Staging for Head and Neck Cancer: Purpose, Process and Progress

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Abstract

With advancing knowledge and new data available, periodic revisions in the TNM staging system is essential. In addition, new disease entities entering in the spectrum of neoplastic diseases demand that a staging system be developed to facilitate their treatment algorithms and outcomes. The most recent revisions in the AJCC/UICC staging system were published in the eighth edition of the AJCC staging manual. This presentation gives a historical background on the AJCC/UICC staging process and highlights major changes introduced in the eighth edition for cancers of the head and neck.

Keywords Staging · Head and Neck Cancer · AJCC · 8th Edition

Purpose

Once the diagnosis of cancer is established, it is only intuitive that clinicians would like to describe the extent of disease at the outset for a variety of reasons including selection of treatment and assessment of prognosis. Staging cancer measures its volume and extent at presentation and puts the clinical problem in proper perspective. Staging allows one to estimate prognosis at the outset and sets realistic expectations on the part of the patients and their families and their treating physicians. Staging cancer allows clinicians appropriate selection of treatment and creates a “yard stick” for comparison of outcomes of therapy, among different treatment modalities, and among institutions and across geographic regions. The concept of cancer staging is not new. Halstead theorized that cancer progression followed an orderly stepwise process beginning from the primary tumor formation to distant metastases, passing through regional lymph nodes, using breast cancer as an example [1]. Based on Halstead’s theory, Steintal in Germany first attempted to clinically stage breast cancer [2]. However, it was not until 1944 that Pierre Denoix

systematically reported the Tumor, Node, and Metastasis (TNM) staging system [3].

To study the validity of the TNM system, the International Union Against Cancer (UICC) appointed a TNM Committee in 1954. Similarly, in the USA, the American Joint Committee for Cancer Staging and End Results Reporting was appointed. Both the UICC and the American Joint Committee met on January 9, 1959, to initiate a dialog and deliberate on developing a cancer staging system. Eventually, a National Conference on Cancer Staging was organized in the USA in 1976, and subsequent to that the first edition of the cancer staging manual was published in 1977 which included only some sites of cancer. The name of the American Joint Committee on Cancer Staging and End Results Reporting was truncated to the AJCC in 1980. The second edition of the cancer staging manual was published in 1983, where several other sites of cancer were added. Since the 1980s, both the UICC staging committee and AJCC have developed increasing collaboration with the ultimate goal of developing a uniform staging system by both organizations with global applicability. A representative of the UICC Head and Neck Committee has served on the AJCC Head and Neck Task Force as the liaison officer for nearly three decades. Up until now, seven editions of the cancer staging manual have been published with improvement in the staging systems in each successive edition with better prognostic accuracy and predictability. Progressively, non-anatomic factors have been added into the staging system, with each successive editions. The most recently published *8th Edition* is a

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culmination of intense work and in-depth discussions between the UICC and AJCC, Head and Neck Committees, where all staging criteria for all head and neck sites are now uniform, resulting in a single staging system approved and accepted by both UICC and AJCC [4]. These revisions in the *8th Edition* of the staging system will go into effect worldwide on January 1, 2018. Going forward, all future revisions in the head and neck staging system will remain uniform for both organizations, with global applicability.

Process

In devising a staging system, several factors come into play, in order to arrive at a balanced and globally applicable staging system. Particularly, complexity, discrimination, and compliance are fundamental issues which must be addressed to make the system, clinically applicable with a high predictive power of prognostication.

Complexity is of particular importance. For example, a highly detailed and complex system, which includes all possible factors impacting on outcome, will be very accurate in predicting outcome. However, the more complex the system gets, it loses its user friendliness and compliance will decline. Thus, a highly complex system will lose its value due to poor compliance. Therefore, any revision in the staging system has to maintain a balance between complexity and simplicity. Based on new knowledge, additional factors impacting on prognosis have to be added to improve the staging system, but by necessity it will be a compromise between the all comprehensive *ideal* and the user friendly *practical*.

Discrimination is an equally important factor to consider in devising or revising the staging system. The data collected should be analyzed in such a way to be able to discriminate different groups in predicting outcomes, and the groups should be more or less equally distributed. For example, we cannot have 80% of all the patients clustered in one stage, and the remaining 20% in the other three stages (II, III, and IV). Ideally, each of the four stages should comprise of approximately one quarter of the entire cohort. This process requires consideration of issues such as (i) hazard consistency, (ii) hazard discrimination, (iii) outcome prediction, and (iv) balance [5].

Compliance is a crucial factor, if the staging system will be used to generate meaningful data. High compliance in the utility of the staging system is necessary to generate large data. A very simple system would be very easy to use and will have very high compliance, but its predictive and prognostic power would be low, and thus it would not be of value. On the other hand, as stated above, a highly complex system would be very accurate and precise, but will have a low compliance. Thus,

again, to achieve high compliance and have high accuracy, it will have to be a compromise between the ideal and the practical.

The 5% rule: Finally, any tumor, factor, issue, or observation which is rare and exceptional and has an incidence of less than 5% is generally not considered for entering into the criteria for the staging system.

Another issue that comes up for discussion is how often should the staging system be revised? Frequent revisions of the staging system should be avoided; otherwise, we will not be able to generate sufficient comparative data to show outcomes of a disease or therapy. On the other hand, new discoveries and new knowledge must be incorporated into the staging system to continually improve it and make it more and more accurate and meaningful.

Over the past four decades, seven editions of the AJCC staging manual have been published at an approximate interval of 6–7 years between each edition. These intervals allow at least 5 years to gather data and analyze the impact of the previous revision, before a new revision takes place. With each successive edition, the staging system has evolved with addition of non-anatomic prognostic factors to the TNM system, along with parallel recording of other prognostic factors and new information, yet not ready for inclusion in the staging criteria. The data collected from such efforts undergo testing and validation before it is introduced into the next revision. One example of such an addition is to include comorbidity in the staging system. Piccirollo used conjunctive consolidation to incorporate comorbidity in the staging system which accounted for performance status, symptom severity, and comorbidity and showed that adding comorbidity improved prognostication over TNM staging alone [6]. Currently, data on comorbidity and lifestyle are entered into the “staging forms,” even though they are not incorporated in the current version of staging. The ultimate goal of the staging effort is to develop *dynamic*, *personalized*, and *prognostic nomograms* for each individual patient, which will have many non-anatomic tumor, patient, and treatment factors, including response to therapy added, in addition to the TNM parameters.

The current staging system by no means can be considered “perfect.” However, it is workable and is considered a work in progress. Taking an example of staging for larynx, the current system is clearly deficient, since it does not incorporate the functional status of the larynx, such as aspiration, laryngeal competency, status of the airway, and dysphagia, all of which impact upon outcome. In addition, patient factors such as lifestyle (smoking and alcohol consumption), pulmonary status, and general medical condition are also not included. Further, the current staging system does not

incorporate “response to therapy.” In addition, the current staging system is “static” and stages the patient at the point of initial diagnosis, and the patient remains in the same stage throughout his/her life. Again, the need for dynamic personalized prognostic nomograms cannot be overemphasized.

Progress

The process of revisions in the staging system has been a very streamlined effort by the AJCC. It has a core committee to oversee and accept/implement changes recommended by the Task Forces for several tumor sites. The charge of the task force is to continually review published literature and compile new information for discussion within the task force which may have a potential impact on the staging of tumors. The data from such publications are validated when feasible using large datasets from the National Cancer Database (NCDB) or Surveillance, Epidemiology, and End Results (SEER) dataset. The task force is made up of a comprehensive group of specialists, consisting of surgical oncologists/head and neck surgeons, radiation oncologists, medical oncologists, pathologists, radiologists, epidemiologists, research scientists, biostatisticians, data managers, registrars, and support staff. It also includes a representative from the UICC Head and Neck Committee, who acts as the liaison person with UICC. The process of review and consideration of incorporation of new information in the revision begins at least 2–3 years prior to final publication of the next edition. A number of subcommittees are appointed to address specific tumors or issues, who deliberate and report to the task force chair. Several face-to-face meetings of the entire task force and numerous conference calls take place during this time. The goal of the task force is to revise the system with incremental improvement, with a focus on global applicability and maintaining harmony between AJCC and UICC. The primary sites that are predominantly treated non-surgically such as the nasopharynx have only clinical staging (cTNM), while sites which are predominantly treated surgically have both cTNM and pathological staging (pTNM). With these goals in mind, the eighth edition of the AJCC staging manual was published in October, 2016. The revised criteria for the staging will be implemented for staging starting January 1, 2018. A detailed description of the changes in the eighth edition with supporting data was published by Lydiatt et al. earlier this year [7]. However, a summary of the major changes is described below. (Revisions and additions are shown in tables below.)

Table 1 T staging of non-melanoma skin cancer, SCC

Tis	Carcinoma in situ
T1	< 2 cm in diameter
T2	2–4 cm in diameter
T3	4 cm in diameter, or minor bone erosion, or perineural invasion or deep invasion > 6 mm
T4	Tumor with gross cortical bone/marrow, skull base invasion, and/or skull base foramen invasion

The most important and significant changes in squamous cell carcinoma of the upper aerodigestive tract cancers are incorporation of pathologic features such as depth of invasion (DOI) in primary tumors of the oral cavity, addition of extra nodal extension of cancer in cervical metastasis, and a separate staging system for HPV +ve oropharynx cancers. Significant changes are also introduced in the staging of non-melanoma skin cancer, nasopharynx cancer, and differentiated cancer of the thyroid gland.

Non-Melanoma Skin Cancer A significant change is addition of perineural invasion in T staging of primary skin cancer. This pertains to upstaging the tumor to T3, if perineural invasion is present regardless of the tumor size. Thus, the new definition for T3 is tumors 4 cm in diameter, or with minor bone erosion *or with perineural invasion or deep invasion > 6 mm* (Table 1).

Nasopharynx Revisions to the T staging of primary tumors include clarification and expansion of the definition of each T stage (Table 2).

Oropharynx The rising incidence of oropharynx (OPC) cancers associated with the human papilloma virus (HPV) has become a major problem. It has the fastest rising incidence among all mucosal head and neck cancers [8]. This tremendous increase in the incidence of HPV positive cancers of the

Table 2 T staging for cancer of the nasopharynx

T0	No primary tumor but EBV + neck nodes
T1	Tumor confined to nasopharynx or extended to the oropharynx, nasal cavity without parapharyngeal space invasion
T2	Tumor with extension to parapharyngeal space and/or adjacent soft tissue involvement (Pterygoids, prevertebral muscle)
T3	Tumor with infiltration of the bony skull base, cervical vertebrae, Pterygoid plates, or paranasal sinuses
T4	Tumor with intracranial extension, invasion of cranial nerves, hypopharynx, orbit, parotid, or extensive soft tissue disease lateral to the lateral Pterygoid muscle

Table 3 N staging for HPV +ve oropharynx cancers

N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph node < 6 cm
N2	Contralateral or bilateral nodes, all < 6 cm
N3	Any lymph node(s) > 6 cm

oropharynx and its unique biological behavior has required that a separate staging system be developed for HPV +ve cancers, in contrast to their traditional tobacco-induced HPV –ve counterparts. HPV positive oropharynx cancers occur mostly in non-smoking, healthy young adults. These cancers show very good response to therapy and have excellent outcomes, even with advanced stage disease, regardless of the type of treatment employed. The T staging for HPV +ve oropharynx cancers remains the same as in HPV –ve cancers and is not changed. But, the N staging for HPV +ve oropharynx cancer has changed, since several studies have shown that the volume and extent of nodal metastases in these tumors do not have the same negative impact on outcome, as it does in other HPV –ve mucosal cancers. The new nodal staging for HPV +ve OPC is as follows: (Table 3).

These changes make all HPV +ve OPC cancers staged between stages 1–3, with stage 4 assigned to only those with distant metastases (Table 4).

Oral Cavity Primary tumors of the oral cavity have been staged traditionally with surface measurements only. Increasing information on the prognostic implication of the Depth of Invasion (DOI) on risk of occult metastases and disease-specific survival has resulted in inclusion of DOI in T staging of primary tumors [9, 10]. Each 5-mm increase in DOI upstages the tumor by one T stage (Table 5).

While it is clinically not possible to accurately assess the DOI, the assessment of DOI by clinical examination/bimanual palpation is acceptable in assigning the primary

Table 4 Stage groupings for HPV +ve oropharynx cancer

When T is...	And N is...	And M is...	Then, the stage group is...
T0, T1, or T2	N0 or N1	M0	I
T0, T1, or T2	N2	M0	II
T3	N0, N1, or N2	M0	II
T0, T1, T2 T3 or T4	N3	M0	III
T4	N0, N1, N2, or N3	M0	III
Any T	Any N	M1	IV

Table 5 T staging for oral cancers

T1	Tumor ≤ 2 cm, DOI ≤ 5 mm
T2	Tumor > 2 cm but ≤ 4 cm, and DOI ≤ 10 mm or tumor ≤ 2 cm, DOI > 5 mm ≤ 10 mm
T3	Tumor > 4 cm or tumor of any size and DOI > 10 mm
T4a	Locally advanced tumor
T4b	Very advanced tumor

tumor as *thin* (< 5 mm), *thick* (5–10 mm), and *very thick* (> 10 mm) for staging purposes. Incorporating the DOI to primary tumor T staging upstaged the tumor in approximately 23% of patients and showed better discrimination among stages in one study [11].

N Staging Up until the seventh edition of the staging system, the size, number, and laterality of nodal metastases were considered for assigning N stage. Increasing information on the “extent” of metastatic disease expressed by extra nodal extension (ENE) led to its incorporation in the revision to the N staging for metastatic carcinoma. The presence of gross ENE upstages the node(s) to N3b. So strong is the influence of ENE on outcome that assigning N3b to nodes with ENE was felt appropriate (Table 6). Addition of ENE to N staging caused stage migration in up to 30% of patients who were upstaged and clearly show worse outcome in one study [11] (Table 6).

Thyroid (Differentiated Carcinoma) There are significant changes made in the staging of thyroid cancer. They are in age at diagnosis, T staging, and N staging. Several cohort

Table 6 N staging for cervical lymph node metastases

N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral node < 3 cm and ENE–
N2	Metastasis in a single ipsilateral or contralateral node 3–6 cm and ENE– or multiple ipsilateral nodes < 6 cm and ENE–, or contralateral or bilateral nodes < 6 cm and ENE–
N2a	Metastasis in a single ipsilateral or contralateral node 3–6 cm and ENE–
N2b	N2b metastasis in multiple ipsilateral nodes < 6 cm and ENE–
N2c	Metastasis in contralateral or bilateral nodes < 6 cm and ENE–
N3a	Metastasis in a single node > 6 cm and ENE–
N3b	Metastasis in a single ipsilateral, multiple ipsilateral, contralateral, or bilateral nodes of any size and ENE+

Table 7 T staging for differentiated cancer of the thyroid

T1	Tumor < 2 cm limited to the thyroid
T2	Tumor 2–4 cm limited to the thyroid
T3a	Tumors > 4 cm limited to the thyroid gland
T3b	Tumor of any size with gross ETE involving the strap muscles
T4a	Gross ETE involving the larynx, trachea, esophagus, recurrent nerve, or soft tissues
T4b	Gross ETE encasing the carotid artery, mediastinal vessels, or prevertebral fascia

studies including an international collaborative validation study showed that age 55 was a better discriminator of outcomes than age 45 [12]. Therefore, age 55 will now be used to risk stratify patients between low- and high-risk groups.

Minor/microscopic extrathyroid extension of primary tumors of the thyroid has no impact on local regional recurrence or disease-specific survival. Hence, *microscopic extrathyroid extension is removed from upstaging the tumor to T3*. Therefore, microscopic extrathyroid extension will no longer affect T staging. The new T categories will thus be as follows: (Table 7).

As far as nodal metastases are concerned, the changes include histological confirmation and distribution of nodal metastases (Table 8).

These changes in staging of thyroid cancer result in stage migration and downstaging of up to 24% of patients with differentiated thyroid cancer and creates more accurate separation of survival curves with better discrimination [13].

The ultimate goal of the AJCC and UICC is to make a progressive move towards creating and using dynamic personalized prognostic nomograms which will incorporate TNM as well as other histomorphological features, molecular markers, non-anatomic prognostic markers, socioeconomic status, lifestyle, and comorbidities, as well as response to therapy. In conclusion, staging is a continuously evolving and dynamic process incorporating new and valid information to improve accuracy and predictive power.

Table 8 N staging for differentiated cancer of the thyroid

N0	One or more cytologically or histologically confirmed benign lymph nodes
N1a	Metastases to level VI or VII lymph nodes (pretracheal, paratracheal, prelaryngeal/Delphian, or upper mediastinal)
N1b	Metastases to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V), or retropharyngeal lymph nodes

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