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

Lyndsay Harris, Herbert Fritsche, Robert Mennel, Larry Norton, Peter Ravdin, Sheila Taube, Mark R. Somerfield, Daniel F. Hayes, and Robert C. Bast Jr

ABSTRACT

Purpose
To update the recommendations for the use of tumor marker tests in the prevention, screening, treatment, and surveillance of breast cancer.

Methods
For the 2007 update, an Update Committee composed of members from the full Panel was formed to complete the review and analysis of data published since 1999. Computerized literature searches of MEDLINE and the Cochrane Collaboration Library were performed. The Update Committee's literature review focused attention on available systematic reviews and metaanalyses of published tumor marker studies. In general, significant health outcomes (overall survival, disease-free survival, quality of life, lesser toxicity, and cost-effectiveness) were used for making recommendations.

Recommendations and Conclusions
Thirteen categories of breast tumor markers were considered, six of which were new for the guideline. The following categories showed evidence of clinical utility and were recommended for use in practice: CA 15-3, CA 27.29, carcinoembryonic antigen, estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, urokinase plasminogen activator, plasminogen activator inhibitor 1, and certain multiparameter gene expression assays. Not all applications for these markers were supported, however. The following categories demonstrated insufficient evidence to support routine use in clinical practice: DNA/ploidy by flow cytometry, p53, cathepsin D, cyclin E, proteomics, certain multiparameter assays, detection of bone marrow micrometastases, and circulating tumor cells.

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INTRODUCTION

The American Society of Clinical Oncology (ASCO) first published evidence-based clinical practice guidelines for the use of tumor markers in breast cancer in 1996. ASCO guidelines are updated at intervals by an Update Committee of the original Expert Panel. The last update of the tumor markers guideline was published in 2000. For the 2007 update, the Panel expanded the scope of the guideline to include a broader range of markers in breast cancer. In addition, the impact of genomic technologies was considered in the Update. While molecular subtyping is still in its infancy, and subgroups are not well defined, the use of multiparameter technologies in clinical practice has considerable potential. The updated recommendations are summarized in Table 1.

<table>
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<th>Table 1. Summary of Guideline Recommendations</th>
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<td>Recommendations for the Use of Tumor Markers in Breast Cancer</td>
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<td>Specific Marker</td>
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<td>uPA and PAI-1 as a marker for breast cancer (Note: This topic is new to the guideline)</td>
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UROKINASE PLASMINOGEN ACTIVATOR AND PLASMINOGEN ACTIVATOR INHIBITOR 1 AS MARKERS FOR BREAST CANCER (Note. This topic is new to the guideline)

2007 recommendation for urokinase plasminogen activator and plasminogen activator inhibitor 1. Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor (PAI-1) measured by ELISAs on a minimum of 300 mg of fresh or frozen breast cancer tissue may be used for the determination of prognosis in patients with newly diagnosed, node-negative breast cancer. IHC for these markers is not accurate, and the prognostic value of ELISA using smaller tissue specimens has not been validated. Low levels of both markers are associated with a sufficiently low risk of recurrence (especially in hormone receptor–positive women who will receive adjuvant endocrine therapy) that chemotherapy will only contribute minimal additional benefit.

Furthermore, CMF-based adjuvant chemotherapy provides substantial benefit, compared with observation alone, in patients with high risk of recurrence as determined by high levels of uPA and PAI-1. uPA and PAI-1 have been evaluated as part of the plasminogen activating system, which includes the receptor for uPA and other inhibitors (PAI-2 and PAI-3). This system has been shown experimentally to be associated with invasion, angiogenesis, and metastasis. 175

uPA and PAI-1: Methodology. Several assay formats for these two markers have been evaluated, including IHC, quantitative real-time reverse transcriptase (RT) -PCR, and enzyme-linked immunosorbent assays (ELISA). 176-178 ELISA, performed on fresh or frozen tissue or cytosolic fractions remaining after biochemical hormone-receptor measurement, is the only method that has been determined to be prognostic. 179 Importantly, all the data from a pooled analysis study 179 and from a prospective randomized clinical trial 180 in which uPA and PAI-1 were used to stratify patients were obtained based on analysis of large tissue sections from tumors that had not been previously biopsied. Although ELISA using tissue from core needle biopsies would be clinically useful, the prognostic value of such a strategy remains to be confirmed. 181 The effects of a prior core biopsy on uPA and PAI-1 levels, which could conceivably alter expression of these tissue-remodeling enzymes, are unknown.

uPA and PAI-1: Literature Review and Analysis

Risk, screening, and monitoring. Currently available data address the impact of uPA and PAI-1 on prognosis for patients with early stage breast cancer. A retrospective study suggests that ductal fluid uPA/PAI-1 levels might be of use for screening or risk recategorization of high-risk women, but these data require verification. 182 There are few if any data regarding monitoring patients with serial uPA/PAI-1 levels. 183-185

Prognosis in Early-Stage Breast Cancer

Several studies have suggested that over expression of uPA and/or PAI-1 have been consistently related to poor prognosis in early-stage breast cancer. These studies suggest that these two factors, combined, are associated with 2- to 8-fold higher risk of recurrence and death. 176,177,186-190 Importantly, studies of node negative patients who did not receive adjuvant systemic therapy suggest that these two markers are very strong prognostic factors, independent of size, grade, and hormone receptor status. 179,190,191