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

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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!

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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

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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

addition, just before every field / every other field delivery, GS coordinates are obtain to estimate the organ motion and target volume repositioning if needed. Daily system implementation was evaluated for 15 patients undergoing IMRT to 72-80 Gy, depending on cases. Early toxicities grades and QOL questionnaire's data were analized.

Results: Sufficient quality DFFP system images of the gold seed were obtained on real time by the X,Y,Z coordinates of the center of a square delineating the seed; the center of the seed. An overall average of 4 system views per treatment fraction, taken from gantry 0 degrees, showed that intrafraction marker displacements were in the range of ± 1mm in 66.8% of delivered fractions. Compared to conventional techniques, in just a small number of all fractions (1/3), DFFP system-guided intrafraction "off range" marker positional corrections could be done, therefore reducing major motion uncertainties. High dose IMRT was well tolerated acutely, without grade 2 complications. Minimal urinary dysfunction and

867 POSTER

Thymidine phosphorylase (TP) expression in tumor cells of metastatic renal cell carcinoma (RCC) patients treated with capecitabine and interferon-alfa2A (IFNa).

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Background: TP is the rate-limiting enzyme that metabolizes 5'-deoxy-5-fluorouridine, an intermediate metabolite of capecitabine, to the active drug 5-fluorouracil (5-FU). Capecitabine is a fluoropyrimidine carbamate capable of exploiting the high concentrations of TP in tumor tissue to achieve activation preferentially at the tumor site, thereby minimising systemic exposure to 5-FU. Purpose of the study was to evaluate level of TP expression in tumor cells and correlation between TP expression and treatment efficacy of capecitabine and IFNa combination as the first line treatment in patients with metastatic RCC.

Material and methods: TP expression was evaluated in tumor tissue of 16 patients with immunohistochemistry assays using monoclonal anti-TP antibody (Roche Diagnostics GmbH). Semi-quantitative analysis by using a scoring system for tumor cells was performed, where staining percentage 0, 1-10%, 11-25%, 26-50%, >50% referred to as 0, 1+, 2+, 3+ and 4+, and staining intensity no staining, low, moderate and high intensity referred to as 0, 1+, 2+ and 3+. Semi-quantitative scores were calculated as sum of staining percentage and staining intensity scores, ranging from 0 to 7. Capecitabine was administered orally at a dose 1,250 mg/m2 twice daily for 14 days followed by 7 days of rest, IFNa was administered subcutaneously 6 million U three times weekly. Tumor measurements were performed after every 6 weeks.

Results: Overall response rate in this group of patients was 31%, all were partial responses, stable disease status was additionally achieved in 33% of patients. High level of TP expression (score e 5+) in tumor was detected in 9 patients from 16 (56%). All semi-quantitative scores and their relation to treatment effects are characterized in table:

		Best response (No. of patients)		
Score	No. of patients	Partial response	Stable disease	Progressive disease
2+	2	1	-	1
3+	2	1	-	1
4+	3	-	1	2
5+	3	-	2	1
6+	6	3	1	2
Total	16	5	4	7

Conclusions: Substantial TP expression in tumor tissue was detected in majority of patients with metastatic RCC. No correlation between TP expression and response to treatment with capecitabine and IFNa is possible to detect in analysed group of patients.

868 POSTER

A tolerance and efficacy study of thalidomide, paclitaxel, estramustine combination for patients with chemotherapy refractory androgen independent prostate carcinoma

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Background: Chemotherapy is effective palliative treatment (Rx) for patients (pts) with androgen-independent prostate carcinoma (AIPCa). Improvement in Rx is required. Results of salvage Rx in pts with AIPCA progressing after prior chemotherapy are under-reported. Preclinical studies indicate synergistic activity with combinations of anti-angiogenesis and cytotoxic agents. Thalidomide (T), an angiogenesis inhibitor, has single agent activity in AIPCa.

Material/Methods: We studied the combination of Paclitaxel (100 mg/m2/week, 2 out of 3 weeks), Estramustine (140 mg po q 8 hrs, 5 days/week, 2 out of 3 weeks) and escalating doses of T (200-400-600 mg/day) in pts with AIPCa, progressing after 1-2 prior cytotoxic regimens. Warfarin 2 mg po qd was given for deep venous thrombosis (DVT) prophylaxis. We considered that a $\geq$ 30% of pts with > 50% post-therapy PSA decline would be a clinically significant threshold of anti-tumor activity of the combination in this setting.

Results: To date, 26 pts [median age 66 (range, 49-80); median Zubrod performance status 1 (range, 0-2)] were entered (10 in the phase I and 16 in the phase II study) and received a median number of 3 (range, 1-8) cycles (C). Pts had 1 (n=18) or 2 (n=8) prior chemotherapy regimens (11 pts with prior Taxane/Estramustine-based Rx; 11 pts with prior Ketoconazole/Adriamycin/Vinblastine/Estramustine). Twenty-five pts are evaluable for toxicity (1 pt developed DVT prior to Rx initiation and did not receive any therapy); 19 are evaluable for response [2 pts were taken off study before 2 C (1 refused Rx after 1 week, 1 developed pneumonia after C1) and 4 pts are too early]. During C1 of the phase I study: at 200 mg/d T, 0 of 3 pts showed grade 3/4 toxicity; at 400 mg/d T, 1 of 4 pts experienced grade 3 neutropenia (< 7 days duration) and 1 of 4 pts had grade 3 edema (relieved promptly by diuretics); at 600 mg/d T, 0 of 3 pts had grade 3/4 toxicity. Of the 18 total pts assigned to the 600 mg/d dose level of T (in both phases of the study), 7 pts tolerated the 600 mg/d continuously, 8 pts tolerated 400 mg/d, 1 pt 200 mg/d, and 2 pts are too early. All dose reductions of T were due to somnolence/fatigue (grade 1-2). Peripheral neuropathy was limited to grade 1. Four of 25 pts developed grade 3/4 DVT (requiring Rx discontinuation in 2 pts), 2 additional pts discontinued Rx due to intercurrent infection, and 1 pt died from sepsis. To date, 15 of 19 (78%, 95% confidence interval 54-94%) evaluable for response pts achieved a sustained (more than 6 weeks duration) > 50% post-therapy decline in PSA, and 3 of 19 pts showed sustained > 80% post-therapy PSA decline. Measurable disease response and improvement in bone pain were seen.

Conclusion: These preliminary results show that a significant number of pts with AIPCa progressing after prior chemotherapy met the threshold of PSA decline considered of clinical significance, thus justifying further study of this combination in AIPCa.

869 POSTER

Gemcitabine (GEM) and oxaliplatin (l-OHP) to treat immunotherapy-resistant advanced renal cell carcinoma (ARCC) patients (pts.): preliminary results of a single institution phase II study

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Background: Pts. with aRCC still have a poor prognosis, with a median survival of approximately 10 months. Due to frequent overexpression of the MDR gene product, P-gp, RCC is a typical chemoresistant tumor, immunotherapy being consequently often used as first-line treatment option; furthermore, at present, there is no standard treatment for immunotherapy-unresponsive pts. Recently, however, combinations of newer chemotherapeutic agents, including GEM and, at a lesser extent, also L-OHP, have been shown to exert some antitumor activity in aRCC. Here we report the preliminary results of an ongoing single-institution phase II study.

Patients and methods: Twenty-five patients with aRCC unresponsive to s.c. IL-2 and IFN-α-based immunotherapy were treated to date with a combination of GEM (1,000 mg/m^2, i.v., days 1 and 8, q21) and L-OHP (90 mg/m^2, i.v., day 1, every 21); treatment was administered for a minimum of 2 cycles before response evaluation; toxicity was recorded at every cycle according to NCI-CTC.

Results: No complete response (CR) were observed, 3 pts. (12%, 95% CI: 2,5-31,2%) achieved a partial response (PR), 8 pts. (32%) had, as their best response, a disease stabilization (SD), while the remaining 16 pts. (56%) progressed (P). All three PR were observed after the first disease re-evaluation, i.e., after 2 cycles. As far as toxicity, treatment was generally well tolerated; indeed, no grade IV toxicity was observed, while grade III toxicity included myelosuppression (in 11 pts., i.e., 44%), neuropathy (in 10 pts., i.e., 40%) and non-neutropenic fever (in 7 pts., i.e., 28%); other, less severe, side effects included, nausea/vomiting, mucositis and fatigue.

Conclusions: Despite preliminary, our results suggest that the combination of GEM and L-OHP cannot improve the objective response rate