Utilization of CellDetect® in bladder cancer diagnosis and recurrence: a prospective comparison with urine cytology and Urovysion FISH

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Introduction

Bladder cancer (BC) has become one of the common cancers globally, ranking 5th most common cancer in Europe, with an estimated 124,000 new cases annually. In addition, due to the high recurrence rates of the disease – rigorous, frequent and long-term surveillance is necessary.

The current methods used for preliminary diagnosis and surveillance of BC recommended by the European guidelines include standard urine cytology (Pap staining) and cystoscopy. Although Pap present high specificity its weaknesses are low sensitivity and high rate of equivocal readouts (i.e., "atypia" or "suspicious"), which limits its value. On the other hand Cystoscopy that is considered gold standard (GS) present low performance in detection of flat lesions. Due to the limitations there is eminent need for a more efficient and sensitive marker for detection of BC.

CellDetect® test is a unique cytochemical stain adding color differentiation without compromising the morphological changes to discriminate between malignant and benign cells based on differences in the metabolic signature. This study summarizes the performance of Pap and the two commercially available tests : U-FISH and CellDetect® when compared to GS in BC diagnosis.

Purpose

The aim of the study was to determine the performance, accuracy and clinical relevance of CellDetect®, in comparison with standard urine cytology and UroVysion FISH (U-FISH), for bladder cancer (BC) detection and management in routinely monitored patients.

Method

Voided-urine samples were obtained from subjects with hematuria or BC patients under routine surveillance. Liquid-based smears were prepared for each specimen, separately stained with Pap, CellDetect® and U-FISH. The smears were blindly reviewed and the performances of all three techniques were compared. Final diagnosis was done using biopsy/cystoscopy/acceptable clinical assessments as gold standard.
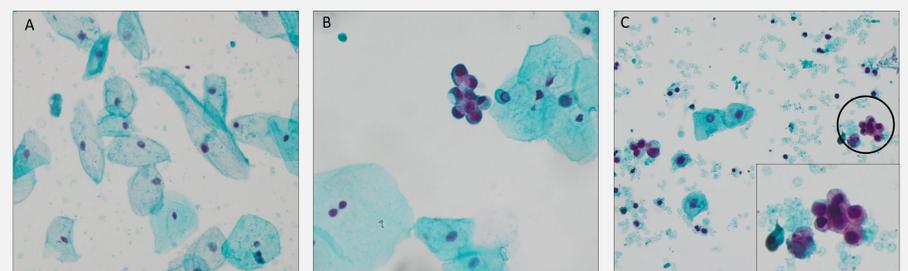

Figure 1: Pictures demonstrating the differentiation between negative and positive cells using CellDetect® technology.
A- Negative result by CellDetect®: cytoplasm of epithelial cells is stained in green and the nuclei in purple/green.
B and C – positive cases in which the nuclei of the positive cells is stained in deep violet (occasionally also the cytoplasm is stained in pink) and show hyperchromasia on top of morphological changes. red blood cells are stained in light green and inflammatory cells in purple/red.

Results

The study included 63 patients. Of those 17 were positive cases and 46 were negative cases, according to the gold standard. Of note that a intended enrichment of PAP cases with "atypia" or "suspicious for malignancy" result was designed. Results shown for this cohort are of 12 months follow up.

Increased sensitivity and accuracy by CellDetect®

The diagnostic accuracy of each test was computed based on determined readings with CellDetect® exhibiting markedly higher sensitivity. Tests performances are summarized in table 1.

	Standard cytology	CellDetect®	U-FISH
Sensitivity	43%	100%	60%
Specificity	95%	85%	67%
Total	31	55	42

Table 1: High sensitivity of CellDetect® when comparing the of overall tests performances

Reduced undetermined reading by CellDetect®

Evaluation was performed on the 24 cases that received an equivocal diagnosis (i.e. "atypia") by standard cytology. Of these cases CellDetect® correctly identified 20 cases (including all 5 positive cases), while U-FISH correctly identified 15 cases.

	CellDetect®	U-FISH
Correct diagnoses	80%	61%
Incorrect diagnoses	10%	23%
equivocal	10%	6%

Table 2: CellDetect® considerably reduces the rate of undermined readings. 80% of standard cytology undetermined readings were correctly diagnosed by CellDetect® while with U-FISH 61% of cases received correct diagnoses.

The rate of determined reading

63 cases were tested with standard cytology out of which only 31 of the cases received determined readings. Out of the 62 eligible CellDetect® cases 55 received determined readings and 42 cases out of 46 tested cases for U-FISH.
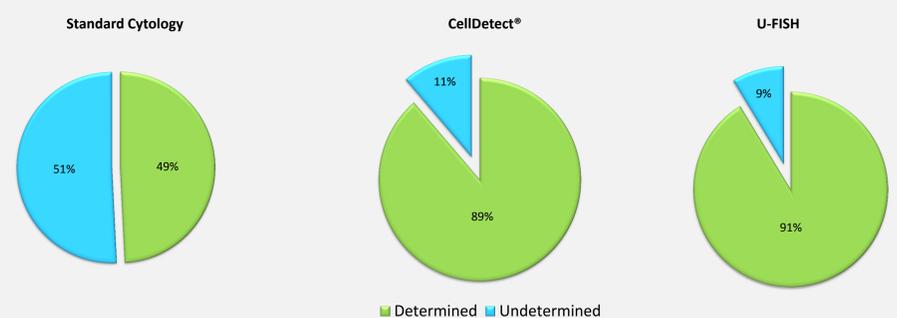

Figure 2: CellDetect® and U-FISH present high levels of determined readings in comparison to standard cytology. The performance of CellDetect® and U-FISH determined readings were similar with 89% and 91% respectively while with standard cytology determined readings where only 49%.
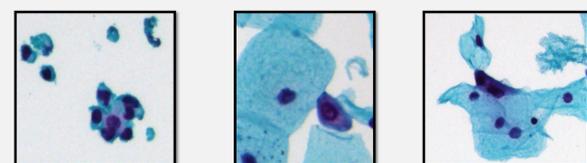
Figure 3: Study cases stained positive by CellDetect® but were missed by PAP. Cases were later confirmed as a low grade tumor by GS. The images demonstrate moderate dysplastic cells highlighted by CellDetect® stain. Positive stain is indicated by hyperchromasia and a deep violet nucleus. Normal cells are stained with a purple nucleus and green cytoplasm.

Conclusions

CellDetect® outperforms both standard urine cytology and U-FISH sensitivities in BC detection, by 57% and 40%, respectively. Additionally, when compared to standard cytology, CellDetect® reduces the number of equivocal readings by 80%. Moreover, though missed by Pap testing, 16% of all cases were positively detected by CellDetect®. Thus, adjunctive testing with CellDetect® may aid in a confirmatory diagnosis of BC.