4022 POSTER

The relationship between age and cancer related outcomes in clinical unilateral T3a prostate cancer

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Objective: According to the guidelines of European Association of Urology (EAU), radical prostatectomy (RP) can be performed in locally advanced disease, PSA serum levels <20 ng/ml, ⩽cT3a, biopsy Gleason score <8 and a life expectancy of more than 10 years. A life expectancy of more than 10 years seems to be an important factor for the treatment of prostate cancer. The purpose of this study is to investigate the relationship between age and outcome in patients with clinical unilateral T3a prostate cancer.
Patients and Methods: Two hundred patients with clinical unilateral T3a prostate cancer detected by digital rectal examination (DRE) underwent RP and bilateral pelvic lymphadenectomy between 1987 and 2004 at our institution. No patient received ADT or RT before RP, while all patients had negative finding on both contrast enhanced computed tomography of the pelvis and bone scan. The patients were categorized into 3 subgroups according to the age at surgery: group 1: ⩽60, group 2: >60 to ⩽70 and group 3: >70 years old. Cox proportional hazard analysis and Kaplan-Meier method were used to analyze biochemical progression free survival (BPFS), clinical progression free survival (CPFS), cancer specific survival (CSS) and overall survival (OS).
Results: Group 1 consisted of 68 patients, group 2 consisted of 96 and group 3 of 36 patients. Between all subgroups, there were no significant differences in preoperative PSA, status of node, surgical Gleason score and pathological stage. Only surgical margin status was significantly different between groups. In the Cox proportional hazard regression analysis, age was not withheld as a significant predictor in BPFS, and CPFS. In the Kaplan-Meier analysis, we found no significant differences between age groups in all survival outcomes (BPFS, CPFS, CSS and OS) (all $p > 0.05$). The projected 5, 10-year CSS and OS are listed in the table.

Survival rate	Age		
	⩽60	>60−⩽70	>70
5-year CSS	97.7%	98.7%	100%
5-year OS	97.7%	94.5%	94.6%
10-year CSS	93.3%	96.9%	82.1%
10-year OS	93.3%	75.8%	66.0%

Conclusion: Age does not influence cancer related outcomes (BPFS, CPFS, CSS) in patients with clinical locally advanced prostate cancer. Thus, RP is an option in motivated healthy elderly patients. However, surgery-related side-effects like urinary incontinence and erectile dysfunction might differ considerably between age-groups. Patient counseling regarding these side-effects is mandatory.

4023 POSTER

Physical and mental health in patients with prostate cancer prior to curatively intended treatment with radical prostatectomy or high-dose radiotherapy

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Background: As a first step of a prospective study we compared the pre-treatment health in patients with prostate cancer (T1−3 M0). They had been allocated to radical prostatectomy (RP) (NX = 139) or radiotherapy (RAD) (pN0 = 252, N+ = 14) after multidisciplinary clinical evaluation.
Materials and Methods: In 405 consecutive men with a PC diagnosis within the last 12 months, risk group was defined based on clinical T-category, PSA and Gleason score. Physical and mental health was assessed by validated self-report instruments (HADS, Fatigue questionnaire, UCLA-PCI and Eysenck Personality Questionnaire).
Results: Compared to the RP group, patients in the RAD group were significantly older and had longer time from diagnosis to survey. They were significantly more depressed, fatigued and neurotic at a moderate level. Significantly fewer RAD patients were in paid work, more reported comorbidity and more were bothered by sexual problems. The distribution of risk groups was different with more RAD patients having high risk features ($p < 0.001$).

Variables	Surgery	Radiotherapy	P	ES[b]
	Mean (SD)	Mean (SD)		
Pre-treatment age	61.7 (6.2)	65.9 (5.6)	<0.001	0.71
Months from diagnosis to survey[a]	3.9 (2.1)	4.8 (1.7)	<0.001	0.47
EPQ-Neuroticism[a]	1.3 (1.4)	1.7 (1.7)	0.04	0.26
HADS-Anxiety	4.1 (2.7)	4.4 (3.0)	0.40	0.11
HADS-Depression[a]	2.4 (2.2)	3.4 (2.8)	<0.001	0.40
FQ-Total fatigue	12.5 (3.2)	13.5 (3.7)	0.004	0.29
	N (%)	N (%)		
In paid work	83 (61)	74 (28)	<0.001	0.65
Comorbid somatic diseases	35 (25)	105 (40)	0.004	0.32
Bother with:				
urine problems	27 (20)	47 (18)	0.58	0.05
bowel problems	14 (11)	25 (10)	0.76	0.03
sexual problems	21 (16)	105 (40)	0.005	0.55
Risk group:				
low + intermediate	133 (96)	151 (57)	<0.001	0.88
high	6 (4)	115 (43)		

[a]Non-parametric test. [b]Effect size (clinically significant if ⩾0.25).

In a multivariate logistic regression with RP as reference, RAD remained associated with Risk group (OR 7.5), not working (OR 2.4), months to survey (OR 1.2) and pre-treatment age (OR 1.1) (all $p < 0.05$).
Conclusions: The study revealed clinically significant pre-treatment differences between the RP and the RAD group. These encompass risk group distribution, age and pre-treatment health status. Comparing the efficacy and toxicity of RP or RAD, these variables must be accounted for. Due to the differences PC patients allocated to RP are expected to display an improved cancer-related outcome as compared to the RAD group.

4024 POSTER

IMRT for high risk prostate cancer based on sentinel node optimised target volume definition – first clinical results

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Background: Whereas cure rates for patients (pts.) with low/intermediate risk prostate cancer (PC) are good, the situation is much more problematic in high risk PC. In parallel with risk of distant seeding, the probability of locoregional lymph node metastasis increases. The RTOG 94−13 trial provided evidence that pts. with high risk of pelvic node involvement (risk >15%) benefit from an additional radiotherapy to the pelvic nodes combined with concomitant hormonal ablation. Since the physiological lymphatic drainage is highly variable, the optimal target volume definition for the adjuvant nodes is problematic. To overcome this limitation, we optimised our target volume by including information derived from pelvic sentinel nodes (SN) identification.
Materials: Pts. with proven PC (risk of pelvic node involvement >15%) were included. To permit a three-dimensional localisation of SN transmission- and emission data were acquired using a gamma camera with an integrated X-Ray device (Millennium VG & Hawkeye®, GE) 1.5−3 hours after injection of ~250 MBq 99mTc-Nanocoll. IMRT planning was done with Hyperion® based on 3 CT's, definition of clinical/planning target volumes (CTV/PTV) and risk organs (rectum, colon, small bowel, bladder, hips) with image fusion of 3 data sets. The detected SN were included into the pelvic CTV additionally. 5−7 gantry angles were used. Dose prescriptions were 50.4 Gy (1.8 Gy daily) to the pelvis and 70.0 Gy (2 Gy daily) to the prostate/seminal vesicles. All pts. received neoadjuvant, concomitant and adjuvant hormonal ablation treatment (3 years).
Results: Since 08/2003 41 pts. (cT1b-4 cN0M0 stage) were treated. No pt. had undergone a staging lymphadenectomy, 5 pts. had undergone transurethral resection. The median initial PSA level was 20.1 (mean 27.5) ng/ml, the mean Gleason Score was 7. With the exception of one all pts. had detectable SN, the numbers of SN per patient ranged from 0 to 13 (median 6). A total of 234 SN could be identified. 31 of 41 pts. (total 77/234 SN, 32.9%) showed SN localisations (perirectal/sacral, ext. iliac, paraaortic) that probably would not have been covered by conventional CTV definition ('geographic miss'). Acute gastrointestinal (GI) and genitourinary (GU) toxicity (RTOG): GU: grade 0 3/41, grade 1 24/41, grade 2 14/41 pts.; GI: grade 0 1/41, grade 1 30/41, grade 2 10/41 pts., no toxicity grade 3 or 4 was seen. With a median follow up of 10.5 month no late toxicity > grade 1 occurred.
PSA outcome: 3 month after IMRT median 0.1 (mean 0.45) ng/ml, 1 year after IMRT median 0.14 (mean 0.21) ng/ml (ongoing hormonablative therapy).

Conclusion: IMRT based on sentinel lymph node identification is feasible and allows pronounced normal tissue sparing. The probability of a 'geographic miss' is reduced. We are planning a prospective trial with dose escalation to the prostate (74−78 Gy) continuing the presented treatment regime.

4025 POSTER

A phase I/II study of sunitinib in combination with docetaxel (dcx) and prednisone (pdn) in patients with metastatic castrate-resistant prostate cancer (mCRPC)

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Background: Sunitinib malate (SUTENT®) is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET and FLT3. VEGFR and PDGFR overexpression are implicated in prostate cancer progression and bone metastasis, respectively; thus, co-administration with sunitinib may improve the antitumor activity of dcx. The objectives of this ongoing phase I/II study are to determine the optimum combination dose (OCD), safety and PK profile of sunitinib combined with dcx + pdn as first-line treatment for mCRPC.
Methods: All pts received a lead-in of sunitinib 50 mg/d for 4 wks to obtain preliminary data on PSA modulation by sunitinib alone. To date, 3 successive cohorts have received dcx 60 mg/m^2 every 3 wks + pdn 5 mg BID and escalating sunitinib doses (cohort 1: 12.5, 2: 37.5, or 3: 50 mg/d) on a 2 wks on/1 wk off schedule. A final cohort 4 (ongoing) is receiving dcx 75 mg/m^2 + sunitinib 37.5 mg/d + pdn 5 mg. DLTs are evaluated during the first 3-wk combination cycle. PK profiles for sunitinib and its metabolite, SU12662, are obtained on day 1 of the lead-in period and day 1 of cycle 2 (with dcx). PK profiles for dcx are obtained on day 1 of cycle 1 (dcx alone) and day 1 of cycle 2 (with sunitinib). Preliminary efficacy is assessed per the PSA Working Group Criteria and RECIST.
Results: Twenty-three pts have enrolled in the 4 cohorts (n = 6, 7, 6 and 4, respectively). To date, 6 pts discontinued due to disease progression and 6 due to AEs; 1 pt died due to disease progression. Three pts have completed 1 year on study and are eligible to enroll in a sunitinib continuation protocol. The median durations of treatment in cohorts 1 and 2 were 6.3 and 6.6 months, respectively. The most common treatment-related AEs were neutropenia (70%), fatigue (44%), anorexia (30%) and diarrhea (30%). Only 1 DLT was observed, a grade 3 hyponatremia in cohort 3. Confirmed PSA response occurred in 9 (39%) pts and objective response in 3 (13%) pts, each with confirmed partial response. At the time of the data cutoff, 2 additional pts had reached a partial response, although unconfirmed.
Conclusions: Sunitinib in combination with dcx + pdn appears to be safe and well-tolerated. Based on these results, the OCD was chosen as sunitinib 37.5 mg/d in combination with dcx 75 mg/m^2 and pdn 5 mg BID. The study is now proceeding to phase II to further assess the safety and efficacy of this regimen in the first-line treatment of mCRPC.

4026 POSTER

Clinical implementation of a novel method of image guided radiation therapy (IGRT) of prostate cancer by "localization of intrinsic isocenter" and "dynamic margin" – retrospective analysis of 3370 adaptive IGRT deliveries using an in-room CT on rails system

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Purposes/Objective: Prostate movements throughout radiation treatment course can be a combination of (a) systematic set up error – the prostate position reverting to the "intrinsic isocenter" which is different from the initial CT simulation isocenter – and/or (b) random error – daily variance of the prostate positions from its intrinsic isocenter.
We developed a novel method of adaptive targeting to localize the "intrinsic isocenter" and to minimize the random errors by varying the treatment margins using a dynamic margin.
Methods and Materials: A total of 3370 IGRT treatment for prostate cancers from 2000 to 2006 formed the basis of this study. The first group – 284 patients had 5 IGRT fractions each. They form the 'no shift' group. The second group – 114 patients had 10 IGRT fractions. The third group of 54 patients had 15 IGRT fractions.
In this approach, the mean and variation of isocentre shift is reviewed after each 5 IGRT fractions. The isocentre was shifted accordingly if the observed "intrinsic isocenter" deviated from its planned position with more than 2 mm. The set up variation with respect to the new intrinsic isocenter is subsequently estimated in each of the next 5 IGRT fractions. The entire setup error data is formed as the basis of "dynamic margin" and updated intrinsic isocenter for the reminding 28 IMRT fractions. This approach follows the "observe-adjust-evaluate" loop method and was validated for the three patient groups.
Results: For the no shift group, 41%, 27%, 26% and 6% of the 1420 CTs have average shifts in the range $\leqslant$2 mm, 2−5 mm, 5−10 mm and $\geqslant$10 mm, respectively. For the second group, 44%, 38%, 14% and 3.7% of the 570 samples have mean shifts in the same 4 ranges respectively. For the third group, the corresponding percentages are 54%, 32%, 13%, and 0.7% respectively. The daily setup uncertainties for these three groups as shown in table 1 demonstrate a monotonic decreasing nature of the mean shifts. Thus 15 IGRT fractions are more effective to reduce the setup variation than 10 and 5 IGRT sessions. Results and methodologies of the dynamic margin will be presented.

Table 1. Setup shifts for three patient groups

Fraction ID	No shift	One shift	Two shifts
1−5 Samples	1420	570	270
S.D. (mm)	5.92	5.95	5.78
6−10 Samples	–	570	270
S.D. (mm)	–	4.36	4.48
11−15 Samples	–	–	270
S.D. (mm)	–	–	3.38

Discussions and Conclusions: Our IGRT method employed a flexible adaptive targeting technique and can be generalized to treatment of cancers other than prostate cancer.

4027 POSTER

Results of the feasibility stage of STAMPEDE: a Multi-Arm, Multi-Stage phase II/III trial in patients with high risk prostate cancer (MRC PR08, ISRCTN78818544)

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Introduction: Most drug trials in prostate cancer (PCa) concentrate on patients with hormone refractory disease. Drugs which work in end stage disease may work better earlier in the disease. STAMPEDE tests 6 treatment approaches for patients with high-risk localised or metastatic PCa who are commencing long-term hormone therapy (HT).
Material and Methods: The trial uses Multi-Arm Multi-Stage (MAMS) methodology. There is an initial UK-based Pilot Stage of 210 patients (for feasibility and safety) followed by 4 Efficacy Stages to ~3,300 patients internationally. Patients are approached before or www.stampedetrial.org).
Results: Pilot Phase accrual was completed in 17 months and 213 patients had been recruited by 31-Mar-07. The main patient barrier to recruitment has been anxiety about chemotherapy but the accrual rate has been satisfactory. The median age is 64 years; 161, 50 & 2 patients have WHO performance status 0, 1 & 2. Of 192 newly diagnosed patients, 44 have T3/4 N0 M0 histologically confirmed adenocarcinoma with PSA > 40 ng/ml or Gleason score 8−10; 128 have N+ or M+ histologically confirmed adenocarcinoma; 20 have multiple sclerotic bone metastases with PSA > 100 ng/ml but no biopsy. An additional 21 patients have been entered having previously relapsed following local treatment & now have either PSA > 4 ng/ml with PSADT 20 ng/ml (n = 4). Safety data from the Pilot Phase will be reviewed by the trial's Independent Data Monitoring Committee in June 2007.
Conclusions: Recruitment to STAMPEDE is feasible and has been well supported by urologists & oncologists, despite the trial's apparent complexity. Patients report liking the 2 stage PIS which provides sufficient information without overload. Despite widespread PSA testing in UK, there are many newly diagnosed patients who meet the trial entry criteria.