Urine as a liquid biopsy

Urine is a waste product that is produced in the kidneys and expelled from the body via the ureters and bladder. Although it is composed primarily of water, small quantities of other constituents such as protein, dead blood cells and toxins may also be present. Urine samples are easy to obtain and allow testing to be performed for a large range of disorders. In the cytology laboratory for example, the examination of cells is carried out to look for signs of infection, inflammation and cancer. Although the presence of blood or abnormal cells is often the result of benign, non-cancerous conditions, they may also be the first indicators of malignancy.

Bladder cancer is the most common cancer of the urinary tract and a leading cause of morbidity and mortality. Early detection and staging of the disease is vital as statistics show that survival rates increase the earlier the cancer is detected. Diagnostic workup for suspected bladder cancer usually commences with physical examination, cystoscopy (the gold standard for detecting and monitoring bladder tumours) and cytological analysis. Urine cytology involves the microscopic assessment of stained epithelial cells that have been shed from the urinary tract (Figure 1).

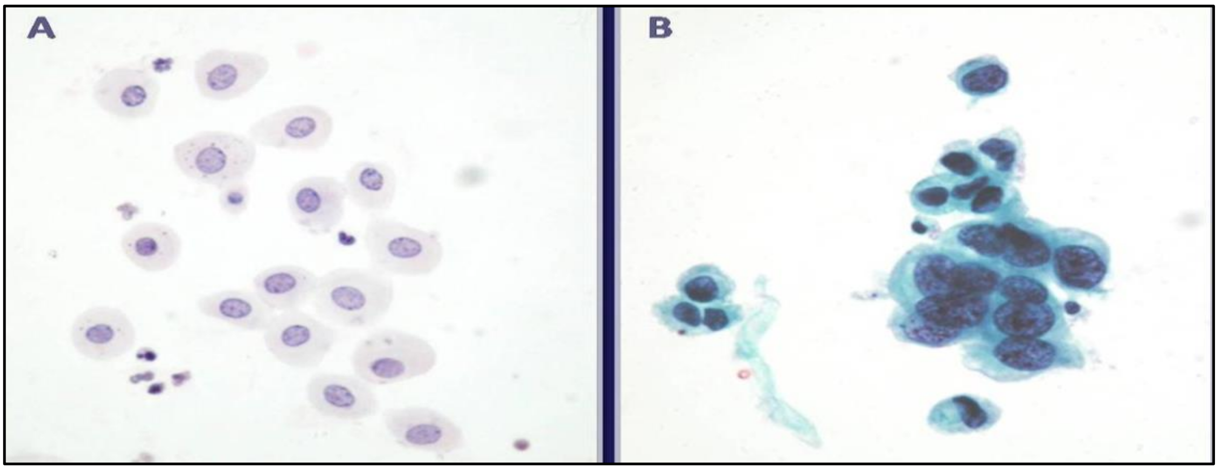

Figure 1. Urine cytology showing (A) normal and (B) malignant urothelial cells

In recent years, the management of urothelial cancer has been revolutionized by the performance of diagnostic tests on fluid samples (liquid biopsies) rather than on tissues. Liquid biopsies are non-invasive alternatives that enable identification of genitourinary and other diseases and cancers by detecting biomarkers in fluid samples such as urine. The ability to diagnose tumours and monitor their progression and response to treatment without the need to obtain a tissue biopsy has been a long-standing goal of disease and cancer management.

The most highly developed technique for liquid biopsies is the analysis of circulating tumour cells (CTCs) which are commonly detected using polymerase chain reaction (PCR) type methods. CTCs are cancer cells that have detached from a primary tumour and travelled via vascular, lymphatic or other means to various parts of the body (Figure 2). They are often detected quite early in the course of the disease and are a fundamental prerequisite to metastasis, offering great potential for both diagnosis and prognostic assessment. Furthermore, the molecular characterization of CTCs and circulating cell-free (cf) DNA can provide considerable information on issues such as the sensitivity of tumours to treatment and potential for developing resistance to anticancer agents.

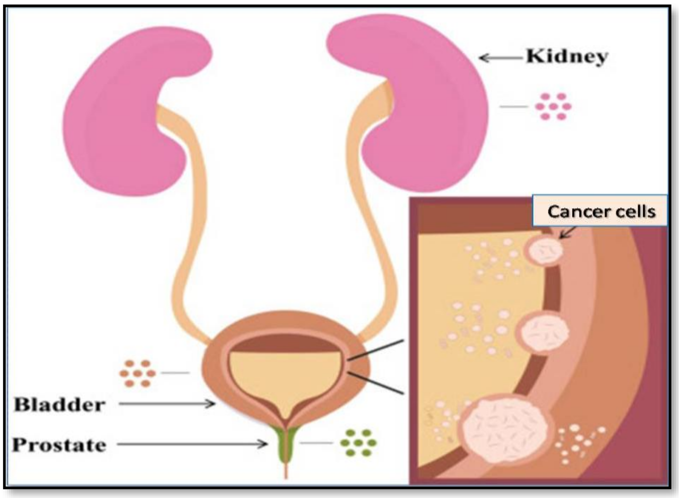

Figure 2. Circulating tumour cells in the urinary system

There is a growing trend towards exploring the value of urine as a liquid biopsy and the use of biomarkers is an important and relevant addition to the current armoury of diagnostic methods. Some biomarkers such as bladder tumour antigen (BTA) offer a sensitivity that often increases with tumour grade similar to that obtained with urine cytology. However, in addition to BTA assays, testing for chromosomal abnormalities can also be carried out using a multi-target, multi-colour system such as UroVysion. This fluorescent in-situ hybridization (FISH) assay is useful for detecting abnormalities in chromosomes 3, 7 and 17 which are known to be altered in bladder cancer cells. Many other biomarkers such as telomerase (TERT) activation, tumour protein 53 (TP53), epidermal growth factor (EGFR) and fibroblast growth factor receptor-3 (FGFR3) mutations are invariably present in the urine of patients with bladder cancer and are often fundamental in the early diagnosis of the disease. Some liquid biopsy studies have also focused on the future of self-sampling and subsequent analysis of urine in the detection of human papillomavirus (HPV) biomarkers in early stage genital cancers. Many of these assays are able to provide valuable information on the morphological and molecular profiling of both primary and metastatic cancer.

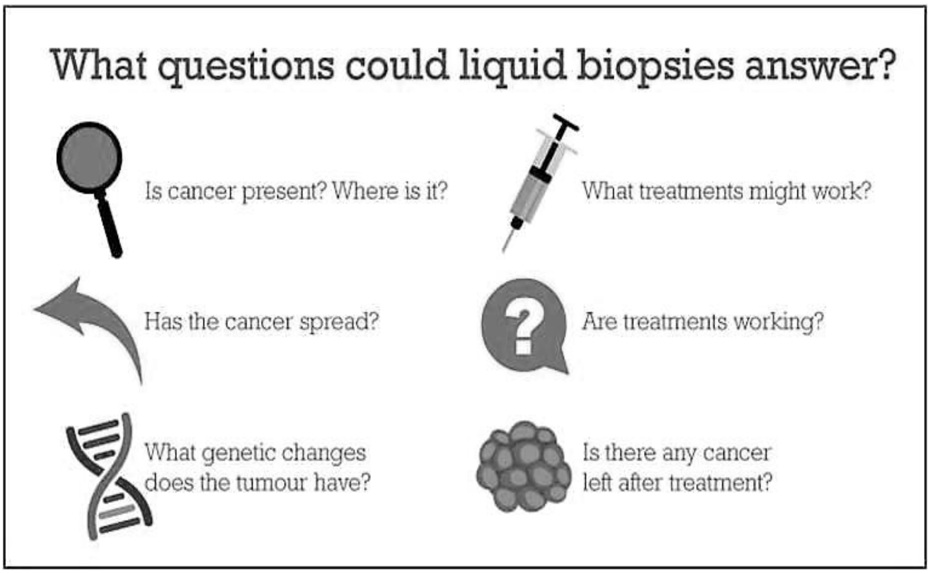

Figure 3. The value of urine as a liquid biopsy

The application of urine as a non-invasive, liquid biopsy has obvious appeal (Figure 3). Urine samples are both practical and easy to obtain and are stable for many days. Because of the large volumes that can be acquired regularly, the availability of both tumour and genomic DNA for testing is often far greater than that which can be obtained from other liquid biopsies such as blood. Since tumours can shed cells in the urine, their DNA becomes available as an important tool in the treatment and monitoring of cancer. Identification (or absence) of specific mutations becomes a valuable indicator of whether a drug is actually performing as it should in destroying the tumour cells. The outlook for urine as a liquid biopsy appears to not only have a great future in cancer diagnosis but also in the treatment response of the patient to targeted therapy.

Further reading

1. A prospective comparison of UroVysion FISH and urine cytology in bladder cancer detection. Lavery HJ et al. BMC Cancer 2017;17:247. https://bmccancer.biomedcentral.com/articles/10.1186/s12885-017-3227-3

2. Detection and surveillance of bladder cancer using urine tumor DNA. Dudley JC et al. Cancer Disc 2019;9(4);500-509. http://cancerdiscovery.aacrjournals.org/content/9/4/500

3. Emerging biomarkers for the diagnosis and monitoring of urothelial carcinoma. Miyake M et al. Res Rep Urol 2018;10:251-261. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6299471/

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5. Techniques of using circulating tumor DNA as a liquid biopsy component in cancer management. Elazezy M & Joosse SA. Comput Struct Biotechnol J 2018;16:370-378 https://www.ncbi.nlm.nih.gov/pubmed/30364656

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