RESEARCH ARTICLE

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Accuracy of Urine Cytology In Detecting Bladder Cancer

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Abstract

One of the most prevalent and deadly cancers in men is bladder cancer. To achieve the best possible outcome, physicians need to diagnose it promptly. The gold standard for diagnosis is tissue biopsy, but this method is invasive. There is another option for non-invasive diagnostic using urine cytology. The purpose of this study was to measure the accuracy of urine cytology in diagnosed bladder cancer patients. This study extracted data from patients medical records in a tertiary hospital in Indonesia from 2009–2019. The diagnostic accuracy was then compared between urine cytology and biopsy as the gold standard. Data on subjects' baseline characteristics and diagnostic accuracy (sensitivity, specificity, PPV, and NPV) were collected. Results were then stratified according to the American Joint Committee on Cancer pathology staging for bladder cancer. Of 124 study subjects, male was more dominant (male,88% versus female, 12%) Seventy-five patients had a T1-tumor stage. Overall, the diagnostic accuracy was as follows:sensitivity, 47.8%; specificity, 90.9%; PPV, 98.2%; and NPV, 14.5%. High-grade tumors were shown to have a higher sensitivity. The highest accuracy was found in the MIBC grade T3, which was 90.68%. For diagnostic accuracy, urine cytology offered high specificity, but low sensitivity. The exploration of other markers is needed to establish a non-invasive but accurate method to diagnose bladder cancer.

Keywords: Bladder cancer, diagnostic, histopathology, sensitivity, urine cytology

Akurasi Sitiologi Urine Dalam Mendeteksi Kanker Buli

Abstrak

Kanker buli merupakan salah satu kanker yang paling sering terjadi pada pria dengan angka mortalitas yang tinggi. Diagnosis yang cepat diperlukan untuk mencapai prognosis sebaik-baiknya. Biopsi jaringan sebagai standar kunci untuk diagnosis saat ini merupakan pemeriksaan invasif. Sitologi urine dapat digunakan sebagai alternatif pemeriksaan noninvasif untuk menegakkan diagnosis. Penelitian ini bertujuan mengetahui tingkat akurasi diagnosis pemeriksaan sitologi urine pada pasien kanker buli. Penelitian ini menggunakan rekam medis seluruh pasien kanker buli di sebuah rumah sakit tersier pada tahun 2009–2019. Akurasi diagnosis dari pemeriksaan sitologi urine dibanding dengan biopsi yang menjadi metode standar kunci diagnosis saat ini. Karakteristik subjek penelitian dan tingkat akurasi diagnosis (sensitivitas, spesifisitas, PPV, dan NPV) dianalisis. Hasil dikelompokkan berdasar atas tahapan kanker buli menurut *American Joint Committee.* Dari 124 subjek penelitian, 88% laki-laki dan 12% perempuan. Tujuh puluh lima pasien tergolong ke dalam kelompok tumor T1. Akurasi diagnosis secara keseluruhan: sensitivitas 47,8%; spesifisitas 90,9%; PPV 98,2%; dan NPV 14,5%. Sensitivitas tertinggi ditemukan pada tahapan tumor paling tinggi. Akurasi tertinggi ditemukan pada jenis tumor MIBC tahap T3, sebesar 90,68%. Sitologi urine memiliki spesifisitas yang tinggi, namun sensitivitas rendah. Pemeriksaan marker non-invasif lainnya mungkin diperlukan untuk menegakkan diagnosis kanker buli yang lebih akurat.

Kata kunci: Diagnosis, histopatologi, kanker buli, sensitivitas, sitologi urine

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Introduction

Cancer of the bladder is ranked as the 10th most prevalent malignancy in the world. Men are four times more often than women to have bladder cancer. In 2008, the incidence of bladder cancer was around 386,000 cases worldwide and had caused over 150,000 deaths. But now, as the prevention, diagnosis, and treatment have been improved, the worldwide mortality rate is falling. Bladder cancer is now the 13th in the rank of most deadly cancer worldwide.[1–3]

The outcome of patients with bladder cancer may be improved by earlier evaluation and intervention. Other studies also stated that worse outcomes were found in patients with delayed diagnosis and treatment, specifically in patients with diagnosis delay of more than three months, particularly in lower stages of cancer.[4] Despite the majority of the cases were presented with the low stage when the diagnosis was made (confined to the mucosa or submucosa), high risk of recurrence and progression to aggressive disease (up to 70% and 30%, respectively) after resection require more prompt diagnostic modalities to minimize the risk of recurrence.[5]

The current gold standard to detect bladder cancer is cystoscopy combined with biopsy. However, one of the main drawbacks of the method is its invasiveness, which may cause a significant degree of discomfort to the patient. Urine cytology was developed as one of the less invasive diagnostic modalities. However, the method has low sensitivity (0–50%), although the specificity is high (up to 99%).[6] Tumor grade, specimen, and sampling are several factors that affect the accuracy of urine cytology. In high-grade urothelial carcinoma, urine cytology served as an accurate diagnostic tool with up to 98% accuracy.

On the other hand, the diagnostic accuracy was less in low-grade urothelial carcinoma. The specificity was 50% with 8.5% sensitivity. Variable results were found in other studies. The sensitivity ranges from 20 to 97.3%, and specificity ranges from 74% to 99.5%.[7] The accuracy and the variable accuracy of this modality were affected by numerous factors. A local population study to ascertain its accuracy was intended to perform in this study. The purpose of this study is to determine the diagnostic accuracy of urine cytology in local populations of West Java with bladder cancer treated in a tertiary hospital. To our best knowledge, this is the first study that performed an accuracy assessment of urine cytology test on the West Java local population.

Methods

A single-centered and diagnostic research study measured urine cytology accuracy in bladder tumors cases. Participants' data were collected from medical records of the Urology Department in a tertiary hospital in West Java (2009–2019). Patients who received both biopsy and urine cytology tests and received treatment in this tertiary hospital were included in this study. Patients without previous confirmation of a diagnosis of suspected bladder cancer without confirmed biopsy results and/or urine cytology results were excluded. The histopathological samples provided from the biopsy may be acquired during the surgery or as part of a routine follow-up schedule.

The Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital gave ethical approval (No.LB.02.01/X.6.5/157/2021). Patients' baseline characteristics include age (years), sex, tumor type, grading, pathology status. The age and sex of the patients were readily collected from the medical records. Tumor types were stratified based on the histopathological reports listed in the medical records. Transitional cell carcinoma (TCC) consisted of urothelial carcinoma. Mixed carcinoma consisted of urothelial carcinoma and another co-existing tumor type, such as papilloma. Carcinoma other than urothelial carcinoma was defined as non-transitional cell carcinoma. The highest diagnosed tumor stage were cases with multiple biopsies and/or urine cytology results. The histopathological reports were classified using a TNM grading system. WHO and The International Society of Urological Pathology (ISUP) 2004 were used to grade non-invasive bladder tumors.

Sensitivity, specificity, accuracy, PPV, and NPV were the diagnosis parameters used in this study. Urine cytology was compared to the histopathological examination (biopsy), which is the gold standard for diagnostic. Positive findings define as atypical cells and carcinoma findings in urine. A non-specific inflammation is concluded as a negative finding. The authors stratified diagnostic parameters based on the pathology stage status.

The characteristics of the subjects are described with descriptive statistics. For the

Table 1 Characteristics of the Patients

Patients' Characteristics	N
Age, Median years (range)	58 (29–79)
Sex	
Male	109 (88%)
Female	15 (12%)
Histological finding	
Transitional cell carcinoma	105 (85%)
Mixed	0 (0%)
Non- transitional cell carcinoma	8 (6%)
Cystitis	11 (9%)
Percentage based on pathology	
Total NMIBC*	75 (64%)
Ta	6 (8%)
Tis	0 (0%)
T1	69 (92%)
Total MIBC**	38 (34%)
T2	20 (53%)
T3	8 (21%)
T4	10 (26%)
Grading	
PUNLMP***	15 (13%)
Low grade	73 (63%)
High grade	28 (24%)

*NMIBC=non-muscle invasive bladder cancer; **MIBC= muscle invasive bladder cancer; ***PUNLMP=papillary urothelial neoplasm of low malignant potential

accuracy of diagnostic, descriptive analysis was done according to the tumor grading stratification.

Results

This study included 124 patients. Table 1 showed the baseline characteristics of patients included in this study.

This study included 109 male patients (88%) and 15 female patients (12%) with a median age of 58 (29–79) years. The most common cancer type found in this study was Urothelial Cell carcinoma. On the other hand, only 4 adenocarcinoma cases, 1 liposarcoma, 1 leiomyoma, 1 squamous cell carcinoma and 1 rhabdomyosarcoma were found. The most frequently found cancer stage in the study was T1, consisted of 69 patients (59%). There were 15 patients (13%) with PUNLMP, 73 patients (63%) with low-grade tumors, and 28 patients (24%) with high-grade-tumor.

Diagnostic accuracy of the urine cytology, described in Table 2, was determined by sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV). ROC analysis was also performed and showed results as summarized in Table 3. The overall diagnostic accuracy of the urine cytology test was as follows: sensitivity 47.8%, specificity 90.9%, PPV 98.2%, and NPV 14.5%.

Table 2 Diagnostic Accuracy

Total	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
	47.8	**90.9**		**98.2**	**14.5**
NMIBC*					
Ta	50	90.9	88.92	75	77
T1	37.7	90.9	61.3	96.3	18.9
MIBC**					
T2	60	90.9	85.92	92.3	55.6
T3	87.5	90.9	90.68	87.5	90.9
T4	60	90.9	88.41	85.7	71.4
Grading					
PUNLMP***	40	90	84.74	85.7	52.6
Low Grade	41	90.9	61.52	96.2	21,7
High grade	79.3	90.9	88.28	95.8	62.5

NMIBC=non-muscle invasive bladder cancer; **MIBC=muscle invasive bladder cancer; ***PUNLMP=Papillary urothelial neoplasm of low malignant potential

Table 3 Area Under ROC Curve

Staging	Area Under ROC Curve (95% Confidence Interval)
Total	0.693 (0.56–0.83)
NMIBC*	
Ta	0.705 (0.42–0.99)
T1	0.643 (0.48–0.80)
MIBC**	
T2	0.755 (0.58–0.93)
T3	0.892 (0.72–1.00)
T4	0.755 (= 0.54–0.97)
Grading	
PUNLMP***	0.655 (0.44–0.87)
Low grade	0.644 (0.49–0.80)
High grade	0.814 (0.67–0.95)

*NMIBC= non- muscle invasive bladder cancer; **MIBC= muscle invasive bladder cancer; ***PUNLMP=papillary urothelial neoplasm of low malignant potential

Overall area under the ROC Curve for urine cytology was 0.693. Urine cytology tests were found to have higher sensitivity in higher tumor stages. Greater sensitivity was seen in high-grade compared to low-grade tumors. According to AJCC Pathology Staging, the highest accuracy was found in MIBC stage T3, which is 90.68%. In WHO 2004 grading, the highest accuracy was found in High Grade in a number of 88.28%. Both MIBC stage T3 and High Grade also had highest Area Under ROC Curve score, which is 0.892 and 0.814 respectively.

Discussion

Bladder cancer is one of the most common cancers in men. It was ranked 10th as the most commonly encountered cancer worldwide. It occurs 4 times more commonly in men than in women.[1,8] The outcomes of patients may potentially be improved with earlier diagnosis and intervention. On average, the risk of mortality and disease progression, such as lymph node involvement (20–90% and 60%, respectively), was greater in patients who had a delayed time between diagnosis and radical cystectomy for more than three months. The risk of recurrence in such patients is higher. The five years mortality is almost 33% of all patients diagnosed with bladder cancer. Hollenbeck et al., in their study, established that patients had a 34% higher risk of death than those treated within 3 months when there is a nine-month delay between diagnosis and intervention. Low-grade tumors and low-stage disease had a higher risk (HR 2.11; 95% CI 1.69–2.64 and HR 2.02; 95% CI 1.54–2.64, respectively).[4] Older age, advanced tumor grade, metastasis to lymph nodes, lymphovascular invasion, and positive soft tissue surgical margins are several risk factors related to lower cancer-specific survival in patients with bladder cancer.[9]

There are various diagnostic methods feasible for bladder cancer. Zhu et al. made a review about the diagnostic accuracy of each available method: urine testing (microscopy, cytology, and markers), cystoscopy, Computed Tomography (CT) scan, and Magnetic Resonance Imaging (MRI). The highest specificity was achieved with a CT scan (77.8–100%), and the most heightened sensitivity was reached with urine microscopy (87–91%). Confirmation of the diagnosis uses the biopsy to obtain the tissue sample.[2] A systematic review from 2 studies held by Kumar et al. and Hajdinjak showed a sensitivity and specificity of urine cytology compared to microscopy examination. Kumar et al[2]. study shows that urine cytology's sensitivity in diagnosing a bladder cancer was only 13.3% with 100% sensitivity. These results are a bit similar to Hajdinjak's, with 42% sensitivity and 96% specificity. Low sensitivity with high specificity was shown in both studies.[2]

Study from Yafi et al. using a prospective method had found that urine cytology had overall low sensitivity (48%); Low-grade tumors had the lowest sensitivity (16%) and increased in high-grade tumors (84%). In contrast, its specificity was high, up to 80%.[5] Diagnostic accuracy was significantly affected by the grading of the tumor. In low-grade urothelial and papillary, sensitivity and specificity were very low, 8.5% and 50%, respectively.[7] The poor interobserver and intraobserver agreement were the other limitations of urine cytology. Reid et al. noted that interobserver and intraobserver agreement had only 77% (95% CI, 72–82%) in their overall accuracy.[10] However, lower specificity and higher sensitivity were found in low-grade tumors in this study. Thus, it may be inferred that diagnostic accuracy was affected by tumor staging greater than tumor grading. The sensitivity and specificity of urine cytology might be affected by the combination of the high stage but low-grade tumors that were found in several patients in this study. The study had yet to assess the agreement of the cases between

interobserver and intraobserver; this may be counted as one of the limitations of this study.

Despite non-invasive and yield compared to the standard biopsy, several studies stated that urine cytology might be vulnerable for some patients and extraneous factors, affecting its sensitivity and specificity to screen and diagnose bladder cancer. Gopalakrishna et al. had noted that diagnostic performance of urine cytology might be significantly affected by age ($p<0.001$), smoking history ($p=0.003$), and sex ($p<0.001$), mainly expressed in increased sensitivity and decreased specificity. Indications for testing, such as hematuria ($p=0.047$ in using logistic regression model of a generalized linear mixed model), were significantly associated with increased sensitivity and decreased specificity.[11] The diagnostic accuracy found in this study was concurrent with other studies: low sensitivity and high specificity. As a screening tool, this would infer that urinary cytology may not be ideal. Other factors may be another hurdle that limits the application of this method, such as patient factors that may significantly affect the sensitivity and specificity of the test, besides its advantage as a non-invasive diagnostic method.

In conclusion, urine cytology had high specificity but low sensitivity. Other markers that accurate yet non-invasive method to diagnose bladder cancer need to be established. Higher diagnostic accuracy is associated with high grade and high pathological staging (according to AJCC). The study results may be affected by intrinsic factors from each patient. However, those were not the subject of this study. Further studies and effort are required to enhance and discover other urine biomarkers with better sensitivity to justify the urine cytology method.

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