Author’s response to reviews

Title: Para-aortic lymphadenectomy in advanced stage cervical cancer, a protocol for comparing safety, feasibility and diagnostic accuracy of surgical staging versus PET-CT; PALDISC trial

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Author’s response to reviews:

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Concerning: PAFS-D-16-00100R1

October 13, 2017
Dear Dr. Dodd,

Thank you very much for your message of September 29, 2017 in which you invited us to re-revise our article entitled "Para-aortic lymphadenectomy in advanced stage cervical cancer, comparing safety, feasibility and diagnostic accuracy of surgical staging versus PET-CT; PALDISC trial."

We would like to thank the reviewers for the effort to again provide us with their valuable comments and suggestions. Please find below our response to each of the points raised.

Reviewer reports:

Reviewer #1: Thank you for responding so carefully and thoroughly to my comments. I feel they have all been adequately addressed, and the manuscript is improved by these changes and those in response to the other reviewers.

Minor Issues:

The only outstanding point I have is a small one - about the use (or otherwise) of FIGO in the abstract. Your change to page 2 line 24 is improvement I think, but then you use the FIGO stage in line 32. Perhaps the best solution is to revert to "FIGO stage IB2, IIA2-IVA" here (line 24) and add "(locally advance stage)" in brackets after it. Then you can use the FIGO stage in line 32 where using the technical terms makes more sense. Perhaps the editors are best placed to advise on this, knowing their readership best.

Authors response

We’ve reverted the said lines to their original state:

Page 2, line 24: added “FIGO stage IB2, IIA2 – IVA” and added “(locally advanced stage)”
Reviewer #2:

Thank you for your revisions. There are only a few minor further changes required in response to your revisions.

page 2: line 37: Please add "outcomes" to the revised text i.e. "Primary safety and feasibility (of surgical staging) outcomes..."

Authors response

As suggested, we’ve added “outcomes” to the revised text:

Page 2, line 37: changed “Primary safety and feasibility of surgical staging” into “Primary safety and feasibility outcomes of surgical staging”

page 9: line 211: add “;” before "estimates will be provided..."

Authors response

As suggested, we’ve added the semicolon to the revised text:

Page 9, line 210: added “;”

page 13: line 295: correct spelling of "assess" (currently "asses")

Authors response

We’ve corrected this typo.

Page 13, line 295: changed “asses” into “assess”

page 13: line 303: the word "result" does not need to be added; instead please just remove "and allocation concealment" from this sentence
Authors response

We agree with the reviewer that “and allocation result concealment” can be left out. As such, we’ve changed the following line:

Page 13, line 308: changed: “As for most surgical trials, blinding and allocation result concealment are not possible.” into ”As for most surgical trials, blinding is not possible.”

Progression to phase 3 trial: Thank you for providing an explanation of the considerations that will be required when deciding whether or not this trial should progress to Phase 3. Please could you add the information in your reply to the discussion section ie "The final decision whether or not a phase 3 trial is deemed safe and necessary is a decision that should be made by a group of experts. This decision should take into account the difference between current standard of care and surgical staging on subjective (quality of life) and objective (time of treatment delay, blood loss, adverse events, etc.) outcome measures, while controlling for confounders and selection bias due to the randomization. In addition, data on both sensitivity and specificity should also be considered. Although this study only includes 15 patients, it is almost a doubling of the currently available number of patients in whom PET-CT was compared to gold standard histology (n=16)."

Authors response

Most of this information was already supplied within the discussion section (page 13). However, based on the response we feel that it could be more clear. Therefore we’ve added part of the reply in our discussion, as suggested.

Page 13, lines 300-303: added “In addition, data on both sensitivity and specificity should also be considered. Although this study only includes 15 patients, it is almost a doubling of the currently available number of patients in whom PET-CT was compared to gold standard histology (n=16). [10]

And page 13, lines 304-306: “These strengths will provide vital information for a group of experts in order to make the final decision whether or not a phase 3 trial is deemed safe and necessary.”
Additional revision:

After a long discussion we have decided to cancel, or at least set the PALDISC study on-hold. This decision was based on a currently too low inclusion rate which is mainly due to a lack of extra inclusion centres and no additional funding for a dedicated coordinator to get more centers in the trial.

After a long discussion, we do believe that the study-protocol itself is of scientific value and would still like to submit the revised manuscript. Especially as the before mentioned reason is a more practical manner related to current logistics than to the study protocol and population itself. By making this protocol publicly available, we can provide the opportunity for other centres to either takeover this study and/or gain more inclusion centers, as well as attend the scientific community on the fact that we are making decisions based on studies with only 16 patients.

As such we have made the following changes:

Page 13, line 314: removed “Completion of the PALDISC trial is expected in 2018.”

Page 14, lines 317-318: changed “Recruitment began in July 2015 and is currently ongoing. A total of 4 patients were enrolled by October 2016.” Into “The PALDISC trial is currently cancelled and further inclusion is on hold due to a too low inclusion rate. Recruitment began in July 2015 and a total of 5 patients were enrolled by October 2017. This low inclusion rate which has led to the cancellation of the study is mainly due to the fact that the incidence of advanced stage cervical cancer is low in the Netherlands and there was only one actively participating centre. With the publication of this protocol we do hope to spark the interest of other centres for such a trial. In addition, we would like to open a scientific discussion on the diagnostic accuracy of the PET-CT for diagnosing para-aortic lymph node metastases as there is currently no study that compares PET-CT positive results to gold-standard histology analyses. The specificity of 83% (95% CI; 52 – 98%) based on only 16 patients implies that possibly 17% of all patients have false positive PET-CT results without PALN metastases. This may lead to misinformed treatment decisions including ‘unnecessary’ extended field radiotherapy with associated comorbidities. As such, more evidence on both the sensitivity and specificity of the PET-CT is warranted.

We hope that the revisions are in agreement with your expectations. However, we can imagine that the change in the trial-status may lead to a reconsideration on whether or not our protocol is
potentially acceptable for publication. As such, please do not hesitate to contact us, should you have any questions or remarks.

Yours sincerely,

On behalf of all co-authors,

Casper Tax M.D.