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# Association Between Urinary Cytology and Pathology for Nontransitional Cell Malignancies of the Urinary Tract

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**Purpose:** Because nontransitional cell carcinoma neoplasms of the urinary tract are rare in Western countries, we examined the association between urinary cytology and pathology evaluations for these tumors.

**Materials and Methods:** An institutional review board approved, retrospective review of a total of 55,946 cytology evaluations in 12,705 patients between 1992 and 2004 was performed for correlation with subsequent histopathology findings. Documented urothelial neoplasms were then correlated with previous cytology results. Nontransitional cell carcinomas were categorized as adenocarcinoma, squamous cell carcinoma and other, including small cell disease, sarcoma, melanoma or lymphoma.

**Results:** All 108 patients with cytology evaluations showing adenocarcinoma had histological evidence of cancer and 86% had adenocarcinoma in the urinary tract. All 110 patients with squamous cell carcinoma on cytology had cancer, including 47% with primary squamous cell disease. All 42 patients with other nontransitional cell carcinomas on cytology evaluation had cancer, of whom 64% had histological concordance. In a separate analysis of 70 patients who had pathologically confirmed adenocarcinoma 57% had positive prior cytology findings, of whom 19% had histological concordance. Of 85 patients with squamous cell carcinoma 81% had positive prior cytology findings, of whom 60% had histological concordance. Of 83 patients with other nontransitional cell carcinomas 70% had positive prior cytology findings, of whom 31% had histological concordance.

**Conclusions:** In our series all patients with nontransitional cell carcinoma cytological results had cancer in the urinary tract. Thus, nontransitional cell carcinoma cytology findings mandate careful urinary tract evaluation. Concordance with histological subclassification on subsequent pathology evaluation ranges from 49% for squamous cell carcinoma to 86% for adenocarcinoma. A majority of patients with nontransitional cell carcinoma malignancies had positive prior cytology findings. However, the concordance with histological subclassification on prior cytology results ranges from 19% for adenocarcinoma to 60% for squamous cell carcinoma.

*Key Words:* urinary tract; carcinoma, transitional cell; urine; cytology; diagnosis

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Of bladder tumors in the Western hemisphere 90% to 95% are TCC. NonTCC neoplasms of the urinary tract include tumors of epithelial origin, such as squamous cell carcinoma, adenocarcinoma and small cell/neuroendocrine carcinoma, tumors of nonepithelial origin, such as sarcoma, lymphoma and melanoma, and metastatic tumors. Of nonTCC tumors squamous cell carcinoma and adenocarcinoma are most frequently reported, comprising 3% to 5% and 0.5% to 2%, respectively, of all primary bladder tumors. All other nonTCC tumors collectively comprise less than 0.5% of primary bladder lesions.<sup>1</sup>

Cytology evaluation of urine specimens is an integral part of screening and surveillance for TCC. In 1945 Papanicolaou and Marshall reported that cytology evaluation of urine sediments was highly specific (24 of 27 cases or 89%) but poorly sensitive (24 of 46 or 52%) for cancers of the urinary tract.<sup>2</sup> Subsequent studies reiterated these findings for TCC,

showing high specificity, especially for high grade tumors.<sup>3-7</sup> In contrast, to our knowledge the diagnostic usefulness of urine cytology for nonTCC malignancies of the urinary tract is not known.

We report the experience at our institution with urinary cytology for nonTCC malignancies of the urinary tract. To examine the diagnostic usefulness of urine cytology we asked 2 questions. 1) If urine cytology reveals nonTCC histology, how often does it diagnose cancer in the urinary tract, specifically a nonTCC tumor of the same histology? 2) If the pathology specimen from cystectomy or TUR shows nonTCC, how often would patients have had previously positive urine cytology findings, specifically those that predicted the same histological finding?

## MATERIALS AND METHODS

We performed an institutional review board approved, retrospective review of a total of 55,946 cytology evaluations in 12,705 patients evaluated at our institution from 1992 to 2004 to identify cytology results of pure nonTCC neoplasms. For study purposes negative urine cytology was defined as one that reported negative and/or atypical cells, while posi-

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TABLE 1. Characteristics of patients with urinary cytology showing nonTCC malignancy

Parameters	AdenoCa	Squamous Cell Ca	Other NonTCC	All NonTCC
No. pts	108	115	50	273
No. data missing	3	5	8	16
Study group (No.)	105	110	42	257
% Symptoms (No./total No.):				
Hematuria	92.4 (97/105)	95.4 (105/110)	100 (42/42)	94.9 (244/257)
Dysuria	26.7 (28/105)	38.1 (42/110)	19.0 (8/42)	28.6 (78/257)
Mean age at cytology (range)	68.0 (39–83)	67.5 (11–92)	62.5 (1–86)	66.7 (1–92)
% Men (No./total No.)	72.3 (76/105)	53.6 (59/110)	71.4 (30/42)	64.2 (165/257)
% Cytology (No./total No.):				
Suspicious	43.5 (47/108)	20 (23/115)	24 (12/50)	30 (82/273)
Pos	56.5 (61/108)	80 (92/115)	76 (38/50)	70 (191/273)

tive urine cytology was defined as one that reported suspicious and/or positive. Reviewing these results documented a total of 43,831 negative and 11,349 positive cytology studies in 3,604 patients. Only cytology evaluations performed at our institution were included in the database.

On reviewing positive cytology findings we considered results reporting mixed histology, such as combined TCC and squamous cell carcinoma or combined TCC and adenocarcinoma, to be TCC with aberrant differentiation and we included them in the TCC group. Only cytology studies with pure nonTCC were classified in this study as cytology results positive for nonTCC. Using these criteria 10,943 cytology studies were classified as positive for TCC, while in 273 patients a total of 406 cytology evaluations were classified as positive for nonTCC.

For all analyses we only examined the results of cytology studies within 6 months of pathological confirmation. In patients with multiple cytology studies during this period histological type was assessed for positive cytology results. No further analysis was performed in patients with negative cytology results or in those with TCC histology. Of the 273 patients 133 (48%) underwent only a single cytology study during the preceding 6-month period and the remaining 140 (51%) underwent 2 cytology evaluations. Of these patients 133 (95%) had 2 concordantly positive cytology studies, while in 7 results were discordant between repeat cytology evaluations for suspicious or malignant cells. All 7 patients had a positive cytology result first, followed by a single negative cytology result before pathological confirmation was obtained.

Cytological findings in 273 patients were then correlated with histopathology findings on subsequent TUR or partial cystectomy/RC. Again, for consistency pathology results reporting mixed histology were considered to be TCC with aberrant differentiation. Of TURs and/or partial cystectomies/RCs 68% were pure TCC, 25% had varying amounts of squamous cell, adenocarcinoma or small cell components and 7% were pure nonTCC.

In a separate analysis we examined prior cytology results in patients with documented urothelial neoplasms on TUR or cystectomy. Our overall database included a total of 6,021 TUR and 1,525 RC pathology specimens in 3,205 patients. After selecting for patients with nonTCC histology a total of 220 TUR, and 160 partial cystectomy and RC pathology specimens in 245 patients comprised our nonTCC database. These data were then correlated with previous cytology findings.

For this analysis nonTCC malignancies were categorized as adenocarcinoma, squamous cell and other, including

small cell disease, sarcoma, melanoma, lymphoma or renal cell carcinoma. The reason for the category, other, was the low incidence of the respective histologies. These lesions included 12 lymphomas, 3 melanomas, 22 small cell carcinomas, 5 renal cell carcinomas and 8 sarcomas. Finally, due to the low incidence of upper tract lesions the association between nontransitional cell malignancies categorized by different urinary tract sites, such as the bladder, ureter, renal pelvis, etc, and urinary cytology findings was not performed.

## RESULTS

A total of 273 patients had cytology findings positive for nonTCC (table 1). In 16 patients no correlation with TUR/RC specimens was available. All 105 patients (100%) with cytology findings positive for adenocarcinoma who had histology data available for diagnosis confirmation had histologically proven cancer in the urinary tract on subsequent evaluation. Of the patients 90 (86%) had adenocarcinoma in the urinary tract, including 13 (12%) with primary or urachal adenocarcinoma of the bladder, 37 (35%) with prostate cancer and 40 (38%) with adenocarcinoma of various primary lesions (ovarian, colorectal or uterine) metastatic to the urinary tract. Only 15 patients (14%) had TCC in the bladder and no evidence of adenocarcinoma in the urinary tract (table 2).

Similarly all 110 patients (100%) with cytology findings positive for squamous cell carcinoma had histological confirmation of cancer in the urinary tract on subsequent evaluation. Of the patients 54 (49%) had squamous cell carcinoma in the urinary tract, including 51 (47%) with primary squamous cell carcinoma of the bladder and 3 (2%) with locally invasive squamous cell carcinoma of the cervix. The other half of this cohort (51% or 56 of 110 patients) had TCC in the bladder, including a significant squamous cell component in 42 (table 2).

TABLE 2. Urinary cytology nonTCC finding vs TUR or partial cystectomy/RC pathology

Urine Cytology	No. Pts	No. Pathological Confirmation (%)	No. Same Histology (%)	No. TCC (%)
AdenoCa	105	105 (100)	90 (86)	15 (14)
Squamous cell Ca	110	110 (100)	54 (49)	56 (51)
Other	42	42 (100)	28 (67)	14 (33)
Totals	257	257 (100)	172 (67)	85 (33)

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