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

Authors:

Casper Tax (casper.tax@radboudumc.nl)
Karin Abbink (karin.abbink@radboudumc.nl)
Maroeska Rovers (Maroeska.rovers@radboudumc.nl)
Ruud Bekkers (ruud.bekkers@radboudumc.nl)
Petra Zusterzeel (petra.zusterzeel@radboudumc.nl)

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Author’s response to reviews:

Dr. Susanna Dodd,
BMC Pilot and Feasibility Studies

C. Tax, MD
Radboudumc dept. of Operating Rooms (715)
P.O. Box 9101
6500 HB Nijmegen, the Netherlands
Tel: +31 24 36 16770
Casper.Tax@radboudumc.nl

Concerning: PAFS-D-16-00100

September 6, 2017
Dear dr. Dodd,

Thank you very much for your message of August 9, 2017 in which you invited us to 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 their valuable comments and suggestions. Please find below our response to each of the points raised.

Reviewer reports:

Reviewer #1: Thank you for asking me to review this manuscript. It is a very worthwhile study with implications for practice if it proceeds to a phase 3 trial. The article is well-written and the study protocol clearly thought out. I have just a few minor issues to point out for the authors' consideration.

Minor Issues:

Generally, there were places where I felt a bit more explanation was needed for the general (non-specialist cancer) readership of this journal e.g. FIGO - needs definition and explanation at first use (and perhaps do not use in the abstract, could just say "late (or advanced) stage" there). There is quite a bit of technical language in the abstract e.g. lymphadenectomy - could be changed to a more lay term and then explained in the body of the manuscript.

Authors response

We’ve tried to clarify the more technical terms by including the proposed revisions as suggested by this reviewer and by making the following adjustments:

Page 2, line 24: changed “FIGO stage IB2, IIA2 – IVA” into “advanced”

Page 4, lines 64-65: added “the International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical cancer. It uses”

Page 5, lines 101-102: added “, i.e. removing the para-aortic lymph nodes by performing a para-aortic lymphadenectomy, “
Page 14, line 321: added “FIGO: International Federation of Gynecology and Obstetrics”

* Title: you may want to explain the PALDISC acronym somewhere, or perhaps not needed?

Authors response

In accordance we added the following sentence:

Page 6, line 114: added “(Para-Aortic Lymphadenectomy In advanced-stage Cervical cancer)”

* Line 25: could add "A small study established a sensitivity and specificity estimate for PALN metastases of..." otherwise the wide CIs are a red flag immediately!

Authors response

In order to make this more clear we included the proposed revision and made the following adjustment:

Page 2, lines 24-25: changed from “Sensitivity and specificity for PALN metastases is 50% (95% CI; 7 – 93%) and 83% (95% CI; 52% - 98%), respectively.” into “A small study established a sensitivity and specificity estimate for PALN metastases of 50% (95% CI; 7 – 93%) and 83% (95% CI; 52% - 98%), respectively.”

* Line 31: it is not clear here that there will be 30 women overall (as opposed to 30 in the intervention arm all receiving surgical staging). Rephrase e.g. by adding "or usual PET-CT staging" at the end of the sentence.

Authors response

To clarify the number of randomised women in total and per treatment arm, we included the proposed revision and made the following changes:

Page 2, lines 32-34: rephrased from “In addition to standard imaging (MRI or CT-scan) with PET-CT, 30 adult women with FIGO stage IB2, IIA2 – IVA cervical cancer will be randomized to receive surgical staging.” into
“In addition to standard imaging (MRI or CT-scan) with PET-CT, 30 adult women with FIGO stage IB2, IIA2 – IVA cervical cancer will be randomized to receive either surgical staging or usual PET-CT staging.”

* Line 59: clarify whether this is 700 new diagnoses across the whole population (and if so, give the rough female adult population in the Netherlands, for those not familiar) or 700 per 100,000 women per year?

Authors response

To be more clear on the incidence and to make it more comparable to incidences from other countries we added the following sentence:

Page 4, lines 63-64: added “or approximately 8.3 new diagnoses per 100,000 women per year in the Netherlands.”

* Line 61: "failure rates" - failure of what? I assume, being able to determine an accurate stage?

Authors response

We have clarified this by making the following adjustments:

Page 4, lines 66: added “accurate staging”

* Line 61: are these FIGO stages or TNM stages referred to here? Non-cancer specialists may not know what these refer to, may be better to say: early / late or advanced, or explain numbers more fully?

Authors response

In order to be more precise we made the following addition:

Page 4, lines 66: added “FIGO”
Authors response

We corrected this typo:

Page 4, line 67: changed “para-oartic” into “para-aortic”

* Line 73: the sentence on sensitivity and specificity is a little unclear - why does it "seem to have" a certain sensitivity and specificity? The following sentence makes it clear that the figures are based on the one small study (ref 8?) but then it is unclear what the other references in the original sentence (i.e. refs 6, 9 and 10) are adding?

Authors response:

due to unknown reasons, the references were not put in correct order. We have corrected this. In addition we have clarified the lines by making the following adjustments:

Page 4, line 80: changed “These broad confidence intervals” into “This uncertainty and these broad confidence intervals”

Page 4, lines 77 – 78 added “PET-CT provides a higher sensitivity and specificity than magnetic resonance imaging (MRI). [8,9]”

Page 4, lines 78 - 80 changed from “For detecting PALN metastasis PET-CT seems to have a sensitivity and specificity of 50% (95% CI; 7 – 93%) and 83% (95% CI; 52 – 98%), respectively. [6,8 - 10]” into “However, for detecting PALN metastasis PET-CT seems to have a sensitivity and specificity of 50% (95% CI; 7 – 93%) and 83% (95% CI; 52 – 98%), respectively. [10]”

* Line 80: In the LILACS trial, if a patient is found to be PET-CT negative (which, if assumed to be accurate, I understood to mean: no nodes found with metastases) then why would they go on to have surgical staging? Clarify or reword.
Authors response

Although we are not the authors or investigators of the LILACS trial, we have tried to be more clear on this, without too much speculations by making the following adjustments:

Page 4 and 5, lines 86-97: changed “However, in the LILACS trial surgical staging is only performed in PET-CT negative patients, assuming that diagnostic accuracy and positive predictive value of the PET-CT are already acceptable.” Into “However, in the LILACS trial surgical staging is only performed in PET-CT negative patients and not in PET-CT positive patients. This may be due to the fact that the PET-CT seems to have a sensitivity of 50% and specificity of 83%, thus possibly being false negative in half of all patients with PALN metastases while being false positive in 17% of all patients without PALN metastases. Or due to the assumption that the specificity and positive predictive value of the PET-CT are already acceptable. Regardless, although missing a PALN metastases due to a false negative result may be more detrimental to survival than ‘overtreating’ patients due to a false positive result, the radiotherapy induced complications can also have a negative impact quality of life of patients. In addition, the confidence interval surrounding the specificity of the PET-CT ranges from 52 – 98%, leading to a large uncertainty. As such, more evidence on both the sensitivity and specificity of the PET-CT is warranted.”

* Line 90: Perhaps add "…diagnostic accuracy of the tests and the clinician's experience with both PET-CT and surgical staging." if this is what you mean here? Do you have a reference for this assertion?

Authors response

Unfortunately we do not have a reference for this assumption for using the PET-CT and/or surgical staging in cervical cancer patients. However, in our experience and as shown in studies from other fields, each and every clinician has a certain learning curve after which a level of more consistent efficiency and accuracy is attained. This is most likely true for interpreting the PET-CT results as well as performing an adequate para-aortic lymphadenectomy. As such we have incorporated the proposed revision by making the following adjustments:
Page 5, line 106-108: changed “The proportion of treatment modifications depends on diagnostic accuracy and experience with both PET-CT and surgical staging.” Into

“The proportion of treatment modifications may depend on both the diagnostic accuracy of the PET-CT as well as a clinician’s experience with interpreting PET-CT results and performing the surgical staging.”

* Line 105: typo - phase 2

Authors response

We corrected this typo:

Page 6, line 122: changed “II” into “2”

* Line 150: typo - optionally

Authors response

We corrected this typo:

Page 8, line 168: changed “optional” into “optionally”

Reviewer #2: Abstract:

Methods/Design: "Data on sensitivity, specificity, negative and positive predictive value of MRI, PET-CT and surgical staging will be documented." should be replaced by "Estimates of sensitivity, specificity, negative and positive predictive value of MRI, PET-CT and surgical staging will be presented with 95% confidence intervals."

Authors response

We have included the proposed revision by changing:
Page 2, line 41-43: changed “Data on sensitivity, specificity, negative and positive predictive value of MRI, PET-CT and surgical staging will be documented.” into

“Estimates of sensitivity, specificity, negative and positive predictive value of MRI, PET-CT and surgical staging will be presented with 95% CI.”

Discussion: "When a phase 3 study is deemed necessary": "When" should be changed to "If" (also in line 100 in the main body of text)

Authors response

We have included the proposed revision by changing:

Page 2, line 52: changed “When” into “If”

Page 6, line 118: changed “When” into “If”

Randomisation, blinding and allocation concealment:

"Blinding and allocation concealment are not possible."

1) Would it be possible to blind the statistical analysts or outcome assessors?

Authors response

Yes, this would be possible. However it would not provide any additional objectivity as the outcome parameters are already objective. As such, the blinding of either the analyst or outcome assessor holds no additional value.

2) Allocation concealment is always possible, as it refers to the concealment of randomised allocation sequence from the randomising team/investigators until the point of randomisation. Methods of allocation concealment include sealed envelopes, telephone or web randomisation. Can the authors describe how the randomised allocations were administered?
Authors response

We agree that the allocation sequence can be concealed. However, this paragraph refers to the outcome of the allocation, which is not concealable. The allocation itself is incorporated in the CASTOR EDC program, as stated on page 7, lines 153-156. In order to be more clear, we made the following adjustment:

Page 7, lines 154-157: changed from “Patients will be randomized equally between surgical staging and standard treatment using a permuted block design per centre. [19] Blinding and allocation concealment are not possible.” Into

“Patients will be randomized equally between surgical staging and standard treatment using a permuted block design per centre, the allocation sequence itself is concealed from the patient, investigator and clinician. [19] Blinding of the patient, investigator and/or observer from the allocation result is not possible.”

Secondary study parameters and analysis:

1) "Including these secondary parameters will make it possible to enter these patients into a subsequent phase 3 trial." Can you explain this sentence, as it suggests that this pilot study is in fact an internal pilot within a larger phase 3 trial?

Authors response

Indeed, this pilot study is designed in such a way that it may be part of a larger phase 3 trial. Given the relative low incidence as well as severity of the disease and its treatment, we feel it is the most efficient and patient friendly approach to think about future research and the (re)usability of their data and goodwill. However, it is not yet proven that a future phase 3 trial is indeed necessary. As such, this phase 2 trial is needed.

To be more clear on this, we have made the following addition:

Page 9, lines 203-205: added “, if the current PALDISC study shows that such a phase 3 study is indeed necessary.”

Page 13, line 303: added “result”
2) Add "estimates will be provided with 95% confidence intervals" to the sentence "Data on sensitivity, specificity, negative and positive predictive value of MRI, PET-CT and surgical staging will be documented in 2x2 tables."

Authors response
We have included the proposed revision by changing:
Page 9, lines 210-211: adding “estimates will be provided with 95% CI”

3) Time to treatment should be estimated using Kaplan Meier estimation, summarised using medians (rather than means).

Authors response
We have included the proposed revision by changing:
Page 9 and 10, lines 212-214: changing from “Difference in treatment delay between the arms, due to surgical intervention and histological analyses will be presented as a mean difference with 95% CI.” Into

“Difference in treatment delay between the arms, due to surgical intervention and histological analyses will be presented using a Kaplan-Meier curve with the corresponding medians and 95% CI.“

Progression to phase 3 trial: How will the authors determine whether or not this study design is feasible, safe and necessary for progression to phase 3 trial? Can the authors add specific criteria for progression to a phase 3 trial?

Authors response
Unfortunately we cannot be more precise than already stated on page 13, lines 298-301. 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).

Editor comments:

Please add "protocol for feasibility trial" to the title.

Please distinguish between "Primary feasibility outcomes" (including feasibility) and "Secondary patient-centred outcomes".

Authors response

We have included the proposed revision by changing:

Page 1, lines 1-2: changed from “Para-aortic lymphadenectomy in advanced stage cervical cancer, comparing safety, feasibility and diagnostic accuracy of surgical staging versus PET-CT; PALDISC trial” into

“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”

Page 2, lines 37-41: changing from “Safety and feasibility of surgical staging will be assessed by calculating means with 95% confidence intervals for: duration of surgery, number of complications, blood loss, nodal yield after para-aortic lymphadenectomy, and treatment delay due to surgical staging. Quality of life and first year survival will be documented and compared between the two groups.” Into

“Primary safety and feasibility of surgical staging will be assessed by calculating means with 95% confidence intervals for: duration of surgery, number of complications, blood loss, nodal yield after para-aortic lymphadenectomy, and treatment delay due to surgical staging. Secondary patient-centred outcomes on quality of life and first year survival will be documented and compared between the two groups.”
Additional revisions

While checking the manuscript, we found a few typos which we also corrected.

Page 3, line 58 “lymh” instead of “lymph”

Page 12, line 285: started with a double ‘space’ instead of a single ‘space’

We hope that the revisions are in agreement with your expectations. Please do not hesitate to contact us, should you have any further questions or remarks.

Yours sincerely,

On behalf of all co-authors,

Casper Tax M.D.