and bad (28%). The data were collected prospectively for 42% of patients. Rectal toxicity was analyzed according to the SOMALENT classification (> Grade 2) and rectal bleeding (at least once episode) at 2, 3, 4 and 5 years. The effects of pts characteristics, DVH (including mean dose) and NTCP models on rectal toxicity at the different follow-ups were assessed using logistic regression (univariate and multivariate analysis). A total of 6 NTCP models were tested: Lyman Kutcher Burman (LKB), logit EUD, Poisson EUD, Kallman, Schultheiss and Parallel models. The parameters of the models were identified using the MATLAB Genetic Algorithm Toolbox and constrained optimization. The performance for predicting toxicity of the models was performed using Efron's pseudo R squared.

Results: Median follow-up was 60 months (range: 6 to 154). Two-, 3-, 4- and 5-year grade >2 toxicity rates were: 15%, 21%, 25% and 30%, respectively. Two-, 3-, 4- and 5-year rectal bleeding rates were: 21%, 28%, 32% and 38%, respectively. Univariate analysis shown following parameters as significant predictor of 4-year grade >2 toxicity: total prescription dose, V_{71} to V_{73} and maximal rectal dose. In multivariate analysis, the remaining factors were total dose, V_{72} and V_{73}. The table shows the parameters of the NTCP models. The NTCP models which probability values are significantly related with bladder toxicities are: LKB, Logit EUD and Poisson EUD models. The model having the better predictive capability is Poisson EUD model.

Conclusions: Both, some DVH parameters and three NTCP models (Poisson EUD model being the most predictive) are useful to assess rectal toxicity and could be used as constrains in IMRT planning.

Table: NTCP of 4 Year rectal toxicity (grade $\geqslant$2)

Model	TD_{50} (Gy)	Volume Effective Factor	Slope Factor	Log-Likelihood (p value)
LKB	79.14	n = 0.0025	m = 0.2705	159.05 (0.0022)
LogitEUD	80.57	n = 0.0063	k = 9.5959	159.08 (0.0022)
PoissonEUD	81.50	n = 0.0063	γ = 2.1618	158.95 (0.0018)

7007 POSTER DISCUSSION

Predictive Models of Bladder Toxicity in Prostate Cancer Radiotherapy

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Background: In case of prostate 3D conformal radiotherapy (3DCRT), the objectives were:

– To identify patients and treatment predictors of bladder toxicity;
– To compare the performance of different Normal Tissue Complication Probability (NTCP) models for predicting bladder toxicity.

Materials and Methods: A total of 436 patients (pts) received 3DCRT for localized prostate cancer to a median total dose of 78 Gy (range: 70 to 80 Gy), 2 Gy/fraction. Pts were selected based on the availability of dose-volume histogram (DVH). Median age was 67 years (45−78). History of abdominal or pelvic surgery, anticoagulant therapy (ACT) and diabetes were observed in 30%, 15% and 6% of pts, respectively. Tumour prognostic groups (D'Amico classification) were: good (7%), medium (65%) and bad (28%). The data were collected prospectively for 42% of patients. Bladder toxicity was analyzed according to the SOMALENT classification ($\geqslant$ Grade 2) and bladder bleeding (at least once episode) at 2, 3, 4 and 5 years. The effects of pts characteristics, DVH (including mean dose) and NTCP models on bladder toxicity at the different follow-ups were assessed using logistic regression (univariate and multivariate analysis). A total of 6 NTCP models were tested: Lyman Kutcher Burman (LKB), logit EUD, Poisson EUD, Kallman, Schultheiss and Parallel models. The parameters of the models were using the MATLAB Genetic Algorithm Toolbox and constrained optimization. The performance for predicting toxicity of the models was performed using Efron's pseudo R squared.

Results: Median follow-up was 60 months (range: 6 to 154). Two-, 3-, 4- and 5-year grade $\geqslant$2 toxicity rates were: 15%, 19%, 24% and 30%, respectively. Two-, 3-, 4- and 5-year bladder bleeding rates were: 6%, 9%, 11% and 16%, respectively. Univariate analysis shown following parameters as significant predictor of 4-year grade $\geqslant$2 toxicity: diabetes, total prescription dose and maximal bladder dose (none of the DVH values). In multivariate analysis, the remaining factor was the total dose. The table shows the parameters of the significant NTCP models.

The NTCP models which probability values are significantly related with rectal toxicities are: LKB, Logit EUD, Poisson EUD and Schultheiss models. The model having the better predictive capability is LKB model.

Conclusions: NTCP models (LKB model being the most predictive) are useful to assess bladder toxicity and could be used as constrains in IMRT planning.

NTCP of 4 Year bladder toxicity (grade $\geqslant$2)

Model	TD_{50} (Gy)	Volume Effective Factor	Slope Factor	Log-Likelihood (p value)
LKB	80.56	n = 0.0920	m = 0.3641	158.12 (0.0038)
LogitEUD	81.00	n = 0.0431	k = 7.6206	157.91 (0.0049)
PoissonEUD	82.19	n = 0.0409	γ = 1.7510	157.88 (0.0045)
Schultheiss	71.38	–	k = 8.2548	160.69 (0.0089)

7008 POSTER DISCUSSION

Twenty-four-month Safety Data From Phase II Studies of Radium-223 Chloride, a First-in-class Alpha-pharmaceutical With a Highly Favorable Safety Profile for Patients With Castration-resistant Prostate Cancer (CRPC) and Bone Metastases

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Background: Radium-223 chloride (^{223}Ra; Alpharadin™) is a first-in-class alpha-pharmaceutical with a potent, highly targeted antitumour effect on bone metastases. Phase II trials assessed the safety and efficacy of ^{223}Ra in patients (pts) with CRPC and bone metastases. Here we report long-term safety data from the end of the treatment period until 24 months after the first injection of ^{223}Ra.

Methods: Two double-blind, dose-response phase II trials (BC1−03 [NCT00667199], BC1−04 [NCT00337155]) and 1 double-blind, placebo-controlled phase II trial (BC1−02 [NCT00459654]) of ^{223}Ra were conducted in 286 pts with CRPC and bone metastases (255 pts received ^{223}Ra;100, 122, and 33 pts in BC1−03, BC1−04 and BC1−02, respectively). Doses varied from 5 to 100 kBq/kg (single [BC1−03] and repeated injections [BC1−02 and BC1−04]). Follow-up safety assessments were performed at months 6, 9, 12, 18, and 24 and included treatment-related adverse events (AEs), hematology, clinical chemistry, potential long-term toxicity, and death. Twenty-four month safety data are available for all 3 studies.

Results: A total of 159 pts were included in this analysis. No pts reported any treatment-related serious AEs during follow-up to 24 months. One patient had mild diarrhea 2 days after receiving an optional second injection of 50 kBq/kg ^{223}Ra at the start of follow-up; it was reported as probably related to the last ^{223}Ra injection. One patient reported lumbar pain after 24 weeks (only treatment-related AEs were reported during follow-up). CTC grade 4 hematologic toxicity was seen in 1 patient each for platelets, neutrophils, WBC, and hemoglobin. Across all studies, 7 pts experienced CTC grade 3 anemia, 5 pts grade 3 thrombocytopenia, and 3 pts grade 3 neutropenia. The BC1−02 study showed no statistically significant difference in hematologic parameters between the ^{223}Ra and placebo groups during follow-up. No patient reported a secondary diagnosis of acute myelogenous leukemia, myelodysplastic syndrome, aplastic anemia, or primary bone cancer. No signs of renal or hepatic toxicity were observed. The frequency and cause of death during follow-up were as anticipated for pts with metastatic CRPC.

Conclusion: Safety data from the 24-month follow-up period support previous findings of the highly favorable safety profile of ^{223}Ra in pts with CRPC and bone metastases. A randomized phase III study, ALSYMPCA, is ongoing worldwide with overall survival as the primary endpoint.

7009 POSTER DISCUSSION

Sensitivity and Specifity to Detect Local Recurrent Prostate Cancer Using Dynamic Contrast Enhanced (DCE) MRI Without Endorectal Coil and MRI Patterns of Post-prostatectomy Recurrence and of Its Response to Salvage Radiotherapy

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Purpose: To determine sensitivity and specifity of dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) without endorectal coil

in detecting local relapse after radical prostatectomy for prostate cancer by analysis of post-prostatectomy fossa appearance in pre- and post salvage radiotherapy DCE-MRI.
Methods and Materials: 33 patients undergoing DCE-MRI without endorectal coil before salvage radiotherapy (RT) without evidence for metastases were selected retrospectively and evaluated using information of post treatment DCE-MRI with an interval $\geqslant$ 12 months and response of Prostate-specific antigen (PSA) after RT, median <0.01 ng/mL (mean 0.02 ng/mL, range, <0.01–0.08 ng/mL). The median PSA at diagnosis of biochemical recurrence before salvage RT was 0.34 ng/mL (mean 0.57 ng/mL, range 0.08- 2.38 ng/mL). Pre-RT DCE-MRI scans were compared with post-RT-DCE-MRI-scans to assess behaviour of any suspicious lesions.
Results: 22/33 patients had 24 enhancing nodules in the post-prostatectomy fossa in pre-RT-DCE-MRI at a median PSA of 0.51 ng/ml (mean 0.74 ng/mL, range 0.11 to 2.38 ng/mL). These pre RT enhancing nodules disappeared in post treatment DCE-MRI while PSA showed biochemical remission after RT. Therefore these nodules were considered as highly specific for macroscopic local prostate cancer recurrence. 11/33 patients had normal post-prostatectomy MRI findings at median PSA of 0.22 ng/mL (mean 0.24 ng/mL, range 0.08 and 0.53 ng/mL) without changes after salvage RT. Calculated sensitivity for the MRI identification of the location of the source of the PSA recurrence within the prostatic bed was 72% per lesion for all cases and reached 100% at PSA-levels >0.53 ng/mL. Specificity was 100%.
Conclusions: Enhancing nodules in the DCE-MRI of the post-prostatectomy fossa can be detected depending on the PSA-level with high sensitivity and specifitiy. Thus DCE-MRI without endorectal coil, which can simultaneously be used for RT planning, may be a valuable tool to detect local recurrence even at low PSA-levels (>0.11 ng/mL), and may be used for dose escalation on macroscopic sites of local recurrence.

7010 POSTER DISCUSSION

The Impact of Rectal Distension Present on Planning Scans on Localized Prostate Cancer Outcomes in the Era of Image-guided Radiotherapy

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Background: Rectal distension (RD) at time of radiation planning has been associated with lower rates of biochemical progression free survival (bPFS). Use of daily image-guided radiotherapy (IGRT) on prostate may overcome prostatic displacement from RD. We review the impact of RD on prostate cancer outcomes in patients treated with daily IGRT.
Methods and Materials: 189 localized prostate cancer patients were treated with daily IGRT on implanted fiducials from 2001–2003. Patients treated with neoadjuvant/adjuvant hormone therapy were excluded. All patients received 79.8 Gy in 42 fractions delivered via 3D conformal radiotherapy (88.9%) or intensity modulated radiotherapy (11.1%). Clinical target volume (CTV) was prostate +/- seminal vesicles. The planning target volume was a 10 mm expansion on the CTV in all directions except for posteriorly where a 7 mm margin was used. Six RD parameters were measured on CT simulation scans: rectal length (RL); rectal volume (RV); average cross sectional area (CSA); superior rectal diameter (SRD); inferior rectal diameter (IRD); and average rectal diameter (ARD). The primary end-point was the impact of the RD on bPFS using the PSA nadir + 2 definition. After adjusting for T-stage (T1 vs T2+) and risk-category (low vs intermediate vs high), associations between bPFS and RD were determined through multivariate analysis using a Cox-proportional hazard model. Secondary end-points were physician scored RTOG acute/late gastrointestinal (GI) and genitourinary (GU) toxicity scores.

Rectal distension parameter	Median distension (range)	Hazard Ratio	95% Confidence Interval
Rectal length	7.9 cm (5.6–12.4)	0.98	0.74–1.31
Rectal volume	49.8 cm^3 (20.9–123.6)	1.00	0.99–1.02
Average cross-sectional area	6.4 cm^2 (3.1–13.4)	1.03	0.89–1.18
Superior rectal diameter	3.0 cm (1.3−6.4)	0.87	0.62–1.21
Inferior rectal diameter	2.6 cm (1.5−4.3)	1.14	0.61–2.10
Average rectal diameter	2.9 cm (2.0−4.3)	0.95	0.47–1.94

Results: Median follow-up was 7.7 years for patients alive at last visit. 84.1% of patients had a T-category of T1a-T2a (T2b/T2c 14.3%; >T2c or Tx 1.6%). Low or intermediate risk disease was 92.6% of patients, while 7.4% had high-risk disease. The 7-year bPFS rate was 78.7%. There were no significant associations between any of the RD parameters and bPFS (see table). Acute GI toxicity grade >2 was 0%. Acute GU toxicity grade >2 was 5.3%. There were 2 events of acute grade 4 urinary obstruction requiring catherization. Late GI toxicity grade >2 was 1.1%. Late GU toxicity >2 was 1.1%. No late GU or GI grade 4 toxicities were reported.
Conclusion: RD does not appear to impact bPFS when patients are treated with daily IGRT on prostate. Severe acute or late toxicity was uncommon and bPFS is consistent with other reports.

7011 POSTER DISCUSSION

Cellular and Humoral Immune System Activation by Sipuleucel-T − Preliminary Data From the OpenACT Phase 2 Trial

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Background: Sipuleucel-T is an autologous cellular immunotherapy designed to stimulate an immune response against prostate cancer. It is made from peripheral blood mononuclear cells (PBMCs) cultured ex vivo with a recombinant fusion antigen, PA2024 comprising prostatic acid phosphatase [PAP] linked to granulocyte-macrophage colony-stimulating factor [GM-CSF]). Sipuleucel-T has demonstrated improved overall survival (OS) in men with asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer (mCRPC). OpenACT is a Dendreon-sponsored Phase 2 trial, designed to further evaluate the safety and immune responses in mCRPC patients (pts). Survival follow-up is ongoing.
Materials and Methods: Sipuleucel-T was administered every 2 weeks (wks) $\times$ 3 and antigen presenting cell (APC) activation (CD54 upregulation) was assessed by flow cytometry. In vivo responses to PA2024 and PAP antigens were assessed at baseline and 2 wks after the 3rd infusion by IFNγ ELISPOT, ^{3}H-thymidine T cell proliferation assays; humoral responses were measured by ELISA. Cytokines were profiled during manufacture of sipuleucel-T and in pt serum before and after treatment (multiplex MSD assay).
Results: 104 pts were enrolled. Following the manufacture of sipuleucel-T, CD54 upregulation was greater at the 2nd and 3rd infusions, suggesting a prime-boost phenomenon. Analysis of the culture supernatants showed an increase in T cell activation-associated cytokines (IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IFNγ, and TNFα) after the 1st infusion. Cytokines associated with APCs (IL-8, IL-12p70, IL-1β, MCP-1, MIP-1β, TARC, and Eotaxin) were elevated. Compared to baseline, humoral responses against PAP and PA2024 after therapy were robust ($P < 0.001$ for both). Post-treatment IFNγ ELISPOT responses to PA2024 and PAP were increased from baseline ($P < 0.001$ and 0.073, respectively) as well as proliferative responses ($P < 0.001$ and 0.003, respectively). Serum cytokines associated with immune activation were increased from baseline (IL-6, TNFα, and IL-10 [$P < 0.05$]). Prior docetaxel exposure (28% of treated pts) did not adversely affect immune responses. Adverse events reported here were comparable to those reported in the pivotal Phase 3 IMPACT trial.
Conclusions: Sipuleucel-T generates a prime-boost immune response in pts with mCRPC by activating the immune system. The humoral response to PAP and newly reported serum cytokine profiles provide support for sipuleucel-T's mechanism of action.

7012 POSTER DISCUSSION

Patients Treated With Sipuleucel-T Who Had Prior Docetaxel Had Positive Immune Responses and Survival Benefit

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Background: Sipuleucel-T, an FDA-approved therapy for men with asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer, has been demonstrated to prolong