

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Additional value of volumetric and texture analysis on FDG PET assessment in pediatric Hodgkin Lymphoma: an Italian multicentric study protocol.
AUTHORS	Lopci, Egesta; Burnelli, Roberta; Elia, Caterina; Piccardo, Arnaldo; Castello, Angelo; Borsatti, Eugenio; Zucchetta, Pietro; Cistaro, Angelina; Mascarin, Maurizio

VERSION 1 – REVIEW

REVIEWER	Michael Fuchs Universit Hospital of Cologne German Hodgkin Study Group Cologne, Germany
REVIEW RETURNED	21-Jul-2020

GENERAL COMMENTS	The manuskript is well written and the study cleary outlined. I suggest to indicate one or two potential limitations of the study.
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REVIEWER	Jennifer Seelisch Division of Hematology/Oncology, Department of Pediatrics, Children's Hospital London Health Sciences Centre, Western University, London, Canada
REVIEW RETURNED	23-Sep-2020

GENERAL COMMENTS	<p>Overall this proposal represents an exciting opportunity to further characterize the role of volumetric and texture analysis on FDG PET in pediatric patients with Hodgkin lymphoma, which may potentially have implications for prognostication. A clear strength is the use of EuroNet-PHL-C2 to provide a large sample size.</p> <p>Background:</p> <ul style="list-style-type: none">- Second paragraph - "The implementation *of* metabolic..."- Metabolic tumor volume is defined well; consider also expanding further the concept of textural parameters within the background (perhaps by introducing radiomics briefly?)- Last sentence - Did you intend - chemotherapy sensitivity vs sensibility? <p>Eligibility Criteria</p> <ul style="list-style-type: none">- 3rd line "two cycles of" is repeated- Throughout the paper you specifically mention using the Italian cohort of patients on EuroNet-PHL-C2 rather than all patients on the study. This should be included in the eligibility criteria. <p>Methodology</p>
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	<p>- Could you expand further on the specific software you are using and any potential limitations of the software?</p> <p>Sample size calculation - 3rd line - "we *expect* to enroll.."</p> <p>Discussion: - "guarantee cure" is too strongly worded</p>
REVIEWER	Veronique Edeline Institut Curie, site Saint Cloud France
REVIEW RETURNED	27-Oct-2020
GENERAL COMMENTS	<p>this is a well written study protocol manuscript. According the the manuscript's review, some dates of the study should be mentionned (starting, planned end of study). This is a research planned on a subgroup of patients treated in a EuroNet trial. The authors should clarify if this ancillary study has been discussed with the sponsor of the global study.</p> <p>minor points: the radiomics study could be detailed and the primary objective (line 55) mention the diagnostic and prognostic role of volumetric assessment. The authors should explain what diagnostic means for them in this objective.</p>

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name

Michael Fuchs

Institution and Country

Universit Hospital of Cologne

German Hodgkin Study Group

Cologne, Germany

Please state any competing interests or state 'None declared':

not declared

Comments to the Author

The manuskript is well written and the study clearly outlined.

I suggest to indicate one or two potential limitations of the study.

Answer: *The authors would like to thank the reviewer for the positive comments and constructive suggestions to our manuscript.*

Reviewer: 2

Reviewer Name

Jennifer Seelisch

Institution and Country

Division of Hematology/Oncology, Department of Pediatrics, Children's Hospital London Health Sciences Centre, Western University, London, Canada

Please state any competing interests or state 'None declared':

None declared

Comments to the Author

Overall this proposal represents an exciting opportunity to further characterize the role of volumetric and texture analysis on FDG PET in pediatric patients with Hodgkin lymphoma, which may potentially have implications for prognostication. A clear strength is the use of EuroNet-PHL-C2 to provide a large sample size.

Answer: *The authors would like to thank the reviewer for the very positive comments to our manuscript.*

Background:

- Second paragraph - "The implementation *of* metabolic..."
- Metabolic tumor volume is defined well; consider also expanding further the concept of textural parameters within the background (perhaps by introducing radiomics briefly?)
- Last sentence - Did you intend - chemotherapy sensitivity vs sensibility?

Answer: *According to the reviewer's suggestion, we have now modified the text.*

Eligibility Criteria

- 3rd line "two cycles of" is repeated
- Throughout the paper you specifically mention using the Italian cohort of patients on EuroNet-PHL-C2 rather than all patients on the study. This should be included in the eligibility criteria.

Answer: *We have now corrected the text based on the reviewer's suggestion.*

Methodology

- Could you expand further on the specific software you are using and any potential limitations of the software?

Answer: according to the reviewers recommendation, we have now added required information in the text.

Sample size calculation

- 3rd line - "we *expect* to enroll.."

Answer: the term has been corrected as suggested

Discussion:

- "guarantee cure" is too strongly worded

Answer: the term has been removed as suggested

Reviewer: 3

Reviewer Name

Veronique Edeline

Institution and Country

Institut Curie, site Saint Cloud

France

Please state any competing interests or state 'None declared':

None declared

Comments to the Author

this is a well written study protocol manuscript. According the the manuscript's review, some dates of the study should be mentionned (starting, planned end of study). This is a research planned on a subgroup of patients treated in a EuroNet trial. The authors should clarify if this ancillary study has been discussed with the sponsor of the global study.

Answer: The authors would like to thank the reviewer for the positive comment. We want also to reassure the reviewer that the study has been discussed and approved by the sponsor. In particular it is approved following the amendment nr. 4 of the EuroNet trial. These data together with the study timeline have been added to the manuscript for more clarity.

minor points: the radiomics study could be detailed and the primary objective (line 55) mention the diagnostic and prognostic role of volumetric assessment. The authors should explain what diagnostic means for them in this objective.

Answer: according to the suggestions, we have now added more details on the radiomics study. As per the diagnostic role mentioned in the study objectives, we intend the capability of added parameters to assess disease presence at different timing. This goes necessarily with the need to assess ability to define treatment response at interim and at treatment end.

VERSION 2 – REVIEW

REVIEWER	Jennifer Seelisch Division of Hematology/Oncology, Department of Pediatrics, Children's Hospital London Health Sciences Centre, Western University, London, Canada
REVIEW RETURNED	03-Dec-2020
GENERAL COMMENTS	Thank you for your revisions. I have no further comments.