Conclusions: Fecal symptoms and intestinal QOL deteriorated during CRT for prostate cancer while global QOL was not affected. Although a number of ano-rectal symptoms improved after radiotherapy, fecal bother and EORTC PR25-bowel symptoms continued to be inferior to pretreatment values throughout follow-up. Reducing ano-rectal symptoms in CRT for prostate cancer might have a positive impact on QOL.

4050 POSTER

Proton radiotherapy for patients with prostate cancer – in the Hyogo Ion Beam Medical Center (HIBMC) experience

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Background: Proton radiotherapy (PRT) is sophisticated treatment modality for prostate cancer that is increasing in Japan. The purpose of this study is to examine clinical results of prostate cancer treated with PRT.
Materials and Methods: From Apr 2003 to Oct 2004, 291 males aged 48−85 (average 69) with histologically-proven cT1−3N0M0 prostate cancer (1997 UICC TNM) received PRT at the HIBMC. Clinical T stage was classified T1a/T1b/T1c/T2a/T2b/T3a/T3b as 2/3/112/80/38/36/20. Initial prostate specific antigen (PSA) level was distributed 1.2 to 222 (mean 17.8 ng/ml). Patients were stratified into three prognostic risk groups: Group A patients had a T1-T2a, PSA < 20 ng/ml, and the percentage of positive prostate biopsies (PPPB) <50%; Group B: T2b-T3, or 20 ng/ml < PSA < 50 ng/ml, or PPPB < 50%; and Group C: PSA > 50 ng/ml irrespective of T factor. 83 of 170 patients in group A received PRT with neoadjuvant androgen ablation (NAA) for 6 months. 101 of 102 in group B were treated by NAA followed by PRT. All of 19 in group C were treated by NAA, PRT and adjuvant androgen ablation. PRT was planned with a 3D planning system using bilateral 2 fields; patients received 74 GyE (gray equivalent, using a relative biologic equivalence factor of 1.1) of protons (190 to 230 MeV) at 2.0 GyE per fraction. GI and GU toxicity was scored according to the RTOG/EORTC Late Morbidity Grading Scale. Overall survival (OS) and biochemical disease free survival rate (Houston definitions: absolute nadir plus 2 ng/ml dated at the call) were calculated by Kaplan-Meier estimates.
Results: Five patients died from other disease in the follow-up period ranging from 28 to 47 months (median 36 months). Biochemical disease free survival rates/OS rates at 3 years was 92%/98% in all cases and was 98%/99%, 90%/97%, 57%/100%, in the group A, B, C, respectively. According to MSKCC risk criteria, three year biochemical disease free survival rates in favorable (n = 62) /intermediate (n = 106) /unfavorable (n = 117) were 100%/98%/83%, respectively. The GI/GU toxicity rates of grade 2 and grade 3 were 4.1%/4.1% and 0%/0%, respectively.
Conclusions: Our proton radiotherapy showed excellent OS and biochemical disease free survival rates in patients with prostate cancer with minimum late morbidities.

4051 POSTER

Long-term effect of radiotherapy of the healthy prostate on Serum-PSA levels

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Background: Prostate-Specific antigen (PSA) is a 34 kilodalton protease exclusively secreted by the epithelium of the prostatic ducts to lyse seminal vesicular protein. Its concentration in the seminal fluid is about 100x higher than in the blood. PSA concentration in serum (s-PSA) is a common indicator for diagnosis, treatment monitoring, and relapse in prostate cancer. Irradiation of the healthy prostate may impair its exocrine function and consequently impact on serum PSA level. On the other hand, prostate cancer regression due to irradiation also affects s-PSA. PSA kinetics after radiotherapy for prostate cancer is a combined result of both. Surprisingly, scarce data exists on radiation induced s-PSA changes in the absence of prostate cancer. Here we present long-term follow-up data of a previously published study (1) on the effect of pelvic irradiation on s-PSA levels.
Materials and Methods: We examined s-PSA in 33 men (median age 62.9 y) who had undergone pelvic irradiation for rectal and anal cancer. These men had no prostatic diseases. The prostate has been inadvertently irradiated in all patients as confirmed by CT-based treatment plans. 26 patients received conventional radiotherapy with 50.4 Gy/1.8 Gy, and seven patients 25 Gy (5 × 5 Gy fractions). Total (free and bound) s-PSA was measured with an immunoassay using monoclonal anti-PSA antibodies (Elecsys PSA assay, Roche; Diagnostics, Mannheim). Blood samples were drawn before, during, and after radiotherapy in regular intervals. In the meantime 9 patients deceased and 14 patients were lost to follow up. In 10 patients long term data were available with a median follow-up of 7.9 (7.2−8.5) years from study entry.
Results: Serum-PSA levels increase steadily within the first weeks of irradiation, peaking at 2−3 weeks with a lg(PSA) excess of 0.37 ($p < 0.01$), i.e. a 2.3 fold increase. At the end of radiation therapy, PSA levels decrease, but are still slightly elevated. On the long term, serum PSA decrease below the initial level, but this decrease is not significant [lg(PSA) = 0.19, $p = 0.26$].
Conclusions: Irradiation of the healthy prostate causes a significant transient increase of serum PSA levels. In comparison to the elapsed time the accumulated dose is of minor importance. On the long term 7−8 years after radiotherapy s-PSA decreased gradually, but this trend was not significant. This decrease may indicate a radiation-induced glandular insufficiency.

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4052 POSTER

MRI-based preplanning in low-dose-rate prostate brachytherapy

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Background: TRUS-based preplanning is inconvenient and uncomfortable due to the insertion of a probe into the rectum and a catheter into the urethra. If similar results as accurate as those obtained through TRUS-based preplanning could be obtained by MRI-based preplanning, then it would be comfortable and convenient for patients. To compare the dosimetric results between MRI-based and TRUS-based preplanning in permanent prostate brachytherapy, and to estimate the accuracy of MRI-based preplanning by comparing with CT/MRI fusion-based postimplant dosimetry.
Methods & Materials: Twenty-one patients were entered in this prospective study with written informed consent. MRI-based and TRUS-based preplanning was performed. The seed and needle locations were identical according to MRI-based and TRUS-based preplanning. MRI-based and TRUS-based preplanning was compared using DVH-related parameters. This analysis included a comparison of the prostate volume, prostate V100(%), prostate D90(%), urethral D30(%), urethral D5(%), urethral V150(cc), rectal V150(cc), and rectal V100(cc). Following brachytherapy, the accuracy of the MRI-based preplanning was evaluated by comparing it with CT/MRI fusion-based postimplant dosimetry. The group comparisons for the volumes and dosimetric parameters were performed using a t test and a p value of <0.05 was considered statistically significant.
Results: Mean MRI-based prostate volume (19.26±8.15 cc) was slightly underestimated (0.73 cc in mean volume) in comparison to TRUS-based volume (20.00±8.71 cc). There were no significant differences in the mean DVH-related parameters except with rectal V100(cc) between TRUS-based and MRI-based preplanning. Mean rectal V100(cc) was 0.74 cc in TRUS-based and 0.29 cc in MRI-based preplanning, respectively, and the values demonstrated a statistical difference.
The postimplant prostate volumes increased by prostatic edema in comparison to preplanning. Postimplant prostate V100 and D90 were decreased in comparison to the MRI-based preplanning. However, there was no statistical difference in the urethral V150(cc), rectal V150(cc), and rectal V100(cc) values between MRI-based preplanning and CT/MRI fusion-based postimplant dosimetry. The rectal V100(cc) value between MRI-based preplanning and CT/MRI fusion-based postimplant dosimetry showed a correlation.
Conclusion: Prostate volume estimation and DVH-related parameters in MRI-based preplanning were almost identical to TRUS-based preplanning. MRI-based preplanning can more accurately predict postimplant rectal dose than TRUS-based preplanning.

4053 POSTER

Comparison of image guidance by megavoltage computed tomography versus simple bone alignment during radiation of prostate cancer

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Background: Helical tomotherapy delivers intensity-modulated radiation therapy and allows image-guidance based on an integrated megavoltage CT (MVCT). Aim of this study was to evaluate the benefit of this image-guidance versus simple bone alignment in radiation of prostate cancer.
Methods and Materials: 10 patients treated for localized prostate cancer with tomotherapy were included. A total dose of 76 Gy was delivered to prostate (GTV). Before each of the 363 fractions a MVCT was performed and the patient was positioned (shift in *x*/*y*/*z*-direction and roll) to match

the prostate with the planning GTV. Prostate and rectum were segmented on each daily pre-treatment MVCT and doses recalculated. To simulate positioning of the patient based on alignment of the pelvic bones (for example with daily x-ray) a software algorithm was used that matches the bones on the daily MVCT to the bones of the planning CT. Doses of the prostate and the rectum for this theoretical bone match position were calculated. Actual treatment and treatment in bone match position were compared with respect to the calculated dose of 95% of the prostate (D95) and absolute rectal volume with dose over 1.5 Gy (rV1.5) in a single fraction. Currently 109 out of 363 fractions are evaluated.
Results: Comparing actual treatment position and theoretical bone match position: average ($\pm$SD) shift between both positions for each fraction was 2.4$\pm$1.7 mm, difference of roll was −0.35$\pm$0.56. Average difference between treatment position and bone match position for D95 was 0.35% and for rV1.5 was 1.6%, both not significant ($p = 0.01$). The confidence interval for the difference of D95 was [0.2%, 0.9%] and for rV1.5 was [16%, 19%] ($p = 0.01$). However improvement of >100% for rV1.5 in treatment versus bone match was possible in 2% of fractions.
Conclusion: Average differences found of delivered dose between positioning based on daily MVCT and positioning based on pelvic bones are small for two reasons: (1) The soft tissue contrast of MVCT is small, which limits GTV alignment during treatment and dose recalculation of GTV after treatment. (2) Interfractional movements of prostate and rectum are complex and sufficient compensation with table shift and rotation is difficult in a number of fractions. However, daily MVCT can avoid high dose rectum radiation of >1.5 Gy in a number of fractions.

4054 POSTER

Placebo-controlled, randomized, phase II study of radium-223 in metastatic hormone refractory prostate cancer (HRPC)

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Background: The alpha emitter radium-223 (Alpharadin^{TM}) is a bone-seeking radionuclide studied as a novel treatment for patients with HRPC and skeletal metastases. Ra-223 showed minimal toxicity in a phase I study [1]. Here we present outcome data from a randomised phase II study with 18 months follow up.
Methods: Patients with CRPC and bone pain requiring external beam radiotherapy were randomized to treatment with 4 injections of either Ra-223 (50 kBq/kg b.w.) or saline (placebo) every 4 weeks. The primary endpoints were change in bone-alkaline phosphatase (ALP) levels from baseline to 4 weeks after last injection (previously reported [2]), and time to occurrence of Skeletal Related Events (SREs). Secondary endpoints included toxicity, PSA progression and overall survival.
Results: 33 patients were randomised to Ra-223 and 31 to placebo. The two groups were well balanced with respect to standard prognostic factors. Mild, transient haematological toxicity was seen after Ra-223. Long term toxicity was not observed. SAEs were reported in 8 patients in the Ra-223 group versus 14 in the placebo group. Based on intention to treat analysis, the median time to PSA progression was 26 versus 8 weeks ($p = 0.048$) for Ra-223 versus placebo, respectively. The median time to first SRE was 14 versus 11 weeks ($p = 0.257$). The hazard ratio (HR) adjusted for baseline covariates was 1.75 (95% CI: 0.97−3.19, $p = 0.065$). The median overall survival was 65.3 weeks versus 46.4 weeks ($p = 0.066$). The HR adjusted for baseline covariates was 2.12 (95% CI: 1.13−3.98, $p = 0.020$). At 18 months, 15 (45%) versus 8 (26%) patients were still alive. Two years survival and long term safety data will be presented at the meeting.
Conclusions: Four injections of Alpharadin were well tolerated, with minimal myelotoxicity, and demonstrated encouraging evidence of efficacy. Larger clinical trials are warranted to study the impact of Alpharadin on the prevention of SREs and on overall survival in CRPC. The bone targeting properties of Alpharadin, may also be applicable to the treatment of skeletal metastasis from other primary cancers.

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4055 POSTER

Hypofractionated stereotactic intensity modulated radiotherapy (IMRT) for prostate cancer with low-metastasic potential

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Introduction: To assess the feasibility, outcome, and toxicity of hypofractionated IMRT in patients with low- to intermediate-risk prostate cancer with <20% risk of metastases.
Material and Methods: From December 2003 to December 2005, 63 patients with non-metastasic prostate cancer and a Roach index [RI% = 2/3PSA + 10(Gleason score − 6)] of <20% were treated with an hypofractionated IMRT protocol using an extracraneal stereotactic repositioning system (Exatrac, BrainLAB) and 6MV X-ray beams from a micro-multileaf collimator-based linear accelerator (Novalis, BrainLAB). A total dose of 56 Gy (14$\times$4 Gy, 2 days a week for a total elpased time of 7 weeks) was delivered to the prostate with or without the seminal vesicles (equivalent to 88 Gy in 2 Gy daily fractions, $\alpha/\beta = 1.5$ Gy). Acute ($\leqslant$6 months) and late ($\geqslant$6 months) genitourinary (GU) and low-gastrointestinal (low-GI) toxicities were scored according to the LENT-SOMA and RTOG scoring systems, respectively. Five-year biochemical disease-free survival (bDFS) was calculated according to the Houston definition for failure (i.e., PSA nadir +2 ng/ml).
Results: Feasibility was optimal as well as preliminary results on tolerance (see table) and bDFS: 89% (5-year) after a median follow-up of 33 months (range, 13−90).

Toxicity	GU		low-GI	
Grade	1	$\geqslant$2	1	$\geqslant$2
Acute	12 (19%)	6 (9.5%)	5 (7.9%)	5 (7.9%)
Late	7 (11%)	2 (3.2%)	12 (19%)	2 (3.2%)

Conclusions: Hypofractionated RT using 56 Gy/14 fractions using stereotactic IMRT is feasible and is associated with a very low risk of $\geqslant$grade 2 acute (<10%) and late toxicity (<5%). Preliminary data may suggest, in addition, optimal bDFS similar to normofractionated treatments with equivalent doses for a similar risk group of patients.

4056 POSTER

Clinical validation of PTV margins used during dose escalated loco-regional IMRT to prostate, seminal vesicles and pelvic lymph nodes

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Background: Determining appropriate PTV margin size is difficult when multiple CTVs move independently. This is particularly challenging when small margins are necessary to limit dose to the adjacent organs at risk. We describe the clinical efficacy of the PTV expansions used during a Phase II clinical trial of escalated-dose IMRT to prostate/seminal vesicles (P+SV) and pelvic lymph nodes (PLN) for high-risk prostate cancer.
Materials and Methods: This retrospective review included data from the first 14 patients treated in the clinical trial. Patients were treated supine and in a vac-cushion with full bladder/empty rectum preparation. PTV margins were: PLN (5 mm), prostate (10 mm except 7 mm posterior) and seminal vesicles (10 mm). Daily isocentre adjustment was performed, by incorporated both offline and online EPI analysis. Twenty-nine daily orthogonal EPIs were reviewed for each patient. The proportion of treatment fractions where the CTVs could not be encompassed within the PTV was determined using pelvic bony anatomy (BA) as a surrogate for PLN position and the centre of 3 intra-prostatic fiducial markers (COM) as a surrogate for P+SV position.
Results: The distribution of CTV excursions outside the PTV for BA and COM is summarised in Table 1. Without any correction strategy, frequent Anterior/Posterior (AP) excursions of the CTVs outside the PTVs occurred. After offline correction of systematic errors, COM excursions were reduced to 2.6%, but BA excursions remained common due to the smaller PTV margin used. Online correction resulted $\leqslant$3% of fractions with an excursion outside the PTVs. Data revealed that excursions for the 2 CTVs were reasonably well correlated ($r^2 = 0.94$ Left/Right [LR], 0.60 Superior/Inferior [SI], 0.82 [AP]) and this allowed the matching strategy to routinely accommodate the displacements of both CTVs.
Conclusions: The PTV margins used here during dose escalated loco-regional IMRT to prostate, SV & pelvic lymph nodes are able to accommodate $\geqslant$97% of CTV displacements when online image guidance is used.