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Changes in prostate volume during permanent brachytherapy with JOD 125 and influence on dose distribution (D 90)

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Background: An increase of the prostate volume during permanent brachytherapy may lead to a clinical relevant dose reduction. The time course and the predominant axis of the volume aberration after seed implantation were determined.

Materials and methods: In 96 patients a CT scan before implantation was compared with examinations taken one day, four and eight weeks after implantion. Computer tomography was performed with a Picker 5000 using 3/3 mm slices. Prostate volume and extension in anterior/posterior, lateral and longitudinal axis was recorded with an AqSim/VoxelQ® workstation. The D 90 values were computed using the Prowess® - planning software.

Results: Following an initial increase of all axes, predominant on the a-p direction, there was a continuous decrease, particularly in the lateral dimension:

Extension	CT 1 (pre)	CT 2 (day 1)	CT 3 (week 4)	CT 4 (week 8)
Ant. / Post. (mm)	38,2	42,2 (+11,5%)	39,4 (+2,9%)	36,9 (- 4,2%)
Lateral (mm)	47,4	49,7 (+ 4,8%)	46,5 (- 2,1%)	43,8 (- 7,2%)
Longit. (mm)	30,5	33,1 (+ 7,5%)	33,0 (+ 7,9%)	32,2 (+ 5,3%)
Volume (ccm)	33,1	37,4 (+13,2%)	32,0 (-3,3%)	28,3 (-11,5%)

Where as the a-p. and lateral extension showed a continuous decrease and sunk below the initial datas, the cranio-caudad extension remained nearly unchanged at least during the first eight weeks. Compared with the initially calculated D 90, this effect resulted in a relative increase of the D 90 (132,8 Gy day 1; 142,4 Gy week 4; 152,5 Gy week 8).

Conclusion: The cranio-caudad volume extension showed the smallest decrease compared with the other spatial axis.

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Effects of 5 alpha reductase inhibitors on prostatic carcinoma cells grown in primary culture

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Background: 5 alpha reductase (5α R) plays a key role in the transformation of testosterone (T) in the more active 5α dihydrotestosterone (DHT). In prostate gland both type I (5α R1) and type II (5α R 2) isozymes are expressed. We tested the effectiveness of two 5α R inhibitors (Finasteride, or MK 906, as specific inhibitor of 5α R2 and MK386, a specific inhibitor of 5α R1) in inhibiting cell proliferation of human PCa cells in primary coltures from prostatic biopsies of different pathologies.

Materials and Methods: We analyzed primary cultures derived from 30 cases of Prostatic carcinoma (PCa), 6 cases of high grade PIN and 6 cases of Benign Prostatic Hyperplasia (BPH). Cultures were analyzed for the presence of Prostatic Specific Antigen (PSA), Androgen Receptor (AR) expression and stromal cell contamination by immunocytochemistry. Androgen dependent cell growth was also analyzed. MK906 and MK386 were kindly provided by Merck Sharp and Dohme.

Results: Both 5α R inhibitors are able to reduce significantly and dose-dependently cell proliferation in prostatic primary cultures inducing a significant increase in apoptotic cell number. IC50 values from MK906 were lower when compared to those observed from MK386 whereas the combination of both inhibitors does not increase their overall effectiveness. Primary cell cultures contained about 30% of stromal contamination. Stromal cell presence was essential for prostatic epithelium proliferation. This can also explain the higher effectiveness of MK906 respect to MK386. In fact, 5α R1 (responsible primarily for androgenic catabolism) is mostly expressed in epithelial cells whereas 5α R2 (responsible for DHT local synthesis and release) is expressed in the stroma compartment,. which provides several paracrine factors and DHT itself to epithelial cells. In addition, the effectiveness of MK386 in primary cultures can be explaned considering that the catabolic products (3α and 3β ADIOLs) generated from DHT by 17β hydroxylases modulates prostatic cell growth. Then the inhibition of 5α R1 can alter the catabolism of DHT generating also high levels of β -estradiol having different proliferative effects in prostatic epithelium.

Conclusions: 5α R inhibitors may have an important role in the inhibition of prostatic cancer proliferation as demonstrated by the effectiveness on both human cell lines and PCa primary cultures. In our experience, data concerning the combination effects with other antiproliferative drugs deserve particular attention and will be presented in the near future for an optimal control of PCa.

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The effect of pelvic lymph node irradiation in salvage therapy for prostate cancer patients with a biochemical relapse following radical prostatectomy

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Purpose: Radiation therapy (RT) as salvage treatment for a biochemical relapse (BCR)following prostatectomy has been controversial, but shown to be of benefit with regards to PSA control. However, the appropriate target volume for RT is not well defined. Here, we compare the results of postoperative RT given to an extended field (EF, prostatic fossa and pelvic lymph nodes encompassing at the least the obturator lymph nodes) or to a limited field (LF, prostatic fossa only) as treatment for those with a post-prostatectomy BCR.

Methods: Between 1987-1999, 68 patients were referred for post-prostatectomy RT for a BCR (defined as 2-3 consecutive rises in PSA following prostatectomy). Of them, 46 were treated with RT alone, with 21 patients treated to a EF and 25 patients were treated to an LF. All patients were treated by four-field technique with simulation films verified for EF and LF coverage. The mean field sizes measured 15 x 14 x 12cm and 10 x 10 x 10 cm for the EF and LF, respectively. The mean doses for the EF and LF were 6300 and 6200 cGy, respectively. After 45 Gy, the field for the EF group was shrunk to cover the prostatic bed only.

Results: The ten year actuarial biochemical disease-free survival rates for the EF and LF were 52% and 47%, respectively (p=0.52). The distant metastasis-free survival (DMFS) was 77% and 78% (p=0.93) and overall survival (OS) was 88% and 68% (p=0.61) for the EF and LF group, respectively. A subset analysis of patients with adverse pathologic histopathologic features on surgery (i.e., positive surgical margins, lymph node involvement, seminal vesicle involvement, extracapsular invasion, or perineural invasion) showed a biochemical disease-free survival of 57% and 44% (p=0.22) for the EF and LF group respectively. The DMFS was 84% and 72% (p=0.93) and OS was 92% and 61% (p=0.37) for the EF and LF group, respectively.

Conclusions: For patients with rising PSA levels after a radical prostatectomy, salvage irradiation is a viable option for biochemical control. Our results suggest that EF radiation with coverage of pelvic lymphatics, shows a trend towards PSA control in those with adverse pathologic features, although statistical significance was not achieved. However, a potential prospective study comparing field sizes could more definitively answer our questions as to how to optimize therapeutic options in the postoperative recurrence setting.

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Expression of bcl-2 and p53 as biomarkers in imprint smears of prostate carcinomas and their prognostic value

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Background: The tumour suppressor gene p53 and the proto-oncogene bcl-2 have been shown to be prognostic biomarkers of cancer recurrence in patients with malignant diseases. The aim of this study, was to evaluate the prognostic significance of the expression of p53 and bcl-2 in smears of prostate adenocarcinomas and the results to compare with other prognostic factors.

Material and Methods: Imprint smear samples obtained from 70 patients immediately after radical prostatectomy for prostatic adenocarcinomas were studied. An immunocytochemical stain was performed using anti bcl-2 and anti-p53 monoclonal proteins. The expression of these proteins was related to the Gleason score, tumour differentiation, stage and PSA levels.

Results: Positive expression for p53 and bcl-2 was observed in 50 (71.4%) and 38 (52.8%) smears, of 70 studied tumours, respectively. Our findings demonstrate that p53 and bcl-2 biomarkers in prostatic adenocarcinoma smears, correlated significantly with the degree of Gleason score ($p<0.001$ for p53 and p:0,005 for bcl-2). When combining p53 and bcl-2 positivity with tumour differentiation there was a significant association between these parameters ($p<0.001$). Overexpression of p53 and bcl-

2, was also associated with increase pretreatment PSA serum levels (>4ng/ml) (p<0.001). The distribution of p53 and bcl-2 expression, in prostate carcinomas, was statistically significant for stages T2a and T2b (p<0.001). On the contrary, no significance for T2c and T3a (p:0.24 for p53 and p:0.61 for bcl-2) was found as for as the histological stage. P53 and bcl-2 proteins had significant prognostic value for the disease free survival, remained an independent prognostic marker by Cox multivariate regression analysis.

Conclusions: The expression of p53 and bcl-2 appears to be an additional significant marker in the field of prognosis and outcome of patients with prostatic adenocarcinoma.

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High-dose ibandronate is effective and well tolerated in the treatment of pain and hypercalcaemia due to metastatic urologic cancer

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Introduction and objectives: Up to 20% of all urological malignancies are complicated by paraneoplastic hypercalcemia due to increased bone resorption and enhanced renal tubular reabsorption. Increased bone resorption is associated with osteolytic bone metastases and severe bone pain in metastatic renal cell and bladder cancer. Bone pain, reduced mobility and decreased quality of life due to osteoblastic metastases still represent a therapeutic dilemma in hormone refractory prostate cancer. Ibandronate is a third generation bisphosphonate with a high analgesic potency and a calcium lowering effect. We undertook a prospective pilot study to evaluate the safety and tolerability of high dose ibandronate in metastatic urological cancer.

Patients and methods: 59 patients (n=45 prostate cancer, n=9 renal cancer, n=5 bladder cancer) with hypercalcemia (n=6, group A) or painful osseous metastases (n=53, group B) were included in the prospective study. All patients had a serum creatinine level greater than 2 mg/dl. Patients in group A also had serum calcium levels greater than 2.8 mmol/l, while patients in group B had a mean pain score of 6.8 using a VAS from 110. In group A, after fluid repletion, ibandronate 6mg i.v. in 500ml glucose 5% was infused over 1 hour and repeated daily until serum calcium levels had normalized (median three infusions, range 25). In group B, ibandronate 6mg was given i.v. for three consecutive days, and continued at 4-week intervals.

Results: In group A, s erum calcium values fell progressively from day 2, reaching a nadir on day 4, and normocalcemia was maintained for 28 days. In group B, bone pain was significantly improved in 44/53 (83%) of the patients, starting on day 2; the mean pain score on day 3 was 2.5 (p<0.001). None of the patients in groups A or B demonstrated an increase in serum creatinine or serum urea nitrogen concentrations. Besides a slight decrease in serum calcium concentrations in 7/59 patients (12%), no alterations in laboratory measures were detected. Eight patients (14%) from groups A and B developed fever and flu-like symptoms as the only therapy-associated side effects. No renal adverse events were reported.

Conclusions: Application of high dose ibandronate results in a significant and fast normalization of serum calcium levels in patients with paraneoplastic hypercalcemia and a significant pain relieving effect in 83% of patients with painful osseous metastases. Despite the intensive dosing schedules of i.v. ibandronate in this study, we did not encounter renal toxicity or any other significant therapy-associated side effects.

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Chemotherapy induced peripheral neuropathy in testicular cancer patients treated with cisplatin,etoposide and bleomycin(PEB)

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Purpose: Evaluation neurological late toxicity in testicular cancer patients (pts) treated with PEB (cisplatin,etoposide and bleomycin) combination chemotherapy (CHT).

Methods: From January l997 to January 2002, 48pts with testicular cancer, were treated in hospital with PEB combination chemotherapy, after orchiectomy received at least 3 cycles of CHT. Median age was 32 (18-64). Were followed for at least 1 year after CHT and retrospectively evaluated for neurotoxicity. All pts had EMG (electromyography) and physical examination by a neurologist.

Results: Only 4 pts had pathological findings of EMG (axonal neuropathy). 8 pts had symptoms with paresthesias at distal extremities, 2 pts have grade I neurological toxicity according to the WHO toxicity scoring system.

Conclusion: We concluded the combination PEB CHT is safe, well tolerated and treatment with 3 cycles did not lead no clinically significant neuropathy.

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Indirubin, the active constituent of a Chinese antileukaemia medicine induces growth arrest and apoptosis in renal cell cancer cells.

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Indirubin is the active ingredient of Danggui Longhui Wan, a mixture of plants that is used in traditional Chinese medicine to treat chronic diseases. The cell permeable Indirubin-3'-monoxime is a selective and potent inhibitor of cyclin-dependent kinases (CDK) and was shown to be active in several hematological tumor models. In this study we investigated if Indirubin-3'-monoxime (Alexis Inc.) can induce apoptosis and tumor cell death in four different, one animal (Renca) and three human (A498, Caki 1, Caki 2), renal cell cancer cell lines. The growth inhibitory properties were evaluated by EZ4U, a cytotoxic assay; whereas induction of apoptosis was determined by flowcytometry of Annexin-V/PI staining during treatment. Further, we investigated a potential synergism of a combined application of Indirubin with Paclitaxel, as this drug targets the mitotic spindle and cell cycle regulation, too. The efficacy of Indirubin-3'-monoxime yielded different results in the cell lines. In Renca, A498 and Caki-1 we found a significant dose and time related, but reversible growth arrest, though not apoptosis. When combined with Paclitaxel, a significant amount of apoptosis was induced, which was higher then with Paclitaxel treatment alone, suggesting that there might be a synergistic effect for the induction of apoptosis. A synergistic effect of a combination of Indirubin-3'-monoxime and Paclitaxel was shown in two cell lines (A 498, Caki-1). In Caki-2, a highly malignant cell line, growth inhibitory efficacy was limited, all three applications (Indirubin-3'-monoxime, Paclitaxel, combination) induced only a minor amount of apoptosis. In summary, Indirubin-3'-monoxime seems a promising candidate for a molecular targeted approach in renal cell cancer therapy. However, its actions alone and with other agents need further evaluation.

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Adjuvant chemotherapy(CHTH) in patients with high-risk urothelial cancer of urinary tract.

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Background: The role of adjuvant CHTH in high-risk urothelial cancer pts is disputable. Adverse prognostic factors are not fully determined.

Objective: the retrospective evaluation of results of adjuvant CHTH in patients (pts) with urothelial cancer of urinary tract after radical surgery.

Patients and methods: From 1994 through 2002 136 pts with urothelial cancer of urinary tract and no residual macroscopic disease following radical surgery with high-risk features for relapse (defined as: grade 3, positive lymphonodes, vascular/lymphatic invasion) received 2 (to 1996) or 3 (to 2001) or 4 cycles of adjuvant CHTH. Median age was 60 (41-76), male/female ratio 115/21. All pts had undergone macroscopically radical operation (7-nephroureterectomies, 3- partial cystectomies, 123-radical cystectomies/cystoprostatectomies). The local status was: pT2-25pts, pT3-87, pT4-24. The nodal status was: pN0-60 pts, pN1-29,pN2-30,pN3-2, in 15 pts the pN status wasn't determined. For 81 pts the median number of excised lymphonodes was 4 (1,30). 40 pts had G2, 96- G3. Vascular/lymphatic vessel invasion was present in 74 of 80 pts in whom this feature was defined. 134 pts received MVC (metotrexate, vinblastine, cisplatin), 2 pts MVCarbo. 9 pts received 1 cycle of CHTH (in 8 cases CHTH was stopped because of toxicity, 1 pt resign of CHTH), 26- 2 cycles, 94- 3 cycles, 6- 4 cycles, 1- 5 cycles.

Results: 54/136 pts (39.7%) are alive with no evidence of disease, 23/136 (16.9%) are alive with PD, 58/136 (42.6%) died of disease. 66/136 (48.5%) relapsed with the median TTP 11.8 mos (2.7-72). The median OS is 17.9 mos (0.6-101).