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Bladder Cancer

UroVysion Compared with Cytology and Quantitative Cytology in the Surveillance of Non–Muscle-Invasive Bladder Cancer

Paula M.J. Moonen [a], *Gerard F.M. Merkx* [b], *Pim Peelen* [a], *Herbert F.M. Karthaus* [c], *Dominique F.C.M. Smeets* [b], *J. Alfred Witjes* [a,*]

[a] *Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands*
[b] *Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands*
[c] *Department of Urology, Canisius Wilhelmina Hospital, Nijmegen, Netherlands*

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Abstract

Objectives: The multitarget fluorescence in situ hybridization probe set Vysis UroVysion, consisting of probes for chromosomes 3, 7, and 17 and for the 9p21 band, was studied to evaluate its value in the follow-up of patients with bladder cancer. The results were compared with conventional cytology and quantitative cytology (Quanticyt). The aim of this study was to evaluate whether UroVysion is a better adjunct to urethrocystoscopy than cytology and quantitative cytology.

Methods: UroVysion, cytology, and quantitative cytology were performed on 113 voided urinary samples of 105 patients under surveillance for non–muscle-invasive bladder cancer. Before urethrocystoscopy or transurethral resection of the bladder, a voided urinary sample was obtained. Results of all tests were compared to evaluate the value of UroVysion.

Results: Sixty-four patients had biopsy-proven urothelial cell carcinoma. Sensitivity and specificity were, respectively, 39.1% and 89.7% for UroVysion, 40.6% and 89.7% for cytology, and 42.1% and 67.9% for quantitative cytology. When the UroVysion test and cytology were combined, sensitivity increased to 53.1%, but specificity decreased to 79.5%. Detection of Ta tumours was equal for cytology and UroVysion (26.7%), detection of T1 and T2–T4 samples by UroVysion was 60% and 50%, respectively. Detection of grade 1, 2, and 3 tumours by UroVysion was 21.4%, 36.8%, and 66.7%, respectively. In four cases the UroVysion test was positive, but no abnormalities were seen at cystoscopy.

Conclusions: Our data suggest that the use of UroVysion provides no improvement over cytology or quantitative cytology in the diagnosis of recurrent non–muscle-invasive bladder tumours.

* Corresponding author. Department of Urology, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Tel. +31 24 3616712; Fax: +31 24 3541031.
E-mail address: F.Witjes@uro.umcn.nl (J.A. Witjes).

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1. Introduction

The range of non–muscle-invasive bladder tumours covers low-, intermediate-, and high-risk tumours. The risk of recurrence or progression for individual patients within this range can be calculated by use of the European Organisation for Research and Treatment of Cancer risk tables [1]. In short, at one end of the spectrum, low-risk tumours are found. Although the mortality risk of these tumours is very small, the recurrence rate is relatively high. At the other end of the spectrum are the high-risk tumours, which also have a high recurrence rate and, even more important, a loss of differentiation, implying a high risk of progression to muscle-invasive disease. Therefore, surveillance is required for all non–muscle-invasive bladder tumours, with a minimum of 5 yr of follow-up for patients with a low-risk tumour and lifelong follow-up for patients with a high-risk tumour. The combination of cystoscopy with cytology is currently used for the surveillance of tumours in all different risk groups. During cystoscopy, papillary tumours are clearly seen, but the high-grade carcinoma in situ (CIS) lesions are readily missed. On the other hand cytology shows a high sensitivity for high-grade tumours, whereas tumours with a moderate or good differentiation are easily missed. Moreover, the results of cytology are not reliable in case of an infection or after intravesical therapy, and the test results are operator dependent. Two important aims in improving the surveillance of bladder cancer patients are (1) adding to the value of cystoscopy and cytology and (2) individualizing the patient's policy. Herewith, for example, the number of unnecessary cystoscopies in low-risk patients can be diminished. For several years urinary markers have been developed and studied for this purpose. In general their sensitivity is higher, compared with cytology, but at the cost of a decreased specificity caused by higher false-positive rates.

The multitarget fluorescence in situ hybridization (FISH) assay shows the enumeration of copies of (parts of) chromosomes in interphase. The multicolor FISH probes allow simultaneous targeting of chromosome 3, 7, and 17 and the 9p21 region in a single cell. Deletions within the short arm of chromosome 3 (3p) have been found in high-grade, muscle-invasive bladder cancer, and numerical abnormalities of chromosome 7 are the most sensitive marker for urothelial cancer detection [2]. The p53 tumour suppressor gene (TSG) was identified on chromosome 17; a mutation in this TSG is associated with higher malignancy grade and stage. Homozygous deletions of the p16 gene at 9p21 are one of the most common alterations in urothelial cell carcinoma and occur early in the development of bladder cancer [3]. The initial results of the FISH assay in the detection of bladder tumours were promising, and the test was approved by the Food and Drug Administration in 2001 for use in monitoring urothelial carcinoma for tumour recurrence. However, clinical implementation remains low, and a clear-cut selection of the patient group that benefits most from this assay remains indefinite.

Quantitative cytology is a method of cellular analysis proven to be superior to urine cytology for the identification of patients at risk for tumour recurrence and progression [4,5]. In short, quantitative cytology is an automated karyometric analysis that is used with a personal computer-based image analysis system. For each analyzed nucleus, the DNA content and the nuclear shape feature PASS are determined. On the basis of these features, patients are divided into risk groups for presence of tumour.

The aim of this study was to determine the value of the UroVysion assay for the patient group *under surveillance* for bladder cancer, and to compare it with conventional urine cytology and quantitative cytology.

2. Methods

Between March 2005 and April 2006, 113 voided urinary samples and bladder wash samples were obtained from 105 patients who provided informed consent. All patients had (a suspicion of) a bladder tumour. An overrepresentation of tumours was used to increase the number of positive samples at the time of collection. Urinary samples were used for routine cytologic examination, sediment, culture and FISH analysis. Quantitative cytology was performed on bladder wash samples [4]. The persons who performed the different tests were blinded to each other's result and to the pathology report. Clinical information was recorded and matched with the results of the tests. All resected tissue was examined by one uropathologist; staging and grading were done according to the TNM classification [6] and World Health Organization 1973 classification [7]. Imaging of the upper urinary tract was performed according to the European Association of Urology (EAU) guidelines. The influence of red blood cells and white blood cells in the sample was studied. Statistical analysis was performed using the Statistical Package for Social Sciences, release 12.0 (SPSS Inc, Chicago, IL, USA).

2.1. *UroVysion*

We used the Vysis UroVysion Bladder Cancer recurrence kit (Abbott laboratories Inc, Hoofddorp, The Netherlands) to perform FISH. In brief, urine samples were spun down (10 min at 1000 rpm) within 24 h from collection. The sample