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

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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 1. Summary of Guideline Recommendations

Recommendations for the Use of Tumor Markers in Breast Cancer

Specific Marker	2007 Recommendation
<i>uPA and PAI-1 as a marker for breast cancer (Note: This topic is new to the guideline)</i>	uPA/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

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

Background:

(uPA)/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: Marker definition.* uPA and PAI-1 are 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 study¹⁷⁹ and from a prospective randomized clinical trial¹⁸⁰ 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}

A pooled analysis of uPA/PAI-1 data collected from 8,377 breast cancer patients was performed by members of the Receptor and Biomarker Group of the European Organisation for Research and Treatment of Cancer.¹⁷⁹ These results demonstrate the reproducibility of the assay among several sites, and they confirm the strong association of over expression of uPA and PAI-1 with recurrence and survival during a median follow-up of 79 months. A subset analysis of node-negative, untreated patients also confirmed the potential utility of these markers for identifying a low-risk cohort in this group.

The first interim report of a prospective trial using uPA and PAI-1 levels to stratify node-negative patients has been published.¹⁸⁰ Five hundred fifty-six node-negative patients were accrued. Those patients whose tumors expressed low levels of both markers were followed in a prospective registry and were not treated with adjuvant chemotherapy. Patients whose tumors showed elevated uPA and/or PAI-1 levels were randomly assigned to adjuvant chemotherapy (CMF) or no adjuvant chemotherapy. In this report the estimated 3-year recurrence rate for 241 patients with low levels of both uPA/PAI-1 was 6.7%, with a median follow-up of 32 months. The recurrence rate for patients with elevated uPA and/or PAI-1 levels who did not receive chemotherapy was roughly double that, and the hazard rate for recurrence in the group for patients treated with adjuvant chemotherapy was 0.56 of that for patients who were not treated.

Other reports suggest uPA and/or PAI-1 may serve as predictive factors for hormone therapy and/or specific types of chemotherapy, but these are uncontrolled studies.^{182,192}

The data support the requirement for both uPA and PAI-1 levels to be performed using ELISAs on whole sections (minimum 300 mg) of fresh or frozen cancer tissue. IHC results do not reliably predict outcomes, and the prognostic value of ELISA using smaller tissue specimens, such as tissue collected by core biopsy, has not been validated.¹⁸¹ Furthermore, in the modern era of frequent pre-excision, diagnostic core needle biopsies, one must interpret uPA and PAI-1 ELISA results with caution.

Future Studies

Studies are underway in Europe to address further the utility of uPA/PAI-1 measurements. In an ongoing prospective clinical trial, patients are randomly assigned to two groups: in one group, they will have clinical decisions regarding adjuvant chemotherapy using uPA/PAI-1 levels; in the other group, these decisions will be made according to existing guidelines. Carefully designed studies addressing the predictive role of uPA/PAI-1 for specific chemotherapy and endocrine therapy are recommended. Finally, components of the urokinase plasminogen activating system appear to be promising targets for future therapeutic studies.