R/M HNSCCs in the recent past [3]. These immune therapies are designed to harness a patient's immune response to fight and eliminate cancer cells. Under normal physiological conditions, checkpoint pathways play a key role in maintaining immune homeostasis by inhibiting the proliferation, activity, and responsiveness of cytotoxic T-lymphocytes. While this is important for attenuating autoimmunity, it also helps cancer cells in evading the immune system. ICIs block immune checkpoint proteins present on T cells from binding to inhibitory ligands present on cancer cell surfaces, thereby preventing cancer cells from suppressing the activity of cytotoxic T cells [4,5]. The immunoreceptor proteins are present on the surfaces of T cells and bind to their respective ligands on antigen-presenting cells (APCs) to downregulate immune system activity [6]. In HNSCCs, inhibitory checkpoint proteins are frequently upregulated, whereas stimulatory checkpoint proteins are

downregulated [7]. The key players in the inhibitory checkpoint signaling pathways include programmed cell death Protein-1 (PD1) and Cytotoxic T-lymphocyte-Associated Protein-4 (CTLA-4) [8]. While PD1 is expressed on activated B cells, T cells, natural killer cells, and myeloid cells, its ligands (PD-L1 and PD-L2) are upregulated in activated leukocytes, myeloid cells, and cancer cells [9]. On the other hand, CTLA-4 is expressed on T cells, and its ligands are expressed on the surface of APCs [10]. By disrupting the checkpoint regulatory pathways, ICIs stimulate cytotoxic T-lymphocyte mediated cancer cell killing, reduce the population of Tregs, and cause the production of cytokines, resulting in a profound inflammatory response within the cancer bed [11].

Some ICIs such as pembrolizumab (anti-PD1 antibody), nivolumab (anti-PD1 antibody), and ipilimumab (anti-CTLA-4 antibody) have been used for the treatment of (R/M) HNSCCs in several large multicentric early- and late-phase clinical trials.[3] While exploring the therapeutic efficacy of anti-PD1 immunotherapy, the results from a phase III trial have revealed that patients treated with pembrolizumab had significantly prolonged Overall Survival (OS) and Progression Free Survival (PFS) [12]. Moreover, considerable upregulation of T cell and interferon-γ-related gene expression have been observed within tumor specimens following pembrolizumab treatment [13]. Several clinical trials (NCT05047094, NCT03440437, NCT03755739) are currently underway whose results are yet to be published.

Recently, an unusual and unfavorable response pattern, colloquially known as tumor *Hyperprogression* (HPD), has been identified in several cancers including HNSCCs after the administration of ICIs. This novel phenomenon is characterized by a rapid worsening and paradoxical acceleration of *cancer* growth after initiating ICIs [14-16]. Several definitions of HPD have been proposed clinically. Champiat et al. [17], defined HPD as a ≥2-fold increase of the tumor growth rate (TGR) before and after initiating ICIs while Kato et al. [18], defined HPD as time-to-Treatment Failure (TTF) <2 months, >50% increase in tumor burden compared to pre-immunotherapy imaging, and >2-fold increase in progression time. The reported incidence of HPD in retrospective studies varies across different solid tumor types from 6% to 29%, with HNSCC having the highest incidence of HPD amongst carcinomas at approximately 9-29% [17,19]. HPD is associated with poor prognosis and shorter survival outcomes [16]. The phenomenon of HPD closely resembles another ICI-induced transient phenomenon known as predominant treatment related changes, colloquially termed as "Pseudoprogression" (PSP) [20]. This favorable response is mediated by an immunotherapy-induced increased in vascular permeability that leads to a profound inflammatory response in the treatment bed. While it may appear to indicate tumor growth, the PsP lesions usually stabilize or resolve spontaneously without further treatment after the initial increases in size [21,22].

While the underlying molecular mechanisms of HPD are not fully understood, some evidence indicates that older age (>65 years of age), amplification of Mouse Double Minute 2 Homolog (MDM2) gene, Epidermal Growth Factor Receptor (EGFR) alterations, increased tumor mutational burden, and modifications in tumor microenvironment caused by tumor ablation or radiotherapy, may contribute to HPD [23,24]. It has been reported that MDM2 amplified cells are more sensitive to TNFα-induced proliferation compared to non-MDM2 amplified *cancer* lines. Mechanistically, MDM2 amplification dramatically alters TNF-alpha signaling pathways, blocking apoptotic signals while simultaneously promoting NFκβ mediated cell growth and proliferation [25,26]. Ultimately, additional proof-of-concept studies are required to improve our understanding of the HPD phenomenon. Taken together, these findings suggest that (R/M) HNSCCs is a heterogeneous group and advocate for a cautious approach while selecting these patients for receiving ICIs.

In the current clinical practice, there is a lack of consensus on the factors which are sufficiently appropriate to identify suitable candidates for participating in ICI trials. Using FDG-PET, an anecdotal study reported that melanoma patients who presented with HPD had significantly higher baseline Metabolic Tumor Volume (MTV), total lesion glycolysis [TLG, product of MTV and mean standardized uptake value (SUV_{mean})], and total measured tumor volume burden [27]. Similarly, an increased risk for developing HPD was observed in non-small cell lung cancer patients receiving ICIs who had higher MTV and harbored increased neutrophil-to-lymphocyte ratio [28]. Some other studies have reported clinical signatures and histopathological/molecular features as potential risk factors for the development of HPD in cancer patients after ICIs administration [29]. Subsequently, these risk factors were used for constructing and establishing prediction models. In one such study, patient age, tumor size, and number of various metastatic lesions were incorporated into the multivariate logistic regression analyses to develop a prediction model with an accuracy of 96% in a patient population of Non-Small Cell Lung Cancer (NSCLC) [29]. In a pan cancer study, Long et al. constructed a predictive model with a training accuracy of 85% and testing accuracy of 81% for the development of HPD using data from 867 patients with 17 different types of solid tumors [30]. While these studies have reported promising findings, some other studies found non-significant associations between clinical biomarkers and HPD development, raising concerns about their utility as robust and reliable biomarkers for predicting HPD [31-33].

Therefore, there is a pressing need for the development of a robust, reliable, and objective prognostic model for risk stratification and individualized decision making (precision prognostics) for HNSCC patients undergoing ICIs. This model will allow selection of "low-risk" patients to potentially receive ICI therapy in future clinical trials (precision therapeutics). On the other hand, "high-risk" patients could be excluded from ICI therapy and instead offered alternative therapies for improving their clinical outcomes and quality of life measures.

Magnetic Resonance Imaging (MRI) is considered as a mainstay in the prediction and evaluation of treatment response in HNSCCs using Response Evaluation Criteria in Solid Tumors (RECIST) based on uni/bidimensional measurements of tumor size or estimation of tumor volumes [34]. However, these metrics using anatomical images alone are not good predictors of treatment response [35-37]. For instance, cancer cells could die without a change in volume (shrinkage). The presence of profound inflammatory response and/or vasogenic edema at the cancer bed and poor delineation of cancer margins further complicate accurate determination of cancer size [38]. The continuous developments in physiologic MRI techniques such as Diffusion Weighted Imaging (DWI), Intravoxel Incoherent Motion (IVIM), and Dynamic Contrast Enhanced (DCE)-MRI have provided new insights into the understanding of tumor biology and microenvironment of HNSCCs.

However, the spatial and temporal heterogeneities present within tumors render the usage of a single diagnostic modality or parameter sub-optimal in the prediction and assessment of treatment response with high accuracy. To address this issue, a multiparametric approach

exploiting the unique strengths of different diagnostic techniques allows a comprehensive assessment of tumor biology and microenvironment. Indeed, several studies have demonstrated the utility of integrated multimodal MRI, FDG-PET [39-41], liquid biopsy [42-44], approach in predicting and evaluating treatment response in head and neck cancers. In the field of MRI, several research groups have been at the forefront in the development, implementation and utilization of DWI [45-51], IVIM [52-55], and DCE-MRI [45,51,56-61], in HNSCC patients and in prediction and evaluation of treatment response to standard CRT in HNSCCs. Collectively, these studies have documented that tumors harboring lower pretreatment Apparent Diffusion Coefficient (ADC) values and higher volume transfer constant (K^{trans}) values are associated with better treatment outcomes and prolonged progression-free and overall survival than those harboring higher baseline ADC or lower K^{trans}. This may be due to the fact that tumors with lower pretreatment ADC and higher K^{trans} values are characterized by greater proportion of viable cells and blood flow, leading to better transport of cytotoxic drugs as well as improved delivery of oxygen at the tumor beds during chemoradiation therapy than tumors with necrotic and hypoxic areas (higher ADC values and lower K^{trans}).

Given that DWI and DCE-MRI are widely available on all clinical MRI scanners irrespective of vendors and field strengths, we believe that use of these well-established techniques may assist in predicting treatment response and risk stratification in HNSCCs. Additionally, availability of consensus guidelines [62,63], and recommendations by Quantitative Imaging Biomarkers Alliance (QIBA) [64], enabling standardization and harmonization of DWI and DCE-MRI acquisition parameters, make these techniques more attractive in routine clinical workflow. Moreover, concerted efforts are required to adopt these imaging tools into clinical settings, including added time for scanning and processing data, which often requires subspecialized knowledge. Efforts should also be made to create user friendly image processing tools to analyze and interpret advanced MRI data. Furthermore, analysis of multiparametric radiomic data from DWI and DCE-MRI derived parametric maps may allow distillation of many variables into a clinically relevant synthesis, potentially aiding in patient stratification and response assessment.

Recently, there has been a significant interest in using circulating tumor (ct)-DNA released by cancer cells into the bloodstream (liquid biopsy) for diagnosis, treatment selection, disease monitoring and risk stratification in various cancers including HNSCCs [42-44,65,66]. As the spatial and temporal heterogeneities present within tumors may render the usage of a single diagnostic modality or parameter sub-optimal in the assessment of treatment response with high accuracy. We believe that a robust and reproducible Clinical Decision Support (CDS) tool comprising of physiologically sensitive DWI, DCE-MRI, and liquid biopsy-derived biomarkers together will allow more accurate prediction of tumor hyperprogression and risk stratification. This has the potential to optimize personalized risk-adaptive therapeutic management decisions in future clinical trials.

Conclusion

In conclusion, immunotherapy offers new hope in the cancer treatment and is slowly and gradually getting FDA approval for the treatment of multiple cancers including HNSCCs. As the treatment is evolving, distinct imaging patterns associated with response and disease progression are emerging and being recognized by the scientific community. In this context, HPD is an unfavorable response pattern characterized by rapid and accelerated tumor growth observed during treatment with anti-PD-1/PD-L1 ICIs in HNSCCs and other cancers. Therefore, HPD should be carefully monitored in HNSCC patients receiving ICIs. If the outcome can be predicted before the commencement of treatment, patients who are at a greater risk for developing HPD could be spared from the unnecessary economic burden and toxic side effects associated with ICIs.

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