Head and Neck Cancer Staging and Prognosis: Perspectives of the UICC and the AJCC

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Abstract

The prognosis of head and neck cancer is determined by numerous factors related to the patient, tumor, and health-care system. For many measures of outcomes, especially the key endpoints of organ preservation, locoregional control, occurrence of distant metastases, and survival, anatomic extent of disease remains one of the most powerful prognostic factors. This is embodied in the tumor–node–metastasis (TNM) classification, which historically has provided a very effective enabling tool to facilitate many elements of prognostication and cancer control. Traditionally, its contribution has been a codified classification and language to describe anatomic stage of disease for use in the clinic, determining eligibility and stratification for clinical trials and treatment protocols, and for comparison and surveillance of treatment results among centers and jurisdictions. More recently, momentum to include nonanatomic factors has grown, partly because it is recognized that anatomic extent of disease does not embrace all dimensions of prognosis. In particular, this relates to the quest to understand the biological dimensions of cancer, the deterministic effects of patient health, and the systems within which treatment is delivered that are needed to achieve more personalized and/or biologically driven therapies. Increasingly, there is a need in head and neck cancer to exploit new biological discoveries to permit modification of treatment and interventions in the clinic for this heterogeneous group of tumors. Because of this, the TNM staging has been criticized due to a perception that it has not been adapted sufficiently to modern needs despite its worldwide adoption. This may stem from the fact that there is no alternative uniform functional framework available to classify nonanatomic predictive and prognostic factors. The prevailing view is to regard TNM as the optimal receptacle for these factors due to its uniform appeal and success. As the field evolves, both anatomic disease extent and other factors, especially those addressing biological behavior of disease, need to be studied in their component domains as well as in combination using an agreed upon enabling taxonomy. An important strategy is to move toward constructing prognostic mod-

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els to modify the current classification, which will not only include the TNM staging information but will also include other parameters of prognosis including comorbidities, lifestyle, and biochemical or genetic markers. In addition, experts in one area (e.g., translational science or clinical trial methodology perhaps) who may rely on TNM may not always consider that the classification provides very different needs for others (e.g., health services research or screening and cancer control initiatives, etc.) and vice versa. Ignoring or dismissing one dimension of prognosis compared to another will not be fruitful and the true contribution of each will remain unappreciated, and the goals of the prognostic factor effort in head and neck cancer may be left unfulfilled.

Keywords
Head and neck cancer • Staging • Prognosis • Prognostic models

9.1 Introduction

In oncology, "to stage" a patient implies two intentions. The first uses clinical examination and investigations to describe the extent of disease to permit a rational treatment strategy to be formulated. The second employs an agreed classification system to categorize the extent of disease within risk hierarchies that predict the outcome following conventional treatment strategies. For the latter, the foremost priority is given to the risk of death and is provided by the joint primary tumor–node–metastasis (TNM) classification of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), a discussion about which will comprise much of this chapter. A challenge is to also consider new methods to enhance prognostic information and determine if these can be incorporated into or complement the traditional anatomically based classification. A variety of candidate areas exist and include features relevant to the host (or patient), the environment of the patient's treatment setting, and, finally, the assessment of the tumor itself, which has tended to receive the most emphasis. For the latter, of particular emphasis is the biological character of an individual tumor or groups of tumors. In this chapter, we discuss the importance of anatomic staging in the management of head and neck cancer and provide some perspective on the scope and application of the TNM classification and how it continues to evolve since its inception in the middle of the last century. A second component will briefly summarize the changes that were introduced in the seventh edition TNM [1, 2]. The final sections of the chapter address newer concepts including the evolving tension between anatomic staging in its current form and the value of nonanatomic methods of prognostication that need to be considered and a discussion of key issues being addressed for development of the eighth edition (see Sect. 9.9).

9.2 Achievements, Challenges/Limitations, and Opportunities of the TNM Staging System

1. Anatomic extent of disease remains one of the most powerful prognostic factors and is embodied in the TNM classification. The hegemony of the TNM results from its ability to stratify disease prognosis and provide a universally applicable and easily reproduced methodology and thus has facilitated many elements of cancer control on a global basis. Anatomic features of locoregional tumor extension are especially important in the head and neck since these underpin the management of these tumors. The static nature of TNM staging (determined at initial diagnosis) is a problem for future prognostication, for example, after several years of recurrence-free survival.
2. A major dilemma in TNM staging is the tension between the notions that frequent revisions would undermine the value conferred by the stability and universality of TNM, but a static formulation of TNM risks falling behind the state of the art in diagnostic techniques, biological concepts, biomarkers, and nonanatomic factors impacting on outcome.
3. Dimensions of prognosis are not uniform and the settings where some factors are useful to consider may not apply to other situations (e.g., early vs. advanced stage, or recurrence vs. first presentation, or important endpoint in head and neck cancer such as survival vs. organ preservation).
4. The TNM remains essential so that newer biological findings can be evaluated in the context of its existing structure. Although it has significant limitations in the era of molecular oncology, it is also needed to provide the framework for advances in biological discoveries when cohorts of patients are evaluated for prognostic or predictive outcomes.

5. Future research should focus on the evolution of biology with advancing stage since this could open the door to the potential for a true molecular-based "staging system." A major achievement of this type could override or complement traditional anatomic staging in some diseases or situations.
6. In considering prognosis in cancer, the UICC and AJCC are also focusing on *host* and *environmental* factors that may be as important as *tumor*-based prognostic factors in some settings.
7. The UICC and AJCC recognize an urgent need to achieve agreement on a new taxonomy and methodology to permit nonanatomic factors to be combined with traditional anatomic classifications while allowing the full impact of both to be explored, adopted, and used without compromise to the other. One future aim to achieve personalization and fluency over time is to move toward a prognostic nomogram, where the TNM anatomic staging will remain an important component. An intermediate step is the creation of prognostic groupings that use validated nonanatomic factors to modify the stage grouping.
8. TNM serves many purposes in cancer care, research, and control, and dismissing one dimension compared to another will not be fruitful since the true contribution of each will remain unappreciated and the goals of the prognostic factor effort in head and neck cancer may be left unfulfilled.

9.3 The Principles of Staging in Head and Neck Cancer

9.3.1 The Importance of Anatomic Staging in Head and Neck Cancer

The challenge for oncologists who manage head and neck cancers is to achieve tumor control while maximizing the opportunities for preservation or restoration of form and function. A dominant pattern of treatment failure of head and neck tumors is locoregional recurrence, making it important to have a clinical staging system that acknowledges this biological behavior and emphasizes the anatomic features of local tumor extension that underpin the management of these tumors. Clinical evaluation is a fundamental part of the assessment (i.e., palpation and visual observation of the head and neck that are almost unique to these sites because of their relative accessibility compared to other disease areas) and together with imaging studies informs a user-friendly language for the extent of disease that can be applied uniformly and consistently on a worldwide basis [3]. This traditional need to classify the extent of disease remains a paramount component of the assessment of patients with head and neck cancer and the basis for many comparisons between groups of patients and the means to develop initial treatment approaches.

As cancer approaches the concept of a chronic disease with survival extending months and years beyond the date of recurrence in selected patients, salvage of initial treatment failure also requires unique attention and diligence. Therefore, disease description at recurrence is important so that the goals of treatment are achieved and includes the ability to plan treatment and compile results that can be compared among centers and jurisdictions separately from the description of the initial treatment. Here again, a codified language to describe treatment and protocol guidelines and permit orderly reporting of results of this adverse setting is needed and is provided by an anatomic stage classification that is tailored to the recurrent scenario which in the TNM system uses the "r" prefix described later.

The TNM staging for head and neck cancer is unusual in that it encompasses multiple sites and disease types with differing etiologies, pathophysiology, and outcomes. Amalgamating all of these heterogeneous diseases into a single staging system is complicated.

9.3.2 The Evolution of the TNM Classification in Head and Neck Cancer

The TNM staging system was first proposed in 1944 by Pierre Denoix at Institut Gustave-Roussy, Paris, France [4]. The first formalization of the classification was developed by the Union for International Cancer Control (UICC) when it published the first of its brochures on cancer of the breast and larynx in 1958, to be followed by that on cancer of the buccal cavity and pharynx in 1963. This led to the classification of additional anatomic sites and their eventual compilation in 1968 as a single booklet, referred to as the *Livre de Poche*, which contained 22 body site classifications and represented the first edition of the TNM staging system [5]. Of central importance in the first edition of TNM were the classifications of head and neck cancer. These originally included buccal cavity, nasopharynx, hypopharynx, and larynx. All contained a common, though now outdated, regional lymph node classification that focused on whether lymph nodes in the neck were palpable or not and used fixity as the criterion for N3. The buccal cavity was subdivided into seven regions and a number of subsites such as "lips (red borders)" with divisions into upper and lower components. Of interest also, the oropharynx was initially allocated as a region within the buccal cavity site and did not achieve independence as a region within the head and neck until the 1974 second edition [6]. Another interesting element was that fixation of the vocal cord was classified as T2 in the first edition and only became T3 in the 1974 second edition classification following a trial period of a new proposal. Also the first edition contained only a limited attempt to combine the three different anatomic components (T–N–M) into groups that might

provide prognostic strata as stage groups. This process was confined to breast and cervix cancer as it was deemed "…in the opinion of the Union an attempt to stage group all sites would at present be immature" [5]. Importantly, this was also modified in the second edition thereby representing the first formal international attempt to prognosticate in head and neck cancer using different elements of extent of disease grouped together.

The American Joint Committee (AJC) was founded in 1959 to complement this work in the USA. Joint classifications were prepared by both organizations and distributed for trial periods before their formal adoption into the TNM classification. In 1977, the AJC introduced a TNM classification of its own [1] which had the potential for two separate classifications. This was recognized early on, and a strong collaboration between both organizations (the AJCC renamed in 1980 and UICC) has continued since, so that both classifications resemble each other as closely as possible. Nowhere is this more apparent than in the classification of the head and neck sites stewarded by the authors of this chapter representing the UICC and the AJCC.

From the outset, the TNM was intended to be an anatomic stage classification describing the anatomic extent of the primary tumor as well as the involvement and extent of regional lymph nodes and distant metastasis. It describes the anatomic extent of cancer and is based on the hypothesis that the probability of survival and the choice of treatment are related to the anatomical extent of the tumor at the primary site (T), the presence or absence of tumor in regional lymph nodes (N), and the presence or absence of metastasis beyond the regional lymph nodes (M). At present, in the head and neck sites, T is almost always divided into four major categories (T1–T4), with a further subdivision into moderately advanced local disease (T4a) or very advanced local disease (T4b). The genesis of subcategorization of T4 into "a" and "b" categories began during the development of the sixth edition of the staging manual, where category "a" was assigned to "resectable" and category "b" was assigned to "unresectable" disease based on the local extension of disease to vital structures. However, with increasing use of "nonsurgical" treatment approaches, the terms "resectable" and "unresectable" were felt to be inappropriate, and the terms "moderately advanced local disease" and "very advanced local disease" were assigned to the "a" and "b" subcategories of T4 tumors. However, the descriptions of the local extent of disease in each subcategory remained the same. A common lymph node classification represented by four categories (N0–N3) with some subcategories is used in almost all the head and neck sites. The T and N categories are also combined with the M categories that indicate the presence or absence of distant metastases to form groups representing stages and that confer prognostic guidance. As noted earlier and continues to be the case, TNM has always needed to evolve with the availability of additional information about outcome, new treatments, or novel ways to evaluate disease and anatomy, including developments in imaging or emerging biological insights about disease behavior or etiology. Almost all clinical trials use anatomic extent, generally represented by the TNM or its elements, to define entry criteria or to control for prognostic imbalance between arms of randomized trials by employing stratification based on anatomic stage [7]. It is also a critical pathway to developing clinical practice guidelines such as those of the National Comprehensive Cancer Network (NCCN) [8] and is a key determinant in identifying patients to be treated by guidelines and for monitoring compliance to guidelines [7].

9.3.3 The Place of Nonanatomic Prognostic Factors and Staging

It is important to recognize that the TNM classification was never intended to capture all elements that are important in determining prognosis or guiding treatment and that a variety of tumor-, host-, and treatment-related external factors are also important and are becoming increasingly so today. One of the ironies of the TNM classification is that it has been immeasurably successful in its goals and has enjoyed worldwide adoption but in recent times has become a target for criticism because of assertions that it has not adapted itself to modern needs [9]. This may stem from the fact that there is no uniform functional framework that can be used to classify nonanatomic predictive and prognostic factors. The tendency seems to have evolved to consider the TNM as the optimal receptacle for these factors presumably due to its uniform appeal and success. This needs to be considered carefully since the problem is not straightforward. Dimensions of the elements of prognosis are not uniform, and the settings where some factors are appropriate to consider may not apply to other situations of the disease. These concepts will be discussed later.

9.3.4 How TNM Is Modified

As discussed already, changes continually take place in the TNM classification because of the need to maintain relevance with current management approaches and to respond to the availability of new data that may be considered in revisions to the classifications. This generally requires evidence of the need for modification and for the most part relies on published data in the literature. Thus, for example, the AJCC and UICC meticulously reviewed the overall TNM classification for all diseases for the seventh edition. This process is being followed in preparation to create the eighth edition as well. In considering change, it is important to reflect on the

fact that any classification or staging system is a "compromise" between the "ideal" and the "practical." The more accurate and, thus by design, the more complex the system is, the less compliance we will observe. One of the basic tenets of the staging system is that it should be applicable and available worldwide, it should be user-friendly, and it should have the ease to have maximum compliance from all parts of the world [10].

The process of revision involves collaboration between both organizations, and that is partly accomplished by a series of disease-specific task forces. A number of resources are available to the task forces, which include a structured process for introducing changes to the TNM classification. The elements of the TNM process include the development of unambiguous criteria for the information and documentation required to consider changes in the classification, establishment of a well-defined process for the annual review of relevant literature, formation of site-specific expert panels, and the participation of experts from all over the world in the TNM review process [11]. For perspective, changes in the seventh edition will be briefly summarized later (see Sects. 9.8.1 and 9.8.2).

In addition some domains, including anatomically based issues, may seem relevant but are not included in the modifications. This may arise because the data supporting the change are not sufficiently strong, or may lack the practicalities to permit its inclusion in a general way, or may not fit into the established structure of the TNM. In order to address the need for awareness of other elements that are not included in the formal classification, the UICC and the AJCC have initiated separate processes with different but complementary goals.

The UICC approach includes a separate publication, entitled the *TNM Supplement, A Commentary on Uniform Use* [12]. The "Supplement" now appears following each revision of TNM. Its purpose is to provide explanations and examples to answer the numerous questions that arise during the daily use of TNM, particularly in unusual cases. It enumerates the recommended criteria for pathological classification (pT and pN). One example in the head and neck is a description of the superior and inferior boundaries of the glottis, since these are not elaborated in the UICC *Livre de Poche* though such items are included in the more expansive AJCC Cancer Staging Manual. Another example concerns the reminder that pathological classification also uses clinical information. Thus, in considering impaired mobility or fixation in the glottis, this information that is evaluated in the clinical T category is also used to define the pathologic TNM (see Table 9.1) [12]. The "Supplement" also contains proposed classifications for new tumor sites and types not yet part of the official UICC and AJCC TNM system and that can be tested by interested investigators with a view to encouraging publication that may result in their subsequent inclusion in the formal classification if the data prove robust. Optional expansions of existing TNM categories are also included in the "Supplement" for those needing to record more detail. An added feature is the "Frequently Asked Questions" chapter, derived from the UICC and AJCC TNM web sites' help desks.

The AJCC has taken a different approach. First, the AJCC staging manual is a more expansive text. Consequently, it is less portable for consultation in the clinic by clinicians, though it provides the reference foundation for the work of cancer registrars in North America. A more compact version is available though is still not as brief and synoptic in presentation as the UICC *Livre de Poche*. In addition, the AJCC has implemented the "Collaborative Staging System" (CS), which acts as a repository of all available prognostic information for current and future use. This process commenced in 2004 and comprises a data collection tool across all US hospital and population registries for cancer staging information [13]. It uses a standardized data dictionary to collect information on T, N, M, and site-specific prognostic and predictive factors. The CS system is built into all cancer registry software systems in the USA. Areas identified for data collection in the head and neck sites include such factors as the actual size of lymph nodes, the location of lymph nodes (e.g., upper or lower neck involvement), the presence of extracapsular spread (ECS), human papillomavirus (HPV) status, and tumor thickness in oral cancers. Many of these are not reliably available by clinical evaluation, but their strength is apparent on pathological examination where they may influence clinical care in significant ways. For example, the presence of ECS is a singularly adverse factor [14] and drives the need for chemotherapy in addition to radiotherapy in the postoperative adjuvant management of cervical lymph node metastases [15]. However, the role of ECS in HPV-positive patients appears to be of less significance [16]. Tumor thickness in oral cavity primary sites is one of the strongest predictors for the risk of lymph node involvement in the neck beyond the formal T staging system [17], thereby influencing the approach to neck management. Other important pathological issues that are not part of the TNM at present include the character of the tumor (e.g., endophytic vs. exophytic) and the nature of the host tumor interface (pushing vs. infiltrating) and the presence of perineural or lymphovascular invasion (LVI) that also impact on the treatment and outcome of patients. In addition to being implemented in some other jurisdictions beyond the USA, ongoing efforts involving the College of American Pathologists (CAP) and the Centers for Disease Control and Prevention (CDC) are revising the CAP Cancer Templates for reporting pathology on cancer specimens to collect core elements on tumor size, extension, nodal involvement, and metastases in the format needed for recording in the CS system. It is also expected that the CS system will be incorporated in the NCI's Cancer Bioinformatics Grid (caBIG) as the accepted standard for

recording data on the extent of disease and stage [13]. In this way, the future potential exists for important elements that influence treatment and prognosis to be analyzed in order to develop prognostic groups that may be able to enhance the existing TNM stage classification.

9.3.4.1 The Unique Case of HPV

The emergence of our understanding of oropharyngeal disease is explosive. The developing evidence suggests that p16-positive cancers of the palatine and lingual tonsils have a significantly better prognosis and behavior that defies our current staging system to quantitate. Later in this chapter, we will address the question of whether HPV-positive oropharyngeal carcinoma is a variation with a better prognosis or a completely separate disease entity.

9.3.5 Specific Designations and Rules in TNM

The staging of head and neck cancer requires the clinician and the cancer registrar to be familiar with an extensive assortment of anatomic sites and subsites. Practitioners and statisticians interested in how results from clinical trials are interpreted and received need to be familiar with the fundamental rules of the TNM classification. The same holds true for everyone involved in interpreting and applying the general results of treatment or in maintaining and addressing consistency in how treatment guidelines are developed, used, and assessed. Depending on an individual's or a group's focus, some of these may seem arbitrary, cumbersome, or even unnecessary. Nonetheless, they embody a uniformity that is applicable to all oncologic disease sites, health professionals, and jurisdictions around the world [3].

A detailed discussion of the rules of TNM is not intended in this chapter. Some basic issues will be known to practitioners such as the fact that the TNM for most mucosal sites is designed for squamous cell carcinoma and minor salivary gland cancer. It is also acknowledged that head and neck oncologists are very familiar with the TNM system though they may not be aware of some of the recent changes described below and may be interested in the current ongoing discussions regarding further modifications to come in the eighth edition. In addition, even experts may not be aware of all of the "fine print" that exists, and a summary of some of the questions and problems that arise in day-to-day usage is provided (see Table 9.1). This is not intended to be exhaustive, and the interested specialist should also consult additional sources mentioned earlier as well as the actual TNM classification publications [1, 2, 12]. Several broader issues merit comment, however. These concern the areas of clinical vs. pathological staging, some additional descriptors within the classification, and the use of grouping of elements to define prognosis.

9.4 Clinical Versus Pathological Staging

All cases should be confirmed microscopically through tissue biopsy of the primary tumor or metastatic lymph node. All cases should receive a *clinical classification* (the TNM or cTNM) based on evidence acquired before treatment through physical examination supplemented by endoscopic and imaging evaluation essential to select and evaluate therapy. Physical examination, radiographs, CT or MRI, PET scan, endoscopy, biopsy, and other relevant examinations including surgical exploration comprise the majority of this evidence. In contrast, *pathological classification* (pTNM) is based on postsurgical histopathological classification and is used to guide adjuvant therapy and provides additional data to estimate prognosis and to calculate end results in those patients that have surgery as part of their treatment regimen. Both should be recorded when available and should not be mixed or considered equivalent since different selection criteria apply to each. In addition, they should contain the same elements.

9.5 Additional Descriptors Used in TNM

The clinical TNM and pTNM classification also contain specific terms to facilitate clinical situations faced by clinicians in the contemporary management of head and neck cancer. Thus, several symbols may be used to facilitate including the m, y, r, and R identifiers (see Table 9.2).

The suffix m, in parentheses, is used to indicate the presence of multiple primary tumors in a single site, whereby the tumor with the highest T category should be classified and the multiplicity or the number of tumors should be indicated in parenthesis, e.g., T2(m) or T2(2) in the case of two tumors (see Table 9.1).

The y symbol is available to classify cases during or following multimodality therapy by identifying the clinical TNM or pTNM category identified by a "y" prefix that designates that the classification refers to the extent of tumor actually present at the time of that examination. Therefore, the y categorization is not an estimate of the extent of tumor prior to multimodality therapy, but is useful for description of TNM during concurrent chemoradiation therapy or after the completion of neoadjuvant regimens [18].

The lowercase "r" symbol is available to describe recurrent tumors and needs to be applied after a disease-free interval (usually in the order of 6 months). Such tumors are identified by the prefix "r" as rTNM or rpTNM and need to be distinguished from the uppercase "R" designation used to describe residual disease following surgical resection as R0 for microscopically clear resections, R1 for microscopic residual disease, and R2 for macroscopic residuum. In some cases, confusion could arise between the uppercase "R2"

Table 9.1 Application of selected rules relevant to the TNM head and neck classification

General issues
For each disease, there should be a clinical (obtained without resection) and a pathological (obtained after surgery) classification that contain equivalent descriptors
Pathological classification (pTNM) is based on evidence acquired before treatment, supplemented or modified by additional evidence acquired from surgery and from pathological examination
Because the designation is based on evidence acquired before treatment, a glottic cancer with a fixed vocal cord will remain a T3 lesion after surgery unless additional evidence of extension of disease is present, such as invasion of thyroid cartilage, to raise the category to the next (i.e., more advanced) level
The pathological assessment of pT and pN requires a resection adequate to evaluate the highest pT or pN category
If there is doubt about whether a tumor should be classified with a higher T or N category, it should be allotted to the lower category (i.e., less advanced) where the available criteria for that case can be reliably applied
The designation X is used for the T or the N categories, if there is inadequate information available to classify the lowest category when disease has been known to be present in that location. The term X is not used for the M category since a clinical exam alone cannot permit assessment of distant metastases. It is also not used for the designation of unknown primary where T0 is the correct convention
T-category issues
Tumors overlapping adjacent areas should be classified according to the site where the bulk of the lesion (epicenter) is located
In the case of multiple primary tumors in one organ, the tumor with the highest T category should be classified and the multiplicity or the number of tumors should be indicated in parenthesis, e.g., T2(m) or T2(5)
In simultaneous bilateral primary cancers of paired sites (e.g., tonsillar carcinomas), each tumor should be classified independently
In unknown primary cancer classification, the designation T0 should be used for the T category. T0 is also used at the time of recurrence of a previous known head and neck cancer (e.g., regional lymph node or distant failure) if there is no evidence of disease recurrence at the primary site, preceded by the descriptor "r"
N-category issues
The regional lymph nodes are the cervical nodes. Midline nodes are considered ipsilateral nodes
The definitions of the N categories for all head and neck sites except the nasopharynx and mucosal melanoma are the same
In oral cavity, larynx, and pharynx cancers, metastases at level VII (those in the anterior superior mediastinum, cephalad to the innominate artery) are considered regional lymph node metastases. The remaining mediastinal lymph node metastases are considered distant metastases
Histological examination of a selective neck dissection specimen will ordinarily include six or more lymph nodes
Histological examination of a radical neck dissection or a comprehensive modified radical neck dissection specimen will ordinarily include ten or more lymph nodes
If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0
When size is a criterion for pN classification, measurement is made of the metastasis, not of the entire lymph node
In unknown primary cancer classification, the designation T0 and the N classification should use that of the site most likely to represent the origin of the tumor

Table 9.2 Selected additional descriptors encountered in the TNM or pTNM of head and neck cancer

m symbol	The suffix m, in parentheses, is used to indicate the presence of multiple primary tumors at a single site. See commentary in Table 9.1
y symbol	In those cases in which classification is performed during or following multimodality therapy, the cTNM or pTNM category is identified by a y prefix
	The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The y categorization is not an estimate of the extent of tumor prior to multimodality therapy
	This convention should typically be used following neoadjuvant therapies and may be most applicable to induction chemotherapy
r symbol	Recurrent tumors, when classified after a disease-free interval, are identified by the prefix r
R classification	The absence or presence of residual tumor after treatment is described by the symbol R as follows
	RX: presence of residual tumor cannot be assessed
	R0: no residual tumor
	R1: microscopic residual tumor
	R2: macroscopic residual tumor
	Typically, these designations are used in surgical resections where microscopic residual tumor (R1) or gross residual tumor (R2) is left behind
	In some situations, the R2 designation may interact with the "r symbol" if macroscopic (gross) residual represents recurrence of previous tumor (see text)

designation for gross residual disease and the lowercase "r" designation that designates recurrent disease since one may eventually merge into the other if sufficient time evolves. This is especially prone during the time to referral to a cancer center for definitive treatment following an initially incomplete excision.

9.6 Lymph Node Classification for Micrometastasis and Sentinel Node Assessment

The regional lymph node classification has recently also been adapted to address subclinical disease. This is particularly relevant in the head and neck to sentinel lymph node assessment where the designation "Sn" has been introduced in the TNM classification (Table 9.3). Therefore, the following designations are applicable when sentinel lymph node assessment is attempted: pNX(sn), sentinel lymph node could not be assessed; pN0(sn), no sentinel lymph node metastasis; and pN1(sn), sentinel lymph node metastasis. Cases with morphological evidence of micrometastasis only, i.e., no metastasis larger than 0.2 cm, can be identified by the addition of "(mi)," e.g., pN1(mi) (see Fig. 9.1). A designation of morphologically evident isolated tumor cells (ITC) can also be used to designate single tumor cells or small clusters of cells not more than 0.2 mm in greatest extent that can be detected by routine H and E stains or immunohistochemistry and is designated as (i+) (see Table 9.3). This overall approach has been validated recently by experts in sentinel lymph node assessment [19].

The approach has been similarly adapted to the situation where no morphological evidence of disease is apparent, but evaluation is based on a molecular assessment of the presence of disease by techniques such as flow cytometry or DNA analysis (see Table 9.3). The term "mol" is used to indicate that such a technique has been employed in the assessment; e.g., pN0(mol−) indicates that no regional lymph node metastasis is present histologically, and there is a negative assessment for nonmorphological findings for ITC. In contrast, pN0(mol+) indicates that no regional lymph node metastasis is identifiable histologically, but there is a positive assessment for nonmorphological findings for ITC. Also, in the situation where these characteristics have been assessed but confined to a sentinel lymph node assessment, the term "Sn" may be used as follows: pN0(mol+)(sn), no sentinel lymph node metastasis histologically, but there are positive nonmorphological findings for ITC. In general, these terms are not commonly used in practice, but are available in the event that these assessments become more uniformly used in the future. It is apparent that the designations (i+) and (mol+) are considered N0 at this time.

Table 9.3 Refinement in description of subclinical disease (most applicable to regional lymph node evaluation using sentinel node biopsy) assessment

Cases with micrometastasis only, i.e., no metastasis larger than 0.2 cm, can be identified by the addition of (mi), e.g., pN1 (mi)	
Isolated tumor cells (ITC) are single tumor cells or small clusters of cells not more than 0.2 mm in greatest extent are designated by the term "i+"	
Molecular detection (nonmorphological findings for ITC) of tumor presence is designated by the term "mol+"	
Sentinel node assessment is described by the use of the suffix "sn" at the end of the classification of a given tumor as depicted below	
The classifications for ITC and molecular detection of tumor should be used and designated as follows	
pN0	No regional lymph node metastasis histologically; no examination for ITC
pN0(i−)	No regional lymph node metastasis histologically; negative morphological findings for ITC
pN0(i+)	No regional lymph node metastasis histologically; positive morphological findings for ITC
pN0(mol−)	No regional lymph node metastasis histologically; negative nonmorphological findings for ITC
pN0(mol+)	No regional lymph node metastasis histologically; positive nonmorphological findings for ITC
When sentinel lymph node assessment is attempted	
pNX(sn)	Sentinel lymph node could not be assessed
pN0(sn)	No sentinel lymph node metastasis
pN1(sn)	Sentinel lymph node metastasis
Cases with or examined for ITC in sentinel lymph nodes can be classified as follows	
pN0(i−)(sn)	No sentinel lymph node metastasis histologically, negative morphological findings for ITC
pN0(i+)(sn)	No sentinel lymph node metastasis histologically, positive morphological findings for ITC
pN0(mol−)(sn)	No sentinel lymph node metastasis histologically, negative nonmorphological findings for ITC
pN0(mol+)(sn)	No sentinel lymph node metastasis histologically, positive nonmorphological findings for ITC

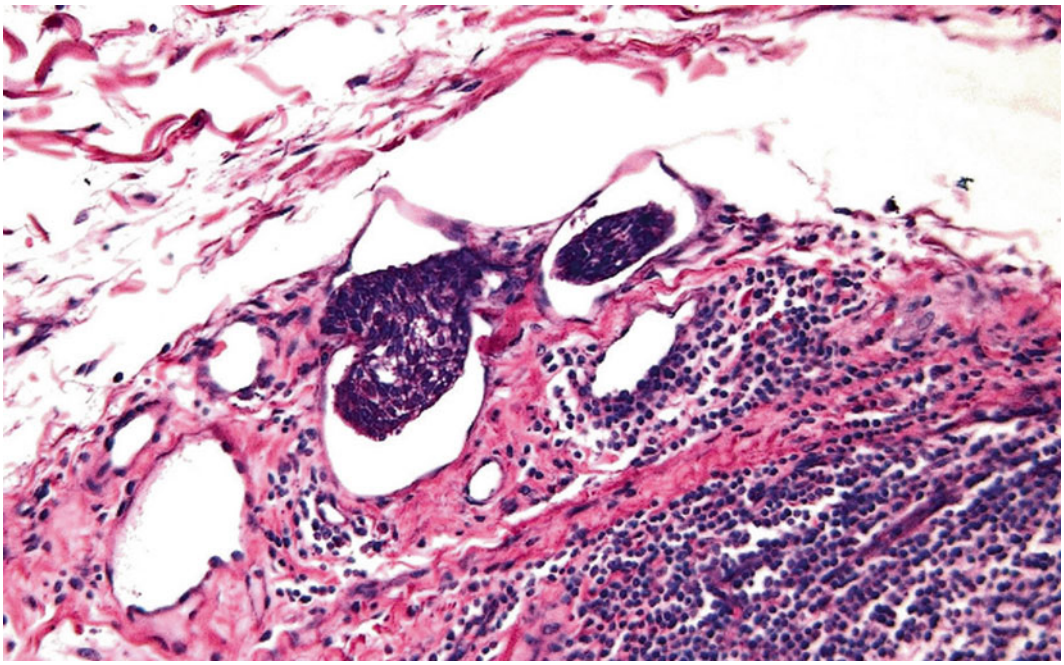

Fig. 9.1 Micrometastasis evident by small clusters of cells not more than 0.2 mm in greatest extent can be detected by routine H and E stains and is designated by the addition of "mi," e.g., pN1(mi) for detection in a single lymph node. Single tumor cell can also be classified using the term isolated tumor cells (ITC) and designated by the use of (i+) (see Table 9.3)

9.7 Stage Grouping

For purposes of tabulation and analysis, it is useful to condense the T, N, and M categories into stage groups. In general, in the TNM system, the groups are based on a hierarchy governed by the degrees of modification of prognosis. For most tumor sites in the body, carcinoma in situ is categorized as Stage 0, tumors localized to the organ of origin as Stages I and II, locally extensive disease and especially spread to regional lymph nodes as Stage III, and those with distant metastasis as Stage IV. In the classification of head and neck tumors, some unique differences exist and will be outlined in the sections that address specific anatomic sites in the head and neck region, most notably in the area of mucosal melanoma, where a new classification was introduced for the first time in the seventh edition, in anaplastic thyroid cancer and in the general head and neck classification where advanced local disease (T4a or b) and extensive regional adenopathy (N2c and N3) will place the case at the highest level of adverse prognosis (Stage IV). The HPV-positive patient will be handled in a unique way, akin to nasopharyngeal carcinoma.

The stage groups are intended, as far as possible, to provide homogeneous groups with distinctive survival rates for the different cancer sites. In addition, there are pathological stage groups if sufficient tissue has been removed for pathological examination to evaluate the highest T and N categories. As discussed earlier, the stage groups have also evolved over time. Originally, in the first edition of the TNM classification, they did not exist, and in the most recent edition, the AJCC and the UICC have introduced separate modified approaches in order to acknowledge the potential importance of nonanatomic factors (see Sect. 9.12.3 later).

9.8 Seventh Edition Modifications to "TNM"

The seventh edition of the TNM staging system became available for wide usage in 2010 [1, 2]. In the head and neck classifications, the most significant changes were the creation of a staging system for mucosal melanoma and fine-tuning of the relatively substantial modifications previously introduced in the sixth edition [20, 21]. Broadly speaking, the changes were intended to reflect current practices of treatment, clinical relevance, and contemporary data as well as providing the opportunity for data to be collected with a uniform classification in situations where this may have been problematic previously.

9.8.1 Recent Modifications to the T Classification

9.8.1.1 Very Advanced Local Disease (T4)

In the seventh edition, the terms "resectable" (T4a) and "unresectable" (T4b) introduced by the AJCC in the sixth

edition [20] were replaced by the words "moderately advanced" (T4a) and "very advanced" (T4b). These changes were made since a significant proportion of advanced-stage epithelial malignancies of the head and neck are being treated nonsurgically, and of those that are surgically treated, criteria for resectability may be subjective and are often dependent on the quality of available imaging studies [22, 23]. The anatomic criteria for the definitions of T4a and T4b, however, remained unchanged. Importantly for our discussion of the eighth edition, the nasopharynx was felt to have insufficient data to permit a subdivision of the T4 category. In particular, there is evidence that minimal invasion of the skull base or minimal cranial nerve involvement is not uniformly prognostically detrimental when determined by imaging assessments [24], further emphasizing the rationale for the importance of clinical evaluation in staging assessments (e.g., of cranial nerves in this instance). This remains an area of significant work in the development of the eighth edition to explore this heterogeneous and unique disease.

9.8.1.2 Nasopharynx T Category

The most apparent changes in T categories in the seventh edition occurred in the nasopharynx (see Table 9.4), a site that underwent no substantive change in the sixth edition TNM. Data over the past decade has demonstrated the relatively consistent finding of the absence of a difference in outcome between T1 and T2a tumors leading to a recommendation for reclassification of patients with soft tissue disease involvement of the oropharynx and nasal fossa to the T1 category [25, 26]. Thus, T2a lesions are now designated T1 and Stage IIA is now Stage I (see Table 9.4).

9.8.2 Recent Modifications to the N Classification

Traditionally, the N classification for cervical lymph node metastasis has been uniform for all sites except the thyroid, nasopharynx, and skin. The N classification for thyroid and nasopharynx is unique to those sites and is based on tumor behavior and prognosis.

An important change for nonmelanoma skin cancer in the seventh edition was the introduction of the N classification used in the remaining head and neck sites and is justified based on a variety of studies that indicate that increasing extent of neck disease is associated with adverse outcome [27]. Indeed this compelling argument has influenced the complete nonmelanoma skin cancer classification to a degree that the head and neck N classification was also used for axillary and inguinal lymph nodes in the seventh edition TNM. For metastatic squamous cell carcinoma, from mucosal primary sites, no major changes were made in the N staging for any site, except that a descriptor has been added. As noted earlier, ECS of disease has been added as ECS+ or ECS− as a descriptor for capture in the CS of the AJCC. These descriptors did not influence the nodal staging system but will likely provide data to permit future revisions of the N classification.

A final point concerning the neck is that the new classification for mucosal melanoma (see below) uses a limited schema restricted to only designating absence (N0) or presence of regional lymph node involvement (N1) without additional categories (see Table 9.5).

9.8.3 The New Classification for Mucosal Melanoma of the Head and Neck

Mucosal melanoma of the head and neck warrants separate consideration, and the approach to these lesions is outlined in a new chapter that introduces a TNM classification for the first time (see Table 9.5). Even small cancers behave aggressively with high rates of recurrence and death [28]. To reflect this aggressive behavior, even the smallest mucosal melanomas confined to the mucosa alone are designated as T3 and those with moderately advanced lesions (involving underlying cartilage or bone) are staged T4a. Very advanced primary tumors are staged T4b. In situ mucosal melanomas are excluded from staging, as they are extremely rare. There is also no T1 or T2 category. It is intended that the availability of a stage classification for this rare, unfavorable, and perplexing disease may facilitate research addressing its etiology, biology, and treatment. In fact, recent work has demonstrated the successful stratification of this system [29, 30].

9.9 The Future of TNM in Head and Neck Cancer

As implied and discussed earlier, the anatomic extent of disease remains one of the strongest and most consistent prognostic factors, especially in head and neck cancer. Multiple reasons for this exist and have been described. As also mentioned, however, its very success seems to have rendered it vulnerable since no alternative overarching strategy has emerged to amalgamate, administer, and process multiple prognostic elements for a given cancer. A major dilemma in TNM staging is that frequent revisions to include new biomarkers, for example, would undermine the value conferred by the stability and universality of TNM, but a static formulation of TNM risks falling behind the state of the art in diagnostic techniques, biological concepts, and biomarkers [31]. In fact, other techniques do exist and should be considered, but a shift in attitude is probably needed to embrace other methods of classification in addition to the TNM system.

Table 9.4 Nasopharyngeal TNM clinical classification (revision in seventh edition)

T – primary tumor			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor confined to nasopharynx or extends to oropharynx and/or nasal cavity		
T2	Tumor with parapharyngeal extension[a]		
T3	Tumor invades bony structures of skull base and/or paranasal sinuses		
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, and orbit or with extension to the infratemporal fossa/masticator space		
N – regional lymph nodes			
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 nodes, 6 cm or less in greatest dimension, above the supraclavicular fossa		
N2	Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa		
N3	Metastasis in lymph node(s) greater than 6 cm in dimension or in the supraclavicular fossa N3a greater than 6 cm dimension N3b in the supraclavicular fossa		
M – distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping (nasopharynx)			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0, N1	M0
Stage III	T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage IVA	T4	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Note: The term "Stage Grouping" is termed "Anatomic Stage/Prognostic Groups" in the AJCC version of the classification [1]
Adapted from Sobin LH, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumors. 7th ed. New York: Wiley; 2010. With kind permission from Wiley
[a]Parapharyngeal extension denotes posterolateral infiltration of tumor

Biological staging for head and neck cancer has been discussed for over two decades. The idea is that the natural history of cancer within an individual is varied and dependent upon many factors related to the tumor itself and the environment- or host-related factors [32]. This concept has gained widespread adoption conceptually, but as a practical matter, it remains to be properly structured for worldwide adoption.

In addition to the area of biomarker discovery, other areas of prognostic importance also exist and in many situations have the capability of equaling or even overcoming effects embodied by traditional areas of cancer classification in terms of disease biology and anatomic disease extent. For example, many nonanatomic factors address issues relevant to the host (i.e., patient) or the environment or setting where the patient is treated and particularly in the context of the availability of treatment or diagnostic assessments, but receive scant attention in the voluminous literature on prognosis that has emerged recently. The role of the health system and treatment factors such as patient volume, expertise of the treating team, distance from treatment facilities, socioeconomic status of the patient, and other factors are also known to influence prognosis. Some of these issues will be discussed to introduce these concepts while recognizing that this field is evolving and immediate solutions have not yet been developed or universally adopted. Broadly, prognostication in cancer can be classified into three domains that address the dimensions of the *tumor*, the *host*, and the *environment*. This traditional classification has been used by the UICC in its publication *Prognostic Factors in Cancer* now in its third edition [33]. In addition, this text has also introduced a tabular format

Table 9.5 TNM classification for mucosal melanoma of the head and neck (a new classification in the seventh edition TNM)

Primary tumor			
T3	Mucosal disease		
T4a	Moderately advanced disease		
	Tumor involving deep soft tissue, cartilage, bone, or overlying skin		
T4b	Very advanced disease		
	Tumor involving the brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures		
Regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastases		
N1	Regional lymph node metastases present		
Distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis present		
Stage grouping			
Stage III	T3	N0	M0
Stage IVA	T4a	N0	M0
	T3–T4a	N1	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Note: The term "Stage Grouping" is termed "Anatomic Stage/Prognostic Groups" in the AJCC version of the classification [1]
Adapted from Sobin LH, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumors. 7th ed. New York: Wiley; 2010. with kind permission from Wiley

for each disease site throughout the body to address these three dimensions but, additionally, has allocated them into three hierarchy tiers to address whether these factors influence treatment of the disease at the present time (based on recommendations in published practice guidelines), whether they add valuable additional information to understand the disease setting without influencing treatment decisions, or finally whether they represent new and promising discoveries that have not yet found a place to put it in the assessment of the disease in the clinic. A modified example of one of the head and neck tabulations is shown in Table 9.6 [33].

Some of these areas will be discussed briefly in addition to some of the challenges in grouping data and using them to prognosticate for the individual patient or in groups of patients. In addition, statistical assessments need ongoing understanding of concepts that address validation in particular. Development of the eighth edition has begun by a careful collection of literature that addresses each of these factors. The task before the committee is to develop a working framework within which these can best be detailed and statistically integrated. As of the writing of this chapter, each of the major issues is being researched by task forces designed to provide meaningful insight and modifications to the current system while respecting the important practical and historical role of TNM anatomic staging.

9.9.1 The Importance of "Nonanatomic" Tumor Factors

9.9.1.1 Introduction of Biologic Prognostic Markers

An interesting editorial [34] noted that the power of the TNM staging system is largely derived from the observation that tumors demonstrating locoregional or distant spread carry a worse prognosis than their less advanced counterparts. The problem is that, while this is true, and it is possible to predict survival based on a particular clinicopathological stage, there are clearly some patients that beat the odds [34]. Unfortunately, the authors also point out that there is also evidence that small tumors can metastasize early in their course and that a surgically resected primary tumor may in fact harbor cells demonstrating metastatic potential. This suggests the possibility to differentiate virulent tumor cells capable of metastasis from nonvirulent tumor cells based on molecular profiling. Molecular evidence may then be used to predict the outcome and treatment needs for an individual patient better than TNM staging. This speaks to the inherent clinical and molecular heterogeneity of cancer we now know that exists and to our inability to predict the behavior of any particular tumor. And so the question can be legitimately posed: will TNM survive the molecular revolution [34]?

We feel that it is unlikely to change for the foreseeable future. In large part, the place of TNM remains secure if only

Table 9.6 Prognostic factors in oral cavity, pharynx, and larynx cancer

Prognostic factors	Tumor related	Host related	Environment related
Essential	T category	Performance status	
	N category	Lifestyle – tobacco/alcohol	
	M category		
	Anatomic subsite		
Additional	Resection margin	Comorbidities	Radiation dose
	Number of involved nodes	Age	Overall treatment time
	Extracapsular nodal extension		Quality of surgery and radiotherapy
	Perineural, lymphovascular invasion		Response to therapy
	Tumor hypoxia		
	HPV status		
New and promising	EGFR expression		
	Surgical molecular margins		
	Osteopontin DNA profiling		

Based on data from: ESMO guidelines for management of SCC of the head and neck 2005 http://oncologypro.esmo.org/Guidelines-Prac...al-Practice-Guidelines/Head-and-Neck-Cancers; National Cancer Institute: Lip and Oral Cavity (PDQ®): Treatment Guidelines 2005 http://www.cancer.gov/types/head-and-neck/hp/lip-mouth-treatment-pdq; Clinical Practice Guidelines in Oncology: Head and Neck Cancer 2005 http://www.nccn.org/professionals/physician_gls/PDF/head-and-neck.pdf; Bourhis J. Oral cavity, pharynx, and larynx cancer. In: Gospodarowicz MK, O'Sullivan B, Sobin LH, eds. *Prognostic Factors in Cancer*. 3rd ed. New York: Wiley; 2006:99–104

for the fact that newer biological findings will need to be evaluated and validated in the context of an existing robust structure such as that provided by TNM, even if it remains imperfect. In addition, TNM is also a worldwide language, at least in head and neck cancer, and it is not possible to replace it in many areas of the world where complex molecular assays are unavailable. It also represents the basis for entry and stratification in many clinical trials [7] to permit the evaluation of new treatments and biomarkers in a manner that reduces the influence of treatment selection bias.

In head and neck cancer, as in all other regions, we are confronted by a large group of potential factors, but their precise place in the management of the disease remains uncertain. Articles are appearing that address a bewildering multitude of potential molecular characterizations of head and neck cancers, often in studies containing only modest patient numbers [35–38]. It is not the purpose of this chapter to discuss these in detail, but broad comments may be useful as we continue to search for the best use of potential biomarkers and explore how to incorporate these important elements that have the potential to profile these tumors in methods that take us beyond pure extent of disease. In the paragraphs that follow, for squamous cell carcinoma of mucosal origin, we have chosen two relatively well-recognized biomarkers, specifically the expression of the epidermal growth factor receptor (EGFR) and of HPV, that could be readily available if needed for clinical management of patients with head and neck cancer in the developed world. Both are being discussed by the head and neck task forces in the process of preparation of the eighth edition TNM. The situations surrounding both biomarkers will be discussed in relation to the proposition that they could replace or enhance the TNM or other prognostic models in the near future.

For some time, it has been recognized that EGFR expression is an independent determinant of survival and a robust independent predictor of locoregional relapse, although not for distant metastasis that is capable of withstanding the scrutiny of rigorous multivariate analysis. However, in one of the original landmark correlative studies of a large series of patients treated with radiotherapy alone, EGFR expression varied considerably among head and neck squamous cell carcinomas, and the study was restricted to the investigation of higher-stage patients (i.e., in excess of 95 % of patients had UICC/AJCC Stage III or IV disease) [39]. A recent meta-analysis of 68 studies suggests that copy number and overall expression of EGFR can predict survival although the magnitude was not dramatic. This suggests that early excitement is slightly dampened and illustrates the need for ongoing assessments and an ability to use selected biomarkers as modifiers of known existing information such as anatomic staging [40].

Thus, the precise impact of this biomarker in the continuum of the different degrees of head and neck cancer disease extension remains unclear. This problem in fact exists in much of the prognostic factor literature, where different factors or prognostic models may be important in subsets of a disease that address issues such as advanced stage as compared to early disease or in different scenarios (e.g., primary vs. recurrent presentations), but it becomes problematic when one wishes to apply them universally across the entire disease spectrum. An additional problem relating to

EGFR expression concerns its true value in the clinic as matters stand today. The initial data suggested that EGFR expression might be considered for selecting patients for more aggressive combined therapies or enrollment into trials targeting EGFR signaling pathways [39]. Strong claims have persisted that it is a promising therapeutic target in head and neck cancer based on the proven efficacy of cetuximab, a monoclonal antibody against EGFR, when combined with radiotherapy in locally advanced cancer (Stages III and IV) [41]. This observation had led to the approval of the drug for this indication on a worldwide basis. However, the role of EGFR-targeting agents in other therapeutic modalities, such as combined chemoradiotherapy or induction chemotherapy, remains to be defined [42]. In addition, and perhaps more disheartening, is the knowledge that the useful effects of cetuximab appear to be divorced from the degree of EGFR expression [42, 43]. The reality is that the majority of squamous cell carcinomas in the head and neck overexpress EGFR, but the clinical responses to EGFR-targeting agents have been modest, and molecular predictors for response to EGFR-targeted therapies have not been identified in the head and neck. Molecular marker studies have shown that mutations in the EGFR gene such as the L858R mutation in the tyrosine kinase portion of the receptor confer sensitivity to EGFR tyrosine kinase inhibitors in non-small cell lung cancer, but positive similar and additional studies in head and neck cancer have proven elusive to this point [42]. Recent data suggests that a negative regulator, the multiadaptor protein mitogen-inducible gene-6 (Mig6), plays an important role in signal attenuation of the EGFR network [44]. Thus, Mig6 may be important in understanding the complex relationship between EGFR and tyrosine kinase inhibition. Although the study is primarily based in cell lines, it is supported by a small clinical cohort as well. Another opportunity is that emerging data suggest that cetuximab may have the ability to elicit immune responses such as antibody-dependent cell toxicity (ADCC), and the search for predictive biomarkers for cetuximab therapy may need to be redefined to include elements of the immune system. Certainly, the response to cetuximab appears to be multifaceted and involves more than a simple inhibition of the EGFR pathway [42], and until the situation becomes clearer and its role more certain, the incorporation of this potentially important biomarker with elements of the TNM remains unresolved. It does seem clear, however, that its place in the prediction of prognosis in head and neck cancer should continue to be evaluated within the established framework of anatomic disease extent, and failure to do so may lead to spurious findings.

In contrast, the AJCC has recently recommended that HPV status in tumor should be assessed in mucosal squamous cell carcinoma of head and neck sites because of the impact it has on the prognosis of some head and neck cancers [1]. These data, together with other factors not included in TNM, have been compiled in the CS for analysis in particular as it relates to prognostic models that take into account various factors. This is an encouraging opportunity since the HPV status has emerged as a major predictor of survival that determines eligibility in multiple randomized trials currently underway investigating various treatment regimens. It is clear that HPV-mediated oropharyngeal cancer is an active field of investigation [44–46]. These tumors seem to have significantly more favorable outcome compared to HPV-negative squamous cell cancer in these locations [47]. These findings have led to HPV being widely accepted as a prognostic biomarker for oropharyngeal carcinomas.

An alternative interpretation is to regard this as an entirely different disease compared to non-HPV-related oropharynx cancer. In essence, it remains unresolved whether it should be considered separately from traditional smoking-related oropharyngeal cancer, and the clinical trials discussed above are designed specifically with this in mind to tailor treatment strategies to these more favorable, and presumably different, cancers. This potentially implies that a different TNM classification could be considered in this disease akin to the way a disease such as NPC is approached where its different etiology, also predominantly viral, and case profile set it aside from other head and neck cancer. Apart from their different etiology, other evidence for considering HPV-related oropharyngeal cancers uniquely includes the characteristic histological description of these tumors as poorly differentiated, often exhibiting minimal keratinization, basaloid features, and clinical features that include noninvasive submucosal primary lesions and lymph nodes with palpable features that resemble those found in lymphoma patients and that appear cystic on computerized tomography (CT) [48]. Recently, it has even been suggested that lymph node involvement carries dramatically less prognostic importance compared to traditional head and neck cancers emphasizing again that it is difficult to evaluate the influence of these important biomarkers unless the evaluation is undertaken within some framework that addresses the extent of disease. Indeed the evidence appears to be that, in this group of patients, a substantial percentage of whom have metastasis to cervical lymph nodes in less advanced primary tumors, the N status, is an unreliable prognostic indicator [49–52]. Again this is reminiscent of the NPC situation where different consideration to N classification has been needed, although the direction of the effect was the opposite due to higher risk of distant metastases in NPC with advanced neck disease.

Additional complexity also exists in relation to racial differences in outcomes for oropharyngeal cancer and that is related to molecular basis of these tumors. Recent data suggests that the adverse outcome of black patients compared to white patients may be explained by the paucity of association with HPV expression in tumors among the black

population [53]. The precise reason for the disparity in HPV expression remains unresolved, but its absence appears strongly associated with significantly less favorable outcome of oropharyngeal cancer in blacks compared to patients where HPV is associated.

Finally, in considering the HPV situation, patients who have HPV-related oropharyngeal cancers but who are smokers appear to retain some of the adverse profile of more traditional head and neck cancer and do not fare as well as *never-smoker* patients [38, 54]. Such "hybrid etiology" cancers appear to be complex, and in this situation, the concept of a biomarker within the spectrum of regular and traditional oropharyngeal cancer may indeed apply. Complicated interplays exist, including additional adverse expression of EGFR that appears to be expressed, possibly through increased hypoxia in the tumor tissues in smokers' cancers [38]. In addition, in their modest cohort of 66 patients, Kumar et al. identified other unexplained variables including an adverse effect of female gender (although only 12 were female) and additional adverse biomarkers. The authors advised additional validation to understand the role of these findings in predicting and guiding therapies. This would also apply to how these findings could be incorporated with TNM staging. Again most of the patients had presented with relatively advanced regional node involvement or with fairly advanced T-category disease rendering it difficult to address the whole spectrum of the disease [38]. To add to this complexity, the interrelationships of these biomarkers further complicate the picture. Just using these two markers, data suggests that the effect of EGFR may be only in those patients that do not harbor HPV. This suggests a relativism that evades the use of hard and fast categories [55].

9.10 Serum Markers

Among mucosal head and neck cancers, NPC has additional uniqueness in possessing a robust circulating tumor marker that can be expected to be employed clinically. One of the uses is the correlation of circulating EBV DNA with disease staging using quantitative real-time polymerase chain reaction (PCR) technology [56]. By means of its production by NPC cells, EBV DNA level has been shown to be more powerful than existing staging system in predicting outcomes by providing an index of disease burden in the individual patient and has been investigated now by numerous authors [57]. In particular, Leung et al. showed that pretherapy circulating EBV DNA load is an independent prognostic factor for overall survival in NPC. Thus, patients with early-stage disease can be segregated by EBV DNA levels into a poor-risk subgroup with survival similar to that of Stage III disease and a good-risk subgroup with survival similar to Stage I disease [58]. Pretreatment serologic antienzyme rate (AER) of Epstein–Barr virus has also been shown as a compliment to TNM staging and may also serve as a serum biomarker worthy of investigation [59]. While this provides an attractive concept, it also faces challenges in whether it can be applied universally at this time, especially in regions where the disease is most prevalent and resources to make it universally available are not as plentiful as in the developed world. A possibility may be to use it presently as an additional tool within clinical trials to augment prognostic assessment and disease monitoring. Also importantly, while it is attractive to consider it as a molecular marker that provides characterization of disease for prognostication, it falls somewhat short of this. As is the case for prostate-specific antigen in prostate cancer staging and in the case of serum markers for testis cancer, both of which are incorporated in the TNM classification [1, 2], these blood assays are considered indicators of disease burden and, in reality, represent surrogates for disease bulk. The same probably applies in NPC since the influence of the circulating marker correlates with the full spectrum of disease extent and the disparity noted above from Leung et al. could be explained by imprecision in estimating the extent of disease in these complex tumors in the region of the skull base.

9.11 Volume as a Predictor

Classification based on tumor volume instead of strict anatomic extent alone has been reported as a significant prognostic factor in the management of head and neck cancer. In turn, this has prompted investigators to suggest the incorporation of tumor volume into the TNM staging system. Indeed an extensive literature has now emerged that addresses this topic, but will not be discussed exhaustively. Much of this knowledge emanates from the treatment of NPC but has also been reported for other head and neck cancers [60, 61]. Nonetheless, if tumor volume is to be used as an independent prognostic factor, the methods for volume measurement need to be standardized [62]. Unfortunately, the technical challenges to routinely implement this in the clinical setting need to be resolved if it is to be used to classify patients using a TNM system. Not only is the measurement of tumor volume a tedious process requiring the tumor to be outlined digitally on cross-sectional imaging, but also the results are prone to difficulties created by both intra- and interobserver discrepancy and the quality of the imaging study. To overcome this problem, several investigators have developed semiautomated systems to reduce interoperator as well as intraoperator variability [62]. In order to overcome the technical and manpower considerations, alternative simpler methods have also been suggested including standard bidimensional measurements [63, 64]. While there seems to be no doubt that tumor volume provides a robust predictor of

outcome in many head and neck cancers, including claims of superiority to TNM in the contemporary era of head and neck cancer treatment, problems with implementing this approach remain. Manpower issues and other problems have not yet been resolved, including the determination of agreed potential cut points that might be used to create a classification that meets the needs of the clinician and scientists. This is also particularly relevant in regions of the world where NPC is most prevalent. In the end it must also be acknowledged that while volume assessment could provide utility if it was introduced, it remains fundamentally a measure of the extent of disease. In addition, the tumor volume of a totally exophytic cauliflower-like cancer does not have the same prognostic implications, as a tumor of the same volume, which is nearly all endophytic. It has been a long-standing observation that exophytic tumors are quite radiosensitive, in contrast to endophytic tumors. Thus, tumor volume, such as assessment of serum markers, is not strictly divorced from the anatomic stage paradigm and does not address many of the problems discussed earlier and that seem to lie at the heart of many of the criticisms of TNM [34].

9.12 Evolution of Biology with Advancing Stage

Another complex problem involving interplay between anatomic disease extent and molecular characterization of disease concerns the potential that disease could evolve in its character as it progresses from early to more advanced stage. While undesirable for patients, and implying the need for more intensive treatment as disease evolves, investigators might readily embrace this concept. Thus, intensified treatment, while often used for anatomically more extensive tumors, could additionally be needed because the disease character has evolved to a more aggressive phenotype. In turn, this also could open the door to the potential for a true molecular-based "staging system." Unfortunately, while the proposal is attractive in concept, few useful examples are available in the head and neck region. Investigation into this important area will need robust translational science activities, grounded in the laboratory and the clinic, where the anatomic stage classification and clinical parameters provide the framework for this evaluation. An example, in laryngeal cancer, is a study intended to address shortcomings in cancer prognostication and treatment due to a lack of methods to adequately address the complexity and diversity of disease. The authors of this study used multiparametric methods to identify specific patterns of disease progression. They investigated, on an exploratory basis, whether genome-wide alterations of loss and gain, using a panel of 122 gene probes (112 unique genes), discriminated between early-stage (Stages I and II) and late-stage (Stages III and IV) laryngeal squamous cell carcinomas. Significant differences between early and advanced stage were apparent for the following genes: ERBB4, CASP2, RECQL4, and BCL7A. Loss of ERBB4 ($P=0.045$) and BCL7A ($P=0.019$) significantly discriminated between early and advanced stages. Gain of RECQL4 copy number ($P=0.043$) was associated with advanced stage; gain of CASP2 ($P=0.043$) characterized early disease, but loss was associated with advanced stage. Problems with this approach include not only the isolated nature of this study, but also the multiple significance testing makes it important to validate the findings independently. The potential that the number of statistical assessments used could result in spuriously significant observations by chance alone appears to have also been recognized by the authors who identified their study as "exploratory" [65].

A related issue with a different application exists within the domain of head and neck cancer staging that embodies the concept of tumor evolution over time. In essence, this, as in the previous example, relies on the fact that carcinogenesis is a multistep process at both the phenotypic and genetic levels. A malignant neoplasm has several phenotypic attributes which commences with the benign and acquires genetic events that carry it through sequential steps that ultimately lead to excessive growth, local invasion, and the ability to form regional or distant metastases [66]. An application of this evolution with some practical clinical consequence relates to the potential to temporally model some of the key genetic events of a cancer and to identify whether different areas of cancer in the same patient could be related to each other or could have descended from each other. A very practical use for this is the potential to identify if pulmonary squamous cell carcinoma in a patient with head and neck squamous cell carcinoma might represent metastatic disease or a second primary. Depending on the approach taken for these two scenarios, it may have profound implications for a patient who may be denied potentially curative treatment when this might be possible if such a lesion is incorrectly declared metastasis. For some time, the ability has been available to achieve this diagnostic distinction using molecular tools for an important element of cancer staging, but as yet it seems not to have been translated actively to the clinic [67, 68].

9.12.1 The Importance of Host Factors

It has been well recognized that features of the host have significant prognostic impact in head and neck cancer. However, with the exception of differentiated thyroid cancer, where patient age is an important factor, the head and neck TNM classification does not take into account any host characteristics.

A consistent feature of the management of laryngeal cancer has been the demonstration that female gender is a powerful and independent favorable factor in addition to other more traditional factors. In a large retrospective series ($n=1252$) from Aarhus University Hospital in Denmark, women had absolute improvements of approximately 10 % compared to men for all cancer-specific outcomes including local control, locoregional, disease-specific survival, and overall survival following curative radiotherapy [69]. Female gender seems to retain this favorable advantage in other sites as well, based on a very large series ($n=3821$) from Germany [70]. For this reason, reports of adverse outcome in HPV-related oropharyngeal cancer in women compared to men are unexpected [38, 71]. While these represent small studies, they raise the possibility of host interactions with the biological process underlying the pathogenesis of head and neck cancer and the subsequent response to treatment. Earlier we have also noted the discrepancy in outcome between black and white patients with oropharyngeal squamous cell carcinoma and the fact that there is a dramatic difference in the association of cancers in these two groups with HPV oncogenesis, and the precise reasons underlying this remain speculative [53]. It is not just a difference in HPV however but a complex interplay between mutational, treatment, and socioeconomic differences [72]. There is also evidence that the status of the host immune system may be relevant and may be an explanation for the unusually favorable outcome of HPV-related oropharyngeal cancer compared to non-HPV-related cancers in this location [73].

Another well-described host-related prognostic variable for outcome in head and neck cancer is comorbidity. Comorbidity is described as "the presence of one or more medical ailments, in addition to the primary tumor but not caused by the primary tumor" [74]. Risk factors for the development of head and neck squamous cell carcinoma, such as smoking and alcohol abuse, contribute to other diseases as well (e.g., cardiovascular, pulmonary, or hepatic diseases). Therefore, comorbidity is to be expected in these patient groups. This has been well established by early work from Piccirillo [75] to more recent reporting of the influence of comorbidity for the first time in hypopharyngeal cancer [76]. Depression has been demonstrated to negatively affect survival as well [77]. Several established validated instruments designed to code and quantify comorbidity are available. These include, in historic order, the cumulative illness rating scale (CIRS) [78], the Kaplan–Feinstein comorbidity index (KFI) [79], the Charlson comorbidity index (CCI) [80], and the index of coexistent disease (ICED) [81].

In a comparative study of these four instruments, the KFI was the most successful in stratifying patients with head and neck cancer [82] though the CIRS appeared to be uniquely robust in another report that addressed laryngeal cancer exclusively managed with surgery [83]. Whether this would apply to patients treated with organ preservation strategies is unclear and emphasizes the context-based nature of some of these analyses that are sometimes overlooked. Nevertheless, a very consistent finding throughout such literature of head and neck cancer is the observation that comorbidity, assessed in various ways, seems to have as significant effect as the stage in understanding the prognosis of patients with these cancers and needs to be considered in designing treatment approaches. These analyses may also provide a framework for amalgamation of the various elements of prognosis into usable prognostic models that may be applicable in a broader perspective. This is discussed in Sect. 9.12.3.

9.12.2 The Importance of Environmental Factors

The relationship between outcome and the environment where the patient with head and neck cancer is treated can be profound, and the reasons underpinning these can be complex. What sets these apart from other prognostic factors is that they exert influence external to the parameters of the host and tumor, but their value relates to their ability to explain reasons for differential outcomes for treatments that might otherwise be expected to be similar. A classification is available and includes factors related to the physician, the health-care system, and society [34]. Each can also be subdivided into treatment-related issues (e.g., expertise, access, and health-care delivery processes), educational issues (e.g., participation in continuing education, development of practice guidelines, and access to information), or quality issues (e.g., quality of treatment, quality of the health-care facility, and access to affordable health insurance). Interested readers should consult the original description for a more detailed review [34].

The problem of environment as a prognostic factor is well exemplified by the report of outcome in a large prospective randomized trial where the technical planning and radiotherapy parameters of almost 700 patients were evaluated by a team of expert head and neck radiation oncologists. This review was undertaken without knowledge of the outcome of the patient or of the arm of the trial on which the patient was treated. In patients who received at least 60 Gy, those with major deficiencies in their treatment plans had a markedly inferior outcome compared with those whose treatment was initially protocol compliant. The 2-year overall survival was 50 % vs. 70 % (hazard ratio 1.99; $P<0.001$), and the 2-year freedom from locoregional failure was 54 % vs. 78 % (hazard ratio 2.37; $P<0.001$) for deficient vs. compliant radiotherapy, respectively. A large variation in the percent of plans with major adverse impact was noted according to country. Even more striking was the correlation between the number of patients entered and the probability of receiving

unsatisfactory radiotherapy. In centers enrolling fewer than five patients, 29.8 % had a predicted major adverse impact compared with 5.4 % in centers enrolling more than 20 patients [84]. A Canadian study of outcomes related to surgeon and hospital volume showed significant relationships. After controlling for clustering and patient/treatment covariates, hospital volume continued to be significant as a predictor of mortality [85].

Another interesting example relates to the availability of modern radiotherapy facilities in the form of access to intensity-modulated radiotherapy (IMRT). The use of IMRT has rapidly become widespread for the delivery of radiotherapy for patients with head and neck cancer in the USA. However, significant geographic variations are apparent in the utilization of IMRT, and patients in census tracks comprising the lowest socioeconomic quartile were less likely to receive IMRT than their more affluent counterparts [86].

Other reports also point out disappointing examples of environmental health-care disparities associated with advanced head and neck presentations in the USA. These are much more likely to be evident in patients without adequate health-care insurance, or individuals, especially blacks, residing in regions with low educational accomplishments or with low median household incomes. Similar findings were seen in patients with laryngeal cancer [87] and oropharyngeal cancer [88]. The authors indicate that it is important to consider the impact of insurance coverage on disease stage at diagnosis and associated morbidity, mortality, and quality of life.

Similar findings on stratified analysis and logistic regression were applied to two million incident cancers (1997–2000) from 32 states representing 57 % of the US population. For a great many cancers, poverty as a factor independently predicts advanced-stage cancer suggesting that improved access and utilization of good medical care might facilitate earlier diagnosis and longer survival [89]. Consistent with these findings is the report of a large series ($n=1231$) of patients with primary squamous cell carcinoma of the oral cavity, pharynx, or larynx diagnosed or treated at the University of Pittsburgh by Kwok et al. [90]. They report that patients with Medicaid/uninsured and Medicare disability were at increased risk of death after a diagnosis of SCCHN when compared with patients with private insurance, after adjustment for age, gender, race, smoking, alcohol use, site, socioeconomic status, treatment, and cancer stage. Similarly, Molina and colleagues studied 20,915 patients with head and neck cancer in the Florida Cancer Data System and showed that African American and poor patients have a dramatically worse prognosis although the disparity is not entirely explained by demographics, comorbidity, or undertreatment [91].

While numerous other factors are also associated with adverse outcome, space does not permit a more detailed discussion of this very important and often overlooked area. Ironically, as implied by the examples shown above, these factors have the greatest potential for remediation with consequent improvement in outcome compared to other prognostic factors, but this can only be accomplished if resource inadequacies and process deficiencies are addressed.

9.12.3 Combining Variables and Validation

The science of prognostic factor assessment is a nascent area that needs to be considered in a broader context. We have seen that the dimensions of prognosis in head and neck cancer cover a wide field, yet there remains uncertainty about how to proceed in our goals of using the extent of this knowledge to its full capability. It does appear that critical dismissal of one dimension as being less useful than another is probably not the solution, nor is it helpful to dismantle a system that is being used successfully worldwide, for nearly half a century, to permit newer elements to be introduced if the framework was not designed to receive them. In general terms, some agreement on taxonomy and methodology is required. Perhaps the adoption of formal terms such as *staging* to describe the anatomic extent of disease and *profiling* to describe the qualitative characteristic of tumors may be a start. The use of the term *prognostic models* could then permit them to be combined in a rational way that allows their full impact to be exploited. These concepts are under active discussion by the UICC and AJCC. Different aspect of these will be discussed below under different rubrics that address the traditional TNM groupings, the use of prognostic indexes, the use of nomograms, and the area of validation and comparison of prognostic models.

9.13 Handling Prognostic Groups Within TNM

In addressing the need to combine different prognostic elements into groups, the UICC and the AJCC took slightly different approaches in the seventh edition TNM classification. The AJCC substituted the term "Anatomic Stage/Prognostic Groups" in place of what were previously termed "Stage Groups" when the elements of TNM are combined together within the TNM in the seventh edition [1]. However, the goal of the new terminology is the same as it was previously, i.e., to create a basic form of prognostic index. The UICC approached this slightly differently in the seventh edition although the intent is identical to the AJCC, namely, to permit the incorporation of validated nonanatomic prognostic factors at present or in the future. The UICC's approach is to use two forms of grouping of component elements [2].

The predominant one is termed "Stage Groups" and contains only anatomic factors for virtually all sites within TNM and represents the same "Stage Groups" as were used in the former sixth edition. Certain diseases that traditionally used some nonanatomic factors, e.g., thyroid cancer where age has been incorporated and sarcomas that included grade, are retained in the "Stage Groups" of the seventh edition to avoid disruption to a classification developed many years ago. However, the incorporation of newer nonanatomic factors is being addressed by the creation of a third dimension within the UICC's version of TNM in the form of "Prognostic Groups." In truth, these are identical to the AJCC's "Anatomic Stage/Prognostic Groups" in the few diseases where this applies, and for all other diseases, the UICC "Stage Groups" are analogous. At present only two diseases have the new "Prognostic Groups" in the UICC version, namely, prostate and esophageal cancer, in both of which pathological grade was recently introduced in the classification. There were no head and neck sites included in this process in the seventh editions. In time, it is possible that the UICC may also modify thyroid and sarcoma so that the anatomic and nonanatomic elements will only be aggregated together in the "Prognostic Groups," and the "Stage Groups" will only contain anatomic extent of disease variables throughout TNM. In this way, anatomic disease extent can be addressed independently in "Stage Groups" or in combination with nonanatomic factors in the "Prognostic Groups," the latter being analogous to the "Anatomic Stage/Prognostic Groups" of the AJCC. Currently discussions are underway as to how best to amalgamate these two ideas and whether to expand these "Prognostic Groups" to head and neck.

A final and more sobering dimension in the area of "Prognostic Groups" or "Stage Groups" is the fact that these are generally developed in a pragmatic rather than pure scientific way. Hence, the literature contains numerous examples of the theme that the TNM stage group classifications, while successful in creating statistically distinct groups, often do not perform as well as other stage grouping systems [92]. Potentially, the future will require some attention to this area of research as well if the groups formulated within the classification are to be considered seriously. Detailed discussion of alternative staging systems is reported in the literature [93].

9.14 Prognostic Indexes

The head and neck literature contains a growing body of reports devoted to combining different elements of prognosis together. Generally, the intention is to focus on a particular setting (e.g., previously untreated patients, patients with recurrent cancer, patients with metastatic disease, early-stage disease vs. more advanced disease, etc.). Usually, the intention is to facilitate decision-making in the management of patients, usually concerning some intervention. Behind most is the goal of generating a quantified prognosis in the form of a score that may be useful to the patient, guiding clinical decisions, or for guiding eligibility for clinical trials tailored to specific treatments and patient types.

Some of the dimensions are appropriate to combine together, but as we have discussed, this can be fluid and variables are highly interdependent. Some factors are not present at baseline. A typical example is the inclusion of the status of resection margins in a model where this variable only becomes available after the first and often most important treatment has been administered (namely, surgery). Thus, it is not only unavailable at baseline, but it also automatically selects out cases with different prognosis based on their likelihood of undergoing a successful resection with clear margins. Cases with positive resection margins can be expected to be already having adverse prognosis from the standpoint of the anatomic extent of disease, but such classifications may still be highly useful in guiding decision-making for the use of adjuvant treatments once the primary treatment has been undertaken. This further illustrates the theme that disease extent must be considered in applying prognostic models, and one cannot necessarily extrapolate to another setting whether it concerns different stages of disease, different anatomic sites, or different scenarios (e.g., primary vs. recurrent cancer).

There is insufficient opportunity to explore the different models that have been developed in the head and neck area, but these include, among others, attention to parotid cancer [94, 95], metastatic nasopharyngeal cancer [96], laryngeal cancer [83], hypopharyngeal cancer [76], and various combinations of cancers of the larynx, oral cavity, and pharynx [74]. Some of these studies were mentioned earlier in the context of comorbidity in Sect. 9.12.1 where many have included comorbidity assessed in various ways combined with the TNM and other elements of anatomic disease extent and included other factors such as age, gender, and some pathological features. An outstanding example of this demonstrates that both claims-based and chart-based reviews have significant predictive capabilities [97]. As yet there is no report that incorporates a robust model that combines molecular characterization of disease (or even host) with more traditional domains, and this type of work is very inviting for the future. As noted some studies have combined different prognostic factors that include biological markers with more traditional parameters such as gender and smoking, but they have not as yet been formulated into a prognostic index to guide decision-making for individual patients or even groups of patients [38, 53].

9.15 Nomograms

Nomograms are widely used for cancer prognosis, primarily because of their ability to reduce statistical predictive models into a single numerical estimate of the probability of an event that is tailored to the profile of an individual patient [93]. Often these use appealing graphical interfaces, commonly displayed by computer, that facilitate interaction with individual patients about their personal disease situation. While widely used in some areas of oncology, especially prostate cancer, there is a small but growing body of literature addressing various questions through the use of nomograms for head and neck cancer [98, 99]. Gross et al. developed a nomogram for guiding adjuvant treatment after surgery for oral cavity squamous cell carcinoma [100]. Notably, this was developed for relatively early-stage resected oral cancer, and this context must be remembered as it is easy to stray from the original basis of the nomogram when using it to discuss problems with patients. So far there is no evidence that this is happening in head and neck cancer, but there may be such instances in other diseases.

The AJCC, in particular, is exploring the use of nomograms to address the potential goal of creating a "continuous prognostic nomogram" for each site and each patient, where the anatomic TNM staging will remain as the fundamental factor, but other important features, such as biomarkers as well as comorbidities, will be included with a weighted score to arrive at a "prognostic score," at any given point throughout the patient's life [10]. In this concept, the prognostic score will be a dynamic "staging and prognostic" tool to accurately reflect each patient's prognosis at the point of inquiry. The beauty of this is that its dynamic nature throughout a patient's life gives an accurate assessment of prognosis, while retaining the static parameters of TNM staging in its construct. This would also be a perfect example of "personalized prognostic model," for each patient. The CS approach implemented by the AJCC will act as a repository of all available prognostic information for current and future use to support this approach. This ambitious project is potentially both welcome and problematic. Clearly, it is important to be able to encompass the multiple dimensions of prognosis in this way, and the concept is certainly meritorious. On the other hand, a limitation is that it largely relates to individual prognosis at this time, and additional development will be needed to address groups of patients since one of the goals of the stage classifications is to be able to compare results across groups, in trials, and among regions. Thus, there is the possibility that two systems of staging and prognostic modeling may be required. One would be an individualized nomogram, and the other would be stage groupings, to compare results and outcomes of groups and for protocol entry. Another challenge concerns the statistical underpinnings of these models that require careful scrutiny, including the degree of uncertainty surrounding the point estimates. This is thoroughly addressed in a review that includes cautionary language that the methodology underlying the construction of nomograms should be understood by clinical users so that prognostic estimates are appropriately communicated [101].

9.16 Validation and Comparison of Prognostic Models

An important aspect to the creation of prognostic indexes concerns the underlying statistical principles and the epidemiological basis for their creation. This area cannot be addressed here, but the reader should be aware of such principles as the generalizability of the index to patients outside the source population. It includes transportability of results beyond the domain where it was created such as transportability regarding geographic location, but also by time or era, which may be more difficult to address with different historical dimension to the data, its assembly, and its use. Other dimensions include clinical and statistical validation. The complex nature of these issues and the assumptions behind the models, including understanding their inherent weaknesses, require attention and are summarized more completely elsewhere [92, 93, 102, 103].

Other elements in understanding prognostic models, and especially when comparing models against each other, concern a variety of concepts in the evaluating process. These include hazard consistency (i.e., homogeneity within strata for the outcome of interest), hazard discrimination (i.e., each stratum chosen should have a statistically distinct prognosis compared to the stratum above and below it for the outcome), outcome prediction (i.e., maximizing prediction accuracy by techniques such as percent of variation in outcome explained by the scheme or by measuring the slope or degree of separation in the mean probability predictions), and balance (where different prognostic strata or groups are relatively even and balanced). These are detailed elsewhere for the interested reader [92, 104].

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