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Non-invasive Detection of Bladder Cancer by UBC Rapid Test, Ultrasonography and Cytology

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Abstract. *Background/Aim: There is a need to diagnose early bladder cancer by non-invasive tests. This study aimed to explore the clinical value of three non-invasive methods, UBC Rapid, ultrasound (US), and urine cytology, separately and in combination, for the primary diagnosis and surveillance of bladder-cancer. Patients and Methods: Urine samples were obtained from 106 patients who presented with symptoms of bladder cancer and patients followed-up after transurethral resection of bladder tumors (TURB). Each patient underwent US, cystoscopy, cytology and UBC Rapid test. The sensitivity and specificity of all methods and combinations were calculated and related to cystoscopy and biopsy. Results: Voided urine samples assayed with UBC Rapid and cytology yielded a sensitivity and specificity of 58.3% and 75.9%, and 57.1% and 98.0%, respectively and for US 76.2% and 98.1%. The combination of all three methods resulted in a sensitivity and specificity of 95.8% and 67.3%, and the combination of UBC Rapid and US, gave a sensitivity of 91.3%, and a specificity of 72.2%, The combination of UBC Rapid and cytology yielded a sensitivity and specificity of 84.6% and 71.2%. Conclusion: Combined use of UBC Rapid, US and cytology improved the sensitivity of bladder cancer detection.*

Bladder cancer is a relatively common cancer, the 9th most malignant tumor and the 13 most common cause of death from cancer (1). Bladder cancer is clinically divided into two subgroups, non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) (2). Approximately 70-75% of newly diagnosed bladder cancer is NMIBC at presentation (3). In NMIBC, the focus is on the tendency to detect recurrence and progression in the high risk bladder cancer patients during monitoring after transurethral resection of bladder tumors (TURB). At the time of diagnosis, more than 25% of the bladder cancer patients already suffer from MIBC and these patients are candidates for a more aggressive surgical procedure (radical cystectomy) (3-5).

Non-muscle invasive cancer disease has a significant lower risk of cancer specific mortality with a better long-term survival compared to MIBC. NMIBC high-grade bladder cancer has a particularly high rate of recurrence and will progress to muscle-invasive disease (6). Bladder cancer is typically diagnosed by cystoscopy followed by pathological examination of suspicious tissue. Cystoscopy is a time-consuming method that also requires an experienced urologist. Furthermore, cystoscopy demonstrates limited sensitivity for flat lesions (CIS tumors) and as it is an invasive procedure, might lead to discomfort for the patients (7). Urine cytology, a non-invasive test for the detction of bladder cancer, is recommended as a standard test in combination with cystoscopy for regular surveillance of patients, with the potential to detect flat lesions not detected by cystoscopy (5, 8). Cytology is very specific but its overall sensitivity is low and its sensitivity is only satisfactory for high grade and CIS tumors (9). Furthermore, the diagnostic accuracy of cytology varies between study centers due to subjective interpretation (10, 11).

There is a need for an easier and non-invasive diagnostic method for measuring easy assessible body fluids instead of tissue specimens. It is of general acceptance that urine might be a good source for bladder cancer specific urinary tumor markers (12).

UBC Rapid is an immunochromatographic point-of-care (POC) test that detects soluble fragments of cytokeratins 8 and 18 in urine, which play an active role in tumor invasion (13-18). The UBC Rapid test is performed at the doctor's office, enabling a better and immediate decision regarding the patient treatment.

The aims of this study were to investigate the diagnostic accuracy of UBC Rapid in patients with primary bladder cancer and patients with a history of bladder cancer, and

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compare it with other urinary tumor markers in high- and low-risk urothelial tumors.

Patients and Methods

In total, 106 patients were recruited at the Hadassah University Hospital, Jerusalem. Demographic and clinical characteristics of the enrolled patients are presented in Table I. Forty-seven patients with primary symptoms of a suspected tumor (hematuria or dysuria) or abnormal findings at image analysis and 59 patients undergoing surveillance for NMIBC after TURB. The initial diagnosis of bladder cancer was based upon cystoscopy and confirmed by histological examination of resected tissue. Tumors were classified as low- or high-grade tumors according to the 2004 WHO classification (19). The control group included patients with a negative cystoscopy after routine oncological control. Exclusion criteria were any kind of mechanical manipulation within 10 days before urine sampling. Furthermore, patients with urinary tract infection (urinedipstick analysis) or urolithiasis were also excluded. All these exclusion criteria might influence the UBC Rapid test to produce false results.

Methods. The reference method was cystoscopy combined with histological evaluation. Cystoscopy was considered positive if a tumor was found or if a suspicious area was observed and histologically verified as a malignancy. Cystoscopy was performed in all patients to diagnose bladder cancer using a flexible cytoscope according to the standard procedure used in the hospital. Ultrasound (US) was conducted by an experienced urologist/radiologist in all patients eligible for the study, using a standard method. If a tumor was observed, its location, size and number of tumors were documented.

Urine samples of all patients were analysed by cytology and UBC Rapid. For cytology, Papanicolaou staining was performed. Microscopic assessment was performed according to the recommendations by Papanicolaou classification (20). Voided urine samples were collected for UBC Rapid analysis (IDL Biotech, Sweden) using visual detection. UBC Rapid is a qualitative POC assay based upon lateral flow and measures the soluble fragment of cytokeratins 8/18 in urine. All UBC Rapid tests were performed as recommended by the manufacturer. The presence of a line after 10 min of incubation was evaluated as a positive test. Patients with positive urine culture (urine infection) were excluded from the UBC Rapid study as urinary tract infection could influence UBC Rapid signal.

Statistical methods. The statistical calculations were performed using IBM SPSS 22. The diagnostic yield of UBC Rapid was assessed with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Contingency tables were analysed with Fisher's exact test or with Chi-square test. Logistic regression analysis was conducted to calculate the sensitivity and specificity of marker combinations; UBC Rapid, US and cytology. Cohen's Kappa coefficient was used to calculate the agreement between the applied analytical methods. The statistical significance level was set at p less than 0.05. All outlayers were included in the analyses.

Ethics. This study was performed according to the Declaration of Helsinki. The study was approved by the local Institutional Review Board (0605-15-HMO).

Table I. *Patient demographics and distribution of bladder cancer by stage and grade*.

Patients characteristics	Patient numbers
Total males	77
Toatal females	29
Age range (years)	38-98
Mean age (years)	69.9
Stage/grade	
pTa	28
pT1	6
pT2-T4	7
CIS	3
G1 (Low grade)	25
G2 (High grade)	17

All invasive tumors were G2, except for one T1 tumor that was G1. All pTa tumors were G1, except for four that were G2.

Written informed consent was obtained from each participant in the study.

Results

Urine specimens were obtained from 106 patients, 47 of whom had symptoms of bladder cancer and 59 were monitored after TURB. After TURB, all patients routinely underwent control cystoscopy. Figure 1 illustrates the study design. Of all 106 cases included in the study, 48 cases were urothelial cell carcinoma (UCC) positive and 58 cases demonstated no tumor, as proven by a negative cystoscopy and/or histological analysis of a biopsy sample.

Among the 48 UCC-positive cases, 25 were low-grade NMIBC, 15 high-grade NMIBC and in 8 cases, no pathological evaluation was assigned. In 39 of the patients with clinically confirmed tumors, all patients showed more than one tumor or tumors exceeding 5 mm. Four patients had one small tumor below 5 mm (Table I).

The sensitivities, specificities, PPVs and NPVs of the individual tests for predicting bladder cancer and bladder cancer recurrence are shown in Table II. For the urinary UBC Rapid visual test, the sensitivity, specificity, PPV and NPV were 58.3%, 75.9%, 66.7% and 68.7%, respectively. Urinary cytology of voided urine yielded an overall sensitivity, specificity, PPV and NPV of 57.1%, 98.0%, 95.2% and 76.6%, respectively.

Ultrasound is a non-invasive method included in the guidelines for diagnosis and surveillance of bladder cancer and therefore, we compared with the UBC Rapid. In some countries, US is applied instead of cystoscopy for confirmation of Bladder Cancer. Ultrasound showed a sensitivity, specificity, PPV and NPV of 76.2%, 98.1%, 97.0% and 83.9%, respectively. However, in this study, ultrasound missed 10 tumors in the 42 bladder cancer patients. Seven of

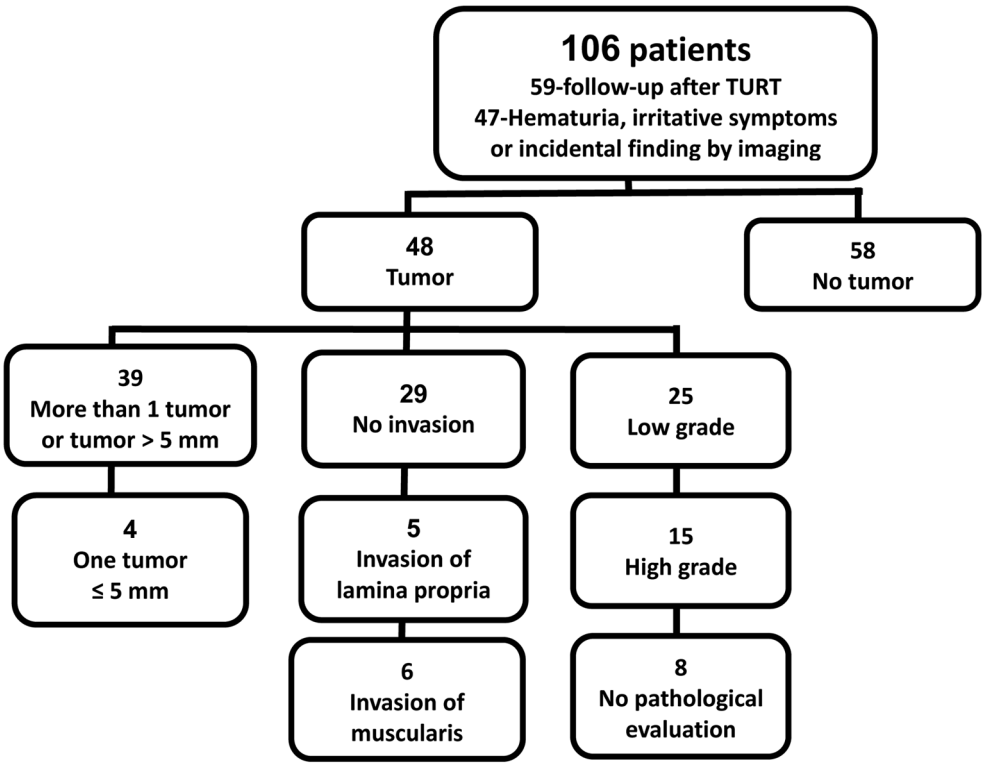

Figure 1. *Flow diagram of patients and eligible urine specimen.*

Table II. *Diagnostic sensitivity, specificity, PPV and NPV of UBC Rapid, cytology, ultrasound and different method combinations.*

	Sensitivity (%)	95%CI	Specificity (%)	95%CI	PPV (%)	NPV (%)	*p*-Value
UBC Rapid	58.3	0.43-0.71	75.9	0.63-0.78	66.7	68.7	<0.001
Cytology	57.1	0.39-0.94	98	0.89-1.0	95.2	76.6	<0.001
Ultrasound	76.2	0.61-0.88	98.1	0.90-1.0	97	83.9	<0.001
UBC Rapid+Cytology	84.6	0.69-0.94	71.2	0.57-0.83	68.8	86	<0.001
UBC Rapid+Ultrasound	91.3	0.79-0.98	72.2	0.58-0.83	73.7	90.9	<0.001
Cytology+Ultrasound	98.6	0.75-0.96	95.7	0.85-0.99	95.1	90	<0.001

these cases were high grade NMIBC tumors and two of these, were missed by ultrasound but identified by cytology. No invasive bladder tumor was overlooked by US.

Table II shows the results obtained by combining the different diagnostic methods. Combining qualitatively UBC Rapid with urinary cytology demonstrated a sensitivity of 84.6% and a specificity of 71.2%, and a PPV and NPV of 68.8 and 86.0%, respectively. A significantly higher sensitivity was obtained with the combination of methods compared to each individual method used alone, but with a markedly lower specificity. The combination of UBC Rapid and ultrasound resulted in a sensitivity, specificity, PPV and NPV of 91.3%, 72.2%, 73.7%, 90.9%, respectively. The combination of cytology and US showed the highest sensitivity, specificity, PPV and NPV of 98.6%, 95.7%, 95.1% and 90.0%, respectively; however, with this combination five low-risk tumors were not detected.

The combination of all three individual diagnostic methods - UBC Rapid, US and cytology resulted in a sensitivity, specificity, PPV and NPV of 95.6%, 67.3%, 72.9% and 94.3%, respectively. With this triple combination, only two low-risk tumors were missed, in one patient with a single 2-mm tumor and in one with a low-grade non-invasive tumor.

If we divide the patients into two groups, those with primary symptoms that are suspicious of tumor, and those at follow-up after TURB, in the first group, there were much

more positive cases (34 patients) than negative cases (13 patients). In this patient group, the combination of US and cytology resulted in a very high sensitivity of 96.8% (95%CI=0.83-1). The specificity was 100% (95%CI=0.69-1), PPV was 100%, and NPV 90.9% ($p<0.001$), significantly higher than the individual methods. The addition of UBC Rapid did not improve the sensitivity in this patient group.

In the follow-up group there were significantly more patients with a negative result (45 cases). Negative results were obtained in 14 patients with a recurrent tumor. In this group, a combination of UBC Rapid and US showed a sensitivity of 92.3% (95%CI=0.64-1). Adding cytology did not improve the sensitivity.

Discussion

The main purpose of this pilot study was to evaluate the clinical usefulness of qualitative UBC Rapid for the accurate diagnosis and monitoring of bladder cancer. The results were compared to those of the urine marker cytology and US methods. The sensitivity of cytology in detecting bladder cancer was reported to be 44% and the specificity 96% (21). Due to the low sensitivity, its clinical value has been disputed (22-24). Therefore, it is necessary to investigate new tests such as UBC Rapid. UBC Rapid with visual detection has been examined in bladder cancer patients with a reported sensitivity in the range of 53.3% to 86.9%, and a specificity of 59.0% to 97.4% (13-18, 25).

UBC Rapid has demonstrated high sensitivity (71.4%) in patients with non-muscle-invasive high grade tumors, with a specificity of 90.9% (17). Carcinoma *in situ* (CIS) is a very aggressive form of non-muscle-invasive urinary bladder cancer (5, 26). CIS is difficult to be detected even with cystoscopy, due to its characterist flat lesions. The sensitivity of UBC Rapid in CIS patients was 86.9%, and the specificity was 90.9% (17). UBC Rapid has the potential to be a more sensitive and specific biomarker for the accurate detection of high-grade non-muscle-invasive and CIS tumors.

Our study is one of many studies that have attempted to find a non-invasive alternative to cystoscopy that can be used in the diagnosis and follow-up of bladder cancer. To the best of our knowledge, a study examining the combination of a POC test with US and cytology, has not been previously published. Most of the studies performed so far have examined the sensitivity and specificity of different methods, however, no method has been found sensitive enough to detect a primary tumor of the bladder or a recurrent tumor during follow-up. The important finding of this study is that it is worth trying to combine a number of non-invasive, simple-to-do methods to achieve sufficient sensitivity. We also found that for patients with different characteristics (patients suspected of primary tumor *vs*. follow-up patients, patients with a low grade *vs*. high grade tumour) different combinations of tests should be applied.

In previously reported studies, the combination of different urinary tumor markers has been reported, which has shown relatively high sensitivity (27-29). Giannopoulus *et al*. (30) examined the combination of BTA STAT (a POC test), UBC ELISA and NMP22 ELISA and found that the triple combination gives a sensitivity of 94.9%, while the combination of UBC ELISA and BTA STAT resulted in a sensitivity of 92.4% (30). However, despite the good results, these assays are not accepted among urologists in the clinical practice, mostly because they are expensive (each patient requires several tumor markers) and require special laboratory equipment and its labor intensive.

A similar bladder cancer study was performed in our ward in 2009, where we found that the combination of US, cytology and the tumor marker CYFRA 21-1 had a sensitivity of 90.5% and a specificity of 67.2% (31). However, serum CYFRA 21-1 level was tested using the ELISA method (32). A similar study in our ward was performed by combining US and cytology with immunohistochemical staining of cells in the urine sediment with Lewis X antigen. The combination showed a sensitivity of 95.2% and a specificity of 82.4%. However, this combination of methods could not be used in practice due to its technical limitations, since immunocytology requires laboratory time and an experienced pathologist.

The results of our study are similar to those reported in other studies regarding the specificity and sensitivity of each individual method (13-17). UBC Rapid showed a sensitivity of 58.3% and specificity of 75.9%. Ultrasound showed a sensitivity of 76.2% and a specificity of 98.1%, and cytology a sensitivity of 57.1% and a specificity of 98.0%. However, no method was sensitive enough by itself, but the combination of the three methods showed high sensitivity (95.6%) and moderate specificity (67.3%). Only 2 of the 45 confirmed tumors were missed, that were low-risk tumors that would have most likely been detected later in the follow-up before they endangered the patient. The combination of UBC Rapid and US showed a sensitivity of 91.3% and a specificity of 72.2%. When we analyzed the results in relation to follow-up patients versus patients with primary symptoms, we found that in the second group the combination of US and cytology gave a very high sensitivity (96.8%) and 100% specificity. The addition of UBC Rapid did not improve the sensitivity, but significantly lowered the specificity to 72.7%. Whereas in the group of follow-up patients, the combination of UBC Rapid and US resulted in high sensitivity (91.3%) and a specificity of 72.2%.

High sensitivity is a very important parameter that has to exist so that tumours are not missed with non-invasive tests. High specificity is less critical, because in the case of a false positive result the patient will undergo an unnecessary cystoscopy at most (who without these tests would have undergone anyway).

The principal limitation of this pilot study is the small number of patients, which restricts the statistical evaluation. In spite of not having randomization or double blindness, the significance of the study, is it's prospective performance and the control group.

This is the first study that tested UBC Rapid in paralel to US.

Conclusion

The sensitivity of UBC Rapid Visual was similar to that of cytology, but the specifity was lower. The combination of US, cytology and UBC Rapid has high sensitivity to detect tumors of the bladder in patients at risk for bladder cancer. In patients with primary hematuria or dysuria, US and cytology might substitute diagnostic cystoscopy, if one of them is positive. In patients under surveillance following resection of a low-grade tumor, US and qualitative UBC Rapid, might be used instead of cystoscopy. The main advantage of UBC Rapid is that it is a non-invasive test, that is easily performed by doctors. If no tumor is found on US but the UBC Rapid is positive, the patient should undergo a diagnostic cystoscopy. Another advantage of the UBC Rapid is that it can be performed during the patient's visit at the doctor and the results can be obtained on the spot.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Barak V and Einarsson R –evaluation of results and their significance, paper preparation. Pode D and Gofrit O – Heads of Urology Department treating bladder cancer patients. Itzkovich D – student, performed UBC tests, statistics, table preparations and summaries for the paper.

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