The Value of Conventional Urine Cytology in the Diagnosis of Residual Tumour after Transurethral Resection of Bladder Carcinomas

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Schlüsselwörter

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Summary

Background: Transurethral resection leads to characteristic histological changes of tissue repair ('TUR cystitis'), which also cause non-specific cytological changes. The aim of this study was to investigate the diagnostic sensitivity and specificity of conventional exfoliative urinary cytology in diagnosing residual urothelial carcinoma after differential transurethral resection. **Patients and Methods:** 417 urinary cytology specimens of all 374 patients undergoing primary (n=326) or secondary (n=91) transurethral resection of urothelial carcinoma of the bladder at our institution between June 1996 and December 1997 were examined. The cytology specimens were stained according to Papanicolaou's method. The sensitivity and specificity of the cytologic diagnosis and of the tumour grading were compared with histological findings. **Results:** The overall sensitivity of urine cytology in tumour detection was 77.6% for primary lesions and 74.5% in the detection of residual carcinoma after transurethral resection. The diagnostic specificity was 77% and 84.3% respectively. The degree of sensitivity was dependent on tumour grade and was lower for well differentiated tumours. After transurethral resection, the sensitivity for grade 1 residual tumours was 11%, whereas it was 54% for grade 1 tumours before primary transurethral resection. **Conclusions:** The inflammatory changes following transurethral resection of primary bladder carcinoma cause reactive cytologic changes that make the diagnosis of well differentiated residual carcinoma more difficult. However, urinary cytology after transurethral resection has the same diagnostic accuracy for medium and poorly differentiated tumours as before primary resection and thus remains a very useful diagnostic tool.

Zusammenfassung

Hintergrund: Transurethrale Resektionen von Blasentumoren führen zu histologischen Veränderungen («TUR Zystitis») im Sinne regenerativer Veränderungen, welche urinzytologisch zu diagnostischen Fehleinschätzungen führen können. Das Ziel unserer Untersuchung war der Vergleich der diagnostischen Sensitivität und Spezifität der Urinzytologie vor transurethraler Resektion mit der bei der Diagnose von Residualtumoren nach transurethraler Resektion. **Patienten und Methoden:** Untersucht wurden 417 urinzytologische Präparate von allen 374 Patienten, die in unserer Einrichtung zwischen Juni 1996 und Dezember 1997 einer primären (n=326) oder sekundären (n=91) transurethralen Resektion von Urothelkarzinomen der Harnblase unterzogen wurden. Die zytologischen Präparate wurden nach Papanicolaou gefärbt. Sensitivität und Spezifität der zytologischen Diagnostik und des Tumorgradings wurden mit den histologischen Befunden verglichen. **Ergebnisse:** Die Sensitivität der Urinzytologie in der primären Tumorerkennung lag bei 77,6% und die für die Diagnose von Residualtumoren nach transurethraler Resektion bei 74,5%. Die diagnostische Spezifität lag bei 77% bzw. 84,3%. Die Sensitivität war abhängig vom Differenzierungsgrad der Urothelkarzinome und war bei gut differenzierten Tumoren am niedrigsten. Nach transurethraler Resektion betrug die Sensitivität der zytologischen Diagnose für G1-Residualtumore lediglich 11%, während sie für G1-Primärtumore bei 54% lag. **Schlussfolgerungen:** Die entzündlichen Veränderungen nach transurethraler Resektion verursachen Veränderungen exfolierter Urothelzellen, welche die zytologische Diagnose von residualen G1-Tumoren erschweren. Die Diagnose mäßig und schlecht differenzierter residualer Urothelkarzinome nach transurethraler Resektion hat dagegen die gleiche Sensitivität und Spezifität wie die bei primärer Untersuchung, so daß die Urinzytologie auch bei der Diagnose von Residualtumoren ein wertvolles diagnostisches Verfahren darstellt.

Introduction

The routine usage of exfoliative urinary cytology was introduced into clinical urology as a diagnostic method for the detection of urothelial carcinoma in the 1970s. The method depends on the fact that the mucosa of the whole urogenital tract undergoes continuous regeneration and that urothelial cells are constantly shed into and excreted with the urine. The same applies to malignant urothelial cells. These exfoliated urothelial cells can be found in normal urine and can be examined microscopically after staining.

Malignant urothelial cells differ microscopically from normal urothelial cells in the appearance of their nuclei. This difference is more pronounced in less differentiated tumour cells.

Urinary cytology is thus a non-invasive method for the primary diagnosis and the follow-up of superficial urothelial carcinoma, which is primarily treated by transurethral resection.

The cytologic diagnosis of residual urothelial carcinoma after transurethral resection has considerable consequences for the patient, since this will necessitate secondary or tertiary transurethral resection, whereas in the absence of residual tumour, the patient can be followed routinely. Thus, a reliable negative cytologic examination after a primary transurethral resection of a superficial bladder carcinoma may spare the patient a secondary transurethral resection.

Urinary cytology is a non-invasive and technically simple diagnostic method, but does require a certain degree of experience, and its diagnostic accuracy depends on this as well as on the quality of staining and the yield of viable urothelial cells.

The examiner-bias of urinary cytology has led to efforts to replace conventional exfoliative cytology in the diagnosis of bladder carcinoma by other urine-based laboratory tests. Automated cytometric methods (e.g. flow cytometry) and immunocytochemical methods are technically more elaborate and have so far been of value only for research purposes. Several methods of detecting tumour-associated antigens in the urine have therefore been proposed as alternative diagnostic methods (cytokeratins, telomerase, NMP-22, bladder tumour antigen). These methods potentially offer technically simple methods of screening for bladder carcinoma. Some of these tests are reported to have a high sensitivity but low specificity in the detection of urothelial cancer [1–3].

In studies of the diagnostic usefulness of the urine-based detection of tumour-associated antigens, these new methods were usually compared with conventional urinary cytology. Often the sensitivity and specificity of cytology reported in such studies was rather low [1–3] in comparison to earlier investigations dealing with the diagnostic accuracy of cytology itself [4, 5].

It is only an assumption that standardised technical methods are more objective and hence more reliable in their results than urine cytology, only because the human factor has been reduced. Urine cytology can lead to false-negative, but rarely to false-positive results.

The value of urinary cytology as a diagnostic method, however, can only be assessed in large studies where cytology is practised as a routine technique. As many other diagnostic and therapeutic methods in medicine, the value of urinary cytologic diagnosis depends on the long-term diligence with which this method is practised.

The aim of this study was to establish the diagnostic sensitivity and specificity of conventional urinary cytology in a large and representative group of patients before and after transurethral resection. After the primary transurethral resection of superficial bladder tumours, which is usually done with curative intent, we routinely perform a secondary transurethral resection 3–4 weeks after the first resection in order to increase the likelihood of complete tumour resection. The cytologic diagnosis of malignant urothelial cells in the urine of patients after a primary transurethral resection with curative intent thus proves the existence of residual tumour.

The assessment of the diagnostic value of conventional urinary cytology in diagnosing residual urothelial carcinoma after transurethral resection is important for two reasons. First, regenerative changes in the bladder wall following transurethral resection lead to cytological changes and artefacts which make the accurate cytologic diagnosis more difficult [6]. Second, the primary urinary cytologic diagnosis of patients referred for surgery with the preliminary diagnosis of a possible bladder lesion can lead to an examiner bias which can falsely increase the diagnostic accuracy of the method. After macroscopically curative transurethral resection of a bladder lesion, the cytologic examiner will be free from any such bias so that the diagnostic value of urinary cytology can be objectively assessed when looking at the sensitivity and specificity of diagnosing residual carcinoma after primary transurethral resection.

Patients and Methods

Between June 1996 and December 1997, urinary cytology specimens were obtained from all patients undergoing transurethral resection of bladder lesions in our department. During this period, 417 transurethral bladder tumour resections were performed on 374 patients. Of these, 78.1% were primary transurethral resections ($n=326$) while 21.8% were secondary resections ($n=91$).

Of the 374 patients, 74% were males ($n=276$) with a mean age of 68.2 years, and 26% were females ($n=98$) with a mean age of 74.1 years.

From all patients, a mid-stream urinary specimen was obtained on the day of admission and fixed with thiomersale [7]. Cell concentration was achieved by centrifugation (4 min at 3000 g). From each urine specimen, two slides were prepared, fixed with alcohol and stained according to the method described by Papanicolaou [8]. The microscopic cytologic examination was done by three different staff members of our department.

The primary transurethral resection of suspicious bladder lesions was done by the so-called differential resection technique: Complete resection of the exophytic lesion or suspicious mucosal area was followed by separate resection of the macroscopically normal margin of the lesion and of the base of the lesion. Thus, three separate specimens were sent for histologic examination after each primary transurethral resection. The routine histological examination of all specimens was done by the Institute of Pathology at the Technical University, Dresden.

A secondary transurethral resection was routinely performed 3–4 weeks after the primary resection in all cases where superficial urothelial carcinoma had been diagnosed by histology after the primary resection, except for cases of pTa G1 lesions. In all cases where the tumour was seen histologically in the resection margins or the tumour base, or in all cases other than the exceptions mentioned, a secondary transurethral resection was also performed.

The *statistical methods* used are those of standard calculation of means, sensitivity and specificity [9].

Table 1. Cytological and histological findings from primary transurethral resections. **A:** Histological results after primary transurethral resections (TUR), tumour stage vs. histological grading. **B:** Comparison of histological and cytological grading before primary TURs

A

Stage	Grade			
	G1	G2	G3	total
pTa	25	19	2	46
pT1	21	73	19	113
pT2	2	33	40	75
pT3	0	11	22	33
pTIS	–	–	11	11
Total	48	136	94	278

B

Histology	Cytology				
	G1	G2	G3	no tumor detected	total
G1	11	10	5	22	48
G2	22	58	26	30	136
G3	3	19	51	10	83
CIS	0	2	6	3	11
Total	36	89	88	65	278

CIS = Carcinoma in situ.

Results

Of the 326 primary transurethral resections, urothelial carcinoma was diagnosed in 85.3% (n=278) and a benign histological diagnosis was made in 14.7% of cases (n=48). Tumour stages and grades based on the histological findings after the primary resections are given in table 1A. The cytologic diagnoses and tumour grades in comparison to the histological findings are given in table 1B.

Thus, in 65/278 cases of histologically proven primary urothelial carcinoma, urinary cytology did not detect any malignancy. This corresponds to 23.4% false-negative cytologic findings for primary bladder tumours in our series.

Of the 159 patients with superficial bladder tumours (pTa and pT1), 113 with pT1 tumours were advised to undergo secondary resection. Of these, 5 were lost to follow-up and 10 patients who presented for secondary resection more than 8 weeks after the primary resection were excluded from analysis. Another 7 patients had no cytological examination done prior to secondary resection, so that a total of 91 specimens from patients before secondary transurethral resection were included in the analysis. For the secondary transurethral resections (n=91), the results of the histological findings and the comparison between histology and cytology are given in tables 2A and 2B, respectively. Of the remaining 59 patients who were histologically found to have residual urothelial carcinoma after

Table 2. A: Histological findings after secondary transurethral resection, tumour stage vs. tumour grading. **B:** Histological grading vs. cytological grading before secondary transurethral resection

A

Stage	Grade			
	G1	G2	G3	total
pTa	4	5	0	9
pT1	5	14	4	23
pT2	0	9	8	17
pT3	0	2	3	5
pTIS	–	–	5	5
Total	9	30	20	59

B

Histology	Cytology				
	G1	G2	G3	no tumor detected	total
G1	0	1	0	8	9
G2	2	18	4	6	30
G3	1	4	9	1	15
CIS	0	1	4	0	5
Total	3	24	17	15	59

the primary transurethral resection, 44 were correctly identified by cytology preoperatively. 15 out of 59 cases of histologically proven residual tumour were not identified cytologically, representing 25.4% false-negative cytologic findings.

The sensitivity of the urinary cytologic diagnosis before and after transurethral resection was clearly dependent on tumour grade (table 3). Before the primary resection, 13 of 94 undifferentiated carcinomas (3 of 11 carcinoma in situ and 10 of 83 exophytic G3 tumours) were missed by cytology. The overall sensitivity in correctly diagnosing G3 bladder carcinoma was 86.1% and markedly higher than for G1 tumours (54.1%) and G2 tumours (77.9%). Before secondary transurethral resection, the relationship was similar: The overall sensitivity in the diagnosis of G3 tumours was 95% (19/20) and for G2 tumours 80% (24/30). However, the diagnostic sensitivity for residual G1 tumours was only 11% (1/9) and thus markedly lower compared to the sensitivity in diagnosing primary G1 bladder carcinoma.

The specificity of urinary cytologic diagnosis in our study (table 4) was 77% for primary diagnosis (37/48 histologically benign lesions were correctly diagnosed by cytology). The specificity of diagnosing residual tumour after transurethral resection was slightly higher with 84.3% (27/32). The benign histological findings after primary resection (n=48) were chronic inflammation (n=35), cystic cystitis (n=8), squamous cell metaplasia (n=3) and one each of inverted papilloma and polypoid hyperplasia. All specimens from the secondary transurethral resection with and without residual carcinoma were reported to show the typical findings of ‘TUR cystitis’.

Table 3. Sensitivity of cytological assessment: Numbers and percentages of urothelial carcinomas correctly identified by urinary cytology before primary transurethral resections

Histological grading	Correctly identified by cytology	Sensitivity of cytology, %
Primary TUR		
G1	26/48	54.1
G2	106/136	77.9
G3	73/83	87.9
CIS	8/11	72.7
Total	213/278	76.6
Secondary TUR		
G1	1/9	11.1
G2	24/30	80.0
G3	14/15	93.3
CIS	5/5	100
Total	44/59	74.5

TUR = Transurethral resections.

Table 4. Specificity of the cytological diagnosis in cases of benign histological findings with primary and secondary transurethral resections

Transurethral resections	Cytological diagnosis	G1	G2	G3	Tumours detected n / %	Total n
Primary	benign histology	7	4	0	37 / 77	48
Secondary	benign histology	2	3	0	27 / 84.3	32

Discussion

The first description of the microscopic detection of malignant urothelial cells in the urine of patients with bladder cancer dates back to the works of Lambl [10] and Sanders [11] published in 1856 and 1864 respectively. Thus, for bladder cancer, urine cytology predates the histological examination of bladder biopsies as a diagnostic method. However, urine cytology did not develop into a routinely useful method until the fundamental cytologic work of Papanicolaou and Marshall [8], published in 1945, and has only since then become an established diagnostic tool for the diagnosis and follow-up of patients with bladder carcinoma. Exfoliative urine cytology is based on the detection of discrete structural abnormalities (changes in nuclear structure and size) of cells isolated from their tissue environment. Urine cytology is neither able to localise a urothelial malignancy nor can it supply information about tumour stage. However, in contrast to randomised bladder biopsies, urine cytology is a detection method for the whole mucosal surface of the urinary tract. The problems which can lead to errors in the diagnosis lie in the nature of the material examined, the biological nature of

urothelial carcinoma and in the visual assessment of stained slides by an examiner. Since urinary cytology can only assess isolated cells shed into the urine, the method is more prone to artefacts caused by the collection, fixation, storage and processing of the material. Good cytological results require the processing of fresh urine [7]. Degenerative cell changes through autolysis and bacterial growth in the urine sample must be avoided. The number of cells shed with the urine can vary considerably inter- and intra-individually and also depends on diuresis, therefore cell concentration techniques are indispensable. The nature of bladder carcinoma provides additional problems. First, highly differentiated superficial bladder tumours (papillomas according to the WHO classification) which are classified as such by their histologic features, have a cytologically benign appearance. Well differentiated urothelial carcinomas (G1) consist of cells with different grades of anaplasia so that the cytologic picture can vary. Second, the degree of exfoliation of malignant cells by any urothelial malignancy can also vary, and the cytologic appearance of cells found in one urine sample will not always be representative of the underlying tumour. And third, errors can occur in the assessment of cytological specimens. Diagnostic mistakes are particularly likely when (i) too much emphasis is placed on nuclear staining characteristics in the absence of distinct changes of the quantitative relation between nuclei and cytoplasm (staining artefacts), (ii) when the diagnosis of malignancy is based on the interpretation of cellular aggregates, and (iii) when the cellular atypia due to regenerative or inflammatory urothelial changes is misinterpreted. Especially reactive cellular changes can make the cytologic diagnosis of urothelial malignancy difficult. Such non-specific changes are those seen after intravesical chemo- and immunotherapy but also inflammatory changes due to other causes. Following transurethral resection of a bladder lesion, tissue regeneration leads to the so-called ‘TUR cystitis’. This reactive-inflammatory response is histologically characterised by neutrophilic infiltration of the urothelium and smooth muscle as well as hyperchromatic nuclear urothelial changes with an increased number of mitotic figures [12]. The changes caused by a marked TUR cystitis can therefore make the cytological detection of residual carcinoma more difficult [6]. However, despite all these potential problems, conventional urinary cytology can diagnose urothelial cancer with a high degree of sensitivity and specificity. Investigations of the diagnostic accuracy of urinary cytology from the 1980s, when this method received increasing attention, showed a global sensitivity in tumour detection of about 70% with a specificity of 78–95% [4, 5, 13, 14]. The sensitivity found in these studies for the detection of G1 tumours was around 50%, for G2 lesions 65–80% and for G3 tumours 85–90%. Thus, the diagnostic accuracy of urine cytology is higher with less differentiated tumours. It also follows that urine cytology is not reliable as a routine screening method since G1 lesions can easily remain undetected. In several recently published studies looking at the value of methods for the detection of urinary tumour-associated antigens, these new methods were compared with conventional urinary cytology in their ability to detect urothelial malignancy

[1–3, 15]. The sensitivity of conventional cytology reported in these studies was much lower than that reported previously. The global sensitivity of tumour detection for their own urine cytology was given by the different authors as 17.7% [15], 23% [1], 28% [3] and 40% [2] only. The sensitivity of detecting G1 tumours in the study of Landmann et al. was only 6% [2], and for G2 and G3 tumours 36% and 79% respectively, while Del Nero et al. [16] found a sensitivity of 37.9%, 44.4% and 80% for G1, G2 and G3 lesions respectively.

These findings are in contrast to older publications on the diagnostic usefulness of urinary cytology [4, 5, 13, 14] and to our own results in the present study. The overall sensitivity of urine cytology in tumour detection in our study was 77.6% for primary lesions and 74.5% after transurethral resection, with a specificity of 77% and 84.3% respectively.

Especially the comparison of the results of cytological examination before the primary and before a secondary transurethral resection allows a reliable assessment of the quality of the cytologic diagnosis, since, on the one hand, the post-operative non-specific changes due to TUR cystitis can make the cytologic assessment more difficult, and, on the other hand, an examiner bias is largely excluded following a macroscopically curative primary transurethral resection. The comparability of the overall sensitivity and specificity in diagnosing urothelial malignancy under these conditions suggests that these figures accurately reflect the value of the method.

The standard by which the results of urinary cytology are out of necessity judged is the result of the histological diagnosis after transurethral resection of a bladder lesion. It is well known that the cytological grading of malignant urothelial cells is subject to a certain degree of error and that well differentiated G1 tumours can be missed by cytological examination in 50% of cases [17]. However, it should be remembered that the histological grading of urothelial tumours is examiner- and experience-dependent as well and can vary considerably when the same histological specimens are examined by different pathologists [18]. When cytological and histological grading of urothelial tumours are compared, this bilateral margin of error must therefore be taken into account, especially since internationally there are several classifications of histological grading of urothelial cancer in use.

The agreement between cytological and histological grading in our series was 86.1% for G3 tumours before primary transurethral resection and 95% before a secondary resection. Thus, poorly differentiated G3 tumours were rarely missed by cytology. The cytological detection rate was markedly lower for medium and well differentiated tumours. The poor sensitivity of only 11% for the diagnosis of residual G1 tumours compared to a sensitivity of 54.1% for primary G1 tumours can probably

be attributed to the non-specific changes caused by the post-operative TUR cystitis which was histologically seen in all specimens from the secondary resections. These post-TUR changes cause urothelial atypia which mimics the cellular changes seen with well differentiated tumours. This may lead to a certain reluctance on the part of the cytological examiners to make the diagnosis of 'residual G1 tumour' in order to avoid false-positive assessments.

The specificity of urinary cytological diagnosis in our series was 77% before primary and 84.3% before secondary transurethral resection. False-positive assessments did not occur in any case with the diagnosis G3 tumour. The high specificity of urinary cytology is generally acknowledged [4, 17]. However, a high specificity of urine cytology of 97% [3] and even 98.9% [15] is also reported by authors who acknowledge a low sensitivity in their own series. The combination of a low sensitivity and a simultaneously high specificity of the cytological assessment reported in these studies suggests that mostly poorly differentiated, cytologically well recognisable tumours were identified. However, the proportion between sensitivity and specificity needs to be well balanced when assessing the results of this method.

In conclusion, in our series urine cytology was found to be a reliable diagnostic tool for the detection of urothelial carcinoma. However, the detection rate is lower for well differentiated tumours, and the non-specific changes of TUR cystitis lead to a rather poor sensitivity in the detection of residual G1 tumours of only 11%. In contrast, the post-operative cytological detection of medium and poorly differentiated tumours is the same as before primary transurethral resection.

There are few studies looking at the reliability of urinary cytology following transurethral resection. Müller et al. [6] reported a decreased accuracy due to TUR cystitis. Our results show that the artefacts caused by TUR cystitis only affect the diagnostic accuracy of residual G1 tumours. Badalament et al. [19] used cytology 3 days after transurethral resection as a predictor of later tumour recurrence in patients with superficial bladder tumours, but did not assess the accuracy of their cytology by other means. In our study, cytology done shortly before a secondary resection was compared with the histological result, thus allowing a good assessment of the diagnostic accuracy.

Whether the decision to perform a secondary transurethral resection can be based on post-operative cytology must remain open to debate at present. Clearly, in cases of G1 tumours this cannot be recommended. For G2 and G3 tumours, secondary transurethral resection may be omitted in selected cases and only if tumour margins and base were free of malignant tissue at the primary resection and if repeated post-operative cytological examinations are negative.

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