Guideline Summary

American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer

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Introduction

ASCO and the College of American Pathologists (CAP) collaborated to produce an evidence-based guideline on optimal testing performance for estrogen receptor (ER) and progesterone receptor (PgR) testing in breast cancer.[1,2] The purpose of the guideline is to improve the accuracy of immunohistochemical (IHC) testing and its utility in determining predictive markers for breast cancer treatment. The ASCO/CAP Hormone Receptor Testing in Breast Cancer Panel was composed of experts in pathology, medical oncology, laboratory medicine, laboratory regulation, and biochemistry as well as a patient advocate.

Overview

Testing for the presence of hormone receptors as part of breast cancer diagnosis is the standard of care and is used to guide therapy decisions. ER/PgR overexpression is associated with clinical outcomes and is an important predictive and prognostic factor. The relationship between target expression (ER/PgR) and efficacy of endocrine therapy is well established. Accurate assessment of ER/PgR status permits informed treatment decisions for targeted therapy, thereby identifying the patients most likely to benefit from endocrine therapy. Accurate test performance is crucial, yet there is evidence of wide variability in test performance and inaccurate results (falsely negative or falsely positive) of up to 20%. The production of the guideline[1] was deemed necessary to improve the status of ER/PgR testing. The guideline makes recommendations on methods of optimal test performance as well as on quality assurance. As we describe, in the case of IHC testing of ER and PgR status, there is no gold-standard assay available.

Discussion

Hormone Receptor Status and Treatment

The guideline[1] recommends that ER and PgR status be determined for all individuals with invasive breast cancers and breast cancer recurrences. The purpose of both tests is to help determine the likelihood of benefit from endocrine therapy for men and women with breast cancer. People with a recurrence of breast cancer should always receive hormone receptor (HR) testing so that treatment decisions can be made based on current biologic information. In the absence of definitive published data, the panel did not make a formal recommendation on ER testing in patients with ductal carcinoma in situ but rather suggests clinician-patient discussion. A previous ASCO/CAP guideline addressed human epidermal growth factor receptor 2 (HER2) testing in invasive breast cancer.[3]

HR positive is the most common breast cancer phenotype worldwide. Therefore, access to accurate and reliable ER/PgR testing and established and relatively affordable endocrine therapies could have a profound impact on breast cancer outcomes in high- and low-/middle-income countries around the globe. Endocrine therapies for women with HR-positive tumors include ovarian ablation (surgical or chemical), selective ER modulators, and aromatase inhibitors. Endocrine therapy is not indicated for women whose tumors do not express either ER or PgR. The predictive role of PgR status is less established than that for ER status, but it may provide predictive value independent of ER status. There exists a small subset of women with tumors that test ER negative/PgR positive; these women may be candidates for endocrine treatment because there is no single explanation for this finding at this time.

Biopsy

Large, preferably multiple, core biopsies of a tumor are preferred for testing if they are representative of the tumor (grade and type) at resection (Appendix Table A1, online only). If core samples are large and representative of the resection specimen, the guideline[1] recommends that these samples be used when possible rather than a surgical specimen for ER and PgR analyses, because such samples are less likely to be exposed to cold ischemia and more likely to be begin pathology processing within a short period of time.

Breast cancer tumor specimens should be fixed for a minimum of 6 hours in 10% neutral buffered formalin (NBF) and for no longer than 72 hours. Additional preparation of the specimen is described in the guideline. If the tumor comes from a remote location, it should be bisected on removal and sent to

the laboratory immersed in a sufficient volume of NBF. Cold ischemia time, fixative type, and time sample placed in NBF must be recorded.

Assay and Laboratory Regulation

In the United States, tests and laboratories are regulated by the US Food and Drug Administration (FDA) and by the Centers for Medicare & Medicaid Services via Clinical Laboratory Improvement Act regulations and are accredited by bodies deemed private accreditors. These private organizations providing accreditation include CAP, the Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations), and COLA (formerly the Commission on Office Laboratory Accreditation).

IHC became the de facto standard method to measure ER and PgR status in formalin-fixed paraffin-embedded tissue in the 1990s. There is a single FDA 510(k)-cleared ER/PgR assay kit, although several antibodies have been cleared as individual reagents by the FDA. These include antibodies 1D5, 6F11, SP1, and ER.2.123+1D5 for ER and antibodies 1294, 1A6, and 312 for PgR.

ASCO and CAP recommend that ER and PgR testing be performed in a CAP-accredited laboratory or in a laboratory that meets the additional accreditation requirements set out within this guideline.[1] CAP will require that every CAP-accredited laboratory performing ER and/or PgR testing participate in a mandatory proficiency testing program beginning as soon as possible. The previous collaboration between ASCO and CAP addressed the technical and analytic issues related to accurate HER2 testing. A set of guidelines were issued that have had a positive impact on evaluation and treatment of women with breast cancer.[3] Cancer specialists of all disciplines (eg, pathologists, surgeons, radiologists doing biopsies, radiation oncologists, and medical oncologists) are encouraged to learn about the accreditation status of laboratories that perform ER/PgR testing and about specimen handling and interpretation requirements, including the new thresholds for positive assays (1% of tumor cells).

Test Performance

The guideline[1] proposes a testing algorithm that relies on accurate, reproducible assay performance. It also specifies elements to reliably reduce assay variation (eg, specimen handling, proper use of controls, and interpretive and reporting criteria). A laboratory performing ER/PgR testing should initially validate its proposed or existing assay against a stable assay of another laboratory, using a clinically validated assay. To be considered acceptable, the results of the assay must be initially 90% concordant for positive ER or PgR and 95% concordant for negative ER or PgR with those of the clinically validated assay. (Concordant refers to the assay result.) See Assay and Laboratory Regulation for quality assurance recommendations.

Test Results

It is recommended that ER and PgR assays be considered positive if there are at least 1% positive invasive tumor nuclei in the sample on testing. The guideline[1] provides additional interpretation, recommending that clinicians consider endocrine therapy in patients whose breast tumors show at least 1% ER-positive cells and withhold endocrine therapy if the amount is less than 1%. It also recognizes that it is reasonable for oncologists to discuss the pros and cons of endocrine therapy with patients whose tumors contain low levels of ER by IHC (1% to 10% weakly positive cells) and make informed decisions based on the balance.

Required Reporting Elements for ER and PgR Analysis

First, the percent/proportion of positive cells: The percent/proportion of invasive tumor cells staining positively should be recorded and reported; all of the tumor containing areas of the tissue section on the slide should be evaluated to arrive at this percentage. The percentage can be arrived at either by estimation or by quantification, either manually by counting cells or by image analysis (computer automated quantification). If the sample is a cytology specimen, at least 100 cells should be counted or used to estimate the percent of HR-positive tumor cells, particularly if the tumor specimen is limited and if the positive staining appears to involve only a minority of tumor cells.

Second, the intensity of staining: The intensity of staining should be recorded and reported as weak, moderate, or strong; this measurement should represent an estimate of the average staining of the intensity of the positively stained tumor cells on the entire tissue section relative to the intensity of positive controls run with the same batch. Intensity is provided as a measure of assay quality over time and also allows for optional composite scoring. Tissue heterogeneity can sometimes be observed.

Third, an interpretation of the assay (≥1% is positive; <1% is negative or uninterpretable): An interpretation of the assay should be provided using one of three mutually exclusive interpretations. The reader should provide an interpretation of the assay based on the following criteria:

- Receptor positive (either ER or PgR): The guideline recommends a cutoff of a minimum of 1% of invasive tumor cells positive for ER/PgR for a specimen to be considered positive. There is no agreement about a range for receptor equivocal, so this term should not be used.
- Receptor negative: Tumors exhibiting less than 1% of tumor cells staining for ER or PgR of any intensity should be considered negative based on data showing that such patients do not receive meaningful benefit from endocrine therapy. The sample should only be considered negative in the presence of appropriately stained extrinsic and intrinsic controls. Testing for any specimen lacking intrinsic elements (normal breast epithelium) that is negative on ER and/or PgR assay should be repeated using another tumor block or another tumor specimen, and the specimen should be reported as uninterpretable rather than negative.
- Receptor uninterpretable: The guideline[1] states that there are no absolute assay exclusions. Nevertheless, a result should be considered uninterpretable if the sample did not conform to the preanalytic specifications of the guideline, the sample was processed using procedures that did not conform to guideline specifications or the standard operating procedure of the

laboratory, or the assay used to analyze the specimen was not validated and controlled as specified in the guideline.

- If ER and PgR status is negative in histologies commonly associated with ER- and PgR-positive results (eg, low grade tumors and tubular, lobular, and mucinous histologic types), then an optional cautionary statement should indicate that although the patient's tumor tested ER/PgR negative, tumors with the same histologic type or grade almost always test positive.

Optional reporting elements are described in the guideline. Briefly, they include a cautionary statement with negative ER/PgR results when histopathology is normally associated with positive ER/PgR results and a composite score (eg, H, Allred, or Quick score).

Special Questions

The guideline[1] also addresses two special questions. First, in view of the lack of definitive published studies on ER/PgR testing in ductal carcinoma in situ, the panel opted not to make a definitive recommendation at this time. Second, although the precise role of PgR in patient management has not been established, the guideline recommends that endocrine therapy not be withheld from women with ER-positive/PgR-negative tumors and that this status not be used to select type of endocrine therapy. Patients with ER-negative/PgR-positive tumors may also benefit from and should be considered for endocrine therapy.

Methodology

ASCO and Cancer Care Ontario conducted a systematic review of medical literature published from 1990 through May 2008 using Medline, EMBASE, and the Cochrane Database of Systematic Reviews. The companion systematic review will be published separately. Cancer Care Ontario will publish separate recommendations/guidelines based on the same systematic review because of differences in the way health care is provided and the way pathology labs operate in the United States and Canada.

The primary outcome of interest of the systematic review was the correlation of ER/PgR status and endocrine treatment benefit (disease-free, progression-free, or overall survival). The evidence available was primarily from retrospective comparative studies. No randomized controlled trials were identified that were designed to assess prospectively the technical aspects of HR testing in breast cancer, although a number of studies involved specimens (slides, tissue blocks) collected during the course of randomized trials that were used for retesting. Much of the literature identified involved variables concerning the preparation, conducting, and analysis of IHC tests. In addition, there was literature about laboratory proficiency/performance and quality assurance.

Additional Resources

A slide set and table showing markers corresponding to clinical presentations are available as Data Supplements (online only) to this article. The full and abridged versions of the guideline[1] are available at www.asco.org/guidelines/erpr. A patient guide is available at www.cancer.net/whattoknow.

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