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Significance of Suspicious Urine Cytology (Class III) in Diagnostic Cystoscopy Follow-up of Bladder Cancer

Mesane Kanserinin Tanısal Sistoskopi Takibinde Şüpheli İdrar Sitolojisinin (Sınıf III) Önemi

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ABSTRACT

Objective: The aim of this study was to determine the appropriate path to follow in the cystoscopic follow-up of patients with suspicious urine cytology but negative malignancy findings on cystoscopy.

Methods: Data of 829 patients with bladder cancer between 2012 and 2023 were retrospectively analyzed. Patient data including age, gender, recurrence, progression, and urine cytology results were analyzed.

Results: Approximately 65% of patients with suspicious urine cytology results had recurrence or progression of bladder cancer at subsequent follow-up. This highlights the importance of urine cytology as a screening tool and demonstrates its effectiveness as a diagnostic tool in detecting bladder cancer. However, it should be noted that even patients with suspicious urine cytology are at risk of developing bladder cancer in the future.

Conclusion: Evaluation of suspicious urine cytology results is an important step in the early diagnosis of bladder cancer. Although the test has diagnostic accuracy, it should be clinically interpreted and used in conjunction with other investigations to determine the patient's cancer status.

Keywords: Suspicious cytology, cystoscopy, bladder cancer

ÖZ

Amaç: Şüpheli idrar sitolojisi olan ancak sistoskopide malignite bulguları negatif olan hastaların sistoskopik takibinde izlenecek uygun yolların belirlenmesi amaçlandı.

Yöntem: 2012-2023 yılları arasında 829 mesane kanserli hastanın verilerinin retrospektif olarak değerlendirildi. Yaş, cinsiyet, nüks, progresyon ve idrar sitolojisi sonuçlarını içeren hasta verileri analiz edildi.

Bulgular: Şüpheli idrar sitolojisi sonuçları olan hastaların yaklaşık %65'inde sonraki takiplerde mesane kanserinde nüks veya ilerleme görülmüştür. Bu durum, idrar sitolojisinin bir tarama aracı olarak önemini vurgulamakta ve mesane kanserini tespit etmede bir tanı aracı olarak etkinliğini göstermektedir. Bununla birlikte, şüpheli idrar sitolojisi olan hastaların bile gelecekte mesane kanseri geliştirme riskiyle karşı karşıya olduğunu belirtmek gerekir.

Sonuç: Şüpheli idrar sitolojisi sonuçlarının değerlendirilmesi, mesane kanserinin erken teşhisinde önemli bir adımdır. Test tanısal doğruluk oranına sahip olsa da, klinik olarak yorumlanmalı ve hastanın kanser durumunu belirlemek için diğer tetkiklerle birlikte kullanılmalıdır.

Anahtar Kelimeler: Kuşkulu sitoloji, sistoskopi, mesane kanseri

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INTRODUCTION

Urothelial carcinoma of the bladder is the 7th most common cancer diagnosed in the male population worldwide. Bladder cancer ranks 10th when both genders are taken into account.[1] The majority of patients with bladder cancer present with a non-muscle invasive disease limited to the mucosa (stage Ta, CIS) or submucosa (stage T1), and this rate is even higher in patients <40 years of age.[2]

In the diagnosis of bladder cancer, a patient history focusing on voiding symptoms and hematuria should be taken. In patients with hematuria, bladder ultrasound and/or computed tomography can be performed during the initial examination. Cystoscopy is required for the gold standard diagnosis in patients with symptoms suggestive of bladder cancer. Urinary cytology has high sensitivity in high-grade tumors. However, low-grade tumors do not have the same sensitivity.[3]

Examination of exfoliated cancer cells in voided urine or bladder-washing specimens yields increased sensitivity for HG and G3 tumors (84%), but not for LG/G1 tumors (16%) [101]. CIS detection has a sensitivity range of 28-100%. Although useful, cytology is best used as an adjunct to cystoscopy in patients with HG/G3 tumors and is not intended to detect LG tumors. Positive voided urinary cytology can indicate urothelial cancer at any location in the urinary tract, whereas negative cytology cannot definitively rule it out.[4,5]

Cytological interpretation depends on the interpretation of the pathologist, and urinary tract infections, low cellular yield, stones, or intravesical installations may preclude evaluation; however, specificity is greater than 90% in experienced hands.[6]

According to the classification of urinary cytological examination with Papanicolaou and Marshal staining, the absence of malignant cells is considered class I-II negative, and the presence of malignant cells is considered class IV-V positive. Class III or suspicious group is controversial; therefore, in clinical practice, suspected urinary cytology requires extensive investigations to rule out the presence of urothelial malignancy.[7] Most urologists treat class III urinary cytology as malignant, resulting in repeated evaluations and follow-up that are inconclusive in most these patients.[8]

The aim of our study was to determine the paths to be followed in the cystoscopic follow-up of patients with suspicious urine cytology and negative for malignancy in cystoscopy.

METHODS

Our research received approval from the Manisa Celal Bayar University Ethics Committee with reference number: 20.478.486/1962, date: 31.08.2023. Following this approval, data on age, gender, recurrence, progression, and urine cytology were retrospectively evaluated for 829 patients who had been monitored for bladder cancer at our urology clinic from 2012 to 2023. The cytology results of the cystoscopy follow-up of patients who underwent trans urethral resection bladder (TUR-B) surgery for bladder cancer were included in the study. Cytological results were classified as benign, suspicious, or malignant. According to the TUR-B pathology results, patients were divided into three groups according to recurrence, progression, or absence of both. Patients were divided into risk groups according to European Urology guideline by using TUR-B pathology results, tumor size, tumor number, recurrence, and age information. The data regarding the number of tumours, tumor diameter, prior recurrence rate, stage of the disease, concomitant CIS and tumor grade were inputted and retrieved from the European Organisation for Research and Treatment of Cancer Bladder Cancer Recurrence and Progression Calculator.[9] The study included patients who underwent at least 1 TUR-B operation and had a minimum of 2 regular cystoscopy follow-ups. Patients with an inadequate number of cystoscopy follow-ups were not considered. Low-risk group patients underwent cystoscopy at 3 and 12 months in the first year after TUR-B. Annual cystoscopy follow-up was performed up to 5 years after the initial operation. After 5 years, patients were no longer included in the follow-up. Patients who were at intermediate or high risk were monitored using cystoscopy every 3 months for the first 2 years following TUR-B and then every 6 months for up to 5 years. Annual follow-up was continued after the fifth year. Blood-washing specimens were taken during cystoscopy and sent to the pathology laboratory. In cases where a mass was detected during cystoscopic follow-up, it was classified as a recurrence, and TUR-B operation was planned without cytological sampling. Following the pathology report, the risk classification was re-evaluated, and a revised follow-up plan was developed. Patients with malignant or suspicious cytological results underwent computed tomography with intravenous opaque administration.

All patients underwent a full urinalysis before undergoing cystoscopy, which was conducted after treating any infections with compatible laboratory or clinical findings. Cystoscopy was performed using a 17-Fr rigid cystoscope and white light. After applying the exclusion criteria, data from 144 patients were included in the study.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences version 26 software. Our study's numerical data did not follow a normal distribution, as determined by the Kolmogorov-Smirnov test. We considered p values below 0.05 significant.

Nominal data, such as gender, risk group, recurrence, progression, and cytology results, were analyzed using the chi-square test. The Kruskal-Wallis test was applied when more than two nominal data points, such as cytology results, were grouped with recurrence and progression scores. On the other hand, the Spearman's correlation test was used when numerical data such as age, follow-up time (months), recurrence, and progression scores were evaluated.

RESULTS

Progression was observed in 17 (11.8%) and recurrence in 74 (51.3%) of the patients included in the study. The mean follow-up time for cystoscopy was 35.12±2 months, and the mean age of patients was 65±9.7 years. During the patient follow-up, the average time to recurrence was 11 months, and progression occurred at 35 months. The distribution of cytology results according to the number of patients with recurrence/progression or not is shown in Table 1, and the distribution of the data according to the pathological results after the first TUR-B operation is shown in Table 2. The study included 128 male and 16 female patients, with no significant statistical difference between the genders. The chi-square test revealed that suspicious or malignant cytology outcomes were associated with recurrence (p=0.00) (Figure 1) and progression (p=0.00) (Figure 2). Comparing suspicious and benign cytology results, patients with suspicious results showed a statistically significant increase in their recurrence score (p=0.020) and progression score (p=0.006). Similarly, when comparing suspicious and malignant cytology results, patients with malignant results showed a statistically significant increase in their recurrence score (p=0.043) and progression score (p=0.00). However, there was no statistically significant difference between the recurrence score (p=0.52) and progression score (p=0.06) for the malignant and suspicious cytology groups. In addition, the cytology results and follow-up periods also exhibited no statistical significance (p=0.68). Upon comparison of benign cytology with suspicious cytology, increased age was statistically correlated with suspicious cytology (p=0.007). However, when comparing malignant cytology with suspicious cytology, there was no statistical difference. There was a positive association between age and both recurrence (p=0.031) and progression (p=0.008) scores. However, no relationship was found between follow-up time and recurrence or progression scores. Risk categories were significantly associated with recurrence and progression scores (p<0.001). Additionally, an increase in age (p=0.006) and follow-up time (p=0.04) was associated with a shift from low- to very-high-risk groups.

DISCUSSION

In the Nabi et al.[10] study, they shared the 2-year follow-up results of patients who presented with hematuria. The mean follow-up period was 15.7 months, and suspicious cytology was associated with malignancy in patients with suspicious urine cytology and no evidence of malignancy at the first follow-up. Results similar to those of the previous study were obtained, but our method differed, and the mean follow-up period in our study was roughly twice as long as that in the previous study. As our research was

Table 1. Distribution of cytology results according to recurrence and progression

	No recurrence or progression	Recurrence	Progression	Total
Benign cytology	34	47	2	83
Suspicious cytology	17	23	9	49
Malign cytology	2	4	7	12

Table 2. Distribution of data according to pathology results after the first TUR-B operation

	N	Mean age	Male	Female	Mean follow-up time (month)	Benign cytology (N)	Suspicious cytology (N)	Malign cytology (N)
PUNLMP	7	55	7	0	2	7	0	0
TaG1	69	66	61	8	33	40	28	1
TaG2	1	62	1	0	84	1	0	0
TaG3	18	59	15	3	44	11	6	1
T1G1	1	57	1	0	90	1	0	0
T1G2	3	59	3	0	84	2	1	0
T1G3	38	69	34	4	35	21	12	5
CIS	7	66	6	1	32	0	2	5

TUR-B: Trans urethral resection bladder

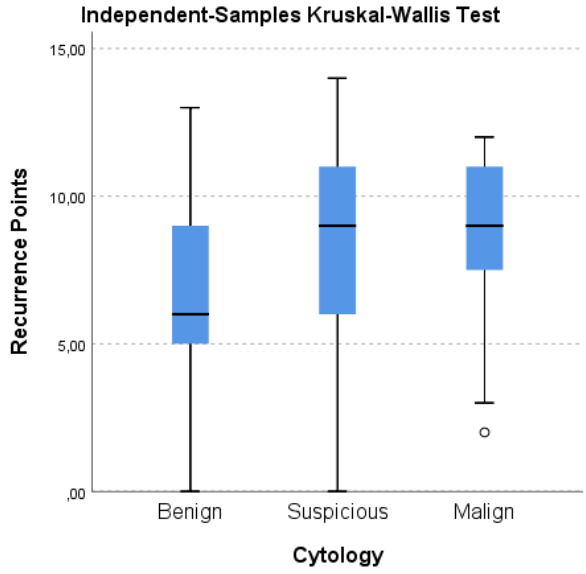

Figure 1. Distribution of recurrence scores according to cytology groups

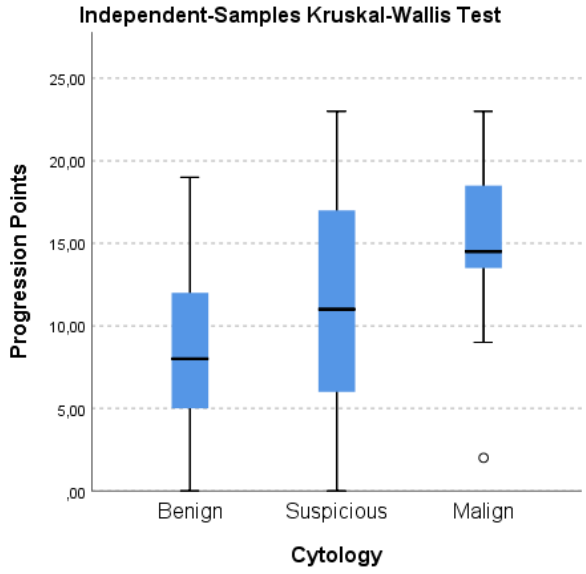

Figure 2. Distribution of progression scores according to cytology

founded on a long-term cystoscopy follow-up of patients who were diagnosed with bladder tumors, it demonstrated that suspicious cytology necessitates careful evaluation in the follow-up after the diagnosis of bladder cancer.

In a study conducted by Raitanen et al.[11], 48.8% of the follow-up patients with suspicious class III cytology exhibited recurrence, implying a significant risk of concomitant malignancy in this group of patients. Similar to our study, 46.9% of patients with suspicious cytology results had recurrence and 18.3% had progression.

In the study by Sternberg et al.[12], retrospective data from 3 years were examined, and in 48.7% of the 111 patients with suspicious urine cytology, simultaneous urothelial carcinoma was detected during cystoscopy. In our study, these patients had a history of urothelial carcinoma and a suspicious cytology result despite no visible mass during cystoscopy. The fact that a similar rate of tumor recurrence was observed in subsequent cystoscopy follow-ups, either early or late, indicates that suspicious cytology should be closely monitored for malignancy.

In Kim et al.'s[13] study, a positive fluorescence in situ hybridization (FISH) test proved to be a substantial indicator of recurrence and progression compared to negative FISH during follow-up of suspicious urine cytology. Nevertheless, there was no connection discovered between FISH result and tumor recurrence in the nearby follow-up period. Discoveries of new diagnostic methods through further studies will substantially expedite the job of urologists, specifically in the follow-up of suspicious cytology.

In a study published by Lebret et al.[14], artificial intelligence algorithms, along with digital image processing (VisioCyt test), were used to identify low- and high-grade urothelial tumors. The recently developed diagnostic method (Phase 1) displayed superior sensitivity compared with standard cytological examination. Should the validation cohort verify these findings, the method holds potential for assisting urologists in the diagnosis of bladder cancer.

In 2016, the working group of The Paris System convened to standardize the reporting system for urinary cytology in a universally acceptable and usable manner. The Paris System underscored the lack of specificity and sensitivity in detecting low-grade urothelial neoplasms, while highlighting improved sensitivity and specificity for identifying high-grade urothelial carcinoma.[15] However, evidence in the literature suggests that urine cytology, as described by Papanicolaou and Marshall, exhibits superior sensitivity compared with The Paris System for detecting high-grade carcinoma.[16]

In our study, we obtained important findings regarding the evaluation of suspicious urine cytology results. Our results showed that approximately 65% of patients with positive suspicious urine cytology results had recurrence or progression of bladder cancer in subsequent follow-ups. These results confirm that this test has a high diagnostic accuracy rate and that urine cytology is an effective screening tool. Furthermore, our study also shows that some patients with negative suspicious urine cytology results still have a risk of bladder cancer in the future. Therefore, urine cytology results alone may be insufficient

for determining a patient's cancer status. They should be evaluated in conjunction with other tests and examinations and considered clinically.

Study Limitations

The limitations of this study are that it is a retrospective study in a small patient population.

CONCLUSION

Evaluation of suspicious urine cytology results is an important step and a valuable tool for early diagnosis of urinary tract cancer. However, the results need to be clinically interpreted and used in conjunction with other examinations. Future studies should investigate the integration of this test with other techniques to improve its diagnostic accuracy and better determine the risk of urinary tract cancer.

Ethics

Ethics Committee Approval: Our research received approval from the Manisa Celal Bayar University Ethics Committee with reference number: 20.478.486/1962, date: 31.08.2023.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Y.E.B., Concept: Y.E.B., T.M., Design: Y.E.B., T.M., Data Collection or Processing: Y.E.B., A.C.A., A.G., Analysis or Interpretation: Y.E.B., Literature Search: Y.E.B., Writing: Y.E.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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