Current Oncology Reports (2019) 21: 52
https://doi.org/10.1007/s11912-019-0799-x

HEAD AND NECK CANCERS (EY HANNA, SECTION EDITOR)

Changes in the 8th Edition of the American Joint Committee on Cancer (AJCC) Staging of Head and Neck Cancer: Rationale and Implications

Daniella Karassawa Zanoni[1] · Snehal G. Patel[1] · Jatin P. Shah[1]

Published online: 17 April 2019

Abstract

Purpose of Review The objectives of this article are to review the major changes in the staging of head and neck cancers and the rationale for the modifications.

Recent Findings Information gathered from various institutional reports lead to a better understanding of the clinical and biological behavior of head and neck tumors, resulting in distinct outcomes, which were used to update the staging system.

Summary This article reviews the changes in the staging of head and neck cancers published in the 8th edition of the AJCC/UICC TNM staging system.

Keywords TNM staging · Head and neck cancer · Squamous cell carcinoma · Thyroid cancer · HPV-related oropharyngeal cancer

Introduction

The American Joint Committee on Cancer (AJCC)/ International Union Against Cancer (UICC) staging system is a tool which provides clinicians across the world with the ability to stage cancer prior to any treatment (cTNM), after surgical resection (pTNM), and at recurrence (rTNM). Staging stratifies patients into various prognostic groups. Based on the stage of the disease, it is possible to select best treatment option, plan the treatment, and estimate prognosis.

In 1944, Pierre Denoix proposed a staging system for solid tumors based on tumor characteristics (T), nodal spread (N), and distant metastasis (M) [1]. The UICC adopted this system in 1954. The AJCC was established in 1958. The UICC and AJCC worked independently for nearly 25 years and had separate staging systems for classification of cancer. The first edition of the AJCC/UICC TNM classification was published in 1987. Since then, the TNM classification has been widely used not only to plan treatment and to reliably estimate the prognosis of patients but also to evaluate treatment results and to compare outcomes between institutions in different parts of the world [1, 2].

The simplicity of TNM staging makes it the most accepted and used system in clinical practice. In order to increase acceptance and compliance, by design, the TNM staging system has to be kept simple and user-friendly. A highly complex staging system may be most accurate, but may not be easy to accept in clinical practice, and thus will have poor compliance. Therefore, some important prognostic information (tumor and host factors) are often not included in the staging system to keep it simple and increase compliance. Each new edition of the AJCC/UICC staging manual incorporates changes and improves the prognostic accuracy and predictability. The major modifications in the 8th edition were changes in the T category for oral cavity cancer by incorporating depth of invasion of the primary tumor; inclusion of extranodal extension in N staging except in p16+ oropharynx cancer and nasopharynx cancer; the division of the pharynx chapter into one chapter for oropharynx (p16−) and hypopharynx, a separate chapter describing the staging system for human papillomavirus related (p16+) oropharyngeal cancer, and a third separate chapter for nasopharynx; new head-and-neck-specific cutaneous malignancy and soft tissue sarcoma chapters; and changes in the age cutoff and N categories for staging of thyroid cancer. These modifications were based on information gathered from various institutional reports leading to a

This article is part of the Topical Collection on *Head and Neck Cancers*

✉ Jatin P. Shah
shahj@mskcc.org

[1] Head and Neck Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA

Table 1 Primary tumor (T) definition for oral cavity cancers

TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm and DOI ≤ 5 mm
T2	Tumor ≤ 2 cm, DOI > 5 mm, and ≤ 10 mm *or* tumor > 2 cm and ≤ 4 cm and DOI ≤ 10 mm
T3	Tumor > 4 cm *or* any tumor with DOI > 10 mm
T4	
T4a	Tumor invades adjacent structures only (e.g., through cortical bone of mandible or maxilla, or involves the maxillary sinus or skin of the face)
T4b	Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

AJCC is currently discussing further refinement of T-stage stratification for small tumors (< 2 cm) with DOI > 10 mm

DOI depth of invasion

From: Amin et al. [3]

better understanding of the clinical and biological behavior of these tumors, resulting in distinct outcomes [3].

Twenty-eight specialists from various disciplines with expertise and knowledge in head and neck cancer biology and staging formed the AJCC Head and Neck Task Force. The group analyzed in detail chapters from the 7th edition and proposed changes to incorporate new information. When the task force recommended changes, additional analyses were performed to confirm if there is available data to support the modifications [4•]. The aim of this article is to review some of the major changes in the staging of head and neck cancers and the rationale for the modifications that were published in the 8th edition of the AJCC/UICC TNM staging system.

Table 2 Clinical assessment of regional lymph nodes (cN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm and ENE−
N2	Metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm and ENE−; *or* metastases in multiple ipsilateral lymph nodes, ≤ 6 cm and ENE−; *or* in bilateral or contralateral lymph nodes, ≤ 6 cm and ENE−
N2a	Metastasis in a single ipsilateral lymph node >3 cm and ≤ 6 cm and ENE−
N2b	Metastases in multiple ipsilateral lymph nodes, ≤ 6 cm and ENE−
N2c	Metastases in bilateral or contralateral lymph nodes, ≤ 6 cm and ENE−
N3	Metastasis in a lymph node > 6 cm and ENE−; *or* metastasis in any lymph node(s) with ENE+ clinically
N3a	Metastasis in a lymph node > 6 cm and ENE−
N3b	Metastasis in any lymph node(s) with ENE+ clinically

From: Amin et al. [3]

Table 3 Pathological assessment of regional lymph nodes (pN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm and ENE−
N2	Metastasis in a single ipsilateral lymph node, ≤ 3 cm and ENE+; *or* metastasis in a single ipsilateral lymph node >3 cm and ≤ 6 cm and ENE−; *or* metastases in multiple ipsilateral lymph nodes, ≤ 6 cm and ENE−; *or* in bilateral or contralateral lymph nodes, ≤ 6 cm and ENE−
N2a	Metastasis in a single ipsilateral lymph node, ≤ 3 cm and ENE+, *or* metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm and ENE−
N2b	Metastases in multiple ipsilateral lymph nodes, ≤ 6 cm and ENE−
N2c	Metastases in bilateral or contralateral lymph nodes, ≤ 6 cm and ENE−
N3	Metastasis in a lymph node > 6 cm and ENE-; *or* metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE+; *or* multiple ipsilateral, contralateral, or bilateral nodes, any with ENE+; *or* a single contralateral node of any size and ENE+
N3a	Metastasis in a lymph node > 6 cm and ENE−
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE+; *or* multiple ipsilateral, contralateral, or bilateral nodes, any with ENE+; *or* a single contralateral node of any size and ENE+

From: Amin et al. [3]

Oral Cavity Cancer

Traditionally, the greatest dimension of the tumor was the most important characteristic for the T stage categories in oral cancer. Since depth of invasion (DOI) has been shown to have

Table 4 Primary tumor (T) definition for nasopharyngeal cancers

TX	Primary tumor cannot be assessed
T0	No tumor identified, but EBV+ cervical node(s) involvement
Tis	Carcinoma in situ
T1	Tumor confined to nasopharynx, or extension to oropharynx, and/or nasal cavity without parapharyngeal involvement
T2	Tumor with extension to parapharyngeal space, and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle

From: Amin et al. [3]

Table 5 Assessment of regional lymph nodes (N) in nasopharyngeal cancers

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), ≤ 6 cm, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), ≤ 6 cm, above the caudal border of cricoid cartilage
N3	Unilateral or bilateral metastasis in cervical lymph node(s), > 6 cm, and/or extension below the caudal border of cricoid cartilage

From: Amin et al. [3]

prognostic implications, with deeper tumors showing an increased risk of nodal metastases and decreased disease-specific survival, this parameter was included in the categorization of T stages in the AJCC 8th edition (Table 1) [5•]. Clinical assessment of accurate DOI can be challenging but differentiation among thin (≤ 5 mm), intermediate (> 5 mm and ≤ 10 mm), and thick (> 10 mm) lesions is usually possible in the hands of experienced head and neck surgeons.

In the past, lip was included in oral cavity primary sites. Lip is now divided into mucosal and cutaneous lip. Mucosal lip is included in oral cavity.

The N category was also modified in the 8th edition. Extranodal extension (ENE) has been shown to have a profound effect on prognosis of most head and neck cancers, except for tumors associated with HPV, and therefore, it was incorporated in the N category [6•]. In order to clinically classify the disease as ENE+, unambiguous evidence of ENE in clinical examination supported by strong radiological evidence ENE must be present. Note that once clinical ENE is detected, the disease is cN3b. In case of doubt, the lower category should be assigned (ENE−) [3]. Clinical and pathological N stage categories for squamous cell carcinomas of the oral cavity and all other head and neck sites (except for HPV-related oropharynx, nasopharynx, melanoma, thyroid, and sarcoma) are described in Tables 2 and 3, respectively.

Table 6 AJCC prognostic stage groups for nasopharyngeal cancers

0	TisN0M0
I	T1N0M0
II	T0N1M0, T1N1M0, T2N0M0, or T2N1M0
III	T0N2M0, T1N2M0, T2N2M0, T3N0M0, T3N1M0, or T3N2M0
IVA	T4N0M0, T4N1M0, T4N2M0, T0N3M0, T1N3M0, T2N3M0, T3N3M0, or T4N3M0
IVB	Any T, any N, and M1

From: Amin et al. [3]

Table 7 Primary tumor (T) definition for HPV-related (p16-positive) oropharyngeal cancers

T0	No tumor identified, but p16+ cervical node(s) involvement
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm
T2	Tumor > 2 cm and ≤ 4 cm
T3	Tumor > 4 cm or extension to lingual surface of the epiglottis
T4	Moderately advanced local disease; tumor invades larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond

From: Amin et al. [3]

Nasopharyngeal Cancer

Nasopharyngeal cancers (NPC) have a unique biology and were given a separate chapter in the AJCC 8th edition. The major changes are the inclusion of a T0 category for patients with Epstein–Barr virus (EBV) -positive metastatic cervical lymph nodes with unknown primary, clarification to avoid ambiguity for the other T categories, and changes in the regional lymph node definition. Unlike the other head and neck cancer sites for which surgery plays an important role in primary treatment, NPC is treated primarily with radiotherapy with or without chemotherapy. For this reason, pathological classification is not relevant in this disease. Tables 4, 5, and 6 describe the tumor, node, and overall stage classification of NPC, respectively [3].

Oropharyngeal Cancer

Human papillomavirus (HPV)-related or p16-positive oropharyngeal cancer (OPC) is a different entity that occurs more frequently in younger individuals, with little or no tobacco exposure, and that usually shows excellent response to treatment even in patients with advanced stage disease. The incidence of OPC associated with HPV has been rising since 1990, and the observation of the diverse clinical and biological behavior of p16-positive OPC versus p16-negative OPC has been reported by many authors [7, 8]. Because it behaves as a completely different disease when compared to p16-

Table 8 Clinical assessment of regional lymph nodes (cN) in HPV-related (p16-positive) oropharyngeal cancers

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes ≤ 6 cm
N2	Contralateral or bilateral lymph nodes ≤ 6 cm
N3	Lymph node(s) > 6 cm

From: Amin et al. [3]

Table 9 Pathological assessment of regional lymph nodes (pN) in HPV-related (p16-positive) oropharyngeal cancers

pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastases in more than 4 lymph nodes

From: Amin et al. [3]

negative OPC, a separate staging system was developed for HPV-related (p16-positive) OPC [9•]. However, the T categories for both p16-positive and p16-negative OPC remain similar. The main differences are the following: Tis is not included in p16-positive OPC; T0 (unknown primary in patients with metastatic nodes tested positive for p16) category is only used in p16-positive metastatic nodes, where the primary is presumed to be OPC, and the T4b category has been removed from p16-positive OPC. Table 7 describes the T categories for p16-positive OPC. The clinical N staging categories for p16-positive disease are shown in Table 8. Ipsilateral nodes (one or multiple), none larger than 6 cm are staged N1. Contralateral or bilateral nodes are classified as N2, as long as none of them is larger than 6 cm. Nodes that are greater than 6 cm are included in N3 category. Pathological staging is only applicable to patients who are treated with surgery. For HPV-related (p16-positive) OPC treated with surgery, an important change in behavior is observed when the number of positive nodes was between 1 and 4 versus 5 or more [3]. This was incorporated in pN staging for p16-positive tumors. The pathological N categories for HPV-related (p16-positive) OPC are shown in Table 9. The clinical and pathological prognostic stage groups are described in Tables 10 and 11.

Cutaneous Carcinoma of the Head and Neck

Staging of skin cancers was developed by a multidisciplinary team to create a system for nonmelanoma skin cancers of the head and neck. It encompasses 82 different types of skin cancers excluding melanoma and Merkel cell carcinoma. The cutaneous lip consisting of the keratinizing epithelium of the vermilion border is included in this classification. In spite of expected diversity among skin cancers that are included in this group, basal cell carcinomas and squamous cell carcinomas are the most common varieties in the head and neck area. A decision was made for a common staging system because it would not be feasible to have a meaningful system for each of the individual histologic types. This new chapter was created to emphasize the importance of staging these tumors in the head and neck area. T categories are based on independent risk factors for poor prognosis [10]. Table 12 describes the T categories for cutaneous carcinomas of the head and neck.

Table 10 AJCC prognostic clinical stage groups for HPV-related (p16-positive) oropharyngeal cancers

I	T0N1M0, T1N0M0, T1N1M0, T2N0M0, or T2N1M0
II	T0N2M0, T1N2M0, T2N2M0, T3N0M0, T3N1M0, or T3N2M0
III	T0N3M0, T1N3M0, T2N3M0, T3N3M0, T4N0M0, T4N1M0, T4N2M0, or T4N3M0
IV	Any T, any N, and M1

From: Amin et al. [3]

Table 11 AJCC prognostic pathological stage groups for HPV-related (p16-positive) oropharyngeal cancers

I	T0N1M0, T1N0M0, T1N1M0, T2N0M0, or T2N1M0
II	T0N2M0, T1N2M0, T2N2M0, T3N0M0, T3N1M0, T4N0M0, or T4N1M0
III	T3N2M0, or T4N2M0
IV	Any T, any N, and M1

From: Amin et al. [3]

Head and Neck Soft Tissue Sarcoma

Sarcomas of the head and neck are separately staged from the general soft tissue sarcomas of the trunk and extremities because that staging system did not suit this anatomic region. The size cutoffs for T are changed to 2 and 4 cm (T1 ≤ 2 cm, T2 > 2 cm and ≤ 4 cm, T3 > 4 cm, T4 tumor invades adjoining structures). Nodal disease is uncommon and is staged as N0 (when no regional lymph node metastases are present or if the lymph node status is unknown) or N1 (lymph node metastasis is present) [3].

Table 12 Primary tumor (T) definition for cutaneous carcinomas of the head and neck

TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm
T2	Tumor > 2 cm and ≤ 4 cm
T3	Tumor >4 cm *or* minor bone erosion *or* perineural invasion *or* deep invasion*
T4	Tumor with gross cortical bone/marrow, skull base invasion and/or skull base foramen invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement

*Deep invasion is defined as invasion beyond the subcutaneous fat or > 6 mm (as measured from granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression

From: Amin et al. [3]

Table 13 Primary tumor (T) definition for papillary, follicular, poorly differentiated, Hurthle cell, and anaplastic thyroid carcinoma

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 2 cm limited to the thyroid
T1a	Tumor ≤ 1 cm limited to the thyroid
T1b	Tumor > 1 cm but ≤ 2 cm limited to the thyroid
T2	Tumor > 2 cm and ≤ 4 cm limited to the thyroid
T3	Tumor > 4 cm limited to the thyroid *or* gross extrathyroidal extension invading only strap muscles
T3a	Tumor > 4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size
T4	Includes gross extrathyroidal extension into major neck structures
T4a	Gross extrathyroidal extension invading subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing carotid artery or mediastinal vessels from a tumor of any size

All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest tumor determines the classification)

From: Amin et al. [3]

Thyroid

Significant changes were made in thyroid cancer staging. Modifying the age cutoff from 45 to 55 years of age [11•] and excluding microscopic extrathyroidal extension from the definition of T3 resulted in downstaging a significant number of patients. Downstaging these patients correctly fitted them into the right group according to their risk for dying from thyroid cancer [12]. Table 13 describes the definition of the primary tumor (T). The definition of nodal metastases is also revised. Metastatic lymph nodes in the central neck (levels VI and VII) are now staged as N1a. Lymph nodes in the lateral neck are staged N1b (Table 14). In the previous editions, all anaplastic thyroid cancers were staged as T4. In this new edition, anaplastic thyroid cancers are classified using the same definitions for T category as differentiated thyroid cancer. Tables 15 and 16 describe the prognostic stage groups for differentiated and anaplastic thyroid cancers, respectively.

Table 14 Assessment of regional lymph node (N)

NX	Regional lymph nodes cannot be assessed
N0	No evidence of locoregional lymph node metastasis
N0a	One or more cytological or histologically confirmed benign lymph node
N0b	No radiologic or clinical evidence of locoregional metastasis
N1	Metastasis to regional nodes
N1a	Metastases to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease
N1b	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph nodes

From: Amin et al. [3]

Table 15 AJCC prognostic stage groups for differentiated thyroid cancer

When age at diagnosis is…	And T is…	And N is…	And M is…	Then the stage group is…
< 55 years	Any T	Any N	M0	I
< 55 years	Any T	Any N	M1	II
≥ 55 years	T1	N0/NX	M0	I
≥ 55 years	T1	N1	M0	II
≥ 55 years	T2	N0/NX	M0	I
≥ 55 years	T2	N1	M0	II
≥ 55 years	T3a/T3b	Any N	M0	II
≥ 55 years	T4a	Any N	M0	III
≥ 55 years	T4b	Any N	M0	IVA
≥ 55 years	Any T	Any N	M1	IVB

From: Amin et al. [3]

Improving the TNM Staging System

The goal of updating the staging system is to use new knowledge about the disease to develop a model to predict outcomes better than the previous editions. Advances in understanding the behavior of the disease and risk factors, as well as new imaging technologies, and emerging new therapies can improve outcomes. For this reason, periodically revising the outcome prediction capability of the staging system is needed. Keeping the staging system as simple as possible is important to make it universally used and to standardize the way head and neck oncologists present and discuss their results. A simple system, however, will not allow for an accurate personalized prognostic

Table 16 AJCC prognostic stage groups for anaplastic thyroid cancer

When T is…	And N is…	And M is…	Then the stage group is…
T1–T3a	N0/NX	M0	IVA
T1–T3a	N1	M0	IVB
T3b	Any N	M0	IVB
T4	Any N	M0	IVB
Any T	Any N	M1	IVC

From: Amin et al. [3]

tool. Nomograms are calculation devices that have been widely tested in a variety of cancers, including in the head and neck [13–19]. This prediction tool is dynamic, personalized, and can predict prognosis individually with a higher accuracy. Therefore, nomograms will likely be widely used in the near future.

Conclusions

Since the 1940s when it was first described, the TNM staging system has been continuously used for cancer prognostication. Its user-friendliness has allowed it to be implemented and used worldwide. With the understanding of many other tumor and host factors that can influence outcomes, it will be challenging to create a tool as simple as the TNM that can incorporate all these factors.

Funding Information This work was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

Compliance with Ethical Standards

Conflict of Interest Daniella Karassawa Zanoni, Snehal G. Patel, and Jatin P. Shah declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Denoix PF. Note on the possible role of the International Union against Cancer in nomenclature, classification, analytical index, bibliography and documentation. Acta Unio Int Contra Cancrum. 1952;8(Special No):92–6.
2. (UICC), T.U.f.I.C.C. *TNM* History*, Evolution and Milestones*. 2017; Available from: https://www.uicc.org/sites/main/files/atoms/files/TNM_History_updated_June2017.pdf.
3. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. editors. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing: American Joint Commission on Cancer; 2017.
4.• Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, et al. Head and neck cancers–major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(2):122–37. **This article describes the most significant modifications of the staging system**.
5.• International Consortium for Outcome Research (ICOR) in Head and Neck Cancer), Ebrahimi A, Gil Z, Amit M, Yen TC, Liao CT, et al. Primary tumor staging for oral cancer and a proposed modification incorporating depth of invasion: an international multicenter retrospective study. JAMA Otolaryngol Head Neck Surg. 2014;140(12):1138–48. **This retrospective study included a large cohort of oral cancer patients from multiple centers in the world and identified optimal cutpoints for depth of invasion. The models that were evaluated in this study were used to define the changes in the T category of the AJCC 8th edition.**
6.• Wreesmann VB, Katabi N, Palmer FL, Montero PH, Migliacci JC, Gonen M, et al. Influence of extracapsular nodal spread extent on prognosis of oral squamous cell carcinoma. Head Neck. 2016;38 Suppl 1:E1192-E1199. **This study evaluated the microscopic extent of extranodal extension and its prognostic implications for oral cancer**.
7. Ang KK, Sturgis EM. Human papillomavirus as a marker of the natural history and response to therapy of head and neck squamous cell carcinoma. Semin Radiat Oncol. 2012;22(2):128–42.
8. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29(32):4294–301.
9.• O'Sullivan B, Huang SH, Su J, Garden AS, Sturgis EM, Dahlstrom K, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. Lancet Oncol. 2016;17(4):440–51. **This study included a large number of patients from multiple centers to create a better staging system for patients with HPV-related oropharyngeal cancer**.
10. Skulsky SL, O'Sullivan B, McArdle O, Leader M, Roche M, Conlon PJ, et al. Review of high-risk features of cutaneous squamous cell carcinoma and discrepancies between the American Joint Committee on Cancer and NCCN Clinical Practice Guidelines In Oncology. Head Neck. 2017;39(3):578–94.
11.• Nixon IJ, Wang LY, Migliacci JC, Eskander A, Campbell MJ, Aniss A, et al. An international multi-institutional validation of age 55 years as a cutoff for risk stratification in the AJCC/UICC staging system for well-differentiated thyroid cancer. Thyroid. 2016;26(3):373–80. **This international retrospective study showed that changing the cutpoint age from 45 to 55 years could prevent overstaging patients with low-risk disease and better estimate prognosis**.
12. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on cancer/tumor-node-metastasis staging system for differentiated and anaplastic thyroid cancer (eighth edition): what changed and why? Thyroid. 2017;27(6):751–6.
13. Chen F, Lin L, Liu F, Yan L, Qiu Y, Wang J, et al. Three prognostic indexes as predictors of response to adjuvant chemoradiotherapy in patients with oral squamous cell carcinoma after radical surgery: a large-scale prospective study. Head Neck. 2019;41(2):301-308.
14. Bobdey S, Mair M, Nair S, Nair D, Balasubramaniam G, Chaturvedi P. A nomogram based prognostic score that is superior to conventional TNM staging in predicting outcome of surgically treated T4 buccal mucosa cancer: time to think beyond TNM. Oral Oncol. 2018;81:10–5.
15. Hay A, Migliacci J, Zanoni DK, Patel S, Yu C, Kattan MW, et al. Validation of nomograms for overall survival, cancer-specific survival, and recurrence in carcinoma of the major salivary glands. Head Neck. 2018;40(5):1008–15.
16. Montero PH, Yu C, Palmer FL, Patel PD, Ganly I, Shah JP, et al. Nomograms for preoperative prediction of prognosis in patients with oral cavity squamous cell carcinoma. Cancer. 2014;120(2):214–21.
17. Pan JJ, Ng WT, Zong JF, Lee SWM, Choi HCW, Chan LLK, et al. Prognostic nomogram for refining the prognostication of the proposed 8th edition of the AJCC/UICC staging system for

nasopharyngeal cancer in the era of intensity-modulated radiotherapy. Cancer. 2016;122(21):3307–15.

18. Ge MH, Cao J, Wang JY, Huang YQ, Lan XB, Yu B, et al. Nomograms predicting disease-specific regional recurrence and distant recurrence of papillary thyroid carcinoma following partial or total thyroidectomy. Medicine (Baltimore). 2017;96(30):e7575.

19. Fakhry C, Zhang Q, Nguyen-Tân PF, Rosenthal DI, Weber RS, Lambert L, et al. Development and validation of nomograms predictive of overall and progression-free survival in patients with oropharyngeal cancer. J Clin Oncol. 2017;35(36):4057–65.