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No difference in treatment outcome between patients with nodal versus extranodal diffuse large B-cell lymphoma

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1st Editorial decision
24-Jul-2022

Ref.: Ms. No. JCTRes-D-22-00034
Outcomes of Patients in Nodal vs. Extranodal Diffuse Large B-cell Lymphoma: An Institutional Perspective
Journal of Clinical and Translational Research

Dear Dr Khan,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the

reviewers to rapidly verify all changes made.

Your revision is due by Aug 23, 2022.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #2: Manuscript JCTRes-D-22-00034 entitled "Outcomes of Patients in Nodal vs. Extranodal Diffuse Large B-cell Lymphoma: An Institutional Perspective" for Journal of Clinical and Translational Research.

This is a retrospective study including patients with Difusse large B cell lymphoma, attended during 5 years in a single Institution in Pakistan.

The number of patients is very limited. However, as an information from a reference center in Pakistan, it could be interesting.

The following recommendations are suggested:

Theses authors describe a higher frequency of extranodal lymphoma (58.47 %), in comparision with the nodal lymphoma (41.52 %). This results are in contrast with those described in the literature, where the primary extranodal lymphoma is not higher that 10-12 %. Authors nedd to clarify this discrepancy.

They must define residual disease, since this is a term used for molecular detection of a hematological neoplasms. The detailed the use of PET-CT, if this method was available in all patients, then the results should be reported according with Deauville & Lugano criteria.

There are manuscript mistakes, for example, page 5: wwereanyzed, variabwaswere, Dwere

The following phrase is confusing: Approximately 17-20 % of patients did not fulfill the requirements for classification as double expressor lymphomas. This means that the authors did additional markers to search double hit lymphomas in patients with double expressor lymphomas (myc /Bcl2 /Bcl6 expression by immunohistochemistry)?

An additional table describing every extranodal site is highly suggested.

If these suggestions are explained, it could be accepted for publication.

Authors’ response

Respected reviewers: Thank you for your time and valuable recommendations.

We have addressed all the suggestions as listed. We hope that this revised manuscript, with the addition of your valuable suggestions, will fulfil the requirement of publication of this work in to your prestigious journal.

RESPONSE SHEET:

This is a retrospective study including patients with diffuse large B cell lymphoma, attended during 5 years in a single Institution in Pakistan.

The number of patients is very limited. However, as information from a reference Centre in Pakistan, it could be interesting.

The following recommendations are suggested:

Comment 1:

These authors describe a higher frequency of extranodal lymphoma (58.47 %), in comparison with nodal lymphoma (41.52 %). These results are in contrast with those described in the literature, where the primary extranodal lymphoma is not higher than 10-12 %. The author needs to clarify this discrepancy.

Response: We have mentioned in our study as (Page 10, Line 4-12)

As per literature, the incidence of primary extranodal disease ranges from around 10-40%, with a gradual increase in incidence seen in more recent studies [20, 21]. Our study also demonstrates a higher percentage of extranodal DLBCL when compared to nodal DLBCL; 58.4% vs. 41.5%. Overall, this is higher than what is reported in the literature [22-24]. The exact cause cannot be

determined; however, one hypothesis may be that as we are a tertiary care centre and tend to see more complicated presentations, therefore, there could be a referral bias. Also, the fact that the differences between nodal V/S extra nodal DLBCL have never been studied in our population, hence this is the first real-world data explaining the possibility of high frequency of extranodal DLBCL presentation in our region.

Comment 2:

They must define residual disease since this is a term used for molecular detection of haematological neoplasms. The detailed the use of PET-CT, if this method was available in all patients, then the results should be reported according to Deauville / Lugano criteria.

Response:

PET CT scan was used in all patients to assess the presence of residual disease. Hence we have mentioned this in our study as (page 6, para-2, and line 1-3)

Residual disease was determined by the PET positivity using the Deauville score. For this study, lesions with a score of ≥4 on PET CT scan by Deauville were considered positive for residual disease.

Comment 3:

There are manuscript mistakes, for example, page 5: wwereanyzed, variabwaswere, Dwere.

Response: Possible error during the submission process. However; we have reviewed and corrected all the manuscript errors.

Comment 4:

The following phrase is confusing: Approximately 17-20 % of patients did not fulfil the requirements for classification as double expressor lymphomas. This means that the authors did additional markers to search double hit lymphomas in patients with double expressor lymphomas (myc /Bcl2 /Bcl6 expression by immunohistochemistry)?

Response: Here we are talking about double expressor (DE) status. We have performed MYC, BCL2, and BCL6 for all patients to classify as to have a double expressor status and a small percentage of patients in our study did not classify as having double expressor status. Hence we have mentioned this in our study as: (Page 5, Line 1-3).

Approximately 17-20 % of patients in both groups did not fulfil the requirements for classification as double expressor lymphoma (DEL).

Comment 5:

An additional table describing every extranodal site is highly suggested.

Response: Thank you for this valuable suggestion.

We have mentioned all the extranodal sites involvement in Table 1, S#7, and Page 5.

2nd Editorial decision
08-Aug-2022

Ref.: Ms. No. JCTRes-D-22-00034R1
Outcomes of Patients in Nodal vs. Extranodal Diffuse Large B-cell Lymphoma: An Institutional Perspective
Journal of Clinical and Translational Research

Dear Dr Khan,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Sep 07, 2022.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Dear authors,

Thank you for submitting a revised draft.

I have perused through the modifications and rebuttal and would like you to add the following to the manuscript:

1) your replies to the reviewer must also be integrated into the correct sections of the manuscript. For example, the fact that PET-CT was employed and the interpretation criteria to determine residual disease is not mentioned in the Methods section. This should be moved from the Results section to the Methods section. Moreover, immunohistochemistry and other protocols used for diagnosis/prognosis (e.g., IPI) and treatment (e.g., lenalidomide, rituximab) should also be explained more elaborately in the Methods.

2) several representative PET-CT images should be included in the manuscript to show residual disease. 'Representative' refers to both types of lymphoma.

3) several representative immunohistochemical stainings (c-Myc, BCL-2, and BCL-6) should be presented in a figure for both types of lymphoma.

4) Please include a detailed CONSORT flow chart to describe the patient cohort inclusion/exclusion and treatment arms (https://www.evscienceconsultant.com/blog/flowchart-of-your-study).

5) Please proofread the manuscript, as it is still replete with linguistic errors and

inconsistencies. Either involve a native speaker, contract a third-party language editing service, or contact the editorial office (m.heger@jctres.com) for language editing and content support.

Thank you,

Michal Heger
Editor

Authors'response

Respected reviewers. Thank you for your valuable suggestions. We have reviewed addressed the following comments and made appropriate changes in the manuscript.

RESPONSE SHEET:

Thank you for submitting a revised draft. I have perused through the modifications and rebuttal and would like you to add the following to the manuscript:

COMMENT 1:

Your replies to the reviewer must also be integrated into the correct sections of the manuscript. For example, the fact that PET-CT was employed and the interpretation criteria to determine residual disease is not mentioned in the Methods section. This should be moved from the Results section to the Methods section. Moreover, immunohistochemistry and other protocols used for diagnosis/prognosis (e.g., IPI) and treatment (e.g., Lenalidomide, rituximab) should also be explained more elaborately in the Methods.

Response:

We have included this in "method section" in our manuscript

All the biopsies were examined and reported by histopathologists and final diagnosis was made. Hence detailed immunohistochemical (IHC) stains were reviewed including complete panel consists of LCA, CD3, CD19, CD20, CD10, CD30, CD22, CD79a, BCL6, BCL2, MUM1,

PAX5, c-MYC and Ki-67. Among these IHC stains, the cutoff scores for overexpression for MYC and BCL2 were ≥ 40% and ≥ 50% respectively. However, the positive standards for BCL6 and MUM1 were 30%. Positron emission tomography (PET) imaging was performed and evaluated to classify patients into stage I-IV based on the Lugano modification of the Ann Arbor classification. page #3 line 21-25 and page 4 line 1-4.

Residual disease was determined by the PET positivity using the Deauville score. For this study, lesions with a score of ≥4 on PET-CT scan by Deauville were considered positive for residual disease. page #4 line 7-9.

International Prognostic Index (IPI) score was calculated by using one point for each variable including age (>60 years), serum LDH above normal, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, Ann Arbor stage III or IV, number of sites of extranodal disease. CNS-IPI score was calculated by using one point for each variable as for IPI with additional one point for kidney and/or adrenal glands involvement. The sum of IPI and CNS-IPI grouped patients into Low, intermediate and high risk categories. page #4 line 21-24 & page# 5 line 1-2.

R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) and REPOCH (Rituximab, Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin) are the most common primary treatment regimen used for both nodal and extra-nodal DLBCL patients. DHAP (Dexamethasone, Cytarabine, Cisplatin), ICE (Ifosfamide, Carboplatin,

Etoposide), Lenalidomide, GemOX (Gemcitabine, Oxaliplatin), GCD (Gemcitabine, Carboplatin, Dexamethasone) with or without Rituximab are some of the other chemotherapy

regimen used in patients (nodal and extra-nodal) who has residual disease after first line primary treatment or those with relapsed/refractory disease. Page #5 line 5-12.

COMMENT 2

Several representative PET-CT images should be included in the manuscript to show residual disease. 'Representative' refers to both types of lymphoma.

Response:

We have included PET-CT images in the manuscript-supplementary data to show residual disease of PET CT image representatives (Fig no 2&3) for both nodal and extra-nodal lymphoma types. Page #8 line 6

COMMENT 3:

Several representative immunohistochemical staining (c-MYC, BCL-2, and BCL-6) should be presented in a figure for both types of lymphoma.

Response:

We have included several representatives of immunohistochemical analysis of Nodal / Extra-nodal DLBCL patients. (Fig no 1) page #3 line 25.

COMMENT 4

Please include a detailed CONSORT flow chart to describe the patient cohort inclusion/exclusion and treatment arms (https://www.evscienceconsultant.com/blog/flowchart-of-your-study).

Response:

We have included a detail CONSORT FLOW CHART to describe treatments received by both EXTRA-NODAL and NODAL groups. Added in supplementary file. Page # 5 line 18-19.

COMMENT 5:

Please proofread the manuscript, as it is still replete with linguistic errors and inconsistencies. Either involve a native speaker, contract a third-party language editing service, or contact the editorial office (m.heger@jctres.com) for language editing and content support.

Response:

We have proofread the manuscript using Grammarly software premium version and native speaker to remove grammatical and linguistic errors and inconsistencies.

3rd Editorial decision
16-Aug-2022

Ref.: Ms. No. JCTRes-D-22-00034R2
Outcomes of Patients in Nodal vs. Extranodal Diffuse Large B-cell Lymphoma: An Institutional Perspective
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Sep 15, 2022.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Dear authors,

Thank you for submitting a revised version of your paper.

I have gone through the changes and appreciate the additions as per my request.

Nonetheless, I do still have a problem with the language editing.

To give you an example of what I am referring to, I will use the abstract alone to point out inconsistencies and errors that must be corrected here and throughout the entire paper before we can publish your paper. Please understand that we want to bring out pristine work only, which will benefit everyone involved in our organization, and particularly past and future authors.

- Nodal vs. Extranodal -> capitalization is incorrect
- Extranodal (background) vs. extranodal (results) vs. extra nodal (results) -> this is inconsistent and wrong spelling
- a sentence shoulkd not start with numerical values; 80 should be written as Eighty at the beginning of a sentence
- 31% vs. 16 % -> why no space and space after value and before unit? This is inconsistent
- "Residual disease was more common in the extranodal group 31% vs. 16 % (p=0.08)" is not a complete sentence; I therefore doubt that a native speaker perused over the paper
- "33.5months" -> this is not 1 word
...and so forth; too many mistakes

Please contract a third-party service or involve a native speaker or contact the editorial office (m.heger@jctres.com) for help.

Good luck,

Michal Heger
Editor

Authors' response

Respected reviewers. Thank you for your valuable suggestions. We have reviewed addressed

the following comments and made appropriate changes in the manuscript.

RESPONSE SHEET:

Thank you for submitting a revised draft. I have perused through the modifications and rebuttal and would like you to add the following to the manuscript:

COMMENT 1:

Your replies to the reviewer must also be integrated into the correct sections of the manuscript. For example, the fact that PET-CT was employed and the interpretation criteria to determine residual disease is not mentioned in the Methods section. This should be moved from the Results section to the Methods section. Moreover, immunohistochemistry and other protocols used for diagnosis/prognosis (e.g., IPI) and treatment (e.g., Lenalidomide, rituximab) should also be explained more elaborately in the Methods.

Response:

The methods have been updated accordingly.

COMMENT 2

Several representative PET-CT images should be included in the manuscript to show residual disease. 'Representative' refers to both types of lymphoma.

Response:

We have included PET-CT images in the manuscript-supplementary data to show residual disease of PET CT image representatives (Fig no 2&3) for both nodal and extra-nodal lymphoma types.

COMMENT 3:

Several representative immunohistochemical staining (c-MYC, BCL-2, and BCL-6) should be presented in a figure for both types of lymphoma.

Response:

We have included several representatives of immunohistochemical analysis of Nodal / Extra-nodal DLBCL patients.

COMMENT 4

Please include a detailed CONSORT flow chart to describe the patient cohort inclusion/exclusion and treatment arms (https://www.evscienceconsultant.com/blog/flowchart-of-your-study).

Response:

We have included a detail CONSORT FLOW CHART to describe treatments received by both EXTRA-NODAL and NODAL groups. Added in supplementary file.

COMMENT 5:

Please proofread the manuscript, as it is still replete with linguistic errors and inconsistencies. Either involve a native speaker, contract a third-party language editing service, or contact the editorial office (m.heger@jctres.com) for language editing and content support.

Response:

The manuscript has been completely rewritten.

3rd Editorial decision
23-Nov-2022

Ref.: Ms. No. JCTRes-D-22-00034R3
No difference in treatment outcome between patients with nodal versus extranodal diffuse large B-cell lymphoma
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.
Please notify our assistant editor/production editor when you receive the proofs if your article should belong to a special issue specifying the issue's title.

Thank you for submitting your work to JCTR.

Kindest regards,

Yao Liu, PhD
Editorial Board Member
Journal of Clinical and Translational Research

Comments from the editors and reviewers: