Histopathologic Prognosis of Thymomas
Another Example of Medical Surrogacy
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DOI: 10.1309/AJCPF4KT2PEXZUSD

Particularly in anatomic pathology, the past 2 decades have witnessed a proliferation of tests that are surrogates for selected analytes of predictive or prognostic interest. Those targets include such moieties as functional hormone receptor proteins and the composition of genes that govern responses to selected growth factors. Common respective examples of those groups are estrogen and progesterone receptor proteins and the HER-2/neu, c-kit, and epidermal growth factor receptor (EGFR) genes.

Thousands of tests are done each year, predominantly through immunohistochemical analysis, to assess the status of such targets in malignant human neoplasms. And yet, immunohistochemical analysis represents an imperfect substitutive method in reference to the goal just mentioned. Immunohistochemistry does not necessarily detect functional hormonal receptors (HRs), and it is suboptimally effective in separating HR-“positive” from HR-“negative” tumors, when compared with the performance of traditional biochemical HR assays. General assumptions also have been made (and accepted) that hold that the increased cellular expression of the proteins related to the neu, c-kit, and EGFR genes—as visualized by immunohistochemical analysis—is an invariable reflection of gene amplification or an activating mutation. Recent publications have demonstrated the fallacy of those suppositions. Increasingly, the published literature shows that fundamental, “first-hand” laboratory tests are incontrovertibly superior to immunohistochemical analysis as medical devices.

Pertinent examples are the dextran-coated charcoal assay (DCCA) for HRs and in situ hybridization or polymerase chain reaction–based blotting techniques for the assessment of gene structure.

This situation speaks to a common tendency that many physicians have, that is, a propensity to exchange scientific rigor—because it demands scrupulous attention to detail—for expediency. If one assessment of prognosis is quicker, cheaper, and less technologically intensive than another, the first will be chosen by practitioners nearly every time. Moreover, that paradigm applies even if the selected test is statistically inferior to others, providing that seemingly convincing rationalizations can be made for its use. Returning to an assertion made in the previous paragraph, it has become clear that the old-fashioned DCCA, if properly performed, gives a more accurate depiction of the likelihood that breast carcinomas will respond to hormonal modulation than does immunohistochemical analysis. However, it is cumbersome to obtain aliquots of frozen tissue in each case of breast cancer and equally problematic to transmit them under controlled conditions to the laboratory. In addition, frozen-section examination of the tissue aliquots is ideally necessary before the DCCA is performed to ensure that tumoral—and not nonneoplastic—material has been sampled for biochemical analysis. Hence, immunohistochemical analysis for HRs in breast cancer is now the dominant method of pathologic evaluation, principally because it is much less “needy” with regard to tissue processing.

There are similar examples of “substitutionary” practice in just about every area of medicine. One of them, concerning the prognostication of thymomas, is touched on in an article in this issue of the Journal by Moran and colleagues. This study clearly shows that spindle-cell thymoma (also called “type-A” in the World Health Organization [WHO] classification scheme) definitely has the ability for aggressive clinical behavior. That conclusion flies in the face of...
counterassertions made in other published studies on thymic tumors. For the most part, the latter analyses have claimed that type-A thymoma was virtually always biologically benign, with a low tumor-stage at diagnosis.

Those articles substituted a histologic classification of thymoma for formal clinical staging of that neoplasm, toward the end of forecasting patient outcomes. As a consequence, thoracic surgeons who embrace that approach currently may eschew open thoracotomies and make treatment decisions that are predicated on the results of imaging studies and WHO schema–based descriptions of thymoma in small biopsy specimens. With due respect to our colleagues in radiology, even the most sophisticated procedures available to them are no equal for intraoperative naked-eye inspection of anatomic structures and appropriate tissue sampling of areas that appear to be abnormal to the surgeon. Furthermore, tiny samples of large tumors are quite likely to be poorly representative of the entire mass.

The “story” behind the WHO categories for thymoma makes the foregoing facts even more interesting. I was privileged to be a member of the WHO committee whose work eventually produced the document on thymic tumors that was authored by Juan Rosai, MD (the committee chairperson), in 1999. Therefore, I was a witness to the discussions that had considered which nosological terminology would be best for such lesions and why. After many months of unproductive and often-testy interactions in the late 1990s, the committee members could not agree on a consensus scheme. Consequently, Rosai made a “command decision” to construct the format himself. His intent was, quite simply, to produce a workable method for the histologic description of thymic tumors. There was no associated suggestion that the resulting WHO classification had, or could have, prognostic usefulness as well.

Despite that fact, articles began to appear shortly thereafter claiming that the Rosai-WHO scheme was, in fact, a prognostic one. Such proposals held that the risk of aggressive behavior predictably escalated as one moved from type A to AB, B1, B2, and B3 tumors.

Those claims are still averred by WHO devotees. However, the current article by Moran and colleagues is one of several that have shown that the Rosai system is not, in fact, a reliable surrogate prognostic construction. But then again, it was not meant to be.

In my opinion, the WHO classification of thymomas can be regarded as an “old man in a new set of clothes.” Almost 50 years ago, Bernatz et al advanced a system for categorizing thymomas that closely parallels the Rosai paradigm conceptually, and the former of those schemes has likewise been shown to lack prognostic usefulness.

I, for one, prefer the straightforward construct advanced by Suster and Moran, virtually contemporaneously with the 1999 WHO publication. The former of those approaches divides thymic tumors into 6 groups, integrating information from surgical observation and histopathologic evaluation: thymoma (WHO types A, AB, B1, and B2 neoplasms), noninvasive and invasive; atypical thymoma (WHO type B3 tumors), noninvasive and invasive; and thymic carcinoma (original WHO type C lesions), noninvasive and invasive. The validity of that model has recently been demonstrated convincingly by Marchevsky et al and Kim and colleagues. Furthermore, it is the stage of the tumors in each histopathologic cluster that is the main determinant of outcome, not their morphologic details. In that vein, Gupta and coworkers have shown that the traditional 4-tiered Masaoka staging system for thymoma also can be condensed into 3 strata, combining original stage I and stage II as revised stage I lesions and retaining original stages III and IV as revised stages II and III. Staging has once again emerged from the fray as the dispositive piece of information for the prognosis of thymomas, and, to reiterate a point made earlier, I believe that formal thoracotomy is necessary to the accuracy of that procedure.

Years ago, an often-shown television commercial asserted that a particular investment firm made money the “old-fashioned way”—they earned it. I believe that the same adage applies to outcomes forecasting for thymic tumors; the most direct and traditional methods are still the best.

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References


