

## **Definitive chemoradiation in locally advanced inoperable esophageal cancer patients – Retrospective analysis of different chemotherapy regimens in a tertiary cancer centre**

Aswin Nagarajan, Begum Yesmin Nureja, Ramya Ravichandar, Rama Ranganathan

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Handling editor:

Michal Heger

*Department of Pharmaceutics, Utrecht University, the Netherlands*

*Department of Pharmaceutics, Jiaxing University Medical College, Zhejiang, China*

Review timeline:

Received: 30 March, 2021  
Editorial decision: 6 May, 2021  
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Editorial decision: 25 July, 2021  
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Editorial decision: 28 July, 2021  
Revision received: 7 August, 2021  
Editorial decision: 12 August, 2021  
Revision received: 17 September, 2021  
Editorial decision: 29 September, 2021  
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1<sup>st</sup> Editorial decision  
06-May-2021

Ref.: Ms. No. JCTRes-D-21-00046

**DEFINITIVE CHEMORADIATION IN LOCALLY ADVANCED INOPERABLE  
ESOPHAGEAL CANCER PATIENTS – RETROSPECTIVE ANALYSIS OF DIFFERENT  
CHEMOTHERAPY REGIMENS IN A TERTIARY CANCER CENTRE**

Journal of Clinical and Translational Research

Dear Dr. Nagarajan,

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 Jun 05, 2021.

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 #1: Comments to the Authors

This original article is focused on comparison of efficacy and safety between TC plus radiation and CDDP plus radiation for inoperable locally advanced EC patients. This article has some problems to evaluate efficacy and safety of two treatments. Therefore, authors need to reconsider description and statistical analysis in this retrospective study.

Major comments

1) In the section of results, there are no data on frequency of histology (ex. SCC, AC) and PS (ex. 0, 1, 2) in this population. These data might affect the results of survival outcomes. Therefore, author should describe these data and perform survival analysis that takes these data into account. Additionally, complete response is an important outcome for inoperable EC patients, too. Authors should clarify these short-time efficacy data in this article. Generally, it is impossible to evaluate efficacy of CRT without these data.

2) In the section of results, there are no data on frequency of adverse events by grade (CTCAE ver 5.0). In clinical practice, 4 or more hematological adverse events and 3 or more non-hematological adverse events are important. Therefore, authors should describe these data. Additionally, febrile neutropenia and esophagitis are important adverse events for patients received CRT, authors should add these data. Generally, it is impossible to evaluate safety of CRT without these data, too.

3) In the section of discussion, authors only describe the list of literatures. Authors should deeply discuss about some questions selected based on precise results.

Minor comments

1) Page 3 of 15, line 43-47, in the section "66 patients with locally advanced inoperable esophageal cancers treated at our center during the study period were retrospectively abstracted from the case records. All the patients had given informed consent during the study period and the study was approved by Cancer Institute Ethics Committee. 24(36%) patients received TC and 42(64%) received CDDP.", these sentences should be described in the results.

2) Page 3 of 15, line 53: "The categorical variables were sex, location, histology, tumor status (T) and Node status (N).", authors should mention the classification (ex. UICC 8th).

3) Page 3 of 15, line 57-Page 4 of 15, line 6. In the section "Chemotherapy regimen consisted of two major groups 1) Cisplatin regimen either 3 weekly CDDP 75mg/m<sup>2</sup> at days 1, 22 and 43 or weekly CDDP 40mg/m<sup>2</sup> at days 1, 8, 15, 22, 29 and 36 and 2) Paclitaxel(50mg/m<sup>2</sup>) and Carboplatin (AUC 2) at days 1,8,15,22,29 and 36. Although the standard protocol followed worldwide for Cisplatin regime is CDDP + 5FU, our institutional policy is to give single agent Cisplatin in definitive setting due to poor compliance of patients with CDDP/5FU regimen.", why does your hospital happen poor compliance of CF-RT? CF-RT is one of the standard treatments for inoperable EC patients all over the world.

Reviewer #2: Definitive chemoradiation is the treatment of choice for locally advanced inoperable esophageal cancers. The standard chemotherapy protocol worldwide is CDDP + 5FU. The main aim of this analysis is to describe the outcomes of definitive chemo radiation with Paclitaxel and Carboplatin (TC) Vs Cisplatin (CDDP) with radiation. My question are as follows. Firstly, Which version is the basis of clinical staging of esophageal cancer in your study? The author didn't explain. Secondly, the standard protocol followed worldwide for Cisplatin regime is CDDP + 5FU, they gave single agent Cisplatin in definitive setting due to poor compliance of patients with CDDP/5FU regimen. This may make us confused whether this group belong to definitive concurrent chemoradiotherapy. They can use capecitabine instead of fluorouracil in this situation. Thirdly on the part of discussion, the side effects of the two groups were not discussed in detail. Only a few articles on concurrent chemoradiotherapy for esophageal cancer are listed.

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Authors' response

#### REBUTTAL LETTER

Ref.: Ms. No. JCTRes-D-21-00046

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Yours sincerely

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Journal of Clinical and Translational Research

**We are grateful for your commentary and suggestions, which we have addressed to the fullest extent as indicated below for your comments**

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1) In the section of results, there are no data on frequency of histology (ex. SCC, AC) and PS (ex. 0, 1, 2) in this population. These data might affect the results of survival outcomes. Therefore, author should describe these data and perform survival analysis that takes these data into account. Additionally, complete response is an important outcome for inoperable EC patients, too. Authors should clarify these short-time efficacy data in this article. Generally, it is impossible to evaluate efficacy of CRT without these data.

**Results. Page 4. Lines 2,3,4,5,6,7,8,14,15.**

2) In the section of results, these are no data on frequency of adverse events by grade (CTCAE ver 5.0). In clinical practice, 4 or more hematological adverse events and 3 or more non-hematological adverse events are important. Therefore, authors should describe these data. Additionally, febrile neutropenia and esophagitis are important adverse events for patients received CRT, authors should add these data. Generally, it is impossible to evaluate safety of CRT without these data, too.

**Results. Page 4. Lines 20,21,22,23,24,25,26,29,30,31,32.**

3) In the section of discussion, authors only describe the list of literatures. Authors should deeply discuss about some questions selected based on precise results.

Discussion. Page 6.Lines 6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22.

#### Minor comments

1) Page 3 of 15, line 43-47, in the section "66 patients with locally advanced inoperable esophageal cancers treated at our center during the study period were retrospectively abstracted from the case records. All the patients had given informed consent during the study period and the study was approved by Cancer Institute Ethics Committee. 24(36%) patients received TC and 42(64%) received CDDP.", these sentences should be described in the results.

Results. Page 3.Lines 31,32,33,34,35.

2) Page 3 of 15, line 53: "The categorical variables were sex, location, histology, tumor status (T) and Node status (N).", authors should mention the classification (ex. UICC 8th).

Patients and Methods. Page 2.Line 27.

3) Page 3 of 15, line 57-Page 4 of 15, line 6. In the section "Chemotherapy regimen consisted of two major groups 1) Cisplatin regimen either 3 weekly CDDP 75mg/m<sup>2</sup> at days 1, 22 and 43 or weekly CDDP 40mg/m<sup>2</sup> at days 1, 8, 15, 22, 29 and 36 and 2) Paclitaxel(50mg/m<sup>2</sup>) and Carboplatin (AUC 2) at days 1,8,15,22,29 and 36. Although the standard protocol followed worldwide for Cisplatin regime is CDDP + 5FU, our institutional policy is to give single agent Cisplatin in definitive setting due to poor compliance of patients with CDDP/5FU regimen.", why does your hospital happen poor compliance of CF-RT? CF-RT is one of the standard treatments for inoperable EC patients all over the world.

Patients and Methods. Page 2. Lines 33,34,35,36,37.

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Patients and Methods. Page 2. Line 27.

Secondly, the standard protocol followed worldwide for Cisplatin regime is CDDP + 5FU, they gave single agent Cisplatin in definitive setting due to poor compliance of patients with CDDP/5FU regimen. This may make us confused whether this group belong to definitive concurrent chemoradiotherapy. They can use capecitabine instead of fluorouracil in this situation.

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Thirdly on the part of discussion, the side effects of the two groups were not discussed in detail. Only a few articles on concurrent chemoradiotherapy for esophageal cancer are listed.

Discussion. Page 6. Lines 6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22.

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2nd Editorial decision  
25-Jul-2021

Ref.: Ms. No. JCTRes-D-21-00046R1  
DEFINITIVE CHEMORADIATION IN LOCALLY ADVANCED INOPERABLE  
ESOPHAGEAL CANCER PATIENTS – RETROSPECTIVE ANALYSIS OF DIFFERENT  
CHEMOTHERAPY REGIMENS IN A TERTIARY CANCER CENTRE  
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 Aug 24, 2021.

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: The main aim of this analysis is to describe the outcomes of definitive chemo radiation with Paclitaxel and Carboplatin (TC) Vs Cisplatin (CDDP) with radiation. The conclusion is that chemoradiation with TC in esophageal carcinoma shows equivalent OS but with improved toxicity profile. The author's modification is acceptable. The article is worth publishing. But it is suggested that English should be improved.

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Authors' response

Ref.: Ms. No. JCTRes-D-21-00046R1

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Journal of Clinical and Translational Research

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**Patients and methods. Page 2 Lines 17,19,20,24,25,26**

**Page 3 Lines 5,6,7,8,20,21,22,23,24,25,26**

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3rd Editorial decision  
28-Jul-2021

Ref.: Ms. No. JCTRes-D-21-00046R2

**DEFINITIVE CHEMORADIATION IN LOCALLY ADVANCED INOPERABLE  
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Your revision is due by Aug 27, 2021.

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 your revision to JCTR.

Unfortunately, the linguistics are still not up to par. To give you several examples, in the abstract alone:

- inconsistent use of "chemoradiation" and "chemo radiation"
- why are Paclitaxel and Carboplatin and Vs and Cisplatin capitalized?
- Don't start a sentence with a number written in numbers, but use letters instead
- 66 patients with locally advanced inoperable esophageal cancers -> why is cancer plural? Should be singular
- 3 years. (p value=0.286). The median survival --> period after years, p value should be spelled p-value, there should be a space before and after equal sign



Please have a native speaker go through the text or reach out to the journal (m.heger@jctres.com) for assistance (paid service).

We cannot accept poorly written papers.

Thank you,

Michal Heger  
Editor

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Authors' response

Ref.: Ms. No. JCTRes-D-21-00046R1

DEFINITIVE CHEMORADIATION IN LOCALLY ADVANCED INOPERABLE  
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Yours sincerely,

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

**We are grateful for your commentary and suggestions, which we have addressed to the fullest extent as indicated below for your comments**

OK, but please make sure the referencing etc. are correct. The editor identified some additional issues that will have to be addressed.

"Hi Michal,

I looked at the manuscript and it covers an interesting topic, but the authors did not use correct referencing techniques nor sources in areas of the manuscript. Language alone is not the only issue."

Thanks!

Answer

Abstract	Page 1. Lines 1,2,3,5,7,9,13,14,17,18,19,21.
Background:	Page 1. Lines 22,23,25,26,27,28,29,30,29,30,1,32. Page 2. Lines 1,2,5,6,7,8,10,11,12.
Patients and Methods:	Page 2. Lines 13,15,18,19,20,21,22,23,25,26,28,29,31,32,33,34,35. Page 3. Lines 4,6,8,14,15,17,18,19,20,23,25,26,27,29,30,31,32.
Results:	Page 4. Lines 1,3,4,5,7,8,9,10,11,12,13,14,15,16,17,18,20,21,22,23, 25,28,30,31,32,33,34,35,36,37,38,39,40. Page 5. Line 1
Discussion:	Page 5. Lines 3,4,12,13,19,20,21,27,29,30,31,32,33,35,36 Page 6. Lines 1,2,3,4,5,6,7,10,11,13,15,17,19,20,21,22,23,26,27,28, 29,32,36,37,38,39.
Conclusion:	Page 7. Lines 1,2.
Conflicts of interest:	Page 7. Line 5.
References:	Page 7. Lines 6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24, 25,26,27,28,29,30,31,32. Page 8. Lines 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18.

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4<sup>th</sup> Editorial decision  
12-Aug-2021

Ref.: Ms. No. JCTRes-D-21-00046R3  
DEFINITIVE CHEMORADIATION IN LOCALLY ADVANCED INOPERABLE  
ESOPHAGEAL CANCER PATIENTS – RETROSPECTIVE ANALYSIS OF DIFFERENT  
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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 11, 2021.

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 Dr. Nagarajan,

Please correct the English as previously indicated.

Engage a native speaker, otherwise we will be going back and forth on this issue till one of us dies.

Thanks,

Michal Heger  
Editor

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Authors' response

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ESOPHAGEAL CANCER PATIENTS – RETROSPECTIVE ANALYSIS OF DIFFERENT  
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Journal of Clinical and Translational Research

Hello Aswin,

Thank you for the payment, it has been received in good order.

Please find attached the edited and proofread version of your paper; both a clean version and a version where the changes have been tracked.

Please address the comments to the best of your ability and then resubmit the manuscript WITH track changes via editorial manager so that I can accept it.

All my best,

Michal.

We are grateful for your commentary and suggestions, which we have addressed to the fullest extent as indicated below for your comments

Abstract: Page 1. Lines 12,16,17.  
Background: Page 2. Line 13.  
Chemotherapy regimen: Page 3. Lines 8,13  
Statistical analysis: Page 4. Lines 8,13  
Results: Page 4. Lines 22,25,30,31.  
Treatment outcomes: Page 5. Lines 13,14.  
Overall survival: Page 5. Lines 27,30.  
Page 6. Line 3.  
Toxicity: Page 6. Lines 6,7,8,9,11,13,14,15,16,17.  
References: Page 7. Reference -5.  
Table 1  
Table 2

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5<sup>th</sup> Editorial decision  
29-Sep-2021

Ref.: Ms. No. JCTRes-D-21-00046R4  
DEFINITIVE CHEMORADIATION IN LOCALLY ADVANCED INOPERABLE  
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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.

Thank you for submitting your work to JCTR.

Kindest regards,

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

Comments from the editors and reviewers: