A retrospective study of paraganglioma of the urinary bladder and literature review

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Abstract

Objective

To retrospect and summarize the characteristics and therapy of paraganglioma of the urinary bladder (PUB).

Method

Patients who underwent the operation in Peking Union Medical College Hospital from January 2012 to December 2021 were reviewed for this retrospective study.

Results

A total of 29 patients, comprising 9 males (31%) and 20 females (69%) were included. The main manifestations were hypertension, palpitation, and micturition syncope. 8 patients had an increased 24-hour urinary catecholamine, and 7 of them were increased norepinephrine. 7 patients’ normetanephrine were increased. 6/18 metaiodobenzylguanidine and 8/22 octreotide imaging were positive. 15 cases took laparoscopic partial cystectomy and 14 took transurethral resection of bladder tumor. Of all the patients, the immunohistochemical index of Melan-A, AE1/AE3 and α-inhibin were negative, while (chromogranin A) CgA, S-100 and (succinate dehydrogenase) SDH B were positive. Ki-67 of 28/29 cases are under 5%, and 1 case whose Ki-67 was 20% was diagnosed with malignant PUB. 25 patients had a regular follow-up, 1 patient died in 1 year after the surgery, 2 patients were lost found, and 2 patients had a recurrence. The symptoms all disappeared or relieved after the surgery.

Conclusion

Transurethral surgery approach fits for PUB tumors whose sizes are under 3cm or that protrudes into the bladder and can significantly reduce the postoperative hospital stay. Early detection and treatment are effective, and regular review is necessary after the surgery.

1. Background

Paraganglioma of the urinary bladder (PUB) is a rare tumor which was first reported by Zimmerman et al. in 1953 [1]. Like all the other paragangliomas, PUB derives from chromaffin tissue of the sympathetic nervous system, however, it only constitutes 0.06% of urinary tumors and about 6%-9.8% of paragangliomas [2, 3]. The tumors can be functional or non-functional, the clinical manifestation of functional tumor mainly includes micturition syncope, hypertension, headache, and palpitation, which are caused by extensively increased endogenous catecholamine (CA) secretions. Due to their rarity and the variable nature of their symptoms, PUBs are commonly misdiagnosed and mistreated. Treatment options
generally include transurethral resection, partial or radical cystectomy. We reviewed the clinical and pathological characteristics of all patients diagnosed with PUB in our hospital over the past 10 years and compared postoperative hospitalization and follow-up with different surgical approaches. This will improve our understanding of PUB and provide help to give the patients a more safety and effective treatment method.

2. Methods

We retrospect patients who was diagnosed with PUB and took an operation in our hospital from January 2012 to December 2021. General information, laboratory and radiology examination, surgery, pathology, and follow-up were detected. All PUB tumors were defined as functional when urine or plasm fractionated catecholamines or fractionated or total metanephrines were elevated above the upper limit of respective reference ranges. Length of stay exceeding the 75th percentile of the total length of stay was defined as an extended length of stay [4]. 24-hour urinary catecholamine was examined in all patients. And patients after 2019 were tested normetanephrine (NMN) and metanephrine (MN) of blood sample in our results, which help us to save time of diagnosis and increase the accuracy. The operative method of PUB was diverse, according to our experience, when the tumor diameter is less than or equal to 3cm, transurethral resection of bladder tumor (TURBT) can be selected, which can ensure the en bloc resection of the tumor and complete removal from the urethra to avoid implantation and metastasis. All tumors were completely resected. All surgical specimens were diagnosed by urologic pathologists. Tumor size was determined based on the largest diameter of the PUB on histopathology. To assess the effectiveness of PUB treatment, long-term follow-up was carried out by reviewing patients in the outpatient clinic or by telephone interviews at intervals of approximately 3–6 months. The follow-up period is calculated from the date of surgery to the date of the last follow-up or death. SPSS 26.0 software was used for data processing and analysis. In this study, measurement data that did not obey normal distribution were expressed by median (M) quartiles (P25 ~ P75), and the Mann-Whitney U test was used for comparison between groups. Count data were expressed by frequency or composition ratio, and the χ2 test was used for comparison between groups. P < 0.05 was considered a statistically significant difference. This study was approved by the Ethics Committee of Peking Union Medical College Hospital, and written informed consent was obtained from all patients.

3. Results

3.1 Patient demographics

In this study, 29 cases of PUB were diagnosed, accounting for 5.7% (29/508) of patients with all paragangliomas treated in our hospital in the same period. The mean age of the PUB patients was 48 years (range, 28–68 years), and these included 9 males (31%) and 20 females (69%) (Table 1). Of the 29 cases, 11 (37.9%) were functional, and 18(62.1%) were nonfunctional. Patients of PUB presented with strong headache (44.9%), palpitation (62.1%), weakness (20.7%) and increasing blood pressure after
urination (41.4%). 2 patients (6.9%) detected the tumor occasionally without any symptom. The longest history of hypertension was over 10 years.

<table>
<thead>
<tr>
<th>Index</th>
<th>Partial cystectomy group</th>
<th>TURBT group</th>
<th>(Z/\chi^2)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46 (39.55)</td>
<td>50 (47.56)</td>
<td>-1.027</td>
<td>0.304</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>5 (33.3%)</td>
<td>-0.272</td>
<td>0.785</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10 (66.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 (71.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative hospital stay</td>
<td>7.7 (6.9)</td>
<td>3.6 (3.5)</td>
<td>-4.232</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prolonged postoperative</td>
<td>Extension</td>
<td>12 (80%)</td>
<td>19.106</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>hospital stay</td>
<td>No extension</td>
<td>3 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-operative recurrence</td>
<td>Recurrence</td>
<td>3 (21.4%)</td>
<td>1.340</td>
<td>0.247</td>
</tr>
<tr>
<td></td>
<td>No recurrence</td>
<td>11 (78.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>13 (100%)</td>
<td></td>
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</tr>
</tbody>
</table>

### 3.2 Treatment

B-ultrasound and enhancement computerized tomography (CT) as traditional ways were taken before the surgery to assess the location and the statement of invasion of the tumor (Fig. 1 & Figure 2). PUB performs an obvious enhancement because of the rich blood supplement. The average size of the largest tumor diameter is 2.57cm. 18 patients took metaiodobenzylguanidine (MIBG) and 6 (33.3%) results were positive. 22 patients took octreotide imaging, and 8 36.3% patients were positive. 2 patients’ MIBG and octreotide imaging were both positive. 68GA PET-CT was taken in 2 patients because metastasis was suspected. The locations of the PUB include right side wall (9 cases, 31.0%), right posterior wall (1 case, 3.4%), right anterior wall (1 case, 3.4%), left side wall (1 case, 3.4%), left posterior wall (4 cases, 13.8%), posterior wall (4 cases, 13.8%), and anterior wall (9 cases, 31.0%). (Fig. 3)

All the 29 patients took the operation in our hospital, with 15 transurethral laparoscopic combined partial cystectomy (Fig. 4) and 14 transurethral resection of bladder tumor (TURBT). Among the transurethral laparoscopic combined partial cystectomy patients, tumor sizes of 8 cases were less than 3cm, all TURBT patients’ tumor were less than 3cm. The mean postoperative hospital stay was 7.7 days in the partial cystectomy patient group and 3.6 days in the TURBT patient group, with a significant difference in
whether the postoperative hospital stay was prolonged in the two groups ($P<0.001$) and no difference in whether there was a recurrence after surgery ($P>0.05$). (Table 1)

### 3.3 Pathology

The pathology historical results of the 29 patients are all paraganglioma of urinary bladder. The immunohistochemical index of Melan-A, AE1/AE3 and $\alpha$-inhibin are negative, while CgA, S-100 and SDHB are positive. Ki-67 is an index which can react the malignant degree of the tumor. In our patients, Ki-67 of 28 cases are under 5%. 1 case whose Ki-67 is 20% was diagnosed with malignant PUB, and the pathology result showed that bladder muscular was invaded and intravascular tumor thrombus formed. (Fig. 5)

### 3.4 Follow-up and Prognosis

Of the 29 cases, 2 patients (6.9%) were lost during follow-up. The remaining 27 patients have a regular review, while 1 patient died in one year after the surgery because of the multiple metastasis through the body and 1 patient recurred after 2 years with a bladder tumor and several lung metastatic foci, and the systolic blood pressure increased higher than 180mmHg. We gave him kinds of alpha receptor blocker to control the blood pressure, and the recurred mass and multiple metastatic foci made no progress. 1 patient recurred 5 years after the surgery with two masses were detected, one in retroperitoneum and the other was before the sacrum. Temozolomide was taken with side reactions of weak and nausea. The symptoms of headache, palpitation, and high blood pressure after urination of 26 patients disappeared after the surgery, and 1 patient relieved the symptoms in one year.

### 4. Discussion

A paraganglioma is a non-epithelial tumor which arises in the paraganglial location. Less than 10% paraganglioma are in the urinary bladder, and the young people are more easily to develop PUB. PUB arise more frequently in the trigone of bladder with an average size of 3.9cm [5]. To the best of our knowledge, we have reported the largest number of PUB patients in one center until now.

The detection and diagnosis of PUB depends on the clinical manifestation of hypertension and radiology examination in the early stage. Some patients’ symptoms may present with headache, paranesthesia, dyspnea, angina, hematuria, and lower urinary tract symptoms [6]. While PUB is always misdiagnosed as bladder cancer unfortunately, especially non-functional tumors with no symptoms. According to our previous literature review, 61.6% PUB patients were misdiagnosed before pathologic diagnosis, and less than 30% were diagnosed before the surgery [7].

Based on the difficulties of the diagnosis of PUB patients, crucial laboratory examinations and image analysis are necessary before the operation. Catecholamine (CA) which is secreted by chromaffin cells including dopamine, adrenaline and norepinephrine are important indexes. The level of these indexes, either in blood or 24-hour urinary sample, are increased in functional PUB, and theses laboratory results can help us to finish the etiology diagnosis before the operation. In our study, all the 3 non-functional PUB patients had a normal level of 24-hour urine catecholamine, NMN and MN. Almost all abnormal
laboratory indexes are NE and NMN increased in functional PUB tumors. This may suggest that increased NE and NMN are specific to PUB tumors.

Image analysis provides localization diagnosis and improves etiology diagnosis. Contrast-enhanced CT and magnetic resonance imaging (MRI) are two basic screening methods. PUB performs a regular shape bladder tumor with obvious enhancement and hyperintense on T2 weighted images (T2WI) [8]. MIBG has a high specificity and sensitivity for detecting paraganglioma, and a previous study found that fluorodeoxyglucose (FDG)-PET has a higher sensitivity than MIBG [9]. Ga-68 DOTATATE PET/CT is reported to find the metastatic paraganglioma of the urinary bladder [10]. However, non-functional PUB is difficult to be detected before the operation because of lack for secreting CA and nontypical symptoms can be found. A case of functional PUB was reported even without radiographic and laboratory feature [11]. Musa Male et al. [12] recommended cystoscopy before the surgery because PUB had a cystoscopic feature of hypervascularization. However, the eventual diagnosis must be based on the histopathology and immunohistopathology after the tumor resection.

Surgery is the most important therapy for PUB. Until now, two main surgical options including transurethral resection and transurethral laparoscopic combined partial cystectomy were applied. Most of the PUB tumors are functional which can be detected in the early stage, and the tumor size was small, transurethral is a safe and better operation approach, about 1/5 patients were treated with TURBT alone [13]. Transurethral laparoscopic combined partial cystectomy is regarded to be used for the tumors who invade the muscle layer of the bladder or even deeper. Transurethral methods can help the surgeons to avoid the injury of the important anatomical structure, such as bilateral ureteral orifice. We can early coagulate the vessel at the tumor base and using short burst to limit the blood pressure fluctuations during the procedure may be beneficial [14]. At present, laser resection and electro-excision are reported to treat PUB which have a good effect [15]. While some suggestions believe that resection rarely leads to a high level of recurrence [16].

In this article, we compare the effects of both partial cystectomy and TURBT on postoperative length of stay and postoperative recurrence. The results showed that the different surgical approaches did not have an effect on postoperative recurrence and that the TURBT procedure significantly reduced the postoperative hospital stay. Moreover, recent findings suggest that TURBT is feasible for tumors less than 3cm in diameter with adequate preoperative preparation [17]. Therefore, we recommend TURBT for PUB smaller than 3 cm, while for larger tumors, partial cystectomy or radical cystectomy can be chosen depending on their invasion of the bladder wall. Pelvic lymph node dissection or biopsy is necessary if metastasis is suspected. However, due to sample size limitations, we were not able to compare the differences between the two surgical approaches separately when the tumor was less than 3 cm. Therefore, more studies are needed to confirm this conclusion. On the other hand, almost all the paraganglioma have a whole regular membrane, and excision extension involves muscularis of the bladder is the key point to respect the tumor completely, and complete excision of the membrane is the most important to avoid or decrease the rate of recurrence.
Pathology is the gold standard to definite diagnosis. Typical paraganglioma performs neuroendocrine markers combined with neuroendocrine markers and negative mesenchymal and epithelial markers. CD56, NSE, CgA, Syn vimentin, SDHB, (Von Hippel-Lindau) VHL, PGP9.5 and S-100 protein are in common use [18]. Typical PUB presents with Melan-A, α-inhibin and AE1/AE3 negative, and CgA, S-100, and SDHB positive in our study. Ki-67 > 5% means a high risk of metastasis. Genetic disorder is another occurrence factor, and SDHB is the most common gene which is associated with the highest rate of metastasis [19].

5. Conclusion

PUB is rare bladder tumor with gradually advanced appropriate diagnosis methods and surgery approaches in recent years. Transurethral surgery approach fits for most PUB tumors whose sizes are under 3cm or that protrudes into the bladder. Early detection and treatment are effective, and regular review is necessary after the surgery.

Declarations

Acknowledgments

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Disclosure

There is no conflict of interest.

References


Figures
Figure 1

The arterial phase enhanced CT scan of the patient whose PUB tumor was located in left posterior wall.
Figure 2

The unenhanced CT scan of the patient whose PUB tumor was located in left posterior wall.
Figure 3

The distribution of different tumor locations of bladder and surgical approach.

Figure 4

In a combined transurethral laparoscopic partial cystectomy, the transurethral approach helps the surgeon avoid damaging important anatomical structures.
The pathology historical results of the 29 patients are all paraganglioma of urinary bladder. The immunohistochemical index of Melan-A, AE1/AE3 and α-inhibin are negative, while CgA, S-100 and SDHB are positive.