

PREFACE

Biomarkers in Breast Cancer: Molecular Diagnostics for Predicting and Monitoring Therapeutic Effect is an updated view of the prognostic and predictive biomarkers in breast cancer written by experts in this field. This book covers the major advancements in the application of novel sophisticated molecular methods as well as the state of the art of the conventional prognostic and predictive indicators.

The first three chapters by Simon, Sweep et al., and Kimel et al. highlight the relevance of appropriate and rigorous study design and guidelines for validation studies on new biomarkers, concerning the standardization with quality control of the assay(s) used for their determination, their clinical development, and the statistical approaches. Of particular importance is the suggested optimized protocol for the HER-2/*neu* FISH assay applied by the NSABP network (1).

Gene expression profiling by tissue microarray is treated in depth in the following two chapters by De Bortoli and Briglia and by Kim and Paik. Recent studies conducted using this methodology have clearly documented the heterogeneous nature of invasive breast cancer within the same pathologic stage and menopausal status. These methods have clearly provided powerful new tools for more accurate individual definition of prognosis. However, much more work remains to be done before standard pathology laboratories can use tissue microarrays to perform tumor marker studies for routine clinical use.

Several individual factors are accepted or appear to be promising for standard clinical care. Of course, the use of estrogen and progesterone receptors (ER, PgR) to predict benefit from endocrine therapy represents the gold standard of tumor markers, and should be tested on every breast cancer tissue (2). More recently, testing for HER-2 status has also become standard to help select whether a patient with metastatic breast cancer should receive trastuzumab (2). Other factors that are still controversial, but are considered standard by some guideline panels, include indicators of cell proliferation as well as the urokinase-type plasminogen activator (PAI)-1 system. These are the topics of the next four chapters written by authors who are among the pioneers and worldwide experts in translational research studies in the field.

The roles of the epidermal growth factor receptor (EGFR) pathway and altered p53 in breast cancer growth and progression and as possible prognostic and predictive indicators are outlined by Ciardiello et al. and by Kandoler and Jakesz, respectively. In addition to trastuzumab, several preclinical and clinical studies suggest that other agents that disrupt the signaling pathways generated by members of the EGFR family may be effective against breast cancer. The ability to identify predictive surrogate biomarkers of response is the key for the rational selection of the patients most likely to benefit from these anti-EGFR compounds.

Moreover, it seems likely that markers of EGFR activity might provide the opportunity for monitoring therapeutic efficacy. The recent demonstration that mutation of the phosphorylation site of the receptor may be predictive of gefitinib activity in patients with non-small-cell lung cancer may represent an important step toward the right strategy for the use of such a class of new anticancer agents (3,4).

Adjuvant systemic therapy has now been clearly shown to reduce the odds of recurrence and death (5,6). However, because of the inaccuracy of currently available prognostic and predictive factors, much of adjuvant systemic therapy, especially chemotherapy, is given inefficiently, either to patients whose cancer was never destined to recur or to those patients whose cancer will recur, but for whom the therapy will not be effective. Enormous work has been directed toward prognosis, with advancements in the field of molecular biology and in the detection of occult metastatic cells distant from the tumor. Hawes et al. and Braun et al. comprehensively cover the methodology, state of the art, pitfalls, and promises of detection of early tumor cell dissemination in breast cancer patients.

Although determination of tumor biology in tissue justifiably garners much interest, the ability to test and monitor for biological changes with a simple blood test is obviously appealing. Chapters 13 and 14 deal with the clinical significance of circulating HER-2/neu and vascular endothelial growth factor (VEGF), these being among the more promising therapeutic targets for approaches based on selective molecular-targeting agents.

We hope this text offers a critical view of the modern approach to the development of surrogate biomarkers of prognosis and responsiveness to selective treatments in breast cancer. We are confident that it will provide useful reading for investigators involved either in laboratory research or in clinical development of prognostic/predictive indicators and of novel molecular-targeted therapy.

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