

# The clinical value of urinary cytology: 12 years of experience with 615 patients

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## Abstract

**Aims**—To analyse the diagnostic value of cytological examination compared with histological findings in a large series of patients (n=615) with tumours of the urinary tract epithelium.

**Methods**—Cytological examinations (n=785) after bladder washing and exfoliative cytology were retrospectively compared and correlated with histological findings. In addition, 1527 bladder washings were obtained during follow up of patients after transurethral resection of bladder tumours.

**Results**—Cytology in bladder washings (overall diagnostic accuracy 66%) provides considerably more information than exfoliative cytology (overall accuracy 49%). Cytological examinations (n=1125) in patients with bladder tumours receiving intravesical cytostatic drugs (for example, mitomycin C) yielded suspicious or positive results in 28% of patients, without being confirmed by endoscopy during follow up.

**Conclusion**—Our results illustrate two major drawbacks of urinary cytology. First, a high rate of false positive results in patients on intravesical chemotherapy. Second, a high rate of false negative results in highly differentiated carcinomas, stressing the need for additional diagnostic tests such as staining with monoclonal antibodies directed against tumour antigens or assessment of ploidy.

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The two main target organs in urological cyto-diagnosis are the prostate and the organs of the urothelial tract because of the incidence of associated malignancies. Although the importance of prostate cytology lies in the primary diagnosis of prostate cancer, cytology of the urothelium is also an established tool in monitoring patients for the development of transitional cell cancer (TCC) after surgery. As early as 1856, Lambl<sup>1</sup> reported the presence of exfoliated tumour cells in the urine of a patient with bladder cancer. Since then, a large number of papers on the accuracy of cytology in TCC have been published, but with differing results.<sup>2-10</sup> The controversies concerning the diagnostic contribution of urinary cytology prompted us to compare, retrospectively, the cytological and clinical findings in a large number of patients with urothelial tract tumours.

Data from more than 600 patients who underwent cytological examination following pathological findings in the bladder and upper urinary tract were reviewed. Over 1200 follow up examinations were carried out to monitor these patients and to provide the clinical correlate to cytology. The results of 12 years of interdisciplinary cooperation between the Department of Urology and the Institute of Pathology at the University of Vienna Medical School permit a series of conclusions to be drawn about the usefulness and limitations of urinary cytology and also permit discussion of the possible clinical implications.

## Methods

### TRANSITIONAL CELL CANCER OF THE BLADDER

Cytology on voided urine (n=342) or bladder washings (n=376) from 548 patients with a total number of 718 TCCs was carried out. Cytological examinations (n=1269) were carried out on an outpatient basis during follow up after transurethral resection or laser surgery for TCC and compared with endoscopic findings.

Cytology specimens were always obtained before surgery or endoscopy. Cytological assessment was performed by different investigators and always without knowledge of histology or endoscopy. Cytology reports were classified as positive, suspicious, negative, or unsuitable for diagnosis. Histology was performed according to World Health Organisation and UICC criteria.

Fifty microlitres of fresh, voided urine were fixed with an equal amount of 50% propyl alcohol. Three specimens were obtained on three consecutive days. After catheterisation and before endoscopy, bladders were washed out with 50 ml physiological saline solution, and the irrigation fluid was aspirated three times and diluted with an equal amount of 50% propyl alcohol.

### TRANSITIONAL CELL CANCER OF THE UPPER URINARY TRACT

Cytology was compared with clinical findings in 67 patients with TCC of the upper urinary tract. The cytological and histological criteria were the same as those for TCC of the bladder. As with TCC of the bladder, voided urine (n=31) was examined after fixation with 50% propyl alcohol on three consecutive days. Irrigation fluid was examined in 36 patients. A urethric catheter was placed with its tip in close proximity to the suspicious lesion, as diagnosed by retrograde pyelography, and 5-10 ml of NaCl were instilled. Irrigation fluid

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**Table 1** Comparison of bladder wash cytology and histological findings in 361 bladder tumours

Cytology	Histology		
	Grade 1	Grade 2	Grade 3
Negative	48%	12%	1%
Suspicious	23%	11%	7%
Positive	29%	77%	92%

**Table 2** Comparison of exfoliative cytology and histological findings in 361 bladder tumours

Cytology	Histology		
	Grade 1	Grade 2	Grade 3
Negative	79%	24%	4%
Suspicious	14%	20%	14%
Positive	7%	56%	82%

was collected by aspiration and diluted with an equal amount of 50% propyl alcohol.

**Results**

Of the 718 urine specimens from patients with TCC of the bladder, 682 (95%) could be used for cytological evaluation (94% of voided specimens, 97% of bladder washings). During follow up, 1557 smears were prepared and 1527 (98%) were suitable for cytological assessment.

Our findings demonstrate that the diagnostic accuracy of cytology of bladder washings (table 1) was noticeably greater than the accuracy of

exfoliative cytology (table 2) using voided urine. However, and irrespective of how the specimen was obtained, the accuracy of cytology was hampered by a low detection rate of grade 1 lesions using cytology alone. Moreover, the accuracy not only depends on the degree of malignancy, but also the depth of invasion (tables 3 and 4). The latter observation was basically drawn from our results in grade 2 lesions, given the known difficulties in diagnosing grade 1 tumours and the relative low number of grade 3 tumours in our series.

A negative result on cytology, corresponding to a negative endoscopy result, was obtained in 84% of the 1243 follow up examinations. Cytology during postoperative monitoring was evaluated according to whether patients received metaphylactic cytostatic treatment. In our series patients with recurrent superficial (Ta and T1) lesions received 20 mg mitomycin C every two weeks for six months, then monthly for another 18 months. The results are as follows:

Agreement between negative endoscopy and negative cytology results (table 5) was noticeably higher in patients without (402 examinations) than in patients with metaphylaxis (1125 examinations). Of the unsuspecting endoscopic findings in patients taking mitomycin C, 28% exhibited suspicious or positive cytology (table 6).

Positive results on cytology prompted us to perform bladder mapping (six biopsy specimens in women and seven in men) in 31 patients to search for an endoscopically undetectable lesion. Although dysplasia was present in 35%, unequivocal evidence of malignancy was not found. No further invasive procedures were carried out, and all patients remained clinically and endoscopically free of recurrence for at least 12 months.

Following cytology of voided urine specimens, 33% (11 of 31) of TCCs of the upper urinary tract were diagnosed (table 7). Stratified by tumour grade, 64% (nine of 14) of all grade 3 carcinomas were detected. By contrast, cytology of bladder washings was successful in diagnosing 66% (24 of 36) of all carcinomas, including 81% (13 of 16) of all grade 3 lesions (table 8).

**Table 3** Comparison of bladder wash cytology and tumour stage in 151 grade 2 bladder tumours

Cytology	Histology	
	Non-invasive (<pT1)	Invasive (>pT2)
Negative	12%	6%
Suspicious	21%	5%
Positive	67%	89%

**Table 4** Comparison of exfoliative cytology and tumour stage in 151 grade 2 bladder tumours

Cytology	Histology	
	Non-invasive (≤pT1)	Invasive (≥pT2)
Negative	35%	15%
Suspicious	19%	21%
Positive	64%	64%

**Table 5** Comparison of exfoliative cytology and endoscopy in 402 examinations during follow up (without metaphylaxis)

Cytology	Endoscopy	
	Negative	Positive
Negative	89%	13%
Suspicious	6%	8%
Positive	5%	79%

**Table 6** Comparison of bladder wash cytology and endoscopy in 1125 examinations during follow up (with metaphylaxis)

Cytology	Endoscopy	
	Negative	Positive
Negative	72%	17%
Suspicious	15%	5%
Positive	13%	78%

**Table 7** Comparison of exfoliative cytology and histological findings in 31 tumours of the upper urinary tract

Cytology	Histology		
	Grade 1	Grade 2	Grade 3
Negative	4	2	2
Suspicious	4	4	3
Positive	–	2	9

**Table 8** Comparison of bladder wash cytology and histological findings in 36 tumours of the upper urinary tract

Cytology	Histology		
	Grade 1	Grade 2	Grade 3
Negative	5	–	–
Suspicious	2	2	3
Positive	3	8	13

### Discussion

In our experience cytology using bladder washings or irrigation fluid has improved the accuracy of an established diagnostic tool. Besides endoscopic and histopathological evaluation, cytology remains one of the cornerstones of bladder cancer evaluation. However, our data from 615 patients confirm several observations that have been reported previously. Cytology suffers from low detection rates in highly differentiated TCC, reported to range from 28 to 44%.<sup>11-13</sup> Promising results in the search for modalities that may complement cytology in low grade tumours were achieved using monoclonal antibodies<sup>14</sup> or analysis of DNA (Simak *et al*, 1994, unpublished data).<sup>15-17</sup> Therefore, it is essential that biological markers are tested against conventional cytology, in both retrospective and prospective analyses.

The clinical value of cytology for primary diagnosis is limited and may benefit only a small number of patients. In this study cytology provided additional clinical information only in patients where there happened to be a discrepancy between the histological grade of malignancy and the grade of differentiation as diagnosed by cytology. Controversial findings like this may be because of the presence of an endoscopically undetectable additional lesion, such as carcinoma in situ. However, less than 3% of our patients presented with highly discrepant histology and cytology findings. This low rate in our series is as difficult to explain as the high incidence of primary carcinoma in situ (that is, few exophytic bladder tumours) in other publications. Observer dependent variability in pathological reports and cytological findings may contribute to these different rates.

The low rate of concomitant carcinoma in situ or severe dysplasia in our series has been reported previously.<sup>18</sup> Ninety patients with a history of superficial TCC underwent primary bladder mapping. Biopsy specimens were taken from healthy looking urothelium. However, dysplastic changes were found in 25% of patients and severe dysplasia in 9% without a clinical or pathological correlate during follow up. Hence, routine mapping in all patients with TCC with endoscopically normal urothelium was abandoned. Since then, only patients with discrepant histology and cytology grades were scheduled for bladder mapping. Histology in this restricted number of patients was always negative.

The situation was quite different in patients undergoing intravesical metaphylactic treatment with cytostatic drugs following transurethral tumour resection. Of the patients without endoscopic evidence of a neoplastic lesion, 28% presented with positive or at least suspicious cytology. Multiple biopsies, repeatedly carried out in 21 patients, consistently failed to confirm the presence of neoplasia. As urothelial changes were always classified as toxic drug effects, bladder mapping in these patients was also abandoned. Alkylating agents such as mitomycin C induce urothelial changes mimicking carcinomas on cytology,<sup>19</sup> although corresponding histologically to dysplasia. Given the frequency of dysplasia, cytology

alone during cytostatic treatment permits only limited conclusions to be drawn with regard to biological activity or aggressiveness of the primary tumour in a large number of patients. Our figures indicate that only clear cut malignant cells should be taken into account, whereas atypical or dysplastic changes should be interpreted with caution. Moreover, the recurrence free interval in patients taking mitomycin C was significantly longer than that in untreated patients,<sup>20</sup> emphasising the low predictive value of dysplasia in these patients.

Biopsy specimens from endoscopically normal urothelium should only be taken for primary diagnosis if cytology gives a higher degree of malignancy than histology—that is, biopsies are indicated only in the presence of suspicious endoscopic lesions. During follow up, even a positive cytology result in patients taking cytostatic drugs should not indicate immediate mapping but rather short term control.

Close cooperation between urologists and pathologists is essential. The diagnostic value of a cytology result is greater when more clinical information is given to the pathologist and standardised protocols are used for the collection and preparation of urine specimens. Finally, cytologic evaluation of bladder washings or irrigation fluid has consistently given superior results than voided urine specimens, as more and better preserved cells are made available for diagnosis.

### Prospects

The use of monoclonal antibodies represents an important enrichment of diagnostic possibilities, enabling the diagnosis of urothelial tumour cells irrespective of their grade of differentiation. Reliable diagnostic parameters are needed mainly in the diagnosis of highly differentiated lesions, known to be extremely difficult to recognise with a light microscope. A non-invasive diagnostic tool such as monoclonal antibodies may ultimately become the mainstay for monitoring patients with TCC permitting a reduction in the number of endoscopies required during follow up. The promising results that have been achieved with several monoclonal antibodies<sup>14</sup> emphasise the need for large scale prospective studies.

Likewise, DNA analysis and assessment of ploidy have been successful for detecting nuclear cell alterations associated with malignant transformation.<sup>21</sup> In our experience single cell cytophotometry has been shown to be superior to flow cytometry when cytology specimens were used. Even bladder lavage or barbotage often produce only scanty samples, and intravesical application of alkylating drugs, such as mitomycin, may further reduce the number of evaluable cells.<sup>22,23</sup> Although flow cytometry has proven to be a valid tool in the evaluation of aneuploidy in solid lesions—that is, histology specimens, single cell cytophotometry does not require a large number of cells (Simak *et al*, 1994, unpublished data). As for monoclonal antibodies, the main advantage of ploidy assessment would be that it is non-invasive.

In conclusion, and given the known polyclonality of TCC,<sup>24</sup> further research should assess whether therapeutic regimens can be adapted to individual risk profiles, based on objective and reproducible criteria such as immunoreactivity to monoclonal antibodies or DNA histograms.

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