Cancer Staging

7

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7.1 Introduction

Informatics is transforming medicine. As electronic medical records (EMR) become ubiquitous throughout the world, government committees hope to sift through scientific data in efforts to prove or disprove the efficacy of medical practice. In this new world, eye cancer specialists will be required to prove efficacy for their methods and "statistical significance" will challenge "the art" of medicine.

We can see the early changes in our meetings, publications, and textbooks [1–3]. Presentations are transitioning from single-center case series to large multicenter retrospective studies [1–9]. Cooperative clinical and eye cancer research organizations are being created [2, 4, 5]. Our journals' instructions for authors are becoming increasingly complex, including more standardization of terms, increased prominence of and requirements for clinical trials, and a greater emphasis on evidence-based medicine.

Staging systems have long served as an important building block for the development of medical evidence. For example, past uveal melanoma staging systems have included Callender's prognostic classification related to histopathology and the clinically driven Collaborative Ocular Melanoma Study (COMS) [6, 7]. Using COMS-staged definitions of "medium" tumor size, plaque radiation was found equivalent to enucleation for the prevention of metastasis [8]. COMS also found no survival benefit to pre-enucleation external beam radiation therapy

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prior to enucleation surgery for "COMS-large" melanoma [9, 10]. Radiation retinopathy has also been staged for risk of vision loss [11].

Retinoblastoma was initially staged for response to radiation therapy by Reese and Ellsworth [12]. Then, as clinical practice evolved away from radiation, others devised classifications to predict retinoblastoma response to chemotherapy [13–15]. Lommatzsch evaluated published TpNM staging to predict mortality [16]. Staging also helped the Intergroup Rhabdomyosarcoma Study succeed in evaluation of treatment [17–19].

Thus, ophthalmic oncology has already benefited from staging to predict metastasis, response the therapy and the evolution of side effects. However, clinical staging also offers an opportunity to define epidemiological factors, biometric findings, as well as results of treatment and their side effects. In sum, staging systems serve as a standardized language for research, clinical practice and interdisciplinary communication. However, only universal staging can serve as a foundation for data collection, sharing for meta-analysis, and determinations of statistical significance.

7.2 Universal Staging and the AJCC–UICC Ophthalmic Oncology Task Force

The American Joint Committee on Cancer (AJCC) together with the Union International for Cancer Control (UICC) prompted the creation of The AJCC–UICC Ophthalmic Oncology Task Force (OOTF) [4, 5]. Its mission was to create a universally accepted staging system for all eye cancers [1]. Though these staging systems would continue to be anatomically based, the OOTF was also charged to provide practice guidelines for clinical data collection as well as pathology. For the first time, evidence-based genetic and molecular biomarkers were to be included for prospective data collection. Most importantly, the OOTF was to be made more robust and "internationalized" with members of the UICC.

7.2.1 The Community

Though past AJCC staging systems were comprehensive, eye cancer specialists did not typically use them. Even when the 6th edition made uveal melanoma staging roughly equivalent to the COMS classification, it failed to attract clinical use. Therefore, it was clear that the OOTF had to be reinvented. Rules, structure, and new concepts were required to guide the 7th edition toward universal acceptance (Table. 7.1).

The 7th edition, AJCC–UICC Ophthalmic Oncology Task Force was expanded to include 46 eye cancer specialists from 11 countries (France, England, Sweden, Finland, the United States of America, Canada, India, Japan, the Netherlands, Hungary, and Germany). Though weighted toward ophthalmic oncologists, orbital adnexal surgeons, and ophthalmic pathologists, the OOTF included input from radiation, medical, and pediatric oncologists as well as nonphysician specialists involved in the care of eye cancer patients [20].

7.2.2 The Process

Starting in 2004, the OOTF embarked on a 5-year peer-review process. Each tumor section (uveal melanoma, retinoblastoma, eyelid carcinoma, conjunctival squamous, conjunctival melanoma, lacrimal gland carcinoma, and orbital sarcoma) was reviewed for clinical methods and pathology techniques. The 7th edition staging system included but was not to be limited to *t*umor, *n*ode, and *m*etastatic (*TNM*) grading. There was general agreement that all changes were to be based on the "best data."

Table 7.1 Basic concepts: there is power in numbers!

What is made by the *community* will be used by the community
Sating systems will function as "*common language*" to collect patient data
Eye tumor specific *electronic medical records* (ETS-EMR) will facilitate prospective, multicenter data collection
Statistically *significant evidence* will be used as threshold to determine the allocation of resources
Database analysis will *improve patient care*

There was an emphasis on statistical significance. As available, evidence-based medicine was incorporated to achieve the highest possible standards.

Each 6th edition AJCC section was reviewed by a committee. Then a team consisting of a clinician and pathologist were tasked with writing a first draft revised staging system. In peer-review fashion, that draft was reviewed by a second, internal clinician pathologist team. Once found acceptable, the text was sent for multiple outside reviewers leading to secondary internal revisions and (in some cases) further external review for internal adjudication of conflicts. Lastly, prior to publication, each section was vetted by the AJCC executive committee, the publisher, and tumor registry representatives.

Despite all our efforts to create community consensus, the OOTF, the AJCC, and UICC all realize that tumor classification will be an ever-evolving process. For example, new biologic factors may help predict cancer outcomes and response to treatment, and they will have to be included in future revisions. As evidence-based and statistically significant data becomes available, it will be evaluated for incorporation into subsequent iterations.

7.2.3 Acceptance

So far, the 7th edition AJCC–UICC staging system has been accepted and used by ophthalmic oncologists, ophthalmic plastic surgeons, radiation oncologists, ophthalmic pathologists, tumor registries, and many related eye cancer specialties. This is in part due to their participation in its creation as well as its general acceptance by the College of American Pathology (CAP), the American Society of Ophthalmic Plastic and Reconstructive Surgeon (ASOPRS), medical journals, associated ophthalmic societies, and organizations [21–23]. To date, over 12 ophthalmic journals now either require or suggest that manuscripts use the 7th edition AJCC staging system in manuscript preparation. Further, over 130 world cancer agencies use the AJCC–UICC staging. This brings ophthalmic oncology into the mainstream of world cancer care.

7.2.4 Impact

7.2.4.1 Language: Do You Speak Ocular Tumor?

Language is defined as the human use of spoken or written words as a communication system. Sharing a common language allows us to communicate our ideas and thus enables progress. In order for the staging system to function as a universal language, it needed to be accepted by the entire community [1]. From this measure, the 7th edition AJCC–UICC staging system has indeed become "universal."

7.2.4.2 Patient Care

This is not a trivial point, because the use of the 7th edition staging system will save lives. For example, when a researcher publishes staged results of a new treatment for conjunctival melanoma, he or she will not only better understand the relative size, location, and distribution of the tumors treated, but can better compare those results against other published clinical studies. Staging will allow the clinician to better understand if the results of two differing treatments are confirmative or dissimilar.

Our clinical decisions are primarily based on ideas and studies and what we have heard in lectures or read in the literature, coupled with our medical experience. Therefore, the quality of those life and death decisions is only as good as the information we acquire. Universal staging will allow us to better categorize and understand that information. Future clinical decisions will be increasingly based on a foundation of defined tumor sizes and distribution.

Speaking "ocular tumor" will also affect informed consent. Much of our time as clinicians is spent explaining the current knowledge and ophthalmic practice to patients. A typical explanation of the risks and benefits includes what has been proven by statistics-based research and what is offered as traditional practice. Universal staging allows us to tell our patients that tumors of certain sizes and locations are more or less likely to respond to specific treatments or exhibit particular side effects [24, 25].

A common eye tumor language will change the way we practice medicine and help us cope with the current medical information explosion. From a time when there was only surgery, radiation, and chemotherapy, we currently have to widen our mindset to incorporate immunotherapy, epidemiology, genetics, and molecular biology (Table. 7.2). All these disciplines and their associated specialists must be linked to determine evidence-based best medical practice. This is particularly difficult for rare diseases like eye cancer, where research funds and statistically significant evidence are scarce. Excellence in ophthalmic oncology will increasingly require a multifaceted approach to individualize and maximize of patient care.

7.2.4.3 Eye Tumor-Specific EMR-Based Database

The evolution of staging systems will generate data fields that will be used to form intelligently structured, eye tumor-specific electronic medical records (ETS-EMR). In turn, this ETS-EMR will be used to link eye cancer specialists throughout the world. A form of this approach called "e-cancer Care" is currently being implemented for retinoblastoma linking Canada, India, and Kenya [26].

To accomplish this, each center will have an overlay ETS-EMR that virtually sits on top of their clinic-specific medical record. Each of these two programs will work symbiotically. That is, each EMR will be able to both withdraw and distribute what information is required to accomplish their individual functions.

Table 7.2 The evolution of cancer care

Since 1500 BC	1903	1940s	Present
Surgery	Surgery	Surgery	Surgery
	Radiation	Radiation	Radiation
		Chemotherapy	Chemotherapy
			Genetics
			Immunotherapy
			Molecular biology
			Epidemiology

Once installed, multiple international centers will be empowered to collect large amounts of equivalent data that can be added to derive statistical significance [20, 21]. This will enable further refinements in staging systems, incorporation of valid genetic and molecular biomarkers, comparisons of commonly used diagnostic and therapeutic methods, as well as monitoring of newly devised interventions.

7.2.4.4 Multicenter Collaboration

Multicenter collaboration will allow recruitment of larger numbers of patients and/or clinical samples in shorter periods of time. They will prevent duplication of effort, loss of resources, and encourage cooperation. In comparison to single-center studies that are particularly sensitive to selection bias, poor quality data collection and analysis; prospective multicenter studies are more likely to be better funded, organized, and thereby higher quality.

Universal staging and multicenter collaboration will accelerate the development of new methods of eye cancer diagnosis and treatment. In this case, speed will save lives. For example, what if by the year 2023, 20 ophthalmic oncology centers had been collecting standardized ETS-EMR data from each and every choroidal melanoma patient encounter for 10 years. This would be the best quality data, derived at the time of the specialist–patient interaction using the community-designed data fields and standards embedded within ETS-EMR. Given each center was able to enter 100 cases per year for 10 years, these 20 centers could draw on a database of 20,000 cases of choroidal melanoma. By the year 2033, it would be 40,000 cases or more. These are unprecedented numbers of choroidal melanoma patients from which we could discover statistically significant epidemiological features as well as differences in efficacy of our methods of diagnosis and treatment. There would also be opportunities to examine large numbers of less common tumors (e.g., adenoid cystic carcinoma of the lacrimal gland, conjunctival melanoma). In addition, consider the value of a database collection of rare therapeutic side effects and their treatments.

What if a future researcher thinks he or she has discovered "a cure" for retinoblastoma? But that researcher's single megacenter treats only 40 new patients per year and they require 1,000 patients for a statistically significant prospective randomized clinical trial. If that researcher were to employ that "new treatment" for each and every patient in their center, it would take 25 years to enroll patients for that one study and may take another 5 years to follow the last patient for local recurrence or metastasis (Table. 7.3). Simply put, it would take an academic career or 30 years to properly study this one treatment. On the other hand, with a multicenter cooperation of 10 centers each recruiting 40 patients per year, prospective recruitment would take just 2.5 years. Even with the additional 5 years of follow-up, multicenter cooperation would reduce the total project time from 30 to 7.5 (a reduction of 22.5 years). Plus, those 25 centers can go on to evaluate the next diagnostic method or treatment after just 2.5 years of recruitment (Table. 7.3). Multicenter cooperation would enable recruitment for up to 12 studies during that same researcher's 30-year career.

Multicenter cooperation could also function as an early detection system for failed treatments. A large database could anonymously collect the few cases from here and there where a treatment failed but was not published. Rather than allowing failed treatments to proliferate and fade away, recording the outcomes of unsuccessfully treated patients will spare future patients to repetition of those suboptimal or failed treatments and keep us from wasting precious resources.

Table 7.3 Testing a new cancer treatment

Single center	Multi-center
40 patients per year ×25 years =1,000 patients	40 patients per year × 10 centers × 2.5 years =1,000 patients
5 years follow-up	5 years follow-up
One study = 30 years	One study = 7.5 years
A lifetimes work testing one treatment hypothesis	Plus another study every 2.5 years or 10 completed studies within 30 years

Lastly, consider the wealth of patient information that can be permanently embedded in an electronic database. A functioning eye cancer bioinformatics grid will not lose data when physicians retire or move elsewhere. Quite the contrary, a functioning bioinformatics grid will gift opportunities for retrospective data analysis for future generations of eye cancer specialists.

7.3 Summary

The OOTF composed of members of the AJCC, UICC, representatives of our journals, and societies have developed universal 7th edition AJCC–UICC staging, a foundational element for an eye cancer bioinformatics grid (http://eyecancerbig.com). Our next step is to provide evidence that these data points and tumor stages are valid. Therefore, the 7th edition system is currently being tested within the framework of large multicenter retrospective studies that will be used to evolve eye cancer staging in the 8th edition, improve universal staging, and serve as a foundational element for the multicenter ETS-EMR eye cancer-specific bioinformatics grid.

Our generation is standing at the forefront of a new medical information age. Many of the advances in medicine will stem from or be enabled by multicenter cooperative data analysis. It is time for ophthalmic oncology to evolve from megacenter to multicenter in the best interest of our patients. Bioinformatics can be used as a tool to improve the standards of our medical practice by supporting evidence-based preferred (the proven) diagnostic techniques and therapeutic options. Cooperation will allow us to speed the wheels of progress, shape the destiny of ophthalmic oncology and, most importantly, save the vision and lives of our patients.

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