Table 1

GI	stool-frequency	mucous/pain	bleeding
II°	3%	2%	21%
III°	1%	0%	1%

Table 2

URO	pollakisuria	nycturia	pain	hematuria	stenosis
II°	9%	23%	9%	5%	0.3%
III°	3%	3%	2%	1%	2%

vesicles, neoadjuvant HT, diabetes, cardiovascular disease, acute toxicity > I°. Univariate predictors for a higher incidence of late side-effects were: GI: prostate dose (p=0.035) and acute toxicity (p=0.005); URO: body mass index (p=0.059), cardiovascular disease (p=0.036) and acute toxicity (p=0.002). Multivariate predictors were: GI: acute toxicity (p=0.004) and prostate dose (p=0.032), URO: acute toxicity (p=0.002) and cardiovascular disease (p=0.023).

Conclusions: The incidence of moderate (III°) rectal or urologic late toxicity after CRT is low (<5%). The occurrence of acute symptoms > I° is a predictor for late II°/III° toxicity.

874 POSTER

Ir192 conformal brachytherapy and external beam radiation (EBR-CU.ir192) with or whithout hormonotherapy for locally advanced prostate adenocarcinoma: the Centre François Baclesse experience

D. Brune, F. Lesaunier, D. Benabid, M. M'vondo, M. Henry-Amar. *Centre François Baclesse, Radiotherapy Curietherapy, Caen, France*

Technique: We use temporary transperineal implantation with 2 to 6, 20 cm divergent needles. Implantation is made in 20 mn with general or rachianaesthesia. Needles are loaded with Ir^{192} (low dose rate, LDR) or linked to a projector (high dose rate, HDR).

Treatment protocol: The first protocol involved 15 Gy LDR Cu.Ir^{192} and 45 Gy pelvic EBR. The second protocol combined 2 x 4.7 Gy HDR Cu.Ir^{192} and 45 Gy pelvic EBR. The maximum dose delivered to urethra was 2 x 9 Gy. Within the prescribed radiation doses, the dose rate had no influence on clinical results as well as on toxicity. In locally advanced tumours (T2b-c,T3a-b), hormonotherapy (androcur, nonsteroid antiandrogens or LHRH agonists) was given to 83 patients because of dysuria, postponed therapy or based on recent published findings. Hormonotherapy duration was less than 6 months in 82% of patients.

Study population: From July 1989 to September 1999, 693 patients were treated of whom 291 presented with locally advanced N0, M0 tumours. 208 patients were given EBR-Cu.Ir^{192} only and 83 EBR-Cu.Ir^{192} and hormonotherapy. The two patient groups were similar for age (71 and 70 years in average) and WHO 2-3 performance status (36% and 37%); they differed for Gleason grade (grade ≥ 7: 35% versus 66%, p<0.001) and *ab initio* PSA level (> 20 ng/ml: 52% versus 81%, p=0.002).

Results: The 7-year cause specific survival rates were 85% and 75% in patients treated with and without hormonotherapy, respectively (p=0.59). The 7-year cumulative rates of local failure were 12% and 21% (p=0.10); that of distant metastases were 29% and 28% (p=0.79) and that of biological failure (PSA > 4 ng/ml) were 68% and 63% (p=0.58), respectively. Hormonotherapy duration (< 6 versus ≥ 6 months) had no statistical significant influence on local failure, distant metastases as well as biological failure rates although a trend was observed for less local failure with prolonged hormonotherapy (0% versus 15%). According to the Soma-Lent system, the 7-year cumulative rates of grade II-III urinary and digestive complications were 27% and 7%, respectively, similar in patients given or not hormonotherapy. Sexual complications could not be studied because of the deleterious impact of hormonotherapy on sexual performance.

Conclusion: The contribution of hormonotherapy to EBR-Cu.Ir^{192} is limited in patients with locally advanced prostate adenocarcinoma. Its impact might only concern the incidence of local failure. The administration of hormonotherapy immediately after radiation therapy only is questioned in the light of its efficacy when given at the time a local failure occurs.

875 POSTER

A prospectively randomized phase II trial of pegylated doxorubicin in hormone refractory prostate cancer

A. Heidenreich[1], P. Olbert[1], J. Goecke[1], F. Sommer[2], U.H. Engelmann[2]. [1] *Philipps - University Marburg, Department of Urology, Marburg, Germany;* [2] *University of Cologne, Department of Urology, Cologne, Germany*

Introduction & objectives: Liposomal encapsulation of doxorubicin (Caelyx™) has been shown to reduce non-specific drug delivery to normal tissues and improve the specific delivery to malignant cells. Caelyx™ may also reduce the peak plasma levels of doxorubicin that may be responsible for toxicity. Since doxorubicin shows response rates of 30% in HRPCA, we conducted a prospective randomized clinical phase II trial to evaluate the feasibility, toxicity and therapeutic efficacy of Caelyx™ in HRPCA.

Patients & methods: 48 patients with progressive HRPCA after hormonal therapy and antiandrogen withdrawal were randomized to receive Caelyx™ at 25mg/m^2 every 2 weeks for 12 cycles (group 1), 50mg/m^2 every 4 weeks for 6 cycles (group 2) and 50mg/m^2 every 4 weeks for 3 cycles followed by 40mg/m^2 every 4 weeks for 3 cycles (group 3). All patients received dexamethason 8mg bid on days 1 through 5 and vitamin B 300mg/day. 38/48 patients (79%) presented with severe pain due to osseous metastases equivalent to a pain score of 7.5 on a VAS ranging from 0 to 10. Therapeutic efficacy was recorded by serial PSA serum measurements, toxicity was recorded according to NCIC/CALBG and EORTC QLQ-C30.

Results: Median age was 68.9 (range 58-79) years; mean follow-up was 42 months. Mean pre-therapeutic PSA was 660.4 (8-6340) ng/ml. An objective response (>50% PSA↓) was observed in 17/25 (68%) patients in group 2 and the mean response duration was 6.5 months. None of the remaining patients developed a PSA response. Significantly more patients in group 2 had a pain response (52.6%) than patients in group 1 and 3 (28.6%, p=0.04). Mean 1-year survival was significantly higher in group 2 (42%) than in groups 1 and 3 (6% and 20%, respectively, p=0.02). Toxicity was severe with 24 pts (50%) demonstrating WHO stage III/IV toxicity. There was a significant difference in the type of toxicity between the different groups. Palmar-plantar erythema developed in 60% of group 1 patients (p<0.0005) whereas tachycardia developed predominantly in groups 2 and 3 (20% and 80%, p<0.0005). There was no dose-limiting cardio- or hematotoxicity.

Conclusions: Pegylated doxorubicin has a high palliative efficacy in HRPCA with painful osseous metastases; a short-term objective response was observed in the 40mg/m^2 group. Caelyx® might be a useful component of chemotherapeutic combination therapy in HRPCA.

876 POSTER

Protein microchips for the analysis of prostate specific antigen

E. Dementieva[1], E. Darii[2], A. Rubina[3], A. Zasedatelev[4], T. Osipova[5], T. Ryabykh[6], A. Baryshnikov[7], A. Mirzabekov[8]. [1] *Engelhardt Institute of Molecular Biology, RAS, Biochip-IMB center, Moscow, Russian Federation;* [2] *Engelhardt Institute of Molecular Biology, RAS, Biochip-IMB center, Moscow, Russian Federation;* [3] *Engelhardt Institute of Molecular Biology, RAS, Biochip-IMB center, Moscow, Russian Federation;* [4] *Engelhardt Institute of Molecular Biology, RAS, Biochip-IMB center, Moscow, Russian Federation;* [5] *N.N.Blokhin memorial Cancer Research Center, RF, RAMS, Institute of Experimental Diagnostics and Therapy of Tumors, Moscow, Russian Federation;* [6] *N.N.Blokhin memorial Cancer Research Center, RF, RAMS, Institute of Experimental Diagnostics and Therapy of Tumors, Moscow, Russian Federation;* [7] *N.N.Blokhin memorial Cancer Research Center, RF, RAMS, Institute of Experimental Diagnostics and Therapy of Tumors, Moscow, Russian Federation;* [8] *Engelhardt Institute of Molecular Biology, RAS, Biochip-IMB center, Moscow, Russian Federation*

Background. DNA and protein microchips found wide application in different fields of fundamental and applied science. Three-dimensional gel-based biochips with immobilized proteins developed by the Engelhardt Institute of Molecular Biology RAS can be used for different types of analysis including immunoassays. The goal of our studies was to create microchip-based technique for quantitative assay of prostate cancer marker, prostate-specific antigen (PSA, total and free) in sera of cancer patients.

Material and methods. Microchips with immobilized antibodies to total and free PSA were manufactured. The chip is an array of three dimensional semi-spherical gel elements separated from each other with hydrophobic surface. For the microchip fabrication, solutions of co-polymerization mixtures containing gel monomers and proteins were spotted on a glass slide by a robot. Diameter of gel drops was 50ñ300 μm depending on a robot pin. Polymerization of gel arrays was carried out under irradiation with UV

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.

877 POSTER

Hormone-refractory prostate cancer in the Lobund-Wistar rat

M. Pollard[1], M. Suckow[2]. [1] *University of Notre Dame, Biolgical Sciences, Notre Dame IN, USA;* [2] *University of Notre Dame, Freimann Life Science Center, Notre Dame IN, USA*

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.

878 POSTER

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

P. Fransson[1], P. Bergström[1], P.-O. Löfroth[2], A. Widmark[1]. [1] *Dept. of Radiation Sciences, Oncology, Umeå, Sweden;* [2] *Dept. of Radiation Sciences, Radiation Physics, Umeå, Sweden*

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.

879 POSTER

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

A. Heidenreich, C. Ohlmann, P. Olbert, A. Hegele. *Philipps University Marburg, Department of Urology and Paediatric Urology, Marburg, Germany*

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.