Peer Review File

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Reviewer A

The paper titled "Multi-criteria optimization reduces small bowel high dose index of the intensity-modulated radiation therapy in cervical cancer patients - individualizing treatment options" is interesting. Dosimetric differences suggest that the I-IMRT plan using the MCO method provides better protection of other OARs and equivalently in PTV coverage, while lowering the high-dose index in the small bowel as much as possible for patients with cervical cancer. However, there are several minor issues that if addressed would significantly improve the manuscript.

Reply: Thanks for your important criticism and suggestions on our manuscript, and we are convinced that thanks to your patient guidance, professional questions, and kind help during the review process, our manuscript has gradually become scientific and complete.

What could be the predominant factor affecting the results of optimization in the MCO IMRT planning? It is recommended to add relevant content.

Reply 1: Thank you for the kind suggestion! we added the content about the predominant factor affecting the results of optimization in the MCO IMRT planning.

"This advanced tool within Eclipse facilitates the creation of Pareto surfaces, which graphically represent the ideal dose distribution, providing physicians and dosimetrists with invaluable real-time dosimetry parameters. One of the pivotal factors significantly influencing the outcomes of optimization in MCO IMRT plans lies in the selection of optimization objectives and the associated weightings. Physicians and dosimetrists play a crucial role in achieving optimal planning for their intended treatment objectives by meticulously adjusting the balance of these specific optimization goals. Consequently, MCO streamlines the process, bypassing time-consuming iterative calculations and assisting physicians and dosimetrists in achieving more favorable IMRT plans."

Thank you very much.

Changes in the text: please refer to Page 2, line 77-86 of the revised manuscript (highlighted version).

There have been many studies on IMRT and cervical cancer. What is the difference between this study and previous studies? What is the innovation? These need to be described in the introduction.

Reply 2: I'm sorry the previous writing was not clear. Thank you for the kind suggestion! In fact, this study aimed to assess the dosimetry diffenence in intensity-modulated radiation therapy (IMRT) plans with or without multi-criteria optimization (MCO) for cervical cancer patients. Specifically, we focus on the utilization of MCO to reduce the impact of high dose indices on the small bowel concerning other optimization objectives, thus providing a rapid approach to achieving individualized IMRT for cervical cancer patients. We had added the content. Thank you very much.

Changes in the text: please refer to Page 1, line 18-20 and Page 3, line 87-96 of the revised manuscript (highlighted version).

It is recommended to label the ABCD mark in Figure 4 in the upper left corner. This way, we can see more clearly.

Reply 3: Thank you for the kind suggestion! We had revised the label of Figure 4 for readers to see clearly. Thank you very much. Please check!

Changes in the text: please refer to Page 8, line 216-217 and Page 3 of the revised manuscript (highlighted version).

The abstract is not sufficient and needs further modification. The research background did not indicate the clinical needs of the research focus.

Reply 4: Thank you for the kind suggestion! We have modified our Abstract as advised.

this study aimed to assess the dosimetry diffenence in intensity-modulated radiation therapy (IMRT) plans with or without multi-criteria optimization (MCO) for cervical cancer patients. Specifically, we focus on the utilization of MCO to reduce the impact of high dose indices on the small bowel concerning other optimization objectives, thus providing a rapid approach to achieving individualized IMRT for cervical cancer patients. We had added the content.

Thank you very much. Please check!

Changes in the text: please refer to Page 1, line 18-20 and Page 1, line 40-41 of the revised manuscript (highlighted version).

What is the dose difference between the MCO plans navigated by physicians and dosimetrists? It is recommended to add relevant content.

Reply 5: I'm sorry I didn't clarify the roles of the physicians and dosimetrists in the MCO planning process. In fact, the physician usually provides clinical guidance and prioritizes clinical goals, while the dosimetrists are responsible for the technical aspects of plan optimization. The two work together to complete the radiotherapy plan. Thank you very much.

What are the biggest strengths and weaknesses of this method? What is the biggest problem faced? It is recommended to add relevant content.

Reply 6: Thank you for the kind suggestion! We have modified the content as advised in discussion. In this study, an analysis of dose differences between I-IMRT and W-IMRT reveals that the application of the MCO method in I-IMRT planning offers superior protection to adjacent OARs. This improvement is achieved while maintaining comparable PTV coverage. Furthermore, the MCO method effectively reduces the high-dose exposure to the small intestine in patients with cervical cancer. Notably, the MCO approach streamlines the planning process by eliminating time-consuming iterative calculations. Thus, it provides a swift and valuable tool for aiding physicians and dosimetrists in the creation of more advantageous IMRT treatment plans. However, this study also has some limitations. Firstly, the patient data for the study were collected retrospectively, with a lack of follow-up for overall survival. This implies a lack of clinical evidence for the association of lowering the small intestinal high dose index with translation into a significant reduction in toxicity in actual clinical practice. In the future, we will collect more case and prognostic information to obtain the correlation between dosimetric parameters and the toxicity of OARs. Secondly, as this is a retrospective study, planning efficiency metrics such as planning time were not evaluated in our study. In the future, we plan to collaborate more closely with clinicians to proactively gather parameters that capture planning efficiency and other relevant metrics. Finally, considering that the precision radiotherapy such as IMRT has inter-fraction and intra-fraction setup errors, respiratory motion, and uncertainties in bladder, rectal, and small bowel positions and filling degrees, the MCO method would be combined with adaptive radiotherapy to achieve more precise tumor treatment and minimize radiation damage to surrounding tissues in the future.Thank you very much. Please check!

Changes in the text: please refer to Page 10, line 289-308 of the revised manuscript (highlighted version).

The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "The incidence and risk factors of acute radiation-induced dermatitis in gynecologic malignancies treated with intensity- modulated radiation therapy, Transl Cancer Res, PMID: 35117217". It is recommended to quote the article.

Reply 7: Thank you for the kind suggestion! Based on your suggestion, we quote this article [Reference 4]. Thank you very much. Please check!

Changes in the text: please refer to Page 12, line 340-342 of the revised manuscript (highlighted version).

8) The number of patient samples in this study is too small, and a large sample study should be added for verification.

Reply 8: Thank you for the kind suggestion! I am sorry that the patient samples in this study are too small. In the future, we will collect more data and patient prognosis, in order to bring better clinical help. Thank you very much. Please check!

Reviewer B

First, the title needs to indicate the comparisons between W-IMRT and I-IMRT and the outcomes of interest in this study. The current title is unclear and inaccurate.

Reply 1: Thanks very much for the critical criticism. We have modified the title to "Advantages of IMRT optimization with MCO compared to IMRT optimization without MCO in reducing small bowel high dose index for cervical cancer patients - individualized treatment options." Please check.

Changes in the text: please refer to Page 1, line 1-3 of the revised manuscript (highlighted version).

Second, the abstract needs some revisions. The purpose did not briefly describe the potential clinical significance of this research focus and what the knowledge gap is. In the methods, the authors need to describe the inclusion of subjects and how these outcomes were measured. The results need to briefly summarize the clinical characteristics of the study sample and report the accurate P values for the comparisons. The conclusion needs comments for the clinical implications of the findings.

Reply 2: Thanks very much for the critical criticism. we have modified our abstract as advised. Please check. This study aimed to assess the dosimetry diffenence in intensity-modulated radiation therapy (IMRT) plans with or without multi-criteria optimization (MCO) for cervical cancer patients. Specifically, we focus on the utilization of MCO to reduce the impact of high dose indices on the small bowel concerning other optimization objectives, thus providing a rapid approach to achieving individualized IMRT for cervical cancer patients. In the methods, We added the inclusion of subjects and also added this section to the patient cohort section of the text Methods and Materials "The patient inclusion criteria were as follows: (1) histopathological confirmation of cervical cancer, (2) underwent IMRT radiation therapy, and (3) a prescribed dose of 180 cGy/28 fractions for the patient."(page 3, line 106-109). At the same time, the accurate P values are added to the result description. The summary "thus providing a rapid approach to achieving individualized IMRT for cervical cancer patients" was added to the conclusions. Thank you very much. Please check!

Changes in the text: please refer to Page 1, line 18-20, 22-24, 33, 36, 37 and 40 of the revised manuscript (highlighted version).

Third, in the introduction of the main text, the authors need to analyze why there is a need to examine the differences between W-IMRT and I-IMRT because the current conclusion should be expected. Please further clarify the clinical questions to be answered in this study and clearly indicate the potential clinical contribution of this study. My further concern is the prognosis between the two groups, which is more important than the current outcomes of this study but the authors did not test this.

Reply 3: Thanks very much for the critical criticism. we have modified our introduction as advised. “there is a notable gap in existing research when it comes to the utilization of the Eclipse MCO project within the context of participation in IMRT planning for cervical cancer radiation therapy. Specifically, there has been limited exploration of the dosimetric effects on adjacent normal tissues and organs when implementing MCO to mitigate high-dose exposure to the small bowel. Therefore, the primary objective of this study is to identify and analyze the dosimetric changes in the treatment target volume and the surrounding organs at risk (OARs) after reducing high-dose exposure to the small bowel through the application of the Eclipse MCO program. This research has the potential to enhance the efficiency of treatment planning and prognosis for cervical cancer radiation therapy, thereby contributing to the overall improvement in the quality of life for patients undergoing such treatment.” Thank you very much. Please check.

I'm sorry that we haven't collected the patient's prognostic data yet. Thank you for your suggestion. We will continue to collect more data in the future to make better discoveries.

Changes in the text: please refer to Page 3, line 87-96 of the revised manuscript (highlighted version).

Fourth, in the methodology of the main text, please describe the research design and sample size estimation procedures. In statistics, please provide the correct threshold P value for statistical significance and indicate whether it is two-sided. Please explain why P<0.01 as statistical significance level. Please describe the test of the normality of the outcome variables.

Reply 4: Thank you very much for your suggestion, we have added the research design and sample size estimation procedures in the methodology "The present study compared the dose parameters of target areas and OARs in IMRT planning with and without MCO. The outcome measures included dose parameters of target areas and OARs, which belonged to a comparison of means between two sample groups. Based on previous research, comparative studies of planning typically require a minimum of 20 study subjects. This study was conducted retrospectively at the Affiliated Cancer Hospital of Shandong First Medical University and recruited 25 patients with cervical cancer who had previously received radiotherapy using the IMRT technique between January 2021 and May 2022." Please check.

About the threshold P value for statistical significance whether it is two-sided, we have made changes "P<0.05 (2-tailed)". I'm sorry we made a mistake. In statistical analysis, we found that there was no P value between 0.01-0.05. We blindly chose the value of 0.01. We have corrected it to "Differences were considered statistically significant when P < 0.05 (2-tailed) ", please check.

About the test of the normality of the outcome variables, according to our previous research and other similar planned comparison studies, most of the dosimetric parameters do not conform to the normal distribution, so most of these studies directly choose the Wilcoxon-signed rank tests when choosing the statistical analysis method. Thank you very much for your understanding. Such as these articles as follow:

1.Sun T, Lin X, Zhang G, Qiu Q, Li C, Yin Y. Treatment planning comparison of volumetric modulated arc therapy with the trilogy and the Halcyon for bilateral breast cancer. Radiat Oncol. 2021;16(1):35. Published 2021 Feb 18. doi:10.1186/s13014-021-01763-z

2.Da Silva Mendes V, Nierer L, Li M, et al. Dosimetric comparison of MR-linac-based IMRT and conventional VMAT treatment plans for prostate cancer. Radiat Oncol. 2021;16(1):133. Published 2021 Jul 21. doi:10.1186/s13014-021-01858-7

3.Richter A, Wegener S, Breuer K, et al. Comparison of sliding window and field-in-field techniques for tangential whole breast irradiation using the Halcyon and Synergy Agility

systems. Radiat Oncol. 2021;16(1):213. Published 2021 Nov 6.

doi:10.1186/s13014-021-01942-y

Thank you very much.

Changes in the text: please refer to Page 3, line 100-103 and Page 5, line 160 of the revised manuscript (highlighted version).

Finally, please consider to review and cite some related papers:

1. Malikova H, Burghardtova M, Fejfarova K, Nadova K, Weichet J. Advanced cervical cancer in young women: imaging study of late and very late radiation-related side effects after successful treatment by combined radiotherapy. Quant Imaging Med Surg 2021;11(1):21-31. doi: 10.21037/qims-20-553.

2. Wu Y, Chong Y, Han C, Kang K, Liu Z, Zhang F. Second primary malignancies associated with radiation therapy in cervical cancer patients diagnosed between 1975 and 2011: a population-based competing-risk study. Ann Transl Med 2021;9(17):1375. doi: 10.21037/atm-21-1393.

3. Wang Y, Zhang L, Liu W, Yang JP, Peng HJ, Zhang JW. Apatinib enhances the antitumor effects of radiation in HeLa cell line mouse model of invasive cervical cancer. Ann Transl Med 2022;10(8):459. doi: 10.21037/atm-22-1442.

4. Wang Z, Ren X, Liu Z, Li Y, Wang T. Multimodality treatment for multiple recurrences of cervical cancer after radiotherapy: a case report. Transl Cancer Res 2022;11(4):943-951. doi: 10.21037/tcr-21-2250.

Reply 5: Thanks very much for the suggestions. we quote the articles.

1. Malikova H, Burghardtova M, Fejfarova K, Nadova K, Weichet J. Advanced cervical cancer in young women: imaging study of late and very late radiation-related side effects after successful treatment by combined radiotherapy. Quant Imaging Med Surg 2021;11(1):21-31. doi: 10.21037/qims-20-553. → **[Reference 1]**

2. Wu Y, Chong Y, Han C, Kang K, Liu Z, Zhang F. Second primary malignancies associated with radiation therapy in cervical cancer patients diagnosed between 1975 and 2011: a population-based competing-risk study. Ann Transl Med 2021;9(17):1375. doi: 10.21037/atm-21-1393. → **[Reference 3]**

3. Wang Y, Zhang L, Liu W, Yang JP, Peng HJ, Zhang JW. Apatinib enhances the antitumor effects of radiation in HeLa cell line mouse model of invasive cervical cancer. Ann Transl Med 2022;10(8):459. doi: 10.21037/atm-22-1442. → **[Reference 6]**

4. Wang Z, Ren X, Liu Z, Li Y, Wang T. Multimodality treatment for multiple recurrences of cervical cancer after radiotherapy: a case report. Transl Cancer Res 2022;11(4):943-951. doi: 10.21037/tcr-21-2250. → **[Reference 7]**

Thank you very much. Please check!

Changes in the text: please refer to Page 11-12, line 332-334, 337-339 and 345-349 of the revised manuscript (highlighted version).