light. Two variants of on-chip PSA immunoassays were used: direct and "sandwich" method. In the direct immunoassay, PSA was immobilized in microchip gel elements, and the microchip was developed with PSA-specific monoclonal antibodies, labeled by fluorescent dye. In the antigen-capture two-site ("sandwich") assay, monoclonal antibodies were immobilized on a chip, and the chips were treated with solutions of PSA or blood sera and developed with labeled secondary antibodies. Fluorescence signals from gel elements were recorded using fluorescent microscope. Fluorescence intensities were plotted versus PSA concentrations to measure PSA in blood serum samples. For the sandwich analysis, the intensity of fluorescence signal from gel elements was proportional to PSA concentration (both total and free) within 0.1ñ50 ng/ml range.

Results. The minimum concentration of detected antigen was 0.1 ng/ml. The data for PSA content in the sera of the patients with prostate cancer obtained by protein biochip analysis were compared with those for commercial kit PSA/Total EIA II Cobas Core (Switzerland). Correlation coefficient between the two methods was 0.99 ($p<0.01$).

Conclusion. The data presented in the work demonstrate a new method for cancer diagnostics by protein microchips. On-chip immunoassay opens the possibility of the analysis of many tumor markers in one sample that allows one to increase the effectiveness of the analysis and minimize the amount of analyzed sample.

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Hormone-refractory prostate cancer in the Lobund-Wistar rat

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Refractory prostate cancer [PC] develops progressively as an irreversible, therapy resistant disease in aging men. Among rapidly replicating tumor cells those that are most remote from their source of oxygen develop anoxic necrosis; and the adjacent hypoxic cells survive through metabolic changes that lead to the refractory disease with associated metastasis and resistance to a wide range of therapeutic agents. Model systems for investigating prevention and therapy of refractory cancers are urgently needed. With high levels of manifested homologies to PC in man, the lobund-wistar [LW] rat mimics clinical prostate cancer in man. LW rats are inherently predisposed to develop metastasizing PC spontaneously by endogenous mechanisms, distinct from cancers that develop following exposures to chemical, physical and biological carcinogens in the environment. Early stages of developing PC are testosterone [T] dependent and reversible by T-deprivation agents and procedures, progressing at ~mid life-span [12 months] to development of the T-independent refractory stage. Small T-independent adenocarcinomas [0.5 cm diameter] can be palpated at age 17 months and grow to ~3cm diameter 2 months later. Expanding foci of necrosis appeared among the anoxic tumor cells and pimonidazole- stained cells were noted among the adjacent cells-the likely origin of the refractory cells. Refractory cells did not respond to T-deprivation [castration, injections of estradiol, nonesterified dihydrotestosterone, diets containing soy protein isolate/isoflavones]. For further characterization of the refactory status of the tumors, hypoxia inducible factor-1[HIF-1], vascular endothelial growth factor [VEGF] and expression of tumor promoter EZH2. Tumor cells derived from primary refractory cancers in LW rats were transplantable to male, to female, and to castrated LW rats. Refractory PC cells produce high levels of urokinase and tissue plasminogen activators; and the metastatic spread of tumor cells to the lungs was suppressed by anti-angiogenic linomide. Prevention of the early T-dependent stage of PC prevented progression to the T-independent refractory stage. This model system of hormone-refractory PC should contribute to studies on pathogenesis prevention, and treatment of the disease.

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3-year prospective patient evaluated urinary and intestinal side effects after stereotactic dose-escalated radiotherapy of prostate cancer with the beamcath(R) technique.

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Background. New data suggest that a higher radiation dose will improve outcome in treatment of localized prostate cancer. However, dose-escalated external beam radiotherapy (EBRT) might on the other hand increase the risk of urinary and intestinal side effects. Since 1997, over 600 patients have been treated with the BeamCath® stereotactic primary boost technique of 4-8 Gy added to conventional 70 Gy EBRT. Late side effects have prospectively been evaluated in the first 195 patients up to 3-years after dose-escalated EBRT.

Method. Urinary and intestinal problems were prospectively evaluated with a validated self-assessment questionnaire, the Prostate Cancer Symptom Scale, PCSS. Two-hundred-eighty-seven patients completed the questionnaire at the 1-year follow-up, and out of those 234 at 3-years after treatment. Pre-treatment mean age was 66 years. One hundred and sixty eight patients were treated with conformal technique up to 70 Gy and 195 were treated with dose-escalated stereotactic BeamCath® technique. Mean total dose in the conformal group ($\leq$70 Gy) was 66 Gy (60.8-70.4 Gy). The dose-escalated group consists of 3 dose levels, 74 Gy (n=68), 76 Gy (n=74), and 78 Gy (n=53).

Results. Dose-escalation with stereotactic EBRT (74-78 Gy) did not increase gastrointestinal or genitourinary late side effects at 3-year in comparison to doses $\leq$70 Gy. Most rectal side effects were increased at 3-years in comparison to pre-treatment values. Blood and mucus in stools were the two most increased problems comparing pre-treatment with the 3-year follow-up. A significant decrease in urgency and starting problems were seen, while urinary incontinence was increased.

Conclusion. Dose-escalation with the stereotactic BeamCath® EBRT technique does not increase the urinary or intestinal side effects in patients with localized prostate cancer treated with conventional doses $\leq$70 Gy.

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Docetaxel (DOC) and mitoxantrone (MIT) in the management of hormone-refractory prostate cancer

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Background: DOC, alone or in combination is one the most active agents in hormone-refractory prostate cancer (HRPCA). The aim of this trial was to determine the response rate of DOC-MIT in patients with asymptomatic HRPCA.

Materials and methods: A total of 72 patients with HRPCA and asymptomatic prostate-specific antigen (PSA) progression were recruited. HRPCA was defined as: serum PSA rise despite antiandrogen withdrawal, 3 consecutive weekly PSA rises, castrate serum testosterone levels. DOC was administered at 60 mg/m^2 and MIT was administered at 8 mg/m^2, every 3 weeks for 6 cycles. A dose reduction was performed for grade 3-4 toxicity. Quality of life (QoL) was assessed after each cycle and 3-monthly thereafter using the EORTC QLQ-30. PSA levels were followed at each cycle and 3-monthly after completion of chemotherapy. The primary endpoint of the study was survival; secondary endpoints were objective PSA response, time to progression, time to the development of pain, as well as safety and QoL.

Results: The mean age of the patients was 65.9 (range: 56-85) years; 68/72 (94.4%) patients were eligible for analysis. The mean PSA level at initiation of therapy was 182.1 (range: 2.0-1680) ng/mL. During therapy, PSA levels were reduced by >50% in 42/68 (62%) patients and stable in 15/68 (22%) patients, whereas PSA progression was evident in 11/68 (16%). Three (4.2%) patients died: 1 case of listerial meningitis developed during grade 4 neutropenia and 2 patients suffered a myocardial infarction during cycle 1. The dosage of DOC-MIT was reduced in 9/68 (13%) patients; neutropenic fever developed in 2/68 (3%) patients and grade 3 leucopenia occurred in 12/68 (18%) patients; there were no significant gastrointestinal side effects. After a median follow-up of 10.5 (range: 5-17) months, 5 (7%) patients have died from disease, 25% of patients have demonstrated PSA progression, and 68% have exhibited stable PSA levels. There was no significant correlation between initial PSA level and objective response. It is too early to report survival data.

Conclusions: The combination of DOC and MIT is well tolerated, has a limited spectrum of therapy-associated side effects and results in a high objective response rate in HRPCA with asymptomatic PSA progression.