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Letter to the editor

## (i) TNM staging for head and neck cancers

### Introduction

Immunity is a robust pillar that bears the brutality of cancer to its threshold and grasps the onus on every aspect of cancer management: aetiology, the progress of the disease, surveillance and the feasibility of treatment options.

The Union for International Cancer Control (UICC) defines the Stage of a tumour based on its anatomical topography. The American Joint Committee on Cancer (AJCC) uses the term prognostic stage group which may also include additional prognostic factors in addition to the anatomical extent of the tumour [1]. TNM staging is an anatomical road map of the tumour focussing on its morphological, geographical and pathological route to metastasis. The current anatomical and pathological staging does not explore the tumour microenvironment, host ecosystem and fails to decrypt the subtle biological interactions at the molecular level. Oncologists are occasionally sceptical, as to why some advanced-stage malignancies can remain dormant for years, while there are rapid progression and death of early cancers.

The immortality of the malignant cells and its relentless capacity to multiply and cause life-threatening illness has prompted clinicians to explore the tumour microenvironment as a new therapeutic target. A tumour is an amalgamation of cancer cells and stroma. The stroma is the skeleton framework in which the cancer cells are enmeshed along with the fibroblasts, myofibroblasts, endothelial cells, and immune cells. The stroma is the driver of tumour progression and has the potential to mould the biology of the tumor [2]. The dense infiltration of the immune cells encircling the tumour plays a vital role in the cascade of tumour progression. In addition, there is overwhelming evidence on the high circulating neutrophil-to-lymphocyte ratio [3] as a robust biomarker of poor clinical outcome in various cancers. Prefix modifiers in TNM have often denoted clinical (treatment naïve, recurrence, re-treatment) and pathological tumour profile but not the immune profile. The (i) TNM staging may help us in understanding the hamlet of immune cells that may have a role in modulating the course of the disease.

**T:** T Cells
**N:** Neutrophils.
**M:** Macrophages.

It is a well-acknowledged fact that cancer outcomes can vary significantly among patients within the same stage. The composition of immune cells that modulate the oxidative damage can influence the course of the disease and the response to treatment. Focussing on the normal immune system and the genetic and epigenetic alterations within the tumour microenvironment [4] are essential. Several published studies have shown that the immune-classification has a prognostic value that may be superior to the AJCC/UICC TNM-classification. Thus, many subsites in oncology have begun incorporating immune scoring as a prognostic factor [5] and a marker to classify cancers, as part of their diagnostic and prognostic workup.

The information gleaned from the immune profile may necessitate the need to reinforce the immune system using Adoptive cell therapies (ACT), Activated T cell therapies, dendritic vaccines, chimeric antigen receptor (CAR) T-cell therapies that are targeted towards immunomodulation [6–8]. This synergistic approach of targeting cancer cells together with the modulation of the immune system may have the potential to result in more sustained outcomes in terms of survival and locoregional controls.

Head Neck cancers are not cryptogenic in nature, they have a well-established tumour progression model with its deleterious impact on the immune system. The addiction profile is well known, and its deleterious impact on the immune system. The archaic practice of multimodality treatment (surgery, chemotherapy, radiation) is a double edge sword that aims for a possible cure and halts metastasis at the cost of a feeble immune system. Oncologists reap the benefits of a cure for a transient period as the tumour cells rebound with vengeance and are no longer shielded by immune cells which get depleted [9]. The composition of immune cells that modulate the oxidative damage can influence the course of the disease and the response to treatment. Focussing on the normal immune system and the genetic and epigenetic alterations within the tumour microenvironment are essential.

The AJCC 8th edition has acknowledged several non-anatomical parameters to assess prognostication. The anatomic morphology of the tumour (size, volume) illustrated in the cTNM staging dictates the surgical plan. The pathological pTNM helps us in understanding the biological behaviour of the tumour (proliferation, the pattern of invasion, lymph node metastases and extranodal extension.) which in turn can influence the selection and aggressiveness of treatment. In the same vein, an understanding of the profile of the tumour in terms of the immune expression could help us in understanding the nascent genetic and epigenetic transitions with a tangible proof for prognostication and therapeutic response. The primary endpoint in the management of oral cancer is the disease-free survival and overall survival which is influenced by the host tumour immune response in addition to the biology of the tumour.

A correlation of patient survival with the tumour characteristics, the pattern of invasion, level of Tumour infiltrating lymphocytes was determined by Wolf et al. [9] who analysed that the higher grades of Tumour invasion were inversely correlated with the tumour infiltration by CD4, CD8 and FoxP3 positive T cells. The high number of tumour infiltrating CD8 T cells in the tumour microenvironment of Head and Neck cancers are commonly seen in tumours of the oropharynx that have a limited growth (small primary) and a better outcome [10–12]. This further lends support to the need for an immunological staging to gauge the prognosis, course of the disease and the modality of the treatment to be chosen.

Several efforts globally are perceptible to incorporate the Immunoscoring into routine clinical practice. A task force has emerged

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from the amalgamation of Society for Immunotherapy of Cancer (SITC), the European Academy of Tumor Immunology, the Cancer and Inflammation Program, the National Cancer Institute, National Institutes of Health, USA and "La Fondazione Melanoma" focusing on Immunoscoring [13] as a New Possible Approach for the Classification of Cancer.

The salvage rates of head and neck cancer are dismal due to over-treatment with multimodality therapy, distortion of anatomy and suppression of the host immune surveillance. iTNM staging would help us in understanding the subtle tumour immune response, tumour heterogeneity, predict the aggressive pattern of invasion and also aim to ameliorate treatment-induced toxic effects and improving the morphological results. We hope the postulations put forward would be taken constructively in the upcoming edition of AJCC emphasizing on a "precision & personalized" approach to cancer staging and setting the stage for the much-awaited immunological TNM staging with prognostic and therapeutic ramifications.

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## Authors' contributions

VR predominantly conceived this review and led the development of the short communication. Both SS and VR wrote the first draft of the letter, VR, AK, GR, SK critically revised and edited successive drafts of the manuscript. SS, VR, AK, GR, SK read and approved the final version of the manuscript.

## Declaration of Competing Interest

The authors confirmed that they have no competing interests.

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