Abstract: Metastasis is responsible for most deaths from cancer. Currently, little is known about the early genetic events in the metastatic evolution. Here we describe the application of a newly developed strategy for an in-depth characterization of genomic changes in micrometastatic cells. Unique tumor cell lines were established from bone marrow of patients with cancer of the prostate and analyzed by multiplex-FISH (M-FISH) and array CGH. M-FISH revealed that the occult disseminated cells were characterized by very complex numerical and structural aberrations. Many of these aberrations resulted in chromosomal gains and losses, such as losses of 8p, 13q, and 18q and gains of 8q, 9q, 20, and the X chromosome, which are typically observed in prostate cancer. Array CGH allowed an unprecedented high-resolution assessment of copy number changes, pinpointing commonly gained or lost regions, which should narrow down the identification of regions critically involved in metastasis. Thus, occult micrometastatic cells are now amenable to detailed analyses of their genome. Markers for prognosis and treatment decisions can now be established.