

## Peer Review File

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### Reviewer A

#### **Comment 1: Did the authors consider MIBG scan for metastatic survey?**

Reply 1: Yes, we considered an MIBG scan for metastatic survey; however, a PET CT did not identify any regional/distant lesions or any demonstrate any avidity to suggest active disease sites. If conventional CT chest/abdomen/pelvis or PET CT showed any suspicious lesions, then an MIBG scan would have been performed, since this has great specificity for neuroendocrine tumors, but low sensitivity. We have included a comparison of the different imaging modalities in the Discussion section (see Page 6, line 166-174).

*Changes in the text: Various diagnostic imaging modalities are available for suspected bladder paraganglioma, including ultrasound, which can be used with color Doppler to investigate vascularity. CT urogram is the gold standard when assessing for gross hematuria or a bladder mass, which will also identify pelvic lymphadenopathy. MRI is more useful than CT to estimate the depth of bladder tumor invasion, and is currently being explored in the setting of VI-RADS (8). MIBG Scintigraphy is highly specific for neuroendocrine tumors but has limited sensitivity, allowing for a high false-negative potential (7). Once a diagnosis is confirmed histologically, this can be considered as part of a metastatic workup if a regional or distant lesion is visualized on CT chest/abdomen/pelvis imaging.*

#### **Comment 2: It is not possible to see the "golden yellow" appearance of a submucosal tumor. The appearance is only revealed after transurethral resection. Therefore, the authors should emphasize that any submucosal mass seen in the bladder should raise concern for paraganglioma and prompt further workup with serum and/or urine metanephrines.**

Reply 2: We agree that this is rarely visualized preoperatively and only after resection begins. We have emphasized this in the Discussion section (see Page 8, line 213-231).

*Changes in the text: Early intraoperative recognition of a golden yellow submucosal mass (classically associated with pheochromocytoma) should prompt a cessation of the resection with close hemodynamic monitoring to avoid a hypertensive crisis, which can introduce significant morbidity due to sudden catecholamine release in patients with functional tumors (4,5,9). The hypertensive crisis can manifest with changes in the patient's vital signs (e.g., tachycardia, hypertension (>180/120 mmHg), diaphoresis, and increased body temperature). These findings can cause neurological emergencies such as acute subarachnoid hemorrhage, intracerebral hemorrhage, hypertensive encephalopathy, and acute ischemic stroke, cardiovascular emergencies such as acute heart failure and aortic dissection, and obstetric emergencies such as pre-eclampsia can also occur. In rare cases, untreated or undetected hypertensive crisis can lead to multi-system organ failure (4). Uslar, et al, in a four decade retrospective review of extirpative surgeries to treat paraganglioma, noted a 42% overall incidence of intra-operative hypertensive crises, with a reduction from 50% in the decade spanning 1990-2000 to 23% in the years 2010-2019 (10). Beilan, et al., considered 80 studies of bladder paraganglioma from 1980 to 2012 encompassing 106*

patients, 65 (61.3%) of whom presented with an increase in catecholamine, metanephrine, or VMA levels (1). Visualization of this golden yellow submucosal mass and/or hypertensive crisis during resection should raise concern for paraganglioma and prompt further workup with serum and/or urine metanephrines.

**Comment 3: The authors should discuss the merits of each approach (i.e. sensitivity/specificity of plasma free metanephrines vs. 24hr urine metanephrines) as part of the diagnostic work-up.**

Reply 3: The merits of using plasma and urine metanephrines have been more fully discussed in the Discussion Section (see Pages 6-7, lines 176-184).

*Changes in the text: Urine and plasma metanephrines may serve as a useful diagnostic tool when pheochromocytoma is suspected. Plasma metanephrines are preferred for initial screening due to higher sensitivity and convenience; however, they are susceptible to false positives and are expensive. In contrast, 24-hour urine metanephrines are highly specific and are less influenced by acute changes in physiology, but are less convenient for patients. According to Waingakar, et al., the sensitivity and specificity for plasma metanephrines are 97% and 96%, while urinary catecholamines are 60% and 96%, respectively (7). We advocate for initial screening with the highly sensitive plasma free metanephrines, and subsequent confirmatory testing with the highly specific 24-hour urine catecholamines and metanephrines.*

**Comment 4: The authors should also list other possible tumor types with this submucosal morphology (i.e., connective tissue tumors such as fibroma, fibrosarcoma, leiomyoma, leiomyosarcoma, etc.).**

Reply 4: We have included this broadened differential of submucosal bladder masses in the Discussion section (see Page 6, line 157-162).

*Changes in the text: Prior to definitive extirpative therapy, clinicians should maintain differential diagnosis for submucosal bladder masses that includes benign etiologies such as fibroma, fibrosarcoma, leiomyoma, leiomyosarcoma, hemangioma, paraganglioma, and neurofibroma; malignancies such as urothelial cell carcinoma, squamous cell carcinoma, and small cell carcinoma of the bladder, as well as inflammatory-mediated conditions such as granulomatous inflammation and amyloidosis (6).*

**Comment 5: The use of the 70 degree lens was only helpful given the location of the tumor, which can be anywhere in the bladder. So, the authors should de-emphasize the use of the 70 degree lens as a universal necessity during the evaluation of bladder paraganglioma.**

Reply 5: The use of the 70 degree lens is important for the identification of this large sessile mass, which was not recognized on two prior negative cystoscopic biopsies. Submucosal tumors are not as easily identified when they are large, anterior, or at the bladder neck, such as this one. A delay in recognition of this mass from his first two episodes of gross hematuria may have allowed the tumor to progress to muscle-invasion, which is why we emphasize this point. A typical papillary mass or a small submucosal mass may

be visualized well with a 30 degree lens, but a 70 degree lens should be utilized when history/physical/labs/imaging suggest that there is likely a bladder mass that is not readily visualized on initial examination.

*Changes in the text: None*

**Comment 6: What is the recommended follow-up/surveillance approach for bladder paraganglioma? The authors should include imaging as well as biochemical testing with serum and urine metanephrines.**

Reply 6: Recommendations for follow-up of patients who have undergone surgical intervention include laboratory testing at 3 months post-resection and cross-sectional imaging studies for 1-2 years (see Page 9, line 247-252).

*Changes in the text:* A definitive surveillance protocol has not been recommended; however, prior studies have recommended a combination of blood/urine studies and cross-sectional imaging. Plasma and urine metanephrines are tested three months after definitive paraganglioma resection, even if these values were not elevated preoperatively. Cross-sectional imaging in the form of CT chest/abdomen/pelvis is performed every 6-12 months for the first few years postoperatively, since recurrence rates may be as high as 15-20% (14).

**Comment 7: Given the rarity of the condition, the authors should include a Table of prior case reports/series previously published in the literature. They should focus on the rate of biochemically active bladder paragangliomas in the literature.**

Reply 7: We have included a table that lists the case reports/series of bladder paragangliomas between 2022-2024, which includes 38 studies. We chose these years due to the advancements in detection, surgical resections, and follow-up. A complete list of all case reports/series published in the literature would be over 100 studies, and does not provide the granularity of biochemical activity that is needed. Among our table, only 2 studies did not report biochemical activity. Although there are 38 studies included in Table 1, our study is one of the first to show intraoperative pictures of the unique golden yellow tumor color, which we believe will educate surgeons to identify this submucosal tumor and avoid intraoperative hypertensive crises in the future. We also highlight the discrete nature of this submucosal tumor through the history of 2 prior negative biopsies and intraoperative pictures, which was only visualized with the use of a 70 degree cystoscopic lens.

*Changes in the text: See Table 1.*

## Reviewer B

1. For references cited in Table 1, please number them according to the first identification of the table. In your manuscript, Table 1 is cited after Reference 8. Thus, all references that first appear in Table 1 should be numbered from 9 and cited consecutively.

**Table 1. Case reports/series 2022-2024 of bladder paragangliomas with biochemical activity.**

<u>Author</u>	<u>Year</u>	<u>Biochemically Active Patients</u>	<u>Total Patients</u>
Bermejo <sup>***</sup> (9)	2024	<u>0</u>	<u>1</u>
Song <sup>***</sup> (10)	2024	<u>0</u>	<u>1</u>
Orsini <sup>***</sup> (11)	2024	<u>1</u>	<u>1</u>
Chen <sup>***</sup> (12)	2024	<u>1</u>	<u>1</u>

**Response: The references have been fixed so that Table 1 begins with reference 9.**

2. Please check. Ensure the authors' names and the publishing years in the citations are the same as in the reference list.
  - According to Waingakar, et al., the sensitivity and specificity for plasma metanephrines are 97% and 96%, while urinary catecholamines are 60% and 96%, respectively (7).
  - 7. Waingankar N, Bratslavsky G, Jimenez C, Russo P, Kutikov A. Pheochromocytoma in Urologic Practice. Eur Urol Focus. 2016;1(3):231-240.

**Response: The authors' names and publishing years have been rechecked and fixed for accuracy.**

- Yu, et al. found a four-year overall survival of 81% and a cancer-specific survival of 91%, with higher mortality rate in patients with synchronous metastases (13).
- 13. K Y, AL E, H O, et al. Presentation, Management, and Outcomes of Urinary Bladder Paraganglioma: Results From a Multicenter Study. J Clin Endocrinol Metab. 2022;107(10).

**Response: The authors' names and publishing years have been rechecked and fixed for accuracy.**

### 3. Figures and tables

- 1) Abbreviations in all figures/tables and legends should be explained.

**Response: The abbreviations in all figures/tables have been explained/expanded.**

- 2) Please confirm that all figures/tables/videos in your manuscript are original; if not, permission is needed from the copyright holder for reproduction. Please respond to this.

**Response: All figures/tables/videos in this manuscript are original.**

- 3) Please confirm the accuracy of data in Table 1.

**Response: The accuracy of the data in Table 1 has been rechecked and confirmed.**

4) Please provide the magnification of Figures 4-7.

**Response: The images are each original magnification x 40, which have been added to the titles for Figures 4-7.**

5) Please check Table 1. Ensure the authors' names and the publishing years in the citations are the same as in the reference list.

<u>Kita</u> <sup>24</sup>	<u>2024</u>	<u>0</u>	<u>1</u>
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24. Kita S, Yamakawa M, Kono R, et al. [NONRISING BLADDER PARAGANGLIOMA SUCCESSFULLY TREATED BY THE OPEN BLADDER SURGERY: A CASE REPORT]. *Nihon Hinyokika Gakkai Zasshi*. 2023;114(1):16-20.

<u>Baron</u> <sup>26</sup>	<u>2024</u>	<u>1</u>	<u>1</u>
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26. Pérez Barón L, Guerrero Acosta N, Granados González G, Aldana JC, Mantilla Espinosa R, Carmona GA. Bladder paraganglioma: Case report and review of the literature. *Radiol case reports*. 2024;19(1):213-217.

<u>Wang</u> <sup>35</sup>	<u>2023</u>	<u>1</u>	<u>1</u>
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35. Wang Z, Liu F, Li C, et al. Case Report: Octreotide plus CVD chemotherapy for the treatment of multiple metastatic paragangliomas after double resection for functional bladder paraganglioma and urothelial papilloma. *Front Oncol*. 2022;12:1072361.

<u>Yu</u> <sup>13</sup>	<u>2022</u>	<u>69</u>	<u>110</u>
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13. K Y, AL E, H O, et al. Presentation, Management, and Outcomes of Urinary Bladder Paraganglioma: Results From a Multicenter Study. *J Clin Endocrinol Metab*. 2022;107(10).

6) Please confirm if the description of Table 1 is correct.

Table 1. Case reports/series 2022-2024 of bladder paragangliomas with biochemical activity.

<u>Zhang</u> <sup>51</sup>	<u>2021</u>	<u>N/A</u>	<u>16</u>
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**Response: The authors' names and publishing years have been rechecked and fixed for accuracy.**