Modifications and recent updates in the 8th edition of tumor node metastasis staging pertaining to oropharynx and oral cavity

INTRODUCTION

The recently released 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual, Head and Neck Section,\(^1\) introduces significant modifications from the prior 7th edition. The following is a summary of the changes between the 7th and 8th editions of tumor node metastasis (TNM) pertaining to the oropharynx and oral cavity.

For all sites, there are separate classifications for clinical and pathological neck nodes. There is a new classification for p16-positive oropharyngeal cancers that have p16 immunohistochemical overexpression.

OROPHARYNGEAL CANCERS

According to the National Comprehensive Cancer Network guidelines,\(^2\) human papillomavirus (HPV) testing is recommended for all oropharyngeal tumors. According to the US National Cancer Institute and Cancer Therapy Evaluation Program, HPV status must be included as a stratification factor for trials including oropharyngeal cancer patients. Much evidence suggests that HPV-positive and HPV-negative oropharyngeal squamous cell carcinomas (OPSCCs) represent distinct subgroups of OPSCC, each with unique epidemiological and biological profiles.\(^3\)

Epidemiologically HPV-positive patients are younger with a median age of 54 years. Less exposure to tobacco and alcohol is seen. Higher socioeconomic status and education is observed. HPV positivity is more prevalent in Caucasians and shows a threefold higher incidence in males than females.\(^4\)

Anatomically, an increased incidence of HPV-associated oropharyngeal cancers is seen in the tonsils and tongue. The preference of HPV for the oropharynx is unexplained but may be related to the unique presence of transitional mucosa in the oropharynx, predominantly found in the tonsillar tissue and which shows histological similarities to the cervical mucosa. Another possibility lies within the genetic features of HPV 16, which accounts for more than 90%–95% of all HPV-associated oropharyngeal cancers, as it may facilitate survival in the tonsillar crypt epithelium. It is also possible that the invagination of the mucosal surface of the tonsil may favor virus capture and maintenance by promoting its access to basal cells (the only dividing cells in the epithelium).\(^5\)

The biology of HPV-positive oropharyngeal cancer is typified by p53 degradation, retinoblastoma protein (RB) downregulation and p16 upregulation. By contrast, tobacco-related oropharyngeal cancer is characterized by p53 mutations, downregulation of p16 and RB upregulation.\(^6\)

Clinically, HPV-positive tumors are more likely to present with early T stage (T1–T2) and higher N stage (usually cystic and multilevel). They have distinct histological features, such as moderate/poor tumor differentiation and nonkeratinizing or basaloid pathology. The incidence of distant metastases was seen to be lower in patients with HPV positive tumours. Furthermore, metastases developed later, with a very different pattern from patients with HPV-negative tumours. HPV-positive oropharyngeal cancer had a 28% reduction in the risk of death and a 49% reduction in the risk of disease recurrence. Secondary primary tumor in patients with HPV-positive cancer is

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very rare and has improved better survival rate compared to patients with HPV-negative tumors.[5,6]

Radiologically, HPV-positive carcinomas often have small or even occult primary lesions with well-defined borders and cystic nodal metastases, whereas HPV-negative primaries more often have poorly defined borders and invasion of adjacent muscle.

HPV-positive oropharyngeal cancer has a significantly improved overall and disease-free survival compared to patients with HPV-negative oropharyngeal cancer patients.

HPV-positive tumors may harbor fewer or different genetic alterations, which can be associated with better response to therapy. HPV-positive tumors have higher radiosensitivity, probably due to intact apoptotic response to radiation. The absence of field cancerization is seen in HPV-positive tumors. Immunologic response may play a role in the improved response to radiotherapy and chemotherapy in HPV-positive tumors (due to the stimulation of immune response directed to viral-specific tumor antigens). Younger age, good performance status and fewer comorbidities of HPV-positive oropharyngeal cancer patients may also contribute to improved survival.[3]

HPV OPSCCs in younger patients with better prognosis and survival rates in comparison to non-HPV OPSCCs have prompted clinicians to address changes in the nonsurgical management according to HPV status. Overall survival rates increase with HPV-positive status, low estimated glomerular filtration rate and high p16. Patients with HPV-negative disease have a poorer prognosis and therefore usually require more intensive treatment.[3]

Due to all these factors, separate clinical and pathologic T category for HPV-associated (p16-positive) oropharyngeal cancer and clinical and pathologic T category for non-HPV-associated (p16-negative) oropharyngeal cancer are the main modification incorporated.

In the clinical stage of N category for non-HPV-associated (p16-negative) oropharyngeal cancer, extranodal extension (ENE) has been added.[1]

ENE is now a variable that impacts “N” staging. Cystic metastasis that stretches, but does not breach, the lymph node capsule should be classified as ENE negative.

ENE specified in all stages and N3a and N3b added: N3a being metastasis in a lymph node larger than 6 cm in greatest dimension and ENE negative and N3b being metastasis in any node (s) and clinically overt ENE positive.[1]

Clinical extranodal extension

The presence of skin involvement or soft-tissue invasion with deep fixation/tethering to the underlying muscle or adjacent structures or clinical signs of nerve involvement is classified as clinical extranodal extension.[6]

Oral cavity cancer

In the T category, T4a and T4b are added.

T4a is moderately advanced local disease: lip, tumor invades through cortical bone or involves the inferior alveolar nerve, floor of the mouth or skin of face (i.e. chin or nose).

Oral cavity

Tumor invades adjacent structures only (e.g. through cortical bone of the mandible or maxilla) or involves the maxillary sinus or skin of the face.

T4b is very advanced local disease, tumor invades masticator space and pterygoid plates or skull base encases the internal carotid artery.[1]

DEPTH OF INVASION

To measure depth of invasion, establish the horizon that is at the level of the basement membrane relative to the closest intact squamous mucosa. The greatest invasion is measured by dropping a “plumb line” from the horizon.

The terms “depth of invasion” and “tumor thickness” have been used interchangeably, which is incorrect.

For example: Depth of Invasion in an Ulcerated Carcinoma - The “tumor thickness” would be deceptively thinner than depth of invasion.[1]

CONCLUSION

The 8th edition of the AJCC Cancer Staging Manual, Head and Neck Section incorporates significant changes based on advances in our understanding of the etiology and certain histologic attributes of tumors. These include a separate staging algorithm for HPV-associated cancer of the oropharynx, changes to the tumor T categories and the addition of tumor ENE to the lymph node category for most sites. We recommend that the 8th edition of the TNM classification be always included in data reporting.

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Conflicts of interest
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