Author's response to reviews

Title: Prognostic significance of interim PET/CT based on visual, SUV-based, and MTV-based assessment in the treatment of peripheral T-cell lymphoma

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Version: 3
Date: 16 January 2015

Author's response to reviews: see over
January 16, 2015

Dear Editor-in-Chief,

We appreciate the constructive review of our manuscript entitled “Prognostic significance of interim PET/CT based on visual, SUV-based, and MTV-based assessment in the treatment of peripheral T-cell lymphoma”. We have responded to the reviewers’ recommendations as described in the accompanied letter and revised a manuscript with changes highlighted. We hope that we have been able to answer properly to the questions/concerns raised by the reviewers and that the revised version of the manuscript will be found acceptable for publication in ‘BMC cancer’.

With best regards,

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Editorial

1) Please update your ethics statement to include the names of the ethics committees that approved your study.

(ANSWER) The name of the ethics committees that approved our study is the Institutional Review Board of Chonnam National University Hwasun Hospital

2) Acknowledgments

(ANSWER) We described the authors contributions in the text as follows: D.H.Y. and J.J.L. designed the study and analyzed data, and S.H.J. prepared the manuscript; B.H.B., J.J.M., S.W.L. and H.S.B. performed the image analysis; S.S.K. supported statistical analysis; J.S.A., Y.K.K., Y.S.C., J.H.M., S.K.S., Y.R.D and H.J.K. critically reviewed the manuscript. All authors read and approved the final manuscript.

In addition, there is no sources of funding.
Reviewer 1

Major compulsory revisions

The main drawback is the presentation of the results. .. you could try to present your results according to the assessment done: I. visual; II. Quantitative; and III, combined

[Answer] As following reviewer’s comment, the authors totally revised the content of Result section. We rearranged the result, and tried to present prognostic significance of interim PET/CT according to the assessment method: I. Patient’s characteristics and outcome; II. Visual assessment and survival prediction; III. Quantitative-assessment and survival prediction; IV. Combined-assessment using three parameters.

All revised sentences were expressed a red-colored, bold characters.

Material and Methods

Q1) P.5/L. 14# Follow-up restaging was done every 3 months during the first year, and every 6 months thereafter. How? Clinically? By PET/CT? How recurrence has been confirmed?

[Answer] The role of post-treatment surveillance using PET/CT is still controversial and is not recommend routinely for clinical practice. Restaging was performed by conventional CT scan. However, if patient was suspected the relapse in the CT image or physical evaluation, we performed PET/CT and tried to confirm the recurrence by tissue biopsy.

Results

Patient’s characteristics

Q2) P.9/L. 10-12 # the numbers regarding treatment are confusion. Of the total of 63 patients, how many underwent chemotherapy? All? And how many underwent IFRT -12 (in the text) or 15 (in the table)?

[Answer] Actually, newly diagnosed patients with T or NK lymphomas were registered with informed consents at the time of diagnosis, but patients who had early progression or treatment-related death (after 1st or 2nd cycle) before the interim analysis were excluded. Precisely, fifty-three patients treated with CHOP/CHOP-like chemotherapy, and ten patients received the other chemotherapy including IMVP-16, EPOCH, and VIDL (Table 1). Patients who treated with
IFRT were fifteen correctly (12 with extranodal NK/T and 3 with other subtypes of T cell lymphoma). To avoid confusion, we amended the result part as follows: Most patients (84.1%) were treated with the CHOP/CHOP-like regimen with a median number of six cycles, and 10 (15.9%) were treated with other induction chemotherapy including IMVP, EPOCH, and VIDL. Fifteen patients, primarily with NK/T cell lymphoma, received a short course of chemotherapy followed by IFRT.

Q3) Why have you included the four patients without interim PET/CT? They should be excluded.

[Answer] Four patients without interim PET/CT were excluded in the analysis of interim PET/CT (total number of patients in figure 2, figure 3, or Table 2 was 59). In addition, we found the data error in figure 3. Number of intermediate responder was 16. This error is corrected in figure 3 as follow:

Q4) Positive metabolic uptake (grade 1-3). It should be negative or (grade 4 and 5).

[Answer] We have amended this sentence as follows: Twenty-four patients (38.1%) were classified as having a positive metabolic uptake (grade 4 and 5) based on the visual assessment using 5-PS.

Q5) You should specify the optimal cutoff value here.

[Answer] To address the reviewer’s comment, we rearranged the result part, and the sentence (P.9/L. 24-25) was deleted in the manuscript.
Q6) P.9/L. 26-27 and P. 10/L 1-3 # What is the rationale for this? You are evaluating the visual and quantitative parameters of interim PET/CT and not of initial diagnostic PET/CT. You have shown the prognostic value of interim PET/CT using visual assessment and the prognostic value of initial PET/CT using quantitative assessment. Or you present the prognostic value of initial PET/CT using all parameters or you only show the prognostic value of interim PET/CT using all parameters (this is the aim of your study).

[Answer] P.9/L. 26-27: This is not a relapse rate according to initial PET/CT but a relapse rate according to visually positivity on interim PET/CT. This part was moved to “visual analysis and survival prediction” of result section.

P. 10/L 1-3 #: As the reviewer’s comment, this article was intended to evaluate prognostic value of interim PET/CT in patients with PTCL. Therefore, we deleted the result for initial PET/CT in this manuscript.

Q7) P.10/L. 9-11 “Seven patients with a positive uptake (grade 4 and 5) based on visual assessment were determined to show false-positive uptake during primary chemotherapy” # How was it proved-biopsy? And, please, list the confounding sites.

[Answer] We described for the false–positive site on interim PET/CT and confirm method (biopsy) in the text. Seven patients indicated the five with nasal-type NK/T cell lymphoma and two with hot uptake in the gastric and colonic region.

Q8) Several p–value are missing (p.10/L.22, 24; P.11/L.9, 23)

[Answer]  

p.10/L.22, 24: As reviewer’s comment, we rearranged the result part. Therefore, some data of this part was deleted in the manuscript, and data of p-value was added as follows; There were no differences in OS depending on histologic subtype, with the exception of anaplastic large cell lymphoma (P = 0.595, Figure 1B). PIT exhibited greater differentiation of survival than IPI (80.8 months in PIT 0-1, 15.0 in PIT 2, and 8.8 in PIT 3-4, P = 0.011, Figure 1D).

P.11/L.9, 23: We added the p-value in the manuscript as follows: “the probability of 3-year PFS in the 33 patients who achieved ΔSUVmax > the optimal cutoff was 52.6% compared with 24.7% in the 26 patients who failed to achieve the optimal cutoff (P = 0.001)”. The clinical outcomes of patients in the favorable group were significantly superior to those of patients in the poor or intermediate responder group (P = 0.002, P = 0.004, respectively, Figure 3A, B).
Q9). P. 11/L. 25 “showed better discriminatory ability for predicting the outcomes than single-parameter assessment” # By which statistic test it has been shown?

[Answer] When the authors had worked up the study protocol, the purpose of Interim PET/CT analysis was aimed to predict the increased risk of treatment failure during or after primary chemotherapy or to modify the therapeutic plans with interim PET-adapted de-escalation of therapy or interim PET-adapted escalation of therapy. However, the definition of the positive cutoff based on the each visual, SUV or MTV assessment had the limitations of predicting the disease progression in interpretations (some patients with negative uptake by visual assessment were classified into poor responder by SUV or MTV-based assessment and opposite interpretation also happened). So, the authors suggested in this study that the interim PET/CT response based on a combined evaluation of three methodological assessments could be an effective predictor for predicting the prognosis and the ability to compensate for the limitations of single interpretation. However, the authors could not show the statistical method, so we rephrased the sentence as following: the subdividing ability for predicting the outcomes compared with single-parameter assessment.

Discussion

Q10). P.12/L.9 # lack of uniformity

[Answer] Did you mean the P. 12/L.13? We corrected this typographical error as follow: the major drawback in these reports was the lack of uniformity or reliable criteria for interim PET interpretation.

Q11). P.13/L. 5-6 “which calculated the tumor volume using delineating the tumor margins with SUV cutoff of 2.54# must be omitted. It has been already mentioned before. Avoid repetitions.

[Answer] As reviewer’s comment, we deleted this sentence in the manuscript.

Q12). P13/L. 6 “could be a prognostic factor for predicting the progression during mid-therapy” It makes no sense. Please rephrase it.

[Answer] We have amended this sentence as follows; was helpful for predicting the progression during mid-therapy.
Q13). P. 13/L. 12-13 “no significant difference was observed between the visual and quantitative assessments for predicting the progression” # this result has not been shown.

[Answer] We showed survival curves for PFS according to the visual and quantitative assessment in the Figure 2. Significant difference was not observed in survival curves for PFS between the visual and quantitative assessment.

Q14). P. 13/L. 22-25 “The definition of positivity using grade 1-2 reported relatively low PPV with high NPV compared to quantitative assessments in ROC analysis. Low PPV of visual assessment could make it difficult to intensify the treatment strategy regarding the concern of overtreatment of a substantial portion in poor responders” # this is not very unclear. PPV of visual assessment (87.8%) is probably not significantly lower than the # SUVmax assessment (92.8%), which could make it difficult to intensify treatment strategy. And the main concern in poor responders is the undertreatment, since they usually require higher doses/more treatment. Please rephrase it.

[Answer] As the reviewer’s comment, the main concern of poor responder is the undertreatment. Therefore, we have amended the sentence to avoid confusion as follow; “The definition of positivity based on visual assessment reported relatively low PPV with high NPV compared to quantitative assessments in ROC analysis. Low PPV could make it difficult to modify the therapeutic plans with interim PET-adapted dose escalation or high-dose chemotherapy in poor responders”

Figures and Tables

Q15). It would be very interesting and valuable include a figure showing one example of the proposed visual and quantitative assessments.

[Answer] When the authors analyzed the interim PET data in the study, several cases had the discrepant results when interpreting poor responder based on each assessment methods. This kind of discrepancy mostly happened in patients with bulky mass, nasal NK/T and gastrointestinal involvement. We firstly planned to present representative case in Discussion part, but those cases make the confusion for role of interim PET in T cell lymphoma. So, we will prepare another short paper for careful interpretation of interim PET depending on anatomical site or disease status.
Reviewer 2

Introduction

Minor essential revisions

Q1) Row 18-21: Please provide a reference

[Answer] As reviewer’s comment, the authors added the reference as follows:


Q2) Final paragraph should equal to abstract

[Answer] To address the reviewer’s comment, we have amended the final paragraph in the introduction part as follows: In the present study, we prospectively investigated the prognostic accuracy of sequential interim PET/CT using visual and quantitative assessment to determine whether it provided prognostic information for the treatment of PTCL.

Discretionary Revisions

Q3) Please provide more references to PET data in peripheral T-cell lymphoma and its controversy subject.

[Answer] There are not many data for prognostic role of interim PET/CT in PTCL. The authors added more references of recently published PET data in introduction part.


Khong PL, Huang B et al. Midtreatment 18F-FDG PET/CT Scan for early response assessment of


Materials and Methods

Q4) Was enrollment consecutive? Why do the authors report clinical information on 63 patients but final analysis was only reported in those 59 patients with an interim PET/CT?

[Answer] Actually, newly diagnosed patients with T or NK lymphomas were registered with informed consents at the time of diagnosis, but patients who had early progression or treatment-related death (after 1st or 2nd cycle) before the interim analysis were excluded. The data of 59 patients who underwent interim PET/CT was used to evaluate prognostic value of visual and quantitative assessment of interim PET/CT.

Q5) Page 7 Row 25-27. The authors should describe how patients that were lost to follow-up coded. How did the authors handle patients who died during the follow-up period? These patients should be considered as censored data. The same holds true for OS. Patients who survive during follow-up should be considered as censored data. Please elaborate.

[Answer] As reviewer's comment, patients who lost to follow-up period were classified as censored data. It is same in analysis of OS data. We additionally described the this comment in the “statistical analysis” part as follow: PFS was calculated from the treatment start time to the first recording of disease progression, death from any cause or loss of follow-up period.

Major Compulsory revisions

Q6) ROC analysis requires dichotomous variables as gold standard. What was the gold standard for this analysis.

[Answer] The authors performed the ROC analysis to evaluate the predictability of disease progression. The status of disease progression was confirmed by direct follow-up examination and data-linkage to hospital death certificate data. The reviewer already knew that the optimal cutoff value is chosen with satisfying best sensitivity and specificity for disease progression.

Q7) Why do the authors use for an analysis of "survival (here, progression free survival time) the univariate analysis of the influence, a process in which the survival time is not included?
The authors carefully answered for this question because we did not fully understand the meaning of question. Primary endpoint of this study is progression-free survival (PFS) because patients with T cell lymphomas could be treated additional intensifications during or after primary chemotherapy. The authors did not mean to compare the efficacy of each assessment method in this study. We added the multivariate analysis in Result section.

Discretionary Revisions

Q8) There are not many predictors included. Thus, a cox regression would be more helpful. this could be also stepwise performed.

As reviewer’s comment, the authors added the multivariate results in Result section:

Multivariate analysis showed that performance status (≥2), visual (5-PS≥4) and combined (poor responder by all three assessments) in interim PET/CT were independent prognostic variables associated with PFS.

Results

As following another reviewer’s comment, the authors totally revised the content of Result section. We rearranged the result, and tried to present prognostic significance of interim PET/CT according to the assessment method: I. Patient’s characteristics and outcome; II. Visual assessment and survival prediction; III. Quantitative-assessment and survival prediction; IV. Combined-assessment using three parameters.

All revised sentences were expressed a red-colored, bold characters.

Major Compulsory Revisions

Q10) Page 9 Row 26/27. The authors write about comparing two percentages. Which test was applied?

Relapse rate between two groups was compared by Pearson’s chi-square test

Q11) Page 10 Row2. The authors compare two means. Please provide a p-value

Because of following another reviewer’s comment, the authors deleted the sentence in the text.
Q12) Page 10 Row. An AUC of 672 is rather low and thus does not allow good discrimination. Please elaborate.

[Answer] The authors totally agree that AUC of 0.672 seems to be low and is only categorized moderate accuracy in ROC analysis. So, we make a double check the significance of the three parameters in Table 2. However, no change was found statistically.

Q13) The authors should provide sensitivity and specificity for the selected cut-off values.

[Answer] The authors described the sensitivity and specificity for the cut-off values according to the assessment method in the Table 2.

Discussion

Major Compulsory Revisions

Q14) Please elaborate this section according recent reports indicating the discordant situation regarding the role of interim PET in PTCL.

[Answer] There are a few reports for predictive value of interim PET/CT in PTCL. We tried to describe the recent studies for prognostic value of interim PET/CT in text as follows: The prognostic role of interim PET/CT in PTCL is less-well established than that in DLBCL. One study reported that negative interim or post-therapy interim PET/CT did not associate with improved the survival In NK-T cell lymphoma.[1] However, some recent studies have suggested that the interim PET response may be also useful for predicting the outcome in PTCL. A retrospective study of mature T-cell and NK/T cell lymphoma reported that patients achieving interim PET/CT negativity showed an improved 2-year PFS and OS compared with those with interim PET/CT positivity.[2] Another retrospective study yielded similar results regarding the prognostic role of interim PET/CT.[3]