The plasminogen activator system is a complex system with multiple interactions and members participating in fibrinolysis, cell migration, angiogenesis, wound healing, embryogenesis, tumor cell dissemination, and metastasis in a variety of solid tumors. Increased levels of uPA and/or PAI-1 in primary tumor tissues of breast cancer patients correlate with tumor aggressiveness and poor clinical outcome. Patients with high tumor tissue antigen content of uPA and/or PAI-1 have a worse probability of disease-free and overall survival than patients with low levels of both of the biomarkers, serving as prognostic markers. The clinical utility of uPA and PAI-1 has been proven on the highest level of evidence (LOE-I). Next to being clinically useful prognostic factors allowing estimates of the course of disease in early breast cancer, uPA and PAI-1 may also serve as predictive factors predicting response to systemic therapy. Node-negative primary breast cancer patients with high uPA/PAI-1 levels benefit significantly from adjuvant chemotherapy. The aim of the ongoing NNBC-3 trial is to determine the benefits of a sequential anthracycline-docetaxel regimen in high-risk node-negative breast cancer patients compared to the current standard of anthracycline-based chemotherapy. At present, uPA and
PAI-1 provide the unique opportunity to allow validated and clinically relevant risk assessment of breast cancer patients, over and above that provided by established risk factors. Therefore, in the evidence-based, annually updated AGO guidelines for breast cancer management, the German Working Group for Gynecological Oncology (AGO) has recommended both biomarkers as risk-group-classification markers for routine clinical decision making in node-negative breast cancer, next to established clinical and histomorphological factors.