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11C-Choline-PET/CT determines potentially curative patients with prostate cancer recurrencies

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Background: The purpose of the study was to assess the utility of 11C-Choline-PET/CT in detecting single pelvic lymph nodes, isolated local recurrence or distant lymph nodes in patients with rising PSA-levels after radical prostatectomy.

Methods: 31 patients (pts.) (age:xm 63.1y, 06/2002 until 02/2003) with rising prostatic specific antigen levels (PSA) after radical prostatectomy (RPE) were investigated. All patients underwent dedicated 11C-Choline-PET/CT examination (GE Discovery LS) from neck to prox. femur region. Data acquisition started 10 min after injecting 1080 Mgq 11C-choline and a non-ionic contrast agent. Image fused PET/CT was used to determine local recurrence or lymph node involvement. All CT detected lymph nodes (lnn.) were measured, localised and compared to PET; in case of focal increased 11C-choline uptake the size of the lnn. was correlated to the SUV. In PET SUV was measured in case of local recurrence, single lnn. relapse or distant lnn.metastasis and correlated to the PSA levels.

Results: All 31 Pts. suffered from rising PSA-levels. In 11/31 pts. PET/CT revealed no additional information, but in these cases the average increase of PSA was very low (0.03 ng/ml/month). In 20/31 pts. 11C-choline PET/CT detected a local relapse (n=4) or lnn. recurrence (n=13) with an average increase/month of 1.59 ng/ml. In 4 pts. rising PSA level indicate a systemic tumor spread out. 9/13 pts.were selected for potentially curative therapy with single lymph nodes. Increasing tumor mass correlated with an increase of PSA. SUV xm in single lnn. metastasis was 2.1, in massive lymph node involvement 3.44 and in local recurence 2.31.

Conclusions: In detecting single lnn. 11C-Choline-PET/CT is superior to CT. 11C-Choline-PET/CT demonstrates isolated local recurrence, neither seen in CT nor in MRI or TRUS. 11C-Choline-PET/CT can separate potential curative patients for surgery or conformal radiation therapy, depending on isolated local recurrence or single manifestation in locoregional lymph node regions.

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Phase II study of low dose thalidomide and interferon-alpha in metastatic renal cell carcinoma (RCC)

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Background: Limited options are available in metastatic RCC. Interferon- ± (IFN) and Thalidomide are active in RCC. Because of the antiangiogenic properties of each agent at low doses, we conducted a clinical trial combining low dose IFN- ± and Thalidomide.

Methods: Since February 2001, 19 patients with progressing RCC, WHO performance Status (P.S) ≤2 consented to receive IFN- ± 3× 10^6 U/day and Thalidomide 100 mg/day. Dose reduction for grade 3-4 toxicity and ≥ grade 2 neuropathy was applied only to IFN- ± at 2 and subsequently 1× 10^6 U/day. Survival times were calculated with Kaplan-Meier survival curves using Epistat 5.0. Responses were assessed by the RECIST criteria*Results:* Pt's Characteristics were: m edian age- 64 (45-81) years, WHO P.S. 1(0-2) and disease free interval of 14.6 (0.8-102.7) months. Metastases occurred in lung-16 (84%), lymph nodes- 7 (36%), renal bed- 6 (30%), bone- 4 (21%), and soft tissue, adrenal or liver each in 2 (10%) Pt's. Six (32%) Pt's received prior IFN- ±, one as an adjuvant. Toxicity data is available in all Pt's. IFN- ± was reduced in 10 Pt's (52.6%) due to 11 grade 3 episodes: asthenia- 6 (37.5%) Pt's, and headache; neutropenia; neutropenic fever and grade 2 tremor; dyspnea, vomiting and vertigo; and gastrointestinal toxicity. Two (10%) Pt's discontinued the treatment due to mild visual cerebrovascular event, and persistent headache. While treated, 1 Pt died unrelated to therapy. Fourteen Pt's are assessable now for response: 3 Pt's (21.4%) achieved Partial Response (lung- 2 and lung + soft-tissue-1), 7 Pt's (50%) obtained stable disease, with an overall non-progression rate of 71.4% (10 Pt's- 95%, CI 41.9% - 91.6%). Over all survival is at a mean of 17.4 (1.4+ - 20.3) months. Sixteen Pt's (84.2%) are still alive.

Conclusion: Low doses Thalidomide and Interferon is feasible and active in metastatic RCC. Further accrual with initial IFN- ± 2× 10^6 is ongoing.

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Urinary incontinence in prostate cancer patients treated with external beam radiotherapy

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Purpose/Objective: To describe the incidence of urinary incontinence among prostate cancer patients treated with external beam radiotherapy (RT) and to investigate associated risk factors.

Materials/Methods: 1192 patients with >= 24 months follow-up were the subjects of this series. All patients received between 50-72Gy in 20-37 fractions (median 66Gy/33#). Post-RT urinary incontinence was scored according to the modified RTOG/SOMA scale: Grade 1- occasional use of incontinence pads, Grade 2 - intermittent use of incontinence pads, Grade 3 persistent use of incontinence pads, Grade 4 permanent catheter. Risk-factors investigated were: age, diabetes, TURP prior to RT, elapsed time from TURP to RT, clinical stage, RT dose and presence of grade >=2 acute GU toxicity. Non-parametric, actuarial univariate (Kaplan-Meier) and multivariate tests (MVA, Cox regression) were performed.

Results: Median follow-up for the group is 52 months(24-109). 34 patients (2.9%) had incontinence prior to RT, which was more common in TURP patients (7.8% vs 1.6% p<0.001). These are excluded from further analysis. 57 patients (4.9%) developed grade 1 incontinence, 7 (0.6%) grade 2, and 7 (0.6%) grade 3. There was no grade 4 incontinence. Actuarial rates for grade >=1and >=2 incontinence at 5 years are 7% and 1.7% respectively. Risk factors on MVA associated with the development of grade 1 or worse incontinence are pre-RT TURP (5-year rates 10% vs. 6%, p=0.026), presence of grade >=2 acute GU toxicity (5-year rates 11% vs. 5%, p=0.002). Age, diabetes, clinical stage, elapsed time from TURP to RT, and RT dose or fraction size were not significant. Patients who underwent post-RT TURP or dilatation for stricture (4.3%), were more likely to develop grade 2-3 incontinence (5-year rate 8% v 1.5%, p=0.0015).

Conclusions: Grade 2 or greater urinary incontinence is rare among patients who have been treated with external beam radiotherapy. Associated risk factors are pre-RT TURP and the presence of increased acute GU toxicity. Post-radiation TURP increases the risk of incontinence five-fold.

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Intravesical gemcitabine in the treatment of intermediate risk superficial transitional cell carcinoma (TCC) of the bladder: a marker lesion study

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Introduction: A phase I study has shown a good tolerability and a high complete response (CR) rate of 2000 mg intravesical gemcitabine administered in BCG resistant patients refusing radical cystectomy. Marker lesion studies in intermediate risk superficial bladder cancer are safe and should always precede phase III studies when assessing the efficacy and tolerability of a new intravesical agent. We designed the following study in order to study the ablative or reductive activity of gemcitabine administered intravesically on a single papillary marker lesion. Side affects and hematological parameters during and after the treatment constituted the secondary end point.

Patients and methods: 24 patients with a history of papillary recurrent Ta-T1, G1-G2 bladder TCC (intermediate risk), a normal upper urinary tract at IVU and no high grade atipia at preoperative urine cytology were consented to undergo a resection of all visible lesions except a single 0,5-1 cm papillary marker lesion. After histological confirmation, 2000 mg in 50 ml saline solution of gemcitabine were administered intravesically for 1 hour weekly for 6 weeks starting the 7th postoperative day. Full blood count, renal and hepatic function, urine culture were assessed before any treatment administration. Postoperative urine cytology, cistoscopy plus cold biopsy of the base of implant or resection of the marker lesion were performed within 2 weeks from the end of the treatment. CR was defined as the absence of any histologically confirmed recurrence of bladder TCC and/or a negative urine cytology. Anything else than CR was defined as non response (NR).

Results: All patients completed the treatment. A mild nausea was reported by 4/20 patients and hypostenia by 2/20. Six patients complained of dysuria. Both full blood count and biochemistry parameters were not significantly altered over the treatment course. We recorded only grade I

toxicity for white blood cells (2 cases), for hemoglobin (1 case) and for platelets (1 case). 19 patients have been evaluated endoscopically so far. CR were observed in 11/18. No case of progression was observed.

Conclusions: Intravesical gemcitabine at the dose of 2000 mg weekly for 6 weeks has an effective ablative action on papillary marker lesions from intermediate risk superficial bladder cancers. Side effects are mild. No significant hematological toxicity has been recorded in our series.

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Proton therapy for invasive bladder cancer: Treatment results of a bladder-preserving therapy with x-ray irradiation and concurrent intra-arterial chemotherapy followed by proton irradiation boost

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Background: In the treatment of invasive bladder cancer, proton beam irradiation having an excellent dose localization to the target may contribute to formulating a treatment regimen with less morbidity and more efficacy in both local tumor control and bladder preservation. We present results of treatments for 23 patients with invasive bladder cancer treated with x-ray irradiation and concurrent intra-arterial chemotherapy followed by proton boost to the primary site.

Material and Methods: Twenty five patients with transitional cell carcinoma of the urinary bladder, cT2-3N0M0, were entered in the present study. All patients underwent transurethral resection of the bladder tumor(s) followed by x-ray irradiation (41.4 Gy in 25 fractions with 10-MV photons) to the small pelvis and concurrent intra-arterial chemotherapy (methotrexate 30 mg/m^2 and cisplatin 50 mg/m^2, 3 courses at 3-week intervals). Upon completion of the treatments, the patients were evaluated with transurethral observation and biopsy. When a patient had no residual tumor, he/she received a boost dose (33 Gy in 11 fractions) with proton beams to the primary sites. When a patient had a residual tumor, he/she underwent radical cystectomy.

Results: Twenty-three of the 25 patients (92%) had no residual tumor at the time of tumor re-evaluation, and hence received proton therapy. The remaining two patients having residual tumors underwent radical cystectomy. Of the 23 patients treated with proton therapy, nine had recurrences; local recurrences in six patients, distant metastases in two and both in one. All local recurrences were controlled with salvage therapies and all of the three patients with distant metastases died of cancer. The 5-year over-all, disease-free and cause-specific survival rates were 61%, 65% and 84%, respectively. The 5-year local tumor control and bladder-preservation rates were 73% and 100%, respectively. It was found by the multivariate analysis that T category and the number of tumors were the significant prognostic factors for the survival ($P<0.01$) and for the local tumor control ($P< 0.05$), respectively. Treatment toxicities of grade 3-4 were found in eight patients; hematologic toxicities in six patients and hemorrhagic cystitis in two.

Conclusions: The present regimen of bladder-preserving therapy for invasive bladder cancer was feasible and effective. Proton therapy contributed significantly in improving local tumor control and bladder preservation.

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Risk-adapted brachytherapy of prostate cancer using J - 125 permanent implantation

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Background: To examine causes of early biochemical recurrence after permanent brachytherapy. Risk factors and therapeutic consequences are worked out.

Materials and methods: After a median time of 14 months four of 112 patients developed biochemical progress. Post planning dosimetry at four weeks after implantation showed a median D 90 of 151,5 Gy (144,8 - 159,3 Gy). Restaging using ^{11}C-Cholin-PET/CT unveiled an isolated relapse in the seminal vesicles. Patients' records were reviewed to figure out common factors. Recurrences to the seminal vesicles were histological proven.

Results: All patients with recurrences had initially histological positive specimen from the base and or mid of the prostate and a PSA between 5 and 10 ng/ml. Depending on these results, we decided to include in these patients the seminal vesicles into the target volume. Up to now 9 patients with the above defined risk factors were treated with permanent brachytherapy according to this regime. Post planning dosimetry showed a minimal dose of 148 Gy in the area of the seminal vesicles. During follow up no change in the acute and late side effects was observed compared to patients receiving brachytherapy to the prostate only.

Conclusion: In patients with histological positive specimen from the base of the prostate should be included into the treatment volume. In addition ^{11}C-Cholin-PET/CT has been included into the staging procedures prior to treatment.

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Evaluation of a superantigen- mediated immune response as therapy for superficial bladder cancer.

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Background: Potent activators of T lymphocytes are toxins produced by Staphylococcus aureus. The characteristics of these Superantigens can be exploited in diseases where strong immunologic responses are required. We initiated this study to evaluate a new approach in an immunomodulating intravesical therapy of superficial bladder cancer.

Material and Methods: We first examined by flowcytometry if SEB (staphylococcal enterotoxin B) can induce Fas-ligand expression on peripheral blood mononuclear cells (PBMC). Second we evaluated cytokine secretion by PBMC with specific ELISAs during SEB treatment and finally investigated if SEB-activated PBMC are able to induce apoptosis in human transitional cell carcinoma cells (TCC) in vitro co-cultures. As proof of concept, we evaluated the toxicity and effects of SEB in a chemically induced transitional cell carcinoma rat bladder cancer model. SEB was administered intravesical once weekly for 6 weeks. Rats with NaCl 0,9% instillation in the same schedule were evaluated as control. Tumor stage, grade and lymphocytic infiltration were assessed on hematoxilin and eosin stained sections. Apoptotic cells in the urothelium and stroma of the bladder were detected by TUNEL. All bladder specimens were stained CD4+/CD8+, ED2 and naphtol AS-D chloroacetate to assess distribution of lymphocytes, macrophages and mononuclear cells.

Results: We demonstrate pronounced time-dependant induction of Fas-ligand on PBMC by SEB. Further, show a massive time-dependant secretion of cytokines IL-2, IFN-gamma and TNF-alpha released from the SEB-stimulated PBMC. In co-culture experiments we demonstrate that SEB-activated PBMC kill TCC cells. TCC cells treated with culture supernatant containing the released cytokines of SEB-treated PBMC demonstrated a minimal response only. In vivo, the toxicity study with up to 100 μg/ml SEB intravesical revealed no side effects of SEB in the animals. For treatment a dose of 10 μg/ml SEB dissolved in NaCl 0,9% vehicle was chosen. Due to narcosis-related deaths, 14/20 animals in the therapy group and 16/20 in the control group were evaluable. Of the SEB treated animals only 3 had a tumor remaining vs. 13 animals with tumor in the control group. In the remaining tumors of the animals in the therapy group, we found a significant amount of apoptosis and a large amount of granulocytes mainly in the urothelium, whereas we found no relevant apoptosis or infiltration of the bladder with lymphocytes and no macrophages in the control group.

Conclusions: The in vitro findings show that SEB induces Fas-ligand expression on immune cells accompanied by a massive release of cytokines kills effectively TCC cells. In vivo, we could validate these anti-tumor observations. Therefore a clinical proof of concept study (first in man) should be initiated.

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Intraoperative and interactive planning for permanent prostate brachytherapy: dosimetric and clinical results

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Background: Permanent seed implantation is a well accepted treatment of early stage prostate cancer. Since end of 2000 the interstitial brachytherapy with iodine-125 seeds is performed at the Medical University Hannover with the so called ProSeed-method. Treatment planning is done with the system VariSeed 6.7 and 7.0. With this new version of the planning system