Estrogen and Progesterone (ER/PgR) Receptor Testing in Breast Cancer

American Society of Clinical Oncology (ASCO) / CAP Guideline Update

Early Online Release Publication: *Archives of Pathology & Laboratory Medicine*

January 13, 2020

Outline

- Introduction

- Key questions and main findings

- Guideline statements (recommendations)

- Guideline development process

- Conclusion

ASCO and CAP unite for guidelines

- **The CAP and ASCO agreed to partner to develop guidelines starting with HER2 testing in breast cancer in 2007.**

- **After this successful venture, the ER/PgR guideline was jointly published in 2010.**

- **The ER/PgR guideline garnered wide-spread attention:**
  - 2,800+ unique citations in publications from more than 99 different countries.

Key questions

- **As recommended by the National Academy of Medicine Standards, ASCO and CAP convened an expert panel to evaluate new evidence and update the guideline.**

- **The key questions the panel sought to answer were:**

  1. **What is the optimum quality assurance, tissue handling, scoring system and reporting for determining potential benefit from endocrine therapy?**

  2. **What additional strategies can promote optimal performance, interpretation, and reporting of IHC assays, particularly in cases with low ER expression?**

  3. **Are other ER expression assays acceptable for identifying patients likely to benefit from endocrine therapy?**

  4. **Should DCIS be routinely tested for hormone receptors?**

Noteworthy changes

- **New recommendation for laboratories to establish a specific standard operating procedure to ensure the validity of low positive (1-10%) or negative (0 or < 1%) interpretations and results.**

- **Correlation of ER staining with the histologic features (as well as attention to other standard quality control measures) is also recommended and unusual/discordant results worked up.**

- **New reporting recommendations are made for cases with 1-10% ER expression (special report comment) to acknowledge the more limited data on endocrine responsiveness in this group and overlapping features with ER negative cancers.**

Noteworthy changes, continued

- **The status of internal controls should also be reported for cases with 0-10% staining (with a special comment for those lacking internal controls).**

- **The utility of PgR testing continues to be largely prognostic in the ER-positive invasive cancer population, but testing using similar principles to ER testing is still recommended for invasive cancers.**

- **The update now recommends ER testing for patients diagnosed with ductal carcinoma in situ, but PgR testing is optional.**

Recommendations

Recommendation 1.1. Optimal algorithm for ER/PgR testing

Updated

Samples with 1-100% of tumor nuclei positive for ER or PgR are interpreted as positive.

For reporting of ER (not PgR), if 1-10% of tumor cell nuclei are immunoreactive, the sample should be reported as ER Low Positive with a recommended comment (see manuscript Table 2; Figure 1).

A sample is considered negative for ER or PgR if <1% or 0% of tumor cell nuclei are immunoreactive.

Recommendation 1.1., continued

A sample may be deemed uninterpretable for ER or PgR if the sample is inadequate (insufficient cancer or severe artifacts present, as determined at the discretion of the pathologist), if external and internal controls (if present) do not stain appropriately, or if pre-analytical variables have interfered with the assay's accuracy (see manuscript Figures 1-4).

Clinicians should be aware of and able to discuss with patients the limited data on ER-low positive cases and issues with test results that are close to a positive threshold.

Strong Recommendation

Recommendation 1.1. discussion

- **Updated with:**
  - clear threshold values for uninterpretable, negative, and positive ER or PgR results
  - new low-positive reporting recommendations

- **Low-positive results should include the suggested comment:**

"The cancer in this sample has a low level (1-10%) of ER expression by IHC. There are limited data on the overall benefit of endocrine therapies for patients with low level (1-10%) ER expression, but they currently suggest possible benefit, so patients are considered eligible for endocrine treatment. There are data that suggest invasive cancers with these results are heterogeneous in both behavior and biology and often have gene expression profiles more similar to ER negative cancers."

Recommendation 1.2. Optimal testing conditions

Large, (preferably multiple) core biopsies of tumor are preferred for testing if they are representative of the tumor (grade and type) at resection. Accession slip and report must include guideline-detailed elements.

Strong Recommendation

Recommendation reaffirmed

Recommendation 1.3. Optimal tissue handling requirements

Time from tissue acquisition to fixation should be as short as possible. Samples for ER and PgR testing are fixed in 10% NBF for 6 to 72 hours. Samples should be sliced at 5-mm intervals after appropriate gross inspection and margins designation and placed in sufficient volume of NBF to allow adequate tissue penetration. If tumor comes from remote location, it should be bisected through the tumor on removal and sent to the laboratory immersed in a sufficient volume of NBF. Cold ischemia time, fixative type, and time the sample was placed in NBF must be recorded.

Recommendation 1.3., continued

As in the ASCO/CAP HER2 guideline, use of unstained slides cut more than 6 weeks before analysis is not recommended.

Time tissue is removed from patient, time tissue is placed in fixative, duration of fixation, and fixative type must be recorded and noted on accession slip or in report.

Strong Recommendation

Recommendation reaffirmed

Recommendation 1.4. Optimal internal validation procedures

This topic is deferred to the forthcoming CAP guideline update, Principles of Analytic Validation of Immunohistochemical (IHC) Assays, once available. There should be initial test validation/verification prior to reporting any clinical samples. Prior to that, previously recommended principles apply (See Fitzgibbons et al and Torlakovic et al.).

Strong Recommendation

Change anticipated

Recommendation 1.5. Optimal internal QA procedures

Updated

Ongoing quality control and equipment maintenance are required.

Initial and ongoing laboratory personnel training and competency assessment should be performed.

Recommendation 1.5., continued

Standardized operating procedures (SOPs) should be used that include routine use of external control materials with each batch of testing and routine evaluation of internal normal epithelial elements or the inclusion of normal breast sections (or other appropriate control) on each tested slide, wherever possible. External controls should include negative and positive samples as well as samples with lower percentages of ER expression (such as tonsil). On-slide controls are recommended.

Recommendation 1.5., continued

Regular, ongoing assay reassessment should be done at least semiannually (as described in Fitzgibbons et al). Revalidation is needed whenever there is a significant change to the test system (Torlakovic et al).

Ongoing competency assessment and education of pathologists is required.

Strong Recommendation

Recommendation 1.5. discussion

- **Update provides more guidance on the use of external controls and on-slide controls.**

Recommendation 1.6. Optimal external proficiency assessment

Updated

The laboratory performing ER and PgR testing must participate in external proficiency testing or alternative performance assessment as required by its accrediting organization.

Strong Recommendation

Recommendation 1.6. discussion

- **Recommendation was updated to remove information about what constitutes satisfactory proficiency assessment. Laboratories are instructed to follow the requirements of their accrediting organization.**

Recommendation 1.7. Optimal laboratory accreditation

On-site inspection every other year should be undertaken with annual requirement for self-inspection.

Moderate Recommendation

Statement Reaffirmed

Recommendation 2.1.

Updated

Laboratories should include ongoing quality control using SOPs for test evaluation prior to scoring (readout) and interpretation of any case as defined in the checklist in manuscript Figure 1.

Strong Recommendation

Recommendation 2.2.

Updated

Interpretation of any ER result should include evaluation of the concordance with the histologic findings of each case. Clinicians should also be aware of when results are highly unusual/discordant and work with pathologists to attempt to resolve or explain atypical reported findings (see manuscript Table 3 as an aid in this process).

Strong Recommendation

Recommendation 2.3.

Laboratories should establish and follow an SOP stating the steps the laboratory takes to confirm or adjudicate ER results for cases with weak stain intensity or $\leq$10% of cells staining (see Supplemental Digital Content Data Supplement 2, Figure 1 for an example SOP).

Recommendation 2.4.

Updated

The status of internal controls should be reported for cases with 0-10% staining. For cases with these results without internal controls present and with positive external controls, an additional report comment is recommended (see manuscript Table 2).

Strong Recommendation

Recommendation 2.1. - 2.4. discussion

The 2010 guideline did not include recommendations for low-ER expression cases.

Figure 1 in the manuscript provides information for scoring (readout) and interpretation to determine ER status in breast cancers, including a checklist for initial quality control.

Table 3 describes steps to confirm/adjudicate results with the histologic findings.

Supplemental Figure 2 describes steps to consider including in the laboratory's SOP.

Recommendation 3.

Updated

Validated IHC is the recommended standard test for predicting benefit from endocrine therapy. No other assay types are recommended as the primary screening test for this purpose.

Strong Recommendation

Recommendation 4.

Updated

ER testing in cases of newly diagnosed DCIS (without associated invasion) is recommended to determine potential benefit of endocrine therapies to reduce risk of future breast cancer. PgR testing is considered optional.

Moderate Recommendation

Recommendation 4. discussion

- **Data on whether PgR testing in DCIS adds predictive or prognostic value beyond that of ER alone are currently lacking. Given the lack of evidence, the panel considers PgR testing of DCIS optional.**

Guideline development process

Guideline process

- **The guideline update was developed by a multidisciplinary expert panel, which included a patient representative and an ASCO guidelines staff with health research methodology expertise.**

- **PubMed and the Cochrane Library were searched for randomized controlled trials, systematic reviews, meta-analyses, and clinical practice guidelines for the period from January 1, 2008 through April 30, 2019.**

- **The searches identified 4,897 abstracts and ultimately, 87 papers met the selection criteria.**

Guideline process, continued

- **The expert panel met in-person to update the recommendations.**

- **The draft recommendations were released to the public for comments April 15-April 29, 2019.**

- **Comments were reviewed and any recommendation not receiving at least 80% were revised.**

- **All changes were incorporated prior to ASCO and CAP approval.**

Steering group members

- **Kimberly H. Allison, MD, FCAP, Co-chair**

- **Antonio C. Wolff, MD, FASCO, Co-chair**

- **M. Elizabeth H. Hammond, MD, FCAP**

- **Mitchell Dowsett, PhD**

- **Lisa M. McShane, PhD**

Expert panel members

- **Lisa A. Carey, MD**
- **Patrick L. Fitzgibbons, MD, FCAP**
- **Daniel F. Hayes, MD**
- **Sunil R. Lakhani, MD, MBA**
- **Mariana Chavez-MacGregor, MD, MS**
- **Shannon E. McKernin**
- **Jane Perlmutter, PhD**
- **Charles M. Perou, PhD**
- **Meredith M. Regan, ScD**
- **David L. Rimm, MD, PhD,**
- **FCAP**
- **W. Fraser Symmans, MD**
- **Emina E. Torlakovic, MD, PhD, FCAP**
- **Leticia Varella, MD**
- **Giuseppe Viale, MD**
- **Tracey F. Weisberg, MD**

References

1. Allison KH, Hammond EH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists guideline update. *Arch Pathol Lab Med*. 2020;144(5):545–563. doi:10.5858/arpa.2019-0904-SA

2. Hammond MEH, Hayes D, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *Arch Pathol Lab Med.* 2010;134(6):907-922.

3. IOM (Institute of Medicine). *Clinical Practice Guidelines We Can Trust*. Washington, D.C.: The National Academies Press; 2011.

4. Fitzgibbons PL, Murphy DA, Hammond ME, et al: Recommendations for validating estrogen and progesterone receptor immunohistochemistry assays. *Arch Pathol Lab Med. 2010*;134(6):930-935.

5. Torlakovic EE, Cheung CC, D'Arrigo C, et al: Evolution of Quality Assurance for Clinical Immunohistochemistry in the Era of Precision Medicine. Part 3: Technical Validation of Immunohistochemistry (IHC) Assays in Clinical IHC Laboratories. *Appl Immunohistochem Mol Morphol. 2017;*25(3):151-159.