The Role of UroMark, a novel urinary assay to detect bladder cancer in the haematuria and surveillance setting.

Work to date

I have performed a systematic review of urinary biomarkers in bladder cancer (BCa) and the manuscript is in preparation. I have also published a review of the management of non-muscle invasive bladder cancer (NMIBC) comparing guidelines from the United States, Europe and Asia in *Cancer Treatment Reviews*.

I have performed a systematic review of urinary biomarkers between June 2016- Jan 2013 which revealed 94 studies (PROSPERO database: CRD42016049918). Data collection is still ongoing and the manuscript is in preparation.

I submitted IRAS for DETECT I (clinicaltrials.gov NCT02676180) which received HRA approval on the 9th March 2016 (IRAS project ID: 179245, REC reference: 16/NW/0150). Between March 2016 till April 2017, I opened 45 sites which recruited 3,600 patients and urine samples collected for 72% of patients (n=2,592). Patient recruitment for this study is now close and clinical data is being cleaned up. At interim analysis of clinical data for 1,869 DETECT I patients reports the incidence of BCa to be 5.2% (visible haematuria= 7.5, non-visible haematuria=1.4%) where older patients ($p<0.001$), males ($p=0.006$) and smokers ($p=0.038$) were associated with BCa but not occupational risk factor ($p=0.745$). Majority of BCa patients were between 60-80 years old. DNA from urine specimens have been extracted and is currently being sequenced. It is expected that this will be completed in December 2016 where data analysis can be performed after.

I submitted IRAS for DETECT II (clinicaltrials.gov NCT02781428) which received HRA approval on 30th August 2016 (IRAS project ID: 203022, REC reference: 16/LO/1044). Between September 2016- August 2017, I opened 44 sites which recruited 490 patients. It is anticipated that the target of 600 urine samples from histological confirmed BCa patients will be reached by December 2017. By June 2017, it is estimated that at least 200 NMIBC patients would have 1 year follow-up. DNA from urine samples will be sequenced thereafter and correlated with clinical findings. I have submitted the trial protocol of DETECT I & II for publication (2nd review *BMC Cancer*).

I have been collecting urine samples from other NCRI bladder cancer trials. In addition to the urine samples from patients with tumour from DETECT II collected so far, urine samples from an additional 48 G1pTa patients (CALIBER) as well as 47 urine samples from PHOTO have been collected. Sequential surveillance urine samples from HIVEC-II collected so far includes 171 baseline urine samples with at least 85 and 68 urine samples with 9 and 12-months follow-up respectively. 30 sequential 3 monthly urine samples for 12 months have been collected from the HYMN study. All the urine samples from these bladder cancer trials will be used to validate the results of the DETECT II surveillance cohort.

I have developed a patient questionnaire and outline of the semi-structured qualitative interview assessing patients' perspectives on cystoscopy and use of urinary test for the detection of BCa with the guidance of Dr Maggie Heinrich (UCL Health Behaviour Research Centre). Both the questionnaire and qualitative assessment is embedded in DETECT II and will commence in September 2017.

Future work

Over the next year, I intend to complete the following:

1) Complete and publish the systematic review on urinary biomarkers.
2) Clean up and analyse the clinical data for DETECT I to report on the incidence of genitourinary cancers in patients presenting with haematuria as well as the diagnostic accuracy of imaging on identifying bladder cancer. This manuscript will be submitted in the next 2 months. Subsequently, I am awaiting sequencing data from Dr Andrew Feber before determining the sensitivity, specificity, negative predictive value and positive predictive value of the UroMark.
3) Complete patient recruitment for DETECT II and sequence urine samples followed by correlation to clinical findings. These results will be validated with urine samples from other NMIBC trials.
4) Commence and complete the patient questionnaire and qualitative assessment of patients' perspectives on cystoscopy and use of urinary test for the detection of BCa. I will interview 20 patients with a first diagnosis of NMIBC to qualitatively assess their perspectives on haematuria investigations. 150 patients will complete the questionnaire.

I am grateful to the Urology Foundation for supporting my work to date.

Published manuscripts over the last year

- Khetrapal P, **Tan WS**, Lamb B, Tan M, Baker H, Thompson J, Sridhar A, Kelly JD, Briggs T The Role of Robotics in the Invasive Management of Bladder Cancer. *Curr Urol Rep.* 2017 Aug;18(8):57. PMID: 28634646
- Hussein AA, May PR, Ahmed YE, Saar M, Wijburg CJ, Richstone L, Wagner A, Wilson T, Yuh B, Redorta JP, Dasgupta P, Kawa O, Khan MS, Menon M, Peabody JO, Hosseini A, Gaboardi F, Pini G, Schanne F, Mottrie A, Rha KH, Hemal A, Stockle M, Kelly J, **Tan WS**, Maatman TJ, Poulakis V, Kaouk J, Canda AE, Balbay MD, Wiklund P, Guru KA. Development of a patient and institutional-based model for estimation of operative times for robot-assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. *BJU Int.* 2017 Jun 16. doi: 10.1111/bju.13934. PMID: 28620985.
- **Tan WS**, Lamb BW, Sridhar A, Briggs TP, Kelly JD. A comprehensive guide to perioperative management and operative technique for robotic cystectomy with intracorporeal urinary diversion. *Urologia*. 2017 Feb 28:0. doi: 10.5301/uj.5000224. PMID: 28256704.
- Feber A, Dhami P, Dong L, de Winter P, **Tan WS**, Martinez-Fernande M, Paul D, Hynes-Allen A, Rezaee S, Gurung P, Rodney S, Mehmood A, Villacampa F, de la Rosa F, Jameson C, Cheng KK, Zeegers MP, Bryan RT, James ND, Paramio JM, Freeman A, Beck S, Kelly JD. UroMark - A urinary biomarker assay for the detection of bladder cancer. *Clin Epig*. 2017 Jan 31;9:8. PMID: 28163793.
- Hussein AA, Saar M, May PR, Wijburg CJ, Richstone L, Wagner A, Wilson T, Yuh B, Redorta JP, Dasgupta P, Shamim Khan M, Menon M, Peabody JO, Hosseini A, Gaboardi F, Mottrie A, Rha KH, Hemal A, Stockle M, Kelly J, Maatman TJ, Canda AE, Balbay MD, Poulakis V, Woods M, **Tan WS**, Kawa O, Pini G, Badani K, Ahmed YE, Wiklund P, Guru KA. Early Oncologic Failure after Robot-Assisted Radical Cystectomy: Results from the International Robotic Cystectomy Consortium. *J Urol*. 2016 Dec 18. pii: S0022-5347(16)31985-1. doi: 10.1016/j.juro.2016.12.048. PMID:27993668.
- **Tan WS**, Lamb BW, Khetrapal P, Tan MY, Tan MEL, Sridhar A, Cervi E, Rodney S, Busuttil G, Nathan S, Hines J, Shaw G, Mohammed A, Baker H, Briggs TP, Klein A, Richards T, Kelly JD. Blood Transfusion Requirement and not Preoperative Anaemia is associated with Perioperative Complications following Intracorporeal Robotic Assisted Radical Cystectomy. *J Endourol*. 2017 Feb;31(2):141-148. PMID: 27901350.
- **Tan WS**, Khetrapal P, Tan WP, Rodney S, Chau M, Kelly JD. A Systematic Review and Meta-analysis of Randomised Controlled Trials of Robotic Assisted Radical Cystectomy versus Open Radical Cystectomy. PLoS One. 2016 Nov 7;11(11):e0166221. PMID: 27820855.
- Khetrapal P, **Tan WS**, Lamb B, Nathan S, Briggs T, Shankar A, Ramachandran N, Freeman A, Mitra A, Kelly JD. Port-site metastases following robotic radical cystectomy: A systematic review and management options. *Clin Genitourin Cancer*. 2016 Jun 29. pii: S1558-7673(16)30163-X. doi: 10.1016/j.clgc.2016.06.012. PMID: 28209455.
- Feber A, Worth D, Chakravarthy A, de Winter P, Shah K, Arya M, Saqib M, Nigam R, Malone P, **Tan WS**, Rodney S, Freeman A, Jameson C, Wilson G, Powles T, Beck B, Fenton T, Sharp T, Muneer A, Beck S, Kelly JD. CSN1 somatic mutations in penile squamous cell carcinoma. *Cancer Res*. 2016 Aug 15;76(16):4720-7. PMID: 27325650.
- **Tan WS**, Lamb BW, Tan MY, Ahmad I, Sridhar A, Nathan S, Shaw G, Hines J, Briggs T, Kelly JD. Complications following Robotic Assisted Radical Cystectomy with Intracorporeal Urinary Diversion: An in Depth Critical Analysis of Technical and Systemic Complications. *Eur Urol Focus*. DOI: 10.1016/j.euf.2016.06.002.
- **Tan WS**, Rodney S, Lamb BW, Feneley M, Kelly JD. Management of Non-muscle Invasive Bladder Cancer: A Comprehensive Analysis of Guidelines from the United States, Europe and Asia. *Cancer Treat Rev*. 2016 May 10;47:22-31. PMID: 27231966.