

# Grading of Transitional Cell Tumours of the Urinary Tract by Urinary Cytology

H. Rübben, J. Bubenzner, K. Bökenkamp, W. Lutzeyer and P. Rathert

Departments of Urology and Pathology of the Rhineland-Westphalian Technical Highschool, Aachen, Federal Republic of Germany

Accepted: August 5, 1978

**Summary.** 1122 cytological diagnoses have been made on 2500 Papanicolaou stained cytological slides from Patients with urothelial carcinomas. The cytological accuracy was 78% for G1 tumours, 94% for G2 and 96% for G3 carcinomas. A histologically diagnosed G1 carcinoma was cytologically G1 in 81% of cases, a G2 carcinoma was recognized in 64% and G3 carcinoma in 48%.

**Key words:** Bladder Carcinoma, Urinary Cytology.

The prognosis of patients with urinary tract tumours depends primarily on the depth of infiltration (stage) and the grade of differentiation of the tumour (grade). This is reflected by the three year survival rate: The percentage of patients dying from the disease increases with increasing depth of invasion and the grade of dedifferentiation. The well differentiated, exophytic, non-invasive urothelial carcinomas have the best prognosis, whereas patients with deeply invasive, moderately well differentiated to poorly differentiated tumours survive three years in less than 30% of the cases (Fig. 1).

The staging procedure includes histological investigation of biopsy material, diagnostic TUR or staging operation, and most important of all, bimanual palpation under general anaesthesia, pelvic angiography, computed tomography or serial cystograms are less useful methods. The grading is assessed on pre-treatment biopsy tissue. A correct histological grading is possible in 95% of cases (5).

The importance of exfoliative cytology in the primary diagnosis of tumours of the upper urinary tract and in the postoperative follow up of patients with urinary bladder tumours has been shown many times (6, 18, 26, 34, 36). The diagnostic accuracy in detecting urothelial carcinomas ranges from 70 to 85% (7, 24). Since it is generally possible to diagnose the grade of dedifferentiation of a tumour from small groups of exfoliated cells, cytology seems to be a good method for grading urothelial tumours.

The value of cytological grading of approximately 600 urinary tract tumours has been investigated in comparison with the histological findings.

## MATERIALS AND METHODS

596 transitional cell tumours of the urinary tract of 247 patients treated between 1969 and 1977 have been investigated retrospectively. The cy-

	G	1	2	3
T				
A		97	90	-
1		92	75	57
2		-	53	27
3		-	28	5
4		-	-	9

N = 346

Fig. 1. Percentage three years survival of urothelial bladder tumours in relation to depth of invasion (T) and grade of dedifferentiation (G) according to the UICC and WHO. Benign Papillomas: 100% (11 cases)

Table 1. Histological (H) and Cytological (C) criteria for evaluation of the grade of dedifferentiation

	H/C	Normal finding Papilloma	G1	G2	G3
<u>1. Growth pattern</u>					
Ramification of papillae	H	-	+	++	+++
Cell layer 6	H	-	+	+	+
Flattening of superficial cell layer	H	-	+	++	+++
Loss of polarisation and orientation	H	-	(+)	++	+++
Solid growth	H	-	-	(+)	+++
Tumour necrosis	H	-	-	-	+
<u>2. Cell structure</u>					
Increase in size	H/C	-	(+)	+	++
Anisocytosis	H/C	-	(+)	++	+++
Loss of cell borders	H	-	(+)	++	+
Increase in nuclear cytoplasmic ratio	H/C	-	(+)	++	+++
<u>3. Nuclear abnormalities</u>					
Loss of transparency	C	-	++	++	++
Anisocaryosis	H/C	-	(+)	++	+++
Hyperchromasia	H/C	-	(+)	++	+++
Coarse chromatin	H/C	-	+	++	+++
Increase in size and number of nucleoli	H/C	-	-	++	+++
Number of mitoses	H/C	-	(+)	++	+++
Atypical mitoses	H/C	-	-	+	++
Infoldings and irregularity of nuclear membrane	H/C	-	(+)	+	+
<u>4. Cytoplasm: non specific</u>					
<u>5. Urinary sediment: non specific</u>					

tological and histological slides have been re-classified without prior knowledge of the previous diagnosis and clinical data. The diagnostic criteria employed were those proposed by the UICC in 1978 (29) and WHO in 1973 (35).

The following diagnostic scheme was used:

1. Normal findings (Pap. I and II.)
2. Atypia with suspicion of malignancy but without proof, grading not possible (Pap. III)
3. Tumour cells, grading possible (Pap. IV. and V.)

G1: well differentiated

G2: moderately well differentiated

G3: poorly differentiated

Anaplastic tumours, squamous cell carcinomas, adenocarcinomas and non epithelial tumours have been excluded from this study. The cytological

specimens have been stained after fixation in 50% alcohol according to Papanicolaou (20, 21, 32).

The diagnostic criteria of the cytological and histological grade of differentiation are shown in Table 1 and are demonstrated in a series of pictures.

## RESULTS

596 tumours from 247 patients have been investigated with 1278 cytological specimens. Two slides were prepared in each case. The results are shown in Fig. 6a. In 376 cases the diagnosis "urothelial carcinoma" was made, in 62 cases the suspicion of malignancy was expressed (Pap.

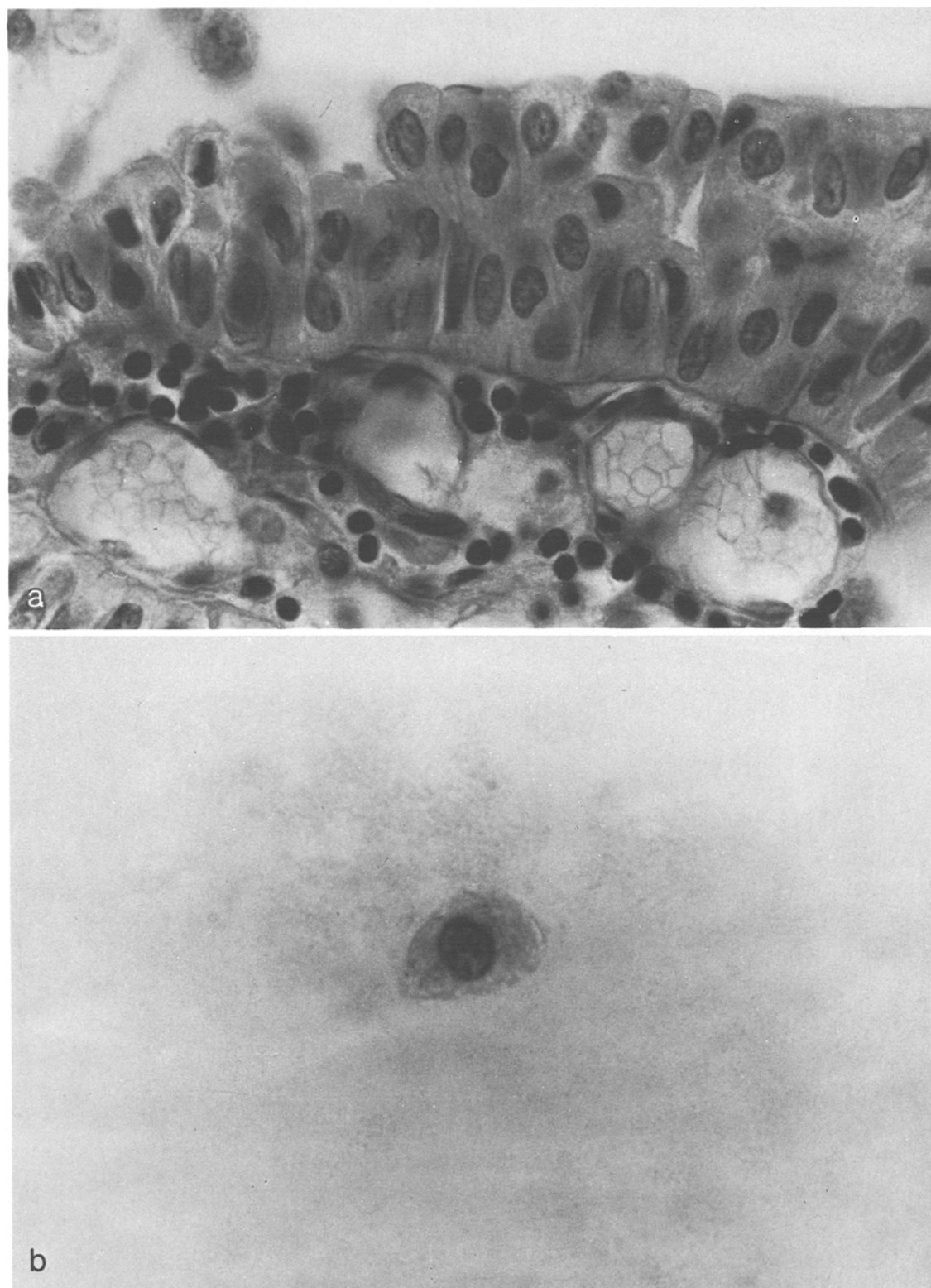


Fig. 2. a Benign Papilloma (GO) 360 X. b Normal urothelial cell 540 X

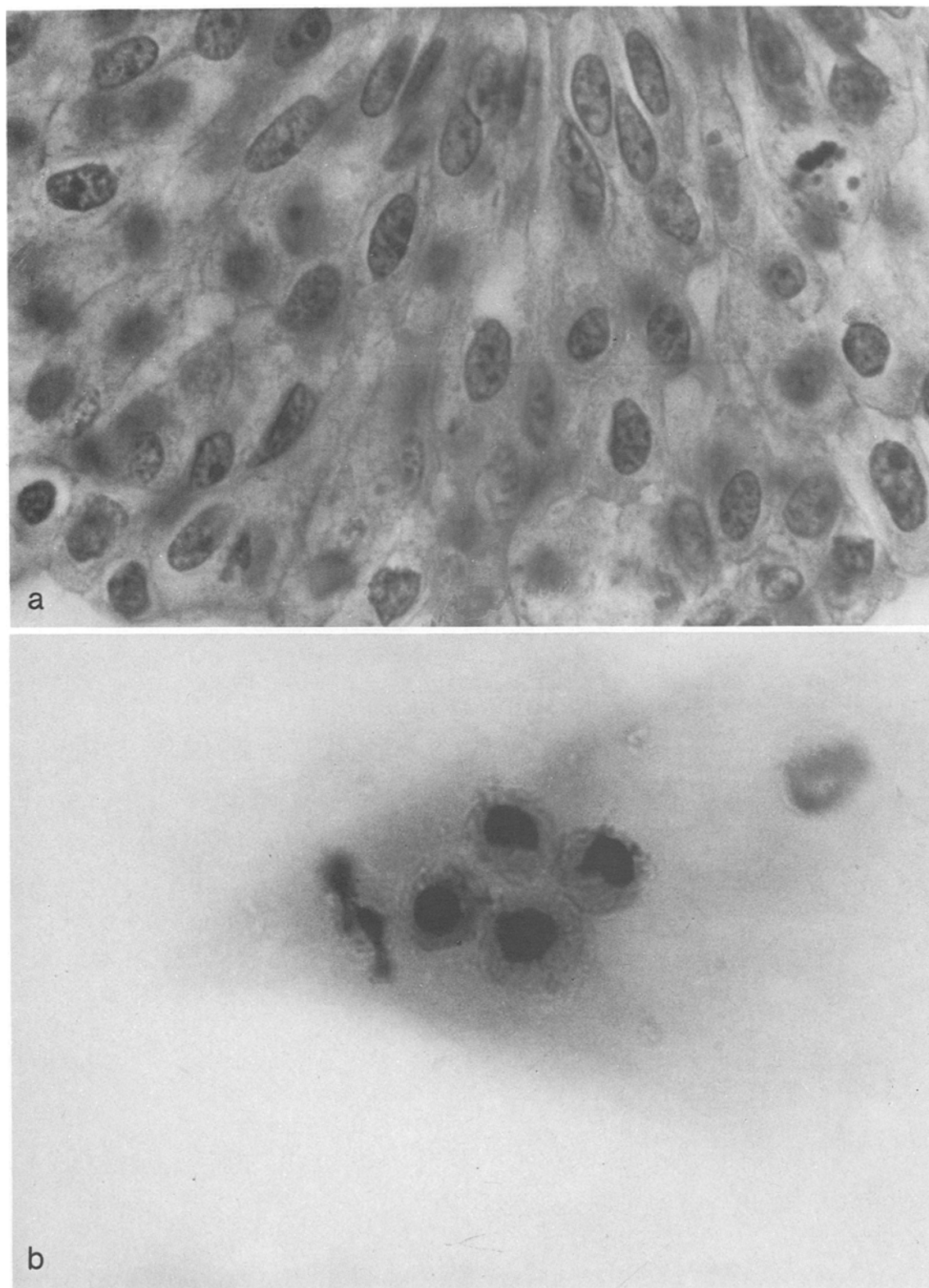


Fig. 3. a Transitional cell carcinoma G1 540 X. b Transitional cell carcinoma G1 540 X

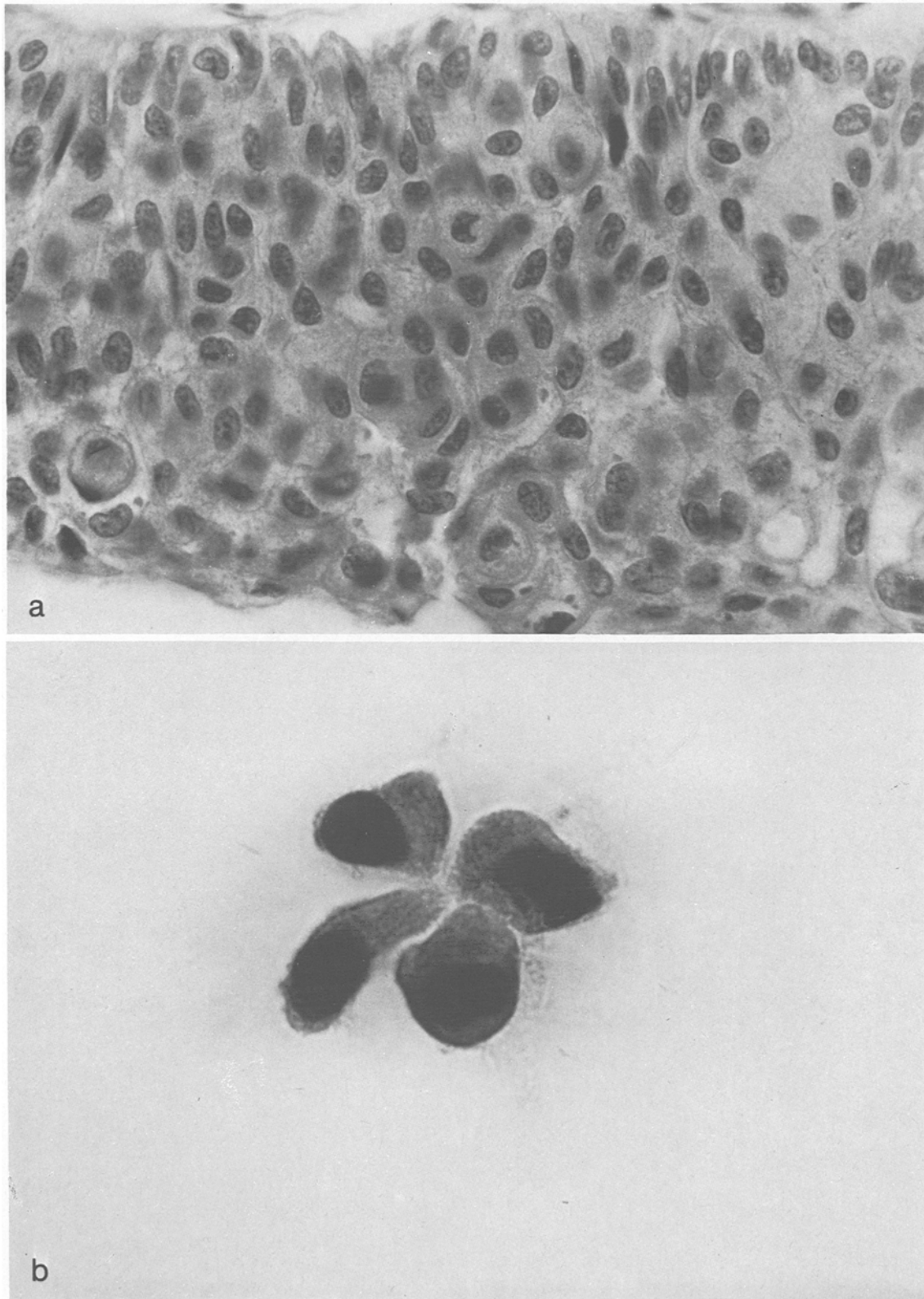


Fig. 4. a Transitional cell carcinoma G2 360 X. b Transitional cell carcinoma G2 540 X

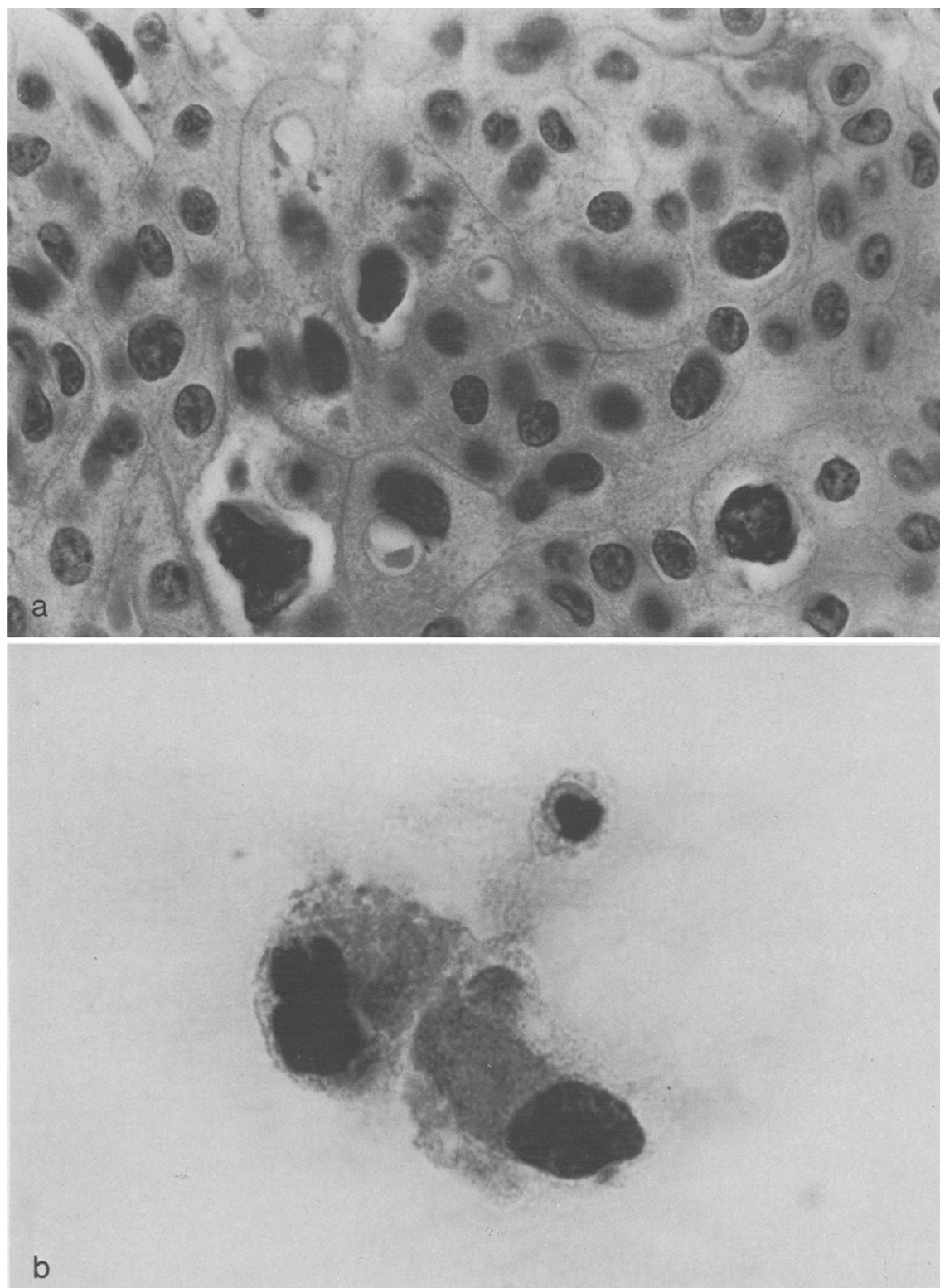


Fig. 5. a Transitional cell carcinoma G3 360 X. b Transitional cell carcinoma G3 540 X

III). 15 diagnoses were proven false positive (4%) 3 of these cases were histologically benign papillomas (GO).

In 47 cases no histological material was available. The diagnostic accuracy ranges between 75% and 90%. If the Pap III diagnoses are included, the accuracy is between 84 and 96%.

In the postoperative follow up of the tumour patients 684 cytological specimens were classified as negative. In 13 cases (2%) tumours diagnosed histologically had not been diagnosed cytologically. The cytological accuracy ranges from 89% to 97% (Fig. 6b).

## DISCUSSION

Exfoliative urinary cytology has been carried out in our clinic since 1965 in the postoperative follow up of patients (24) with epithelial tumours of the urinary tract (14, 23, 27).

The accuracy of cytological diagnosis is 70-85%. Tyrkkö, in a recent review study, including results of 24 investigators, reports an average of 67,7% correct positive diagnosis in 1819 cases. In addition in 9,3% the suspicion of malignancy was expressed. Tyrkkö refers to 9 authors regarding the possibility of recognising cytologically benign papillomas with an accuracy of from 0 to 50%. This reflects not only a different evaluation of the cytological findings but also the different histological nomenclature used, which makes the comparison of cytological findings impossible. According to Broders (1922) 3% of urothelial tumours were classified as benign (4); Franksson's (1950) classification designates 30 - 40% as benign papillomas (9) and Bergkvist (1965) gives a percentage of 21% benign papillomas (2).

Without judging the quality of the different classifications, there is no question that, for diagnostic and therapeutic purposes, a single classification should be used. The combination of the two classifications of the UICC (1978) and the WHO (1973) seems to be at the present time the most useful form to describe the neoplastic diseases of the urinary tract, not only because they are known world wide but also since they offer the possibility to document staging, grading and mode of spread. In addition they cover precancerous stages and non neoplastic abnormalities (29, 35). The cytological accuracy ranges from 78 to 96% for positive findings in cytoscopically proven tumours and from 89 to 98% in the postoperative follow up of tumour free patients. The range of spread is explained by cytological findings without histological correlation.

When excluding these cases the accuracy for

	a			
	Positive	Negative	PAP3	Technically inadequate
Correct	314	596	23	156
False	15	13	10	
Without correlate	47	54	29	
	376	684	62	156

b				
Cytol. findings	False	Without correlate	PAP III	Correct
Positive %	4	12	6	78-90
Negative %	2	8	1	89-97

N = 1122

Fig. 6b. 1122 cytological findings in comparison to cystoscopic and histological diagnosis

Histology	G 1	G 2	G 3
Cytology positive %	78	94	96
Incl. PAP 3	90	100	99

Fig. 7. Cytological accuracy in regard to histological grade of dedifferentiation G1-G3

Histology	G 1	G 2	G 3
Cytology G 1	81	26	16
G 2	18	64	36
G 3	1	10	48

Fig. 8. Comparison of cytological and histological grading

positive findings is 89% and 97% for negative findings. This figure for negative findings is high by comparison with other series (3, 11, 22, 30, 31) and is explained by the fact that in our study was limited exclusively to known tumour patients and that the ratio of positive to negative findings was approximately 1 to 2. A general

screening test would show more false positive findings (10, 24).

The diagnostic accuracy increases with decreasing grade of differentiation (Fig. 7). This has been shown in the literature before (1, 7, 12, 13, 19).

There is an unexpectedly high percentage of cytologically diagnosed G1 carcinomas in our material. Koss (12, 13) and de Voogt (32) have repeatedly pointed out that well differentiated carcinomas can be diagnosed cytologically. On the other hand false negative findings in G1 carcinomas are frequent (7, 28). Here too, discrepancies are partly due to different classifications. We believe that G1 tumours can be diagnosed primarily by their loss of nuclear transparency. Even when this criterion is applied strictly there will not be more false positive findings.

The possibility of grading urothelial tumours following the WHO recommendations has, to our knowledge, not been investigated in a large study. The decreasing accuracy with decrease in grade of differentiation can be explained as follows:

1. Generally only two slides were available of one tumour in the retrospective study whereas in routine cases 6 slides are prepared.
2. A poorly differentiated tumour exfoliates cells of different grades of differentiation in decreasing number: poorly differentiated cells are observed less frequently than G1 and G2 cells. The diagnosis of cancer can be made but the grade of differentiation is underestimated.

The benefit of cytological grading is remarkable: Cytological undergrading has no consequence since preference is given to the histological diagnosis. A cytological diagnosis indicating a higher grade of malignancy than the histological biopsy should be taken very seriously. Multiple biopsies have in many cases extended the diagnosis and changed the therapeutic approach (16, 17, 25, 33).

Even multiple biopsies however do detect abnormalities only in relatively small parts of the urinary bladder. Here lies the main advantage of exfoliative cytology, especially in regard to the carcinoma in situ, which is difficult to diagnose endoscopically and yet is observed with increasing frequency (13, 16, 17, 33).

Although from a statistical point of view no final conclusions can be drawn from the few cases investigated, it is remarkable, that 5% of all positive cytological findings add important information to the histological results, predict the clinical course and can be proven histologically by further sections taken from the initial biopsy material or further cuts of the material embedded. These results can be well understood remembering the fact that Farrow doing 21 cystectomies after cytological diagnosis could prove cancer in each case histologically (8) and Marshall was

able to demonstrate a urothelial carcinoma endoscopically 20 years after an initial cytological diagnosis of malignancy (15).

## CONCLUSIONS

1. 85% of urothelial carcinomas can be diagnosed cytologically. This high degree of accuracy justifies urinary cytology in the postoperative follow up of tumour patients.
2. Diagnostic accuracy increases with decreasing grade of differentiation.
3. Cytological grading is an important part of the routine diagnosis of urothelial carcinomas. Preference should be given to the cytological findings for they give a more reliable guide to prognosis than the histological diagnosis, and cytology shows a higher grade of malignancy.

## REFERENCES

1. Allegra, S. R., Broderick, P. A., Corvese, N. L.: Cytologic and histogenetic observations in well differentiated transitional cell carcinoma of bladder. *Journal of Urology* 107, 777 (1972)
2. Bergvist, A., Ljungqvist, Q., Moberger, G.: Classification of bladder tumours based on the cellular pattern. *Acta Chirurgica Scandinavica* 130, 371 (1965)
3. Beyer-Boon, M. E., De Voogt, H. J., Van der Velde, J. A., Brussee, J. A. M., Schallberg, A.: The efficacy of urinary cytology in the detection of urothelial tumours. Sensitivity and specificity of urinary cytology. *Urological Research* 6, 3 (1978)
4. Broders, A. C.: Epithelioma of the genitourinary organs. *American Surgeon* 75, 574 (1922)
5. Busch, C., Engberg, A., Norlen, B. J., Stenkvis, B.: Malignancy grading of epithelial bladder tumours. *Scandinavian Journal of Urology and Nephrology* 11, 143 (1977)
6. Eriksson, O., Johansson, S.: Urothelial neoplasms of the upper urinary tract. *Acta Cytologi* 20, 20 (1976)
7. Esposti, P. L., Zajicek, J.: Grading of transitional cell neoplasms of the urinary bladder from smears of bladder washings. A critical review of 326 tumors. *Acta Cytologica* 16, 529 (1972)
8. Farrow, G. M., Utz, D. C., Rife, C. C.: Morphological and clinical observations of patients with early bladder cancer treated with total cystectomy. *Cancer Research* 36, 2495 (1976)
9. Franksson, C.: Tumours of the urinary

- bladder. *Acta Chirurgica Scandinavica*, Supplementum 151, (1950)
10. Hartmer-Schilling, B.: Die Exfoliativzytologie als Screening-Test für Harnwegstumoren. Diss. RWTH Aachen 1977
  11. Kern, W.H.: The cytology of transitional cell carcinoma of the urinary bladder. *Acta Cytologica* 19, 420 (1975)
  12. Koss, L.G.: Tumours of the bladder. Atlas of tumor pathology, 2nd series, Fasc. 11. Washington D.C.: Armed Forces Institute of Pathology 1975
  13. Koss, L.G.: Cytology in the diagnosis of bladder tumour. In: The biology and clinical management of bladder cancer. London: Blackwell 1975
  14. Lutzeyer, W., Schiffer, A.: Exfoliative cytodiagnosis as a screening test in bladder tumours. *South African Medical Journal* 6, 1219 (1971)
  15. Marshall, V.F., Seybolt, J.F.: Early detection but delayed appearance of a bladder tumor. *Journal of Urology* 118, 175 (1977)
  16. Melamed, M.R., Voutsas, N.G., Grabstald, H.: Natural history and clinical behaviour of in situ carcinoma of the human urinary bladder. *Cancer* 17, (1533) (1964)
  17. Melamed, M.R., Grabstald, H., Whitmore, W.F.: Carcinoma in situ of bladder: Clinicopathologic study of case with a suggested approach to detection. *Journal of Urology* 96, 466 (1966)
  18. Naib, Z.M.: Exfoliative cytology of renal pelvic lesions. *Cancer* 14, 1085 (1961)
  19. Orell, S.R.: Transitional cell epithelioma of the bladder: Correlation of cytologic and histologic diagnosis. *Scandinavian Journal of Urology and Nephrology* 3, 93 (1969)
  20. Papanicolaou, G.N., Marshall, V.F.: Urine sediment smears as a diagnostic procedure in cancers of the urinary tract. *Science* 101, 519 (1945)
  21. Papanicolaou, G.N.: Atlas of exfoliative cytology. Cambridge, Massachusetts: Harvard University Press 1954
  22. Prall, R.H., Wernett, C., Mattlock, M.: Diagnostic cytology in urinary tract malignancy. *Cancer* 29, 1084 (1972)
  23. Rathert, P., Lutzeyer, W.: Zytodiagnostik bei Harnwegserkrankungen. In: Aktuelle Diagnostik von Nierenerkrankungen. Kluthe, R., Oechslen, D. (eds.). Stuttgart 1974
  24. Rathert, P., Rübben, H., Lutzeyer, W.: Urinzytologie: Stellenwert in Diagnostik und Verlaufskontrolle des Blasenkarzinoms. Verhandlungsberichte der deutschen Gesellschaft für Urologie, Stuttgart 1977 (in press)
  25. Rübben, H., Lutzeyer, W., Bubenzer, J.: In preparation
  26. Say, C.C., Hori, J.M.: Transitional cell carcinoma of the renal pelvis: Experience from 1940 to 1972 and literature review. *Journal of Urology* 112, 438 (1974)
  27. Schiffer, A., Lymberopoulos, S., Charvat, A.: Vergleichende Zytodiagnostik in der Urologie, *Zeitschrift für Urologie* 6, 367 (1968)
  28. Tyrkkö, J.: Exfoliative cytology in the diagnosis and follow-up of urothelial neoplasms. *Scandinavian Journal of Urology and Nephrology* 19, 11 (1972)
  29. UICC: TNM Klassifikation of malignant tumours. Geneva 1978
  30. Umiker, W., Lapidus, J., Sourenne, R.: Exfoliative cytology of papillomas and intraepithelial carcinomas of the urinary bladder. *Acta Cytologica* 6, 255 (1962)
  31. Umiker, W.: Accuracy of cytologic diagnosis of cancer of the urinary tract. *Acta Cytologica* 9, 186 (1964)
  32. Voogt, De, H.J., Rathert, P., Beyer-Boon, M.E.: Urinary cytology. Phase contrast microscopy and analysis of stained smears. Berlin 1977
  33. Voutsas, N.G., Melamed, M.R.: Cytology of in situ carcinoma of the human urinary bladder. *Cancer* 16, 1307 (1963)
  34. Wiggishof, C.C., McDonald, J.H.: Urinary exfoliative cytology in tumors of the kidney and ureter. *Journal of Urology* 102, 1707 (1969)
  35. WHO: World health organization. Histological typing of urinary bladder tumours. International histological classification of tumours. Tenf 1973
  36. Zincke, H., Aguilo, J.J., Farrow, G.M., Utz, D.C., Khan, A.U.: Significance of urinary cytology in the early detection of transitional cell cancer of the upper urinary tract. *Journal of Urology* 116, 781 (1976)

Prof. Dr. W. Lutzeyer  
 Urologisches Institut  
 der RWTH Aachen  
 D-5100 Aachen  
 Federal Republic of Germany