Evidence-Based Medicine, Medical Decision Analysis, and Pathology
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Recent advances in molecular pathology and other technologies such as proteomics present pathologists with the challenge of integrating the new information generated with high-throughput methods with current diagnostic models based mostly on histopathology and clinicopathologic correlations. Parallel developments in the field of medical informatics and bioinformatics provide the technical and mathematical methods to approach these problems in a rational manner. However, it remains unclear whether pathologists or other medical specialists will become primarily responsible for the development and maintenance of these multivariate and multidisciplinary diagnostic and prognostic models that are hoped to provide more accurate, individualized patient-based information. Evidence-based medicine (EBM) and medical decision analysis (MDA) are relatively new disciplines that use quantitative methods to assess the value of information, differentiate fact from myth, and integrate so-called best evidence into multivariate models for the assessment of prognosis, response to therapy, selection of laboratory tests, and other complex problems that influence individual patient care. We review from an epistemological viewpoint the current approach to information in pathology and describe some of the concepts developed by the practitioners of EBM and MDA. HUM PATHOL 35:1179-1188. © 2004 Elsevier Inc. All rights reserved.

Key words: evidence-based medicine, decision analysis, pathology.

Abbreviations: UICC, International Union Against Cancer; SCLC, small cell carcinoma; NSCLC, non-small cell carcinoma; EBM, evidence-based medicine; MDA, medical decision analysis.

DO PATHOLOGISTS, INTERNISTS, AND SURGEONS READ COMPARABLE LITERATURES?

A review of the current medical literature may reveal information that is surprising to some pathologists. For example, there is a significant gap in perception regarding the features of neoplasms that are felt to be important by pathologists and those on which internists and surgeons tend to focus. For example, the most recent edition of Prognostic Factors in Cancer, published by the International Union Against Cancer (UICC), categorizes, in a chapter written principally by oncologists, lung neoplasms into small cell carcinoma (SCLC) and non-small cell carcinoma (NSCLC). In contrast, the World Health Organization classification of the same neoplasms, written by pathologists, is substantially more comprehensive and lengthy. The UICC considers only general tumor categories (SCLC vs. NSCLC), tumor stage, and resection margin to be essential pathological prognostic factors. Tumor grade and vessel invasion are listed as “additional” prognostic factors, whereas the factors “cells in mitosis,” “lymphoid infiltration,” “angiogenesis,” and “molecular markers” are said to be “new and promising.” The clinical implication of the last of those determinants is left largely to the imagination of the reader, and therapeutic decisions are structured around the doctrinaire SCLS versus NSCLC paradigm and tumor staging.

With that in mind, one might ask pragmatically whether it is cost effective for pathologists to spend time and resources to subclassify pathological lesions by criteria that are said to have limited clinical relevance. Similarly, should one document a variety of morphological features that are not used in determining patient care? Which of the “additional” and “new and promising” prognostic factors are truly useful, and should they be integrated into future patient management? Who should be responsible for integrating this information? There is no overriding external pressure at the present time to answer these questions, but they will likely pose greater challenges in the future as our clinical colleagues and hospital administrators become educated regarding the concepts of evidence-based medicine.

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hospital administrators are interested in the clinical value of discrete packets of information on the basis of quantitative techniques rather than that of history, tradition, and other considerations. EBM includes several methods that evaluate the validity of information with the overall goal of integrating scientifically sound information that is collected from various sources into diagnostic and therapeutic guidelines.9,10,12,15,21 MDA uses a variety of mathematical tools, mostly based on Bayesian probability theory, to “reason with uncertainty”.20,22

THE CURRENT STATE OF THE ART OF PATHOLOGY PRACTICE: AN EPistemological VIEW

Epistemology is the branch of philosophy that studies knowledge itself and attempts to address fundamental questions pertaining to it; for example, what distinguishes true or adequate knowledge from false or inadequate information?23-25 Longstanding theoretical questions can be translated into inquiries regarding scientific methodology. For example, which is the best method for integrating variables into an adequate theory or model, and how does one optimally evaluate the relative values of competing theories or models? These queries are now being considered in many disciplines with a practical intent. Computer scientists are developing software that is intended to simulate the human capacity to use knowledge in an intelligent way.20 Hospital administrators are interested in computer models that assess the accuracy and cost-effectiveness of various diagnostic and therapeutic modalities.26-28 New disciplines of cognition such as decision analysis theory, artificial intelligence, and MDA are being used in engineering, business, and medicine for the analysis and development of cost effective solutions to diverse problems.8 Quantitative methods are being used to integrate complex multivariate information in precise, comprehensive, and cost-effective multidisciplinary guidelines for diagnosis, treatment, estimation of prognosis, and response to therapy.29-37

An epistemological approach to the current practice of pathology would involve the formulation of basic questions regarding existing methods and their intended purposes, a review of the limitations of current practices, a consideration of what kind of new information is necessary in the construction of diagnostic models, and a discussion of how these issues might be addressed more effectively in the future.

NEED FOR AN evidence-based approach IN PATHOLOGY; DECISION analysis THEORY IN INTEGRATION OF COMPLEX INFORMATION

Pathology is certainly not the only clinical specialty that is being challenged by an explosion of information. Our colleagues in other areas face similar problems in using new diagnostic procedures and in assimilating new medications and other treatments. EBM and MDA have been developed to address these challenges with quantitative methods derived from statistics, epidemiology, and information science.9,38 A survey of the Internet with a standard search engine yields a robust representation of EBM-related literature, as well as a surprisingly long list of professional societies (e.g., the Decision Making Society, the Society for Medical Decision Making), commercial firms, and university departments that are engaged in the study of medical information with mathematical and computer tools.10,31,39 Surprisingly, there have been few entries concerning EBM and MDA in the pathology literature, even though laboratory medicine has a long tradition of a statistical approach to the interpretation of medical tests.31,40

The following review considers some basic principles of these disciplines and suggests potential applications in pathology-related research and practice. It is beyond the scope of this article to review those topics comprehensively from an epistemological perspective. However, we will discuss a few selected questions in an attempt to stimulate interest in this subject, as well as the basic concepts of EBM and MDA.

What Is the Difference Between a Disease, a Clinicopathologic Syndrome, and a Pathologic Entity?

Pathology evolved, in the latter half of the 19th century and the first half of the 20th century, as a discipline that was devoted mainly to the study of diseases and their pathogenesis, integrating the results of gross inspection, various forms of microscopy, and selected experimental methods.2-5 Diseases were categorized into groups such as cardiomyopathies, collagen vascular diseases, or malignant neoplasms according to their presumed cellular lineages or causations.

However, patients with conditions stratified in this manner do not necessarily have a similar natural history or respond to treatment in a comparable manner. Moreover, it is obviously difficult to etiologically classify neoplastic and nonneoplastic conditions that are apparently idiopathic. These have often been grouped into clinicopathologic “syndromes” or “entities”.3 As such, “pathologic entities” equate with groups of cases with reproducible clinicopathologic findings and similar clinical evolutions. They become accepted in clinical practice when they can be correlated with outcomes, in studies that are validated by the use of descriptive statistical methods such as univariate or multivariate survival statistics, analysis of variances, and others. These techniques compare the survival rates or other characteristics of patient groups but do not reliably provide information for individuals in those populations.41

From a Bayesian perspective, a critical review of clinicopathologic “entities” raises question regarding the validity of some results generated by the model just.
described,\textsuperscript{20,22} For example, the definition of such disorders has often been based on the study of small patient cohorts, without consideration of the overall frequency of the pathological entity being studied, the prior probability of a particular outcome, the distribution of the patient population (normal, Poisson, other), and other factors that influence the results of prognostic-predictive models.\textsuperscript{41} Moreover, the development of reliable classification and prognostic multivariate models requires the division of data into a \textit{training set} that is used to develop the model and a \textit{holdout test set} of cases that are used to validate hypotheses. This approach has seldom been applied in the existing literature in surgical pathology and cytopathology.\textsuperscript{28,33,42}

What Kind of Information Is Provided in Pathology Reports: Diagnosis, Prognosis, Predictions of Response to Therapy, or Combinations Thereof?

The term \textit{outcome} has not been used consistently in the medical literature.\textsuperscript{9} It has been used to describe phenomena that occur without medical intervention or after treatment. Moreover, the results of observational studies have frequently been extrapolated in attempts to correlate observations with prognosis and justify the clinical usefulness of the research, without proper consideration of the limitations of statistical tests briefly reviewed in this article.\textsuperscript{43,44} Outcomes are defined in EBM as discrete, measurable clinical events that affect the survival or quality of life of patients.\textsuperscript{9,12-14,17,20,45,46}

A \textit{prognosis} is an estimate of the probable natural history of a disease over time.\textsuperscript{6,9} Therapy, the scope of the disease process (ie, stage), and other comorbid clinical variables may alter the prognosis of a single patient with any particular pathological entity. However, it is extremely difficult to control for such factors in clinicopathologic studies that describe relatively small cohorts, and therefore, such analyses often present information with limited clinical relevance. \textit{Predictive} factors are used to provide an estimate of the probable response of patients with a given disorder to a particular therapy.\textsuperscript{35,47} This may well be independent of prognosis, as exemplified by temporarily successful surgery or by a response to medications that is followed ultimately by death caused by the disease in question.

Current classification schemes of pathological entities attempt to provide information on the diagnosis of diseases, as well as prognostic-predictive assessments, but do so with variable degrees of accuracy. For example, the unadorned diagnosis of “squamous cell carcinoma” does not provide precise information regarding disease behavior, as applied either to patient groups or individuals. Outcomes for individual patients with a particular tumor type are influenced location, grade, stage, treatment modalities, patient performance status, and other features. Conversely, some individuals with very different disorders obviously may share similar prognoses.

In practice, this problem is addressed by reporting both the diagnosis and other predetermined, disease-specific, prognostic-predictive features that are felt to be relevant. However, it is becoming increasingly more challenging to decide which data to include from immunohistochemical and molecular studies as those assessments grow in number and scope and are linked with new clinical interventions that may or may not be effective therapeutically. The evolution of pathology reports on breast cancers illustrates this problem. A decade ago, standard practice was to report the tumor cell type, tumor size, margin status, and a few, if any, additional details in regard to malignant mammary tumors. Currently, these reports are expected to be much more detailed, often including information regarding various prognostic-predictive markers such as the status of estrogen and progesterone receptor, Her2-neu gene amplification, cell proliferation indices, and others.\textsuperscript{6,48} Narrative or synoptic reports with this information often provide contradictory prognostic-predictive assessments in that they list some features that suggest a good outcome and others that prognosticate an unfavorable clinical course. No current and generally accepted guidelines exist to effectively integrate information of this type into comprehensive outcome models.

What Is the Level of Precision of Pathology Reports?

The problem of interobserver and intraobserver variability in the diagnosis of a variety of lesions has been well documented\textsuperscript{49} and will not be reviewed in detail here. Many diseases show a relatively broad spectrum of pathological changes, reflecting the biologic evolution of the disorder. One may render diagnoses readily if individual specimens show classical morphological features; in contrast, those that have incompletely developed histological images that may be shared with other conditions are often difficult or impossible to recognize with absolute certainty.\textsuperscript{50}

Another real drawback is that the prognostic precision of anatomic pathology is suboptimal in some clinical contexts, even when dealing with so-called definitive diagnoses. For example, patients with surgically treated stage I NSCLC have 5-year survival rates ranging from approximately 60% to 70%, and those with moderately differentiated stage I colonic adenocarcinoma have survivals approximating 90% at the same point in time.\textsuperscript{51-53} Nonetheless, we presently have no effective means to consistently and prospectively identify individuals in either group who will go on to die of their tumors.

The advent of molecular markers and the use of the mathematical tools that are briefly described in the next section of this article is likely to allow for the development of “prognostic scores” or “recurrence scores” that will accurately and precisely quantify the likelihood of cancer recurrence and response to various therapeutic modalities. For example, the National Surgical Adjuvant Breast and Bowel Project and Genomic Health Inc. recently presented at the 26th Annual San Antonio Breast Cancer Symposium the
results of a large multicenter study validating a “recurrence score” for node-negative breast cancer patients based on a multigene assay.48

Can Reports Using the Current Benign-Intermediate-Malignant Paradigm Precisely Describe Individual Outcomes Of Tumors With Potentially Variable Clinicopathologic Attributes and Clinical Courses?

Obviously, a full consideration of the issues raised by this question is beyond the scope of this discussion. Current classification schemes in oncology and pathology principally use binary designations such as benign-malignant or favorable-unfavorable. This paradigm is especially difficult to apply for the prognostication of lesions that rarely behave in a “malignant” manner. Indeed, that problem has engendered the use of tertiary diagnostic labels such as low-grade malignant potential, borderline tumor, and tumor of uncertain biological potential.57-60 Patients with such entities often show a spectrum of outcomes and responses to therapy, seriously challenging the notion that we can effectively label and predict the outcome of individual patients with examples of neoplasms that exist on a continuum.

Do More Data Always Provide Better Information? What Criteria Determine Which New Tests in Anatomic Pathology Truly Provide Cost-Effective, Valuable, and Reliable Data?

It is well known in statistics that a large number of variables may impair the accuracy of multivariate models.57 This paradox stems from the inclusion in the calculations of excess, autocorrelated data, often termed data overfit or data shrinkage, and from certain assumptions on which various statistical methods are predicated. For example, most investigators will accept a probability at the 5% level \( (P = 0.05) \) as sufficient to negate the null hypothesis. This statement implies that there is only a 5% probability that 2 events being studied are associated only by chance. Nevertheless, it is in fact possible to develop hypotheses including 2 variables that meet this requirement but that can be proven to be mechanistically independent of one another. This problem becomes increasingly problematic when statistical models involve multiple variables. False conclusions also can occur when procedures developed for the study of normally distributed populations are applied to paranormal populations and when sample sizes are inadequate to answer particular questions. Other potential sources of error in statistical analyses are discussed in statistics and EBM textbooks.6-10

In reality, the characteristics of populations, 95% confidence-interval methods for assessing heterogeneity (eg, the Mantel-Haenszel test), and other details concerning data distribution are seldom included in medical publications.41 Similarly, procedures that may correct for some of the afore-cited problems are rarely applied. Moreover, although the use of multivariate models has been equated generically with high statistical quality in the medical literature, validating methods such as jackknife analysis, or assessment of holdout data, are scarce in this context. That issue has been considered in a preliminary fashion in some experimental studies on prognostic models by using logistic regression, linear discriminant analysis, artificial neural networks, and other tools for addressing statistical uncertainty.29-33,42

EVIDENCE-BASED MEDICINE

EBM has been defined by Sackett and associates as “the integration of best research evidence with clinical expertise and patient values.”6-10,58-60 It is an evolving discipline that applies the analytical and quantitative methods of statistics, epidemiology, and information science (“informatics”). The overall goal of EBM is to replace the traditional authority-based paradigm of medical education with an analytical approach predicated on the analysis of information by quantitative methods. The best evidence collected from the literature is integrated with personal experience into protocols or guidelines that affect clinical practice. They, in turn, are evaluated and modified thereafter at regular intervals, with the aim of improving their utility as more data become available.

EBM evolved as a discipline in the United States and the United Kingdom in the 1970s, after the realization that systematic reviews of factual evidence were necessary to test the putative validity of new observations in medicine.39,67 EBM is already a well-established discipline that is now taught in many medical schools and in graduate programs at several universities. Several centers have been dedicated to the development of practical medical practice guidelines based on best evidence, such as the Cochrane collaboration at Oxford University and the Centre of EBM at McMaster University.11,59 EBM courses, books, and other educational resources are also widely available at the present time.8,10

There has been limited application of EBM in pathology.21,40 Most attempts at providing standardized reporting information to practicing pathologists have been via published protocols devised by professional societies, such as the Cancer Protocols developed by the College of American Pathologists (CAP) or the Reporting Recommendations by the Association of Directors of Surgical Pathology and Anatomic Pathology.68-70 Those documents were written by groups of pathologists with selected subspecialty experience, based on their opinion and interpretation of current practices in their fields of interest. This approach may be effective, but it is based on semisubjective authority rather than on best evidence taken from a systematic analysis of controlled reports or clinical trials.

The CAP has also sponsored several multidisciplinary consensus conferences, in which groups of specialists in different medical fields convened to perform
systematic reviews of the literature, discussed salient problems, identified best evidence, and proposed guidelines for their clinical management. These sessions have closely approximated the general idiom of EBM.

HOW IS MEDICAL INFORMATION APPROACHED FROM THE STANDPOINT OF EBM?

Sackett & associates have suggested the use of 5 steps for the integration of designated best-research evidence with clinical expertise and clinical values. The first involves the formulation of specific questions regarding diagnosis, prognosis, causation, and other aspects of any given clinical problem. The second concerns a search for information in the scientific literature that specifically addresses those questions. The third step involves a critical appraisal of the validity of the evidence and of its impact, applicability, and usefulness in clinical practice. The fourth step requires incorporation of best evidence from several reliable sources, along with personal clinical experience, for the development of algorithms or protocols that can be used for the diagnosis and management of individual patients with the disorder in question. Finally, the fifth step is an evaluation of the effectiveness and efficiency of those recommendations. Gross summarizes the first 4 steps of Sackett et al by using the acronym FRAP: framing evidence-based questions, retrieving relevant evidence, appraising the quality and appropriateness of the evidence, and using patient-based decision making.

Framing Evidence-Based Questions

Evidence-based questions ideally attempt to address those issues that are most relevant to the materials being studied. For example, Sackett and colleagues have suggested that 3 general queries be used for the assessment of “prognostic” information: “Is the evidence valid?,” “Is it important?,” and “Can it be applied to individual patients?” The first of those queries can be subdivided into further questions: “Was the sample of patients assembled at the same point of the disease?,” “Was the follow-up period sufficiently long and complete?,” and “Were results validated with a group of test (holdout) cases?” Similarly, the second question of Sackett et al can be extended as follows: “How likely are the outcomes over time?” and “How precise are the prognostic estimates?” The third query, regarding the relevance of the evidence to individual patients, prompts the following additional questions: “Are the study patients similar to those of the ‘user of guidelines’ physician?” and “Will the evidence in hand have a significant impact in managing the disease in question?”

Retrieving Relevant Evidence

It is beyond the aim of our discussion here to attempt to provide guidelines for retrieval of medical information from PubMed, MEDLINE, CancerLit, and other Web-based sources. EBM uses several formats to summarize such into evidence summaries that provide an estimate of precision and reliability.

Appraising Quality and Appropriateness of Medical Evidence

The quality and appropriateness of medical evidence is ideally assessed with quantitative tools. Many of those are well known in the clinical laboratory but have not been consistently applied in anatomic pathology. EBM includes measures of sensitivity, specificity, negative and positive predictive values, likelihood ratios, receiver-operator curves, misclassification rates, and others. Sensitivity is the proportion of patients with a disease who have a positive test, whereas specificity is the proportion of patients without a disease who have a negative test. The positive predictive value of a test is the proportion of patients with a positive result who actually have the disease, whereas negative predictive value represents the proportion of patients with a negative test who are actually free of disease. Likelihood ratio (LR) associated with a positive test calculates the probability that the finding is seen in diseased patients, divided by the probability that it is present in healthy people; the posttest odds of disease are equal to the pretest odds of disease, multiplied by the LR. Pathologists have only sporadically used these tools as aids in the interpretation of quantitative or semiquantitative data in surgical pathology and cytopathology.

Evaluating the Quality of Published Studies in the Medical Literature

The medical literature includes many descriptive studies that include single case reports, large observational analyses involving many patients, and scientific studies in which a hypothesis is tested prospectively with appropriate controls. Observation-based publications are definitely valuable, but they suffer potentially from biases caused by case selection, reporting methods, characteristics of control groups (“healthy cohort effect”), and other factors (Table 1). Particularly when there is an interest in assessing the effects of a particular therapy, some workers in EBM have advocated the exclusive use of randomized clinical trials. The latter view is felt by some to be too extreme and certainly does not apply to most clinical problems of interest to pathologists. However, EBM does raise interesting questions that could yield new approaches to the use of
specimen-based data in improved diagnostic and prognostic models in the future.

Ebell\textsuperscript{10} has proposed a system for classifying published medical evidence into 4 levels, with grade I being the best (most reliable). Grade I studies are those that include data validated with a test group that is from a different and distinct population than that from which the training cohort was taken. For example, a classification or a prognostic rule might be developed in 1 group of patients and validated in another. Grade II studies report data that are obtained from the same population, the members of which are divided into independent training and validation subsets and evaluated prospectively. Grade III analysis also include training and validation subsets from the same population, but data are collected contemporaneously rather than prospectively. Grade IV studies are those in which the training group is also used as the validation group. According to this scheme, most studies in the pathology literature would probably be classified as grade IV and are particularly vulnerable to the problems listed in Table 1.

Patient-Based Decision Making

As mentioned earlier, advocates of EBM have attempted to organize best evidence from the scientific literature and their own experience into algorithms, protocols, or rules that address individual patient care. Pathologists may benefit from emulating this approach in future efforts at constructing “patient-based” prognostic and predictive models. For example, immunostains are most often used to distinguish between various neoplasms in a descriptive manner. Studies using immunostains in the pathology literature usually list the percentage of lesions that label for particular epitopes, as well as the sensitivity, specificity, and predictive values of such markers in narrow morphological contexts.\textsuperscript{74,75} However, few studies have assessed LR or other probabilistic measures as applied to panels of markers in selected differential diagnoses.\textsuperscript{29,76-78} At an even more basic level, the relative statistical values attending particular morphological findings has seldom been analyzed in the same fashion, to our knowledge.

In contrast, several prognostic scoring models or “rules” that integrate multivariate pathological, clinical, imaging, and other information are being developed by other specialists.\textsuperscript{10} For example, Kattan et al\textsuperscript{34} and other investigators\textsuperscript{35,36} have developed pretreatment nomograms that combine clinical and pathological data from prostate cancer patients and predict 5-year probability of metastasis.

MEDICAL DECISION ANALYSIS

There is now an interest in understanding the concept of intelligence, as a result of advances in computer technology.\textsuperscript{26,28} Several cyberapproaches have attempted to simulate the abilities of the human brain with mathematical tools such as algorithms, multivariate statistics, artificial neural networks, fuzzy logic, and Bayesian belief networks.\textsuperscript{30,31} The ubiquity of personal computers has also broadened the use of statistical tools, as made available in spreadsheet and other software. These advances have led to the development of new applications in business, military, engineering, medicine, and other fields and to the growth of decision analysis as a distinct discipline.\textsuperscript{79}

Briefly, the latter field concerns itself with quantitative methods for integrating complex and uncertain information into multivariate models. They can provide computerized classifications analogous to diagnoses, forecasts of future events (prognosis), and various simulations that allow users to assess probable outcomes of various options (practice patterns) in a quantitative manner.

These techniques have been used selectively in pathology for the development of computerized methods of diagnoses (eg, automated instruments for screening cervicovaginal cytology smears).\textsuperscript{74} They also have been applied in developing multivariate prognostic methods that are based on artificial neural network technology and multivariate statistics.\textsuperscript{60}

DEVELOPMENT OF THE DATABASE INFRASTRUCTURE NEEDED TO PERFORM POPULATION-BASED STUDIES OF LARGE PATIENT COHORTS

The future development of diagnostic and prognostic tools based on MDA techniques requires the availability of large amounts of data, necessary for the design of grade I and II studies. That type of information is difficult to collect, and a need exists for pathologists to improve the manner in which the information in pathology reports is stored in laboratory information systems.\textsuperscript{80,81} Current text information is fraught with incomplete data and somewhat inaccurate terminology that is difficult to gather with data-mining tools. Ideally, reports of the future could be structured so that data were stored as discrete elements, using uniform terminology and quantitative methods. They could then be shared among different laboratories using a common format and could be stored in centralized or distributed data repositories. Several initiatives are currently exploring procedures for mining text-based data, for developing common terminology (such as SNOMED CT), and for accruing centralized collections of tissues and data in the United States.\textsuperscript{82,86}

EXAMPLES OF THE APPLICATION OF EBM AND MDA CONCEPTS FOR THE EVALUATION OF CURRENT PROBLEMS IN PATHOLOGY

Assessment of the Clinical Relevance of New Immunohistochemical and Molecular Tests in Clinicopathologic Subsets of Patients With a Disease

A critical review of the literature regarding the use of “new and promising” prognostic-predictive markers,
such as the immunohistochemical assessment of invasive breast carcinomas for overexpression of the HER-2/neu/c-erbB-2 gene, provides a good example of how pathology practice could benefit from a more critical approach to the incorporation of new tests into practice.

The Her-2/neu gene codes for a transmembrane tyrosine kinase receptor that is closely related to the epidermal growth factor receptor. Its overexpression may inhibit apoptosis in neoplastic cells and promote tumor growth, properties that suggested in the 1980s the potential prognostic value of this test. Trastuzumab, a chimeric mouse-human monoclonal antibody that specifically blocks the intracellular activity of Her-2/neu in vivo in neoplastic cells, was developed as a therapeutic agent. The possible value of Her-2/neu as a predictive test was described in the late 1990s. The US Food & Drug Administration approved in 1998 a commercial immunostaining kit that can be used for indirect detection of Her-2/neu amplification.

There is still no general consensus view about for which tumor types the Her-2/neu abnormalities provide a reproducible prognostic-predictive test. Breast carcinoma has probably been the most extensively studied in this context, and Her-2/neu immunostaining has now been mandated by oncologists in many US medical centers for all new breast cancer specimens, irrespective of tumor grade, stage, or histological type, or patient age. However, this type of blanket policy is probably wasteful and is certainly not supported by current best evidence. For example, lobular carcinomas, special-type breast cancers (eg, mucinous and tubular carcinomas), and low-grade invasive conventional ductal carcinomas are highly unlikely to overexpress Her-2/neu. The prognostic value of this test is limited in patients with stage I tumors at presentation. The value of the Her-2/neu test as a predictive indicator of clinical response to trastuzumab is also controversial in selected clinical scenarios. For example, several studies have shown that at best, approximately 65% of women with positive Her-2/neu immunostaining results will benefit clinically from antibody therapy. Furthermore, the duration of their response is limited, even when trastuzumab is coupled with conventional chemotherapy. The indiscriminate assessment of all invasive breast carcinomas for Her-2/neu immunoreactivity is based on the assumption that all patients with the disease will inevitably develop metastasis, that nonimmunotherapeutic approaches to the treatment of metastasis will be ineffective, and that all Her-2/neu–immunoreactive neoplasms will be trastuzumab responsive. Each of those assumptions is poorly supported by the aggregated literature on this topic, as summarized by Taucher et al. In addition, the commercial kit for HER-2 immunostaining may not reliably predict gene overexpression, and in situ hybridization may be a preferable technique for its detection.

In summary, a review of the best evidence available about the use of Her-2/neu immunostains as a prognostic-predictive test provides substantial arguments against the generalized use of this test in all patients with this neoplasm and suggests the need for more cost-effective guidelines that are based on an EBM approach.

Integration of Pathologic Diagnoses and Histopathologic Features With Clinical, Imaging, and Biochemical Data Into Multivariate Prognostic and Predictive Models for Cancer Patients

A detailed review of this topic is beyond the scope of this review article, but there have been multiple attempts at combining a pathologic diagnosis, prognostic features observed with histopathology, clinicoradiologic information (eg, stage, sex, performance status), and serum biochemical markers into predictive rules or therapeutic algorithms. For example the province of Ontario in Canada has a longstanding program in collaboration with experts at McMaster University: the Program of Evidence-Based Care. This program has published multiple guidelines. Urologists routinely use the tables developed at Johns Hopkins School of Medicine for the management of prostate cancer patients. Partin tables integrate serum PSA, Gleason score in needle biopsies, and clinical stage to predict the likelihood of extraprostatic extension, seminal vesicle involvement, and other adverse features in subsequent radical prostatectomy specimens. Haese and associates, from the same institution, have more recently developed, with statistical tools and neural networks, multivariate prognostic models that combine 10 biopsy pathologic parameters and 2 clinical parameters for the management of patients with clinically localized prostatic cancer. These models were validated by using data from 2 institutions. Similar multivariate clinicopathologic prognostic models probably can be developed for patients with other neoplasms as pathologists and other specialists become more familiar with the basic concepts of EBM and MDA and analyze the data from their patients with some of the methodology described in this review.

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