Guideline Summary

American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer

Context

ASCO convened an expert panel to produce this 2007 update of its recommendations for the use of tumor markers in breast cancer.[1] The previous guideline on this topic was published in 2001.[2]

Updated 2007 Recommendations

Table A1 (online-only supplement; also available at www.asco.org/guidelines/breasttm) presents a complete summary of the updated recommendations.

Breast Cancer Tumor Markers

The panel considered evidence regarding 13 categories of breast tumor markers, six of which were new within the guideline. The following categories showed evidence of clinical utility, and the panel recommended some applications for use in practice: CA15–3, CA27.29, carcinoembryonic antigen (CEA), estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor (HER-2), urokinase plasminogen activator (uPA), plasminogen activator inhibitor (PAI) -1, and certain multiparameter gene expression assays. The following categories demonstrated insufficient evidence to support routine use in clinical practice: DNA flow cytometry-based proliferation, p53, cathepsin D, Ki67, cyclin D, cyclin E (or other markers of proliferation), proteomics, certain other multiparameter assays, detection of bone marrow micrometastases and circulating tumor cells (Table 1).

Markers Addressed in Previous Editions of This Guideline

CA15–3 and CA27.29

CA15-3 and CA27.29 are serum tumor markers that measure circulating MUC-1 in peripheral blood. 75% to 90% of patients with metastatic disease will have elevated MUC-1 levels. While it is likely that these have prognostic value, their role in the management of early-stage breast cancer is unclear. Therefore, the evidence does not support a recommendation of CA15-3 or CA27.29 for screening, diagnosis, or staging. In addition, although studies have shown that an increase in CA15-3 or CA 27.29 after primary and/or adjuvant therapy can predict recurrence in advance of other symptoms or tests, there is limited evidence and no completed or current prospective randomized trials demonstrating that detecting and treating early metastatic findings using these tumor markers impact the most significant outcomes. Therefore, they are not recommended, which is in line with the ASCO guideline for follow-up and management of patients with breast cancer.[3]

The recommendation for monitoring patients with metastatic disease during active therapy with CA27.29 or CA15-3 used in conjunction with diagnostic imaging, history, and physical examination has not changed.

CEA

CEA levels increase less commonly than MUC-1 levels. Data suggest that evaluating one of the MUC-1 assays and also CEA initially in a patient with metastatic disease is reasonable. If the MUC-1 assay is elevated, monitoring CEA has no role, but if not, then CEA levels may provide supplementary clinical information for monitoring response to treatment as long as it is done with clinical and radiographic investigations.

ER and PgR

ER, and probably PgR, content are associated with favorable prognosis and are highly predictive of benefit from endocrine treatment in both the adjuvant and metastatic settings. Research continues to show benefit from testing for these receptors (which is done with primary or metastatic tumor specimens). A change from the 2001 guideline regards using these markers with ductal carcinoma in situ (DCIS). Although ER negativity is associated with a worse outcome in patients with DCIS, it is not an independent predictor with high nuclear grade and necrosis. The Update Committee does not recommend the use of the estrogen receptor status as a predictor of outcome in patients with DCIS or elect treating with, or withholding, tamoxifen in a patient who undergoes breast preservation.

DNA Flow Cytometry–Based Proliferation

If an experienced laboratory uses the flow cytometry technique (with primary or metastatic tumor specimens) to determine *S* phase with a validated method, it appears that an elevated *S* phase fraction and a worse outcome are associated. However, technical and methodological issues complicate the implementation of DNA flow cytometry to determine *S* phase. Because of the technical variation in and inconsistent data on testing this marker, results produced by all methodologies cannot be endorsed. Routine use of flow cytometry to make clinical decisions is not recommended.

Immunohistochemically Based Markers of Proliferation in Breast Cancer

Additional markers of proliferation (proliferation markers researched for measurement on tissue include Ki67, cyclin D, cyclin E, p27, p21, thymidine kinase, and topoisomerase II) have

Table 1. Breast Cancer Tumor Markers

Diagnosis	Recommended		Not Recommended
	Test Name	Purpose	Test
Newly diagnosed primary invasive	ER/PgR test	To predict response to endocrine treatment in adjuvant setting	—
	HER-2 test	To predict response to trastuzumab and predict response to anthracycline-based adjuvant therapy	
Metastatic	ER/PgR test	To predict response to endocrine treatment in metastatic setting	
	HER-2 test	To predict response to trastuzumab in the metastatic setting	
	CA15–3 and CA27.29 (in conjunction with diagnostic imaging, history, and physical examination)	To monitor during active therapy	Do not use CA15–3 and CA27.29 alone
	CEA (in conjunction with diagnostic imaging, history, and physical examination)	To monitor during active therapy	Do not use CEA alone
Newly diagnosed primary invasive node–negative and ER+ and/or PgR+	Oncotype DX	To determine prognosis in women who will receive adjuvant tamoxifen	Other multiparameter gene expression assays
	uPA and PAI-1 test	To determine prognosis, guiding use of CMF-based adjuvant chemotherapy	
Newly diagnosed primary invasive node–negative and ER− and/or PgR−	uPA and PAI-1 test	To determine prognosis, guiding use of CMF-based adjuvant chemotherapy	—
Recurrent primary invasive	HER-2 test	To predict response to trastuzumab and to predict response to anthracycline-based adjuvant therapy	ER/PgR test Oncotype DX uPA PAI test
DCIS	n/a	n/a	ER/PgR test

NOTE. Table includes only tumor markers for which guideline recommend selected applications. Table does not include those tumor markers the guideline did not recommend in any application: DNA flow cytometry-based proliferation, p53, Cathepsin D, Cyclin E and other immunohistochemically-based proliferation, proteomics, detection of bone marrow micrometastases, and circulating tumor cells.
Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; HER-2, human epidermal growth factor receptor; CEA, carcinoembryonic antigen; uPA, urokinase plasminogen activator; PAI, plasminogen activator inhibitor; DCIS, ductal carcinoma in situ; n/a, not available.
This Table is derived from recommendations in the ASCO 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer. The Table is a practice tool based on ASCO practice guidelines and is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients. This tool does not purport to suggest any particular course of medical treatment. Use of the practice guidelines and this table are voluntary. The practice guideline and additional information are available at http://www.asco.org/guidelines/breasttm.

been measured by immunohistochemistry to determine their prognostic and predictive value in breast cancer. There is a lack of standardization of assay reagents, procedures, and scoring. This guideline concurs with an exceptionally thorough review that concluded that these markers are not recommended for clinical practice.

HER-2

Most, but not all, trials show that use of HER-2 amplification/overexpression and/or shedding of extracellular domain as a prognostic factor is associated with worse prognosis in patients who have not received systemic therapy. The role of this marker purely to determine prognosis in clinical practice is unclear, however, since outcomes are so heavily influenced by subsequent therapy. The Update Committee does not recommend the measurement of HER-2 on the primary tumor by any method or measurement of the extracellular domain in the serum for *solely* determining a patient's prognosis.

However, as an indicator of possible benefit from trastuzumab, the measurement of HER-2 amplification or overexpression in the primary or metastatic tumor continues to be recommended. The recently published ASCO-CAP (ASCO–College of American Pathologists) guideline for

methodology and accreditation of assays for HER-2 overexpression provides details.[4]

Most trials of CMF (cyclophosphamide, methotrexate, fluorouracil) adjuvant therapy suggest that patients with HER-2–positive tumors benefit less from CMF than do patients with HER-2–negative tumors. However, other trials show that CMF may impart some benefit for women with HER-2–positive tumors, but adding an anthracycline further improves prognosis. Patients whose tumors overexpress HER-2 may actually benefit from anthracycline-based chemotherapy more than from CMF. Therefore, the Update Committee recommends anthracycline-based adjuvant chemotherapy for a patient with HER-2–overexpressing breast cancer if adjuvant chemotherapy is indicated, the patient has no contraindication to an anthracycline, and trastuzumab administration is not planned.

The benefit of taxane-based adjuvant therapy for HER-2–overexpressing tumors is controversial. For example, some studies suggest improved response to docetaxel or paclitaxel, while others suggest relative resistance. The benefit of taxane-based treatment in this group is not established, and therefore, not recommended.

Evidence suggests that in patients with ER+/HER-2–positive tumors, the relative benefit from antiestrogens or aromatase inhibitors is likely to be lower than for those with ER+/HER-2–negative cancers. However, it may vary by type of hormonal agent, and randomized trials do not agree. Overall, there are insufficient data to support the use of HER-2 as a predictor of response to endocrine therapy.

Finally, the association between circulating extracellular domain (ECD) of HER-2 as a possible surrogate marker, and predictive factor, for HER-2 positivity is intriguing. Despite this, lack of high-quality studies and consistent findings hamper use of circulating HER-2/ECD. These are prerequisites to understanding the precise utility of this marker in evaluation or monitoring of patients with breast cancer. The panel does not currently recommend use of this marker.

p53

Research suggests that *p53* mutations are associated with worse outcomes. Most studies analyzing p53 may be strongly biased in one direction or another because they have not taken therapy into consideration. The results from recently reported studies are insufficient to change the recommendation from the 2000 version of the guideline because they have not established the prognostic or predictive clinical utility of p53.

Cathepsin D

Trials show some association between increased cathepsin D levels and treatment response, and also between increased levels and recurrence. But generally, the studies of cathepsin D measured by immunohistochemistry are variable, with no assay standardization and inconsistent associations with outcome, and with little regard to the confounding effects of systemic therapy.

Markers New to This Guideline

uPA and PAI-1

Several studies indicate a possible association between uPA and PAI-1 and the possible value of these factors for prediction or prognosis. Persons with increased levels of these markers have a higher risk of recurrence or death, and these markers can be used together to determine prognosis and whether a patient might have a sufficiently favorable prognosis to avoid chemotherapy. One prospective randomized clinical trial does show that patients with elevated uPA/PAI-1 levels benefit from adjuvant chemotherapy.

The use of measuring uPA factors is limited to ELISA using a minimum of 300 mg of fresh or frozen tissue. One must interpret uPA and PAI-1 test results from core biopsies or from formalin-fixed paraffin-embedded tissue with caution, since no studies have demonstrated that these markers, when measured in these types of tissues, are prognostic. Components of the urokinase plasminogen activating system appear to be promising targets for future therapeutic studies.

Cyclin E

Several studies have considered cyclin E as a prognostic factor with elevated levels associated with poor prognosis. This has not, however, resulted in methods useful for clinical practice. Further properly designed studies are required.

Proteomic Analysis

From 1996 through 2007, more than 200 articles were published addressing proteomics and breast cancer. Many of these are methods articles; those that address clinical utility had retrospective designs. The studies do illuminate the heterogeneity of breast cancer and advance understanding of its relevant subclasses. But since mostly retrospective studies produced these promising results, larger, well-designed prospective studies are required. At present, none of the proteomic profiling techniques has been validated sufficiently for use in patient care.

Multiparameter Gene Expression Analysis

Several studies have linked multigene expression signatures in breast cancer with clinical outcomes, and the literature continues to debate its molecular subtypes. In newly diagnosed patients with node-negative, estrogen receptor–positive breast cancer, the Onco*type* DX assay can be used to predict the risk of recurrence in patients treated with tamoxifen. The algorithm used to calculate this recurrence score was developed using data from at least one prospective therapeutic trial and validated in a second in which marker utility was a secondary study objective, achieving level of evidence I.

Onco*type* DX can be used to identify those patients with a low recurrence score, who might avoid chemotherapy because of the very small potential benefit. In addition, patients with high recurrence scores seem to achieve relatively more benefit from adjuvant chemotherapy (specifically [C]MF) and tamoxifen than from tamoxifen alone.

Data are currently insufficient to comment on whether these conclusions generalize to hormonal therapies other than

tamoxifen, or if this assay applies to other chemotherapy regimens. Investigations continue regarding the precise clinical utility and appropriate application for other multiparameter assays, such as the MammaPrint assay, the "Rotterdam Signature," and the "Breast Cancer Gene Expression Ratio." No published or planned studies address the use of multiparameter gene expression assays for early detection, screening, or monitoring, so there is no recommendation for use of these technologies for these purposes.

Bone Marrow Micrometastases

The fate of breast cancer micrometastases in the bone marrow and their clinical significance for individuals are controversial. It is agreed that bone marrow micrometastases predict a higher risk of relapse and worse survival in early-stage breast cancer. But, in most cases, the patient with bone marrow micrometastases already has characteristics that will cause their oncologist to treat with adjuvant therapy, without considering the presence or absence of bone marrow micrometastases. The data do not suggest that a patient with bone marrow micrometastases in the presence of a small, low-grade, node-negative breast cancer has a sufficiently worse prognosis to justify making differential recommendations for adjuvant therapy.

Circulating Tumor Cell Assays

From 1996 through 2006, approximately 400 publications reported on the methodology of detection of circulating tumor cells (CTC)—cells in serum that possess a specific tumor type's antigenic or genetic characteristics—in breast cancer. The presence of these cells in a patient with breast cancer may predict the presence of a micrometastasis or an aggressive primary tumor. There is not enough published evidence to establish clinical use of this factor. The measurement of CTC should not be used to make the diagnosis of breast cancer or to influence any treatment decisions in patients with breast cancer. Similarly, the use of the recently US Food and Drug Administration–cleared test for CTC (Cell Search; Veridex, Warren, New Jersey) in patients with metastatic breast cancer cannot be recommended until further validation.

Methodology and Discussion

The Panel completed an updated review of data published since 1999 through February 2007. The Panel reviewed literature from searches of MEDLINE and the Cochrane Collaboration Library. For the new markers, the review included data published from 1966 to February 2007.

It is important to realize that many management questions have not been comprehensively addressed in randomized trials, and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results.

Accordingly, ASCO considers adherence to this guideline to be voluntary, with ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

Additional Resources

The full-text version of the guideline was published online in the *Journal of Clinical Oncology* (doi:10.1200/JCO.2007.14.2364). Additional resources including a patient guide, summary tables, Breast Cancer Tumor Markers Matrix, and summary slide set can be accessed at www.asco.org/guidelines/breasttm.

The ASCO 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer were developed and written by Lyndsay Harris, Herbert Fritsche, Robert Mennel, Larry Norton, Peter Ravdin, Sheila Taube, Mark R. Somerfield, Daniel F. Hayes, and Robert C. Bast Jr for the American Society of Clinical Oncology Tumor Markers Expert Panel.

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