Paraganglioma of the urinary bladder: review of the contemporary literature

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Abstract

**Background:** Paraganglioma of the urinary bladder is a rare tumor. Herein we sought to review the contemporary literature on paragangliomas of the urinary bladder.

**Materials and Methods:** A comprehensive review of the current literature was conducted by accessing the NCBI PubMed database and using the search terms “paraganglioma, bladder.” This search resulted in the identification of 186 articles published between January 1980 and April 2012 of which 79 articles were ultimately included in our analysis.

**Results:** Paragangliomas usually occurred in young adult Caucasians (mean age, 43.4 years; range, 11-84 years). According to the literature, the most common symptoms and signs of paragnangliomas of the urinary bladder were hypertension and hematuria. Of the 68 cases that commented on catecholamine production, 82% of patients had biochemically functional tumors. Unfortunately, complete tumor stage was only available on 7.2% of patients, while definitive grade was not reported throughout. Approximately 17% of patients were treated by transurethral resection alone, 70% by partial cystectomy and 11% by radical cystectomy. The 67 patients with follow-up information had a mean follow-up of 37 months. At the time of last follow-up, 11 (16%) had disease recurrence, 9 (13%) had metastasis, and 58 (87%) were alive.

**Conclusions:** Paragangliomas of the urinary bladder tend to be functional and occur mostly in young adult Caucasians. Patients with localized tumors have an extremely favorable prognosis
and may be managed by less aggressive modalities, whereas patients with metastatic disease have a significant reduced survival rate despite aggressive treatment.

**Keywords:** paraganglioma, bladder, treatment, diagnosis, prognosis
Background

Paraganglioma of the urinary bladder is a rare tumor that originates from chromaffin tissue of the sympathetic nervous system associated with the urinary bladder wall. These tumors of the sympathetic nervous tissue may be non-functional or functional, \textit{i.e.}, secrete catecholamine causing paroxysmal hypertension, palpitation, and micturition syncope \cite{1}. Typically these tumors possess the capacity to invade and thus are deemed malignant, yet lack mitoses and cellular dissociation that are usually associated with malignant tumors \cite{2}. Numerous, small series case reports have been published in the English literature since it was first reported in 1953 by Zimmerman \textit{et al.} \cite{3}. Herein we sought to review the contemporary literature on paraganglioma of the urinary bladder in hopes of further clarifying presentation, treatment options and outcomes of patients with paragangliomas of the urinary bladder.

Materials and Methods

A review of the current literate was conducted by accessing the NCBI PubMed database \url{http://www.ncbi.nlm.nih.gov/pubmed}. Filters applied in an advanced search include: the search terms of “paraganglioma, bladder”; English language; human subjects 18 years of age and older; publication dates of January 1980 to April 2012. \textbf{Figure 1} illustrates the work-flow of the comprehensive literature review. This search delivered 186 results from which 33 articles were excluded (31 did not have abstract available online for review and 2 entries were not case reports) thus 153 abstracts were reviewed. Of these abstracts, fifty-three were excluded. The top two reasons to exclude articles at this stage included, the paraganglioma did not involve the urinary bladder or the article was not a case report. A total of 121 articles were then reviewed in
Patient characteristics were divided into “primary” and “secondary” demographics for ease of data recording. Reasons for exclusion included missing any primary demographic (patient age, sex, presenting symptoms, type of surgery) or more than three secondary demographics (patient race, catecholamine levels, tumor size, tumor grade and stage, last follow up). Due to failure to report primary demographics and/or secondary demographics, an additional 25 articles eventually were excluded from final analysis. Thus the final analysis comprised 79 articles that reported on 97 patients.

Results

Using strict review criteria, 79 articles on paraganglioma of the urinary bladder were identified on Pubmed and were incorporated in our analysis, which included 97 patients [4-82]. The demographics and presenting symptomology are summarized in Table 1. The mean patient age was 43.4 years (range, 11-84 years). The male-to-female ratio was 1.16 to 1. The most common symptoms were hypertension (50.5%), headache (50.5%), hematuria (46.4%) and syncope/palpitations (43.3%). Micturition attacks were reported in 54.6% of patients.

Average tumor size was 4.0 cm (median 3.5, range 1-9.1). Few studies (n=7) reported exact tumor stage by the TNM criteria and tumor grades were not reported throughout. Of the 97 patients, 56 (57.7%) were noted to have a functional paraganglioma as evident by elevated VMA, metanephrine and/or catecholamines. Furthermore, limited articles reported on CD56, Chromagranin A, and synaptophysin immunohistochemical staining.

The most commonly reported treatment for patients with paraganglioma of the urinary bladder was partial cystectomy (70.1%). Other treatment options for localized/locally advanced
paraganglioma of the urinary bladder are illustrated in Table 2. Mean follow of the cohort is 36.9 months (range 0.75-372). Eleven patients (11.3%) were noted to develop a recurrence of the tumor. Metastatic recurrence was noted in nine patients (9.3%). Eight patients (8.2%) were deceased at last follow-up. Specifically of the eight patients who died, three (3.1%) presented with locally advanced or metastatic disease. Thus, patients who presented with localized paraganglioma of the urinary bladder have a significantly improved survival compared to patients who presented with locally advanced/metastatic disease.

Discussion

Paraganglioma (aka pheochromocytomas) of the urinary bladder are exceedingly rare tumors accounting for less than 0.05% of all bladder tumors and less than 1% of all pheochromocytomas. In the genitourinary tract, the urinary bladder is the most common site for paragangliomas (79.2%), followed by the urethra (12.7%), pelvis (4.9%), and ureter (3.2%) [82,83]. Furthermore, approximately 10% of all extra adrenal pheochromocytomas are malignant [83]. Since this is such a rare condition, limited, large reports are available to direct clinical decision making. We extensively reviewed the English literature on this subject and report the largest analysis of paragangliomas involving the urinary bladder.

Symptoms reported in the current literature range from the typical micturition attacks of headache and palpitations to more abstract signs such as paraesthesias and dyspnea. While our patient lacked some of the more common presenting symptoms of bladder paraganglioma, e.g., hypertension, he did have hematuria and lower urinary tract symptoms, testifying to the variability in which this disease can present itself. Furthermore, the consequences of hypertension itself may muddle the initial diagnostic picture of these patients. Patients often seek
medical attention only when their hypertension has become so advanced as to cause syncope, retinopathy, or intracranial hemorrhage [84]. Physicians must constantly be wary of an undiagnosed paraganglioma in the setting of unexplained hypertension or associated symptoms.

Just over 70% of patients included in our literature review underwent partial cystectomy as a means of primary treatment, similar to our patient. Including those who underwent radical cystectomy, over 82% of patients were treated with aggressive surgical excision. Approximately 3% of patients with reported follow-up died due to their cancer, illustrating that good survival rates can be achieved with the above therapies. It is important to note, however, that over 20% of patients did have recurrence or metastases at the last known follow-up. In the face of metastatic paraganglioma, surgical treatment is rarely curative. It may adequately prolong survival by reducing comorbid conditions (i.e. hypertension) and reducing tumor burden, but adjunct therapies are usually indicated [84]. Thus patients should be counseled according to their individual presentation and disease status.

The main limitations of our study relate to its retrospective nature and the large disparity among reporting styles of various institutions. The lack of uniformity on how oncologic cases are presented makes it difficult to characterize the true disease course of bladder paraganglioma. Information such as patient race, diagnostic findings, and laboratory values should be included whenever possible to better illustrate the pathophysiologic process. The complete tumor stage and grade are vital additions to any oncologic case report. Utilizing standard reporting criteria will enable future investigations to better collect and analyze information from individual case reports.

In summary, paragangliomas of the urinary bladder tend to be functional and occur mostly in young adult Caucasians. Initial presentation is extremely varied in these cancers,
necessitating a low threshold of suspicion in the face of hypertension or hematuria. Patients with localized tumors have a favorable prognosis and may be managed by less radical modalities, whereas patients with metastatic disease have a significantly reduced survival rate. Moving forward, it would be helpful to standardize the reporting guidelines of paragangliomas cases to better understand the natural process and outcomes.

**List of abbreviations**

AUA – American Urological Association

VMA - vanillylmandelic acid

H&E - Hematoxylin and eosin

IHC – immunohistochemical

**Competing Interests**

The authors declare that they have no competing interests.

**Authors Contributions**

All authors have read and approved the final manuscript.

Jon Beilan, BS Acquisition of data, statistical analysis and drafting manuscript

Adrienne Lawton, MD Pathologic interpretation of case report and acquisition pathologic images

Julio Hajdenberg, MD Analysis of data and drafting of manuscript

Charles J. Rosser, MD, MBA Study concept and design, drafting of manuscript
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None
References


### Table 1 Demographics and presenting symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients (M:F)</td>
<td>97 (1.16:1)</td>
</tr>
<tr>
<td>Males</td>
<td>52</td>
</tr>
<tr>
<td>Female</td>
<td>45</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>43.4</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>11-84</td>
</tr>
<tr>
<td>Presenting symptom(s)</td>
<td></td>
</tr>
<tr>
<td>Micturition attacks</td>
<td>53 (54.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49 (50.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>49 (50.5)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>45 (46.4)</td>
</tr>
<tr>
<td>Syncope/palpitations</td>
<td>42 (43.3)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>19 (19.6)</td>
</tr>
<tr>
<td>Micturition disturbances (e.g., urgency, dysuria)</td>
<td>10 (10.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (9.3)</td>
</tr>
<tr>
<td>Abdominal/flank pain</td>
<td>6 (6.2)</td>
</tr>
<tr>
<td>Dyspnea/chest pain</td>
<td>5 (5.2)</td>
</tr>
<tr>
<td>Malaise</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>Incidental finding</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (11.3)</td>
</tr>
<tr>
<td>Commented on Catecholamines</td>
<td>68</td>
</tr>
<tr>
<td>↑ VMA, metanephrine, catecholamines</td>
<td>56 (57.7)</td>
</tr>
<tr>
<td>Unknown/not mentioned</td>
<td>29 (29.9)</td>
</tr>
<tr>
<td>Commented on Tumor size</td>
<td>71</td>
</tr>
<tr>
<td>Mean (cm)</td>
<td>4.0</td>
</tr>
<tr>
<td>Median (range) (cm)</td>
<td>3.5 (1.0-9.1)</td>
</tr>
</tbody>
</table>
Table 2 Primary treatment modalities for 97 patients with localized/locally advanced paraganglioma of the urinary bladder

<table>
<thead>
<tr>
<th>Procedure</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TURBT</td>
<td>17 (17.5)</td>
</tr>
<tr>
<td>Partial Cystectomy</td>
<td>68 (70.1)</td>
</tr>
<tr>
<td>Radical Cystectomy</td>
<td>12 (12.4)</td>
</tr>
</tbody>
</table>
Table 3 Follow Up Data

<table>
<thead>
<tr>
<th>Variables</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up (months)</td>
<td>36.9</td>
</tr>
<tr>
<td>NED at follow up</td>
<td>55 (56.7)</td>
</tr>
<tr>
<td>Recurrence at follow-up</td>
<td>11 (11.3)</td>
</tr>
<tr>
<td>Metastasis at follow-up</td>
<td>9 (9.3)</td>
</tr>
<tr>
<td>Mortality: all-cause</td>
<td>8 (8.2)</td>
</tr>
<tr>
<td>Disease-specific-mortality</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>Unknown followup</td>
<td>31 (32)</td>
</tr>
</tbody>
</table>
**Figure 1**

**Pubmed advanced search**
- Search terms: paraganglioma, bladder
- Language: English
- Subjects: Humans, 18+ yrs old
- Publication date: 01/01/1980 to 04/16/2012

186 Search results

153 Abstracts examined

121 Articles examined

79 Articles included

31: Abstracts unavailable online
2: Entries are not case reports

31: PG not specifically in urinary bladder
16: Entry not a case report
4: PG found with additional malignancy
1: PG examined post-mortem
1: Unable to obtain article online

25: Article did not include key data about the patient(s)
9: PG not specifically in urinary bladder
4: PG found with additional malignancy
2: Report is a recurrence, not initial tumor presentation
1: Entry is not a case report