

Characteristics of Bladder Cancer in Dr. Sardjito General Hospital Yogyakarta: a 5-Year Report

*Fitra Hardian Prisnamurti, Ahmad Zulfan Hendri, Aria Danurdoro**

Division of Urology, Department of Surgery, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia

ARTICLE INFO

Received : 14 May 2021
Reviewed : 18 June 2021
Accepted : 06 October 2021

Keywords:

bladder cancer, clinical characteristics, Indonesia

ABSTRACT

Background: Bladder cancer is the eleventh most common malignancy worldwide and the sixth cancer in men. Bladder cancer shows a male predominance with a sex ratio of 4:1. Most bladder cancers are transitional cell carcinoma, and the other tumors are squamous cell carcinoma, adenocarcinoma, and rare entities like small cell carcinoma. Clinical stage and grade are the most critical determinants of the prognosis of bladder cancer. Therefore, this study aims to evaluate the characteristics of bladder cancer in Dr. Sardjito General Hospital, Indonesia.

Methods: We reviewed the medical records of patients with bladder cancer admitted to Dr. Sardjito General Hospital Yogyakarta from January 2015 until December 2020. The data were about demographic characteristics, clinical presentation and staging, grading and staging based on pathological examinations results, and cancer management.

Results: This study found 282 patients with bladder tumors. Fifty patients did not meet the inclusion criteria so the remaining 232 patients consisted of 169 male patients (72.8%) and 62 female patients (27.2%). The stages of tumors when the patients first came in were T1 diagnosed in 46 patients (22.7%), T2 diagnosed in 81 patients (40%), T3 diagnosed in 11 patients (5.4%), and T4 diagnosed in 64 patients (31.6%). A total of 30 patients were found to have secondary bladder tumors. The pathological anatomy results showed that 177 patients (76.2%) had transitional cell carcinoma and 33 patients adenocarcinoma (14.2%). All patients had undergone Transurethral Resection of Bladder Tumor (TURBT) for diagnosis and staging, followed by definitive treatment. It consisted of TURBT and chemotherapy bladder instillation in 46 patients (19.8%), radical cystectomy in 84 patients (36.2%), partial cystectomy in 4 patients (1.7%), and multimodal therapy (en-bloc transurethral resection of bladder tumors (ERBT) and chemotherapy) in 26 patients (11.2%). There were 72 patients (31%) who underwent TURBT alone.

Conclusions: From a 5-year study, we found similar results with previous studies that the most common bladder histopathological result is urothelial carcinoma. However, most patients presenting to our hospital have higher stages and grades, requiring radical treatment. These differences warrant a larger and more comprehensive, multi-center study in Indonesia.

*Corresponding author:

Aria Danurdoro

Division of Urology, Department of Surgery, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia
danurdoroaria@gmail.com

INTRODUCTION

Bladder cancer (BCa) is the most frequent entity among urinary tract malignancies [1]. It compromises the physical, psychological, and social aspects of the quality of life, causing significant economic and public health burdens in developed regions and less-developed and developing countries [2]. According to The Global Burden of Disease study performed in 2017 (GBD 2017), the global and regional burden of BCa is immense [3]. The prevalence and mortality rates differ according to

geographic, socio-cultural, and economic variations across the globe [2]. GLOBOCAN 2018 data published that the incidence rate of bladder tumors (per 100.000 people/year) in the world for men reached 9.5, and in women 2.4 while the incidence rate of bladder tumors in Southeast Asia was 4.6 for men and 1.1 for women [4]. In 2020, there were 18,911 new cases of bladder tumors in Southeast Asia. Although the prevalence and mortality rates of BCa are higher in developed regions, it remains a significant health problem in relatively less-developed countries, including Indonesia [3].

The two commonly recognized risk factors of bladder cancer are smoking and exposure to synthetic aniline dye intermediates such as beta-naphthylamine and benzidine. Indonesia has a high smoking prevalence of 71% in men among the general population in Central Java only. Batik is an Indonesian traditional textile product, in which Yogyakarta is one of the centers of the batik industry. The increasing use of synthetic dyes in batik production, such as aniline, raises concern about its carcinogenic effects. The elevated count of smokers and repeated exposure to occupational carcinogens will presumably increase the incidence of bladder cancer in Yogyakarta.

The previous study mentioned the characteristics of Indonesian bladder cancer patients in a tertiary hospital in Bandung, West Java, Indonesia. However, the genetic phenotype may vary even among Indonesians, which may influence the study results. Also, more descriptive data are needed to complete the previous study and build better epidemiology data on bladder cancer in Indonesia.

To date, there is a lack of actual and updated information on bladder cancer characteristics in Indonesia's regions. This study aimed to describe the characteristics of patients with bladder cancer admitted to Dr. Sardjito General Hospital Yogyakarta from January 2015 until December 2020. Having this information enables us to obtain a more detailed incidence rate and risk factor analysis for bladder cancer.

METHODS

This study had a retrospective and descriptive design. The medical records of patients diagnosed with bladder cancer based on histopathological results hospitalized in Dr. Sardjito General Hospital Yogyakarta between January 2015 and December 2020 were collected and analyzed.

This study data were taken in Dr. Sardjito General Hospital from March 1, 2020, to March 31, 2021. All the patients who met inclusion criteria were included in the study sample. The inclusion criteria for cases consisted of having a medical record and a clinical diagnosis of bladder cancer based on radiographic, pathologic, or cytological findings alone or in combination with one another. The exclusion criteria consisted of not having the pathological result and bladder cancer patients who have previously been diagnosed at Dr. Sardjito General Hospital. Variables collected were demographic aspects including the number of patients, age, gender, the ratio of men to women, diagnostic aspects including chief complaint, urine cytology, clinical staging, tumor grading, and pathology examination results, as well as the therapeutic aspects. We defined secondary bladder cancer as a tumor not primarily originated from the bladder. It is commonly categorized

as a direct extension of tumor from surrounding organs, metastasis, and lymphoma/leukemias. The collected data were analyzed to determine the overall number of bladder cancer, the ratio between male and female patients, age characteristics, the patient's chief complaints, stage, and grading of histopathology results, as well as a treatment performed. All analysis results are displayed in tables and described narratively.

Most of the patients in this study were referred from another hospital. We did not re-examine them in our hospital if they had already had the urinary cytology results. Consequently, some of the urinary cytology data from the previous hospital are not available in our medical records.

RESULTS

From January 2015 until December 2020, there were 282 patients diagnosed with bladder cancer. Fifty patients did not meet the inclusion criteria. The demographic data are summarized in **Table 1**. The total subjects consisted of 169 men (72.8%) and 63 women (27.2%). The ratio of men to women was 2.68: 1. The average age of patients was 59.3 years. The age of the majority ranged between 41 and 60 years. The chief complaints of most patients were gross, painless, intermittent hematuria (195 patients, 84%), urinary retention or other complaints (19 patients, 8.3%), and chronic dysuria (18 patients, 7.7%).

There were a total of 232 bladder tumor patients studied. One hundred seventy-seven patients (76.3 %) had pathology results in the form of transitional cell carcinoma (TCC) with details of the histopathological degrees of 113 high grade, 62 low grade, and 2 Papillary urothelial neoplasms of low malignant potential (PUNLMP). Adenocarcinoma was found in 33 patients. Squamous cell carcinoma was found in 16 patients. There were two patients with embryonic rhabdomyosarcoma PA, two patients with endometrioid carcinoma, one patient with rhabdomyosarcoma, and one patient with carcinosarcoma.

Most bladder cancer patients were in an advanced stage, above T2, when diagnosed (186 patients, 80.2%). The details are T2 in 81 patients (40.1%), T3 in 11 patients (5.4%), and T4 in 64 patients (31.7%). The early-stage (T1) classified as NMIBC occurred in 46 patients (22.8%). A total of 30 patients had infiltration of tumors from other organs (secondary tumor).

According to TCC invasion to muscle, 127 patients (71.8%) showed a pathology result as muscle-invasive while 46 patients (26%) had no evidence of muscle invasion. Four patients (2.2% of all samples) had no data record of muscle invasion. Urine cytology was performed in 92 patients (39.7 %) showing negative results or no malignant cells (34 patients, 37%), inflammatory cells (24 patients, 26%), atypical cells (3 patients, 3.3%), and malignant cells (31 patients, 33.7%).

Table 1. Profile of bladder cancer patients

Categories	n = 232	%
Sex		
Male	169	72.8
Female	63	27.2
Age (years)		
Range	2-86	
Mean ± SD	59 ± 13	
Age groups (years)		
<18	3	1.3
19–40	8	3.4
41–60	110	47.4
61–80	105	45.3
>80	6	2.6
Chief complaints/symptoms	195	84.0
Gross, painless, intermittent hematuria	18	7.7
Chronic dysuria	19	8.3
Urinary retention		
Histopathology		
Transitional cell carcinoma	177	76.3
High grade	133	63.8
Low grade	62	35.0
PUNLMP	2	1.1
Adenocarcinoma	33	14.2
High grade	13	39.4
Low grade	12	36.4
PUNLMP	8	24.2
Squamous cell carcinoma	16	6.9
High grade	9	56.2
Low grade	3	18.8
PUNLMP	4	25.0
Others	6	2.6
Clinical staging		
T1	46	25.9
T2	81	45.7
T3	11	6.2
T4	64	36.2
Secondary tumor	30	16.9
TCC invasion to muscle		
Yes	127	71.8
No	46	26.0
Without information	4	2.2
Urine cytology result (n=92)		
Malignant cell	31	33.7
Atypical cell	3	3.3
Inflammatory cell	24	26.0
Normal	34	37.0
Not performed	85	48.0
Definitive treatment		
TURBT alone	72	31.0
TURBT + intravesical cytostatic instillation	46	19.8
Partial cystectomy	4	1.7
Radical cystectomy	84	36.2
TURBT + chemotherapy + radiotherapy	26	11.1
Urinary diversion after radical cystectomy (n=84)		
Ileal conduit	42	50.0
Transureterocutaneostomy	39	46.4
Neobladder	3	3.6

PUNLMP, Papillary urothelial neoplasm of low malignant potential; TCC, Transitional cell carcinoma; TURBT, Transurethral Resection of Bladder Tumor

All bladder cancer patients underwent the TURBT procedure to confirm the diagnosis and stage and determine the next definitive treatment options. The definitive therapy consisted of either TURBT, followed by intravesical instillation of cytostatic agents eight times once a week, partial cystectomy, radical cystectomy, radiotherapy, and chemotherapy, or multimodal therapy. There were 72 patients (31%) who underwent TURBT alone, 46 patients (19.8%) underwent TURBT followed by intravesical cytostatic instillations eight times once a week, 4 patients (1.7%) underwent partial cystectomy, and 84 patients (36.2%) underwent radical cystectomy. A total of 26 patients (11.2%) underwent multimodal therapy, maximal TURBT followed by chemotherapy and radiotherapy. Among the eighty-four patients who underwent radical cystectomy, 42 (50%) of them underwent ileal conduit, 39 patients underwent transureteroureterostomy (TUUC), and three patients underwent neobladder as the urinary diversion.

The pie chart of Figure 1 should explain the distribution of the age, gender, symptoms, staging, pathological results, muscle invasiveness status, therapy of the primary tumor and types of urinary diversion in this study.

DISCUSSION

The ratio of men to women with bladder cancer in Dr. Sardjito General Hospital from January 2015 until December 2020 was 2.68: 1. This result is not much different from that of Abdih et al. [5] study, studying bladder cancer patients in Dr. Soetomo General Hospital Surabaya in 2014 with the ratio of men to women of 4.2: 1. In 2020, Globocan reported that the incidence of bladder cancer in Southeast Asia for men was 4.6 per 100,000 population while for women was 1.1 per 100,000 population. In general, the worldwide incidence of bladder cancer in men is 9.5 per 100,000 population and in women is 2.4 per 100,000 population, which means the men to women ratio is 3.96:1 [4].

Based on the results obtained, gross, painless, and intermittent hematuria as chief complaints are most found in bladder cancer patients (84%), followed by urinary retention (8.3%) and chronic dysuria (7.7%). Shephard et al. studied the visible hematuria that existed in 2,595 of 4,915 bladder patients (53%). Approximately 9% of complaints of dysuria, abdominal pain, and constipation were found in approximately 7% and 6% of bladder cancer patients [6].

There is a total of 232 bladder tumor patients studied; 177 patients (76.3 %) had pathology results in the form of transitional cell carcinoma (TCC) with details of the histopathological degrees of 113 high grade, 62 low grade, and 2 Papillary urothelial neoplasms of low malignant potential (PUNLMP). Adenocarcinoma was found in 33 patients, and squamous cell carcinoma was

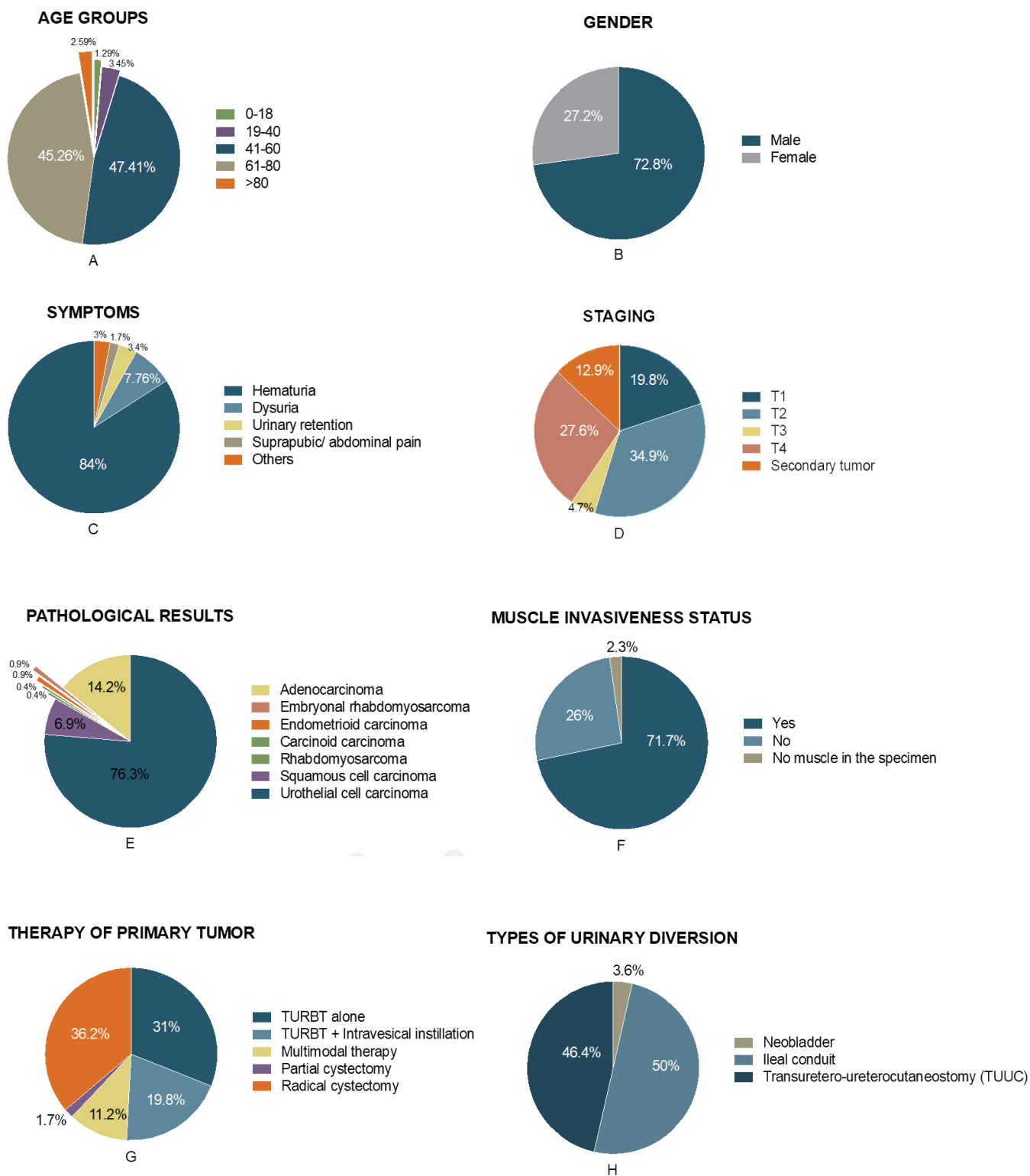


Figure 1. Pie-chart showing the demographic and clinical characteristics of bladder cancer patients included in the study. (A) Age distribution; (B) Gender distribution; (C) Symptoms distribution; (D) Staging distribution; (E) Histopathological results distribution; (F) Status of muscle invasiveness distribution; (G) Therapy of primary tumor distribution; (H) Types of urinary diversion after radical cystectomy (RC) distribution.

found in 16 patients. Based on the data in the United States, 95% of patients with bladder cancer obtained histopathological results in the form of transitional cell carcinoma (TCC), 3% of cases with squamous cell carcinoma, and 2% of cases of bladder cancer with histopathological results of adenocarcinoma. In the Asian race, 75% of bladder cancer cases are TCC, and 18% of cases of bladder cancer are squamous cell carcinoma [7].

Dr. Sardjito General Hospital is the referral hospital in Yogyakarta province; therefore, patients with bladder cancer who come are mostly at an advanced stage. Bladder cancer patients were in the advanced stage when diagnosed (above T2 in 156 patients, 77.2%) with the details of T2 in 81 patients (40.1%), T3 in 11 patients (5.4%), and T4 in 64 patients (31.7%). Meanwhile, 46 patients (22.8%) were diagnosed at an early stage (T1) and classified as NMIBC. There were 30 patients diagnosed with the secondary tumor. These are consistent with the results from the study in Dr. Soetomo General Hospital Surabaya in 2014 that bladder cancer patients were in an advanced stage when diagnosed [5].

There was a total of 177 TCC patients studied. The results of pathology showed that there were 127 patients (71.8%) with tumor cells invading muscle, 46 patients (26%) with non-invasive tumors, and four patients (2.6%) with no information on the histopathological results of whether the tumor had invaded the muscles. The results of this study are different from the literature; based on Babjuk et al. (2020), about 75% of new patients with bladder tumors were firstly found to have non-invasive muscles, and 25% were found to have invasive muscles [8].

Urine cytology was performed on 92 patients (39.7%). The remainder did not perform urine cytology or was not documented in the medical record, showing negative results or no malignant cells (34 patients; 37%), inflammatory cells (24 patients; 26%), atypical cells (3 patients; 3.3%), and malignant cells (31 patients; 33.7%). Urinary cytology recognizes tumor cells that have been shed from the urothelium into the urine. The specificity of voided cytology ranges between 78 to 100% while the sensitivity for high-grade disease and carcinoma-in-situ (CIS) may be ranged between 12 to 84.6 % [9]. Nevertheless, the main drawback of urine cytology is its low sensitivity to identify low-grade neoplasms (roughly around 55%) [10]. There are two possible explanations for this. First, tumor cells of the low-grade tumors are not routinely exfoliated into the urine due to their cohesive characteristics. Second, and presumably more critical, low-grade tumor cells have identical cytomorphology to normal urothelial cells microscopically. Thus, although increased cellularity and papillary fragments in a urine sample may suggest the presence of a low-grade lesion, it is crucial to set aside another possibility of urothelial hyperplasia due to either infection, stone, or instrumentation [11].

All patients with bladder tumors at Dr. Sardjito General Hospital underwent TURBT for diagnosis and tumor staging, followed by definitive therapy. Definitive therapy for bladder tumors includes TURBT alone in 72 patients (31%), TURBT followed by intravesical instillation of 1-series chemotherapy in 46 patients (19.8%), partial cystectomy in 4 patients (1.7%), radical cystectomy in 84 patients (36.2%), and TURBT followed by chemotherapy and radiotherapy in 26 patients (11.2%).

Intravesical chemotherapy installation at the Dr. Sardjito General Hospital uses an anthracycline class of drugs, namely doxorubicin, following the local health insurance policy (JKN) policies. Intravesical chemotherapy is carried out at the clinic of Dr. Sardjito General Hospital in a dose of 50 mg in 50 ml saline every week for a total of 8 courses. Some patients with advanced stages refuse suitable definitive therapy, especially for radical cystectomy, and some patients miss the follow-up after TURBT alone.

The muscle invasion is ruled out as an essential diagnostic step in BCa since the whole management between non-muscle and muscle-invasive patients could be completely different. Overall, patients with muscle-invasive TCC are prognostically less favorable [12]. For non-muscle invasive bladder cancer, the current standard of care is TURBT followed by intravesical chemotherapy (in particular Mitomycin C or epirubicin) or immunotherapy [bacillus Calmette-Guérin (BCG)] [8]. However, the availability of this agent is limited in Indonesia. Radical cystectomy (with pelvic lymphadenectomy and urinary diversion) or radical radiotherapy is the current gold standard treatment for muscle-invasive TCC. There is a place for neoadjuvant chemotherapy prior to the definitive treatment of muscle-invasive TCC with the recommended regimen of cisplatin-based combination chemotherapy. In the case of metastatic diseases, palliative chemotherapy is the first-choice treatment [13].

Systemic cisplatin-based chemotherapy is used along with TURB and radiotherapy as part of multimodal therapy (bladder-conserving strategy). For the External Beam Radiotherapy (EBRT), the technique used is soft-tissue matching and image guidance with the total target dose for curative EBRT of 64–66 Gy.

There are several limitations to our study. First, some data were not available in our medical records, especially laboratory results from the previous hospital. Second, the intravesical mitomycin-C or BCG as the standard treatment for high-risk non-muscle-invasive bladder cancer was not routinely performed. Most of our patients were national health insurance users, and mitomycin-C & BCG therapy is currently uncovered. Alternatively, we used intravesical Adriamycin therapy although comparative studies indicate it is not as effective as mitomycin-C or BCG.

CONCLUSIONS

Based on this study, we conclude that most bladder cancer characteristics in the Urology Department of Dr. Sardjito General Hospital Yogyakarta are in the advanced stage when diagnosed, and some of the patients receive only TURBT and refuse any further definitive treatments. More extensive studies, nationwide and prospectively data collected, will help us understand the current epidemiology of bladder cancer in Indonesia.

DECLARATIONS

Ethics Approval

The study was held after approval from the Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada (study number KE/FK/0111/EC/2021).

Competing of Interest

The authors declare no competing interest in this study.

Acknowledgment

Not applicable.

REFERENCES

1. Antoni S, Ferlay J, Soerjomataram I et al. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. *Eur Urol*. 2017;71(1):96–108.
2. Richters A, Aben KKH, Kiemeny LALM. The global burden of urinary bladder cancer: an update. *World J Urol*. 2020;38(8):1895–904.
3. He H, Xie H, Chen Y, et al. Global, regional, and national burdens of bladder cancer in 2017: estimates from the 2017 global burden of disease study. *BMC Public Health*. 2020;20(1):1–9.
4. Global Cancer Observatory: Cancer Today. [<https://gco.iarc.fr/>].
5. Abdih MA, Djatisoesanto W, Hardjowijoto S. Profile of Bladder Transitional Cell Cancer in Soetomo Hospital Surabaya. *Indones J Urol*. 2014;21(2):1–6.
6. Shephard EA, Stapley S, Neal RD, et al. Clinical features of bladder cancer in primary care. *Br J Gen Pract*. 2012; 62(602):598–604.
7. Payandeh M, Sadeghi M, Sadeghi E. Characteristics of patients with transitional cell carcinoma of the urinary bladder in Kermanshah Province, Iran. *Iran J Cancer Prev*. 2015;8(6):23–26.
8. Babjuk M, Burger M, Compérat E et al. EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS). *EAU Annu. Congr. Amsterdam 2021* 2021.
9. Yafi FA, Brimo F, Auger M, et al. Is the performance of urinary cytology as high as reported historically? A contemporary analysis in the detection and surveillance of bladder cancer. *Urol Oncol Semin Orig Investig*. 2014;32(1):27.e1–27.e6.
10. Piaton E, Decaussin-Petrucci M, Mege-Lechevallier F, et al. Diagnostic terminology for urinary cytology reports including the new subcategories “atypical urothelial cells of undetermined significance” (AUC-US) and “cannot exclude high grade” (AUC-H). *Cytopathology*. 2014;25(1):27–38.
11. Sullivan PS, Chan JB, Levin MR, Rao J. Urine cytology and adjunct markers for detection and surveillance of bladder cancer. *Am J Transl Res*. 2010;2(4):412–40.
12. Kayama E, Kikuchi E, Fukumoto K, et al. History of Non–Muscle-Invasive Bladder Cancer May Have a Worse Prognostic Impact in cT2–4aN0M0 Bladder Cancer Patients Treated With Radical Cystectomy. *Clin Genitourin Cancer*. 2018;16(5):e969–e976.
13. Witjes JA, Bruins M, Cathomas R, et al. EAU guidelines on muscle-invasive and metastatic bladder cancer. *EAU Annu. Congr. Amsterdam 2021*, 2021.