

Dear Reviewers:

Thank you for the time and effort you have spent reviewing our paper. We are pleased to note that you have found our research interesting and pointed out some problems to help us improve the quality of our work. We have carefully evaluated the critical comments and thoughtful suggestions, responded to these suggestions point-by-point, and revised the manuscript accordingly. With regard to the reviewers' comments and suggestions, we wish to reply as follows:

**Reviewer 1**

**Major Comment 1:** P2, lines 19-20 and P6, lines 16-18. "11% (7/61 patients) had irreversible adverse reactions", In Table 1, the number of yes for radiation toxicities is 4. Is this discordance correct?

**Reply:** Thank you for underlining this deficiency. It was our mistake that caused the error in the Abstract. Thirty-eight percent (23/61 patients) had no radiation toxicity after radiotherapy, 56% (34/61 patients) experienced radiation toxicity that resolved after treatment, and 6% (4/61 patients) had irreversible adverse reactions. The corresponding results have been corrected in the Abstract (P3, lines 27-29 and P9, lines 8-10).

**Major Comment 2:** P2, line 25 and discussion. "O-ring Halcyon Linac could achieve a better therapeutic effect on the target volume". They should describe the comparison of the efficacy of Halcyon with that of conventional delivery system in discussion.

**Reply:** Thank you for your suggestion. In our study, four patients were evaluated as having progressive disease (PD) due to distant metastasis, but no increase in the irradiated target tumour volume was observed when separately evaluating the local response. This finding demonstrated the effectiveness of Halcyon for the local control of cancer. In the previous literature, there have been few evaluations of the efficacy of a specific machine in the field of radiotherapy. Early disease-control outcomes in patients treated with Halcyon were comparable to published reports with no recurrences in the radiation field, although with a relatively short median follow-up<sup>1,2</sup>. Gupta<sup>3</sup> found 13.56% local (with or without distant metastasis) first recurrence in neoadjuvant chemotherapy followed by concomitant chemoradiation for cervical cancer. The small cohort of cervical cancer patients in our abdomen group all showed complete response, demonstrating a good start to long-term

survival. We have added this part in Discussion (P11, lines 4-15).

**Major Comment 3:** P4, lines 2-3 and Table 1. The concurrent therapy should be indicated in table 1.

**Reply:** We are grateful for the suggestion. We have added this part in Table 1.

**Minor Comment 1:** P8, line 22. Does a word of “irritated” mean “irradiated”?

**Reply:** Thank you for underlining this deficiency. There was a spelling mistake and the word “irritated” was actually “irradiated”. We have completed the replacement in manuscript (P10, lines 29).

**Minor Comment 2:** P9, line 42. “organs at risk” is after 2nd appearance and should be “OARs”.

**Reply:** We have completed the correction of “OARs” (P13, lines 5).

## **Reviewer 2:**

**Major Comment 1:** The conclusion & discussion: “O-ring Halcyon Linac could achieve a better therapeutic effect” should be based on a comparison with the therapeutic effect of other systems, however, the clinical outcomes of other systems were not provided in this study, other than mechanical/dosimetric comparison in literature review.

**Reply:** Thank you for your suggestion. In our study, four patients were evaluated as having progressive disease (PD) due to distant metastasis, but no increase in the irradiated target tumour volume was observed when separately evaluating the local response. This finding demonstrated the effectiveness of Halcyon for the local control of cancer. In the previous literature, there have been few evaluations of the efficacy of a specific machine in the field of radiotherapy. Early disease-control outcomes in patients treated with Halcyon were comparable to published reports with no recurrences in the radiation field, although with a relatively short median follow-up<sup>1,2</sup>. Gupta<sup>3</sup> found 13.56% local (with or without distant metastasis) first recurrence in neoadjuvant chemotherapy followed by concomitant chemoradiation for cervical cancer. The small cohort of cervical cancer patients in our abdomen group all showed complete response, demonstrating a good start to long-term survival. We have added this part in Discussion (P11, lines 4-15).

**Major Comment 2:** The version of Halcyon system should be described. Accordingly,

please also specify the modulation resolution of MLC, and image guidance modality used for the patients involved, which may influence the patient outcomes.

**Reply:** We are grateful for the suggestion. Halcyon version 2.0 was implemented in our institution. The modulation resolution of MLC is 0.5 cm and the image guidance modality is fast kilovoltage cone beam CT (kV-CBCT) guidance. We have added these parts in the manuscript (P5, lines 12 and P6, lines 1-2).

**Major Comment 3:** Why dose Halcyon have “potential radiobiology advantages” since it is still based on X-ray?

**Reply:** Thank you for your comment. The decrease of biologic effect if delivery of dose fractions takes more than a few minutes has been recognized in the literature. Fowler et al<sup>4</sup> used linear-quadratic (LQ) model to study the extension of fractionated irradiation time and the equivalent biological dose of interval irradiation in intensity modulated radiotherapy (IMRT). The results showed that the effect on cell killing was significantly reduced and the biological effect was reduced if the delivery of 1 fraction irradiation time exceeded more than half an hour. Wang et al<sup>5</sup> indicated that fraction delivery times in the range of 15-45 min may significantly decrease cell killing, and the prolongation of fractionated irradiation time will significantly affect the therapeutic effect of IMRT. The ultra-high dose rate radiotherapy (FLASH-RT), with a dose rate  $\geq 40$  Gy/s and a treatment time less than 1 s, can effectively control the tumour and further reduce the toxicity to normal tissues as compared with conventional dose rate radiotherapy<sup>6</sup>. Overall, these studies demonstrate that shortening the duration of delivery of dose fractions has high radiobiology advantages. The Halcyon system has a series of breakthrough innovations, such as two times faster leaf speed (5 cm/s), four times faster collimator rotation (2.5 RPM), and four times faster gantry speed (4 RPM), and compulsive image guide, which effectively reduce treatment time. In addition, shorter treatment time means less organs movement, which can achieve more accurate coverage of dose to target volumes and better protection of OARs. So, Halcyon have “potential radiobiology advantages”.

**Major Comment 4:** Method session, please specify what ‘feelings’ about the operating the equipment were recorded, and how they were quantified objectively. The corresponding results were missing.

**Reply:** Thank you for underlining this deficiency. The Halcyon system supports automatic couch shifting to replace manual isocentre shifting and faster image-guided procedures, which shortening the duration of delivery of dose fractions. We designed questionnaire on how the therapist felt about operating the equipment in our institution, the results showed that the Halcyon platform has the advantages of a relatively simplified operation process, easy operation, high work efficiency, and faster treatment speed. However, considering the manuscript word limit and the fact that this part had little to do with the topic of study (mainly related to effects of radiotherapy, irradiation toxicity and quality assurance), we have deleted this part and revised it in the manuscript.

**Major Comment 5:** Table3, the std and range of portal dosimetry results for chest and abdomen were missing. In addition, why is the passing rate for chest only 89.7%, which is not clinically acceptable?

**Reply:** Thank you for your suggestions. In chest and abdomen groups, the case number of portal dosimetry verification we performed for each group is one, and the results showed 89.7% and 96%. So, the std and range of portal dosimetry results for chest and abdomen only have one set of data.

TG 218<sup>7</sup> suggested universal action limits: the  $\gamma$  passing rate should be  $\geq 90\%$ , with 3%/2 mm and a 10% dose threshold. In our institution, we adopted stricter standards. For portal dosimetry, gamma evaluation criteria of 2%/2 mm with a 10% dose threshold were used. We set it at 10% during initial machine acceptance testing and commissioning data validation. The passing rate for chest was only 89.7%, which did not meet the low dose threshold and was therefore clinically unacceptable.

**Major Comment 6:** The lower ranges of spine and total were also very low (both 88.6%) for portal dosimetry, but the corresponding Arccheck results were much higher (93.6% and 93.8%) under the same criteria of 2%/2mm? Please double check the data, or put the explanations in the discussion session.

**Reply:** Thank you for your comment. Dosimetric verification of Halcyon plans was performed using quality assurance procedures such as portal dosimetry, Arccheck and point dose measurements to verify the system delivery accuracy. But each plan may not be performed all three quality assurance procedures. For instance, one plan in spinal group only

had been performed PD verification (the results showed 88.6%), and the other two verifications were not performed. Therefore, the results proposed by the reviewer did not come from the one plan.

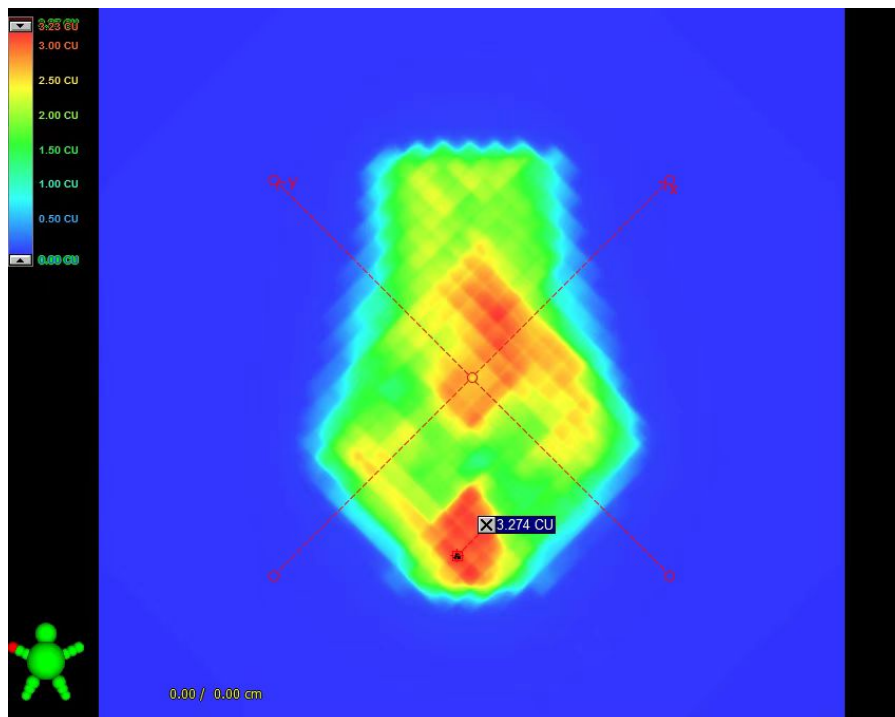
**Minor Comment 1:** The average gamma passing rates with a 2% dose difference and 2 mm distance-to-agreement for IMRT/VMAT/SRT plans were Arccheck 96.4(%) and portal dosimetry 96.7(%). Please also complement units throughout the manuscript when applicable.

**Reply:** Thank you for your comment. We have complemented units in the manuscript (P4, lines 2-3).

**Minor Comment 2:** please use the same scale (3.27 CU or 3.23 CU) for the two subfigures. Anatomic site should be described for the figure.

**Reply:** We are grateful for the suggestion. However, if we set the scale to 3.23CU, the part over 3.23CU in subfigure will appear as black dots, as shown in the following Figure 1. The scale for one subfigure cannot set to 3.27CU, because its upper limit is 3.23CU. In addition, the scale of the two subfigures had little difference, which can make a certain comparison. Therefore, we decided to use primary Figure.

We have added the anatomic site information in the Figure.



**Figure 1** The part as 3.274CU in one subfigure appeared as black dots.

## REFERENCES

1. Chopra S, Gupta S, Kannan S, et al. Late Toxicity After Adjuvant Conventional Radiation Versus Image-Guided Intensity-Modulated Radiotherapy for Cervical Cancer (PARCER): A Randomized Controlled Trial. *J Clin Oncol*. 2021;39(33):3682-3692.
2. de Boer SM, Powell ME, Mileskin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. *The Lancet Oncology*. 2019;20(9):1273-1285.
3. Gupta S, Maheshwari A, Parab P, et al. Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial. *J Clin Oncol*. 2018;36(16):1548-1555.
4. Fowler JF, Welsh JS, Howard SP. Loss of biological effect in prolonged fraction delivery. *Int J Radiat Oncol Biol Phys*. 2004;59(1):242-249.
5. Wang JZ, Li XA, D'Souza WD, Stewart RD. Impact of prolonged fraction delivery times on tumor control: a note of caution for intensity-modulated radiation therapy (IMRT). *Int J Radiat Oncol Biol Phys*. 2003;57(2):543-552.
6. Buchsbaum JC, Coleman CN, Espey MG, et al. FLASH Radiation Therapy: New Technology Plus Biology Required. *Int J Radiat Oncol Biol Phys*. 2021;110(4):1248-1249.
7. Miften M, Olch A, Mihailidis D, et al. Tolerance limits and methodologies for IMRT measurement-based verification QA: Recommendations of AAPM Task Group No. 218. *Medical physics*. 2018;45(4):e53-e83.