The combination of urine Pap cytology with immunocytochemical detection of minichromosome maintenance protein 2 (MCM-2) in patients with visible haematuria identifies most bladder cancers

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Introduction & Objectives: The gold standard for diagnosis and follow up of bladder cancer remains flexible cystoscopy with its associated morbidity and cost. As such, there is continued interest in the development of additional, complementary biomarkers. We have previously demonstrated that identification of MCM-2 positive urothelial cells in the urine may be useful in the diagnosis of bladder cancer. MCMs are normally restricted to the basal proliferative compartments of epithelia; ectopic expression is a characteristic feature of malignancy and pre-malignancy. In this study, we set out to establish if combining urinary MCM-2 and urine cytology leads to greater detection rate in diagnosis of new bladder cancer and in patients undergoing cystoscopic follow-up.

Material & Methods: Patients attending urology clinics with visible or gross haematuria (VH) and those undergoing cystoscopic surveillance (CS) were recruited from 5 centres in the UK. In total 50 and 107 patients were recruited from the VH and CS clinics, respectively. Urothelial cells were collected from voided urine using the SurePath liquid based platform and two slides were prepared, one of which was stained by Papanicolaou and the other by MCM-2 antibody.

Results: In the VH cohort using a threshold of 50 MCM-2 positive cells (based on ROC curves analysis) in a cytology slide preparation as the positive cut-off for the presence of cancer gave a sensitivity 94.4% (95% CI, 74.2, 99.0), specificity of 87.5% (95% CI, 71.9, 95.0%) and a negative predictive value (NPV) of 96.5%. Combining MCM-2 and urine cytopathology yielded sensitivity of 100%, specificity of 84.4% (95% CI, 68.3, 93.1) and a NPV of 100%.

Within the CS group 200 MCM-2 positive cells (based on ROC curves analysis) on a slide as a cut off for cancer gave a sensitivity 86.1% (95% CI, 71.3, 93.9), specificity of 88.7% (95% CI, 79.3, 94.2) and NPV of 96.3%. Combining MCM-2 and urine cytopathology revealed a sensitivity of 86.1% (95% CI, 71.3, 93.9), specificity of 84.5% (95% CI, 74.4, 91.1) and a NPV of 92.3%.

Combining urine cytology with MCM-2 allowed identification of 78.6% and 100% of G2 and G3 tumours, respectively, in the CS group and all grades of cancers in the VH group.

Conclusions: Identification of MCM-2 positive cells in urine is a non-invasive, reproducible test with high degree of accuracy. Its combination with urine cytology can reliably identify most patients with bladder cancer who present with visible haematuria. MCM-2 is also able to identify most patients with recurrence of bladder cancer in the cystoscopic surveillance group. Further large scale studies are required to validate these results and establish the role of MCM-2 in diagnosis of bladder cancer.