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Original article

Clinical significance of functional and anatomical classifications in paraganglioma of the urinary bladder

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Abstract

Objectives: Paragangliomas of the urinary bladder (PUBs) are challenging catecholamine-producing neuroendocrine tumors. We aimed to facilitate their diagnosis and treatment by functional and anatomical classifications.

Materials and Methods: Between April 2007 and September 2017, 31 cases from 2 centers were retrieved, in which the patients were pathologically diagnosed with PUB. Besides classifying them into functional and nonfunctional PUBs, functional PUBs were further subclassified into typical functional PUB (with typical symptoms and elevated catecholamines/metabolites levels) and atypical functional PUB. Anatomically, they were classified into submucosal, intramural, and subserosal PUBs.

Results: Functionally, these cases comprised 17 (54.8%) functional and 14 (45.2%) nonfunctional PUBs. Functional PUBs had significantly larger diameters than nonfunctional PUBs ($P < 0.01$). Of the 17 functional PUB cases, 8 were further subclassified into typical functional PUB, of which 4 were diagnosed without cystoscopy. Anatomically, these cases comprised 14 (45.2%) submucosal, 13 (41.9%) intramural, and 4 (12.9%) subserosal PUBs. Intramural and subserosal PUBs had significantly larger diameters and were more likely to be functional than submucosal PUBs ($P < 0.05$). Cystoscopy failed to detect the tumor in all patients with subserosal PUB. Besides all patients with intramural or subserosal PUB, 1 patient with submucosal PUB underwent partial cystectomy. The remaining 13 patients with submucosal PUB underwent transurethral resection of bladder tumor, 5 of whom required extra surgical intervention.

Conclusions: By functional classification, omitting cystoscopy is feasible in the diagnosis of typical functional PUBs. By anatomical classification, intramural, and subserosal PUBs tend to be large and functional. Moreover, negative cystoscopic findings are not sufficient to exclude subserosal PUBs. Finally, not all submucosal PUBs are amenable to transurethral resection of bladder tumor.

Keywords: Paraganglioma; Urinary bladder; Cystoscopy; Cystectomy; Transurethral resection

1. Introduction

Paragangliomas of the urinary bladder (PUBs) are rare and challenging catecholamine-producing neuroendocrine tumors. Instead of arising from adrenal medullary as pheochromocytomas, PUBs arise from the chromaffin tissues of the sympathetic ganglia in the bladder wall [1]. PUBs account for approximately 0.06% of bladder tumors [2,3] and 79.2% of genitourinary paragangliomas [4]. Due to their unique location, PUBs are prone to be compressed during micturition, potentially causing burst release of catecholamines (CAs) and corresponding symptoms. Owing to their rarity and symptomatic variability, PUBs are commonly misdiagnosed and incorrectly treated, which is risky or even life-threatening due to the potential malignant properties [2] and cardiovascular events [5].

According to their clinical characteristics, PUBs are classified into functional and nonfunctional types [2]. However, it

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is unclear whether the functional classification may clarify the controversy regarding the use of cystoscopy in the diagnosis, as different functional types of PUBs seems pose uneven diagnostic difficulties and cystoscopy-related risks.

In addition, the anatomical characteristics of PUBs remain inadequately elucidated, especially for those not protruding into the bladder cavity and easily missing on cystoscopy. However, the classification according to the anatomical characteristics may be clinically practical for diagnosing and choosing surgical approaches.

Therefore, further studies are required to address the above issues. Herein, a series of 31 PUB cases were retrospectively reviewed. The clinical significance of functional and anatomical classifications in PUBs was analyzed.

2. Materials and methods

2.1. Patients and data

This study was approved by the institutional review boards of Tongji Hospital of Huazhong University of Science and Technology and that of the First Affiliated Hospital of Zhengzhou University. Between April 2007 and September 2017, patients pathologically diagnosed with PUB were retrieved from the 2 centers. Their clinical features including age, sex, symptoms, and symptomatic triggers were collected. Diagnostic data, such as tests for CAs/metabolites, imaging examinations, and cystoscopic findings were documented. Additionally, surgical approaches, prognostic results, and histories of misdiagnosis were reviewed.

2.2. Functional classification

According to the diagnostic efficacies, we categorized the main clinical manifestations into typical and atypical symptoms. The typical symptoms referred to (1) micturition-triggered symptoms of hypercatecholaminemia, including paroxysmal hypertension (HTN), headache/dizziness, palpitation, perspiration, and syncope. The atypical symptoms included (2) sustained secondary HTN (without evident fluctuation, normalized postoperatively), (3) hematuria, and (4) no symptom. Functionally, according to the symptoms, we classified PUBs into functional PUB [with either (1) or (2)] and nonfunctional PUB [with neither (1) nor (2), but with either (3) or (4)]. Further, when functional PUBs presented with both (1) and elevated CAs/metabolite levels, they were further subclassified into typical functional PUB, otherwise into atypical functional PUB.

2.3. Anatomical classification

Anatomically, we classified PUBs into 3 types. (1) Submucosal PUB was located beneath the mucosa and protruded into the bladder cavity (Fig. 1AI, AII, and AIII). (2) Intramural PUB was located beneath both the mucosa and serosa and protruded into the bladder and pelvic cavities, showing a growth pattern between submucosal and subserosal PUBs (Fig. 1BI, BII, and BIII). (3) Subserosal PUB was located beneath the serosa and protruded into the pelvic cavity (Fig. 1CI, CII, and CIII).

2.4. Statistical analysis

Associations between functional types and tumor diameter, age, sex, and hematuria were statistically analyzed. Associations between anatomical types and tumor diameter, functional types, and hematuria were also statistically analyzed. Either Mann-Whitney U test or Student's t test was used to test the continuous variables. Either Fisher's exact test or chi-square test was used to test the categorical variables. Statistical analyses were processed using SPSS version 24 (Chicago, IL). Two-tailed P values <0.05 were considered statistically significant.

3. Results

3.1. Findings regarding functional classification

The clinical features and their differences between the 2 functional types are summarized in Table 1. Functionally, these cases comprised 17 (54.8%) functional and 14 (45.2%) nonfunctional PUBs. Functional PUBs had significantly larger diameters than nonfunctional PUBs (2.9 cm [interquartile range: 2.6−4.9] vs. 1.9 cm [interquartile range: 1.0-−.6], $P < 0.01$). In addition, age, sex, hematuria, and number of lesions were not significantly associated with functional types.

Among the 17 functional PUB cases, 8 (with typical symptoms and elevated CAs/metabolite levels) were further subclassified into typical functional PUB, of which 4 received preoperative diagnosis without cystoscopy. Of the remaining 9 functional PUB cases, 6 were further subclassified into atypical functional PUB (4 with typical symptoms but without elevated CAs/metabolite levels, 2 without typical symptoms and presenting only with sustained secondary HTN), and 3 could not be further subclassified (with typical symptoms but without available results for CAs/metabolites).

3.2. Findings regarding anatomical classification

The clinical features and their differences among the 3 anatomical types are summarized in Table 2. Anatomically, these cases comprised 14 (45.2%) submucosal, 13 (41.9%) intramural, and 4 (12.9%) subserosal PUBs. Intramural and subserosal PUBs had significantly larger diameters (3.5 ± 1.8 cm vs. 4.7 ± 2.2 cm vs. 2.1 ± 1.3 cm, $P < 0.05$) and were more likely to be functional (76.9% vs. 100% vs. 28.6%, $P < 0.01$) than submucosal PUBs. However, hematuria and the number of lesions were not significantly associated with anatomical types.

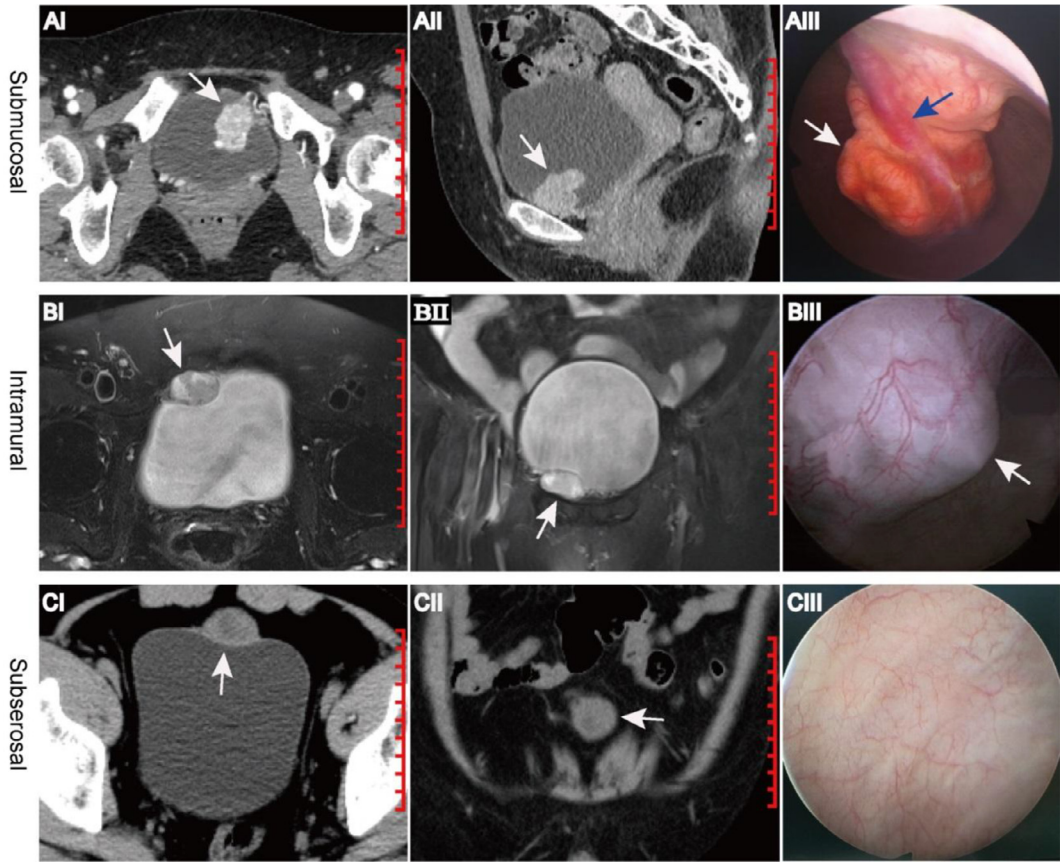

Fig. 1. Imaging and cystoscopy of different anatomical types of PUBs. AI (axial contrast-enhanced CT) and AII (sagittal CT) demonstrate a solid irregular tumor protruding into the bladder cavity; AIII (cystoscopy) reveals a conspicuous hypervascular (blue arrow) nonpedunculated tumor covered with congestive mucosa. BI (axial MRI, T2WI) and BII (coronal MRI, T2WI) demonstrate a solid oval tumor protruding into both the bladder and pelvic cavities; BIII (cystoscopy) reveals a nonpedunculated tumor (intravesical portion) covered with normal mucosa, and the profile is less conspicuous than that of a submucosal PUB. CI (axial CT) and CII (coronal CT) demonstrate a solid globular tumor protruding into the pelvic cavity, whereas CIII (cystoscopy) reveals a normal bladder cavity.

CT = computed tomography; MRI = magnetic resonance imaging; PUB = paraganglioma of the urinary bladder; T2WI = T2-weighted imaging. (Color version available online.)

Cystoscopy failed to detect the tumor in all the 4 patients with subserosal PUB. One patient with submucosal PUB and all patients with intramural or subserosal PUB underwent partial cystectomy. Of the 14 patients with submucosal PUB, 13 underwent transurethral resection of bladder tumor (TURBT). However, of them, 2 required further partial cystectomy for tumor residual, and 2 (suffered from unexpected hypertensive crisis during TURBT) turned to partial cystectomy after antiadrenergic intervention. Moreover, 1 patient needed surgical hemostasis for massive hemorrhage after TURBT.

3.3. Misdiagnosis

Histories of misdiagnosis and consequences are summarized in supplementary Table. Only 19.4% (6/31) of patients were precisely diagnosed before cystoscopy, all of whom were patients with typical functional PUB. Misdiagnoses included primary HTN, bladder cancer, undetermined bladder mass, and anxiety disorder.

3.4. Prognosis

Table 3 shows the initial operations and prognostic results for all patients (mean follow-up: 56.6 ± 36.2 months, 1 patient was lost). Five (16.1%) patients were confirmed with malignant PUB based on the metastasis in the nonchromaffin tissue. Three of them died in the 54th, 82th, and 94th postoperative month. Furthermore, 2 (6.5%) patients were pathologically (vascular invasion) and clinically (new lesion detected) suspected with malignant PUB.

4. Discussion

Owing to their rarity and symptomatic variability, PUBs are frequently misdiagnosed. As our group has shown, misdiagnosis frequently leads to severe consequences. Cystoscopy is commonly performed for diagnosing general bladder tumors. However, the use of cystoscopy for diagnosing PUBs is controversial due to its diagnostic values [6–8] vs. lethal

Table 1
Clinical features and their differences between the 2 functional types.

Variable	Overall	Functional PUB	Nonfunctional PUB	*P* value
Number of patients (%)	31	17 (54.8)	14 (45.2)	–
Age at initial operation (y)				
Mean ± SD	43.9 ± 15.2	44.6 ± 16.8	43.1 ± 13.6	0.798
Range	10−71	10−68	27−71	–
Sex (%)				
Male	20 (64.5)	13 (76.5)	7 (50.0)	0.153
Female	11 (35.5)	4 (23.5)	7 (50.0)	
Max tumor diameter (cm)				
Median	2.7 (IQR: 1.9−4.0)	2.9 (IQR: 2.6−4.9)	1.9 (IQR: 1.0−2.6)	**0.005**
Range	0.7−7.6	1.8−7.6	0.7−5.0	–
Number of lesions (%)				
Yes	1 (3.2)	0 (0)	1 (7.1)	0.451
No	30 (96.8)	17 (100%)	13 (92.9)	
Symptoms (%)				
Typical symptoms				
Paroxysmal HTN	15 (48.4)	15 (88.2)	–	–
Headache/dizziness	13 (41.9)	13 (76.5)	–	–
Palpitation	14 (45.2)	14 (82.4)	–	–
Perspiration	5 (16.1)	5 (29.4)	–	–
Syncope	4 (12.9)	4 (23.5)	–	–
Atypical symptoms				
Sustained secondary HTN	2 (6.5)	2 (11.8)	–	–
No symptom	9 (29.0)	–	9 (64.3)	–
Gross hematuria				
Yes	7 (22.6)	2 (11.8)	5 (35.7)	0.198
No	24 (77.4)	15 (88.2)	9 (64.3)	
Symptomatic triggers (%)				
Micturition	13 (41.9)	13 (76.5)	–	–
Micturition & defecation	2 (6.5)	2 (11.8)	–	–
None	16 (51.6)	2 (11.8)	14 (100.0)	–
CAs/metabolites (%)				
Positive	8 (25.8)	8 (47.1)	–	–
Negative	4 (12.9)	4 (23.5)	–	–
Not available	19 (61.3)	5 (29.4)	14 (100.0)	–

CAs = catecholamines; HTN = hypertension; IQR = interquartile range; PUB = paraganglioma of the urinary bladder; SD = standard deviation.
p value = 0.005 (< 0.05).

Table 2
Clinical features and their differences among the 3 anatomical types.

Variable	Overall	Submucosal PUB	Intramural PUB	Subserosal PUB	*P* value
Number of patients (%)	31	14 (45.2)	13 (41.9)	4 (12.9)	–
Max diameter (cm)					
Mean ± SD	3.0 ± 1.8	2.1 ± 1.3	3.5 ± 1.8	4.7 ± 2.2	**0.016**[a]
Range	0.7−7.6	0.7−5.0	1.0−7.6	2.8−7.4	–
Gross hematuria (%)					
Yes	7 (22.6)	3 (21.4)	4 (30.8)	0	0.614
No	24 (77.4)	11 (78.6)	9 (69.2)	4 (100.0)	
Functional types (%)					
Functional PUB	17 (54.8)	4 (28.6)	10 (76.9)	4 (100.0)	**0.006**[b]
Nonfunctional PUB	14 (45.2)	10 (71.4)	3 (23.1)	0	
Number of lesions (%)					
Multiple	1 (3.2)	1 (7.1)	0	0	1.000
Solitary	30 (96.8)	13 (92.9)	13 (100.0)	4 (100.0)	
Cystoscopy (%)					
Positive	23 (74.2)	14 (100.0)	9 (69.2)	0	–
False-negative	4 (12.9)	0	0	4 (100.0)	–
Omitted	4 (12.9)	0	4 (30.8)	0	–

PUB = paraganglioma of the urinary bladder; SD = standard deviation.
[a] Analysis of least significance difference: intramural vs. submucosal, $P = 0.034$; subserosal vs. submucosal, $P = 0.010$; subserosal vs. intramural, $P = 0.228$.
[b] Intramural vs. submucosal, $\chi^2 = 6.3$, $P = 0.012$; subserosal vs. submucosal, $P = 0.023$; subserosal vs. intramural, $P = 0.541$.

Table 3
Initial operations and prognostic results of the 3 anatomical types.

Variable	Overall	Submucosal PUB	Intramural PUB	Subserosal PUB
Initial operation (%)				
Partial cystectomy	18 (58.1)	1 (7.1)	13 (100.0)	4 (100.0)
TURBT	13 (41.9)	13 (92.9)	0	0
Metastasis (%)				
Yes	5 (16.1)	1 (7.1)	3 (23.1)	1 (25.0)
Suspected	2 (6.5)	0	1 (7.7)	1 (25.0)
No	24 (77.4)	13 (92.9)	9 (69.2)	2 (50.0)
Recurrence (%)	4 (12.9)	1 (7.1)	2 (15.3)	1 (25.0)
Death (%)	3 (9.7)	1 (7.1)	2 (15.3)	0

PUB = paraganglioma of the urinary bladder; TURBT = transurethral resection of bladder tumor.

risks [9,10]. Functional classification of PUBs may provide a possible compromise based on different functional types with uneven diagnostic difficulties and cystoscopy-related risks, whereby cystoscopy can be used for nonfunctional PUBs and atypical functional PUBs but not for typical functional PUBs. TURBT is a surgical treatment for some PUBs [2,11,12]. However, as nonepithelial tumors, rigorous indications are required for choosing TURBT [7]. Therefore, classification of the anatomical types is clinically important. In this study, we aimed to use functional and anatomical classifications to guide the diagnosis and treatment of PUBs.

In our study, we used symptoms as the basic classifying criteria for functional classification. Most patients (88.2%) with functional PUB had micturition-triggered symptoms of hypercatecholaminemia, which were characterized by an explicit symptomatic trigger and paroxysmal attack. These symptoms are highly specific, along with elevated CAs/metabolite levels, which appear to be diagnostic for functional PUBs. Therefore, we defined these typical symptoms as the classifying criteria for typical functional PUBs. Furthermore, a few patients (11.8%) with functional PUB presented only with sustained secondary HTN, closely mimicking primary HTN. Notably, they underwent hypertensive crisis during TURBT. Given its nonspecificity and misleading characteristics, sustained secondary HTN was defined as the classifying criterion for atypical functional PUBs. Hematuria was not taken as a classifying criterion because it was not catecholamine-related and not significantly associated with functional types.

Our findings suggest that intramural and subserosal PUBs have significantly larger diameters and are more likely to be functional than submucosal PUBs. Presumably, with larger surface area, the larger PUBs sustain higher intravesical pressure and tend to shift outward, thereby anatomically manifesting as intramural or subserosal PUBs. Additionally, larger PUBs may produce more CAs and sustain higher mechanical pressure during micturition, resulting in burst release of CAs, thereby symptomatically manifesting as functional PUBs. Furthermore, our findings suggest that functional PUBs have significantly larger diameters than nonfunctional PUBs. Maybe their larger surface area results in shifting outward and presenting with intramural or subserosal PUBs as the above mentioned.

We assumed that elderly or male patients are more sensitive to CAs, thereby symptomatically manifesting as functional PUBs. However, age and sex were not significantly associated with functional types (Table 1). Moreover, we inferred that submucosal PUBs are more like to invade the mucosa and result in hematuria than subserosal and intramural PUBs. Unexpectedly, the anatomical types were not significantly associated with hematuria (Table 2). The age, sex, and incidence of hematuria in our series are largely different from that reported by Zhai et al. [2], which denotes the heterogeneity. Thus, studies with larger sample size are still needed.

Tests for CAs/metabolites should be routinely conducted for all patients with suspected PUB [11,13]. Elevated CAs/metabolite levels are potent proofs of functional PUBs. Therefore, we defined them as the classifying criteria for typical functional PUBs. However, normal CAs/metabolite levels are not adequate to exclude PUBs due to the possibility of false-negative results and nonfunctional type.

On magnetic resonance imaging (MRI) or computed tomography (CT), PUBs are characterized by solitary intensely enhanced solid masses with round or oval profiles (Fig. 1AI, BI, and CI) [14,15]. Six of our patients with typical functional PUB were correctly diagnosed by combining their imaging characteristics with typical symptoms. As anatomical imaging modalities, MRI and CT are effective in determining tumor size, location, profile, blood supply, and adjacent tissue/organ. In our study, the anatomical classification was primarily based on MRI or CT. Due to its better soft tissue contrast and multiple parametric imaging, MRI is superior to CT [9,16], particularly in determining metastasis of the lymph node and continuities of the mucosa and serosa (compare Fig. 2A and B with Fig. 1AI and AII). Functional imaging is instrumental in determining the functional types [2] and metastases of PUBs [6].

Cystoscopically, submucosal PUB (Fig. 1AIII) is conspicuous and can be globular or irregular and pedunculated or nonpedunculated, but frequently manifests as a solitary hypervascular solid mass covered with normal or bleeding

mucosa. Intramural PUB (Fig. 1BIII) is not as conspicuous as submucosal PUB and is characterized by a hemispheric nonpedunculated bulged mass. The mucosa is usually normal, and bleeding may occasionally occur. In contrast, subserosal PUB (Fig. 1CIII) is nearly undetectable and presents with a normal bladder cavity. Consequently, diagnostic information provided by cystoscopy diminishes from submucosal PUB to intramural PUB and further to subserosal PUB.

Although cystoscopy is the gold standard for diagnosing general bladder tumors, for diagnosing PUBs, its limitations are noteworthy. First, cystoscopy may provoke a fatal catecholamine crisis, e.g., hypertensive crisis [17,18], catecholamine cardiomyopathy [19], and severe arrhythmia [11]. In addition, capturing the entire tumor profile with cystoscopy can be challenging due to the deep location. In particular, subserosal PUB is easily missed on cystoscopy, therefore posing limited clinical significance. False-negative cystoscopic findings are reported sporadically [9,20–23]. Furthermore, due to the deep location and hypervascular lesion, cystoscopic biopsy of PUBs may result in false-negative pathological diagnosis (too superficial) or massive hemorrhage (too deep). Finally, the incapability of conclusively determining the benign or malignant properties of PUBs with biopsy and the risk of triggering catecholamine crisis also limit the use of cystoscopy [24].

Bypassing cystoscopy is reasonable in the diagnosis of typical functional PUBs due to low diagnostic difficulties and high cystoscopy-related risks. Together with typical symptoms, elevated CAs/metabolite levels seem adequate to establish the qualitative diagnosis. In addition, in certain subserosal and intramural PUB cases, differential diagnosis from bladder cancer may be achieved with MRI or CT, according to the continuous mucosa (Fig. 2A and B), distinct location (Fig. 1CI), and intense enhancement [16] (Fig. 1AI). Furthermore, the role of cystoscopy in localized diagnosis can be largely substituted by imaging examinations. MRI and CT are even superior to cystoscopy in determining the anatomical relationship between the tumor and the pelvic tissue/organ. Most importantly, typical functional PUBs are easy to develop cystoscopy-triggered catecholamine crisis.

Compared to typical functional PUBs, nonfunctional PUBs are more challenging to diagnose due to the absence of typical symptoms, normal CAs/metabolite levels, and low sensitivity to functional imaging [2,11]. Meanwhile, cystoscopy is relatively safe for nonfunctional PUBs without risks of catecholamine crisis. Therefore, cystoscopy and biopsy should be performed if the imaging characteristics of PUBs are present.

The diagnosis of atypical functional PUBs also can be difficult. Patients with atypical functional PUB may present only with sustained secondary HTN or with typical symptoms but without elevated CAs/metabolite levels. In the above cases, cystoscopy should be considered but only after antiadrenergic intervention. Moreover, anatomical and functional imaging may provide with some diagnostic clues.

Apart from the rarity, symptomatic variability, and false-negative cystoscopic findings, poor cystoscopic vision (e.g., evident gross hematuria or mucosa invasion) potentially results in misdiagnosis. Furthermore, the imprecise consulting department is another important factor potentially leading to misdiagnosis. Due to the main symptoms in the cardiovascular and nervous system, patients with functional PUB often initially visit cardiologists or neurologists, who frequently neglect the association between the symptoms and micturition.

Antiadrenergic intervention should be administered to all patients with typical or atypical functional PUB to prevent catecholamine crisis, which is the most common and risky intraoperative complication. Drastic fluctuation in intraoperative blood pressure was absent in our patients with nonfunctional PUB, albeit without antiadrenergic intervention, which seemed unnecessary.

The primary surgical approaches for PUBs include partial cystectomy and TURBT, whereas the former seems more reliable and preferred over the latter [25]. As nonepithelial tumors, choosing TURBT for PUBs should be based

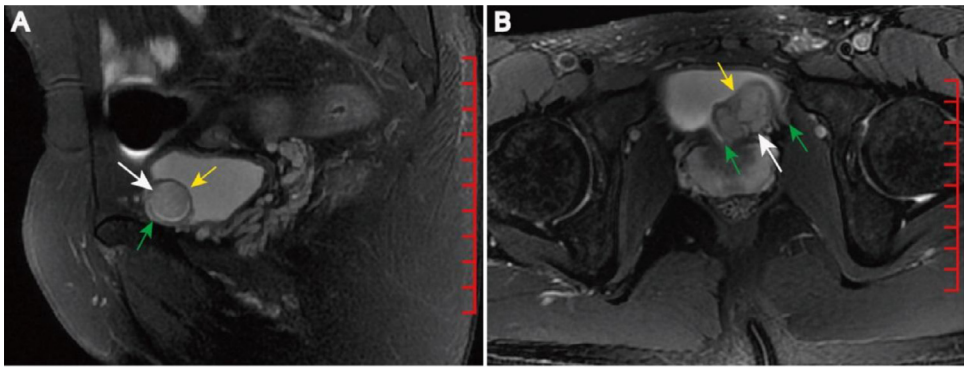

Fig. 2. MRI of PUBs. Both A (sagittal MRI, T2WI) and B (axial MRI, T2WI) demonstrate the gaps between the tumors and the mucosae as well as the continuities of mucosae (yellow arrow). A shows the continuous serosa (green arrow), while B does not.

MRI = magnetic resonance imaging; PUB = paraganglioma of the urinary bladder; T2WI = T2-weighted imaging. (Color version available online.)

on rigorous indications [7]. Anatomically, TURBT is not suitable for intramural or subserosal PUBs. It is only an option for small and pedunculated submucosal PUBs, due to the difficulty of complete resection (deep lesion), risk of bleeding (hypervascular lesion), and consequence of tumor residual (potential malignancy). Moreover, radical cystectomy should be considered for large or confirmed malignant PUBs.

Among the 5 malignant PUB cases in our study, 4 involved recurrence before metastasis. Therefore, recurrence may be a predictor of malignant PUB. The true malignant incidence is probably >16.1%, considering our 2 highly suspected malignant cases. It is higher than the malignant incidence in other studies (6.0%−11.1%) [2,20,26], which may be related to our longer follow-up. One of our patients experienced recurrence and subsequent metastasis until the eighth postoperative year. Recurrence after 10 postoperative years has also been reported [2,27]. Thus, lifelong follow-up is required to detect late recurrence and metastasis.

Apart from pathological examinations and tumor size, genetic mutation is another potential predictor of malignant PUB [26,28]. Increasing studies have proven that PUB is a hereditary syndrome, which may involve genetic mutation of succinate dehydrogenase subunit B [26] and Von Hippel-Lindau [28].

Our study used functional and anatomical classifications of PUBs to guide the diagnosis and treatment by determining the necessities of cystoscopy and surgical options. The factors associated with functional types of PUBs were identified, highlighting the risk factors of catecholamine crisis. Finally, a diagnostic and therapeutic algorithm for PUBs was proposed (Fig. 3).

Our study has several limitations. First, the associations between levels of CAs/metabolites and functional types as well as anatomical types cannot be compared due to the

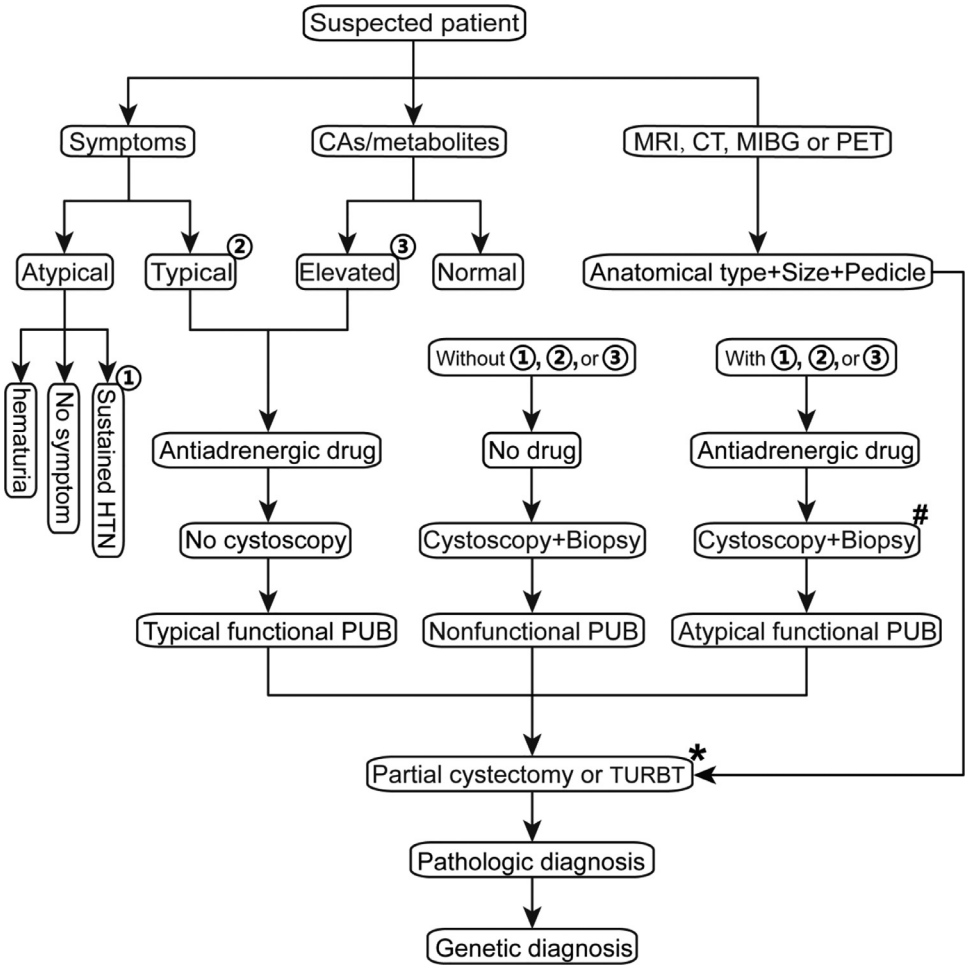

Fig. 3. Proposed diagnostic and therapeutic algorithm for PUBs.

#If the drastic fluctuation in blood pressure is observed during cystoscopy or biopsy, atypical functional PUB should be considered, and biopsy should be avoided or terminated.

*TURBT is only optional for small and pedunculated submucosal PUB.

CAs = catecholamines; CT = computed tomography; HTN = hypertension; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; PET = positron emission tomography; PUB = paraganglioma of the urinary bladder; TURBT = transurethral resection of bladder tumor.

nonuniform and inadequate data. Second, owing to the limitations of nonrandomized surgical options, nonuniform follow-up duration, and small sample size, statistical analysis for determining the association between surgical approaches and prognosis is invalid.

5. Conclusions

Functional and anatomical classifications of PUBs are instructive for the diagnosis and treatment. By functional classification, cystoscopy can be omitted for typical functional PUBs while is recommended for nonfunctional PUBs and atypical functional PUBs. In addition, functional PUBs are more likely to be larger than nonfunctional PUBs. By anatomical classification, intramural and subserosal PUBs tend to be large and functional compared to submucosal PUBs. Moreover, cystoscopy can easily miss subserosal PUBs; thus, it has limited clinical significance. Finally, among submucosal PUBs, only those small and pedunculated are amenable to TURBT.

Conflict of interest

All authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urolonc.2019.01.027.

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