Urinary Biomarkers: Mitigating Diagnostic Delays of Bladder Cancer in the COVID-19 era

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Word Count: 1013 words

Figure Count: 1

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The COVID-19 pandemic has caused a devastating impact to healthcare services worldwide. In the United Kingdom, the six-week wait for a cystoscopy has increased by more than 500 percent, from 1270 in February, to 8190 in April 2020. This is a worrying trend with an impact on both new diagnoses and surveillance of previously treated bladder cancers.

The European Association of Urology (EAU) has issued guidelines to cope with the evolving dynamics of the pandemic, stratifying patients into traffic-light surveillance pathways based on initial tumour grade and presence of haematuria (Figure 1). The adapted guidelines prioritise patients with high-risk tumours for cystoscopies, while suggesting that patients with low or intermediate risk tumours, who remain asymptomatic, have their cystoscopies deferred by six months[1]. This decision was made on a balance of probable benefits and risks, both to minimise exposure of patients to a hospital environment and to deliver a scarce resource to those who are most at need.

Despite these guidelines, individual patients are unlikely to be reassured by delays, and we will inevitably miss some diagnoses in this game of probability. This period of uncertainty calls for timely action and innovation. Urinary biomarkers have featured in the diagnosis and surveillance of bladder cancers for many years and we should explore expanding their role in the context of the pandemic. In particular, markers may be a useful tool in patients with low- and intermediate-grade tumours where a surveillance cystoscopy has been deferred; abnormal results are then flagged and the patient scheduled for a biomarker-stratified diagnostic cystoscopy (Figure 1). A sensible use of biomarkers for the surveillance of patients with a lower possibility of recurrence is beneficial on several fronts: (a) it helps detect a recurrence which would otherwise be missed from a deferred

cystoscopy, (b) it provides a layer of reassurance to the patient, and (c) it minimises exposure of a potentially vulnerable patient to the hospital setting by collecting the urine samples at home, or at the primary health care centres, thus reducing a need to come into the hospital. There is robust clinical rationale to support this strategy, considering that this premise is being explored by the UroFollow trial, which began participant recruitment before prior to the pandemic [2].

The ideal test for surveillance should be sensitive, specific, and easy to perform. It should also be reasonably cost-effective and utilise a broadly available assay with a quick turnaround time. There are currently six urinary assays approved by the US Food and Drug Administration (FDA) for clinical use in conjunction with cystoscopy – NMP22 ELISA, NMP22 BladderChek, UroVysion, immunocyte (UCyt+), BTA-TRAK and BTA-STAT. While widely available, many of them suffer from a high false positive rate in inflammatory conditions affecting bladder mucosa, leading to overdiagnosis, and thus resulting in further strain to a service that is already scarce [3].

In July, the UK National Health Service approved the use of ADXBLADDER to help with the diagnosis and surveillance of bladder cancer. It detects the presence of MCM5, -a biomarker not influenced by infections or inflammation, and is twice as sensitive as urine cytology in the context of surveillance. It boasts an impressive negative predictive value of 92-99% and utilises a standard ELISA assay with a 2-hour rapid turnaround time.

Despite proving superior to urine cytology, the overall performance of ADXBLADDER remains relatively low, with a sensitivity of 51.9% and a specificity of 66.4% [4]. Conversely, the URO17™, a test that has recently been published, shows tremendous promise in its diagnostic capability. This immunocytochemical test detects

presence of oncoprotein Keratin 17, a protein involved in the replication cycle of malignant cells, in urothelial cells which has shown a sensitivity of 100% in detection of both recurrent bladder cancer[5] and new bladder cancers from hematuria patients. The specificity of URO17 in the detection of bladder cancer in recurrent and new bladder cancer was 96% and 92.6% respectively. These recent studies suggest that URO17™ could be a sensitive and specific test for Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP), as well as both papillary and nonpapillary carcinomas, providing diagnostic value in cases that could be missed by urine cytology. Additionally, URO17™ can be tested in patients presenting with haematuria, a cohort that had not been previously included in other K17 studies, thereby expanding its utility in the surveillance population. It should be noted that the immunocytochemical assay test required for URO17™ is easily adaptable to existing instrumentations, and utilises the same cytology samples as used in urine cytology, thereby allowing its seamless integration into clinical practice[5,6].

Whilst many biomarkers have been identified, their individual limitations have made them ineligible to overcome the highly reliable nature of gold standard cystoscopy. Using a panel of multiple biomarkers to improve each individual biomarker's shortcoming has been considered, however, this defeats the principle that a screening test should be simple, accessible and reasonably cost effective. A 2018 meta-analysis highlighted that two biomarkers showed strong potential: Orosomucoid-1 (ORM1), and the serine protease HtrA-1 [7]. Of 14 single protein biomarkers, these two have been identified to show the highest sensitivity and specificity percentages of detecting bladder cancer across the board. ORM1 with a sensitivity of 92%, specificity of 94%, and a ROC of 0.965

(3), and HtrA-1 with a sensitivity and specificity of 93% and 96% respectively (4). Both protein biomarkers are tested using ELISA of collected urine samples, once again allowing the use of existing lab infrastructure.

Urinary biomarkers have been overlooked for many years due to a perceived lack of sensitivity and a high rate of false positivity. Significant improvements in this area have been made in recent times, and the inevitable diagnostic delays as a result of the COVID-19 pandemic require that we adapt our practices in a timely fashion. We propose that particular attention be devoted to transposing the use of these biomarkers to clinical practice, to help mitigate the backlog of diagnostic procedures in these pressing times. We propose that urinary biomarkers should be incorporated in the surveillance of bladder tumours and resources should be focused on clinical trials involving these biomarkers to get a head-to-head comparison.

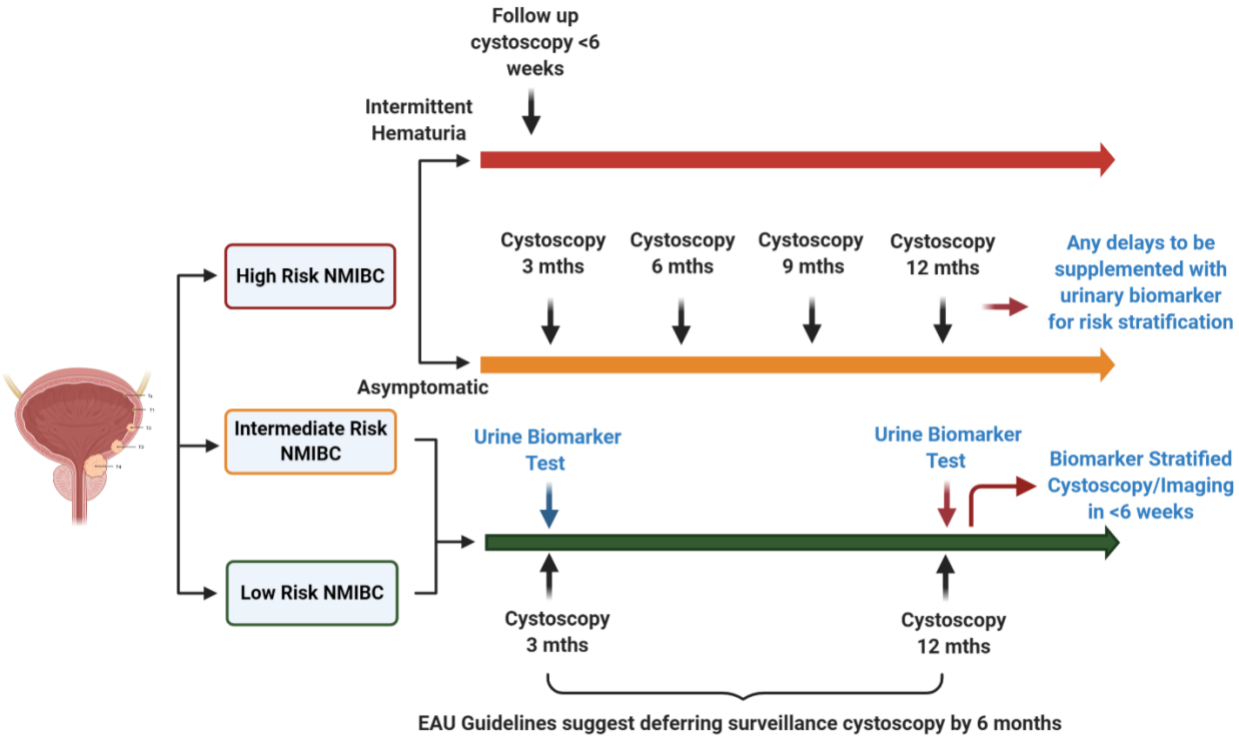

Figure 1 Schematic of Proposed Surveillance Scheme Based on EAU Guidelines in the COVID-19 Pandemic within 12 months of transurethral resection Hypothetical timepoints for urine biomarker test highlighted in blue, alongside biomarker-stratified cystoscopy or imaging in the context of an abnormal urine biomarker test.

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