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Pathologic staging of tumors: pitfalls and opportunities for improvements

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Stage remains the most important prognosticator of most cancers. In the era of personalized medicine, as the determination of individual characteristics of a given tumor becomes increasingly more important, stage is perhaps one of the best ways to individualize the management of a patient. In the United States, reporting of the American Joint Committee on Cancer/Union for International Cancer Control TNM stage of tumors has all but become a mandate, linked to accreditation of laboratories by College of American Pathologists (CAP), as well as the maintenance of cancer center designations of institutions awarded by the National Cancer Institute and the American College of Surgeons' Commission on Cancer. Providing the stage is now also being considered one of the main "quality indicators" and is linked to reimbursement by insurers. Following suit, many laboratory information system programs have also now integrated CAP synoptic protocols into their software. These regulatory requirements and increasingly widespread usage of staging protocols have also brought to light the imperfections of the current staging protocols. Some are due to the inherent nature of the staging process, which attempts to segregate a continuum (which cancers are) into distinct clusters, which is not always possible. Additionally, although some of the parameters used in staging are evidence-based, many are arbitrary or based on assumptions or logistic progression models. Moreover, some parameters such as the spread of a tumor beyond an organ may seem valid at the theoretic level but are difficult to use in daily practice, for example, for organs without a well-defined capsule. The most problematic issue, however, is the fact that the pathologists are now being asked to incorporate into "pathologic stage" the information that they are not savvy about or cannot verify themselves, such as serum prostate-specific antigen levels or vocal cord paralysis. This current issue of *Seminars in Diagnostic Pathology* deals with the pitfalls in pathologic staging of common and challenging cancers. In this series of articles written by experts who deal with pathologic staging on daily basis, the authors highlight the problematic aspects of staging in routine practice, discuss the ways these can be dealt with, and also provide a platform for future discussions and improvements in tumor staging.

Importance of pathologic staging: current state

In the era of personalized medicine, proper staging of cancers has gained even more importance as the best means to assess the potential outcome of the disease, as well as the stratification of the patients into appropriate management algorithms. For most tumor types, stage still remains the strongest determinant of clinical outcome. Pathologists are now required to provide the stage for any malignant tumor they diagnose. This is required not only by the College of American Pathologists (CAP) as a part of the laboratory accreditation but also by the National Cancer Institute and the American College of Surgeons in the accreditation of Cancer Centers. Recently, reimbursement is also being in-

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creasingly linked to the providing of cancer stage as a quality indicator. In fact, some of the stage-related parameters are also used as quality indicators for other disciplines, including surgery. For example, the number of lymph nodes (LNs) identified in an oncological resection specimen is used as a means to assess the adequacy of the operation, and tracked as one of the parameters to evaluate surgeons. Accordingly, staging of tumors has almost become a mandate. Many laboratory information systems have now incorporated the CAP staging protocols into their software. Although many software provide flexibility in the reporting of stage, allowing the user to make modifications on challenging cases; some do not allow the finalization of the pathology report unless all staging parameters are entered verbatim as indicated in the program as dictated by the CAP protocols, which takes away the possibility of modification in nonfitting situations, which are not uncommon. This highly rigid and regimented approach used by the laboratory information systems is also preferred by academic institutions for the purpose of future data collection. This lack of flexibility can hinder the individualization of the stage for a given patient, and emphasizes the importance of further clarification of subtle, but not uncommon, situations that are encountered in daily practice. For example, a breast cancer that invades the dermis and adnexal structures of the skin but not the epidermis itself may not exactly qualify as T4, nevertheless requires documentation and may need to be incorporated in the management of the patient. Thus, it is now even more important than before that the established "protocols" are clear, accurate, and practical. Although the Union for International Cancer Control (UICC) Web page (http://www.uicc.org/resources/tnm-frequently-asked-questions) is an excellent source for some of the questions, several others remain unclarified.

Which tumors to stage?

In the latest (seventh) edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, neuroendocrine tumors (NETs) and gastrointestinal stromal tumors (GISTs) are now (finally) included in the list of malignancies to be staged.[1] Until recently, because these are relatively indolent malignancies, and their low-stage/low-grade examples often behave in a benign fashion, many clinician practitioners have erroneously dismissed these as benign tumors. However, recent studies with long-term follow-up have shown that even the seemingly benign end of the spectrum of these lesions can have recurrences and metastases. Therefore, there is now developing consensus that these are malignant neoplasms, albeit low grade, and therefore the whole spectrum of NETs and GISTs is now staged and graded as any other malignancy.

Although inclusion of these tumors in the staging protocols was a major step forward in recognizing and properly recording the malignant nature of these neoplasms, we believe there is still work to do in establishing the right protocols for these cancer types. For example, for the NETs, AJCC has mostly adapted the corresponding organ protocols that had been created for the ordinary (non-neuroendocrine) cancers of these organs, without taking into account the natural and biological characteristics of NETs. In this regard, the staging systems proposed by the European Neuroendocrine Tumor Society may prove to be superior because they are based on studies with more evidence-based data.[2,3] This needs to be further analyzed for the NETs of each organ system.

Common pitfalls in pathologic staging

Combination of stage and grade

In oncological pathology practice, stage typically refers to the physical extent/spread of the tumor, whereas grade assesses its histologic and biological/biochemical characteristics. Although they often correlate closely, nevertheless these two parameters are typically kept separately because they are independent of each other. A low-grade tumor can be discovered at an advanced stage and conversely a high-grade tumor at an earlier stage, and these have different implications. Unfortunately, for staging of some of the tumor categories such as the GISTs, the stage- (size of tumor) and grade- (mitotic rate) related criteria have been combined to determine a final stage in a formula that is, in our opinion, highly limiting the information that can be gained by using these two parameters separately, and then combining them afterward. This combining also hinders the assessment of the individual value of these parameters toward future betterment of the staging systems. A similar problem existed previously for the NETs but was recently addressed through international consensus discussions[4] and now separated in the WHO-2010[5] as well as in the seventh edition of the AJCC.[1]

Similar situation also exists for hepatocellular or renal cell carcinomas, where a not-necessarily stage-related parameter, vascular invasion, has been incorporated in the T-stage.[1] It can be argued that, similar to histologic grade, it may be more appropriate to regard vascular invasion separately from the stage, as it reflects a different biological characteristic rather than the physical advancement level of the tumor. It should be noted here that the authors are very much in favor of using prognostic indices (formulas and overall stages) into which stage, grade, and adjunct prognosticators such as vascular invasion can be incorporated independently. However, for such prognostic indices to be accurate and relevant, the relative values of these independent parameters have to be well characterized, and this requires their separate notation in the current staging systems, so that more data can be accumulated for future. A good example is the Nottingham Prognostic Index, which