Introduction of the 7th Edition Eyelid Carcinoma Classification System From the American Joint Committee on Cancer–International Union Against Cancer Staging Manual

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● Context.—The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer commissioned the Ophthalmic Oncology Task Force to modify and update the ophthalmic chapters of the 7th edition of the AJCC Cancer Staging Manual.

Objective.—To review the existing eyelid carcinoma chapter in the 6th edition of the AJCC Cancer Staging Manual for its clinical and research utility and to seek evidence-based revisions with the strongest medical foundation to use in updating the anatomically based TNM cancer staging system manual.

Data Sources.—The 4-year Ophthalmic Oncology Task Force consisted of 45 tumor specialists from 10 countries and an extensive internal and external peer review process. The 10-member Carcinoma of the Eyelid team included a diverse group of international authors. The group included extensive representation by clinicians, pathologists, surgeons, radiation therapists, and cancer registrars, all with advanced, ophthalmic cancer–related areas of subspecialty. Data sources included the above expertise applying a worldwide medical literature search, with no discrimination based on language, country of origin, discipline source, specialty source, or surgical practice.

Conclusions.—Revisions were made to the TNM classification in areas with the strongest basis in evidence and practical effect. Lymph node staging data were expanded markedly to reflect its significant prognostic value. T3 and T4 were redefined and stage groupings were added that applied current understanding in tumor biology, respected site-specific risk factors, and provided greater correlation with the common language of the overall AJCC Cancer Staging Manual. Evidence-based biomarkers and data-field modifiers were included to capture additional pathologically and clinically substantiated prognostic factors.

(Top Pathol Lab Med. 2009;133:1256–1261)

The American Joint Committee on Cancer (AJCC) was established in 1959 to develop classification systems for cancer, including staging and the reporting of outcomes. The AJCC has a diverse and multidisciplinary membership. Its classification and staging of cancer are widely accepted in oncology disciplines. The International Union Against Cancer reaches an additional 103 countries worldwide and hundreds of international member organizations. The AJCC’s cancer staging handbook is used throughout the world as a common language for cancer staging, based upon a (primary) tumor, (regional) lymph node, and (remote) metastasis (TNM) classification system. Sharing a common language is the first step toward expansion of the worldwide database for eyelid carcinomas, and it allows the sharing of new concepts in tumor management and biology.

The Ophthalmic Oncology Task Force was commissioned by the AJCC to update the ophthalmic cancer sections for the 7th edition of the AJCC Cancer Staging Manual. This article serves as an introduction to the chapter on eyelid carcinoma and specifically highlights the differences between the 6th edition and 7th edition.

MATERIALS AND METHODS

We used an evidence-based, peer-reviewed process to identify TNM staging factors worthy of inclusion and to justify the proposed modifications for the 7th edition. We strived to pool data from the most inclusive scope of published literature and to improve on the common TNM staging language to meet the needs of a broad spectrum of clinicians and scientists. We specifically aimed at proposing only modifications that could be applied in almost all regions of the world. The required data had to be easily recordable and reproducible, regardless of the possible variations in available health care resources. The 4-year Ophthalmic Oncology Task Force consisted of 45 tumor specialists from 10 countries. This body of international ophthalmic cancer experts served as a secondary level of internal peer review. The 10-member Carcinoma of the Eyelid team included a diverse group of international authors. The group included extensive representation by clinicians, pathologists, surgeons, radiation therapists, and cancer
registrar, all with advanced, ophthalmic cancer–related areas of subspecialty. The chapter was written by designated committee members and then peer-reviewed by several independent experts in the field in a primary, secondary, and tertiary reviews process. By design, the review integrated the broadest range of discipline input. Suggested revisions by coauthors and reviewers were discussed and implemented based on the strength of the scientific evidence, our mission focus for the AJCC Cancer Staging Manual, vigorous peer review by diverse areas of specialty, and final consensus between the committee and lead authors.

RESULTS

The “Carcinoma of the Eyelid” chapter underwent modifications in both the 6th and 7th editions of the AJCC Cancer Staging Handbook. The main update for the 6th edition was the designation of a site-specific listing for infiltration of adjacent structures, designated as T4. The specific listing included bulbar conjunctiva, sclera, globe and deeper structures including perineural spread, orbital invasion, bone invasion, and invasion into the paranasal sinuses and the central nervous system. Inclusion of any of the above-named adjacent structures classified the tumor as T4 in the 6th edition.

Although the 6th edition chapter on “Carcinoma of the Eyelid” attempted to expand the defining features of adjacent infiltration, it fell short on practical applications. For example, in the 6th edition, an eyelid carcinoma with bulbar conjunctival extension, which was amenable to globe-preserving surgical resection, fell into the same T4 category as a tumor with deep orbital invasion that would be amenable only to orbital exenteration. A nonresectable tumor with deep central nervous system invasion would also be a T4 in the 6th edition classification. In the 7th edition, we have tried to improve the practical, surgical correlation of TNM factors, with the level of tumor aggression (Tables 1 and 2).

The 7th edition redefined and subdivided T3 and T4. These revisions were based on strong, historic, site-specific, pathology-driven databases, such as the Armed Forces Institute of Pathology database, as well as current literature from a broad scope of pathologic, surgical, and clinical perspectives. This evidence-based foundation supports primary tumor (T3 and T4) revisions that are more predictive of tumor behavior and the effect on patients. For a patient, surgeon, pathologist, and tumor registrar, there is a huge difference between the evidence-based features of a T1 lesion requiring local excision, and a T3b tumor associated with clear margins following exenteration. T3 for many carcinomas is generally defined by greater depth of invasion, greater tumor size, and invasive features, such as perineural invasion, which correlate with the need for a more radical excision. T4 is defined as a tumor that is not surgically resectable anatomically because of the extent of local or regional infiltration.

In the AJCC Cancer Staging Manual, designation of medial canthal carcinomas presents a unique clinical challenge, given the higher risk of deep orbital invasion and invasion into the nasal cavity and paranasal sinuses. In the 7th edition, the anatomic description of the primary site was expanded to include carcinomas of the periorbital region, including medial and lateral canthal carcinomas. Stage groupings are another major modification in the 7th edition (Table 3). Primary carcinoma of the eyelid is categorized into 4 stage groupings. Stage I refers to an eyelid carcinoma limited to the eyelid. Stage II refers to an eyelid carcinoma with involvement of adjacent structures but that is surgically resectable without removal of the globe. Stage III refers to any tumor that also includes the presence of regional lymph node metastasis; a locally
advanced tumor requiring an enucleation or orbital exenteration; or an anatomically nonresectable tumor. Stage IV refers to any tumor that also includes the presence of distant organ metastasis.

The “Carcinoma of the Eyelid” chapter in the 7th edition1 markedly expands the data collection on lymph node status. Submitting surgeons and tumor registrars are requested to confirm the source of the lymph node data, that is, whether it was a clinical diagnosis, a radiographic finding, or a pathologically confirmed lymph node status1 (Figure 1, A and B). There is a “Sentinel Lymph Node Biopsy (SLNB)” section within the newly acquired biomarker database. Was SLNB performed? Was carcinoma present? Were there findings of abnormal lymph nodes identified on clinical or radiographic examinations?

“Evidence-Based Biomarkers” and “Data Field Modifiers” are 2 new sections in the 7th edition,1 included in the chapter for “Carcinoma of the Eyelid.” Biomarkers have the strongest basis in evidence, and in this chapter, pathologically confirmed risk features, such as neurovascular or lymphatic invasion, are covered. The “Data Field Modifiers” section captures highly associated clinical features, such as a history of human immunodeficiency virus or multiple carcinoma syndromes. The TNM staging criteria, the biomarkers, and the data field modifiers are designed to work in practical harmony as noted by the following case presentation.

REPORT OF A CASE

A 72-year-old woman presented with an infiltrative upper eyelid mass, which, on incisional biopsy, proved to be a poorly differentiated sebaceous carcinoma. Wide excision was performed with additional map biopsies of the conjunctiva in adjacent quadrants. A SLNB was performed, and the sentinel lymph node findings were negative for metastasis. The largest tumor dimension was 12 mm. There were multiple, high-risk, histologic features
including tumor necrosis, pagetoid spread, perilymphatic spread, and neurovascular infiltration (Figure 2, A and B). Findings from a systemic workup, including computed tomography of the chest, abdomen, and pelvis, were negative for metastatic disease. The patient had a 20-year history of multiple, primary, visceral, and skin carcinomas. The sequential list of primary carcinomas included 2 primary colon carcinomas separated in time by 5 years, resulting in first a left, and then a right, hemicolectomy. She had also presented with pathologically distinct endometrial carcinoma and multiple basal cell and squamous carcinomas of the face, arms, and back. All previous carcinomas during 20 years were successfully resected. The pelvis was augmented with external-beam radiation therapy. A diagnosis of Muir-Torre syndrome was definitively established with the finding of sebaceous carcinoma of the eyelid after 20 years of a multiple carcinoma syndrome. Our patient is currently alive and well, 4 years later, with limited new squamous carcinomas of the skin on her chest and scalp found by close total-body carcinoma observation and early preventive care.

The AJCC TNM classification of this patient’s sebaceous carcinoma of the eyelid was T3apN0M0. Perineural involvement elevated the T stage from T2b to T3a. Her stage grouping was thus stage II, indicating that resection sparing the globe was possible. Biomarker results were recorded and included perineural invasion. Data field modifiers indicated a SLNB was performed, and there was no clinical, radiographic, or SLNB evidence of nodal infiltration. Data field modifier points were captured for a clinical history of multiple carcinomas, most specifically, Muir-Torre syndrome.

COMMENT

It was important that we remained true to the mission of the AJCC cancer staging handbook and to the mandate to the Ophthalmic Oncology Task Force to revise and update the 7th edition.1 Our goal was to provide an evidence-based revision to the cancer-staging manual that was practical and concise. The clear, simple language can be understood and applied worldwide.

The AJCC Cancer Staging Handbook allows clinicians to communicate and report outcomes of cancer treatment in a uniform, reproducible, and effective fashion.1,2 Despite the availability of AJCC classifications for ophthalmic tumors for several decades, there is remarkably little published data in the ophthalmic literature on their use for any of the ophthalmic tumors, including eyelid carcinomas.

One objective of the Ophthalmic Oncology Task Force for the 7th edition was to encourage an inclusive, diverse process among an international group with expertise in ophthalmic oncology. We wanted the process to be inclusive and to stimulate eventual acceptance of the final product. We refer the reader to an article in this issue entitled, “The 7th Edition AJCC Staging System for Eye Cancer: An International Language for Ophthalmic Oncology,” by Paul T. Finger, MD. Dr Finger presents the scope of current domestic and international support for the 7th edition AJCC-UICC Classification System, and the value of a common language in ophthalmic cancer staging.

The eyelid carcinoma chapter in the 7th edition attempts to make the classification more relevant to real-life clinical situations and to make the handbook correlated with new insights about the clinical and biologic behavior of eyelid carcinomas.3

No revision is perfect. This is a process in which we look to the future while achieving our task force goals based on current evidence, open diversity, critical peer review, and the practical cohesive mission of the AJCC Cancer Staging Manual.1

Some questions appear disparate only to resolve calmly when we look at the overall context of the AJCC Cancer Staging Handbook.1 To my pathology colleagues, I apologize in advance for discussing how vital a specimen submission form can be. I am sure at your hospital or service you have resolved this issue. For my clinical and surgical colleagues, we have seen the ebb and flow of the role of subspecialists and how our services overlap. We celebrate the diversity. In the high and low tides of ophthalmic pathology history, there will always be advocates and equally talented individuals who question the need for a site-specific chapter within AJCC. Rather than engage in these historic discussions, I would prefer to illuminate 3 areas of concern with more concrete resolution. These areas are also addressed in the general principles of pathologic tissue handling and within the AJCC Cancer Staging Handbook approach.3

Three Practical Questions

1. How will the data be coded for an invasive carcinoma of the eyelid, brow, and face?

- Surely, we need only 1 staging system of all skin carcinoma.

- Are cancers of the ophthalmic site truly a unique group of cancers?

The issue of why the entire “Ophthalmic Site” has been accepted as a distinct site-specific location for many editions relates to the unique tumor biology and anatomic pathophysiologic nature of ophthalmic oncology.

Answers to questions of correct tissue identification are concrete and largely resolved within tissue processing protocols. The submitting surgeon with the greatest knowledge of the patient is responsible for the tissue submission form and proper labeling of the specimen. If the submitting surgeon identifies the primary tissue as right eyelid from wide excision, then the specimen is accessioned as “right eyelid from wide excision.” Rarely does a pathologist override a submitting tissue identification. Such an override would require an alert report in many institutions.

2. What does the tumor registrar do if a diagnostic biopsy is performed and the patient declines radical surgery for an invasive tumor?

- Does this cause problems with a pathologic staging classification?

- What does an eyelid carcinoma, nonresectable, T4 really mean?

- “Our hospital can fully excise these tumors; therefore, it is not really nonresectable.” Who determines T4 status?

If an incisional diagnostic biopsy is performed, the anatomic tissue is coded as an incisional diagnostic biopsy. (Dear pathology colleagues, I again beg your pardon for stating the obvious for a normal diagnostic biopsy protocol.) The pathology report for that specimen would not contain an AJCC “Carcinoma of the Eyelid” staging comment. Variations in capability between surgical hospitals and cancer centers of excellence are important topics for a given patient or surgeon. However, in the greater scope of cancer treatment, the AJCC Cancer Staging Manual is designed to be of benefit worldwide in a variety of settings.
with a variety of capabilities. The term nonresectable is intentionally flexible to allow for the judgment of the treating surgeon, who may be providing care for a highly infiltrative tumor in a region of the world with incredibly limited assets and a population that lives on the margin.

Pathologically speaking, a nonresectable tumor (T4) is defined by a “final” radical excision specimen with carcinoma infiltration at the surgical margin. Future editions may choose to subdivide anatomic from nonanatomic levels of T4. Even that idea will find proponents for further discussion of the ever-expanding limits of anatomic boundaries for resection.

3. Why does the “Ophthalmic Site: Eyelid Carcinoma” chapter have a different definition of T3 and T4 from other unique sites, such as for head and neck carcinomas?

- Why do the stage groupings for eyelid carcinoma not match the criteria for head and neck carcinoma?
- What is the most common definition of stage IV carcinoma in the AJCC Cancer Staging Handbook?

The most common definition of stage IV carcinoma in the AJCC Cancer Staging Handbook is distant metastatic disease. We made a conscious decision to use the same definition of stage IV, distant metastatic disease, for “Carcinoma of the Eyelid.” We followed the same common language for stage III disease, representing regional nodal disease or, at minimum, invasive carcinoma requiring radical excision, such as an exenteration, with or without clear surgical margins.

These definitions are most consistent with the language of the AJCC Cancer Staging Handbook and are strongly supported by an evidence-based review.

The carcinomas of the head and neck are in a unique site. They do have different primary tumor and staging definitions. In the head and neck stage grouping, distant metastatic carcinoma is not the principle defining feature of stage IV disease. There are historic, tumor biology, and anatomic reasons for this TNM and staging approach. Patients with head and neck carcinomas suffer more midline tumors with the potential for bilateral lymph node drainage into a series of nodal basins. Further insight into this unique carcinoma site can be gained by reading the chapters of the AJCC Cancer Staging Manual and reviewing the referenced supportive literature. Approaches to tumor factors and to staging criteria do vary by site.

One limitation of the 7th edition may be in the classification of periorbital carcinomas, particularly medial canthal carcinomas. This anatomic location is known to be associated with a high risk of local and regional recurrence and invasion into the orbit, nasal cavity, and paranasal sinuses. Carcinomas of the medial canthus may require a unique biomarker status. There are limits and trade-offs in the number of data points that can be obtained in a succinct cancer staging manual or chapter. The data inclusion and decision tree is a dynamic process. As the 7th edition is rolled out for validation studies in clinical practice, classification of medial canthal lesions probably will deserve further refinement.

We have gained considerable understanding of lymph node staging for eyelid carcinoma in recent years, particularly for squamous cell carcinoma, Merkel cell carcinoma, and sebaceous carcinoma. Clinical examination and imaging studies can fail to detect microscopic lymph node metastasis in up to 25% of cases of head and neck squamous cell carcinoma and 32% of head and neck Merkel cell carcinomas. A similar body of evidence is developing for these high-risk tumors of the eyelid and is worthy of collecting data field modifier findings and inclusion within the TNM classification analysis. Elective lymph node dissection carries significant morbidity and is probably not justified in all patients with eyelid carcinoma.

Sentinel lymph node biopsy has emerged as a less-invasive surgical procedure that allows for sampling the first-order lymph nodes draining the tumor bed, with less morbidity than a full lymph node dissection. A positive SLNB provides critical staging information and can help select patients who may benefit from additional treatments. The 7th edition specifically asks for information regarding how the lymph nodes were evaluated, separating clinical, imaging, and pathologic confirmation.

The information, captured within the entire framework of the new 7th edition of the AJCC Cancer Staging Manual chapter on “Carcinoma of the Eyelid” can be helpful in consideration of adjuvant therapies, such as postoperative radiation therapy to the eyelid or to the regional lymph node basins. The AJCC classification and stage groupings can help with the rational design of prospective trials evaluating these treatment options for more advanced-stage patients or for tumors with high-risk features.

We recommend implementation of the latest edition (7th edition) of AJCC classification for eyelid carcinomas into the practice of all surgeons and clinicians who manage eyelid carcinomas throughout the world. We encourage investigators who conduct studies reporting outcomes for eyelid carcinoma to define tumors based on AJCC classification and stage groupings, so that fair and reproducible comparisons can be made between treatment modalities and among various studies and centers.

We thank all authors and reviewers for the 7th edition of the AJCC Cancer Staging Manual chapter “Carcinoma of the Eyelid,” including: Chair, Paul T. Finger, MD; Darryl J. Ainbinder, MD; Christian Wittekind, MD; Leonard M. Holbach, MD; Zeynel A. Karcigolu, MD; Bita Esmaeli, MD; John H. Boden, MD; John B. Halligan, MD; Tero Kivelä, MD; Robert A. Mazzoli, MD; and the 45 members of the AJCC-UICC Ophthalmic Oncology Task Force who served as primary, secondary, and tertiary peer reviewers.

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