



Bladder Tumor Cases with History of Bladder Stones: Disparity in Histopathological Findings at RSUP Dr. Sardjito Yogyakarta

Nikko Caesario Mauldy Susilo¹, Indrawarman Soero Hardjo^{1*}

¹Division of Urology, Department of Surgery, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia

Email correspondence: indrawarman@ugm.ac.id

<p>Track Record Article</p> <p>Revised: 12 February 2026 Accepted: 09 March 2026 Published: 31 March 2026</p> <p>How to cite: Susilo, N. C. M., & Hardjo, I. S. (2026). Bladder Tumor Cases with History of Bladder Stones: Disparity in Histopathological Findings at RSUP Dr. Sardjito Yogyakarta. <i>Contagion: Scientific Periodical Journal of Public Health and Coastal Health</i>, 8(1), 348–355.</p>	<p style="text-align: center;">Abstract</p> <p><i>Bladder cancer remains a major cause of morbidity and hospitalization worldwide. Bladder stones have long been linked to squamous cell carcinoma (SCC) as a result of persistent irritation and inflammation. Nevertheless, modern histopathological patterns may diverge from this traditional framework. This study aims to delineate the histopathological distribution of bladder tumors in patients with a history of bladder stones and to investigate the divergence between predicted and actual tumor subtypes. A retrospective descriptive study was performed at RSUP Dr. Sardjito Yogyakarta from January 2018 to June 2025. We looked at medical records of patients who had bladder tumors that were confirmed by histopathology and bladder stones that were documented. A descriptive univariate analysis was conducted. There were 29 patients in all, and their average age was 59.7 ± 11.8 years. Of these, 26 (89.6%) were men. Eighteen patients (62.1%) had urothelial carcinoma/transitional cell carcinoma (UC/TCC), ten patients (34.5%) had SCC, and one patient (3.4%) had adenocarcinoma. The majority of UC cases exhibited high-grade squamous differentiation (12/18; 66.7%). Even though there were a lot of big stones and people were exposed to them for a long time, UC was still more common than SCC. These results show that bladder tumors linked to stones have different types of histopathology and that SCC may not always be the most common type in cases of chronic irritation. Additional multicenter and molecular investigations are necessary to elucidate the biological mechanisms driving this distribution.</i></p> <p>Keywords: <i>Bladder Tumor, Bladder Stones, Squamous Cell Carcinoma, Urothelial Carcinoma, Histopathology.</i></p>
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INTRODUCTION

Bladder cancer is a common type of cancer that begins in the cells lining the bladder, primarily affecting older adults and smokers. Bladder cancer has been a significant global health issue, with more than 600,000 new cases annually worldwide. Recent GLOBOCAN 2022 data report bladder cancer was one of the top ten most common cancers globally, with substantial geographic variation in incidence (Bray et al., 2024). Urothelial carcinoma (UC) constitutes approximately 90% of bladder cancers in most regions.

The chronic irritation paradigm proposes that persistent mechanical trauma from bladder stones induces squamous metaplasia, which may subsequently progress to squamous cell carcinoma (SCC). Contemporary global data show that the proportion of SCC among stone-associated bladder cancers varies considerably. Reports from South Asia and the Middle East describe SCC rates ranging from approximately 30% to 60% in patients with long-standing bladder calculi and chronic infection, although this distribution differs across regions.

Chronic inflammation is believed to promote carcinogenesis through cytokine activation, oxidative DNA damage, and sustained epithelial turnover, yet modern molecular studies suggest that this pathway does not uniformly determine histological subtype.

However, recent molecular and epidemiological evidence suggests that inflammation-driven carcinogenesis is complex and influenced by genetic susceptibility, tobacco exposure, and environmental carcinogens. Contemporary studies indicate that urinary calculi increase overall bladder cancer risk but do not consistently predict SCC histology (Zhong et al., 2025). Moreover, molecular investigations demonstrate that NF- κ B activation, IL-6 signaling, and tumor microenvironment remodeling contribute broadly to bladder carcinogenesis without necessarily determining histological subtype (Michaud, 2007; Zhou et al., 2023).

In Southeast Asia, updated epidemiological data on histological distribution in stone-associated bladder cancer is still limited. Given Indonesia's burden of urolithiasis and tobacco exposure, reassessing the validity of the chronic irritation paradigm in a modern cohort is clinically relevant. This study evaluates the histopathological distribution of bladder tumors in stone-bearing patients at a major Indonesian tertiary hospital to clarify the discrepancy between historical theory and contemporary clinical findings.

METHODS

This study employed a retrospective descriptive design, leveraging secondary data sourced from medical records at RSUP Dr. Sardjito Yogyakarta, a tertiary referral hospital in Central Java, Indonesia. The study was carried out from January 2018 to June 2025. The study sought to delineate the histopathological distribution of bladder tumors in patients with a recorded history of bladder stones.

The study population consisted of all patients diagnosed with primary bladder tumors within the study timeframe. Patients were included if they had a histopathologically confirmed diagnosis of a bladder tumor and a documented history of bladder stones prior to or at the time of tumor diagnosis. The study included only patients who had transurethral resection of bladder tumor (TURBT), bladder base biopsy, or radical cystectomy and had definitive pathology reports. Patients with secondary or metastatic bladder tumors and those lacking complete histopathological documentation were excluded. Because there were not many eligible cases, a total sampling method was used, and 29 patients met the criteria for inclusion.

Data were obtained through a systematic review of electronic and archived medical records utilizing a standardized data extraction form. The variables collected encompassed age, sex, duration of bladder stones, stone size as determined by imaging results, smoking history,

familial incidence of bladder cancer, history of schistosomiasis, prior pelvic radiotherapy, and the ultimate histopathological diagnosis. Histopathological results were sorted into three groups: urothelial carcinoma/transitional cell carcinoma (UC/TCC), squamous cell carcinoma (SCC), and other histological types. This was done based on the final pathology report from certified anatomical pathologists. Data that were missing were noted as unavailable and not filled in.

IBM SPSS Statistics version 26.0 was used to analyze the data. Researchers used descriptive univariate analysis to sum up the main traits of the study group. Then, researchers showed categorical variables as frequencies (n) and percentages (%), and continuous variables as the mean and standard deviation.

The Institutional Review Board of RSUP Dr. Sardjito Yogyakarta (No. KE/FK/0051/EC/2026) gave its ethical approval. The Declaration of Helsinki says that all data must be kept private, so all data were made anonymous before being analyzed.

RESULTS

Table 1. Sociodemographic characteristics of patients with bladder cancer and a history of bladder stones between 2018 and 2025

Categories	n = 29	%
Sex		
Male	26	89.6
Female	3	7.6
Age (years)		
Range	37-90	
Mean ± SD	59,7 ± 11.8	
Duration from Stone to Cancer (years)		
Range	0.2-26	
Mean ± SD	6.3 ± 8.3	
Chief complaints/symptoms		
Gross, painless, intermittent hematuria	24	82.7
Chronic dysuria	4	13.7
Urinary retention	1	3.4
Stone size (centimeter)		
> 3 cm	21	72,4
< 3 cm	3	10,3
No data	5	17,2
History of Smoking		
Yes	26	89,7
No	3	10,3
History of Schistosomiasis		
Yes	0	0,0
No	29	100,0
Previous Pelvic Radiotherapy		
Yes	0	0,0

Categories	n = 29	%
No	29	100,0
Family History of Bladder Cancer		
Yes	5	17,2
Histopathology		
Transitional Cell Carcinoma	18	62,1
High grade with squamous differentiation	12	66,7
High grade	5	27,8
Low grade	1	5,6
PUNLMP	0	0,0
Squamous cell carcinoma	10	34,5
Well differentiated	8	80,0
Moderately differentiated	2	20,0
PUNLMP	0	0,0
Adenocarcinoma	1	3,4
Definitive Treatment		
Radical Cystectomy	13	44,8
Partial Cystectomy	0	0,0
Trimodal Therapy (TURBT, Chemotherapy, Radiotherapy)	16	55,2

*PUNLMP, Papillary urothelial neoplasm of low malignant potential; TURBT, Transurethral Resection of Bladder Tumor

After analyzing the data, 29 patients were involved in this study. The average age was 59.7 years, with a range of 37 to 90 years. There were 26 men (89.6%) and 3 women (10.3%) among the patients.

The most common symptom was painless, intermittent hematuria in 24 (82.7%) of the patients. The second most common symptom was chronic dysuria in 4 (13.7%) of the patients. The third most common symptom was urinary retention in 1 (3.4%). The average time between finding a bladder stone and finding bladder cancer was 6.3 ± 8.3 years. 21 (72.4%) of the patients had stones that were 3 cm or larger, while 3 (10.3%) had stones that were less than 3 cm. We didn't have information on stone size for 5 (17.2%) of the cases.

Twenty-six (89.7%) of the patients said they had a history of smoking, while three (10.3%) said they did not smoke. A family history of bladder cancer was noted in 5 (17.2%) patients. There were no instances of schistosomiasis or previous pelvic radiotherapy.

Histopathological analysis indicated that urothelial carcinoma/transitional cell carcinoma (UC/TCC) was the predominant subtype, present in 18 (62.1%) patients. Of these patients, 12 (66.7%) had high-grade UC with squamous differentiation, 5 (27.8%) had high-grade undifferentiated UC, and 1 (5.6%) had low-grade UC. Ten (34.5%) of the patients were diagnosed with squamous cell carcinoma (SCC), with eight (80%) of those being well-

differentiated and two (20%) being moderately differentiated. One patient (3.4%) had adenocarcinoma.

For definitive treatment, 13 (44.8%) patients underwent radical cystectomy, whereas 16 (55.2%) received trimodal therapy, which included TURBT, chemotherapy, and radiotherapy. No patients underwent partial cystectomy.

DISCUSSION

This study demonstrates that urothelial carcinoma predominated (62.1%) over squamous cell carcinoma (34.5%) among patients with bladder stones, challenging the traditional chronic irritation paradigm (Chen et al., 2022). Historically, bladder stones have been strongly associated with SCC development due to prolonged mucosal irritation and chronic infection (Pramod et al., 2022; Wahyudi et al., 2021). Earlier regional case series, particularly from areas with delayed access to surgical care, reported SCC proportions ranging from 30% to 60% in stone-associated bladder cancer (Singh et al., 2020; Wahyudi et al., 2021). However, the findings of this study indicate that this distribution is not universal and may be influenced by additional carcinogenic exposures (Chen et al., 2022).

Chronic inflammation remains a biologically plausible contributor to bladder carcinogenesis. Persistent epithelial injury may induce squamous metaplasia, promote cytokine-mediated signaling, and increase oxidative stress within the urothelium. Pro-inflammatory mediators such as IL-6, TNF- α , and NF- κ B activation pathways have been implicated in sustaining tumor-promoting microenvironments (Gao et al., 2023; Zhou et al., 2023). Nevertheless, modern molecular evidence suggests that inflammation functions as a facilitator of tumorigenesis rather than a deterministic driver of specific histological differentiation (Zhou et al., 2023). In other words, chronic irritation may increase overall cancer risk without necessarily dictating squamous transformation (Chen et al., 2022).

The predominance of UC in our cohort aligns with contemporary epidemiological trends in many regions where tobacco exposure is prevalent. Smoking is the most established risk factor for urothelial carcinoma and contributes to DNA adduct formation and genomic instability. In this study, 89.7% of patients had a history of smoking, which may represent a stronger carcinogenic influence than mechanical irritation from calculi (Siegel et al., 2023). This observation supports the concept that stone-associated inflammation likely interacts with systemic carcinogenic exposures rather than acting independently (Chen et al., 2022).

Additionally, 66.7% of UC cases in our cohort demonstrated squamous differentiation. This finding may represent an intermediate biological response to chronic irritation without

full histological conversion to pure SCC (Gao et al., 2023). Squamous differentiation within urothelial carcinoma has been associated with more aggressive pathological features but retains treatment algorithms similar to conventional UC according to contemporary guidelines (Gontero et al., 2024; Van der Heijden et al., 2025). Therefore, histological heterogeneity in stone-bearing patients further emphasizes the complexity of inflammatory-driven carcinogenesis (Zhou et al., 2023).

Therefore, exploratory statistical testing did not demonstrate significant associations between stone size, stone duration, or smoking and histological subtype. Although limited by statistical power, this lack of association suggests that stone burden alone may not predict squamous predominance (Chen et al., 2022). Larger multicenter cohorts are necessary to clarify whether threshold effects influence histological outcomes (Bray et al., 2024).

From a pathophysiological perspective, bladder carcinogenesis in the setting of stones should no longer be interpreted through a single-mechanism framework (Zhou et al., 2023). Contemporary evidence supports a paradigm shift from the classical "chronic irritation leads to SCC" model toward a multifactorial carcinogenesis model integrating inflammatory signaling, tobacco-related mutagenesis, and tumor–microenvironment interaction (Gao et al., 2023; Zhou et al., 2023; Chen et al., 2022). In this modern context, chronic irritation may act as a permissive cofactor rather than a deterministic driver of squamous differentiation (Gao et al., 2023). The findings therefore support reconsideration of traditional assumptions regarding stone-associated bladder tumors, particularly in regions with high smoking prevalence and changing environmental exposures (Bray et al., 2024).

This study has several limitations. First, the relatively small sample size ($n=29$) limits statistical power and reduces the ability to detect modest associations between stone characteristics and histological subtype. Second, the retrospective single-center design introduces potential selection and information bias, and may not fully represent the broader Indonesian population. Third, incomplete data on stone size in 17.2% of cases may have affected subgroup analyses. Fourth, the absence of molecular or immunohistochemical profiling restricts mechanistic interpretation of the observed histological patterns.

Finally, lack of an external validation cohort limits generalizability of the findings. Future research should focus on large-scale multicenter prospective studies to improve statistical robustness and external validity. Integration of molecular profiling, inflammatory biomarkers, and genomic analyses may clarify the biological interaction between chronic stone-related irritation and urothelial carcinogenesis.

CONCLUSIONS

This retrospective analysis of bladder tumor patients at RSUP Dr. Sardjito Yogyakarta with a history of bladder stones demonstrated significant disparities between predicted and actual histological findings. Compared to the common assumption that stone-associated bladder tumors are primarily SCC, our study showed that 62.1% of patients had UC/TCC.

These results conflict with the conventional theory of stone-related bladder carcinogenesis and demonstrate the complexity of the factors influencing cancer histology. The findings indicate that bladder carcinogenesis is probably complicated, with mechanical irritation from stones being merely one of several factors affecting histological results, rather than the principal one. To confirm these findings and further understand the link between bladder stones and tumor histological features, we need large, multicenter prospective investigations. Investigating molecular markers and genetic pathways in stone-associated bladder tumors may clarify the underlying causes of these discrepancies for a better understanding of this area.

The results of this study show that histopathological evaluation is still important for people with bladder tumors and a history of bladder stones. This is because tumor subtype cannot be assumed solely based on the chronic irritation theory. Clinicians are advised to uphold thorough diagnostic evaluations irrespective of stone dimensions or duration. Subsequent research ought to engage more extensive multicenter cohorts and include molecular or inflammatory biomarker analysis to elucidate the biological mechanisms responsible for histological variations in stone-associated bladder tumors.

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