

The Role of Exfoliative Cytology in the Management of Bladder Carcinoma

P. L. Esposti¹, F. Edsmyr¹, and B. Tribukait²

¹) Radiumhemmet, Karolinska Sjukhuset and ²) Institute of Radiobiology, Karolinska Sjukhuset Stockholm, Sweden

Summary. Cytological analyses of bladder washings from 974 patients with disorders of the urinary tract are reported. The cytological findings were compared with the clinical and histological diagnoses. The histological grading of bladder tumours was based on the classification proposed by Bergkvist et al. No false positive diagnosis of malignancy was made in the 320 patients without tumour growth. The five cases with positive cytology had histologically verified carcinoma *in situ*. The frequency of cytological diagnosis of cancer increased with the histological grade of malignancy in the 428 patients with bladder neoplasm. Carcinoma was graded in smears according mainly to the degree of epithelial atypia. A comparison with the histological grading was attempted. Of 226 cases of bladder carcinoma treated with supervoltage irradiation, 108 had persistence or recurrence of carcinoma. The clinical diagnosis was cytologically confirmed in 92 per cent of these cases.

Key words: Exfoliative cytology - Bladder neoplasms - Malignancy grading.

The urinary tract is lined with transitional epithelium (urothelium). This is a pluristratified (three to seven layers of cells), non-keratinized epithelium. The urothelial cells vary in size and shape from the basal layer to the surface. The basal layer exhibits small, round cells with scant cytoplasm and dark, round nuclei. Intermediate cells show larger often elongated nuclei and a cytoplasmic tail reaching down to the basal layer. At the surface large cells exhibit abundant cytoplasm and often more than one nucleus (so-called umbrella cells).

Exfoliated cells from the urinary tract can easily be processed for study of urinary disorders. The analysis of cells from sediments of voided urine or bladder washings is of particular importance in the diagnosis of epithelial tumours of the urinary bladder.

MATERIAL AND METHODS

At the Department of Urology, Karolinska Sjukhuset, the routine investigations in patients with disorders of the urinary tract include, as a rule, cystoscopy, when samples of urine

and bladder washings are taken for cytological analysis.

Experience has shown that cellular preservation was better and the number of epithelial cells higher in bladder washings than in urine and in the last years the cytological smears have been prepared almost exclusively from wash-outs. The smears are prepared as previously described (3, 4). The cellular sediment obtained by centrifugation and fixed with methanol, was mixed with an adhesive solution containing pectin as recommended by Rofe (6). The dry slides were stained according to the Papanicolaou method.

In tumour cases the cytological findings were compared with the histological sections from tumour biopsies. Each tumour was graded histologically according to the severity of deviation of the cell pattern from normal transitional epithelium, as suggested by Bergkvist et al. (1). This classification, consisting of five grades (0-4) is essentially similar and comparable to the classification proposed by WHO (8). Carcinomas Bergkvist grade 4 malignancy are generally called anaplastic carcinomas in the WHO classification.

The present study includes 974 patients,

Table 1. Cytological reports in 428 bladder tumours

Cytological report	Histological diagnosis		
	Grades 0-1	Grade 2	Grades 3-4
Non-malignant	56	49	11
Suspicious	12	23	16
Malignant	2	80	179
Total	70	152	206

Table 2. Cytological reports correlated with histological invasiveness in 152 neoplasms of the urinary bladder grade 2

Cytological report	Histological grade 2		
	Non-invasive	Possibly invasive	Invasive
Non-malignant	29	11	9
Suspicious	8	6	9
Malignant	4	16	60
Total	41	33	78

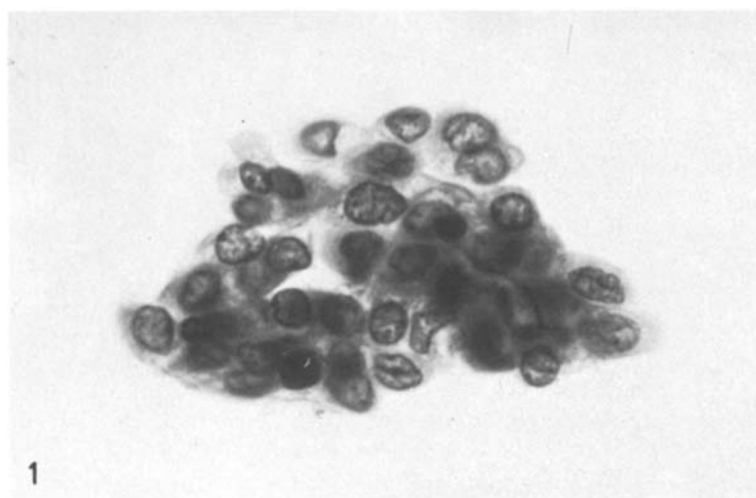


Fig. 1. Cluster of carcinoma cells with low-grade nuclear atypia in bladder washings from a case histologically diagnosed as urothelial carcinoma grade 2a. (X 800)

from two consecutive groups treated at Karolinska Sjukhuset, during the periods 1964-1970 and 1974-1976.

RESULTS

In 320 patients no papillary or solid tumour was found in the bladder. The clinical diagnoses were miscellaneous e. g.: bacterial cystitis, urinary calculi, prostatitis.

Benign cells were reported in 297 cases, suspicious cells in 18 cases, and carcinoma cells in five cases. In all these five cases carcinoma in situ was eventually shown by histological examination of repeated biopsies.

A cytological diagnosis was available in 428 cases of cystoscopically and histologically verified bladder tumour. The cytological findings are correlated with the histological diagnoses in Table 1. Only about 3% of cases

of papillary tumours grade 0-1 showed carcinoma cells in the smear. More than 50% of grade 2 and the majority of grade 3-4 tumours had a cytological report of malignancy. Grade 2 neoplasms appear cytologically to be an intermediate group between papilloma and frank carcinoma. The evidence of invasive tumour growth, often combined with a more accentuated cellular atypia in histologic sections, is well correlated to frequency of malignant cells in smears (Table 2).

An attempt to assess the cytological grading of malignancy in cells exfoliated from bladder neoplasms has been made and the results published in an earlier paper (5). Cells were graded according to the severity of deviation from normal urothelium as low-grade, moderate or high-grade (Figs. 1-3). In this grading nuclear details of malignancy were considered together with the amount of individual carcinoma cells, as compared to cell clusters present

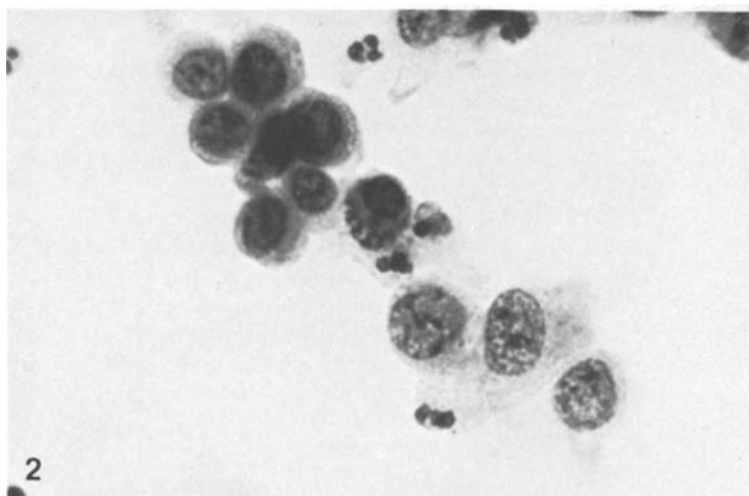


Fig. 2. Cluster of carcinoma cells with moderate nuclear atypia in bladder washings from a case histologically diagnosed as urothelial carcinoma grade 2b. (X 800)

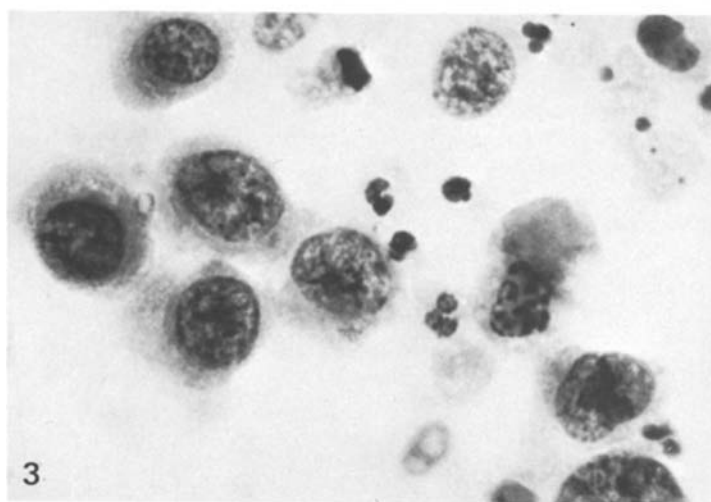


Fig. 3. Dissociated carcinoma cells with high-grade nuclear atypia in bladder washings from a case histologically diagnosed as urothelial carcinoma grade 3. (X 800)

Table 3. Cytological atypia in smears of 220 cases of bladder carcinoma of histological grades 2-4 (in per cent)

Cytological atypia	Histological grade		
	2		3-4
	a ^a	b ^b	
Low-grade	60	-	-
Moderate	40	70	10
High-grade	-	30	90

^a non-invasive neoplasms grade 2 with slight atypia

Table 4. Cytological malignancy and clinical follow-up in 226 patients after radiotherapy for bladder carcinoma

Clinical Follow-up	No. of Patients	Cytological malignancy	
		no. of patients	per cent
No response to therapy	40	38	95
Recurrence	68	61	90
Suspected recurrence	31	14	45
No recurrence	87	3	3.5

^b possibly invasive or invasive neoplasms grade 2 with more severe nuclear atypia

Table 5. Time lag between cytological and clinical detection of recurrence of bladder carcinoma in 37 patients

No. of cases with malignant cytology	Delay before clinical detection
19	6 months
8	6 - 12 months
3	13 - 24 months
4	25 - 36 months
2	34 - 48 months
1	49 - 60 months

in the smears. Table 3 shows the correlation of cytological atypia with histological grade in 220 cases of bladder carcinoma.

Supervoltage irradiation was given to 226 patients with carcinoma of the urinary bladder (2). Malignant cells were found on cytological examination in 116 patients during clinical follow-up from three months to several years after radiotherapy. The correlation between cytological malignancy and the presence of tumour is shown in Table 4. The cytological follow-up revealed malignant cells in the smears of 3 out of 87 patients without clinically detectable tumour growth after radiotherapy. That a cytological report of malignancy can precede the clinical detection of recurrence is shown in Table 5. In 37 patients the cytological detection preceded the clinical diagnosis of recurrence. The time lag varied from a few months to several years.

CONCLUSIONS

The study of exfoliated cells is useful in screening patients with symptoms from the urinary tract. In 320 patients without a clinically evident neoplasm, no false positive diagnoses of cancer were made. The five cases without tumour and with positive cytology were eventually diagnosed histologically as carcinoma *in situ*.

In cases with primary, untreated bladder tumours, the frequency of cytological diagnosis of cancer increased with the histological grade of malignancy. From the results of our study, as in previous studies, there is some indication that grade 2 tumours without invasion and with less severe atypia (2a) may, like grade 0 and 1 tumours, not be truly progressive. While smears from bladders with neoplasms grade 0, 1 and 2a contain malignant cells in less than 10 per cent of the cases,

the number of cytologically positive smears from cases with tumours grade 2b (invasive) and grades 3 and 4 increases to 70 to 90 per cent. For a clearer understanding of this problem other methods may be required, such as cytophotometric analysis of DNA content of exfoliated urothelial cells (7, 9).

The morphological changes occurring in irradiated cells do not seem to increase the danger of a false positive diagnosis of recurrent bladder carcinoma. The cytological diagnosis of recurrence often precedes the clinical detection of the tumour growth and the interval can vary from few months to several years.

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P. L. Esposti, M. D.
Radiumhemmet
Karolinska sjukhuset
S-104 01 Stockholm 60/Sweden