Summary and Conclusion

- UBC® is a urinary marker measuring the cytokeratins 8 and 18
- UBC® is a non-invasive indicator of tumor cell activity in urine
- UBC® demonstrates high diagnostic sensitivity in low-stage and low-grade bladder tumors
- UBC® is a stage-specific marker in urine for detection of bladder cancer
- UBC® may serve as a reliable complementary tool during patient followup, and thus reduce the number of cystoscopies performed
- UBC® provides the physician with early signals of tumor recurrence during treatment monitoring
- UBC® supports therapy decisions to optimize patient management

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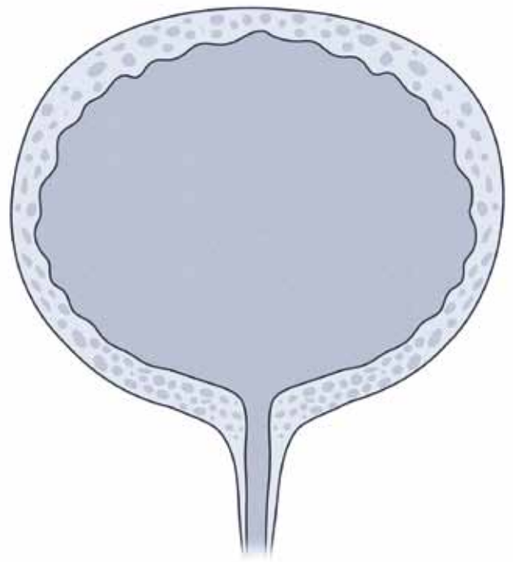
UBC®
For accurate tumor status

UBC® in Bladder Cancer



For detection and monitoring of bladder cancer

The cytokeratin marker UBC® is an indicator of tumor cell activity that provides the clinician with earlier signals regarding disease outcome.

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Background bladder cancer

The most frequently detected malignant tumor in the urinary tract is bladder cancer. Ninety percent of bladder tumors originate from transitional epithelial cells, which cover the internal bladder wall.

The risk of developing bladder cancer is three to four times higher in men than in women and it increases with smoking, industrial chemicals and other carcinogens. Of particular prognostic importance is the pathological classification of bladder carcinomas into superficial (Ta/Tis/T1) or muscle invasive (T2-T4) carcinomas. More than 50% of recurrent tumors do not infiltrate the muscle layer, but bladder carcinomas still have a relatively high rate of recurrence. Superficial recurrences can be identified by urological investigations, but the situation is different with invasive recurrence.

The mainstay of treatment is transurethral resection of the tumor (TURT), sometimes combined with intravesical chemotherapy and/or radiotherapy. The current practice of long-term follow up of patients with bladder cancer is cystoscopy to identify recurrence at an early stage and treat it before it reaches an advanced stage.

According to the American Cancer Society, there is a five-year survival rate of 95% for bladder cancer when diagnosed in its early stages. If diagnosed at an advanced stage, however, the five-year survival rate can be less than 10%. More importantly, bladder cancer has one of the highest rates of recurrence. It is estimated that as many as 70% of bladder cancer cases will recur, and of those, as many as 30% progress to a dangerous tumor. Tests for early detection and patient monitoring are therefore crucial.

Testing for Bladder cancer

Cystoscopy is the method most generally used for the detection and monitoring of bladder cancer. This consists of introducing an instrument through the urethra, which allows visual inspection of the bladder inner wall.

Cystoscopy is used to examine symptomatic patients presenting abnormal urinary cytology, hematuria or other symptoms related to bladder cancer. The current standard method for non-invasive detection of bladder cancer is urine cytology. Urine cytology has a high specificity, but a very low sensitivity (below 30-40%), and this varies according to stage and grade. Tumor markers are potentially useful in diagnosis of bladder cancer, monitoring the course of the disease and detecting recurrences.

A higher sensitivity may be achieved by analyzing urine, from patients with bladder tumors, with UBC and compare with urine cytology. UBC appears to be a useful marker for diagnosis and clinical management of bladder cancer patients.

Cytokeratin Filaments

All eucaryotic cells have cytoplasmic cytoskeletal structures known as intermediate filaments. The cytoskeletal network is responsible for the mechanical integrity of the cell and is critical during cellular processes such as cell division, motility and cell-to-cell contacts.

More than 20 different cytokeratins have now been identified, of which cytokeratin 8, 18 and 19 are the most abundant in simple epithelial cells. The cytokeratins are epithelial cell specific, and the cytokeratin pattern is usually preserved during the transformation of normal cells into malignant cells.

UBC® Assays

UBC (Urinary Bladder Cancer) is an immunoassay designed for the determination of soluble cytokeratin 8 and 18 fragments in urine from urothelial tumors. UBC is available as quantitative immunoassays (UBC ELISA and UBC IRMA).

UBC ELISA assay is a solid-phase, two-site immunoassay using two monoclonal antibodies as catcher in the microplate well. In UBC IRMA assay, soluble cytokeratin 8 and 18 fragments are reacted with a bead coated with two monoclonal antibodies.

Patient samples and standards are incubated with the immobilized monoclonal antibodies and simultaneously with labeled polyclonal antibodies (detector antibodies). The cytokeratin antigens are detected by color development (HRP-labelled polyclonal antibodies) or by bound radioactivity (^{125}I-labelled polyclonal antibodies).

Test precision is established to below 10% variability between assays, and less than 5% variability within assays. UBC is a marker of tumor cell activity in urine.

UBC® for detection of bladder cancer

The most common symptom of bladder cancer is intermittent hematuria, detected either visually or by urinanalysis. Less than 10% of patients with these symptoms have bladder cancer.

Bladder cancer is a disease with a high prevalence and potential for improved survival with early detection. UBC indicated a sensitivity of 87%, at a specificity of 86%, when measured in urine from patients with active transitional cell carcinoma of the bladder.

Comparing the diagnostic efficiency of UBC to other urine markers in ROC analysis revealed a higher sensitivity for UBC at the same specificity. UBC appeared to have the lowest rate of false positive results when comparing with other cytokeratin markers. At a specificity of 93%, UBC demonstrated a sensitivity of 58%, and in the same patient material NMP22 showed a sensitivity of 47% at a specificity of 80%. UBC is also related to histological grading of bladder cancer; UBC is increased by 66% in GI tumors, 43% in GII tumors and 50% in GIII tumors.

When comparing UBC with BTA and voided urine cytology (VUC), UBC showed an overall sensitivity in urine of 90% (specificity 70%) compared with 57% for VUC and 44% for BTA. In another study, UBC demonstrated higher sensitivity than cytological examination of urine (77% versus 44%). While cytology remains the standard urine-based diagnostic method, the additional use of UBC testing may also be useful in the early identification of locally advanced bladder tumors.

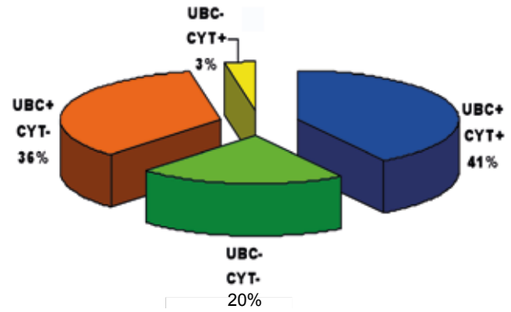
UBC® for monitoring bladder cancer

When bladder cancer has been diagnosed, the superficial tumor is removed by surgery.

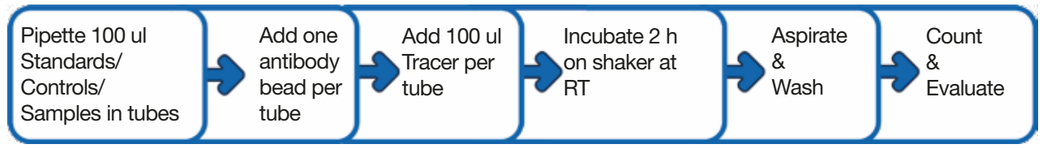
Patients with low risk for recurrence are included in a program based on regular cystoscopic examinations. In patients with a high risk for recurrence (local as well as spread disease), a more aggressive management is applied, such as intravesical immunotherapy or chemotherapy to delay further recurrence, as well as more frequent cystoscopic examinations.

Cystoscopy creates discomfort for patients and is also expensive. UBC can provide urologists with valuable information that will influence medical decisions in the management of bladder cancer patients. UBC may not replace cystoscopies, but can guide the use of this invasive method. Monitoring patients with UBC could lead to a more cost-effective use of cystoscopy.

Sensitivity of UBC and Cytology in TCC bladder cancer patients

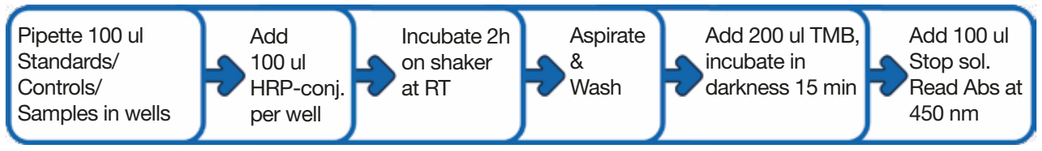


UBC® IRMA assay procedure



Soluble fragments of cytokeratins 8 and 18 are reacted with a bead coated with monoclonal antibodies, and simultaneously with isotope labelled affinity-purified polyclonal antibodies.

UBC® ELISA assay procedure



Soluble fragments of cytokeratins 8 and 18 are reacted with a microplate well coated with monoclonal antibodies, and simultaneously with HRP-conjugated affinity-purified polyclonal antibodies.