BJUI

BAUS Annual Meeting, 23–26 June 2014

Best Academic Paper Session

Monday 23rd June
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09:00–10:00 Room 3A
BEST ACADEMIC PAPER SESSION
Chair: Professor Rob Pickard
Papers 1–6

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1

Goliath – RCT evidence that Greenlight 180-W XPS provides benign prostatic hypertrophy (BPH) patients with better return to stable health status within 24 hours, and shorter length of stay, than TURP. United Kingdom results

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Introduction: TURP is regarded as the gold standard in the surgical treatment of BPH. In 2010, NICE reported that there was insufficient data to draw conclusions concerning the clinical effectiveness of Greenlight photoselective vaporisation of the prostate (PVP). We now have results from the largest multinational RCT, the GOLIATH study, comparing PVP (using the180-W XPS) to TURP.
Patients and Methods: 269 patients (88 from UK) were treated by PV or TURP. The ability to perform the procedures as a daycase for PVP and TURP were compared with respect to length of stay and time until return to stable health status, which measures the time to when a patient is fit for discharge, irrespective of actual length of stay. We present the UK results.
Results: 70.8% (34/48, 95% C.I. 55.9–83%) UK PVP patients had return to stable health status within 24 h, compared to 20% (8/40 95% C.I. 9.1–35.6%) TURP patients ($P < 0.001$). The mean length of stay was 28.8 (±21.5 (standard deviation)) hours for the PVP patients compared to 52.0 (±21.3) hours for TURP patients ($P < 0.001$), for interquartile range and 95% CI see below:

Table 1 (1).

Length of stay	PVP	TURP
Interquartile range	24.0 to 32.2	39.3 to 56.8
95% CI	22.6 to 35.1	45.2 to 58.8

Conclusion: These results clearly show a significant difference in return to stable health status and reduced hospital stay in favour of PVP patients. This will positively impact as a benefit for health providers, in reduced hospital length of stay bed costs.

2

Long term follow up of a prospective randomised trial of Hexylaminolevulinate (HEXVIX®) photodynamic diagnosis (PDD) assisted versus conventional white-light transurethral resection (TURBT) in newly presenting non-muscle invasive bladder cancer (NMIBC)

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Introduction: Despite Hexvix PDD improving bladder tumour detection, a randomized trial in newly presenting bladder tumours did not demonstrate reduced recurrence in the first year post-resection. We now report longer-term follow-up with 3-year recurrence and progression rates from the trial.
Methods: 249 patients with newly presenting suspected NMIBC were enrolled between March 2005 and April 2010, and randomized to receive either Hexvix-PDD assisted or white-light (W/L) TURBT, with single shot Mitomycin-C in both arms. Operations were performed by 3 specialized bladder cancer teams. All data was prospectively collected.
Results: 129 patients received Hexvix-PDD assisted TURBT and 120 patients received W/L TURBT. 185 of 249 patients had NMIBC (Hexvix – 97, W/L – 88). Final histological distribution was similar in both groups. Of those who completed 3-month follow up, 17/86 (20%) in the Hexvix group and 14/82 (17%) in the W/L group recurred ($P = 0.70$). Of those recurrence-free at 3 months who completed 1-year follow up, 10/63 (16%) in the Hexvix group and 15/67 (22%) in the W/L group recurred ($P = 0.38$). Of those recurrence-free at 1 year who completed 3-year follow up, 5/47 (10.6%) in the Hexvix group and 7/46 (15.2%) in the W/L group recurred ($P = 0.51$). 3/97 (3.1%) in the Hexvix group and 4/88 (4.5%) in the W/L group progressed to muscle invasive disease at 3 years ($P = 0.61$).
Conclusions: Despite improving the accuracy of bladder cancer diagnosis, Hexvix PDD has not been shown in this

trial to reduce the recurrence or progression rate of NMIBC at 3 years' follow-up.

3

Epigenetic Drivers of Penile Squamous Cell Carcinoma Development

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Penile cancer is a rare disease in the developed world, with only 500 new cases diagnosed in the UK per year, however, presents a significant burden in developing countries. Other than a potential HPV driven process, little is known about the molecular epi-genetic alterations defining the development of Penile Cancer (PeCa). We have carried out a genome wide analysis of DNA methylation in penile cancer to accurately catalogue the epigenetic alterations associated with the development and progression of this disease.
Genome wide methylation profiling of 30 primary PeCas and matched normal, identified 6933 epigenetic (4935 Hypermethylated, 1998 Hypomethylated) potentially involved in PeCa development and progression, including in key tumour suppressor genes such as CDO1 & WT1. Methylation analysis identified a CpG Island Methylator Phenotype (CIMP), which had a significant ($P < 0.0001$) association with lymph node metastasis, furthermore we defined an epigenetic classifier that could accurately predict the presence lymph metastasis with a AUC of 89% in a training cohort and 86% in an independent validation cohort. Finally, as with other cancers, infection with oncogenic HPV represents a significant cause of PeCa. We defined a 25 gene epigenetic signature, which could accurately discriminate HPV infected tumors in penile, head and neck and cervical cancers with an AUC of 96%.
In summary these data represent the most comprehensive assessment of alterations driving the development of penile cancer. We have defined alterations which may have utility in the clinical management of penile cancer patients and potentially other HPV driven tumours.

4

Hes6 drives a critical androgen receptor (AR) transcriptional program to induce castration resistant prostate cancer (CRPC) through activation of an E2F1-mediated cell cycle network

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Background: CRPC is poorly characterized and heterogeneous and while the AR is of singular importance, other factors such as c-Myc and the E2F family also play a role in later stage disease. Hes6 is a transcription co-factor associated with stem cell characteristics in neural tissue, but its role in cancer remains uncertain.
Methods: We created a Hes6 and luciferase expressing cell line model for xenografting in NSG mice and bioluminescent monitoring. Expression microarray and ChIP sequencing permitted investigation of the molecular landscape underpinning the cellular effects of Hes6. We generated a 61 patient CRPC TMA and meta-analysed 285 prostate cancers from public sets to profile the Hes6 regulome in aggressive human disease.
Results: We found that Hes6 is up-regulated in aggressive human prostate cancer and is regulated by c-Myc and AR. Hes6 drives CRPC growth by enhancing AR transcriptional activity in the absence of ligand binding. The AR is preferentially directed to a regulatory network enriched for other transcription factors including E2F1. We found a physical interaction between E2F1 and both Hes6 and AR, with increased occupancy of AR at E2F1 target sites in the presence of Hes6. In the clinical setting, we uncovered a Hes6-associated signature that predicts poor outcome in prostate cancer, which can be pharmacologically targeted by inhibition of PLK1, part of the Hes6 regulome, with restoration of sensitivity to castration.
Conclusion: We have therefore shown for the first time the critical role of Hes6 in the development of CRPC and identified its potential in patient-specific therapeutic strategies.

5

INPP4B Knockdown Confers Cisplatin Sensitivity in Bladder Cancer

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Introduction: Neoadjuvant cisplatin-based chemotherapy is recommended for all patients with muscle invasive bladder cancer, although up to 70% of cancers may be cisplatin resistant. Inositol Polyphosphate 4-phosphatase type II (INPP4B), which modulates Phosphatidylinositide 3-kinase (PI3K) signalling is implicated in chemoresistance. We hypothesise that up regulation of INPP4B is associated with cisplatin resistance in bladder cancer.
Materials and Methods: INPP4B methylation profiling was performed in 48 muscle invasive bladder cancer patients who received neo-adjuvant chemotherapy and two paired cisplatin resistant and sensitive cell lines (RT112, EJ). Protein quantification for INPP4B was performed using Western blot assay. Polethylenimine (PEI) transfection with lentiviral shRNA was used to create stable INPP4B knockdowns in RT112 and RT112CP. INPP4B knock down was confirmed by Quantitative RT-PCR. Tetrazolium (MTT) assay was used to quantify cell death due to cisplatin treatment.
Results: INPP4B was found to be differentially methylated in cisplatin resistant cell lines. Western blot analysis confirmed over expression of INPP4B in cisplatin resistant cell lines compared to their sensitive parental line. Quantitative RT-PCR showed that INPP4B expression was reduced by 36% in knockdown cell lines compared to controls. Reduced INPP4B expression in cisplatin resistant cells resulted in a significant increase in cell death upon treatment of 150 μM ($P = 0.010$) and 200 μM ($P = 0.038$) of cisplatin, but did not appear to affect the paired sensitive cell lines.
Conclusions: INPP4B is implicated in cisplatin resistance in bladder cancer and may be able to predict which patients will response to cisplatin-based chemotherapy.

6

Factors predicting local recurrence of penile carcinoma (PC) – An analysis of risk factors, patterns of recurrence and outcome

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Introduction: There is limited guidance on management and outcome from recurrent PC. The aim of this study was to determine risk factors and recommend management strategies for recurrent disease.
Materials and Methods: A retrospective study of 416 penile cancer patients treated between 1999–2013, 45 patients (10.8%) developed recurrence. Predictors including age, presentation, tumour stage, grade, subtype, lymphovascular invasion, positive lymph nodes, extranodal spread, management and relationship with outcome were assessed using multiple regression analysis. Kaplan-Meier (KM) curves were constructed. Chi-squared and Fisher's exact tests were used to determine differences between local and regional/distant recurrence groups. P values <0.05 were taken as statistically significant.
Result: Mean age was 64.2 years. Mean time to recurrence was 759 days (range 52–3958). Twenty-four (53.3%) recurrences occurred in the first 2 years. Twenty-six (57.8%) were local recurrences, 11 (42.3%) being node positive. Significant predictors of overall survival were histology ($P = 0.037$) non-basoloid having the better survival, grade ($P = 0.037$) higher grade correlating with poorer survival, time to recurrence ($P = 0.01$) longer time to recurrence giving better survival. KM curves demonstrated a significant difference between survival in the local and regional/distant recurrence groups. Local recurrence did not have a negative impact on survival, with 2 (7.7%) deaths from PC. Five year survival was 83.3% in the local group versus 23.1% in the regional/distant group.
Conclusion: There remains a significant risk of recurrent PC, even after 2 years from primary treatment. In particular men with adverse histopathogical factors should remain under long term surveillance. Men with early regional/distant recurrence have a poorer prognosis.