PATHOLOGY ONCOLOGY RESEARCH
Vol 3, No 1, 1997

Science Press Publishing Ltd. TUDOMÁNY KIADÓ

ARTICLE

Changing Pattern of Bladder Cancer Cytology

(Haynal Imre University Experience)

Ferenc KISS,[1] Ferenc SALAMON,[1] József RÓZSAHEGYI[2]

[1]Institute of Pathological Anatomy, [2]Department of Urology, Haynal Imre University of Health Sciences, Budapest

Urinary cytology reports of 151 patients with histologically verified tumors from the periods 1981-1985 and 1991-1995 were analyzed. No significant change in the overall sensitivity of tumor detection (76% and 76.8%, respectively) was found. In the group of well-differentiated (G0-G1) tumors, however, 60% of the more recent cases were cytologically positive or suspicious, 23% more than ten years ago. A decrease in the detection rate of G2 tumors in the last period (72% versus 89%) was probably caused by false negative reports due to frequent inflammatory changes in the specimens. Poorly differentiated (G3-G4) transitional cell tumors resulted in a high rate of positive cytological diagnoses (93% in both periods). In cases with negative cytology at clinical suspicion of tumor, repeated sampling increased the detection rate of G0-G1 lesions from 53% up to 60%. Optimal sampling and preparation technique, cytopathologists training and improved follow-up of patients are preconditions of sensitive and specific urinary cytology. (Pathology Oncology Research Vol 3, No1, 47–50, 1997)

Key words: urinary cytology, sensitivity, transitional cell neoplasms

Introduction

Urinary oncocytology became a generally accepted investigation in Hungary only in the last few decades.[15] The main cause of aversion to this non-invasive, relatively inexpensive method was a limited overall sensitivity at detection of transitional cell tumors.

Limitation of sensitivity is primarily due to the cytomorphological characteristics of transitional cell tumors. Well-differentiated papillary neoplasms (G0-G1) often exfoliate cells in the urine, which lack distinctive signs of atypia, at least at the routine microscopic investigation. On the other hand, severe inflammatory change, bleeding or necrosis accompanying bladder neoplasms may result in false negative cytology reports. Apart from these features, urinary cytology is an accurate indicator of urinary tract tumors, especially of poorly differentiated forms, invasive neoplasms, and carcinoma in situ.[10]

Received: Sept. 15, 1996, accepted: Nov. 22, 1996

Correspondence: Ferenc KISS, MD; 2nd Institute of Pathology, Semmelweis University of Medicine; Üllői út 93, H-1091 Budapest, Hungary. Tel: (36) (1) 215 7300, Fax: (36) (1) 215 6921, E-mail: kf@korb2.sote.hu

Therefore, the method represents an acknowledged tool in the complex diagnostics of urothelial tumors. Retrospective analysis of the cytological reports in comparison with histology may serve as quality control. In order to find patterns of failure, we decided to analyse data from two five-year periods at our institution.

Material and methods

During the time interval 1981-1985, 370 urine samples from a total of 223 patients were cytologically investigated at our department. An additional series of 745 cytological specimens from 512 patients were evaluated in a second period, 1991-1995. Samples of voided urine were prepared by conventional cytocentrifugation and Giemsa staining. In the most recent period, Papanicolaou-stained specimens were also available.

87 patients out of the first series and 86 out of the second series had comparable pretreatment cytological and histological reports. 67 patients from 1981-1985 and 84 from 1991-1995 had histologically verified transitional cell tumors. All but three of these tumors were located in the bladder, including two cases of primary carcinoma in situ. Two urothelial tumors of the renal pelvis and one pap-

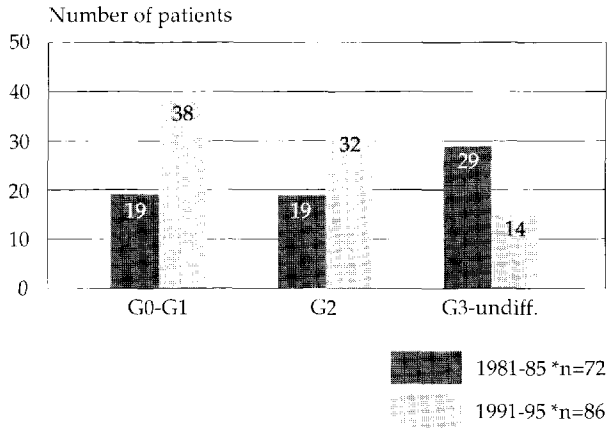

Figure 1. Frequency distribution of transitional cell tumors according to histologic grades.

illary carcinoma of the ureter were those observed outside the bladder.

Transitional cell neoplasms were categorized into well-differentiated (G0 and G1), intermediately differentiated (G2), and poorly-differentiated (G3 and G4/undifferentiated) groups. Cytological reports included negative (not suspicious of tumor), suspicious (atypical cells, suggesting neoplastic lesion), and positive diagnoses (cytological evidence of tumor). For statistical evaluation, "suspicious" reports were considered together with the positive ones, both for sensitivity and specificity computing.

The sensitivity of cytology at tumor detection was obtained by dividing the number of positive cytology reports by the number of all patients with positive histology. Sensitivity was indicated as an overall figure for all patients in each period, and for each histologic grade, as well. The specificity of the method was expressed as the quotient of cases with negative cytology against all histologically negative cases.

Tumors with positive urinary cytology other than transitional cell neoplasms included 5 cases of renal cell carcinoma, and 1 case of secondary adenocarcinoma (colon cancer with propagation to the bladder). These neoplasms were excluded from the statistical analysis.

Results

The distribution of transitional cell tumors by histological grades is depicted in *Fig.1*. In the period 1991-1995, the frequency of well-differentiated (G0 and G1) tumors in our material was twice as high as 10 years earlier. The number of neoplasms with intermediate differentiation (G2) has also increased in the latest years. Poorly differentiated carcinomas, in contrast, showed a substantial decrease both in number and proportion.

Statistical evaluation considering positive and false negative cytology reports showed a practically unchanged overall sensitivity (76%, 1981-1985; 76.8%, 1991-1995) (*Fig.2*). In the group of well-differentiated neoplasms (G0 and G1), however, the sensitivity of the method increased to 60.1%, which was 23.1% higher than in the earlier period. Carcinomas of intermediate differentiation (G2) could be detected at a 72% sensitivity in the more recent years. This latter figure was 17% lower than the corresponding value in the years 1981-1985. In the group of poorly differentiated carcinomas (G3 and G4/undifferentiated), we found a 93% sensitivity in both series.

The impact of repeated sampling on the cytologic detection of tumors could be evaluated only for the 1991-1995 series (*Table 1*) since in the earlier files there were only sporadic cases with repeated cytology. According to the available data, a 7% increase in cytological sensitivity could be achieved by repated sampling at well-differentiated (G0-G1) urothelial tumors.

***Table 1.* Impact of repeated sampling on the sensitivity of urinary cytology**

	G0-G1	G2	G3
First cytology	53%	70%	91%
Second cytology	60%	71%	93%
Third cytology	60%	72%	93%

The overall specificity of urinary cytology could not be reliably ascertained for the time period 1981-1985, since 3 patients with positive and 7 patients with suspicious reports were lost follow-up. For the more recent series, we have found an 86% specificity, which includes 4 false positive cases (3 suspicious and 1 positive report).

Discussion

Analysis of our performance in cytologic detection of bladder tumors showed an equal 76% overall sensitivity in the earlier and the more recent years. The frequency of low

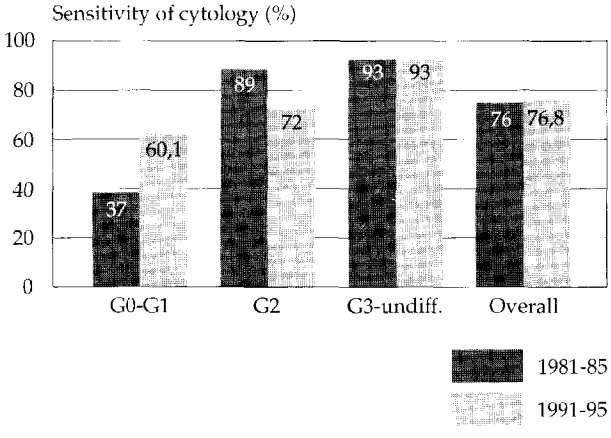

Figure 2. Sensitivity of urinary cytology (%), 1981-1985 versus 1991-1995.

grade tumors in our material, however, doubled for the period 1991-1995, with a simultaneous decrease in poorly differentiated carcinoma cases. The last feature may point to a pattern change in the diagnostic evaluation.

Sensitivity is a crucial point for oncocytological investigations, since early detection of tumors is generally associated with favorable prognosis. The overall sensitivity of urinary cytology, however, reflects dissimilar morphological characteristics of two groups of transitional cell tumors.[8]

The cells of well-differentiated papillary tumors (G0-G1) often display only slight cytological atypia, so they are mostly indistinguishable from normal urothelial cells. Light microscopic recognition of such lesions may be facilitated by the presence of characteristic (although not specific)[1] cell clusters (*Fig.3*). Reported figures of cytological tumor detection rate in this group range from 0 to

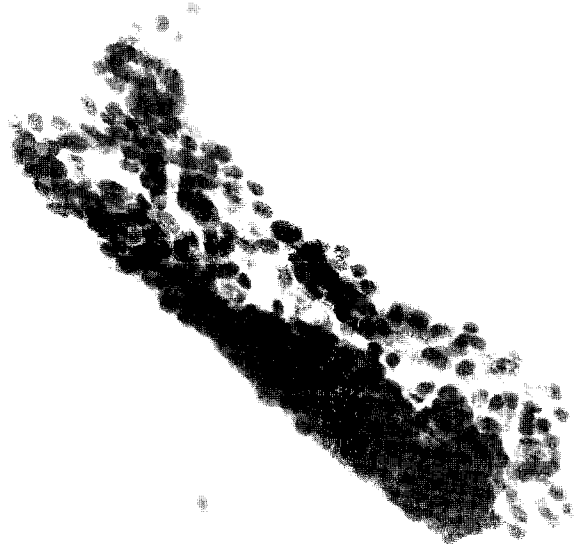

Figure 3. *Cluster of cells suggesting papillary urothelial tumor from urinary cytology. Papanicolaou, 400x*

86%.[13,14] Our finding of improved sensitivity to such tumors in the last few years may be explained by the introduction of Papanicolaou staining, as well as by our growing experience with these tumors. Although the great majority of these neoplasms are not invasive (stage Ta),[10] early detection may contribute to successful treatment or at least prevent early appearance of recidives.

Urothelial tumors of intermediate and poor differentiation (G2, G3 and G4/undifferentiated), on the other hand, display considerable atypia and cellular polymorphism. In a series by Koss,[8] the sensitivity of cytology was 71% with G2 tumors, 94% with G3 tumors, and 100% with non-papillary carcinoma in situ.

A decrease in sensitivity of cytology at G2 tumors in the recent files was an unexpected feature of our study. A review of the corresponding specimens revealed that in the false-negative cases, a high amount of inflammatory cells, with reactive and degenerative urothelial cells were almost invariably present. These features were infrequent in the 1981-1985 files. We conclude that, beyond technical problems,[5] cytologic underdiagnoses due to misinterpretation of cells with abnormal cytology have probably caused the failures.

These findings urges us to check the processing technique (very cell-rich sediments should be diluted appropriately). Anti-inflammatory treatment may help to obtain specimens with less disturbing "background" cells. The diagnostitian should not underestimate cytological atypia in voided urine specimens, when inflammatory changes (other than those with viral infection or after BCG treatment) are present. At the investigation of separated urine from the pyelon, however, a higher frequency of "suspicious" cell clusters due to instrumentation artifact is expected.[7,8]

An advantage of urinary cytology is easily repeatable sampling. Thus, a number of urothelial tumors with initially negative cytology can be detected in subsequent specimens[4]. In our relatively small series, an increase of sensitivity by 7% occured with the second sampling, in the category of well-differentiated papillary tumors.

We believe that more frequent and systematic application of repeated urine sampling would further improve the efficacy of cytologic tumor detection in our area. The calculated specificity of our cytology reports was 86%. This figure may point to a relatively low diagnostic accuracy, when compared to the 88%-100% specificity values, as indicated in the literature.[8,9] As a matter of fact, this value was obtained with only a few false positive reports, out of a limited number of histologically negative cases. Considering that there were more than a hundred (!) negative samples without histologic control, but with no clinical evidence of tumor in both analyzed periods, we assume that a higher number of biopsies in these cases would have resulted in a higher specificity. We found no tumors of the upper urinary tract with initially "false positive" cytology. The possible influence of concomitant urothelial atypia[6] on false positive reports could not be specified because systematic biopsy mapping has not been done for all cases.

Posttreatment cytologic specimens after BCG, chemotherapy and irradiation were not included in the statistical evaluation because the number of them was too low for a comparison. According to Wiener et al[16] a considerable decrease in the diagnostic accuracy of cytology after such treatments is to be expected. In conclusion, our findings suggest that urinary cytology remains a valuable tool in the detection of urinary bladder cancer. Its simplicity, low cost and non-invasive nature should be emphasized. In some instances, cytology may disclose otherwise undetected tumors, even in the new era of flow cytome-

try and specific bladder carcinoma antigens.[2,3,12] In order to improve diagnostic accuracy, careful sampling, standardized preparation technique, continuing training of cytologists and improved follow-up of the patients are all necessary.[11]

Acknowledgement

The authors wish to thank Professor Attila Bajtai, M. D., Ph.D. (present address: Uzsoki County Hospital, Budapest) for his contribution of and valuable instructions on the 1981-85 cytological study.

References

1. *Andrion A and Boffetta P:* Diagnostic criteria and terminology in urinary cytology. Cytopathology 5:62-63, 1994.
2. *Billerey C, Lamy B, Bittard H, et al:* Flow cytometry versus urinary cytology in the diagnosis and follow-up of bladder tumors: critical review of a 5-year experience. World J Urol 11:156-160, 1993.
3. *Chow NH, Tzai TS, Cheng HL, et al:* Urinary cytodiagnosis: can it have a different prognostic implication than a diagnostic test? Urol Int 53:18-23, 1994.
4. *Farrow GM:* Urine cytology in the detection of bladder cancer: A critical approach. J Occup Med 32:817-821, 1990.
5. *Gamarra MC and Zein T:* Cytologic spectrum of bladder cancer. Urology 23 (Suppl): 23-26, 1984.
6. *Harving N, Petersen SE, Melsen F and Wolf H:* Urinary cytology in the detection of bladder tumorus. Influence of concomitant urothelial atypia. Scand J Urol Nephrol Suppl. 125:127-131, 1989.
7. *Kannan V and Bose S:* Low grade transitional cell carcinoma and instrument artifact. A challenge in urinary cytology. Acta Cytol 37:899-902, 1993.
8. *Koss LG:* Diagnostic cytology of the urinary tract.Lippincott-Raven Publishers, Philadelphia, New York, 1996. pp. 124-148.
9. *Mondal A and Banerjee DK:* The reliability of urinary cytology in the detection of tumours of urinary bladder. J Indian Med Assoc 90:265-267, 1992.
10. *Murphy WM:* Current status of urinary cytology in the evaluation of bladder neoplasms. Hum Pathol 21:886-896, 1990.
11. *Nielsen KT, Lund L, Mommsen S and Olesen S:* How do we follow patients with Ta grade I-III bladder tumors in Denmark? Scand J Urol Nephrol Suppl 172:27-31, 1995.
12. *Pu YS, Tsai TC, Hsieh TS, et al:* Role of urinary cytology and urinary deoxyribonucleic acid flow cytometry in the diagnosis of bladder cancer. J Formos Med Assoc 93:216-221, 1994.
13. *Schoonees R, Gamarra M, Moore R and Murphy G:* The diagnostic value of urinary cytology in patients with bladder carcinoma. J Urol 106:693-696, 1971.
14. *Shenoy UA, Colby TV and Schumann GB:* Reliability of urinary cytodiagnosis in urothelial neoplasms. Cancer 56:2041-2045, 1985.
15. *Törzsök F, Koór S and Erényi Á:* Exfoliative cytological examination of the urinary tract by membrane filter technic (in Hungarian). Orv. Hetil. 147:1807-1812, 1986.
16. *Wiener HG, Vooijs GP and van't Hof-Grootenboer B:* Accuracy of urinary cytology in the diagnosis of primary and recurrent bladder cancer. Acta Cytol 37:163-169, 1993.