

Diagnosis and management of intradiverticular bladder tumours: A pooled analysis of 498 cases

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Summary

Objective: Intradiverticular bladder tumors (IDBT) are uncommon clinical entities. We reviewed the literature for clinical presentation, diagnosis and therapeutic options to establish recommendations for diagnostic and therapeutic management.

Methods: Bibliographic research was performed using PubMed from database inception until October 15, 2022. A pooled analysis was performed of 498 patients with IDBT presented in the literature. The evaluation included patient sex, age, diagnostic methods, symptoms, localization of the tumor, tumor staging, tumor histopathology, treatment, and the presence of recurrence. To express results, descriptive statistics were used appropriately.

Results: The mean age at diagnosis was 64.81 years (range 49 days to 84 years). The ratio between men and women was \approx 24:1, suggesting a male predominance (85% male, 3.6% female).

The most common presenting symptom was gross hematuria (60.88%). Most of the patients had cystoscopy (56.85%) and intravenous or computed tomography urography (52.01%).

Regarding tumor staging, most of the patients were diagnosed with pT1 tumors. For the histopathology of IDBT, 87.95% of the specimens were transitional cell carcinomas and in 10.84% there were concomitant CIS. Regarding the treatment, radical cystectomy was chosen in 34.34%, partial cystectomy in 26.66%, diverticulectomy in 15.95% and transurethral resection of bladder tumour (TURBT) in 16.36% of the patients.

Conclusions: Most common diagnostic tool for IDBT seems to be cystoscopy followed by computerized tomography urogram. Due to the absence of muscle layer in the diverticulum and the high-grade histology of most of them at diagnosis, cystectomy is the first therapeutic choice. However, for patients that are not considered appropriate candidates or for those presenting with low-grade and low volume tumors, TURBT is a good option.

KEY WORDS: Intradiverticular bladder tumors; Bladder diverticular carcinoma; Urothelial carcinoma; Bladder diverticulum.

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INTRODUCTION

Bladder diverticula are outpouchings of the bladder wall devoid of a functional muscularis propria lining (1). The lack of a muscle layer results in a loss of contractility, which in turn results in urine stasis in the diverticulum. This chronic irritation can lead to chronic inflammation and an increased risk of neoplasms, owing to a prolonged

exposure to carcinogens such as aromatic amines from cigarette smoke (1). Intradiverticular bladder tumours (IDBT) account for approximately 1% of all urinary bladder tumors (2). Therefore, they pose a unique diagnostic and therapeutic challenge. Considering the scarcity of intradiverticular bladder tumours it is not surprising that there are no standard guidelines for the diagnosis and management. We performed a pooled analysis of 498 cases of intradiverticular bladder tumours collected from the international literature, in order to completely characterize the entity in relation to epidemiological, medical and surgical aspects.

METHODS

This review was conducted in accordance with the PRISMA guidelines (*Preferred Reporting Items for Systematic Reviews and Meta-Analysis*) (3). Bibliographic research was performed using PubMed from database inception until October 15, 2022. The following medical subject heading terms were used in combination with Boolean operators (AND, OR, NOT): bladder diverticulum, bladder diverticula, intradiverticular, bladder tumor, bladder cancer, carcinoma. Two independent reviewers (K.S, T.L) screened all the articles retrieved by the initial search. All disagreements were resolved with discussion, and final decision was reached by consensus with a third reviewer (P.A.). Reference lists were systematically searched for potentially eligible, missed studies. Fifty-nine articles were found in total. Among these, we spotted 498 well-documented cases of intradiverticular bladder tumors (Figure 1) (1, 4-61). Retrieved articles were carefully studied and a database with the patients' characteristics was made (*see Supplementary Materials*). The database included sex, age, diagnostic methods, symptoms, localization of the tumor, tumor staging, tumor histopathology, treatment and recurrence. The cases that fulfilled most of these criteria have been included in the statistical analysis. Excluded studies met \geq 1 of the following criteria: (a) irrelevant to the subject studies, (b) studies published in a non-English language, (c) reviews and meta-analyses, and (d) editorials, perspectives, and letters to the editors. An ethical approval is not required because this study is a review of the existing international literature. To express results, descriptive statistics were used appropriately.

No conflict of interest declared.

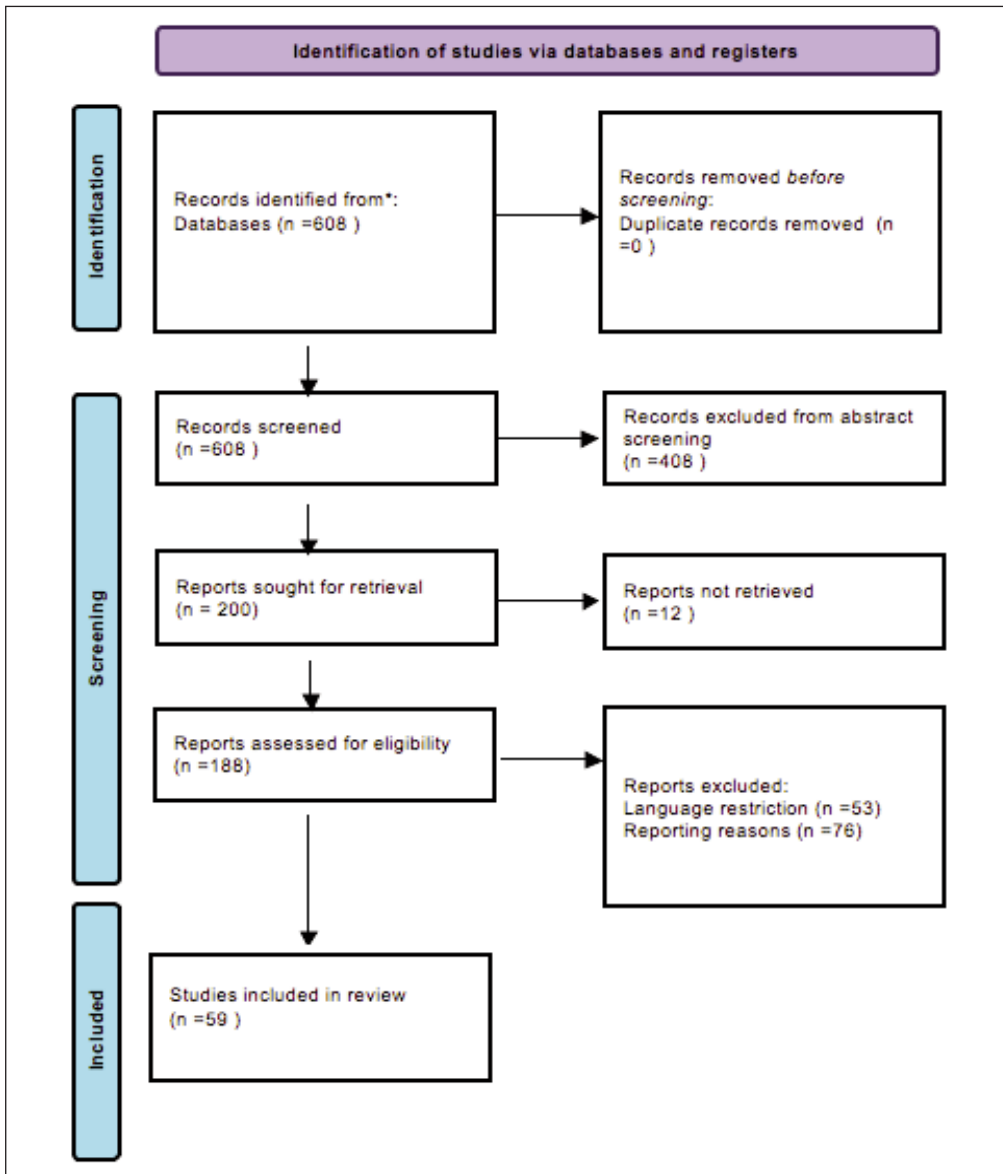


Figure 1. Flow chart of papers selection.

RESULTS

Characteristics of IDBT were determined concerning sex, age diagnostic methods, symptoms, localization of the tumor, tumor staging, tumor histopathology, treatment and recurrence.

Gender

Concerning gender, 85% of the patients were male (431 patients), while 3.6% were female (18 patients). There were no data regarding gender for 49 patients. The ratio between men and women was $\approx 24:1$, suggesting a male predominance in the reported IDBT population.

Age

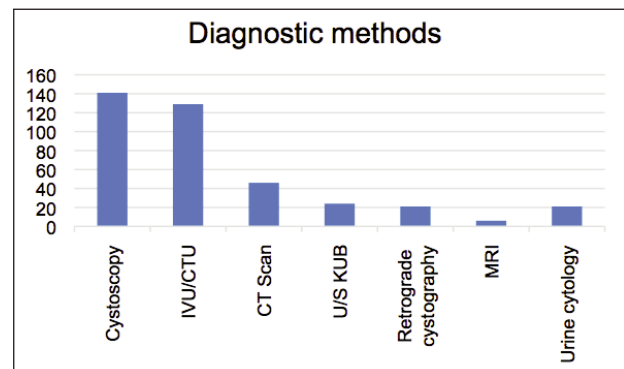
Mean age of the population was 64.81 years, ranging from 49 to 84 years. It is concluded that IDBT most frequently appeared in age range from 60 to 70 years.

Diagnostic methods

The most useful tool was cystoscopy (141/248 patients, 56.85%), followed by intravenous/computed tomography

urography (IVU/CTU) (129/248 patients, 52.01%) as shown in Figure 2. Other imaging techniques used were computed tomography (CT) scan (46/248 patients,

Figure 2. Diagnostic methods.



18.54%) and ultrasound (U/S) of *Kidneys, Ureters, and Bladder* (KUB) (24/248 patients, 9.67%); retrograde cystography (21/248 patients, 8.46%) is still of great importance for the diagnosis of IDBT. Last but not least, *magnetic resonance imaging* (MRI) can be a helpful tool for the differential diagnosis of IDBT. In the laboratory tests, 21 of 248 patients (8.46%), underwent a urine cytology test for the detection of IDBT.

Presenting symptoms

IDBT can present with a wide variety of symptoms, ranging from gross hematuria to symptoms of *urinary tract infections* (UTI). Our statistical analysis has shown that the most frequent symptom is gross hematuria (151/248 patients 60.88%). Eight patients presented with microhematuria (3.22%), 8 patients had frequency (3.22%) and 11 had dysuria (4.43%). *Lower urinary tract symptoms* (LUTS), obstructive symptoms, urinary retention, hydronephrosis, pain, loss of weight and UTI were found in 23 (9.27%), 15 (6.04%), 2 (0.8%), 7 (1.4%), 6 (2.82%), 2 (0.8%) and 14 (5.64%) patients respectively.

Tumor localization

Pooled analysis included limited data concerning tumor localization that was mentioned in only 66 patients. Most common site was right lateral wall (19/66 patients, 28.78%), while left lateral wall was the second one (16/66 patients, 24.24%). IDBT appeared above right and left orifice in 9 and 8 patients respectively (13.63% and 12.12%). Nine patients (13.63%) had an IDBT in the posterior wall. The base of the bladder (2/66 patients, 3.03%), dome (1/66 patients, 1.51%), anterior wall (1/66 patients, 1.51%) and trigone (1/66 patients, 1.51%) represent rarer locations of IDBT.

Tumor staging

Regarding tumor staging, most of the patients were diagnosed as pT1 tumors (117 patients), followed by those diagnosed with pT2 tumors (33 patients). Patients with pTa, pT3 and pT4 tumors were 2, 19 and 1 respectively. Pooled analysis of tumor grade using *low grade* (LG)/*high grade* (HG) and G1/G2/G3 classification resulted in 28 patients with LG tumors, 128 patients with HG tumors, 15 patients with G1 tumors, 24 patients with G2 tumors and 31 patients with G3 tumors.

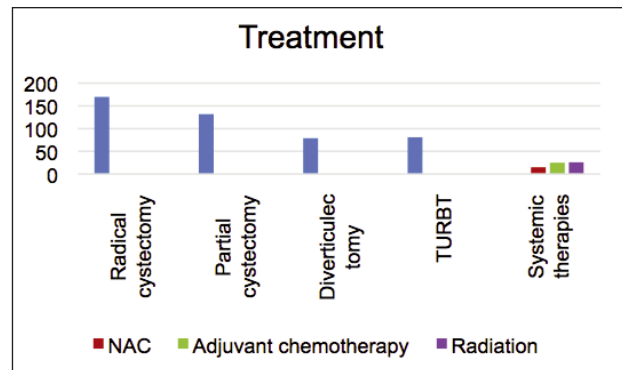
Tumor histopathology

In relation to histopathology of IDBT, most of them presented as *transitional cell carcinomas* (TCC) (438 patients, 87.95%). Squamous cell carcinomas come followed with 26 patients (5.22%). Small cell carcinomas, adenocarcinomas and sarcomatoid carcinomas were 8, 6 and 8 cases respectively. Worth of mention is the presence of concomitant *carcinoma in situ* (CIS) in 54 patients (10.84%).

Treatment

Regarding the treatment applied, radical cystectomy has been chosen in 170 of 495 patients (34.34%), whereas partial cystectomy in 132 patients (26.66%). Seventy-nine (79) patients underwent diverticulectomy (15.95%). Transurethral resection of bladder tumor (TURBT) was performed in 81 patients (16.36%) and out of them 14

Figure 3.
Treatment.



(2.82%) had also intravesical therapy as part of their treatment. Systemic therapies such as neoadjuvant chemotherapy, adjuvant chemotherapy and radiation were applied in 15 (3.03%), 25 (5.05%) and 26 (5.25%) patients respectively. Figure 3 summarizes all the above treatments.

Recurrence

Pooled analysis resulted in a recurrence rate of 19.07% (95 patients).

DISCUSSION

Intradiverticular bladder tumors are uncommon clinical entities, with only few studies reported in the literature. Their rarity make diagnosis and management a unique challenge. They were first described by *Targett* in 1896 (62) and account for approximately 1% of bladder tumors. IDBT seem to have a male predilection (male: female ratio, 24:1) and they more frequently appear in the sixth decade.

The diagnosis of IDBT is usually like that used for other tumors of the bladder, based on the cystoscopy and imaging findings. In some patients the anatomy of the bladder diverticulum may not help to perform a cystoscopy (narrow neck of the diverticulum). However, in most cases cystoscopy is the main diagnostic test used and cannot be excluded from the diagnostic procedure. A variety of imaging techniques can be used to evaluate IDBT. Ultrasonographically, IDBT present as a mostly echo-free outpouching that protrudes outside the urinary bladder outlines with an echogenic soft-tissue lesion projecting inside it. It has been found that ultrasonography is useful for diagnosing larger tumors but its sensitivity is poor if the IDBT is < 1 cm in diameter (63). In our review ultrasonography was reported as a useful tool for the first assessment of hematuria related with IDBT but further imaging techniques were usually needed such as CT scan and CT urography. CT gives further details regarding extravesical extension and tumor stage. Among laboratory tests, urine cytology, due to its low sensitivity for low-grade tumors, has not been used very often (8.46%).

IDBT display a great variety of symptoms. The majority of cases present with gross hematuria. Hydronephrosis and pain can also appear due to obstruction of ureteric orifices. LUTS and symptoms of urinary tract infections are

common mostly because of the presence of the diverticulum rather than the tumor itself. Our study supported the assumption that the most common clinical manifestation of IDBT is gross hematuria, while LUTS are the second most frequent clinical presentation.

Regarding location of IDBT, it extends from lateral wall to the dome. The majority arise from right and left lateral wall followed by those above the ureteric orifices.

Most of the tumors reported in our study were TCC high grade and more specifically pT1 ones. Although squamous cell carcinomas were not even close in numbers to the TCC they cannot be overlooked, as they represent a not so rare manifestation (5.22%).

Regarding treatment all scientists agree that IDBT should be excised when diagnosed. The main surgical approach was radical cystectomy (34.34%) followed by partial cystectomy (26.66%). The predominance of high-grade, that was mentioned before and the recurrence rate of 18.67% which many times resulted in an upstaging of the tumor were the main reason for that choice. Interestingly, Voskuilen *et al.* (11), in their retrospective study, presenting the largest series of IDBT published so far, showed that although upstaging was frequent in the patients that underwent partial rather than radical cystectomy, there was no difference in overall survival. In another study from Kong *et al.* (12) including 36 patients, 28 of them had partial cystectomy or diverticulectomy as primary treatment without compromising cancer related survival. Similar results are presented in two more studies (13, 16). Golijanin *et al.* (16), supported that patients with low or high grade Ta tumors may be treated conservatively (either by complete TUR or partial cystectomy) providing a close surveillance after treatment. In a more recent study Bourgi *et al.* (13), concluded that conservative management is feasible even in high grade tumors or in patients presenting with CIS. In view of these facts, a fair number of patients were treated with less radical approaches such as diverticulectomy (15.95%) or TURBT (16.36%). They usually presented with low-grade and low volume tumors.

In our review, most of the studies included were case reports or small case series with insufficient case number and short follow-up time. Multiple case reports indicated that poor outcome was the result of difficult and delayed diagnosis, leading to early invasion and advanced disease at presentation. That was the reason for the predominance of radical cystectomy as therapeutic approach. There was also a correlation of the year of published studies and the treatment applied. In the past it was widely accepted that IDBT had an ominous prognosis so the management was more radical. Data from most recent studies have questioned the benefit of radical approach for IDBT, shifting the primary treatment to less invasive techniques.

We acknowledge that the present study had several limitations. The major limitations were the retrospective nature of the studies included, the large numbers of case reports and the lack of long follow-up time in most of them. However, to the best of our knowledge this is the first attempt to present a thorough review of a clinical entity that was much overlooked in the published literature.

CONCLUSIONS

Most common diagnostic tool for IDBT seems to be cystoscopy followed by CTU. The relative rarity of IDBT makes their management challenging because as there is no clear consensus about it. Although cystectomy seems a much more morbid procedure compared to less invasive techniques such as TURBT, the absence of muscle layer in the diverticulum and the high-grade histology of most of them, makes it the most likely therapeutic choice. However, it has been proved that less invasive techniques such as partial cystectomy, diverticulectomy or TUBT can be applied in wisely selected patients with similar clinical outcomes.

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