**Results:** Differences between benign prostatic hyperplasia and prostatic carcinomas was observed in high level of expression of PKC isoforms alpha, and delta ($p < 0.001$). PKC isoforms alpha, and delta were elevated in prostate cancer (97%) and in poorly differentiated carcinomas (80%) and reduced to well differentiated prostatic carcinomas and prostate hiperplasia. The frequency of elevated PKC isoforms alpha, and delta expression was higher in tumours with Gleason score >5 ($p < 0.001$).
**Conclusions:** These results indicate that both PKC alpha and PKC 98delta may aid in prominence between benign and malignant prostatic diseases.

**883** POSTER

**Phase I trial of sorafenib (BAY 43–9006) in combination with interferon alpha-2a in patients with unresectable and/or metastatic renal cell carcinoma and malignant melanoma**

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**Background:** Sorafenib (BAY 43–9006) is a novel, oral multi-kinase inhibitor that acts on both the tumour and the vasculature by targeting Raf kinase and the receptor tyrosine kinases VEGFR-2 and PDGFR-β. In Phase II/III trials, sorafenib significantly prolonged progression-free survival versus placebo, and had a favourable safety profile in patients with renal cell carcinoma (RCC). This Phase I, single-centre, open-label study was designed to determine the safety profile and maximum tolerated dose (MTD) of sorafenib in combination with interferon alpha-2a (IFN).
**Patients and methods:** Patients with metastatic RCC or malignant melanoma who were refractory to standard therapy were enrolled. Following a 2-week period of IFN alone, patients received 28-day cycles of continuous oral sorafenib 200 mg (cohort 1) or 400 mg bid (cohorts 2 and 3), with subcutaneous IFN 6 MIU (cohorts 1 and 2) or 9 MIU tiw (cohort 3). Patients continued on treatment until disease progression, unacceptable toxicity or death. Primary endpoints were the safety profile and MTD of combination therapy. Secondary endpoints included RECIST-evaluated best tumour response, changes in tumour vascularization by Doppler US, and various immunological parameters.
**Results:** Twelve patients with RCC and one patient with melanoma received treatment in cohorts 1 ($n = 4$), 2 ($n = 3$) and 3 ($n = 6$). Patients' characteristics were: median age 59 years (range 25–76); ECOG 0:1, 77%:23%; prior systemic anticancer therapy, 92%; prior IFN, 69%; $\geqslant 3$ metastatic sites, 92%. To date, no dose-limiting toxicities have been reported for patients in any cohort. Common grade 1 and 2 drug-related adverse events occurring in 10 evaluable patients during combination treatment were: fatigue (90% of patients); diarrhoea (80%); nausea (50%); dry skin, hand–foot skin reaction, pruritus and anorexia (40% each). One patient in cohort 2 experienced drug-related grade 3 asthenia; however, this decreased to grade 2 in Cycle 2. One patient in cohort 1 withdrew on Day 6 of Cycle 1 due to grade 2 asthenia and anorexia. No deaths have been reported. Of the nine evaluable patients, stable disease was achieved in five RCC and one melanoma patient, with tumour shrinkage in 5/6 clear-cell RCC patients.
**Conclusions:** This combination was safe and well tolerated. The recommended dose for Phase II trials is continuous oral sorafenib 400 mg bid and IFN 9 MIU tiw. Complete data will be updated at the meeting.

**884** POSTER

**The role of amifostine on late normal tissue damage induced by pelvic radiotherapy with concomitant gemcitabine: in vitro study**

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**Background:** In this invitro study; we aimed to assay the role of radioprotective effect of amifostine on late normal tissue damage induced by pelvic radiotherapy with concomitant gemcitabine, by histopatologic and quantitative methods.
**Material and methods:** Fifty-six male Wistar albino rats were randomly divided into seven experimental groups (8 rats per group) (I) gemcitabine (25 mg/kg) alone (GM) (II) radiation+gemcitabine (25 mg/kg) (RT+GM) (III) radiation+gemcitabine (25 mg/kg)+amifostine (200 mg/kg) (RT+GM+AF) (IV) radiation+amifostine (200 mg/kg) (RT+AF) (V) sham radiation (S) (VI) amifostine (200 mg/kg) alone (AF) (VII) radiation alone (GM). Irradiation was given to the pelvic region with a dose of 20 Gy/5 fractions/5 days with Co60 gamma rays. A single dose of AF (200 mg/kg) was given intraperitoneally 30 minutes before the first day of irradiation. A single dose of GM (25 mg/kg) was injected intraperitoneally 24 hr before the first day of the radiotherapy. TGF-beta levels in plasma were assessed before the beginning of the treatment and 1 week after the treatment. All animals were sacrificed at the end of 4$^{th}$ month. Pathological examination was performed and the tissue collagen content was measured for bladder and rectal tissues.
**Results:** 52 animals that were alive at the end of the follow up period were analyzed. 35 animals (68.6%) revealed grade I-III late effect in histopathological examination and 5 of them were severe. We observed grade III colitis in 1, bladder fibrosis in 4 animals. In histopathological evaluation, bladder fibrosis and colitis was seen significantly higher in RT+GM groups than the other groups respectively ($p = 0.0027$, $p = 0.0005$). In groups that AF was used, collagen content of bladder and rectal tissue was lower than the other groups ($p = 0.02$ and $p = 0.04$). Although, the collagen contents of bladder and rectal tissues were lower in RT+GM+AF group than RT+GM group, this difference was not significant. The difference between pre-RT and post-RT levels of TGF-B1 was not significant in all groups.
**Conclusion:** By histopathological and quantitative methods we determined that, addition of amifostine to the pelvic radiotherapy with concomitant gemcitabine can reduce the late bladder and rectal damage. We couldn't show the relationship between plasma TGF-B levels and histopathological radiation injury in pelvic tissues.

## *Publication*
## Genitourinary cancer

**885** PUBLICATION

**Selective organ preservation in muscle-invasive TCC of the bladder: a biological approach**

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**Introduction:** 1400 new cases of T2/T3 TCC bladder are diagnosed in the UK annually. Cystectomy alone is associated with 20–30% local failure rate and raises QoL issues, as reconstruction may not be available/ possible. Neo-adjuvant chemotherapy (neo-CT) has a 5% 5 year absolute survival benefit. (ABC Meta-analysis Collaboration 2003 Lancet;361:1927–34) and pathological response to treatment is associated with outcome (Splinter et al. 1992 J Urol;147:606–8). A pilot study of selective bladder preservation, giving radiation to patients with pathological down-staging after neo-CT is discussed.
**Materials and Methods:** Patients with T2/T3 TCC bladder received 3 cycles of neo-CT (accelerated MVAC) followed by rigid cystoscopy 2 weeks later. Patients down-staged to $\leqslant$pT1 received radical radiotherapy (64 Gy/32 fractions). Cystectomy was reserved for poor pathological responders ($\geqslant$pT2). Response and toxicity were evaluated.
**Results:** 24 patients were treated (2000–2004). pCR were seen in 12/25 patients (48%), and pTa/pT1 in a further 7/25 (28%). 21 (88%) patients underwent bladder preservation. After a median of 18 months follow up (8–34) 6 patients have died (metastatic bladder cancer 2, other causes 4) and 1 has required salvage cystectomy for invasive recurrence. 16 (67%) are alive in remission (3 after treatment for superficial disease). Of surviving patients; 15(83%) are alive with an intact bladder. Toxicity has been low with episode of grade 4 bowel toxicity reported.
**Conclusion:** Selective bladder preservation in patients with favourable pathological response to neo-CT represents a realistic option to cystectomy and merits further evaluation in a multi-centre study.

**886** PUBLICATION

**Impact of post-implant evaluation by different slice intervals using CT-based dosimetry in prostate brachytherapy**

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**Purpose:** To compare the CT-based post-implant dosimetry by 1 mm slice intervals versus 5 mm slice intervals.
**Material and Method:** Twenty-one patients treated with permanent prostate brachytherapy were selected for this study.
The CT volume was based on each slice intervals calculated from the contours of the prostate on day 0. One radiologist randomly repeated the contouring and evaluation three times for each slice interval at weekly intervals. Post-implant dosimetry was performed and the DVH were calculated to report the reconstructed prostate volume (pvol), prostate

V100, prostate D90. The coefficient of variation (CV) of post-implant pvol was calculated from each slice interval. Then intra-observer variation was evaluated by comparing the CV for 1 mm and 5 mm intervals. The radiologist subjectively scored each image based on the quality of the CT images. Each image was assigned a score from 3 to 9 points (3 = poor, 6 = moderate, 9 = good).
**Result:** The mean planning TRUS pvol was 19.34±8.30 cc standard deviation (SD). The mean post-implant pvol by 1 mm slice was 18.75±6.68 cc, by 5 mm was 24.48±7.78 cc. The difference in mean values was 4.82 cc ($p < 0.05$). The mean ratio of post-implant: planning prostate V100 from 1 mm was 0.80±0.19, while that from 5 mm was 0.75±0.13. The difference in mean value was 0.06 ($p < 0.05$). The mean ratio of post-implant: planning prostate D90 from 1 mm was 0.70±0.20, while that from 5 mm was 0.62±0.15. The difference in mean value was 0.06 ($p < 0.05$). The mean coefficient of variation (CV) of post-implant pvol from 1 mm was 15.25±7.62%, while that from 5 mm was 8.81±4.23%. The difference in mean values was 7.79% ($p < 0.05$). The mean score of 1 mm was 5.11 and that of 5 mm was 7.22. The difference in mean values was 1.9 ($p < 0.01$).
**Conclusion:** The difference between post-implant pvol from 1 mm and 5 mm slice intervals significantly impacted the post-implant dosimetry. Because the prostate volume outlined by using 1-mm was smaller than that by using 5 mm, the prostate volume was underestimated; and therefore, the prostate V100 and D90 were overestimated.
The quality of CT images from 1 mm was significantly worse than that from 5 mm. The intra-observer variation (the coefficient of variation) of post-implant prostate volume from 1 mm was significantly greater than that from 5 mm. Using 5 mm slice intervals to outline the prostate is significantly more accurate and reproducible than using 1 mm slice intervals.

**887** PUBLICATION

**Postchemotherapy pelvic chemoradiotherapy for metastatic transitional cell carcinoma of the bladder**

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**Background:** Intrapelvic sites of disease in patients with metastatic transitional cell carcinoma (TCC) of the bladder can be a source of significant morbidity. Consolidative radiotherapy (RT) has improved local control in other tumors with high local recurrence rates but has not been well studied in urothelial cancer. In this retrospective analysis, we report the efficacy, toxicity and pattern of failure of this approach.
**Materials and Methods:** Patients treated for stage IV TCC at the London Health Sciences Centre between January 1, 1996 and December 31, 2003, who had either had an unresected primary bladder tumor or pelvic recurrence or metastases, and who received consolidative pelvic chemoradiotherapy following at least a partial response to systemic chemotherapy were identified and their charts reviewed. Patients were excluded if RT was strictly of palliative intent following pelvic recurrence or progression. Primary outcomes of interest were the pelvic failure rate and time to pelvic failure. Secondary outcomes were time to disease progression, overall survival, pattern of first failure, pelvic morbidity and chemoradiotherapy toxicity.
**Results:** Twelve patients were identified and median followup was 15.6 months. Three patients relapsed in the pelvis, yielding a pelvic failure rate of 25%. The median time to pelvic failure was 12.8 months. Overall, nine patients developed progressive disease and died, with a median time to disease progression of 9.8 months. At last followup, three patients were alive and free of recurrent or progressive disease, with a median disease-free survival of 52.8 months. The median overall survival of all patients was 15.6 months. The major severe acute toxicity of chemoradiotherapy was myelosuppression; however, symptomatic cytopenias were infrequent. The most common acute non-hematologic toxicities were diarrhea and nausea. Five patients experienced chronic radiation toxicity. There were no life-threatening toxicities.
**Conclusions:** Consolidative chemoradiotherapy following systemic chemotherapy appears to be feasible and safe in selected patients, and may improve local disease control and reduce pelvic complications. Postchemotherapy chemoradiotherapy intended to reduce pelvic morbidity deserves further study in patients with metastatic TCC and pelvic involvement.

**888** PUBLICATION

**Commonly used serum tumor markers in patients with invasive urothelial cancer**

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**Background:** No valid serum marker is currently used in patients (pts.) suffering from urothelial cancer. Moreover, only a few studies exist reporting data for the behavior of commonly used tumor markers in these pts. The circulating serum tumor markers CEA, Ca 125, Ca 19–9, β-HCG, and AFP have been measured in pts with invasive urothelial cancer.
**Material and methods:** 142 pts. with transitional-cell urinary bladder cancer entered this study. 56 pts had disease confined to the bladder ($T_{1-4a}N_0M_0$, clinical stages I, II, III), and 86 had metastatic disease (clinical stage IV). Thirty-three healthy volunteers constituted the control arm. Serum levels of CEA, Ca 125, Ca 19–9, β-HCG, and AFP were estimated prior to the therapeutic approach for all pts and during chemotherapy for the pts with metastatic disease.
**Results:** There was no correlation of all estimated tumor marker levels with tumor differentiation. Pts with high CA 19–9 and β-HCG levels showed unfavourable overall survival. A clear statistic difference has been found in all (except CEA) circulating tumor markers between the two groups of pts with local and metastatic disease (ANOVA t-test, CA 125, $p = 0.012$; CA 19–9, $p < 0.0001$; βHCG, $p = 0.011$; AFP, $p = 0.001$). Moreover, in the subgroup of patients with metastatic disease receiving chemotherapy, only β-HCG levels correlated with the response to treatment.
**Conclusion:** Among the commonly used serum tumor markers CEA, Ca 125, Ca 19–9, β-HCG, and AFP, only β-HCG seems to be a helpful marker indicating the neoplastic burden and chemotherapy response in pts with invasive bladder cancer.

**889** PUBLICATION

**Clinical results of high-dose-rate Iridium-192 brachytherapy combined with external beam radiotherapy for localized prostate cancer**

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**Background:** In recent years, high-dose-rate (HDR) brachytherapy combined with external beam radiotherapy (EBRT) has come to perform for localized prostate cancer in Japan. The aim of this study is to report the clinical control rate of patients with HDR brachytherapy combined with EBRT for localized prostate cancer.
**Material and methods:** We enrolled 33 patients treated with HDR brachytherapy combined with EBRT between July 1999 and June 2002. Patient age ranged from 55 to 81 years (mean 73). Of the 33 patients, 9, 11, and 13 belong to low risk (stage <T2c, prostate-specific antigen (PSA) <10 ng/mL, and Gleason score <7), intermediate risk (stage <T3a, 10 ng/mL <PSA <20 ng/mL, and Gleason score <8), and high risk group (stage = T3, PSA >20 ng/mL, or Gleason score >7), respectively. Nine patients had received neoadjuvant hormonal therapy, which was stopped at the beginning of RT in all cases. Patients in this series were treated on two protocols. In the initial protocol, patients in high risk group were treated with HDR brachytherapy to 18 Gy in 3 fractions and whole pelvis EBRT to 45 Gy in 25 fractions, and patients in other groups were treated with HDR brachytherapy to 18 Gy in 3 fractions and prostatic EBRT to 40 Gy in 20 fractions. In the second protocol, patients were treated with HDR brachytherapy to 18 Gy in 3 fractions and prostatic EBRT to 40 Gy with an added staging lymphadenectomy to rule out lymph node metastasis for patients in high risk group. We used the American Society for Therapeutic Radiology and Oncology consensus definition for biochemical failure, and the Radiation Therapy Oncology Group (RTOG) guidelines for acute and chronic toxicities. Follow-up ranged from 36–71 months (median, 57 months).
**Results:** No patients in low and intermediate groups had biochemical failure. In high risk group, 2 patients had died of heart failure and malignant lymphoma, respectively, with no biochemical failure, one patient had died of distant metastasis, and 2 patient had bone metastases with no symptoms of local recurrence. Two patients experienced RTOG Grades 3 and 4 late radiation toxicities for the gastrointestinal system, respectively. Grade 3 urethral stricture was observed in 2 patients. Acute toxicity has been modest. Conclusions: HDR brachytherapy combined with EBRT is a very effective treatment for intermediate and high as well as low risk patients. However, in order to achieve more reliable results, additional long-term follow-up is required.