invariant over the same time period. Ser15-p53 foci were not observed in ATM-/- fibroblasts (GM05823) cells, but are present in Nijmegen Breakage Syndrome fibroblasts (GM07166). Current experiments are underway to correlate the number of ser15-p53, rad51 and rad50 foci in a panel of fibroblasts with biochemical DNA rejoining assays (CFGE) and overall cell survival and may possibly provide a predictive assay for mammalian cell radiosensitivity.

Genitourinary cancer

571 ORAL

Bicalutamide ('casodex') 150 mg as adjuvant to radiotherapy in localised or locally advanced prostate cancer

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Objectives: The efficacy and tolerability of bicalutamide ('Casodex') 150 mg (a non-steroidal antiandrogen) as immediate therapy or as adjuvant to therapy of curative intent in localised or locally advanced prostate cancer has been evaluated in the world's largest randomised, double-blind clinical trial programme in prostate cancer.

Patients and Methods: Prostate cancer patients (n=8113) with negative bone scans were enrolled from N. America (n=3292), Scandinavia (n=1218), and Europe, S. Africa, Australia and Mexico (n=3603). Patients were randomised to receive bicalutamide 150 mg/day (n=4052) or placebo (n=4061), plus standard care of radical prostatectomy (55%), radiotherapy (17%) or watchful waiting (28%). Objective disease progression was determined by bone scan, CT scan, ultrasound or MRI. Deaths from any cause in the absence of progression were counted as objective progressions. PSA progression was not a criterion for objective progression. A planned, pooled analysis of all 3 trials was performed on an intent-to-treat basis using a Cox proportional hazards regression model for progression-free survival.

Results: At a median follow-up of 3 years, bicalutamide 150 mg plus standard care significantly reduced the risk of disease progression by 42% compared with standard care alone (HR 0.58; 95% CI 0.51, 0.66; $p<<0.0001$). Of 922 patients with objective progression, 363 progressed on bicalutamide and 559 on standard care alone. Reductions in risk were seen across the entire patient population, regardless of underlying therapy (radical prostatectomy, radiation therapy or watchful waiting) or disease stage. Of the 1,358 patients who received radiotherapy, 178 patients progressed (75 bicalutamide; 103 standard care alone). The most frequently reported side effects of bicalutamide were gynaecomastia and breast pain. Survival data were immature with 6% overall mortality and <2% of patients dying due to prostate cancer.

Conclusions: Radiotherapy with adjuvant bicalutamide 150 mg, in men with localised or locally advanced prostate cancer, reduces the risk of disease progression. These findings are consistent with those reported by Bolla, showing that adjuvant hormonal treatment with goserelin ('Zoladex') and radiotherapy reduced disease progression and significantly improved overall survival compared with radiotherapy alone.

'Casodex' and 'Zoladex' are trade marks of the AstraZeneca group of companies

References

[Bolla M et al. Eur Urol 1999;35:23-25.]

572 ORAL

A randomised trial of two radiotherapy schedules in the adjuvant treatment of stage I seminoma (MRC TE18)

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Background: Adjuvant post-orchidectomy radiotherapy (RT) cures the majority of patients (pts) with stage I seminoma, but as approximately 80% would remain relapse-free on surveillance alone, minimising RT - and hence morbidity and second cancer risk - is a worthwhile aim.

Methods: Pts were randomised within 8 weeks (wks) of orchidectomy to receive 20 Gy in 10 fractions over 2 wks or 30 Gy in 15 fractions over 3 wks. They were asked to complete a symptom diary card daily for 4 wks after starting RT and weekly for a further 8 wks, and quality of life forms (EORTC QLQ-C30+testis cancer module) at 0,3,6,12 and 24 months. The primary endpoint was the relapse-free rate.

Results: Between Jan 1995 and Jan 1998, 625 pts were randomised from 45 centres worldwide. The groups were well balanced with respect to baseline characteristics and 98% of pts in each treatment group received their allocated treatment. Four wks after the start of RT significantly more 30Gy patients reported moderate or severe lethargy (20% vs 5%) and an inability to carry out normal work (46% vs 28%), however by 12 wks, levels in the randomised groups were similar. With a median follow-up time of 37 months, 8 relapses have been reported in the 30 Gy group and 10 in the 20 Gy group (HR=1.27, 90% CI (0.58, 2.8)). The difference in 2 year relapse rates is 0.3%, 90% CI (-1.9%, 2.5%) i.e. the probability that true difference exceeds 2.5% is < 5%. A further 393 patients have been randomised with respect to the same RT doses within a subsequent trial (MRC TE19) of whom 6 (30Gy 5;20Gy 1) have relapsed; analysing all 1018 patients the difference in relapse rates at 2 years is 0.8% in favour of the 20 Gy group, with the upper 90% CI excluding differences of more than 1.3%.

Conclusions: This randomised trial has confirmed that 20 Gy in 10 fractions is unlikely to produce relapse rates more than 2% higher than for standard 30Gy RT and reductions in morbidity enable patients to return to work more rapidly.

573 ORAL

Quality of life (QL) in patients with good prognosis metastatic malignant germ cell tumour (MGCT): comparison of 4 chemotherapy schedules (EORTC 30941/MRC te20)

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Aim: To compare by a 2x2 factorial design QL after 3 or 4 cycles BEP (Bleomycin/Etoposide/Cisplatin) chemotherapy, being applied over 3 or 5 days. Methods: In 30941/TE20 (JCO, 19; 1629, 2001) QL was evaluated by the EORTC QLQ C-30 questionnaire (version 2.0) and a testicular cancer (TC) module prior to chemotherapy and at 3, 6 and 12 months thereafter. A mixed model was applied for statistical analysis of QL patterns during the first year. Statistically significant changes of ~10 effect points were defined as clinically significant.

Results: 666 of 812 patients were evaluable for QL. Global QL is significantly decreased at month 3 in all groups relative to baseline, the impact is less for 3-cycle regimens and is more for 3-day regimens. The best tolerated regimen appears to be 3 cycles/5days. There was a significant worsening at 3 months for physical, role and social functioning and for fatigue, dyspnoea and appetite loss. Nausea/vomiting at 3 months was worst for the 4 cycles/3days regimen and was best for the 3cycles/5days regimen. Tinnitus was much increased at 3 months with the 4 cycles/3days regimen. Sexual problems were more frequent during treatment on the 4 cycle regimens. Recovery of side effects was rapid after discontinuation of chemotherapy except for peripheral neuropathy (PN) and Raynaud phenomena (RP) which were worst at the 6 months assessment. One year after treatment start, QL was generally slightly better than at treatment start without differences between the 4 schedules. Role and emotional function were even better than at diagnosis, whereas PN and RP remained clinically relevant problems, as was tinnitus, if 4 cycles were given during 3 days.

Conclusion: If 4 BEP cycles are needed, chemotherapy should be given during 5 days per cycle to maintain optimal QL during chemotherapy and up to 1 year after treatment. Problems with nausea/vomiting and tinnitus at 3 months can be reduced if BEP chemotherapy is applied as a 3 cycles/5 days regimen.

574 ORAL

Favourable psa outcome in patients with large prostates or moderate risk prostate cancer treated by a combination brachytherapy and neoadjuvant hormonal therapy

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Purpose: Patients with localized prostate cancer electing permanent brachytherapy may have an inferior outcome if they present with a large

prostate or moderate to high risk disease. Neoadjuvant hormonal therapy (NHT), while well studied in patients receiving external beam radiotherapy, has not been adequately assessed in the implant patient.

Methods: 151 men with T1-T2 prostate cancer were treated with 6 months of LHRH agonist plus an anti-androgen (3 months prior to and 3 months after implant) in conjunction with either I-125 (160 Gy) or Pd-103 (124 Gy) seeds. There were 76 (50.3%) with PSA < 10 ng/ml, 58(38.4%) with PSA >10-20 and 17(11.3%) with PSA > 20 ng/ml. Clinical stage was T2a or less in 76 and 100 (66.2%) had a Gleason score < 6. 35/151 (23.2%) were treated with NHT because of prostate size > 50 cc while the rest received NHT because of presenting PSA > 10 ng/ml, stage > T2a or Gleason > 6. Median follow up was 4 years (range 2-9.5 years). PSA failure was calculated with actuarial methods using 3 consecutive rises (ASTRO definition) or a PSA > 1.0 ng/ml.

Results: Of the 151 patients, 17 (11.3%) experienced a PSA failure. The six-year likelihood of being free from PSA failure was 88%. The 6-year PSA freedom from failure rate for patients with a PSA < 10 was 95%, PSA >10 to 20 was 86% and PSA > 20 was 69% (p=0.01). A similar benefit was seen for those with PSA < 15 vs > 15 (91% vs 78%, p=0.04). Gleason score did not influence outcome, with 89% free of failure vs 86% (p=0.5) for 6 or less vs score 7 or greater. There was a trend to improved outcomes for lower stage patients; with stage T2a or less 92% free of failure vs 84% (p=0.07) in higher stage patients.

Conclusion: Low risk prostate cancer patients (PSA < 10 ng/ml) who present with large prostates and require NHT to downsize the gland have an excellent (95%) freedom from PSA outcome following permanent brachytherapy. Intermediate risk patients presenting with a PSA < 15 can also be successfully managed with 6 months of hormones plus seed implantation. This 6-month NHT/brachytherapy regimen, which has been found to preserve potency in 70% of men (Stock et al. J. Urol. 165:436, 2001), should be considered an effective treatment option for these two groups. High risk patients (PSA > 15) might further benefit with the addition of external beam irradiation or longer hormonal therapy treatment.

575 ORAL

Diethylstilbestrol (DES) in hormone resistant prostate cancer (HRPC): PSA response, palliative benefit and survival

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The use of DES as first line treatment of advanced prostate cancer has declined due to thromboembolic side effects. The precise mechanism of its activity in HRPC remains controversial, but suggestion of a direct cytotoxic effect led us to explore its use in HRPC. We report our experience with DES in patients failing androgen suppression. We have treated a total of 243 patients (median age: 72; range: 45-93) with advanced PC after failing androgen suppression (LHRHa or orchidectomy) with DES between August 1992 and August 2000. 189 patients had metastatic and 54 patients locally advanced disease. Median time since initial hormonal treatment was 30 months (2.3-161). Median number of previous hormonal manoeuvres was 2 (1-6), antiandrogens if used were withdrawn >1 month before DES with subsequent biochemical or clinical progression. Median pre-DES PSA was 258 ng/ml. DES (1mg: 127 patients; 3mg: 115 patients) plus low dose aspirin (75 mg) was given following breast bud radiotherapy (8 Gy). Median treatment duration was 3.4 months. Some fall in PSA was seen in 77.5% of men. PSA response of >50% compared to baseline confirmed on 2 measurements at least 3 weeks apart, was seen in 29.1% of patients (1 mg: 26.1%; 3 mg: 32.4%). 17% had a partial response and 38% stable disease according to NPCP criteria. Of patients with bone pain, 33% had a more than 1 point and 14% a more than 2 point decline in EORTC pain score. Median time to biochemical progression was 4.6 months. Median survival was 9.6 months [1 year: 38.9% (3.2-45.6); 2 year: 15.5% (10.2-21.8)]. Survival was significantly better in patients with >50% reduction in PSA (p<0.0001). Thromboembolic complications were seen in 11% of all patients. DES at 1 or 3 mg daily can give useful palliative responses equivalent to chemotherapy after failure of standard hormonal therapy in HRPC. The degree of PSA fall correlates with survival.

576 ORAL

Comparison of real time intra-operative dosimetry to post-implant ct control: a multicenter study of prostate brachytherapy quality outcomes:

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Purpose: Permanent seed implantation has become a popular treatment option for localized prostate cancer. The goal of the implant should be to deliver 140 Gy or greater to 90% of the prostate gland (D90) in all cases. Two implant methods available are the pre-plan technique and the ProSeed method, which utilizes intra-operative dose adjustment to optimize dose calculations. This study evaluated the initial experience of the first 5 European centers to perform the ProSeed method.

Methods: Data from 132 patients with stage T1-T2 prostate cancer who were treated by iodine-125 implantation from July 1,2000 to August 20, 2001 was analyzed. Peripheral needles and seeds were placed according to rules previously developed for this technique. After needle placement, US images were acquired into a modified treatment planning system (VariSeed 6.7) and actual needle and seed positions were registered. Interior needles and seeds were placed according to dose optimization rules as determined by the planning computer. Quality control was taken one month later from CT images. Doses to 95% and 90% of the prostate (D95 and D90), 30% of the urethra (U30) and the volume (cc) of rectum covered by 160 Gy (VR 160) for the real time intra-operative dosimetry (RTP) were compared (t-test) to the CT dosimetry (PID) results.

Results: Median patient age was 66 years (range 51-76), median PSA was 9 ng/ml (range 3.9-35) and median Gleason score was 5 (range 2-7). Mean prostate volume prior to needle placement was 40.7 cc (range 10-72), after needle placement at time of image capture was 42.9 cc (range 22-72, p=0.264) and for CT dosimetry was 52.3 cc (range 33-73, p=0.09). Dosimetry results were as follows for RTP vs PID respectively: the mean D95 were 176 vs 162 (min 150 vs 125, max 203 vs 202, p=0.0007), the mean D90 were 187 vs 184 (min 165 vs 140, max 231 vs 240, p= 0.28), the mean U30 were 199 vs 257 (min 165 vs 190, max 265 vs 318, p= 0.00003), and the mean VR160 were 0.617 vs 1.05 (min 0 vs 0.01, max 3.82 vs 2.91, p=0.78) respectively.

Conclusions: These data represent the initial European experience with the ProSeed implant method. All patients received the minimum required D90 dose (>140 Gy) and safe urethral and rectal doses. The data demonstrates that intra-operative dosimetric adjustment can assure quality control during the procedure.

577 ORAL

Bone alkaline phosphatase & extent of skeletal disease burden in a clinical trial of atrasentan are predictive of clinical disease progression in hormone refractory prostate cancer

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Purpose: Bone alkaline phosphatase (BAP) is a marker of tumor induced bone remodeling in metastatic prostate cancer. We hypothesized that baseline BAP correlates with skeletal burden of disease on bone scan in hormone refractory prostate cancer (HRPCa) and can provide prognostic information about clinical disease progression.

Methods: 288 HRPCa patients were randomized in a double blind study of atrasentan, an oral, selective ETA receptor antagonist. Patients were followed until time of clinical progression (TTP) defined as a disease-related event requiring intervention, disease-related pain requiring opiate therapy, or new lesions on imaging studies. Baseline evaluation included BAP (stratified by EORTC criteria) and the quantitative Bone Scan Index (BSI) (stratified by criteria of Sabbatini et al.).

Results: 219 patients had both baseline BAP and BSI values (median BAP 36.4 IU/L, <ULN; median BSI 1.43%). BAP and BSI values were highly correlated (r=0.80, p<0.001). Patients with low BAP (< 1.25 X ULN) had a small tumor burden, median BSI 0.51%, while patients with high BAP (~5 X ULN) had a large tumor burden, median BSI 10.5%. Both BAP and BSI correlated with TTP (see table). Median TTP was delayed by 9.6 weeks (p=0.021) in patients treated with 10 mg atrasentan. Furthermore,