Author’s response to reviews

Title: EPIDEMIOLOGICAL AND HISTOPATHOLOGICAL PROFILE OF MALIGNANT MELANOMA IN MALAWI

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Author’s response to reviews:

Dear Editor,

We are grateful to the reviewers for their thoughtful comments on our manuscript “Epidemiological and Histopathological Profile of Malignancy Melanoma in Malawi” (CPAT-D-18-00045). We’ve addressed their major concerns in the revised submission and believe that their feedback has substantially improved our manuscript.

In the revised manuscript, we have added two additional authors, who have contributed substantially to the work at Kamuzu Central Hospital. To incorporate their feedback, some additional minor edits have been made throughout the manuscript. All changes, both those requested by the reviewers and the minor additional changes have been highlighted through the text. In addition, we provide a point-by-point response to the reviewers’ feedback below.

Thank you for your continued consideration of our manuscript. We look forward to hearing from you.
Sincerely,

Maurice Mulenga (MBBS, FCPATH (SA) Anat)

REVIEWER 1

We thank Reviewer 1 for her enthusiasm for the work at KCH and for her helpful feedback.

Abstract
Page 2, line 40 - Rather than citing studies about what it already known (also was not able to find a reference supporting your first line in the abstract), why not focus on what is not known and what this article can contribute?
* The first sentence has been deleted. Instead, the Abstract introduction now emphasizes that most studies of melanoma have focused on lighter-skinned individuals. We agree with the reviewer that this approach better emphasizes the value of our description of group of black African patients with melanoma in sub-Saharan Africa.

Page 3, lines 16-31 (conclusion) - What does your information add to the medical literature? The last sentence of your conclusion should be a call to action or should provide some sort of interpretation of your data. Please think of your readership. Why should physicians be interested in this paper? We agree with the reviewer that it is critical to emphasize the clinical and public health significance of our observations.
* In the revised manuscript, the Abstract’s Conclusions now emphasize that (1) melanoma may be under-appreciated in black Africans and (2) presentation at late stage in our cohort suggests an opportunity to translate increased awareness into earlier intervention.

Literature on melanoma in black African-Americans is not sparse; in this manuscript please include citations of previous literature that would suggest that there would be any difference between melanoma subtypes/prevalence in black African-Americans and melanoma in black Africans.
* In the revised manuscript, we have several references to literature on melanoma in sub-Saharan Africa (South Africa, Togo, Nigeria, Tanzania, Cameroon, Kenya, Sudan). In addition, we emphasize that clinical experience with melanoma in African-Americans may not predict disease epidemiology for a number of reasons. First, African-Americans and black Africans are not genetically identical populations (Tishkoff et al., Science, 2009. 324(5930):1035-1044). Second, as emphasized in our original text, some apparent melanoma risk factors (e.g. chronic trauma) are not shared between these populations. These points are emphasized in the Introduction and Discussion in the revised manuscript.

Introduction
Page 4, Line 6. Your reference #1 does not support this statement. Please cite the correct source, specify whether the data is from worldwide population-based databases or otherwise, which country or countries is this data from, and what racial/ethnic populations were included in the database.
* In order to more accurately reflect the global implications of this manuscript, we have instead referenced the GLOBOCAN database.
Results
In general, when providing the % of cases of each type, please also include the number of cases next to the percentage
* The number of cases has been added next to percentages

Please consider splitting up your data in Table 2 into several different tables, for improved readability.
*The data in Table 2 has been modified into a different table that is easy to read

Page 5, Line 30 - this article is not about benign melanocytic lesions, why not just start by saying how many melanocytic cases were analyzed?
* Deletion of the statement about benign melanocytic lesions has been done

Page 5, line 41: Information about % from a metastatic site should be in a separate paragraph
* This information is now in a separate paragraph

Page 6, Table 1 - The information regarding table 1 seems irrelevant. Tables are needed to summarize data in this article, but not for the data presented in table 1.
* Table 1 and its associated paragraph has been deleted

Page 8, Figure 2 - Seems unnecessary to include in this paper.
* Figure 2 has been deleted

Page 9, Table 2 - The headings for tables should be more robust and include the population studied, where it was studied at, years studied. There should be footnotes at the bottom of the table with the abbreviations used in the table. Did you mean to include lentigo maligna in this analysis? Lentigo maligna is melanoma in situ; are you focusing the study on only invasive melanomas and that is why your study number is 76? If you want to include lentigo malignas, please change your number to 77 and specify that you were examining invasive melanomas as well as melanomas in situ.
* The headings for the tables have been expanded to include required information
* Lentigo maligna is added in the analysis and the number of cases increased to 77 as suggested.

Accordingly a statement is included describing invasive and in-situ melanoma.

Discussions
Please say why this study is important; many studies have been done on melanoma across many different races/ethnicities, including blacks. Is there any scientific reason for not assuming similar rates of melanoma between blacks in other countries (e.g., African-Americans) and blacks in Africa?
* As explained above, we emphasize that clinical experience with melanoma in African-Americans may not predict disease epidemiology for a number of reasons. First, African-Americans and black Africans are not genetically identical populations (Tishkoff et al., Science, 2009. 324(5930):1035-1044). Second, as emphasized in our original text, some apparent melanoma risk factors (e.g. chronic trauma) are not shared between these populations. These points are emphasized in the Introduction and Discussion in the revised manuscript.

Page 10, Line 26: please consider delete the info about albino patients, as this information is not related to the current study
* This statement and corresponding references have been deleted
Page 10, line 44: please include a separate "limitations" section or paragraph rather than weaving these limitations into the discussion
* A separate section on limitations has been created

Page 11, line 5: please elucidate more on how this conclusion was made
* The conclusion has been explained.

Page 11, line 18: source #36 - how could this statement be made if you were not comparing the rates of ALM between blacks in Africa vs blacks on other continents?
* Yes. The comparison was made and a several sentences have been added following line 18.

Page 12, lines 2-15: I would not think this is that surprising, as it may be a difference of whether growth pattern is included in the pathology report - a rapidly-growing nodular melanoma can arise within acral lentiginous melanoma and proliferate more deeply in the skin. Acral melanomas can start out as patches with radial growth and then develop a more nodular, vertical, growth pattern.
* I agree. And these lines have been modified.

Conclusion
Again, what does your information add to the medical literature? The last sentence of your conclusion should be a call to action or should provide some sort of additional interpretation of your data.
* The conclusion has been completely revised to communicate the paucity of pathologically confirmed melanoma data in sub-Saharan Africa.
* The last 3 sentences address calls to action on melanoma cases and early diagnosis.

REVIEWER 2

We thank Reviewer 2 for the positive comments on manuscript that we find encouraging
Divide and specify number of patients according to plantar area and nails.

* There was limited clinical information to allow such a division. Most cases lacked detailed clinical information on the specific location of the tumour precluding comparison to prior publications. For example, most biopsies indicated foot as a primary site without specifying whether this is plantar and/or nail. Although the presence of glabrous skin and nail was helpful in histopathological evaluation, extensive ulceration often obstructed histological features that may have otherwise facilitated more specific localization.

*This has been added as one of the limitation of the study.

The number of patients with hand lesions

*8 cases had hand lesions. This has been included in the new table (table 1)

Reason for the abrupt increase of patients in 60-69years, especially male.

* BCG and infections as a reason for the increase has been deleted in the manuscript
*The abrupt increase of patients in 60-69 year age group could be attributed to the predominant ALM
histopathological subtype which also is common in males than females. And according to WHO occurs in older population than superficial spreading and nodular melanoma. This has been explained in the manuscript.