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.

860 POSTER

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

M. Hata[1], N. Miyanaga[2], K. Tokuuye[1], K. Ohara[1], Y. Saida[3], S. Sugahara[1], K. Kagei[1], T. Hashimoto[1], H. Akaza[2], Y. Akine[1]. *[1] University of Tsukuba, Radiation Oncology, Tsukuba, Japan; [2] University of Tsukuba, Urology, Tsukuba, Japan; [3] University of Tsukuba, Radiology, Tsukuba, Japan*

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.

861 POSTER

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

P.M. Messer[1], H.-W. Gottfried[2], N.M. Blumstein[3], E. Schneider[1], E.M. Röttinger[1]. *[1] Ulm University, Department of Radiation Oncology, Ulm, Germany; [2] Ulm University, Department of Urology, Ulm, Germany; [3] Ulm University, Department of Nuclear Medicine, Ulm, Germany*

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.

862 POSTER

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

P.L. Willert[1], F.G.E. Perabo[1], D.H. Schmidt[1], M. Sitzia[1], E. Wardelmann[2], A. Von Rücker[3], A. Wirger[4], P. Albers[1], S.C. Müller[1]. *[1] University Hospital, Dept. of Urology, Bonn, Germany; [2] University Hospital, Institute of Pathology, Bonn, Germany; [3] University Hospital, Institute of Clinical Biochemistry, Bonn, Germany; [4] Medical University, Dept. of Urology, Luebeck, Germany*

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.

863 POSTER

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

R. Baumann[1], A. Warszawski[1], S. Machtens[2], J.H. Karstens[1]. *[1] Medical University Hannover, Department of Radiotherapy, Hannover, Germany; [2] Medical University Hannover, Department of Urology, Hannover, Germany*

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

an interactive dynamic dose calculation is possible. Dosimetric and clinical data will be shown.

Methods: Up to now 119 patients underwent a permanent seed implantation. 84 patients were planned intraoperative with the system VariSeed 6.7 on the basis of transrectal ultrasound images. For 35 patients an interactive treatment planning has been performed with the VariSeed 7.0 where a dynamic dose calculation is possible. Implant quality is checked for all patients by post-implant CT-based dosimetry six weeks after the implantation.

Results: A comparison between the intraoperative and the postoperative dose calculation of the first 84 patients results in differences up to 20% in the D90 (dose covering 90% of the volume) and V100 (volume receiving the prescribed dose) for the prostate. Because of the possibility to adjust the position of each needle and each single seed during the implantation using the planning system VariSeed 7.0 differences of nearly 5% in the dose distributions are possible between the interactive planning and the preplanning. Thus the differences between the D90 for the interactive dynamic dose calculation and the D90 of the post-implant CT-based dosimetry are much less for the 35 patients planned with the new version of the planning system.

Conclusion: The analysis of the data of the 84 patients planned with the system VariSeed 6.7 shows obvious differences between the intraoperative dose calculation and the CT-based dosimetry. These differences in the dose distribution are much more smaller for the patients planned with the new version of the planning system (7.0). It is very important to adjust the position of each needle and seed to its real location to guarantee a homogenous dose distribution enclosing the whole prostate. According to this the dose at the organs at risk can be better calculated and the side effects are less.

864 POSTER

Intravenous (IV) vinorelbine (VRL) plus hormone therapy (HT) versus hormone therapy alone in hormone-refractory prostate cancer (HRPC). Final report of a randomised phase III study

R.P. Abratt[1], D. Brune[2], M.A. Dimopoulos[3], J. Kliment[4], J. Breza[5], P. Selvaggi[6], P. Beuzeboc[7], T. Demkow[8], S. Oudard[9]. [1] *Groote Schuur Hosp., Cape Town, South Africa;* [2] *Centre F. Baclesse, Caen, France;* [3] *Alexandra Hosp., Athens, Greece;* [4] *Comenius Univer. Medical School, Bratislava, Slovak Rep.;* [5] *Je Senius School of Medicine, Martin, Slovak Rep.;* [6] *Osp. Policlin. Consorziale, Bari, Italy;* [7] *Institut Curie, Paris, France;* [8] *M. Sklodowska Curie Memorial Cancer Center, Warsaw, Poland*

Background: VRL produced sustained PSA decline and durable clinical benefit in phase II studies. Its moderate toxicity profile is well tolerated in elderly patients.

Material and methods: 414 patients received either IV VRL 30 mg/m2 on days 1 and 8 every 3 weeks combined with HT, consisting of hydrocortisone 40 mg/day + aminoglutethimide 1000 mg/day, or HT alone. Eligible patients had metastatic, progressive disease after androgen deprivation, PSA > 10 ng/ml and Karnofsky score (KPS) > 60%. The primary endpoint was progression-free survival (PFS). All responses and dates of progression were independently reviewed. EORTC QLQ-C30 questionnaires were scheduled every 3 cycles.

Results: Median age was 69 (range: 48-87). The median number of cycles was 6 (1-36) in the test arm versus 4 (1-40) in the control arm. The median relative dose-intensity of VRL in the test arm was over 90%. Intent-to-treat analysis of PFS showed a significant prolongation in the IV VRL arm: 6 month PFS rate of 34.4% versus 23.7%, median of 3.75 versus 2.93 months [p=0.061 in the logrank test (2-sided, a = 10%), p=0.005 in the test adjusted for predetermined prognostic factors]. Significant factors in the multivariate Cox model included hemoglobin (p=0.004), KPS (p=0.020), and alkaline phosphatase (p=0.001). PSA response rate (decline > 50% for 6 weeks) was also significantly higher in the test arm: 30.1% versus 19.2% (p=0.01), as well as clinical benefit response: 30.6% versus 19.2% (p=0.008). Aminoglutethimide did not impact on PFS in either arm. Survival was not different: 12 and 18 month survival rate of 56.1% and 41.1% in test arm vs 57.7% and 40.1%; median at 14.7 vs 15.2 months. Toxicity was low. Grade 3 - 4 neutropenia (25.6%), neutropenic infection (3%) and constipation (3%) were seen in the test arm only.

Conclusion: IV VRL plus hydrocortisone offers a new effective and safe therapeutic option for the treatment of HRPC.

865 POSTER

Comparison of ultrasound assisted implantation of the prostate using a look-up nomogram versus ultrasound assisted intraoperative 3D computer optimization: improved conformality with improved urethral and rectal dose volume histogram: it's time to move forward!

A. Raben[1], H. Chen[2], A. Grebler[3], J. Geltzeiler[4], I. Kesleman[5], S. Litvin[6], A. Hanlon[7], J. Yang[8], S. Sim[9]. [1] *Radiation Oncology,* [2] *Shore Urology, Monmouth Medical Center, Long Branch, USA*

Purpose: We have employed a 3D computer planning system with intraopertive dose optimization and feedback in an effort to improve target conformality and reduce urethral and rectal doses. We report our preliminary dosimetric outcome with this approach and compare our results to our prior experience with a standard lookup nomogram.

Materials and Methods: 114 patients (pts) with favorable risk prostate cancer underwent ultrasound guided brachytherapy using Iodine-125 sources, from 1998 through 2002. Sixty-nine pts (Gr 1) were implanted using a transperineal approach with a standard look-up nomogram. Pts in Gr1 were prescribed a dose of 160 Gy without dose constraints on the urethra and rectum using a modified peripheral loading technique. Forty-five pts (Gr 2) were recently implanted with a transperineal technique using a computer dose-optimization program with real-time feedback. Pts in Gr 2 had pre-determined urethral (V150 < 35%), and rectal dose constraints (V110 < 1.5 cc) placed and prostate dose range (140-180 Gy) prior to the implant. Dosimetric outcome was compared between both groups for differences.

Results: For Gr 1 and Gr 2 (3D), there was no difference in the median pre-implant gland volume (33 cc vs 35 cc; p=0.31), median mCi/seed strengths (0.4 vs 0.45 mCi; p=0.23), or median D90 at post-implant day 30 (165 Gy vs 160 Gy; p=0.26). However, for Gr 2 (3D), the median total mCi's implanted (26 vs 33 mCi; p<0.0001) and the median number of seeds implanted (67 vs 83; p<0.0001) were significantly less. At day 30, the median V150 urethra for Gr 1 was significantly higher than for Gr 2 (3D) (63% vs 17%; p<0.0001) respectively. Similarly, the median V110 rectum for Gr 1 was significantly higher than that in Gr 2 (1.93 vs 0.26 cc; p<0.0001). The percent of pts with D90 > 180 Gy was 29% in Gr 1, compared to 16% in Gr 2 (p=0.08). No difference was observed in the percent of pts with D90 < 140 Gy (14% Gr 1 vs 9% Gr 2, p=0.56). A V150 urethra > 35% was observed in 88% of pts in Gr 1 compared to 29% in Gr 2, p<0.0001. The percent of pts with V110 rectum > 1.5 cc in Gr 1 and Gr 2 was 57% and 13%, respectively, p<0.0001. Pre-and post-implant IPSS scores, and post-implant RTOG GU and GI symptom index scores were obtained in both groups. For Gr 1, the median pre- and post-implant IPSS scores were 5 and 6 at a median f/u time of 25 months. Late RTOG GU morbidity includes 20% with grade 2 symptoms, 2% grade 3, and 2% grade 4. For Gr 2, median pre- and post implant IPSS scores are 4 and 8. To date, 29% are experiencing grade 2 GU symptoms at a median f/u time of 6 months, with no grade 3-4 symptoms. RTOG GI sxs for Gr 1 include 5% grade 2, 0% grade 3, and 2% grade 4. For Gr2, only 3% have grade 2 sxs, with no grade 3 or 4 sxs.

Conclusions: The introduction of a 3D computer optimization program with real-time dosimetric feedback of the target volume during prostate seed implantation resulted in significantly lower urethral and rectal doses while achieving excellent target coverage. Pre-determined dose constraints were effectively maintained in a majority of patients. Additional follow-up will determine if these improvements will lead to a more favorable morbidity profile without compromise of biochemical control.

866 POSTER

A novel system for high-dose radiotherapy for localized prostate cancer using a dual X-ray fluoroscopy and amorphous silicon flat panels system

K. Britton Gallardo, Y. Takai, K. Nemoto, Y. Ogawa, M. Mitsuya, S. Yamada. *Tohoku University, Radiation Oncology department, Sendai, Japan*

Purpose: This study comprises the clinical implementation of a new system mounted on the gantry of a linear accelerator, a dual X-ray fluoroscopy and paired flat panels system (DFFP system) for the settings of a dose escalation protocol.

Material and Methods: The DFFP system consists of a dual fluoroscopy that has been adapted to the gantry's left-right side at 45 degrees from beam axis each and paired flat panels with x-ray sensors opposing the x-ray sources. The image acquisitions of an implanted gold seed in the prostate are obtained at 15-30 frames per second and gold seeds (GS) coordinates, intrinsically recognized as the pixel position on the flat panels. At treatment, the isocentered GS coordinates allow precise positional verifications. In