The value of urine cytology in the diagnosis of bladder cancer

Cytopathological correlation

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ABSTRACT

الأهداف: تحديد قيمة علم خلايا البول في تشخيص سرطان المثانة من خلال مقارنة نتائج السيتولوجي والنسيجي.

الطريقة: استعرضنا بأثر رجعي قاعدة بيانات مختبرنا لجميع المرضى الذين يعانون من تشخيص الأنسجة(خزعة المثانة) من سرطان المثانة خلال الفترة من يناير 2007م حتى ديسمبر 2011م. واعتبر تشخيص الأنسجة المعيار الرئيسي وقورنت نتائج علم خلايا البول مع نتائج خزعة المثانة. واعتبرت الخزعات المحتوية على سرطان المثانة إيجابية. وقد تم تحليل كافة البيانات باستخدام الحزمة الإحصائية للعلوم الاجتماعية.

النتائج: راجعنا نتائج 191 مريضاً. كانت نتائج علم خلايا البول ايجابية للسرطان في 70 حالة (36.6%) وسالبة في 19 (9.9%). واعتبرت مائة وحالتين (53.4%) المشبوهة للسرطان. وكشف فحص الأنسجة أن هناك 82 حالة (42.9%) من درجة منخفضة الخباثة (TCC) و 64 حالة (33.5%) من TCC عالية الخباثة. وكانت سبع حالات (3.7%) إيجابية عن الأورام الخبيثة الأخرى غيرTCC. وكانت الحساسية الشاملة وخصوصية علم خلايا البول 94.1% و 26.3%، على التوالي. كانت حساسية علم خلايا البول لTCC منخفض وعالي الخباثة 18.3% و 51.3%، على التوالي. كانت الخصوصية لكلا الصنفين 26.3%.

خاتمة: كانت حساسية علم خلايا البول عالية للأورام من الدرجة العالية في الخباثة من الدرجة منخفضة منها. الحساسية العالية لعلم خلايا البول يظهر أنه لا يزال أداة قيمة في تشخيص سرطان المثانة.

Objectives: To identify the value of urine cytology in the diagnosis of bladder cancer by comparing cytologic and histologic findings.

Methods: This study was conducted from January to December 2012 at the Department of Pathology, Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia. The laboratory database was retrospectively reviewed for all patients with a histopathological diagnosis of urothelial carcinoma (UC) between January 2007 and December 2011. Histopathological diagnosis was considered the gold standard, and urine cytology findings were correlated with the results of bladder biopsy. Biopsies with low- and high-grade lesions were considered positive. All data were analyzed using the Statistical Package for Social Sciences.

Results: We reviewed the results of 191 patients. Urine cytology results were positive for malignancy in 70 cases (36.6%) and negative in 19 (9.9%). One hundred and two cases (53.4%) were considered suspicious for malignancy. Histopathological examination revealed that there were 82 cases (42.9%) of low-grade UC, and 64 cases (33.5%) of high-grade UC. Seven cases (3.7%) were positive for malignancies other than UC. For urine cytology, the overall sensitivity was 94.1%, and 26.3% specificity. The sensitivity of urine cytology for low-grade was 18.3%, and 51.3% for high-grade UC. The specificity for both grades was 26.3%.

Conclusion: This study shows that sensitivity of urine cytology is higher in high-grade UC than in low-grade UC. The high sensitivity of urine cytology confirms that it is still a valuable tool in bladder cancer diagnosis.

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Over the last 6 decades, urine cytology has become an important diagnostic tool in the screening and follow-up of patients with urothelial carcinoma (UC). However, there is a high variability in the diagnostic accuracy of urine cytology as reported in studies conducted worldwide.[1-5] This makes the accuracy of urine cytology questionable, especially with the emergence of several ancillary diagnostic techniques,[6,7] that are claimed to be more sensitive, particularly in the detection of low-grade urothelial neoplasms.[7] This includes the multicolor multi-target fluorescence in situ hybridization (FISH) UroVysion™ test (Abbott Molecule Inc., Des Plaines, IL, USA), which was initially approved by the FDA for surveillance of patients with bladder cancer, and later for detection of bladder cancer in persons with hematuria, in whom bladder cancer was suspected.[8-12] In spite of newer modalities, urine cytology testing is still practiced in most medical centers within the region due to its lower cost when compared to these new tests. We carried out a retrospective study to compare the results of urine cytology with those of bladder biopsy in order to confirm the value of urine cytology in the diagnosis of UC.

Methods. This study was conducted from January to December 2012 at the Pathology Department of King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia. We retrospectively reviewed the database of all patients with a histological diagnosis of UC between January 2007 and December 2011. Patients were included if they had prior corresponding urine cytology within one year of histopathological diagnosis. We excluded patients with insufficient biopsy or urine cytology samples. Histopathological diagnosis was considered negative for biopsies with normal histology and inflammatory reactive changes; it was considered positive for those with low-grade and high-grade lesions. Low-grade lesions included dysplasia and low-grade UC, while high-grade lesions included carcinoma in situ and high-grade UC. Histopathological grading was based on the degree of differentiation as defined by the World Health Organization classification of urothelial neoplasms.[13] All urine cytology specimens were single voided urine samples that were centrifuged and stained with Papanicolaou stain. Results of urine cytology were classified according to the recommendation of the Papanicolaou Society of Cytopathology[14] for urine cytology procedures, and reporting into inadequate, negative, suspicious, and positive for malignancy. All urine cytology specimens with a diagnosis of atypical cells were either considered "negative for malignancy," if cellular changes did not raise any unwarranted suspicion (changes mostly due to inflammation - reactive atypia), or included in the category of "suspicious for malignancy" if cellular changes were suggestive of dysplasia or malignancy (suspicious atypia). In cases where the patient had more than one urine sample obtained for examination, the worst urine cytology result was considered. The study protocol was approved by the Biomedical Ethics Research Committee of King Abdulaziz University.

Data were analyzed using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA). For purposes of statistical analysis, the "inadequate" group was excluded and "suspicious" cases were included in the "positive for malignancy" category. Histopathological diagnosis was considered the reference (gold) standard and urine cytology findings were correlated with the results of bladder biopsy. We calculated the overall sensitivity and specificity of urine cytology according to the different histological grades of UC.

Results. We reviewed the results of 191 patients. Of the 191 patients, 170 were men. The mean age of the patients was 60 years (range; 25-95 years). As shown in **Table 1**, urine cytology results were positive for malignancy in 70 cases (36.6% [20 cases of low grade UC, 49 cases of high grade UC, and one case of malignancy other than urothelial malignancy]), and negative in 19 (9.9%). One hundred and two cases (53.4%) were considered suspicious for malignancy. There was no cytologically inadequate specimen. Histopathological examination revealed that there were 82 cases (42.9%) of low-grade UC, and 64 cases (33.5%) of high-grade UC. Seven cases (3.7%) were positive for malignancies other than transitional carcinoma, namely squamous cell carcinoma and adenocarcinoma. **Table 2** shows the results of cytology and histology when "suspicious" cases were included in the "positive for malignancy" category. The overall sensitivity was 94.1% and specificity of urine cytology 26.3%. Its sensitivity for low-grade was 18.3%, and 53.1% for high-grade UC.

Discussion. Several studies have evaluated the accuracy of urine cytology in the diagnosis of bladder cancer. However, there are no data regarding the efficacy of urine cytology in the Saudi literature. As a

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Table 1 - Cross tabulation of cytology and histology diagnoses in a study conducted at the Pathology Department of King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia.*

Cytology diagnosis	Histology diagnosis				Total
	Negative	Low-grade UC	High-grade UC	Other malignancies	
Negative	10 (26.3)	3 (3.7)	4 (6.2)	2 (28.6)	**19 (9.9)**
Suspicious	25 (65.8)	52 (63.4)	23 (35.9)	2 (28.6)	**102 (53.4)**
Low-grade UC	2 (5.3)	15 (18.3)	2 (3.1)	1 (14.3)	**20 (10.5)**
High-grade UC	1 (2.6)	12 (14.6)	34 (53.1)	2 (28.6)	**49 (25.7)**
Other malignancies	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	**1 (0.5)**
Total	**38 (19.9)**	**82 (42.9)**	**64 (33.5)**	7 (3.7)	**191 (100.0)**

UC - urothelial carcinoma. *Data are presented as frequency (%). p=0.0001 for χ^2 test

result, the findings of our study were compared with those from other studies conducted in other developed and developing countries.[15-18] The reported sensitivity of urine cytology in these studies varied between 21.1 and 62.0%, lower than the 94.1% in our study (**Table 3**), thus demonstrating better detection rates at our hospital. We also achieved a higher sensitivity (53.1%) for high-grade lesions compared to the 46.3% reported by Brimo et al,[18] and 51.0% by Yafi et al.[5] Conversely, the specificity of urine cytology in our study (26.3%) was lower than in other studies, where the authors reported specificity rates of 98.6%[17], and 85%.[18] The low specificity of cytology in our study is most likely due to a high false positive rate. This results from the fact that in our institution, we prefer to label samples as "suspicious for malignancy" rather than "negative for malignancy" so that physicians are encouraged to request for further investigations, and subsequently diagnose cases that might have been otherwise considered "negative for malignancy".

Table 2 - Summary of cytology and histology results of a study conducted at the Pathology Department of King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia (N=191).

Cytology	Histology		Total
	Negative	Positive	
Negative	10 (26.3)	9 (5.9)	**19 (9.9)**
Positive†	28 (73.7)	144 (94.1)	**172 (90.1)**

Data are presented as frequency (%). †This represents all cases that were "positive for malignancy" and those that were "suspicious".

The diagnostic accuracy of urine cytology depends on many factors. It is reportedly high in patients who are symptomatic, or being followed after bladder cancer diagnosis and treatment.[19] In general, it is reported that papilloma and papillary urothelial neoplasms of low malignant potential cannot be reliably diagnosed regardless of the inclusion of several key cytologic findings. Urine cytology sensitivity increases with the grade of the tumor, and it varies from 26-90% for grade 1, increases to 80% for grade 2, and to 95% for grade 3. The specimen type has also been shown to affect the accuracy of urine cytology.[19] Findings from studies that used voided urine specimens demonstrated low sensitivity and high specificity rates. Raab et al[20] and Brimo et al,[18] for example, reported sensitivity values of 49.2%[20] and 44.2%,[18] and specificity values of 89%[20] and 82%.[18] The sensitivity of bladder washing cytology was slightly higher than that of urine cytology, with rates ranging from 66-77%.[21] Although the specificity of cytology in bladder washings is high (97%),[8] it suffers from low sensitivity, especially in the case of low-grade papillary tumors.[22]

Table 3 - Comparison of sensitivity and specificity rates of a study conducted at the Pathology Department of King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia compared with those of other studies.

Studies	Year	Sensitivity (%)			Specificity (%)		
		Overall	Low-grade	High-grade	Overall	Low-grade	High-grade
Current study		94.1	18.3	53.1	26.3	26.3	26.3
Bhuiyan et al[15]	2003	62.0	NA	NA	NA	NA	NA
Karakiewicz et al[16]	2006	26.0-65.0	NA	75.6	NA	NA	97.1
Talwar et al[17]	2007	21.1	9.5	18.1	98.6	NA	NA
Brimo et al[18]	2009	29.6	8.1	46.3	85.0	85.0	85.0
Yafi et al[5]	2013	NA	10.0	51.0	83.0-88.0	NA	NA

NA - not applicable

Our findings showed that there were 9 false negative and 28 false positive test results. In one report, errors in cancer diagnosis were reported to occur in up to 11.8% of all reviewed cytologic-histologic specimen pairs.[23] These discrepancies are generally due to combined sampling and interpretation failure in one, or the other specimen.[23,24] False negative test results are known to arise as a result of the inability to sample some lesions (as is the case in voided urine specimens, which may not contain shed neoplastic cells), or to difficulties in diagnosing some tumor types.[25,26] The reasons for false positivity include catheterization, inflammation, viral infection (polyomavirus), chemotherapy, and a positive cytology result in the presence of a negative biopsy.[27] However, a positive cytology in the presence of a negative biopsy is not always indicative of a false positive diagnosis since urine cytology is known to pick up carcinoma in situ, while cystoscopy may remain negative. Given that cytology allows sampling of the entire urinary tract, a positive urine cytology may point towards malignancy in the upper urinary tract rather than in the urinary bladder per se. This highlights the importance of providing a detailed history to the reporting cytologist or histopathologist.

In a cytopathologic correlative study such as this, the interval between cytology and subsequent biopsy is critical in determining the accuracy of cytology. More discrepancies should be expected between the 2 results if the interval is longer as the initial cytology results may not reflect the pathologic state of the urothelium at the time of biopsy. Thus, we believe that the maximum interval of one year between cytology and biopsy results that we allowed may have affected our results.

This study had some limitations. First, we considered histology as the gold standard and excluded all patients who had insufficient biopsy specimens, thus increasing the likelihood of missing cancer cases. Second, the small number of cases and the interval of one year considered between cytology and histology testing in our study may be too long, and it may affected the sensitivity and specificity rates in our study.

In conclusion, the sensitivity of urine cytology was 94.1%, whereas the specificity was 26.3%. Its sensitivity for high-grade tumors was higher than that for low-grade lesions, while the specificity was the same in both grades. Although the specificity of urine cytology is low, its high sensitivity shows that it is still a valuable tool in the diagnosis of bladder carcinoma, especially in general hospitals, where newer modalities have not yet been established. Larger studies may be required to better study specificity and sensitivity of urine cytology.

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