Detection of urothelial carcinoma using selected urine-DNA methylation biomarkers in patients with gross hematuria: A prospective, single-center study

Run-Qi Guo, M.D.; Geng-Yan Xiong, M.D.; Xue-Song Li, M.D.; Kai Zhang, M.D.; Li-Qun Zhou, M.D.

Department of Urology, Peking University First Hospital. Institute of Urology, Peking University. National Urological Cancer Center, Beijing, China.

Background
- Hematuria is the most common symptom of urothelial carcinomas (UC) but is often idopathic.
- Cystoscopy is expensive which involves considerable patient discomfort, and conventional urine cytology for non-invasive UC detection and disease monitoring suffers from poor sensitivity.
- Previously, we identified that the methylation status of CDH1, HSPA2, RASSF1A, GDF15, BRCA1, THBS1 and TMEF22 in tissue samples was associated with tumor stage, grade and lymph node status in upper tract urothelial carcinomas (UTUC).
- Remarkably, a different panel (CDH1, SALL3, THBS1, TMEF2, VIM and GDF15) identified UC in patients with gross hematuria with 0.89 sensitivity and 0.74 specificity, and sensitivity (0.91) and specificity (0.92) could be achieved when cytology was included.

Objective
- We aim to evaluate the performance of genes selected from a previous study in detecting UC especially among patients with gross hematuria, as well as UTUC and bladder carcinoma separately, in voided urine samples.

Methods
- Using methylation-sensitive PCR, we examined the promoter methylation status of ten genes in voided urine samples among 473 patients at our institution, including 217 UC patients and 256 control subjects.

Results
- The final combination of VIM, CDH1, SALL3, TMEF2, RASSF1A, BRCA1, GDF15 and ABCG6 identified UC with a sensitivity of 0.83 and a specificity of 0.60.
- Receiver operating characteristic curves for the urinary biomarkers in urothelial carcinomas
  - A panel of selected genes (CDH1, HSPA2, RASSF1A, TMEF2, VIM and GDF15) identified UTUC with a sensitivity of 0.82 and a specificity of 0.68.
  - A panel of selected genes (VIM, RASSF1A, GDF15 and TMEF2) identified bladder carcinoma with a sensitivity of 0.82 and a specificity of 0.53.
- Receiver operating characteristic curves for the urinary biomarkers in upper tract urothelial carcinomas (left) and bladder carcinoma (right).

Conclusions
- The selected urine-DNA methylation biomarkers are reliable, non-invasive, and cost-effective diagnostic tools for bladder carcinoma and UTUC, especially among patients with gross hematuria.

Acknowledgements
- This work was supported by grants from the Collaborative Research Foundation of Peking University Health Science Center and National Taiwan University, College of Medicine (BMU20120318), Natural Science Foundation of Beijing Municipality (7152146) and the Clinical Features Research of Capital (No.Z151100004016173).