PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparative Efficacy and Safety of Treatments for Localized Prostate Cancer: An Application of Network Meta-Analysis.
AUTHORS	Xiong, Tengbin; Turner, Rebecca; Wei, Yinghui; Neal, David; Lyratzopoulos, Georgios; Higgins, Julian

VERSION 1 - REVIEW

REVIEWER	Glenn Bauman London Regional Cancer Program London, Ontario, Canada I am co-author on one the papers cited in the analysis (Chin) and participated as an investigator on another (Lukka)
REVIEW RETURNED	18-Nov-2013

GENERAL COMMENTS	The author's should be more explicit in what their definitions of "conventional radiotherapy" "Low dose" and "High dose" radiotherapy assume - what are the dose ranges and how did the account for/correct for differences in fractionation schemes in assigning trials to each category. The links for conventional radiotherapy to observational management are through one study comparing a small number of patients (<100) randomized between RP and XRT both with long term adjuvant therapy in locally advanced disease. This trial is also controversial within the GU community and is not widely cited. Thus this indirect comparison may not be very robust or appropriate (see other comments re: comparing between risk stratification and use of ADT) I have reviewed this purely from a clinical perspective and do not have the expertise to comment on the rigor or appropriateness of the statistical techniques employed. The author's appropriately caution conclusions about the comparisons given the sparse dataset analysed. The methodology is unique and did allow interesting and important comparisons to be made where gaps in direct randomized controlled comparisons exist. I have a couple of concerns about the methodology: For the toxicity endpoint the RTOG scale is used but this is not appropriate for comparing toxicity between radiotherapy and surgery options as the RTOG scale doesn't include incontinence as part of the scale and this is the most common adverse GU event post-prostatectomy. This endpoint (continence) is also pertinent to cryotherapy as well.

	The studies included variable use of anti-androgen therapy and includes mixtures of low, intermediate and high risk men and there was no attempt made to correct for these potential biases (for example an indirect comparison of one treatment among low risk men linked to a treatment in high risk men through an intermediary would not be a valid comparison) For the comparisons there should be some description of the comparability of the risk strata and use of ADT. Finally, the authors identify a lack of randomized comparisons involving brachytherapy but omitted the following study (which I think would qualify for their review): 1: Giberti C, Chiono L, Gallo F, Schenone M, Gastaldi E. Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study. World J Urol. 2009 Oct;27(5):607-12. At the very least, the author's should acknowledge in their discussion the variability in risk categories and hormone use as limitations of the comparisons in their analysis.

REVIEWER	Michael Cookson University of Oklahoma School of Medicine United States of America
REVIEW RETURNED	22-Nov-2013

GENERAL COMMENTS	In lieu of pertinent randomized controlled trials comparing modalities for prostate cancer treatment head-to-head, the authors reviewed 39 reports from RCT's and compiled a network analysis to study the risks and benefits of each modality as it relates to 4 outcome variables: overall mortality, cancer-specific mortality, GI and GU toxicities. The authors rightly state that using network analysis is valuable for design of future RCT's. It should serve as a template for further comparative efficacy studies. However, there were several limitations of such an analysis that bear mention. 1. More information should be given regarding the variables used to calculate heterogeneity between trials. For instance, was median Gleason score used? A few other possible confounders are listed below. If not included in the stratification, they should be listed in a separate limitations paragraph in the conclusion. a. The RCT's included in the analysis spanned several decades. For instance, one of the two trials comparing prostatectomy to observation accrued patients between May 1967 and March 1975, when the techniques for radical prostatectomy were very different than the contemporary era. This should be mentioned in the discussion. b. The trials contained disparate populations with regard to age, proportion of men with high risk disease, smoking status, comorbidities, etc. These confounders limit the ability to compare across different studies. The clinical stage was considered in the analysis but does not adequately stratify risk for prostate cancer. This should be included as a limitation. c. Over the past 25 years, an incredible stage migration has occurred in the stage of men diagnosed with prostate cancer. Partly for this reason, oncologic outcomes for each definitive treatment modality have improved continuously over this time period. Any analysis comparing studies from several different eras necessarily carries a bias as a result. The authors should include this as a

	limitation. d. The use of hormonal therapy does not appear to be accounted for in the model, which should be included as a limitation. 2. The oncologic outcomes selected, 5-year overall and cancer-specific mortality, are not ideal for localized prostate cancer, as it tends to have a protracted course. In general for men with localized disease, only those with very high risk features would be at risk for death in this interval in the PSA era. The authors should change the sentence in the abstract: “There was no evidence of superiority… all-cause mortality” to “There was no evidence of superiority for any of the compared treatments in respect to all-cause mortality after 5 years.”

REVIEWER	Huseyin Naci Research Fellow, LSE Health, London School of Economics, London, UK Fellow in Population Medicine, Department of Population Medicine, Harvard Medical School, Boston, MA 'I have previously co-authored a paper with one of the authors of this paper (JH).'
REVIEW RETURNED	22-Jan-2014

GENERAL COMMENTS	The statement in the abstract "These findings highlight the importance of informed patient choice and shared-decision making about treatment modality and acceptable trade-offs between different outcomes" is not discussed in the discussion section of the paper. The authors may wish to expand their discussion around these issues. • The authors have done a commendable review and synthesis of the existing evidence on the available treatments for localized prostate cancer. In general, this is a very nicely written paper with strongly executed methods. It reads very well and the approach to analysis is clear. • One question that might require reframing in the introduction and discussion sections is whether the authors should be presenting their work as an application of network meta-analysis (and hence highlighting the benefits of adopting this statistical approach) or whether they are addressing a purely clinical question to which network meta-analysis provides a suitable methodological framework. The methods and results sections of the paper are more aligned with the latter approach whereas the discussion section seems to highlight the importance of using network meta-analysis. As the authors state in their abstract, the primary objective of this paper is “to evaluate the comparative efficacy and safety of different treatments for patients with localized prostate cancer.” Hence, the statement “Network meta-analysis may be useful to optimize the power of evidence synthesis studies once data from new randomized controlled studies in this field are published in the future” may not be entirely suitable for the conclusions of this paper. • On a related note, the authors may wish to expand their discussion on the clinical implications of their findings. • The authors have done a great job in explaining their methods. This section of the paper is detailed and clear. The only comment I have is related to the primary assumption of their analysis. Network

	meta-analyses require an assumption of similarity across the pooled set of studies in terms of patient population and study characteristics. Significant deviations in study characteristics such as outcome definition and assessment or patient population can result in biased estimates of comparative effectiveness – particularly if these factors are relative treatment effect modifiers. The authors should address the following questions: o What are important baseline study-level characteristics that may have impacted the results (i.e., relative treatment effect modifiers)? Have the authors evaluated the similarity across the pooled set of studies on the basis of these study-level characteristics? A brief discussion on the similarity of the included studies is warranted. o It is important to acknowledge that there is always the risk of unknown imbalances in relative treatment effect modifiers and accordingly the risk of residual confounding bias in network meta-analyses, even if all observed effect modifiers are balanced. The authors should acknowledge this as a limitation of their analysis. • I have no comments on the results section of the paper (and the tables/figures).

REVIEWER	Guobing Lu University of Bristol, UK
REVIEW RETURNED	24-Jan-2014

GENERAL COMMENTS	It has not been fully described about how to check the evidence consistency on a single loop on the odds ratio scale. This is a well-performed network meta-analysis (NMA) for comparing efficacy and safety of 8 treatments for localized prostate cancer, which reports transparently the whole NMA process, including literature search, data extraction, statistical analysis, and result analysis. The results in tables 1-5 clearly show an important advantage of NMA over the ordinary pair-wise meta-analysis by providing full comparisons between all possible pairs of treatments, no matter whether direct comparisons have been made in available trials. I also like the idea of incorporating information about heterogeneity from external data sources into the NMA. The following points I would like the authors to consider: 1. P.9, Lines 9-13: The statement “For each ‘loop’ ……we computed the difference between estimates from direct and indirect evidence”; and P.12, Lines 44-46: “No inconsistency was detected in our estimates of the difference between direct and indirect evidence”. It is not clear what you mean precisely by “the difference” on a loop. For example, consider a loop A-B-C-A. There are 3 odds ratios, i.e., OR(A,B), OR(A,C) and OR(B,C), and we denote the direct estimates by OR^dir(A,B),etc, and NMA estimates by OR^nma(A,B), etc. Then, to assess evidence inconsistency on the loop, one may check the consistency equation (CE) (Lu & Ades, 2006, JASA, 101:pp.447-459), which, on the OR scale, should be in a quotient or product (but not a difference) form: OR(A,C)/OR(A,B)=OR(B,C) or equivalently, OR(A,C)= OR(A,B) x OR(B,C) Clearly, the NMA estimates satisfy the CE, but the direct estimates

	may not. So evidence consistency associated with a single loop can be assessed by checking whether the direct estimates can satisfy the CE or not. In your case, there are two evidence loops, i.e., L1: Conventional Rad, Conformal LD Rad, and Conformal HD Rad; L2: Prostatectomy, Observational Management, Conformal LD Rad, and Conventional Rad. It is easy to check, using the results in table 1, For the NMA estimates, we have 0.86 x 0.96 = 0.82, i.e., NMA estimates satisfy the CE. And for the direct estimates, we have 0.92 x 0.96 (=0.88) is close to 0.87. Thus, informally, we can say that evidence on L1 is consistent. In similar way one can check the evidence consistency on L2 (which may not be so consistent as L1). 2. In tables 1, 3-5, please mention that the reported estimates are posterior means (not the posterior medians) with 95 Credible Intervals (CI). 3. P.9, Line 30-33; P.23, Lines 36-43: about the use of informative priors for heterogeneity variance. Please note that, similar idea was suggested by Lu and Ades (Biostatistics 2009, 10, 4, pp.279-805) for incorporating prior correlation information into mixed treatment comparison meta-analysis. 4. P.2, Line 38-39: "There are no evidence of superiority for any of the compared treatments in respect of all-cause mortality". May an error-bar plot based on the NMA estimates in table 1 be helpful for visualizing this?

VERSION 1 – AUTHOR RESPONSE

Reviewer Name: Glenn Bauman
Institution and Country London Regional Cancer Program
London, Ontario, Canada
Please state any competing interests or state ‘None declared’: I am co-author on one the papers cited in the analysis (Chin) and participated as an investigator on another (Lukka)

The author's should be more explicit in what their definitions of "conventional radiotherapy" "Low dose" and "High dose" radiotherapy assume - what are the dose ranges and how did the account for/correct for differences in fractionation schemes in assigning trials to each category.

Response: Many thanks for the suggestion. We have now specified the definitions for "conventional radiotherapy", "Low dose" and "High dose" on page 12, and the details have been shown in the Appendix 2.

The links for conventional radiotherapy to observational management are through one study comparing a small number of patients (<100) randomized between RP and XRT both with long term adjuvant therapy in locally advanced disease. This trial is also controversial within the GU community and is not widely cited. Thus this indirect comparison may not be very robust or appropriate (see other comments re: comparing between risk stratification and use of ADT)

Response: We think you refer to the study by Akakura, which compared prostatectomy and

conventional radiotherapy with a cohort of 95 patients (Figure 3 and Appendix 2). We assessed the quality of this study and the results showed it was without high risk of bias. The small sample size will be appropriately reflected in the statistical precision of our treatment effect estimates. Nevertheless, we now integrate your concern into the discussion.

I have reviewed this purely from a clinical perspective and do not have the expertise to comment on the rigor or appropriateness of the statistical techniques employed.

The author's appropriately caution conclusions about the comparisons given the sparse dataset analysed. The methodology is unique and did allow interesting and important comparisons to be made where gaps in direct randomized controlled comparisons exist.

Response: Thank you for this positive comment about the paper.

I have a couple of concerns about the methodology:

For the toxicity endpoint the RTOG scale is used but this is not appropriate for comparing toxicity between radiotherapy and surgery options as the RTOG scale doesn't include incontinence as part of the scale and this is the most common adverse GU event post-prostatectomy. This endpoint (continence) is also pertinent to cryotherapy as well.

Response: We appreciate the reviewer’s professional insight about this issue. The RTOG scale had been used to define the late gastrointestinal and late genitourinary toxicity in the included studies, we don’t think our analyses were wrong although the scale doesn’t include some specific measurement to cover all the multiple treatments; we have addressed this as a limitation in the discussion on page 24.

The studies included variable use of anti-androgen therapy and includes mixtures of low, intermediate and high risk men and there was no attempt made to correct for these potential biases (for example an indirect comparison of one treatment among low risk men linked to a treatment in high risk men through an intermediary would not be a valid comparison) For the comparisons there should be some description of the comparability of the risk strata and use of ADT.

Response: Thanks for pointing out this important issue which indeed needs to be acknowledged. We have added a paragraph from page 23 to page 24 to describe the issues as study limitations. We appreciated that there was heterogeneity across the study populations in terms of severity of disease and ADT use. However, we only included studies that used ADT for both treatment arms within a trial or for neither treatment arm.

Finally, the authors identify a lack of randomized comparisons involving brachytherapy but omitted the following study (which I think would qualify for their review): 1: Giberti C, Chiono L, Gallo F, Schenone M, Gastaldi E. Radical retropubic
prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective
study. World J Urol. 2009 Oct;27(5):607-12.

Response: We identified this study in our searches but excluded it from our analyses because it did not report any of the outcomes we analysed, only biochemical failure, biochemical disease-free survival and quality of life. This is now clarified on page 11.

At the very least, the author's should acknowledge in their discussion the variability in risk categories and hormone use as limitations of the comparisons in their analysis.

Response: We have integrated this point with other comments above and acknowledged these issues in the discussion, pleases see the paragraphs on page 23 and page 24.

Reviewer Name: Michael Cookson
Institution and Country University of Oklahoma School of Medicine
United States of America
Please state any competing interests or state ‘None declared’: None declared

In lieu of pertinent randomized controlled trials comparing modalities for prostate cancer treatment head-to-head, the authors reviewed 39 reports from RCT's and compiled a network analysis to study the risks and benefits of each modality as it relates to 4 outcome variables: overall mortality, cancer-specific mortality, GI and GU toxicities. The authors rightly state that using network analysis is valuable for design of future RCT's. It should serve as a template for further comparative efficacy studies. However, there were several limitations of such an analysis that bear mention.

Response: Many thanks for the comments.

1. More information should be given regarding the variables used to calculate heterogeneity between trials. For instance, was median Gleason score used? A few other possible confounders are listed below. If not included in the stratification, they should be listed in a separate limitations paragraph in the conclusion.

a. The RCT's included in the analysis spanned several decades. For instance, one of the two trials comparing prostatectomy to observation accrued patients between May 1967 and March 1975, when the techniques for radical prostatectomy were very different than the contemporary era. This should be mentioned in the discussion.
b. The trials contained disparate populations with regard to age, proportion of men with high risk disease, smoking status, comorbidities, etc. These confounders limit the ability to compare across different studies. The clinical stage was considered in the analysis but does not adequately stratify risk for prostate cancer. This should be included as a limitation.
c. Over the past 25 years, an incredible stage migration has occurred in the stage of men diagnosed with prostate cancer. Partly for this reason, oncologic outcomes for each definitive treatment modality have improved continuously over this time period. Any analysis comparing studies from several different eras necessarily carries a bias as a result. The authors should include this as a limitation.
d. The use of hormonal therapy does not appear to be accounted for in the model, which should be included as a limitation.

Response: We have integrated these points and acknowledged these issues in the discussion as study limitations. Please see the added paragraphs on page 23 and page 24.

2. The oncologic outcomes selected, 5-year overall and cancer-specific mortality, are not ideal for localized prostate cancer, as it tends to have a protracted course. In general for men with localized disease, only those with very high risk features would be at risk for death in this interval in the PSA era. The authors should change the sentence in the abstract: "There was no evidence of superiority… all-cause mortality" to "There was no evidence of superiority for any of the compared treatments in respect to all-cause mortality after 5 years."

Response: Many thanks for pointing out this omission and we have made the changes accordingly.

Reviewer Name: Huseyin Naci
Institution and Country Research Fellow, LSE Health, London School of Economics, London, UK

Fellow in Population Medicine, Department of Population Medicine, Harvard Medical School, Boston, MA
Please state any competing interests or state 'None declared': 'I have previously co-authored a paper with one of the authors of this paper (JH).'

The statement in the abstract "These findings highlight the importance of informed patient choice and shared-decision making about treatment modality and acceptable trade-offs between different outcomes" is not discussed in the discussion section of the paper. The authors may wish to expand their discussion around these issues.

Response: Many thanks for pointing out this omission and we have made the changes accordingly.

• The authors have done a commendable review and synthesis of the existing evidence on the available treatments for localized prostate cancer. In general, this is a very nicely written paper with

strongly executed methods. It reads very well and the approach to analysis is clear.

Response: Many thanks for the positive comments.

• One question that might require reframing in the introduction and discussion sections is whether the authors should be presenting their work as an application of network meta-analysis (and hence highlighting the benefits of adopting this statistical approach) or whether they are addressing a purely clinical question to which network meta-analysis provides a suitable methodological framework. The methods and results sections of the paper are more aligned with the latter approach whereas the discussion section seems to highlight the importance of using network meta-analysis. As the authors state in their abstract, the primary objective of this paper is "to evaluate the comparative efficacy and safety of different treatments for patients with localized prostate cancer." Hence, the statement "Network meta-analysis may be useful to optimize the power of evidence synthesis studies once data from new randomized controlled studies in this field are published in the future" may not be entirely suitable for the conclusions of this paper.

Response: Our aim was to apply the established methodology used in network meta-analysis to an area of clinical practice where no such previous studies existed. In doing so our aim was to both summarise existing evidence; 'map out' gaps in comparative evidence with the aim to help motivate the design and conduct of future comparative studies; and develop an approach 'primed' for subsequent updating and incorporation of future trials, including Protec-T study.

• On a related note, the authors may wish to expand their discussion on the clinical implications of their findings.

Response: We have expanded some discussion accordingly; please see the paragraphs on page 23 – 25.

• The authors have done a great job in explaining their methods. This section of the paper is detailed and clear. The only comment I have is related to the primary assumption of their analysis. Network meta-analyses require an assumption of similarity across the pooled set of studies in terms of patient population and study characteristics. Significant deviations in study characteristics such as outcome definition and assessment or patient population can result in biased estimates of comparative effectiveness – particularly if these factors are relative treatment effect modifiers. The authors should address the following questions:
o What are important baseline study-level characteristics that may have impacted the results (i.e., relative treatment effect modifiers)? Have the authors evaluated the similarity across the pooled set of studies on the basis of these study-level characteristics? A brief discussion on the similarity of the included studies is warranted.
o It is important to acknowledge that there is always the risk of unknown imbalances in relative treatment effect modifiers and accordingly the risk of residual confounding bias in network meta-analyses, even if all observed effect modifiers are balanced. The authors should acknowledge this as a limitation of their analysis.

Response: We have integrated these points and acknowledged these issues in the discussion as study limitations. Pleases see the added paragraphs on page 23 and page 24.

• I have no comments on the results section of the paper (and the tables/figures).

Reviewer Name: Guobing Lu
Institution and Country University of Bristol, UK
Please state any competing interests or state 'None declared': None

This is a well-performed network meta-analysis (NMA) for comparing efficacy and safety of 8 treatments for localized prostate cancer, which reports transparently the whole NMA process, including literature search, data extraction, statistical analysis, and result analysis. The results in tables 1-5 clearly show an important advantage of NMA over the ordinary pair-wise meta-analysis by providing full comparisons between all possible pairs of treatments, no matter whether direct

comparisons have been made in available trials. I also like the idea of incorporating information about heterogeneity from external data sources into the NMA.

Response: Many thanks for the positive comments.

The following points I would like the authors to consider:

1. P.9, Lines 9-13: The statement “For each ‘loop’ ……we computed the difference between estimates from direct and indirect evidence”; and P.12, Lines 44-46: “No inconsistency was detected in our estimates of the difference between direct and indirect evidence”.

It is not clear what you mean precisely by “the difference” on a loop. For example, consider a loop A-B-C-A. There are 3 odds ratios, i.e., OR(A,B), OR(A,C) and OR(B,C), and we denote the direct estimates by OR^dir(A,B),etc, and NMA estimates by OR^nma(A,B), etc. Then, to assess evidence inconsistency on the loop, one may check the consistency equation (CE) (Lu & Ades, 2006, JASA, 101:pp.447-459), which, on the OR scale, should be in a quotient or product (but not a difference) form:

OR(A,C)/OR(A,B)=OR(B,C) or equivalently, OR(A,C)= OR(A,B) x OR(B,C)

Clearly, the NMA estimates satisfy the CE, but the direct estimates may not. So evidence consistency associated with a single loop can be assessed by checking whether the direct estimates can satisfy the CE or not.

In your case, there are two evidence loops, i.e.,
L1: Conventional Rad, Conformal LD Rad, and Conformal HD Rad;
L2: Prostatectomy, Observational Management, Conformal LD Rad, and Conventional Rad.

It is easy to check, using the results in table 1,
For the NMA estimates, we have 0.86 x 0.96 = 0.82, i.e., NMA estimates satisfy the CE.
And for the direct estimates, we have 0.92 x 0.96 (=0.88) is close to 0.87. Thus, informally, we can say that evidence on L1 is consistent.

In similar way one can check the evidence consistency on L2 (which may not be so consistent as L1).

Response: This is the approach we took, only we computed differences on the log odds ratio scale rather than ratios on the odds ratio scale and we examined the differences formally by taking account of the precision of the estimates. Although the estimated difference between the direct and indirect estimates in L2 was non-zero, the confidence interval was wide and so we do not draw conclusions either way. We now clarify that computations were performed on the log scale. Many thanks.

2. In tables 1, 3-5, please mention that the reported estimates are posterior means (not the posterior medians) with 95 Credible Intervals (CI).

Response: This has been done accordingly.

3. P.9, Line 30-33; P.23, Lines 36-43: about the use of informative priors for heterogeneity variance.

Please note that, similar idea was suggested by Lu and Ades (Biostatistics 2009, 10, 4, pp.279-805) for incorporating prior correlation information into mixed treatment comparison meta-analysis.

Response: We have now cited this paper on page 24 accordingly.

4. P.2, Line 38-39: "There are no evidence of superiority for any of the compared treatments in respect of all-cause mortality".

May an error-bar plot based on the NMA estimates in table 1 be helpful for visualizing this?

Response: We thank the reviewer for this comment. We agree that figures are very useful to visualize

the results. However, as there are 37 estimates (including direct and indirect comparisons) available for all-cause mortality, in this paper we prefer to keep numerical results in a table.

VERSION 2 – REVIEW

REVIEWER	Glenn Bauman London Regional Cancer Program London Health Sciences Centre Western University London, Ontario, Canada
REVIEW RETURNED	20-Mar-2014

GENERAL COMMENTS	The author's do not include a randomized controlled trial of RP vs. Brachytherapy that would be important I think in terms of augmenting their literature search. I would recommend they include or at least explain why this study was excluded: World J Urol (2009) 27:607–612 Appropriate revisions based on original comments save for the concern about the brachytherapy study

REVIEWER	Huseyin Naci London School of Economics I previously authored a paper with one of the authors (JH).
REVIEW RETURNED	19-Mar-2014

GENERAL COMMENTS	The authors have successfully addressed my previous comments on their submission. I thank them for their responsive revision.

REVIEWER	Guobing Lu University of Bristol, UK
REVIEW RETURNED	29-Mar-2014

- The reviewer completed the checklist but made no further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer Name: Huseyin Naci

Institution and Country London School of Economics
Please state any competing interests or state ‘None declared’: I previously authored a paper with one of the authors (JH).

The authors have successfully addressed my previous comments on their submission. I thank them for their responsive revision.

Response: Thank you.

Reviewer Name: Glenn Bauman
Institution and Country London Regional Cancer Program
London Health Sciences Centre
Western University
London, Ontario, Canada
Please state any competing interests or state ‘None declared’: none declared

The author's do not include a randomized controlled trial of RP vs. Brachytherapy that would be important I think in terms of augmenting their literature search. I would recommend they include or at least explain why this study was excluded:

World J Urol (2009) 27:607–612

Appropriate revisions based on original comments save for the concern about the brachytherapy study

Response: We did identify this study in our searches but excluded it from our analyses because it did not report any of the outcomes we analysed – the paper only reported results in biochemical failure, biochemical disease-free survival and quality of life. This is now clarified on page 11 (number 56 in the reference list).

Reviewer Name: Guobing Lu
Institution and Country University of Bristol, UK
Please state any competing interests or state ‘None declared’: None declared

No further comments.

Response: Thank you.