Heterogeneity in Prostate Cancer: Prostate Specific Antigen (PSA) and DNA Cytophotometry

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Abstract. Background: The heterogeneity in prostate cancer is the reason for the difficult diagnosis and prognosis of this tumor. In this study, we looked for a correlation between prostate specific antigen (PSA), tumor staging and DNA cytophotometry. Materials and Methods: Twenty-two prostates (pT1-T4) from patients with prostate cancer, who underwent radical prostatectomy, were examined. Preoperative PSA and postoperative DNA image cytometry, after 2-8 needle biopsies out of each organ, were evaluated. Results: The prostate cancer tissues showed, in DNA stemline-interpretation according to Fu, in homogenous diploid tumors an average PSA level of 3.8 ng/ml, and, in homogenous aneuploid tumors, a level of 14.0 ng/ml. Tumors with heterogeneous DNA patterns with a majority of aneuploidy had an average PSA level of 85.6 ng/ml, and heterogeneous tissues with a majority of diploidy a level of 10.9 ng/ml. Conclusion: Only the stemline-interpretation of Fu after DNA cytophotometry is efficient for diagnosis of prostate cancer, and allows prognostic statements of the disease.

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Materials and Methods

The serum PSA level (ng/ml) was determined before operation. The operation included radical retropubic prostatectomy and local lymph node dissection of the fossa iliaca ambiateral. The histopathological findings showed 2 x T1 G1, 6 x T2 G2/3, 12 x T3 G2/3 and 2 x T4a G3 (UICC 1992). Two cases had local lymph node metastasis (N1). After the operative procedure, the prostate was cut into 2-8 discs, depending on the size of the organ. With the aim of reducing the known heterogeneity of the prostate cancer, the material for DNA measurement was taken out of every disc by needle suction biopsy. The region of the biopsies was determined arbitrarily. Consequently, 2-8 DNA measurements per prostate were obtained, according to the number of discs.
DNA cytophotometry. After staining according to Papanicolaou, cells were treated with 4N HCl and counterstained according to Feulgen (7) for DNA cytometric measurement. The DNA from a minimum of 250 nuclei of diagnostic cells was evaluated, calibrated to 30 autologous lymphocytes (reference cells). For semi-quantitative DNA examination, the TV-based image analysis system “Cires 3.1” (Zeiss/Kontron, Munich, Germany) was used. The interpretation of every DNA measurement was done according to three different schemes. The single-cell-interpretation (SCI) is routinely performed according to Boecking, detecting DNA aneuploidy when three or more cells hold a DNA value ≥5c (5cEE). The conventional stemline-interpretation (SLI) will show DNA aneuploidy for a stemline >2.2c. Thereby, the stemline (modal value) will be correlated to DNA values of diploid reference cells. Fu (8) defines his SLI as DNA aneuploidy when the stemline is above 2c +/– 2c x (2 x coefficient of variation from the reference cell population).

Results

In the first analysis, we determined the three different DNA interpretation models (SCI of Boecking, SLI of Fu and conventional SLI) for each DNA measurement. These results were correlated to the histopathological findings and to the PSA of each patient and organ (Table I). For two of the three DNA interpretations, SCI of Boecking and conventional SLI, no correlation, either with the PSA level or with the staging or the grading systems (pT, M, N and G, UICC 1992) was found. For SLI of Fu, the highest average PSA levels were found in the group of homogenous aneuploid DNA patterns, as well as in the group with a majority of aneuploid DNA patterns next to diploid ones (heterogeneous) (Table II). The group of homogenous diploid DNA patterns and the heterogeneous groups with a majority or equality of diploid DNA patterns had lower average PSA levels. There was no correlation of the SLI of Fu to the histopathological findings, similar to both other DNA interpretations.

Discussion

Digital rectal examination, transrectal ultrasound examination and determination of PSA are common methods in the identification and control of progression under treatment for prostate cancer. However, these methods can not predict further progression of the tumor at the beginning of the treatment because of the heterogeneity in prostate cancer. Some tumors are androgen-sensitive; other tumors are androgen-independent. DNA cytometry can provide information about the tumor biology and behavior of the prostate cancer. Tavares et al. reported an association between the status of DNA ploidy and the survival of patients with prostate cancer. Diploid or tetraploid tumors were associated with a longer survival than aneuploidy or non-tetraploid tumors.
In our study, the correlation of DNA ploidy analysis with histopathological and clinical parameters was examined. Three different DNA interpretation models (SCI of Boecking, SLI of Fu and conventional SLI) were described. No correlation for two of the three DNA interpretations (SCI of Boecking and conventional SLI) with the PSA or the staging and grading systems (pT, M, N and G, UICC 1992) was found. Only the stemline-interpretation of Fu after DNA cytophotometry showed a correlation between PSA and DNA ploidy in the tumor cells, but did not correlate with the histopathological findings. Our results are at variance with the results of Mora et al. (9), who described a correlation of DNA aneuploidy and high proliferative fraction with high Gleason grade and adverse prognosis, but not with the PSA level in Stage B prostate cancer (T2, N0, M0). Badalament et al. (10) demonstrated that DNA ploidy correlated significantly with pathological stage; aneuploidy was identified more frequently in patients with Stages C and D1 tumors. Significant racial differences were found in that study with respect to DNA ploidy, mean DNA indices, and mean PSA values. Our data also demonstrated a typical problem with different models of DNA cytophotometry; the results are variable for the exact DNA ploidy status. For example, a patient with pT3a N0 G2 prostate cancer with a serum PSA of 10.1 ng/ml shows in SCI of Boecking a homogenous diploid status, in SLI of Fu a heterogeneous status with a majority of diploidy and in conventional SLI a homogenous aneuploid status (Table II), so the evaluation of the progressive character of the prostate cancer from this patient is not possible. Jones et al. presented a sensitivity in DNA cytometry from 50% to 61% in aneuploid tissues of prostate cancer (11).

### Conclusion

By using the SLI method of Fu, information about the differential diagnosis and evaluation of the progressive character of prostate cancer can be obtained. Further studies with larger numbers of patients have to be performed for a final estimation of the correlation between DNA ploidy, malignancy and pathological and clinical parameters within the framework of a better diagnosis, therapy and prognosis of prostate cancer.

### References


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### Table II. DNA stemline-interpretation of Fu of 22 prostate cancer cases as homogenous and heterogeneous DNA patterns correlated to PSA values (mean and range).

<table>
<thead>
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<th>Homogenous DNA</th>
<th>Heterogeneous DNA</th>
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<tr>
<td></td>
<td>Tiploid</td>
</tr>
<tr>
<td>n=22</td>
<td>6</td>
</tr>
<tr>
<td>PSA mean (ng/ml)</td>
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<tr>
<td>PSA range (ng/ml)</td>
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