and Flutamide 250 mg tds) starting 2 months prior to RT; or 6 months MAD starting 5 months prior to RT.
**Results:** Between June, 1996 and February, 2000, 818 men were randomised at 19 Australian and New Zealand centres. 802 were eligible for analysis. In comparison to RT alone 3 months MAD reduced local failure [LF]: HR 0.55 ($p = 0.001$), improved biochemical failure free survival (Houston method) [BFS]: HR 0.71($p = 0.003$), clinical disease free survival [DFS]: HR 0.66 ($p < 0.001$) and freedom from salvage therapy [FST] HR 0.73 ($p = 0.024$). In addition to producing even greater improvements in LF: HR 0.41($p < 0.001$), BFS: HR 0.57($p < 0.001$), DFS: HR 0.55 ($p < 0.001$), FST: HR 0.52 ($p < 0.001$) 6 months MAD also reduced distant failure [DF] HR 0.66 ($p = 0.04$) and produced a significant improvement in cause specific survival: HR 0.58 ($p = 0.048$). In this treatment arm patients with "high risk" cancer also experienced a strong trend towards improved overall survival: HR 0.66 ($p = 0.066$).
**Conclusions:** Six months MAD administered prior to and during RT improves all outcomes in patients with locally advanced P.C.
Further follow-up is necessary now to estimate the size of survival benefits precisely.

**808** ORAL

**PSA doubling time calculated early on following PSA relapse predicts for subsequent death from prostate cancer**

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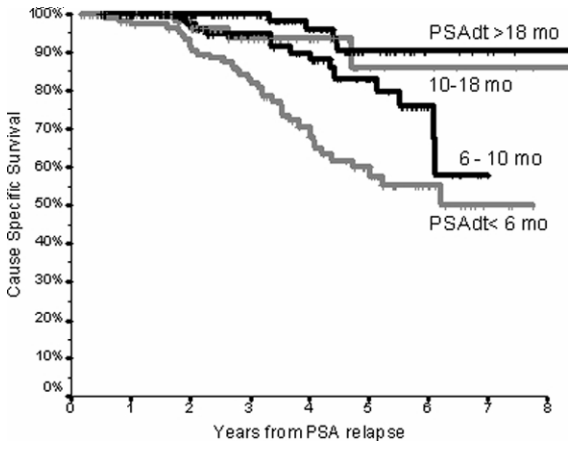
**Background:** PSA doubling time (PSAdt) has been shown by several groups to be a strong predictor of death from prostate cancer (CSS), when PSA relapse has occurred after radiation therapy. However most reports have calculated the PSAdt using all available data from an initial rise up until the time of secondary intervention. In this study we explore whether an early derived PSAdt, using PSA results from the first PSA to breach a level of 1ng/ml to the PSA level that triggers the PSA relapse definition (trigger PSA) could also predict for survival, and thus help to identify early those men who may potentially benefit from intensified intervention.
**Material and methods:** From a prospective database of men treated with external beam radiation therapy established in 1994 of over 1850 men, patients were selected for inclusion if they had a biochemical relapse by the new RTOG-ASTRO ('lowest PSA to date plus 2') definition. For each patient the PSAdt was calculated from the first PSA to exceed 1ng/ml post-radiation and the PSA that triggered the relapse definition (trigger PSA). For patients whose first PSA post-nadir was the trigger PSA, the nadir PSA was used. The PSA relapse slope (ln(2)/PSAdt) was split into quartiles and included in Kaplan Meier and Cox regression for cause specific survival, timed from the trigger PSA time point.
**Results:** 390 men fulfilled the selection criteria. The median time to secondary intervention after trigger PSA was 12 months. The median PSAdt was 9.4 months. The 5 year CSS (timed from trigger PSA) was 77%. In those with PSAdt faster than 6 months the 5 year CSS was 60% ($p < 0.0001$) compared with 83% for 6–10 months ($p = 0.03$), 86% (10–18 months, reference value) and 90% for >18 months ($p$ = ns), see figure. Multivariate analysis showed faster PSAdt, higher T stage, and higher Gleason grade to be independent factors predictive of prostate death. Initial PSA and the use of neoadjuvant or adjuvant androgen ablation were not significant. Earlier intervention in those who have been treated ($n = 256$, 66%) was associated with worse survival ($p = 0.036$).




**Conclusions:** PSAdt calculated on the basis of early serial results between 1ng/ml and the PSA that triggers relapse predicts for CSS. Patients with PSAdt faster than 6 months have very poor survival, whereas those with PSAdt of slower than10 months do relatively well. Men who received early secondary intervention appear to do worse, presumably due to case selection for intervention of the worst prognosis patients. Those with fast PSAdt may benefit from intensification of therapy such as the early use of chemotherapy. Conversely those with slow PSAdt may not require intervention.

**809** ORAL

**Longitudinal observations of QOL changes in men receiving intermittant androgen suppression treatment for prostate cancer; an Australian GUOG study**

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**Objective:** Health related quality of life (HQOL) research is a means of broadening the assessment of treatment effects. This longitudinal study investigated the dynamic change to quality of life (QOL) and testosterone dependant physiology in men commencing an intermittent maximal androgen blockade program (MAB).
**Patients and methods:** Two hundred fifty men were accrued to the multi-centre study of IAB (Eulexin® 250 mg TDS, Lucrin® 22.5 mg depot) ceasing treatment after 9 months if PSA <4 ng/ml, and restarting when PSA >20 ng/ml. QOL was assessed every 3 months for 30 months using the EORTC QLQ-C30 and Prostate 26 module.
**Results:** Data completion for the whole study was >99%. At baseline, our cohort was less symptomatic and had better function than the EORTC reference cohort, which may be related to a shift in clinical practice over time. Testosterone suppression (AS) lead to a significant reduction in global HQOL and deterioration in most function and symptom scales, maximal in the first 3 months. Thirty one percent (79 men) required adjustment of Eulexin dose at 3 months. Apart from a temporary increase in diarrhoea score (a recognised side effect) this adjustment was not a factor for any other symptom or function change. During the off treatment period, median time for Testosterone recovery was 9.3 months. There was a trend of progressive improvement in HQOL that paralleled testosterone recovery and was slower than the rate of deterioration during the treatment phase. Median time to re-treatment (141 men) from end of treatment was 14.5 months. Maximum recovery of HQOL occurred most frequently by months 9–12.
**Conclusion:** Whilst the magnitude of mean change to scale scores was small, there was a consistent and simultaneous deterioration during MAB and improvement during androgen recovery over many separate scales. Older men are more likely to show an impaired testosterone recovery, and this was paralleled by a slower HQOL recovery. Newer methods of analysis to describe results in a way that has meaning to the individual patient are warranted.

**810** ORAL

**Risk and risk factors of renal impairment in hormone refractory prostate cancer (HPRC) patients with bone metastases (BM) treated with Zoledronic Acid (ZA)**

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**Background:** To quantify the risk of renal impairment and identify the associated risk factors in HRPC patients receiving ZA for BM.
**Material and methods:** A comprehensive medical record review was performed, using both electronic databases and paper records, in a large tertiary oncology center. Results of creatinine tests conducted outside of the center were obtained through patients' community physicians. Patients were included in the study if they were $\geqslant$18 years old, actively treated at the center, had HRPC with BM, received at least one ZA infusion in the period from 12/1999 to 4/2005, and had at least one creatinine reading before and after the first ZA infusion. The observation period began on the date of the first ZA infusion and ended on the last center visit date or last creatinine test date, whichever occurred later. The renal impairment outcome was defined as an increase of $\geqslant$0.5 mg/dL and $\geqslant$1.0 mg/dL over baseline creatinine value (defined as the final creatinine serum test prior to beginning ZA treatment) if the baseline value was <1.4 mg/dL and

⩾1.4 mg/dL, respectively; or any doubling of the baseline serum creatinine. Risk factor analysis was conducted using multivariate Poisson regression to adjust for varying patient observation periods.
**Results:** Among the 122 eligible patients, the mean observation period was 422.3 days, with an average ZA treatment period of 367.2 days (mean 10.7 infusions per patient). The mean age at the first ZA infusion was 70.1 years. About 59% of the patients discontinued ZA treatment, 21% of whom due to renal complications. Twenty-nine patients (23.8%, 95% confidence interval: 16.2%-31.3%) had renal impairment during treatment, and the risk of renal impairment increased with an extended duration of ZA therapy (<6 months: 22.5%; ⩾12 months: 23.5%; ⩾24 months: 31.3%). Risk factor analysis found that a significantly greater risk of renal impairment ($p < 0.05$) was associated with: increasing age at ZA initiation (relative risk [RR] = 1.1 per additional year), cigarette smoking (RR = 2.1), a history of prior renal disease (RR = 4.6), hypercalcemia (RR = 4.0), benign prostate hyperplasia (BPH) (RR = 3.0), diabetes mellitus (DM) (RR = 2.9), and treatment with anti-hypertensives (RR = 2.6).
**Conclusions:** In a naturalistic clinical setting, nearly one-quarter of the ZA-treated patients experienced renal impairment; this renal risk is much higher than previously reported in clinical trials. The risk of renal impairment increases with ZA treatment duration. Older age, smoking, antihypertensive therapy, and a history of renal disease, hypercalcemia, BPH or DM are also associated with an increased renal toxicity risk in ZA-treated HRPC patients.

**811** ORAL

**ASCENT: A double-blinded randomized study of DN-101 (high-dose calcitriol) plus docetaxel vs. placebo plus docetaxel in androgen-independent prostate cancer (AIPC)**

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**Background:** High doses of 1.25-dihydroxycholcalciferol enhance the antitumor activity of multiple classes of chemotherapy in preclinical cancer models and showed encouraging Phase 2 results in combination with docetaxel for the treatment of AIPC. DN-101 is a new high-dose oral formulation designed to conveniently and reliably deliver the high 1.25-dihydroxycholcalciferol concentrations required for cancer therapy.
**Methods:** Patients with progressive castrate metastatic prostate cancer, no prior chemotherapy, and adequate organ function received weekly docetaxel 36 mg/m$^2$ iv for 3 weeks of a 4-week cycle with either 45 μg DN-101 or placebo orally 1 day prior to 36 mg/m$^2$ docetaxel.
**Results**: 250 patients were randomized 1:1 at 48 sites in the US and Canada. Baseline characteristics were similar for both arms. Any grade 3/4 adverse event occurred in 58% of DN-101-treated patients and 70% of placebo-treated patients. Most common grade 3/4 toxicities in the DN-101 and placebo-treated arms were neutropenia (10% vs. 8%), fatigue (8% vs. 16%), infection (8% vs. 13%) and hyperglycemia (6% vs. 12%). PSA response within 6 months (the primary endpoint) occurred in 58% of DN-101 patients and 49% of placebo patients ($p = 0.16$). Overall, PSA responses were seen in 63% of DN-101 patient and 52% of placebo patients ($p = 0.07$). The median survival for DN-101 treated patients has not been reached and is estimated at 23.5 months. The observed median survival was 16.4 months in placebo treated patients. With the specified adjustment for baseline characteristics of performance status and hemoglobin, therapy with DN-101 was associated with a statistically significant survival benefit (HR 0.67, $p = 0.035$).
**Conclusions:** The addition of weekly DN-101 did not increase the toxicity of weekly docetaxel with trends suggesting improved safety by several parameters. The trend favoring DN-101 plus docetaxel over placebo plus docetaxel for PSA response did not reach statistical significance, however, in a secondary endpoint of overall survival, DN-101 therapy was associated with a substantial improvement in overall survival that was statistically significant in a prospectively planned multivariate analysis that adjusted for baseline characteristics.

## *Poster presentations* (Wed, 2 Nov)
## Genitourinary cancer

**812** POSTER

**Measuring the accuracy of ultrasound-guided fiducial marker placement in reference to prostatic anatomy using MRI: Implications for high-precision radiotherapy**

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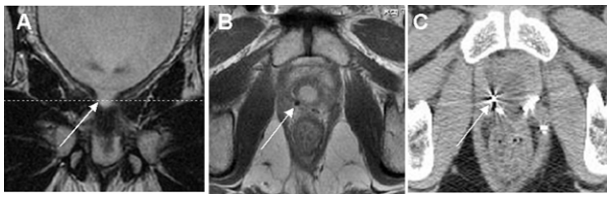
**Background:** Techniques in high precision external beam radiotherapy for prostate cancer are increasingly integrating the use of internal fiducial markers. Literature supports their role 1) as surrogates to prostate gland position during daily online image-guidance, 2) as common landmarks in multi-modality image registration, and 3) as a strategy to mark the location of the prostatic apex and/or urethral anastomosis otherwise invisible on treatment planning CT images. In order to determine the validity of the latter strategy, we sought to measure the spatial accuracy of ultrasound-guided marker placement in reference to anatomical boundaries using MRI.
**Methods:** Twenty patients with prostate cancer underwent trans-rectal ultrasound-guided placement of a gold fiducial marker approximately 1 week prior to CT simulation and investigational MRI examination. Twelve patients with a new diagnosis of prostate cancer had a marker placed immediately above the prostate apex. MRI examination consisted of axial GRE and T2-FSE images (slice thickness 2 mm). The distance between the Z MRI coordinate of the fiducial marker (identified on GRE images) and the visualized prostatic apex (identified on T2-FSE images) was measured and compared to the reported distance measured on ultrasound at the time of placement. Eight patients destined to receive adjuvant or salvage radiotherapy after radical prostatectomy had a marker placed immediately lateral to the urethral anastomosis under ultrasound-guidance. MRI examination consisted of 3 mm axial FRFSE proton density (B) and coronal T2-weighted FSE (A) image acquisitions. The distance between the Z MRI coordinate of the anastomosis (identified on the coronal images as a distinct signal change between urethral sphincter and bladder junction-A) and the fiducial marker (identified on axial FRFSE images-B) was measured.




**Results:** The difference between the reported and measured distance from the fiducial marker to the prostate apex ranged from 0–3 mm, with a mean error of 1.42 mm (SD 1.16 mm). The distance between the fiducial marker and the post-prostatectomy urethral anastomosis ranged from 0–6 mm, with a mean error of 3 mm (SD 2.77 mm). In both instances, the mean error lies within that expected from slice-thickness volume averaging on axial MRI and CT image.
**Conclusion:** Fiducial markers can be accurately placed in reference to prostatic anatomy using trans-rectal ultrasound guidance, and are valid surrogate anatomical markers of the prostate apex and post-prostatectomy urethral anastomosis in CT-based target definition. In those instances where MRI is not available for treatment planning, a margin of 2–3mm accounting for the error introduced by slice-thickness volume averaging may be considered.

**813** POSTER

**Longitudinal evaluation of quality of life and rectal toxicity in patients with conformal radiation therapy for prostate cancer**

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**Background:** To prospectively evaluate quality of life (QoL) and rectal toxicity in patients with conformal radiation therapy (CRT) for localized prostate cancer.