

# Inflammatory myofibroblastic tumor of the bladder: Computed tomographic features

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**Abstract.** Inflammatory myofibroblastic tumor (IMT) is a rare tumor with intermediate biologic potential, in which lack of understanding often poses difficulties in preoperative diagnosis and treatment. The aim of the present study was to characterize the computed tomography (CT) features of the bladder IMT. The CT images of nine pathologically confirmed bladder IMT were retrospectively reviewed. All patients underwent both unenhanced CT and contrast-enhanced CT. The diameter, location, contour, growth pattern, margin, boundary, density and enhancement pattern of the lesions were assessed. The mean Ki67 value of an irregular blood clot was 18% and that of no blood clot was 12%. A total of eight (89%) patients had one tumor and 1 (11%) patient had multiple tumors. An endophytic growth pattern was observed in 4 (44%) patients, an exophytic growth pattern in 2 (22%) patients, and a mixed growth pattern in 3 (33%) patients. The tumor manifests morphologically as either polypoid (n=5), or cauliflower-like (n=1) soft-tissue mass with a wide base in the cavity, or a limited thick-walled (n=3). The tumor margins were smooth (n=8) or lobulated (n=1), and the tumor boundaries were either clear (n=7) or ill-defined (n=2). The lesions showed either ring-shaped (n=3) or heterogeneous (n=6). The polypoid and cauliflower-like soft-tissue mass showed a symmetrical change in the center of the lesion after enhancement. The bladder IMT is mostly a single polypoid nodule in the superior wall, mostly endophytic growth, with ring-shaped enhancement and symmetrical change after enhancement as its characteristic manifestations.

## Introduction

Since the first report by Brunn in 1939 as a primary myofibroblastic tumor of the lung (1), an inflammatory myofibroblastic tumor (IMT) has been acknowledged as a distinctive, though rare, intermediate soft tissue tumor that commonly in the orbit and lung (2,3). Although previously believed to be proliferative lesions deriving from submucosal stroma, of low or indeterminate malignant potential (4), IMT is now considered to be different from pseudotumor for the distinct histological and molecular features, specifically characteristic cellular spindle cell proliferation alongside mutations in the anaplastic lymphoma kinase (ALK)-1 gene loci (5), and there has been an increasing incidence to be found in the pelvic cavity, head and neck, trunk, retroperitoneum, abdomen and limbs (6).

An IMT diagnosis is characterized by the lymphocytic infiltrate and spindle myoepithelial cell proliferation (7). Coffin *et al* (8) described the IMT with three different histological patterns, which may be present simultaneously within a single specimen. Based in fact that IMT is considered as a low malignant potential neoplasm, surgical resection is the first choice of treatment, and several studies proved that successful resolution with radiotherapy, chemotherapy, steroids, or even non-steroidal inflammatory drugs (2,4,9). According to a previous study, ~50% of tumours present with ALK overexpression, which is considered to identify the characteristics and provide the opportunity for targeted therapy (10). Although the exact incidence remains unclear, it has been reported that the recurrence rate and distant metastasis rate of IMT are low (recurrence: 2% in pulmonary, 25% in extrapulmonary sites; metastasis: less than 5%) (3).

Since the first study of a thirty-two-year-old woman of bladder IMT in 1980 (11), the bladder has become one of the common sites of the tumor involving urinary system, and more than 200 cases of bladder IMT were reported mostly in the ophthalmologic and pathologic literature. Due to the lack of specificity clinical symptoms and laboratory results, a preoperative imaging-based examination is very important for determining bladder IMT and selecting appropriate ways to manage conditions of patients requiring emergency treatment (including bladder cancer and lymphoma) (6). However, to the best of our knowledge, there are seldom studies systematically analyzing the CT features of bladder IMT in the radiology literature. The purpose of the present study was to describe the characteristic CT findings of 9 patients with bladder IMT confirmed by pathology.

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*Abbreviations:* CT, computed tomography; IMT, inflammatory myofibroblastic tumor

*Key words:* bladder cancer, inflammatory myofibroblastic tumor, X-ray computed tomography, diagnosis

## Materials and methods

**Patients.** The study was exempt from the Institutional Review Board of the first Hospital of Zhengzhou University. The written informed consent was waived by the Institutional Review Board because this is a retrospective study. Between 2011 and 2021, a review of medical records based on the pathology records and the PACS system of our institution revealed patients with bladder IMT proved on pathologic examination, and the requirement for written informed consent was waived in this retrospective study.

**CT evaluation.** The pelvic CT scans (Discovery CT750HD; GE Healthcare) were typically obtained after the bladder had a sensation of urine (Fig. 1) and intravenous administration of non-ionic iohexol (iopromide, 370 mg/ml, GE Medical Systems, 1.5 ml/kg, and 5 ml/s) by a dual-head pump injector (Medrad, Inc.; Bayer AG), with a section thickness of 5 mm and a pitch of 1.5.

**Image analyses.** All CT images were reviewed blindly by two abdominal radiologists with 3 and 6 years of experience at AW4.6 workstation (GE Healthcare). The following CT features of the bladder IMT were assessed: i) Diameter of the lesion, ii) location of the lesion (posterior wall; superior wall; front wall; left wall; right wall), iii) contour of the lesion (polypoid; cauliflower-like; limited thick-walled), iv) growth pattern of the lesion (endophytic; exophytic; mixed), v) margin of the lesion (smooth; lobulated), vi) boundary of the lesion (clear; ill-defined), vii) density of the lesion on non-enhancement CT scan (low density; iso-density; slightly high density), viii) presence of non-enhancement low-density area within the lesion (homogeneous; heterogeneous), ix) type of enhancement of the lesion (ring-shaped; heterogeneous) and x) degree of enhancement of the lesion (significant; moderate; mild). The lesion showed a symmetrical change in the center of the lesion after enhancement: taking the base of the lesion as the tangent position, and making the median line perpendicular to the base of the lesion, it could be observed that the lesion showed a symmetrical change. In addition, the clinical data (including age, sex and symptoms) were also recorded by the review of medical records.

## Results

**Patient characteristics.** The nine patients (four men and five women) who were evaluated were 7-75 years old (mean age, 40 years). The most common presenting clinical symptoms were gross hematuria (9/9), followed by frequent urination (4/9) and painful urination (4/9). Relevant history included appendicitis resection (1/9) and nephrotic syndrome (1/9). Of the 9 patients, 6 (67%) had irregular blood clots in the bladder. The mean Ki67 value of the presence of an irregular blood clot in the bladder was 18% and that of no blood clot was 12% (Tables I and II).

**CT findings.** The CT findings showed that 8 (89%) patients had one tumor and 1 (11%) patient had multiple tumors. The bladder IMT size ranged from 1.3x2.1 to 4.8x5.1 cm<sup>2</sup>. Tumors occurred in the posterior wall in 2 (22%) patients, 5 (30%)

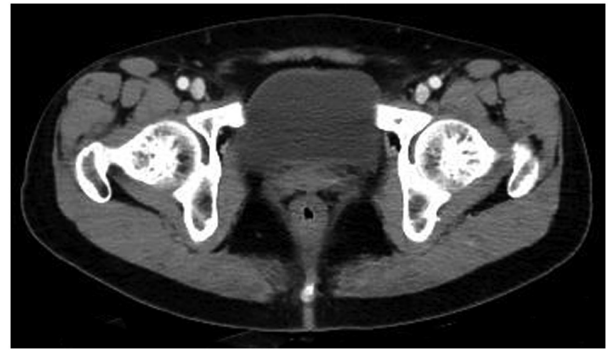


Figure 1. Computed tomography image of normal bladder.

patients had tumors occurred in the superior wall, 1 (11%) patient had tumors occurred in the front wall, and 1 (11%) patient had tumor occurred in the left wall (Figs. 2-5). An endophytic growth pattern (Fig. 3) was identified in 4 (44%) patients, an exophytic growth pattern (Fig. 2) was observed in 2 (22%) patients, and a mixed growth pattern (Fig. 5) was revealed in 3 (33%) patients. The tumor manifests morphologically as either polypoid (n=5), or cauliflower-like (n=1) soft-tissue mass with a wide base in the cavity, or a limited thick-walled (n=3) in the bladder. The tumor margins were smooth (n=8) or lobulated (n=1) and the tumor boundaries were either clear (n=7) or ill-defined (n=2).

The unenhanced CT examination of the lesions revealed either low density (n=4), iso-density (n=3), or slightly high density (n=1), and density was either homogeneous (n=3) or heterogeneous (n=6). The enhanced CT examination of the lesions showed either ring-shaped (n=3) or heterogeneous (n=6), and the degree of enhancement was either significant (n=6), or moderate (n=3). The enhancement pattern was persistent (n=9). In addition, all polypoid and cauliflower-like soft-tissue masses showed a symmetrical change in the center of the lesion after enhancement on the CT image.

## Discussion

IMT is a rare tumor with intermediate biological potential. It is characterized by irregular proliferation of spindle cells in a mucoid to the collagenous stroma, inflammatory infiltration mainly composed of plasma cells and lymphocytes, and occasional mixing of eosinophils and neutrophils (12). Since the first description of IMT in 1939, the understanding of its biological and clinical characteristics has undergone significant changes (9). Based on morphological and histopathological features, IMT used to be described as fibrous histiocytoma, plasma cell granuloma, inflammatory pseudotumor, inflammatory fibroid polyp, fibroxanthoma, xanthoma and xanthogranuloma (9). At present, in the fourth edition of the World Health Organization Classification of Soft Tissue and Bone Tumors, IMT is classified as an intermediate tumor lesion (invasive, occasionally metastatic) (10). Microscopic examination showed that IMT is a tumor with myxoid/vascular type, compact spindle cell type, and hypocellular fibrous type, which could easily lead to misdiagnosis, including inflammatory malignant fibrous histiocytoma, leiomyosarcoma, gastrointestinal stromal tumor rich in inflammatory cells

Table I. Summary of CT findings for nine patients with IMT of bladder.

Patient	Sex	Age, years	Clinical Symptom(s)	Diameter (mm <sup>2</sup> )	Location	Number	Contour	Growth pattern	Margin	Boundary	Tumor Uniformity	Type of enhancement	Ki67 (%)
1	Female	63	Gross hematuria, frequent urination, painful urination	48x51	Posterior wall	One	Polypoid	Exophytic	Lobulated	Ill-defined	Ring-shaped	Persistent	5
2	Female	60	Gross hematuria, painful urination, irregular blood clot	33x34	Superior wall	One	Cauliflower-like	Endophytic	Smooth	Clear	Ring-shaped	Persistent	5
3	Female	35	Gross hematuria, irregular blood clot	33x34	Superior wall	One	Polypoid	Endophytic	Smooth	Clear	Ring-shaped	Persistent	20
4	Male	28	Gross hematuria, frequent urination, painful urination, irregular blood clot	34x48	Superior wall	One	Polypoid	Exophytic	Smooth	Clear	Ring-shaped	Persistent	30
5	Female	14	Gross hematuria, irregular blood clot	22x19	Superior wall	One	Polypoid	Endophytic	Smooth	Clear	Ring-shaped	Persistent	20
6	Male	35	Gross hematuria, frequent urination, irregular blood clot	44x47	Front wall	One	Limited thick-walled	Mixed	Smooth	Clear	Heterogeneous	Persistent	30
7	Female	7	Gross hematuria, painful urination, irregular blood clot	29x32	Left wall	One	Polypoid	Endophytic	Smooth	Clear	Ring-shaped	Persistent	20
8	Male	75	Gross hematuria, frequent urination, irregular blood clot	35x48	Posterior wall	One	Limited thick-walled	Mixed	Smooth	Clear	Heterogeneous	Persistent	15
9	Male	47	Gross hematuria	13x21	Superior wall	Multiple	Limited thick-walled	Mixed	Smooth	Clear	Heterogeneous	Persistent	10

Table II. Summary of clinical manifestations for nine patients with IMT of bladder.

Patient	Sex	Age, years	Immunohistochemistry	Operation	Other treatment	Follow-up time	Follow-up method	Prognosis
1	Female	63	CK <sup>+</sup> , Vimentin <sup>+</sup> , SMA <sup>+</sup> , CD34 (Vascular <sup>+</sup> ), LCA (Stove <sup>+</sup> )	Cystoscopy		1 month	Ultrasound	No recurrence
2	Female	60	Desmin (Individual <sup>+</sup> ), ALK <sup>+</sup>	Transurethral resection of bladder tumor		1 month	Ultrasound	No recurrence
3	Female	35	CK <sup>+</sup> , EMA <sup>+</sup> , ALK <sup>+</sup> , SMA (Stove <sup>+</sup> ), CD30 (Minority <sup>+</sup> )	Partial cystectomy		3 months	Bladder endoscopy	No recurrence
4	Male	28	CK <sup>+</sup> , EMA <sup>+</sup> , ALK <sup>+</sup> , Vimentin <sup>+</sup> , SMA (Stove <sup>+</sup> ), CD68 (Scattered <sup>+</sup> )	Partial cystectomy and pelvic lymph node dissection		7 months	CT, ultrasound, Magnetic resonance imaging	No recurrence
5	Female	14	AE1/AE3 (Weak <sup>+</sup> ), CD34 (Vascular <sup>+</sup> ), ALK <sup>+</sup> , SMA <sup>+</sup> , Desmin (Stove <sup>+</sup> )	Transurethral resection of bladder tumor	Bladder perfusion therapy	2 months	Bladder endoscopy	No recurrence
6	Male	35	SMA (Stove <sup>+</sup> ), Desmin (Stove <sup>+</sup> ), ALK (Stove <sup>+</sup> )	Transurethral resection of bladder tumor plus partial cystectomy		19 months	Bladder endoscopy, CT, ultrasound	No recurrence
7	Female	7	ALK <sup>+</sup> , AE1/AE3 (Partial <sup>+</sup> ), SMA (Partial <sup>+</sup> ), Desmin (Partial <sup>+</sup> )	Bladder tumor excision		2 months	Ultrasound	No recurrence
8	Male	75	CK7 <sup>+</sup> , CK20 (Epithelial <sup>+</sup> ), SMA <sup>+</sup> , ERG (Partial <sup>+</sup> ), GATA-3 <sup>+</sup>	Rod-shaped prostatic dilatation plus electrotomy of bladder neck and mouth		1 month	Magnetic resonance imaging	No recurrence
9	Male	47	AE1/AE3 <sup>+</sup> , CD117 (Stove <sup>+</sup> ), Vimentin <sup>+</sup> , CD99 <sup>+</sup> , P53 (60%)	Laparoscopic radical cystectomy and <i>in situ</i> cystectomy		4 months	CT	No recurrence

CT, computed tomography; ALK, anaplastic lymphoma kinase-1.

and solitary fibrous tumors (13). The diagnosis of IMT can be consolidated by immunohistochemical analysis (13). IMT tumor cells characteristically stain positive for ALK-1 in 87.5% cases, smooth muscle actin (SMA) in 90% cases, pan-cytokeratin focally in >50% cases, and desmin in ~50% cases (14). In addition, a young woman diagnosed as having IMT of the urinary bladder showed the expression of CD10 in a recently published study (14). The pathogenesis of the tumor remains unknown, and it may be related to infections, immunosuppression, chemotherapy, radiotherapy, local trauma and autoimmune disorders (15). In addition, several diseases, including Crohn's disease, congenital neutropenia, gastrointestinal stromal tumor, and pregnancy have been related to the development of IMT (16). Previous studies have reported the correlation between ALK-1 gene expression and

local recurrence, distant metastasis, and overall prognosis of IMT patients (17-20). Moreover, in certain studies (8,21,22), the bladder IMT was associated with the Epstein-Barr virus, bacteria such as *Campylobacter Equi*, the human herpes virus HHV8, *Campylobacter jejuni*, *Escherichia coli*, trauma, radio- and steroid therapy. Previous studies reported that a history of inflammation in the bladder, previous instrumentation, radiation, or a history of surgery was a potential cause of IMT (6). One patient in the present study had a history of appendicitis resection, and one patient had a history of nephrotic syndrome; however, it could not be confirmed whether the surgery was considered to be a causative factor of IMT, because the lesion occurred in the other parts of the pelvis.

There have been certain case reports of bladder IMT, but the shortcomings are obvious. As this tumor is a rare tumor,

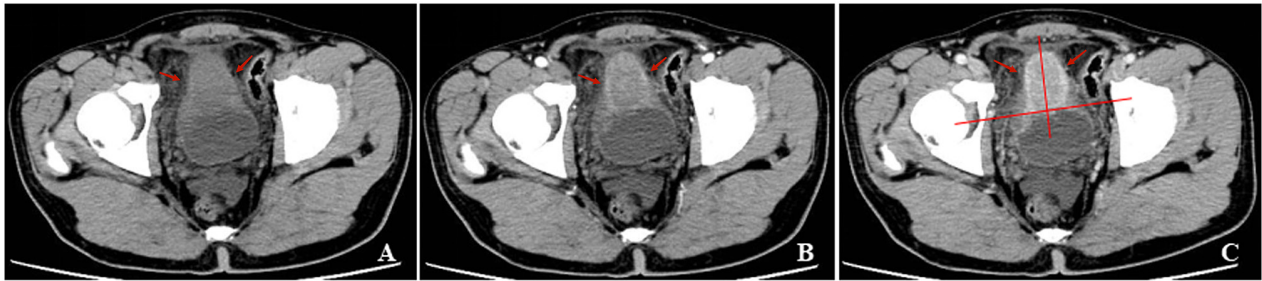


Figure 2. A 28-year-old man with gross hematuria, frequent urination, painful urination and irregular blood clot. (A) Unenhanced CT scan of the bladder showed a polypoid soft-tissue mass with an exophytic growth pattern on the superior wall, with homogeneous density. (B and C) Contrast-enhanced CT scans revealed ring enhancement on the margin of lesion and symmetrical change in the center of the lesion. CT, computed tomography.

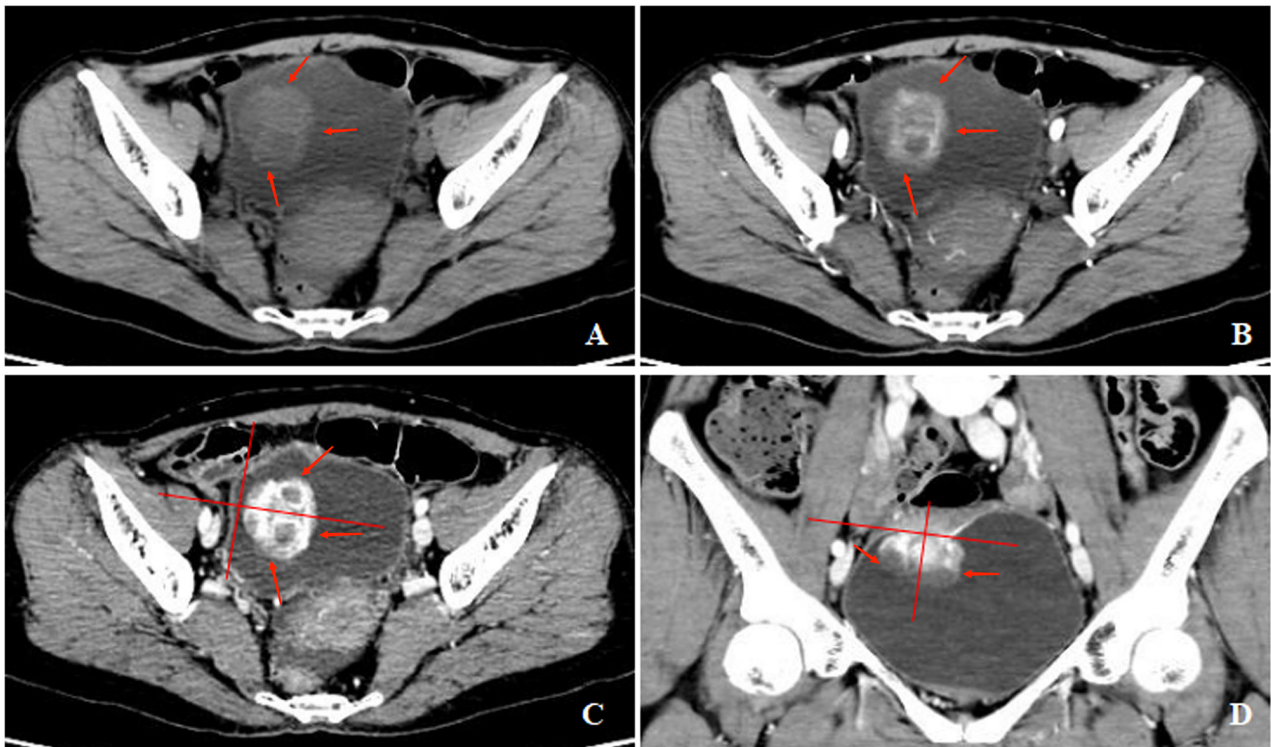


Figure 3. A 60-year-old woman with gross hematuria, painful urination, irregular blood clot. (A) Unenhanced CT scan of bladder showed a cauliflower-like soft-tissue mass with an endophytic growth pattern on the superior wall, with homogeneous density. (B-D) Contrast-enhanced CT scans revealed heterogeneous enhancement of the lesion and symmetrical change in the center of the lesion. CT, computed tomography.

it is easy to be misdiagnosed and missed. At present, there is a lack of literature studies on the systematic analysis of imaging manifestations of bladder IMT, leading to a lack of understanding among clinicians. Therefore, the clinical imaging data of 9 patients were systematically analyzed and combined with previous literature studies, some new insights were found, aiming to improve our understanding of bladder IMT.

The bladder IMT is uncommon accounting for less than 1% of all bladder tumors (23). The distribution of 182 IMT of the bladder was 51.7% in the female patients, and 48.3% in the male patients, with a mean age of  $38.9 \pm 16.6$  years, according to Teoh *et al* (24). In a previous study by Harik *et al* (25), the age of onset of bladder IMT ranged from 7 to 77 years (average 47 years), and the incidence rate of male patients was 3.2 times that of female patients. According to a previous study (6), the

average age of onset of bladder IMT was 53 years old, and the incidence rate of male patients was slightly higher than that of female patients. In the current study, the age of patients ranged from 7 to 75 years (average, 40 years), and the proportion of women preferring men to women was 4:5. Due to the limited number of cases, this demographic difference in the study may be caused by selection bias.

The most common clinical symptoms of patients with bladder IMT are anemia and gross hematuria, accompanied by pain occasionally during urination (6,26). In addition, there was one case report by Harik *et al* (25), which had no clinical symptoms. Due to the rarity of this tumor, it is not always possible to predict the presence of IMT preoperatively based solely on clinical and radiological findings (24).

CT is a common examination method for bladder space-occupying lesions, and it has been reported in the





Figure 4. A 35-year-old man with gross hematuria, frequent urination, irregular blood clot. (A) Unenhanced CT scan of bladder showed a limited thick-walled with a mixed growth pattern on the front wall, with homogeneous density. (B and C) Contrast-enhanced CT scans revealed heterogeneous enhancement of the lesion.



Figure 5. A 47-year-old man with gross hematuria. Coronal computed tomography scan of bladder shows multiple polypoid soft-tissue mass on the superior wall.

literature on the detection, diagnosis and differentiation of bladder lesions as well as the judgment of curative effect. Since bladder IMT is a rare tumor, if some typical imaging diagnostic information can be obtained before treatment, it will be helpful to develop treatment methods and improve the prognosis of patients. Therefore, it is very necessary to systematically analyze the imaging findings of bladder IMT.

Due to its rarity, the CT-based analysis of the bladder IMT remains largely unknown. Lack of understanding often brings difficulties to the preoperative diagnosis and treatment of such tumors. Therefore, it was decided to systematically review the bladder IMT and focus on image-based analysis. Usually, the tumor is identified as a polypoid or cauliflower-like soft-tissue mass with a broad base on the CT image. Occasionally, narrow-base polypoid lesions, nodules, or limited thick-walled bladders have been reported (6,27,28). In the present study, tumors of 5 patients (30%) were located in the superior wall, and 2 (22%) patients' tumors were located in the posterior wall, which was more similar to the distribution reported by Liang *et al* (6). In addition, it was found that 8 of the included patients (89%) had well-defined boundaries, and in the aforementioned study (6), more than five-six of patients also had a well-defined tumor in the bladder. Thus, well-defined tumors were considered to be a feature of the bladder IMT on CT imaging. In the present study, there was a patient with a tumor invasion in the perivesical soft tissue of the bladder. According to the results of the histopathological examination, it was confirmed that it is caused by inflammatory changes. Liang *et al* (6) proposed that the relationship between the number of lesion and biological behavior needed further investigation. In the current study, there were eight patients with one

lesion, and one patient with multiple lesions. The present data showed that there was no significant relationship between one lesion and bladder IMT. Liang *et al* (6) stated that endophytic tumors are more common in bladder IMT. In addition, there have been previous studies that early-stage bladder IMT can appear as a limited thick-walled bladder (27,28). Similarly, the present series of studies revealed that endophytic tumors were more common than exophytic tumors; 44% of the cases were endophytic, 11% exophytic and 22% mixed growth pattern.

Although blood clot is a non-specific sign of any bladder tumor and can be observed in other diseases such as hemorrhagic cystitis, the present study aimed to analyze the relationship between blood clots in the bladder and Ki67 value of the bladder IMT. Of the 9 patients, 6 (67%) had irregular blood clots in the bladder and 9 (100%) had gross hematuria. Therefore, the presence of irregular blood clots in the bladder was considered to be helpful in the diagnosis of bladder IMT (6). The mean Ki67 value of an irregular blood clot of the bladder was 18 and that of no blood clot was 12. It was found that a large Ki67 value appeared to be related to the irregular blood clot.

To expound the relationship between Ki67 value and the prognosis of patients with bladder IMT is of great value for improving the prognosis of patients. However, due to the limited sample size included in the present study and the time of follow-up, the prognosis assessment was limited. This is a limitation to the current study. As a result, sample size will be further accumulated to analyze the relationship between Ki67 value and the prognosis of patients with bladder IMT in future studies.

Although it is not a pathological diagnosis, it has been reported that ring enhancement is the most significant feature

of bladder IMT, because more tumor cells gather at the edge of the lesion, accompanied by inflammatory cell infiltration and a relatively rich blood supply (6). Similarly, all 9 lesions in the present study showed homogeneous or heterogeneous enhancement, and six of the nine lesions also showed ring enhancement on CT imaging. It is interesting to note that all polypoid and cauliflower-like soft-tissue mass exhibited a symmetrical change in the center of the lesion after enhancement on the CT image, which had not been reported before. It is considered that symmetrical enhancement may be the clue of the bladder IMT diagnosis. In the present study, all 9 lesions were examined with CT-enhanced examination, intense enhancement at arterial phase scanning, followed by progressive enhancement at intravenous phase scanning. The possible reason is the presence of a contrast agent in the interstitial space in the center of the lesion (6).

The bladder IMT is often difficult to diagnose correctly before surgery, leading to unnecessary radical bladder resection. The analysis may be due to: i) The clinical symptoms and signs are not characteristic, ii) Clinicians and radiologists have no or insufficient knowledge of it and iii) Preoperative cystoscopy is often due to insufficient materials, resulting in a low rate of diagnosis.

Surgical treatment of the bladder IMT is preferred, and the appropriate surgical method should be determined after a comprehensive examination and full evaluation before surgery. Based on the presence of inflammatory cell infiltration in the pathological tissue of the bladder IMT, anti-infection therapy can play a role in reducing the tumor, so perioperative anti-inflammatory measures should be strengthened. The selection of surgical methods should be comprehensively evaluated according to the size of the tumor and the extent of bladder invasion. Although transurethral resection of bladder tumor has the advantages of less trauma and faster recovery, a multicenter study (24) showed that the rate of second surgery after surgery was 21%, markedly higher than the rate of 2% in patients who underwent partial cystectomy. Total cystotomy should be carefully selected considering the patient's condition, tumor size and invasion degree. Chemotherapy after bladder IMT is controversial. Among the 9 patients admitted to our hospital, 1 patient with preoperative biopsy tendency to bladder malignant tumor received bladder perfusion therapy, and the remaining 8 patients did not receive bladder perfusion therapy after the operation. It remains to be verified whether bladder perfusion could reduce the recurrence rate. It has been reported that prednisone, COX-2 inhibitors and other anti-inflammatory drugs have a favorable effect on bladder IMT in children before surgery (29).

The prognosis of bladder IMT was favorable. The nine patients in the current group were reviewed after surgery for bladder endoscopy, CT, ultrasound and magnetic resonance examination. The follow-up time was 1-19 months. No recurrence or distant metastasis was observed in all patients. It has been reported that the recurrence rate and distant metastasis rate of IMT are 2-25% (3). Although most bladder IMTs are benign tumors and still have malignant potential, it is recommended that patients should be reexamined by cystoscopy every 3 months after surgery for 2 years. Then, ultrasound and CT have performed annually.

In conclusion, the bladder IMT had certain characteristic CT findings that differ from other bladder lesions. The present study of cases suggested that there may be a certain relationship between Ki67 value and radiology features of the bladder IMT, but the number of cases is limited, and further study is needed for in-depth analysis.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

PL primarily wrote the manuscript. JG and PL critically reviewed the paper and revised it. JG and PL confirm the authenticity of all the raw data. PL and XR performed the database search and literature review. PL, BZ and XR analyzed the data. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

The study was exempt from the Institutional Review Board of the first Hospital of Zhengzhou University (Zhengzhou, China). Written informed consent was waived by the Institutional Review Board since this is a retrospective study.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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