

# Feasibility of Use of the 8<sup>th</sup> Edition of the American Joint Committee on Cancer Staging for Head and Neck Cancers in Indian Scenario: An Evaluative Study

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## Abstract

**Introduction:** Inclusion of depth of invasion (DOI) and a separate classification for human papillomavirus (HPV)-associated Oropharyngeal Cancers (OPCs) are two of the many major changes in the 8<sup>th</sup> edition of the American Joint Committee on Cancer staging system. After more than 2 years of implementation, the authors found the need to evaluate if the Indian clinicians found it feasible to apply the system in their practice and if the same has influenced their decision-making. **Methods:** The survey was done in the form of a questionnaire which was distributed personally and via the internet to 100 clinicians. Seventy-two clinicians responded to the questionnaire. The results were analyzed and frequency distribution was computed. **Results:** Eighty-three percent of the clinicians experienced that palpation of the tumour was not a reliable method to determine the DOI. The common issues stated by the clinicians were difficulty in assessing DOI in certain subsites of the oral cavity (most commonly retromolar trigone–83%), inability to determine DOI in patients with trismus, and inability to correlate pathological and clinical DOI. Thirteen percent of the clinicians did not rely on radiological tools for measuring the DOI. Seventy percent of the clinicians did not perform a P16 assay for patients with oropharyngeal cancers. Fifty percent of the clinicians preferred chemoradiotherapy for early HPV positive oropharyngeal cancers. **Discussion:** Based on the results of the survey, the authors recommend a need for more interpretative guidelines and methods for determining the DOI. The authors also emphasize the need for determining HPV status for all oropharyngeal carcinomas.

**Keywords:** Classification, mouth neoplasms, neoplasm staging, oropharyngeal neoplasms, P16 protein

## BACKGROUND

The 8<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC) staging system was published in 2017 and was applied for all cases diagnosed on and after January 1, 2018.<sup>[1]</sup> The major changes in the eighth edition include:

1. Inclusion of depth of invasion (DOI) of oral cavity cancers
2. Upstaging of nodal staging based on extranodal extension
3. Reclassification of oropharyngeal cancers based on human papillomavirus (HPV) expression
4. Testing for HPV and Epstein–Barr virus (EBV) in all cases of cervical metastasis of unknown origin.

It has been recognized since the early work of Spiro *et al.* that the prognosis of the diseases becomes worse as the thickness of the tumour increases.<sup>[2]</sup> It is now a well-accepted fact that DOI is more representative of tumour infiltration than the tumour thickness. Increase in DOI is known to increase the risk

of nodal metastasis and recurrence.<sup>[3,4]</sup> However, difficulty in measuring DOI clinically in certain subsites and interobserver variability makes this parameter challenging to assess.<sup>[5]</sup>

In the recent times, there has been a rise in the HPV-associated oropharyngeal cancers.<sup>[6]</sup> In the 8<sup>th</sup> edition of the tumour, node, and metastasis (TNM) staging system, AJCC recommends

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determination of P16 status of all oropharyngeal cancers to classify the HPV-positive cancers separately, owing to the better prognosis that HPV-positive oropharyngeal cancers offer in comparison to those which do not demonstrate HPV.<sup>[7]</sup> It has been stated that in the Indian scenario, lack of infrastructure for immunohistochemistry (IHC) in certain facilities and low socioeconomic status make application of this system slightly difficult.<sup>[5]</sup> Affordable cancer diagnosis and treatment are one of the challenges faced by the Indian public health system.<sup>[8]</sup> This makes approach of patients and hence the clinicians slightly varied toward cancer diagnosis and treatment than that in the developed nations.<sup>[5]</sup>

We conducted a nationwide survey to evaluate feasibility and the use of recent AJCC staging of the head and neck among clinicians actively involved in the treatment of head and neck cancers, the area of focus being measurement of DOI in oral cavity cancers and HPV determination in oropharyngeal cancers.

## METHODS

This was an evaluative cross sectional study. The study duration was 3 months. The data were collected through a questionnaire [Table 1] consisting of 7 questions, distributed personally and via the internet. A total of 100 clinicians across India were approached to participate in the study, of which 72 clinicians responded. Inclusion criteria included those clinicians actively involved in diagnosis and management of head and neck cancers. The questionnaire was validated by an internal committee from the institutions where the study was designed. The question 1 and question 2 were aimed to identify if the clinicians were able to measure the DOI with ease and if they experienced greater trouble in measuring DOI in any specific subsites of the oral cavity. Question 3 explored if the clinicians relied on imaging for assessing the DOI. Question 4 enquired if there was any change in treatment strategy due to the upstaging of oral cavity cancers on inclusion of DOI. Question 5 focused on whether clinicians determined HPV status of all oropharyngeal cancer patients they encounter. Question 7 asked the clinicians their choice of treatment for HPV-positive early oropharyngeal cancers. Since the study did not involve comparison of any variables or groups, statistical analysis was not performed. The responses were analyzed and frequency distribution was computed.

## RESULTS

The question-wise results were as follows:

As a response to question 1, 78% of the respondents answered that they did not feel that palpation of the tumour was a reliable method to measure the DOI. Twenty percent of the respondents stated that it was not precise and 13% of respondents felt that it was subjective and had inter observer variability. Pain and gag reflex made examination difficult, as reported by 13% of respondents. Twenty-eight percent of the respondents found it difficult to palpate DOI

**Table 1: Eighth edition of the American Joint Committee on Cancer feasibility questionnaire**

Questions
1. Do you feel palpation of the tumor is a reliable method to measure the DOI? A. Yes B. No. If No, then what problem do you face?
2. Do you use any specific clinical technique to measure the DOI? A. Yes. If yes, then which technique? B. Nothing specific
3. Are you able to clinically estimate the DOI in all the subsites of oral cavity? A. Yes B. No. If No, in which of the following subsite is it difficult to estimate DOI clinically a. Tongue b. Buccal mucosa c. Hard palate d. GBS e. Alveolus f. Lip g. RMT h. FOM
4. Do you use radiological tools to measure DOI? A. Yes B. No
5. What treatment do you recommend for a tumor that is 3 cm in size and >10mm in clinical DOI? A. Single modality B. Multimodality
6. Do you check HPV status routinely in all your oropharyngeal cancers? A. Yes B. No. If No, then why? a. Patient not willing b. Expensive c. Not available in our setup d. Does not help in treatment planning
7. What treatment modality do you use to treat early oropharyngeal cancers? A. TORS B. Chemotherapy + Radiotherapy

DOI: Depth of invasion, RMT: Retromolar trigone, TORS: Transoral robotic surgery, GBS: Gingivo-buccal sulcus, FOM: Floor of Mouth

in certain subsites of the oral cavity. Some of the respondents also reported that DOI was difficult to measure in tumours invading the hard tissues.

Question 2 inquired if the clinicians were able to clinically estimate the DOI in all the subsites of oral cavity and if not, which are the subsites where they encounter difficulty. Ninety-two percent of the respondents were not able to clinically estimate the DOI in certain subsites. The sites where DOI was most difficult to assess were retromolar trigone, hard palate, alveolus, and gingivobuccal sulcus.

As a response to question 3, 87% of the respondents agreed to be relying on radiological tools for measuring the DOI.

Question 5 inquired regarding their preferred modality of treatment for a tumour that is 3 cm in size and >10 mm in

clinical DOI. Ninety percent of the respondents opted for multimodality treatment.

On analyzing responses to question 6, it was found that 70% of the respondents did not advise HPV determination as a routine practice. The reasons behind this were IHC not being available in their setup, test being expensive, unwillingness of the patient, and the fact that there is no conclusive evidence to alter the treatment plan in these cases.

While replying to question 7, 50% of the respondents preferred to opt for chemoradiotherapy whereas 30% opted for transoral robotic surgery [TORS] as the choice of treatment for HPV positive early oropharyngeal cancers. The rest 20% of the respondents did not respond to question 6.

## DISCUSSION

Staging forms a pivotal role in establishing the diagnosis, treatment plan, and prognosis of cancer.<sup>[9]</sup> Accurate staging forms a basis for interdisciplinary communication and research.<sup>[10]</sup> AJCC in collaboration with the Union for International Cancer Control has formulated a system known as TNM, which is popularly used worldwide for clinical and research purposes.

The 8<sup>th</sup> edition of the AJCC staging system was published in 2017 and was applied for all cancer cases diagnosed on and after January 1, 2018. Significant changes have been made in the head and neck staging system in the eighth edition, based on the changing nature of cancers and advanced research in the field.

DOI has been discussed extensively in the literature as an independent prognosticator of survival and recurrence in oral cavity cancers.<sup>[11,12]</sup> Ebrahimi *et al.* in their multicenter retrospective study demonstrated a significant association between DOI and disease-specific survival.<sup>[3]</sup> As a result, AJCC incorporated DOI in the T criteria for oral cavity cancers in 2016, which was earlier defined by only a two-dimensional measurement of tumour diameter. Inclusion of DOI leads to upstaging of certain tumours with a small diameter but increased DOI. Seventy-eight percent of the respondents of the present survey found palpation of the tumour unreliable for measuring the DOI. Reasons stated for the same were subjectivity, pain when palpating the posterior areas, gag reflex, trismus, and inability to assess DOI in the intrabony component of the tumour. Ambiguity in measurement of the clinical depth by palpation makes one dependent on the imaging for determining the DOI. 87% of the respondents used imaging as a supplementary tool to determine the DOI. MRI is as an acceptable modality for measuring the DOI.<sup>[13]</sup> However, inflammation and peritumoural edema tends to overestimate the depth in postcontrast MRI. Vidiri *et al.* have established a good correlation between radiological depth measured through contrast MRI and pathological depth. However, their study consisted of a small sample size of 43 and they insisted on measurement of DOI within 1 min of

injecting the contrast (early postcontrast phase) for accurate calculation of DOI.<sup>[8,14]</sup> AJCC gives clearcut guidelines for the measurement of DOI histologically through a plumb line.<sup>[1]</sup> However, it has been observed that DOI measurement in large tumours is associated with high interobserver variability and ambiguity.<sup>[15]</sup> This may obviate the primary aim of staging. Kano *et al.* in their validation study for modified AJCC staging for oral cavity cancers have suggested to improvise the method of measurement of histopathological DOI in larger tumours of the tongue.<sup>[16]</sup>

Ninety percent of the respondents preferred multimodality treatment for a tumour that is 3 cm in size and >10 mm in clinical DOI. Addition of DOI as fundamental criteria in T staging leads to restaging of certain tumours. A tumour 3 cm in size, >10 mm in depth, which was classified as T2 in the 7<sup>th</sup> edition staging system, would now be classified as T3 as per the eight edition, taking into account the depth of the tumour. A tumour that migrates to Stage III from Stage II may need to be considered for multimodality treatment which would otherwise have been subjected to a single modality treatment and observation.<sup>[17]</sup> Probably, with this fact in mind, 90% of the respondents in our survey have opted for multimodality treatment. However, Ebrahimi *et al.* in their retrospective study in a cohort of 1409 patients with tumour diameter  $\leq$ 4 cm concluded that there was no association between DOI and disease-specific survival in such patients. Thus, they have advised against the use of DOI as sole criteria for postsurgical radiotherapy and thus multimodality treatment in the absence of other adverse features in patients with tumour size  $\leq$ 4 cm.<sup>[18]</sup>

In the seventh edition staging system, the staging of oropharyngeal cancers represents the behavior of cancers caused due to tobacco and alcohol and does not differentiate those associated with HPVs. High risk (HR-HPV) associated Oropharyngeal Cancers (OPCs) have a different biology than their non-HPV counterparts.<sup>[17]</sup> Subset analysis of several clinical trials has shown that HPV-positive OPCs have a better prognosis and overall survival compared to HPV-negative ones.<sup>[7,19,20]</sup> This led to the introduction of separate staging system for HPV-positive OPCs in the eight edition of AJCC manual. The recent literature shows that 25% of the oropharyngeal carcinomas are associated with HR-HPV.<sup>[11-13]</sup> A meta-analysis by Mehanna *et al.* has reported an incidence of HPV in OPCs as 47.7%.<sup>[21]</sup> However, there are sparse data regarding the prevalence of HPV in nontobacco-associated OPCs in India, since the majority of the patients with Head and Neck Squamous Cell Carcinomas (HNSCCs) are tobacco users.<sup>[22]</sup>

There are several methods available for the detection of HPV, of which detection of P16 by IHC and detection of HPV DNA by polymerase chain reaction are being more commonly done. P16 detection by IHC has been suggested by the AJCC as an acceptable tool.<sup>[1]</sup> P16 is overexpressed in HPV-positive cases and hence is used as a surrogate marker for HPV. IHC test is less expensive and easily available than the other

tools.<sup>[22]</sup> As per the consensus recommendations provided by the Indian Cooperative Oncology Network, HPV DNA testing in addition to P16 IHC would be desirable but can be considered optional.<sup>[22]</sup> Seventy percent of the clinicians who responded to the survey did not routinely check the HPV status of patients with oropharynx carcinoma. Majority of them claimed to be lacking the necessary infrastructure for performing the tests. Furthermore, the test deemed to add to the cost which was not acceptable to the patients, especially those from low socioeconomic class. In view of a proven favorable prognosis of HPV-positive OPC, deescalation of treatment has been suggested for these patients to decrease the toxicity and morbidity associated with the conventional treatments.<sup>[23]</sup> The various modalities proposed for deescalation are lower dosage of radiotherapy, replacement of chemotherapy by targeted therapy, and minimally invasive therapy. However, deescalation is currently not recommended outside of a clinical trial.<sup>[23]</sup>

In the concluding question of the survey, 30% of the respondents preferred TORS for early oropharyngeal cancers whereas 50% of them preferred a conventional chemoradiotherapy. TORS is now deemed a viable surgical option for carcinoma oropharynx due to the good oncologic, functional, and survival outcomes.<sup>[24,25]</sup> HPV-positive OPC with their proven favorable prognosis could qualify for treatment with TORS. The ORATOR trial has compared radiotherapy versus TORS and neck dissection in patients with T1-T2 lesions and positive for P16. The authors have interpreted that radiotherapy had a better swallowing-related quality of life compared to the TORS group; however, the difference did not represent a clinically significant change. They suggest to inform the patients regarding both the treatment options.<sup>[26]</sup> TORS is available only in few centers across India. Furthermore, the clinicians trained in TORS are few. This could be the reason behind clinicians still opting conventional chemoradiotherapy compared to TORS in early OPC.

## CONCLUSION

Feasibility of applying the 8<sup>th</sup> edition of the AJCC staging for head and neck cancers has been discussed widely in the recent literature.<sup>[6,19]</sup> This survey is first of its kind assessing the feasibility and ease of implementation of Eighth edition of AJCC staging in Indian scenario. The survey reflects a need for more interpretative guidelines and methods for determining the DOI. It also emphasizes the importance of determining HPV status for all oropharyngeal carcinomas.

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## Conflicts of interest

There are no conflicts of interest.

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