Reviewer#1

SPECIFIC COMMENTS TO AUTHORS

"Relationship of anal cancer recurrence and smoking" Comments on the paper by Kevin R McMahon et al   submitted to the Review for World Journal of Oncology _____   Author : P.N. Lee   Date : 27th February 2023   The authors describe the results of a study of 95 patients admitted to a single, community hospital with anal cancer between 2010 and 2021.   I found the paper difficult to follow due to lack of detail presented. In the first place, the name of the hospital should be given directly in the paper, rather than being guessed from the affiliation of the authors.

Reply: While I appreciate your input, I do not think it is standard to include the name of the hospital in the methods section; therefore, I did not include it. I do not think including adds any benefit, and potentially takes away from the paper.

When was the information collected on whether the patients were never, former or current smokers?

Reply: Information was collected on smoking status at time of diagnosis when they were included in the cancer registry. I updated the manuscript to make this more clear.

I imagine at the time the patients were originally admitted and diagnosed with the anal cancer, though this should be clarified.

Reply: Information was collected on smoking status at time of diagnosis when they were included in the cancer registry. I updated the manuscript to make this more clear.

Also "smoking" of what?   Cigarettes?   Or does it include pipe and cigar smoking?

Reply: Cigarette smoking. I have updated the manuscript to make that more clear.

It is noted that there was "non-response" for 37 of the 95 patients.   What does this mean? Does this mean there was no follow-up of these patients, the patients coming in initially for the original diagnosis and treatment but never coming in again?

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Reply: Non-response is defined by persistence of disease following treatment. The manuscript was updated to make this more clear.

What is the definition of recurrence and to which population does it apply?

Reply: I have updated the manuscript to make it more clear that recurrence was defined as someone who had evidence of disease after previously not having evidence of disease.

Recurrence sounds to me as if it can only apply to those who were thought to be cured after the initial diagnosis. Was this the case?

Reply: Correct. I have updated the manuscript to make it more clear that recurrence was defined as someone who had evidence of disease after previously not having evidence of disease.

As regards death, was it known for every patient whether they were dead or not by the end of the study period, even if the data were not available on the hospital records?

Reply: Yes, it was known if a patient had died or not by the end of their follow up period. There was no difference in length of follow up between groups as listed in Table 1.

Presumably, it would be easy enough to find out whether a patient diagnosed in say 2012 with anal cancer had died by 2021, even if the hospital records did not contain the information. Would it not be of interest to analyze deaths certified as being from anal cancer as well as all deaths?

Reply: The database does not specifically list the cause of death; therefore, I do not have access to this data.

The analyses of death and recurrence would be much better conducted using Cox regression with adjustment for age and sex. Clearly patients diagnosed in 2010 would have a much increased chance of dying by the end of the follow-up period (say 2020) than those diagnosed in 2021. The Cox regression would automatically take time to death into

account. In the tables, p-values are given and bold fonts indicate "statistical differences from the other groups". This is unclear. One can do tests to answer various different tests

1) Does the response vary between the 3 groups (on 2 degrees of freedom)?

Reply: With regards to Cox regression, as mentioned in the paper, there was no difference between smoking groups and mortality; therefore, including a Cox regression to show the same thing does not add any value. For recurrence, with their only being 9 events, it is not an appropriate test to include given the small sample size. I adjusted the table and the description in order to make the findings more clear. I also added a description of the testing into the Methods section to make that more clear.

2) Does the response vary between former and never smokers?

Reply: Yes, the response varies between current and never smokers. I have updated the table and the manuscript to make this more clear.

3) Does the response vary between current and never smokers?

Reply: Yes, the response varies between current and never smokers. I have updated the table and the manuscript to make this more clear.

4) Does the response vary between current and former smokers

Reply: No, there was no difference between current and former smokers. I have updated the table and the manuscript to make this more clear.

5) Does the response vary between current and former smokers combined and never smokers?

Reply: From a recurrence standpoint there was a difference between current and former smokers combined as compared to non-smokers. This can be inferred from the data presented given that each one differed individually. I have updated the manuscript to make it more clear how the groups relate to one another. However, statistically speaking, we did not want to divide the groups into different subgroups as it increases the risk of error from multiplicity. We believe our current presentation of the data is

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more statistically sound than dividing or combining groups for further analysis.

Reading the Table 2 recurrence results for example, is one to infer that a bold figure for former smokers means that their recurrence rate is statistically different both from that of never smokers and from that of current smokers. This seems to be implied by the statement about bold font, but does not actually appear to be true?

Reply: There was no difference in recurrence between the former and current smokers. But there was a difference when compared to the never smokers. The manuscript was updated to make this more clear.

You have a variable called "response to therapy". Would it not be of interest to compare death rates in those who did or did not respond to therapy?

Reply: This was done, and the result is included in table 3. There was no difference in mortality rate between groups in the non-responders.

Details should be included (and taken into account) as to when the actual anal cancer was diagnosed, e.g. in grouped periods such as 2010-12, 13-15, 16-18 or 19-21 by smoking group.

Reply: The study size is not large enough to do this. It would dramatically increase the risk of statistical error.

Finally I wonder whether the word "and" in the title of the paper should be replaced either by "to" or "with".

Reply: I have updated the title to read: Relationship between anal cancer recurrence and cigarette smoking

Reviewer#2

Specific comments to authors

Dear Author, thanks for the opportunity to review your paper. The issue is very

interesting although the sample size do not allow definitive conclusions. HPV status is an essential factor in determining prognosis of anal cancer and response to treatment but unfortunately such data are unavailable. This is not negligible. In addition HPV infection is worsened by smoking habits. Please make more extensive comments on these aspects, including relevant references.

Response:

Thank you for your comments. Yes, I agree that it would be ideal to have HPV status for the cohort. Unfortunately, the database did not include this data point and do to the de-identified nature of the database; we cannot go back and pull more data. Despite this shortcoming, this is the second largest study examining the relationship between anal cancer treatment outcome and smoking. Additionally, the other two studies examining this topic did not have meaningful data on HPV status either. I have included a paragraph to acknowledge our data's shortcoming and explain its relevance in the current literature.

Revision reviewer

Specific comments to authors

It is now basically fine following the revisions made. The only corrections I think should be made relate to making it clearer that "smoking" refers to "cigarette smoking". I think the following corrections should be made: Abstract: Background. Final sentence should end   "...recurrence and cigarette smoking." Abstract: Aim. Add "cigarette" before "smoking status" Tables 1, 2 and 3. In the heading, replace "Tobacco use" by "Cigarette smoking" That is all.

Response:

The manuscript was changed to make it more clear that the study examined cigarette

smoking. The title was changed to include the word cigarette smoking. The abstract background and aim were changed to include cigarette smoking. The core tip section was changed to include cigarette smoking. Tables 1, 2, and 3 were changed to include cigarette smoking in the heading.