Introduction to the Imaging and Staging of Cancer

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KEYWORDS

• Staging • Squamous cell carcinoma • American Joint Committee on Cancer • Ultrasound
• Computed tomography • Magnetic resonance imaging • Positron emission tomography
• Fine-needle aspiration

KEY POINTS

- Cancer staging is how clinicians describe the state of the disease, predict prognosis, help determine best treatment, and interpret outcomes.
- Although several staging systems are available, the most widely used is the tumor node metastasis (TNM) system developed by the American Joint Committee on Cancer.
- Knowledge of normal anatomy and the myriad appearances of variations in anatomy is the basis of accurate tumor staging.
- Cross-sectional imaging is complementary to the clinical examination for accurate staging.

THE TUMOR NODE METASTASIS STAGING SYSTEM

Cancer staging is the common language by which clinicians describe the state of the disease, predict prognosis, help determine best treatment, and interpret outcomes. Although there are several staging systems available, the most widely used is the tumor node metastasis (TNM) system developed by the American Joint Committee on Cancer (AJCC) in collaboration with the International Union for Cancer Control (UICC).[1] The first AJCC staging manual was published in 1977, and because the manual is revised every 6 to 8 years, the AJCC seventh edition published in 2010 (AJCC7) is the current version. The manual is available as a 650-page book, a small handbook, and on CD-ROM. The AJCC manual is organized by body part, and head and neck is the first anatomic area covered.

The TNM system categorizes each patient's disease based on location, size, and extent of the primary tumor (T), location, number and extent of nodal metastases (N), and presence of distant metastases (M). Thus, the basis is anatomic. Factors that affect prognosis such as human papillomavirus (HPV) 16 status, the smoking or drinking history, or comorbidities are important, but have not yet been incorporated into the staging system.

Tumors can be staged at various points through the treatment cycle. Specifically, clinical stage is at presentation before treatment, pathologic stage is after surgery, and posttherapy stage is after first course of nonoperative therapy, whether radiation, systemic, or both. The initial clinical stage remains the most significant factor to determine prognosis and additional therapy, and is the stage used in reporting survival statistics. The initial clinical stage often appears in every clinical and follow-up report. Thus, even years later and even if a patient is free of disease, clinical notes list the patient as a TNM stage.

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Despite the nearly universal use of the TNM staging system and the widespread availability of AJCC manuals in both written and electronic versions, in our experience, diagnostic radiologists rarely include the anatomic stage of the primary tumor in the formal written imaging interpretation. That listing the stage in the dictation is the exception rather than the rule is puzzling. Because the AJCC staging system is anatomic, with the exception of mucosal or skin lesions, the best opportunity to accurately stage the patient is by interpretation of the modern imaging. Even endoscopic biopsies are limited in determining deep extent of head and neck cancer. Why, then, do even subspecialty-trained radiologists hesitate to commit to an anatomic stage in each of their dictations?

The answer, as with any significant medical question, is multifactorial, and likely is related to lack of knowledge regarding normal anatomy, patterns of tumor appearance and spread, and important locations of tumor extension that would change clinical staging. Normal head and neck anatomy is complicated, with small structures present in compact regions. The presence of some structures, such as cranial nerves, can be appreciated only by knowing normal anatomy, because they are so small as to evade visualization with current imaging equipment. Tumor resection and subsequent reconstruction to restore normal function and obtain adequate cosmetic result make follow-up imaging even more difficult.

In the past, the radiologist has had to rely on a frequently illegible blurb of a history on an imaging request form. With the advent of the electronic medical record, the radiologist has access to the clinical signs and symptoms to help their review of the imaging. For example, a history of pain along cranial nerve V2 distribution prompts a second look at that relevant anatomy.

Knowledge of normal anatomy and the myriad appearances of variations in anatomy is the basis of accurate tumor staging. Comprehensive review of head and neck anatomy is not the goal of this issue of *Clinics*. Instead, our goal is to show how the AJCC manual can be a guide to interpreting computed tomography (CT) or magnetic resonance (MR) imaging of the patient with head and neck cancer. Only with a thoughtful interpretation and dictation, clearly delineating the local extent of a primary head and neck tumor, can the radiologist offer a precise description of a tumor following guidelines of AJCC, giving value to the referring clinician, tumor board members, and the patient.

Consider the patient presenting with a mass in the tonsil. The referring clinician is likely aware of the mass, so a final dictation just confirming the mass is of little value. Frequently in our head and neck tumor board (HNTB), we see outside dictations that say "Impression: Large tonsillar mass, correlate clinically, tumor cannot be excluded." Questions that remain include size ("large" is vague and of little use when following the patient), whether there is extension to the base of tongue, soft palate, or pterygoids (all of which may affect whether the patient goes for surgery or the target volumes for the radiation oncologist) and does tumor approach, invade, or surround the internal carotid artery (a finding of tremendous prognostic significance that has direct bearing on the operability of the lesion, particularly in the era of transoral resections)? The interpretation offers little guidance for staging, and therefore no direction for treatment plan or prognosis for the patient. Is the patient a surgical candidate? Are radiation and chemotherapy more appropriate for treatment? Is the tumor curable? What is the prognosis? These pertinent questions arise in the HNTB, and the imaging interpretation is critical to answering the questions that the clinicians should be asking. In turn, a multidisciplinary HNTB significantly affects patient care, and the opportunity to actively participate in the HNTB should not be missed.[2]

Table 1 is current staging for cancer of the oropharynx from AJCC7. Because the tonsil is a subsite of the oropharynx, **Table 1** should be used by the radiologist to offer a clinical stage based on imaging. Instead of reporting a large tumor, notice that gradations of size that affect tonsillar cancer stage are 2 cm or smaller (**Fig. 1**), more than 2 to less than 4 cm (**Fig. 2**), or greater than 4 cm. Report the actual tumor size as opposed to only the T stage.

Note that T1 and T2 are based exclusively on size. For T3 stage, size is important, greater than 4 cm, but presence of tumor on the epiglottis is important. More precisely, extension to the mucosal surface facing the oropharynx (the lingual surface) is another critical observation (**Fig. 3**). Therefore, both size and extension to the lingual epiglottic surface should be mentioned.

For all head and neck subsites, the T4 staging is now divided into "moderately advanced," or "very advanced" local disease. T4 tumors by definition have extended out of the boundaries of that subsite and involve surrounding sites. For staging a T4a oropharyngeal tumor, the radiologist must be able to identify the supraglottic larynx, extrinsic tongue muscles (the hyoglossus, styloglossus, genioglossus, and mylohyoid muscles), medial pterygoid muscle, hard palate, and mandible, because extension to 1 or more of those sites

Table 1
AJCC7 oropharynx primary site staging

	Primary Tumor (T)
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but not >4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to the lingual surface of epiglottis
T4a	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible[a]
T4b	Very advanced local disease. Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

[a] Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.

From Edge S, Byrd D, Compton C, et al. AJCC cancer staging manual. 7th edition. Chicago: Springer; 2010. p. 41–56; with permission.

infers the T4a stage (Fig. 4). T4b or "very advanced local disease" means that an oropharyngeal tumor has invaded the lateral pterygoid muscle or pterygoid plates, the lateral nasopharynx, skull base, or is circumferential around the internal carotid artery.

Because of its detail, the AJCC staging manual is a wonderful guide for cross-sectional image interpretation, and facilitates generating a useful, value-added CT or MR dictation for a patient with cancer of the tonsil. Overall, using the AJCC

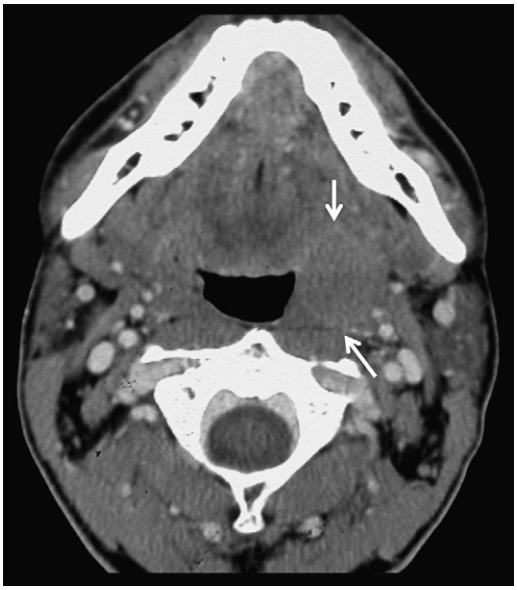

Fig. 2. Oropharyngeal SCC, tonsil subsite, stage T2 N0. Left tonsil mass (*arrows*) is greater than 2 cm, but less than 4 cm in maximum diameter.

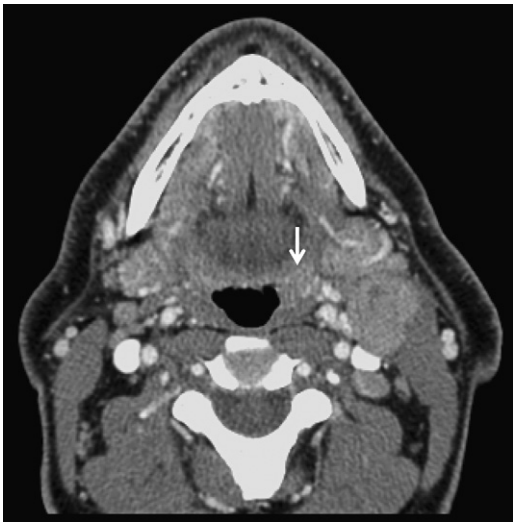

Fig. 1. Oropharyngeal SCC, tonsil subsite, stage T1 N2b. Small left tonsil mass (*arrow*) is less than 2 cm. Notice bulky left anterior and posterior IIA adenopathy. Patient was a nonsmoker and tumor was HPV-16 positive.

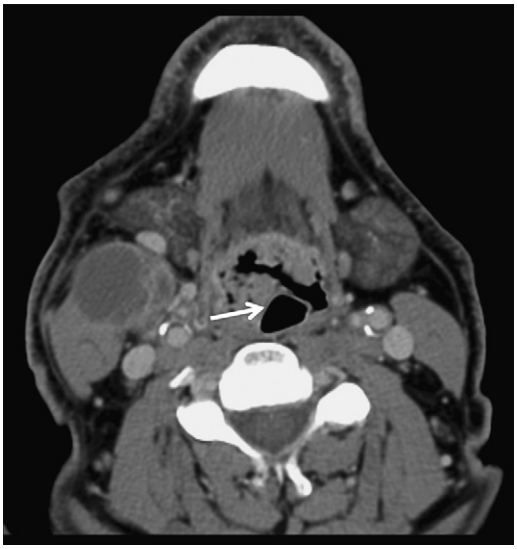

Fig. 3. Oropharyngeal SCC, tonsil subsite, stage T3 N2a. Right tonsil mass extends inferiorly to involve the lingual surface of the epiglottis (*arrow*). Bulky necrotic ipsilateral IIA nodal mass is also present.

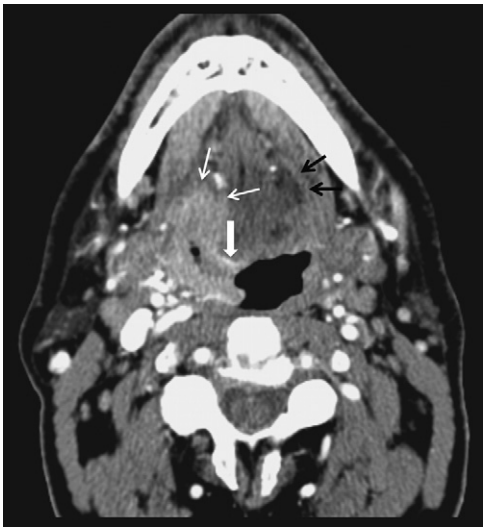

Fig. 4. Oropharyngeal SCC, tonsil subsite, stage T4a. Right oropharyngeal mass likely originated in tonsil, and has extended to base of tongue (*thick white arrow*) and to floor of mouth (*thin white arrows*), an oral cavity site. Note normal left hyoglossus muscle, an extrinsic tongue muscle (*black arrows*). Tumor has replaced right hyoglossus muscle. Based on involvement of hyoglossus muscle, tumor is staged as T4a or moderately advanced local disease.

manual guides the radiologist in making the most useful interpretations of the imaging.

NODAL STAGING

Nodal staging has a significant impact on prognosis for patients with head and neck cancer.[3–5] Designation of N0 denotes no metastatic adenopathy, and N1, N2, and N3 describe increasing number and size of nodes. Nodal staging can be pathologic, either by fine-needle aspiration (FNA) or surgical node dissection, or by imaging if there is unequivocal cross-sectional or metabolic [^{18}F] fluorodeoxyglucose (FDG)-positron emission tomography (PET) evidence of disease. For example, a patient with a new neck mass may undergo FNA of the node, and the diagnosis of squamous cell carcinoma (SCC) may be made. A search for the primary tumor via conventional physical examination, imaging, and endoscopy follows. If multiple nodes are present on CT, MR imaging, or PET-CT, the nodal staging can be designated even if pathologic FNA is not performed on each node. It is crucial to evaluate the imaging carefully and accurately; treatment decisions are frequently made based on imaging.

The standard anatomic nodal description used universally by health care professionals should be routinely adopted by radiologists (**Table 2**).[6,7] This description of node location is used in the head and neck regardless of location of the primary cancer. Node groups that are not covered by the standard nodal system but may be involved with head and neck cancer are suboccipital, retropharyngeal, parapharyngeal, buccinator or facial nodes, preauricular, periparotid, or intraparotid.[1]

Cross-sectional imaging, although critical to nodal staging, carries poor sensitivity for detecting subclinical nodal metastases, especially micrometastases.[8] Microscopic nodal metastases cannot be detected by any current imaging modality. Size and central necrosis are criteria used routinely to detect macroscopic disease. Central nodal necrosis (in the absence of acute suppurative nodal infection) always denotes macroscopic metastatic disease. Nodal size is less sensitive for detecting metastasis, and less specific, because normal reactive nodes are variable in size. Choosing 8-mm to 10-mm short or long axis diameter as the size criteria for reporting

Table 2
AJCC oropharynx and hypopharynx lymph node staging

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, $\leq$3 cm in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N2a	Metastasis in single ipsilateral lymph node >3 cm but not >6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N3	Metastasis in a lymph node >6 cm in greatest dimension

From Edge S, Byrd D, Compton C, et al. AJCC cancer staging manual. 7th edition. Chicago: Springer; 2010. p. 41–56; with permission.

a node as positive likely has high sensitivity, but low specificity, because many normal reactive nodes can be more than 10 mm in diameter. PET-CT has greatly improved nodal staging[9] but reactive nodes can be metabolically active on PET. A neck dissection has the best sensitivity for nodal staging, but nonsurgical management of neck disease is currently the mainstay for SCC of several subsites. The staging system takes into account the macroscopic staging of the neck, and the probability of subclinical disease should not lessen the radiologist's diligence in evaluating the neck. The radiologist should make every attempt to accurately stage the neck, using any imaging available as well as understanding the patterns of nodal metastasis.

Lymphatic drainage for head and neck cancer is frequently predictable, and nodal staging can be more precise when the radiologist is familiar with the drainage patterns for anatomic subsites.[8,10] In a patient with head and neck squamous cell carcinoma (HNSCC), metastases to nodes in levels II and III are common, whereas nodes in level V are less likely to harbor SCC metastases.

One change between the AJCC sixth edition and the current edition is that a descriptor has been added for extracapsular spread (ECS) of nodal disease, denoted as ECS+ or ECS–.[1] When describing a node that is likely pathologic, the radiologist should attempt to determine ECS. Clinically, ECS manifests as a neck mass that is fixed to overlying skin, surrounding muscle, or fibroadipose tissue, or has signs of cranial nerve extension. Radiographically, ECS can be presumed if the nodal margins are irregular or there is surrounding perinodal stranding and induration.[11,12] ECS of disease carries a poor outcome compared with intact nodal capsule.[13–15]

LIMITATIONS TO CROSS-SECTIONAL STAGING

Imaging is not perfect, and the best radiologist knows the limitations of each modality. In the head and neck, each separate subsite has imaging constraints that are specific for both location and modality. These constraints are discussed elsewhere in this issue. A common imaging limitation (tumor boundaries) deserves special mention.

Lesion size is a critical factor that is generally the major criterion that determines stage. The ability to define boundaries of a lesion with imaging is essential, and is related to several factors, including lesion size, vascularity and enhancement, and contrast between the mass and surrounding normal tissue. When mucosal lesions in the head and neck are small and superficial, with no deep invasion, even the best CT and MR imaging do not depict the mass. In that case, the formal interpretation could say, for example, "although there is a known lateral oral tongue mass, the contrast-enhanced CT is normal." Similarly, if there are no large or necrotic cervical lymph nodes in the locations routinely involved with a certain tumor subsite, the final impression should read "no significant cervical adenopathy, nodal disease is N0."

It should be obvious that accurate staging requires high-quality CT and MR imaging techniques. Careful attention to parameters that determine resolution and decrease artifacts, and intravenous contrast amount and timing, are necessary because they affect the accuracy of staging. Technologists should instruct the patient to remain still in the scanner, breathe normally during scan acquisition, and align the head and neck so that images are relatively straight, to optimize comparison of the normal and abnormal sides. In general, for both CT and MR imaging, slice thickness of 3 mm or less is necessary.[16] Thinner slices are important for coronal or sagittal reconstruction, because tumors of virtually every subsite have invasion patterns best appreciated in the nonaxial plane. For example, extension of a supraglottic mass across the laryngeal ventricle is best depicted in the coronal plane. Destruction of the extracranial surface of the sphenoid bone is often seen only in a nonaxial plane.

CT scan acquisition times are so fast that unless there is a built-in delay to obtain images, the CT may be optimized for CT angiography and not a soft tissue study. We have found a longer delay best for CT neck imaging because it allows for mucosal enhancement and showing tumor boundaries. The longer delay is best to detect nodal necrosis.

The current trend is to obtain PET-CT for initial staging of head and neck cancer, a practice that is supported in the literature.[17,18] Combined anatomic and physiologic imaging improves detection of the unknown primary and more accurately stages nodal disease than either technique alone. At our institution, all patients presenting with a new HNSCC undergo PET-CT for staging. One exception is a T1 glottic laryngeal carcinoma, which is accurately staged at endoscopy and has a low propensity for nodal metastases. For almost all other malignancies of the head and neck, the PET portion is interpreted by the nuclear medicine physicians, the contrast-enhanced CT by the head and neck radiologists, and 2 separate dictations are generated after the 2 groups consult with each other. If the findings on the PET and CT are concordant, that is mentioned in the final report. If the PET and CT are discordant (eg, if a metastatic node is detected on PET but has no malignant CT

characteristics), a comment is made about which modality is more likely to be accurate or a method to resolve the difference is offered, typically an image-guided FNA.

AJCC7

Two important changes were made for staging head and neck cancer in the most recent edition. First, the terms "resectable" and "unresectable" were replaced with T4a "moderately advanced" and T4b "very advanced" when referring to the primary site. For virtually all the head and neck subsites, tumor encasing the internal or common carotid arteries upstages to T4b. For oral cavity cancer, extension to the masticator space, pterygoid plates, or skull base also describes T4b disease. For an oropharyngeal primary, tumor invading the lateral pterygoid muscles, pterygoid plates, lateral nasopharynx, or skull base describes T4b disease. For the larynx and hypopharynx, tumors invading the prevertebral space or fascia or extending to the mediastinum are T4b descriptors. T4 nasopharyngeal staging, which is not subdivided into a or b, includes intracranial extension, cranial nerve involvement, hypopharyngeal or orbital extension, or invasion of the infratemporal fossa or masticator space.

Therefore, to incorporate the changes into practice, it is important for the interpreting radiologist to be familiar with the boundaries of each of the subsites, and to be able to identify the carotid artery, masticator space, the pterygoid plates, relevant muscles, the mediastinum, and the prevertebral space.

LIMITATIONS TO AJCC7 AND ANATOMIC STAGING

Because the revision cycle for staging is 6 to 8 years, scientific discoveries may occur that are not incorporated into the staging system. Thus, nonanatomic and biologic factors such as tumor type and grade, and HPV status, for example, are also considered when planning treatment. Anatomic characteristics remain the basis of staging, but additional factors are increasingly recognized as important when predicting prognosis. Although tumor stage, based on local and distant disease, has historically predicted survival, the molecular biology and status may play a more important role in determining prognosis and survival.[19] An HNTB, comprising specialists from all disciplines, therefore, is the single best way to assess each individual patient.

Pathologic characteristics of an individual tumor are not reflected in TNM staging. After biopsy or tumor resection, specifics of the tumor can be described: the degree of tumor differentiation (well, poor, or undifferentiated), presence of perineural invasion, and tumor vascularity, or microvascular density. Treatment recommendations from the HNTB therefore take more than just TNM stage into consideration.

There are important molecular factors that affect tumor development, and tumor resistance to radiotherapy and chemotherapy. The most important new development in head and neck cancer is the recognition of sexually transmitted HPV as a factor in HNSCC of the oropharynx. Base of tongue and tonsil cancers are associated with HPV-16 infections.[20,21] HPV-16 and HPV-18 have been recognized for many years as associated with cervical cancer, but the association with oropharyngeal cancer has been confirmed relatively recently. When there is HPV-16 infection, viral oncoproteins E6 and E7 inactivate p53 and pRb, both tumor suppressor proteins, disturbing cell cycle regulation.[22–24] Patients with HPV-16–associated oropharyngeal cancer, compared with tobacco-associated and alcohol-associated cancer, tend to be younger, and generally have a better prognosis. Proto-oncogenes that code for proteins promoting cellular proliferation, tumor suppressor genes that inhibit cellular proliferation, and a variety of growth factors that change the local microenvironment are all important in prognosis but are not routinely reflected in TNM staging.

HNSCC is therefore biologically heterogeneous, from patient to patient, and tumor environment in the same patient likely differs significantly on the molecular level within the primary lesion itself.

SUMMARY

It should be obvious that imaging-trained and subspecialty-trained radiologists, in combination with the physical examination and pathologic specimen, are essential to stage head and neck cancers (other than skin). The ear, nose, and throat surgeon or radiation oncologist can identify the primary site if there is a mucosal lesion, and can report palpable neck nodes. But these are crude measures of a head and neck tumor, and only cross-sectional imagers can determine the size or local extent of a tumor, and small necrotic or metabolically active nonpalpable lymph nodes. The exception is a T1 superficial mucosal tumor, best staged by direct visualization. When there is no deep invasion, CT or MR imaging may be normal, but even a normal study helps to confirm a T1 lesion.

The objectives of this issue of *Clinics* are to clearly describe the anatomic subsites of the head and neck, summarize the factors that can help stage a tumor in each of the subsites, and emphasize the anatomic structures that the radiologist must examine before assigning a stage. With AJCC7 as a guidebook, staging head and neck cancer is the subspecialty-trained radiologist's responsibility.

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