Receptor tyrosine kinases play an important role in malignant transformation of epithelial cells by activating signal transduction pathways important for proliferation, invasion and metastasis. In a pilot study (n = 40), we evaluated expression of the c-Met and Her2/neu receptor tyrosine kinases and the c-Met ligand hepatocyte growth factor/scatter factor (HGF/SF) in primary breast cancers and their lymph node metastases using both conventional immunohistochemistry and confocal immunofluorescence. Neither c-Met and HGF/SF nor Her2/neu expression correlated with established prognostic factors such as age, lymph node involvement, estrogen receptor (ER), progesterone receptor (PR), tumor size, or grade. Both staining methods confirmed a significant correlation between c-Met overexpression and a high risk of disease progression. Furthermore, among tumors with c-Met overexpression, only 50% also overexpress Her2/neu, thus identifying a subset of patients with aggressive disease in addition to Her2/neu. Median disease-free survival in patients with c-Met overexpressing tumors was 8 months compared to 53 months when c-Met expression was low (p = 0.037; RR = 3.0). This significant impact of c-Met on tumor aggressiveness independent of Her2/neu was also confirmed by
multivariate analysis. In conclusion, the role of c-Met expression as a prognostic variable and consequently as an interesting target for novel therapeutic approaches deserves further analysis in a larger cohort of patients.