Author's response to reviews

Title: Pheochromocytoma of the urinary bladder: a systematic review of the contemporary literature

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Author's response to reviews: see over
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RE: BMC Urology manuscript

Dear Editor,

It is with great pleasure that I resubmit my manuscript entitled ‘Paraganglioma of the urinary bladder: review of the contemporary literature’ to be considered for publication in BMC Urology. We found the reviewers’ comments to be quite provocative and thought provoking. With this said, we have revised the manuscript based on the reviewers’ comments. Attached is a point-by-point response to each comment from the reviewers. We are very excited about these findings and hope that the manuscript will be favorably reviewed by the BMC Urology. If you should have any questions or concerns, please do not hesitate to contact me.

Regards,

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Below are our responses to the editor’s and reviewers’ comments.

1. Abstract
Can you please provide more information in the Background section of the Abstract. Could you please describe why they did this study to give the reader a better idea of the study rationale - not just that paraganglioma of the urinary bladder is a rare tumor.
This was added to the abstract.

2. PRISMA
Can you please adhere to the PRISMA guidelines when conducting a systematic review. Please confirm within the Methods section that you have followed PRISMA guidelines. The PRISMA checklist can be found here, [http://www.prisma-statement.org/2.1.2-%20PRISMA%202009%20Checklist.pdf](http://www.prisma-statement.org/2.1.2-%20PRISMA%202009%20Checklist.pdf).
We will assess your manuscript against the checklist, so could you please complete this document and include it as an additional file for our consideration.
Yes our review adhered to PRISMA guidelines. This was noted in the manuscript and the PRISMA guidelines are included in the submission.

3. Formatting
You now have an opportunity to ensure that your manuscript is formatted correctly and conforms to the journal style ([http://www.biomedcentral.com/info/ifora/medicine_journals](http://www.biomedcentral.com/info/ifora/medicine_journals)). It is important that your files are correctly formatted.
This was performed.

4. Obviously, most pheochromocytomas are benign. Discuss the histologic features the authors used to assign a malignant phenotype.
Seeing that this is a review of the literature, we relied on each published works’ findings. Pathologic interpretation and reporting in these studies were very heterogeneous, and thus a more uniform method of reporting findings should be adopted by journals to report these tumors. This was commented in the manuscript.

5. Can the authors reference in the materials and methods how paragangliomas/pheochromocytomas should be graded? Should the standard TNM staging system apply to these tumors given that tumorigenesis does not originate within the urothelium? Would malignant tumors harbor greater potential for distant progression as they have more ready access to abundant lymphatic and vascular channels within the lamina propria or muscularis propria?
This is a great question and we have taken the opportunity to expand on this in the discussion section.
There is no standard TNM staging for pheochromocytoma and paraganglioma, however the National Cancer Institute divides the staging of pheochromocytomas and paragangliomas into three categories:
- Localized (apparently benign) disease.
- Regional disease.
- Metastatic disease. The most common sites of metastasis for pheochromocytoma or extra-adrenal paraganglioma are lymph nodes, bones, lungs, and liver.
The NCI also lists four pathologic qualities that are associated with malignancy:
- Large tumor size.
- Increased number of mitoses.
• DNA aneuploidy.
• Extensive tumor necrosis.

“In the absence of clearly documented metastases, no combination of clinical, histopathologic, or biochemical features has been shown to reliably predict the biologic behavior of pheochromocytoma. If no definite malignancy is identified, pathology generally provides insufficient prognostic information regarding the likelihood of recurrence or metastasis. These tumors cannot be considered benign by default; patients require continued lifelong surveillance.”
[http://www.cancer.gov/cancertopics/pdq/treatment/pheochromocytoma/HealthProfessional/page3]

6. Results: Can the authors elaborate in the results or in the discussion sections the therapeutic options for metastatic recurrence or progression (i.e. mitotane)? Furthermore, were patients with functional tumors more likely to demonstrate aggressive biology?
This is another great question/comment. We have briefly included a section on therapeutic options in the discussion section. Furthermore, only 15 of the 106 patients included in this analysis were noted to have recurrence and/or metastasis. Of these 15, twelve had functional tumors, and the other three cases’ functional statuses were unknown. Therefore a connection between functionality and disease prognosis is impossible to decisively calculate based on our systematic review.

7. Discussion: Here is where the authors make first mention of “their patient”. Thus, this appears to be a case report and a review of the literature. If a case report, the case should be described. Or, the authors can simply review the literature without mention of their case. Choose one approach or the other.
We are sorry for this oversight on our part. Initially this manuscript started at as a description of our patient with paraganglioma and a review of the literature. However the editorial office requested that we have two separate papers (one a case report and another a review of the literature). This typo, a hold over from the original manuscript, was corrected.

8. The authors suggest that good survival can be achieved with aggressive surgical resection. As only 10% of patients are thought to have malignant features to begin with, I think the better statement might be that symptomatic control is best achieved with surgical resection in the majority of patients as benign disease would not be expected to impact survival (unless functional tumors promote adverse medical events contributing to the patient’s death). The authors need to revise these statements in the discussion.
This has been revised.

9. Discussion: The authors argue for more accurate reporting of stage and grade. However, is tumor stage and grade truly important when the majority of tumors are benign?
This is a great comment and we understand the reviewer. However we believe a more uniform method of reporting should be adopted even if it is only to help the physicians communicate with one and another.

10. Discussion: Does surgical resection most commonly result in resolution of symptoms? Do patients with functional tumors who subsequently develop local or metastatic recurrence, experience a return of their symptoms?
This is a great question, unfortunately, this information is only sporadically reported within the analyzed case reports, and thus we cannot draw definitive conclusions regarding these points.
11. What do the authors recommend for postoperative surveillance. How might this differ for patients with benign, equivocal, or malignant tumors? Are serum biochemical studies performed as part of surveillance in patients with functional or nonfunctional tumors? Discuss the frequency of follow-up as well as any role for surveillance cystoscopy, or surveillance imaging (i.e. CTs, MRIs or MIBG scans).

This is another great question. With a lack of high quality data and the lack of organizational guidelines (e.g., EAU, NCCN, AUA) we are left with our own opinions on this subject. Guidelines on post-op surveillance:
- Functional (any stage): check labs within 1 month post-surgery, then Q6 mo x 2 years.
- Regional or metastatic: check labs and axial imaging; Q3 mo x 1 year, then Q6 mo x 1 year then Q12 mo x 3 years.

12. As the authors state that they have performed the most extensive review to date, rather than calling for standardized reporting guidelines, could they make recommendations regarding what actually should be reported or standardized?

This has been added to the discussion section.

13. Materials and Methods: Consider revising to allow figure 1 to speak for itself rather than duplicating the information from the figure in the written manuscript.

Figure 1 was revised and repetitive text within manuscript was removed.

14. Results: explain if diagnosis is usually first established with TURBT or bladder biopsy?

Unfortunately, the information necessary to answer this question was not recorded. Upon cursory review of our included case reports, it is apparent that many authors neglect to differentiate between a bladder biopsy conducted in the office setting and a TURBT conducted in the operating room.

15. Results: Tables 2 and 3 should be deleted and simply reported in the results section.

Tables 2 and 3 were deleted.

16. Discussion: Suggest using the more common and recognized term pheochromocytoma earlier in the manuscript (i.e. background).

This was changed.

17. It is unclear why the start date for search criteria was chosen as 1980 especially since many of the articles on this subject were published before that date.

Over the past few decades, we have had significant improvements in the surgical and medical care of the oncologic patient. Thus we chose to assess a more contemporary, and thus relevant, cohort of studies.

18. Generally, absence of on-line availability of an abstract is not an exclusion criteria for a literature review.

We agree, usually the lack of online availability does not serve as exclusion criteria, however, articles with limited abstracts tended to be of extremely poor quality and at times were difficult to acquire.

19. Excluding 2 manuscripts because they were not case reports - what were these articles and why were they excluded?
Both manuscripts (listed below) are published responses to previous case reports of pheochromocytomas of the urinary bladder. As these case reports were included in our literature search as their own entries, we did not want to count these included patients more than once in our statistical analysis.


20. The statement "Using strict review criteria," is subjective - consider removing from results section.
This phrase has been removed.

21. The statement "Metastatic recurrence was noted in nine patients (9.3%)." would imply that no patients presented with metastatic disease. Is that true?
Yes, interestingly there were only two case reports that reviewed patients presenting with disease recurrence. This may represent bias in the reporting of cases that offer a more interesting and educational story.

22. There have been other review articles for paragangliomas in bladder that were not mentioned. Please consider including these manuscripts and commenting on why this review improves upon previous reports.
In addition to the review by Tsai et al (2010) we included the review by Deng et al (2010) as well. Our study improves upon previous reports in a number of ways:
• Tsai et al includes one study dating back to 1911, and then eleven between 1989 and 2000. Our study includes 80 studies between 1980 and 2012, offering a better view for analyzing contemporary statistics.
• We have a total of 106 patients included in our study, the most of any literature review to date. Tsai et al, for example have 53.
• Our review uses a multitude of demographics to depict the disease process of bladder paragangliomas, including presenting symptoms, tumor functionality and size, and treatment modality. Furthermore, we include as much follow-up data as possible, with a mean follow-up of 34.6 months.


23. Would clarify in the introduction that paraganglioma is also known as pheo.
This was added.

24. For all continuous variables in tables and manuscripts, please include range or interquartile range
This was added. Also note for Catecholamines, as authors reported on a variety of lab values, we took an increase in any of these values (i.e. serum or urine tests) as positive, and thus cannot provide a range for these measurements.

25. table 1, consider including the denominator for the variables.
   This was added.

26. Please, the authors need to fix some points in the discussion section. For Example please divided with subtitle the discussion sections such as Symptoms, surgical treatment, follow-up....
   This is a good suggestion, however, the format example provided by BioMed Central does not contain sub-titles within the discussion section.

27. Give more details regarding the prognostic factors;  
The subset of patients in our study who experienced recurrence (N=15) and disease-specific mortality (N=4) is too small to make a conclusive connection between pre-operative characteristics and disease prognosis. However we did add a comment regarding prognosis into the discussion section.

28. In the paragraph of the results in the abstract please correct "paragnangliomas"
   This was corrected.