CHAPTER 7

DETECTION OF HER-2/NEU CEP 17 MUTATIONS AT INVASIVE BLADDER CANCER


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INTRODUCTION

Transitional cell carcinoma (TCC) of the urinary bladder is the eighth most common cancer in Germany; the tumor varies greatly in its biological behavior. Of superficial TCC (Ta, T1), up to 70% will eventually be recurrent; 10 to 15% will progress to muscle invasion (≥ T2). About 50% of patients with muscle-invasive bladder tumors subsequently develop metastases.

TCCs of the bladder include a heterogeneous group of tumors, and the underlying genetic changes are incompletely defined. Chromosomal alterations in bladder cancer have been studied by several methods. Cytogenetic studies showed that the most common aberrations are: isochromosome 5p, trisomy 7, monosomy 8 and 9, and deletion of 11p. Molecular genetic methods provide a powerful tool in studies of genomic DNA. Interphase cytogenetic studies with FISH enable the detection of numerical and structural chromosomal aberrations directly in cell nuclei.
The most common alterations of bladder cancer by this technique are on chromosomes 1, 3, 7, 9, 11, and 17.\textsuperscript{17,25}

Activation of growth factor receptors plays a major role in the pathogenesis of bladder cancer. The human HER-2/neu oncogene, localized on chromosome 17p21, encodes a transmembrane growth factor receptor with a molecular weight of 185,000 kDa (p185). The protein consists of an internal cytoplasmatic structure with tyrosine kinase activity, a short hydrophobic transmembrane section, and an extracellular ligand-binding domain.\textsuperscript{20} This extracellular ligand-binding domain is heavily glycosylated and has a 44\% sequence homology with human epidermal growth factor receptor. Overexpression of the epidermal growth factor receptor seems to be correlated to tumor grade, progression, invasiveness, and survival.\textsuperscript{22,27} Aneuploidy of HER-2/neu seems to be correlated with a higher grade of bladder tumor differentiation.\textsuperscript{19} There are also HER-2/neu aberrations for the salivary gland,\textsuperscript{36} ovary,\textsuperscript{37} stomach,\textsuperscript{41} endometrium,\textsuperscript{31} and prostate\textsuperscript{21} known as prognostic markers for disease-free and overall survival. Allelic loss of tumor suppressor genes on chromosome 17p has been implicated in the progression of breast cancer.\textsuperscript{24}

To establish whether HER-2/neu is related to the invasiveness of TCC, we analyzed its gene status in a series of bladder carcinomas at different stages. The second aim was to define the value of FISH compared to DNA image cytometry in diagnosis of bladder cancer.

**MATERIAL AND METHODS**

**Patients**

The study included 39 patients (31 males, 8 females) with bladder tumors or suspicion thereof. Median age was 63 years (range: 33 to 86). All patients were treated by cystoscopy or differentiated transurethral resection.\textsuperscript{5} At the time of diagnosis, 19 patients had a tumor (TaG1-T3aG3) and 20 had none, but 9 of those 20 had one in prehistory (TaG1 to T2G3) (Table 1). For later evaluation, we divided the groups into superficial (Ta, T1) and invasive (T2, T3) bladder cancer.

For DNA image cytometry and FISH examinations, we took cytospins out of urine voiding or bladder washings before operation (stored to 4°C).