Peer Review File

Article information: http://dx.doi.org/10.21037/tcr-20-1196

Comment: First, this manuscript is lacking of novelty that make it different from the other published studies (listed in the attachment). The feasibility of using DIR dose composite of EBRT and ICBT has been published in many manuscripts.

Then, the conclusion is conflicting with the results. It recommended DIR dose composite while it showed no significance in all DVH parameters between DIR and straight addition. Then what is the motivation of using DIR dose composite if it gives similar results but may suffer from higher fusion uncertainty and more human labor compare to "simple straight addition"?

Reply: The accurate evaluation of cumulative dose distributions at the targets in the combined EBRT and ICBT is still a challenge for clinicians, specifically for patients with uncontrolled or recurrent tumors who require secondary radiotherapy. In this study, we focused on the evaluation of cumulative dose distributions on targets and DVHs in combined radiotherapy for cervical cancer using DIR in clinical practice. Although it showed no significance in all DVH parameters between DIR and straight addition, DIR-based dose accumulation was significantly helpful to visually show the cumulative dose distribution in the target area to clinicians in combined radiotherapy for cervical cancer in routine clinical settings. Therefore, we recommended DIR dose composite.

Changes in the text: we have modified our text as advised (see Page 4, line64-67; Page 5, line90-92; Page 14, line293-296) with yellow color

Attachment:

Comment 1: Page 2, line 50: The unit “GyEQD2” is not very informative and commonly used. A better way of presenting could be “Gyα/β=10” as presented in Figure 3.

Reply: we have modified our text as advised (see Page 3, line46, 47)

Changes in the text: Page 3, line46, 47 with yellow color

Comment 2: Page 4, para 1. This manuscript is about using DIR for EBRT and ICBT. First, a literature review on the application of DIR in dose composite should be discussed in the background. Then, there are published studies about using DIR in EBRT and ICBT dose composite (listed below). Those references should be cited and the novelty of this study needs to be highlighted. In other words, what are the key points of this manuscript that make it different from the other published studies.

[1] E. Flower et al. Deformable image registration for cervical cancer brachytherapy dose accumulation: Organ at risk dose–volume histogram parameter reproducibility and anatomic position stability. Brachytherapy. 2015

[2] SV. Jamema et al. Uncertainties of deformable image registration for dose accumulation of high-dose regions in bladder and rectum in locally advanced cervical cancer. Brachytherapy. 2015

[3] E. Flower et al. Deformable Image Registration (DIR) for Cervical Cancer Brachytherapy: A Comparison of the Reproducibility of Three Different Methods and the Effects of DIR on the Anatomical Stability of OAR DVH Parameters. Brachytherapy. 2016

[4] Heerden et al. Potential Added Value of Structure-Based Deformable Image Registration for Dose Accumulation in External Beam Radiotherapy and Brachytherapy in Cervical Cancer. Brachytherapy. 2016

[5] Z. Xu et al. Appropriate Methodology for EBRT and HDR Intracavitary/Interstitial Brachytherapy Dose Composite and Clinical Plan Evaluation for Patients with Cervical Cancer. Practical Radiation Oncology. 2019

Reply: In this study, we focused on the evaluation of cumulative dose distributions on targets and DVHs in combined radiotherapy for cervical cancer using a commercially available DIR algorithm (MIM Maestro®) (9) in clinical practice. We have modified our text as advised (see Page 4, 5 line77-92).

Changes in the text: Page 4, 5 line77-92 with yellow color

Comment 3: Page 4, line 87: Is it 50.4Gy to the whole pelvis or it is SIB with 45Gy to the whole pelvis and 50.4Gy to the parametrium, please specify.

Reply: It is 50.4Gy to the whole pelvis including the parametrium in our center (see Page 5, line 98, 99)

Changes in the text: Page 5, line98, 99 with yellow color

Comment 4: Page 4, line 91: It is better to mention the after loader unit instead of just saying Ir192 source so that the readers can have better picture of the source (i.e. mechanical design, source dimensions)

Reply: we have modified our text as advised (see Page 6, line109,110)

Changes in the text: Page 6, line109,110 with yellow color

Comment 5. Page 4, line 103: Please refer the guideline for OAR dose constraints (ABS or EMBRACE II?). What about the constraints for bladder, sigmoid, and bowel, were they following any constraints?

Reply: The dose prescriptions and target coverages were modified based on the dose constraints for D2cc of 90 $Gy_{\alpha/\beta=3}$ to the bladder and 70 $Gy_{\alpha/\beta=3}$ to the rectum according to Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology (GEC-ESTRO) recommendations. (see Page 6, line114-118)

Changes in the text: Page 6, line114-118 with yellow color

Comment 6: Page4, line 109: the title is not appropriate for the description below. It has nothing to do with DIR imaging. It is better to use "CT for Treatment Planning" or "CT simulation"

Reply: we have modified our text as advised "Computed tomography simulation"(see Page 7, line122)

Changes in the text: Page 7, line122 with yellow color

Comment 7: Page6, line 129: remove "(6)"

Reply: we have modified our text as advised (see Page 7, line141)

Changes in the text: Page 7, line141

Comment 8: Page6, line 135: please explain more on the DIR. It looks like the DIR quality was visually verified. Were there any artifacts (gas or metal artefacts) that affected the registration?

Reply: Patients were required to defecate before being treated to avoid gas artifacts. Rectal dilatation was confirmed by treatment planning CT of EBRT and ICBT. If gas is found in the rectum during ICBT, gas drainage is performed to reduce rectal expansion. Subsequently, CT is performed again. (see Page 8, line150-153).

Changes in the text: Page 8, line150-153 with yellow color

Comment 9: Page 7, line 139: EMBRACE II has constraints on D90 and D98 which are more relevant to local control. Please refer to the reference below:

The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies.

Reply: we have modified our text as advised (see Page 8, line161-162)

Changes in the text: Page 8, line161-162 with yellow color

Comment 10: Page 7, line 139: please explain how the "simple straight addition" was performed. There are two potential ways: (1) rigid image registration based straight addition where there will be one final D90; (2) straight parameter addition of D90 from each fraction of ICBT and EBRT without image registration. This is based on the worst-case scenario that all hot spots are overlapping.

Reply: We used the first way: rigid image registration based straight addition where there will be one final D90. (see Page 8, line162-164)

Changes in the text: Page 8, line162-164 with yellow color

Comment 11: Page 8, line 167: better to present the results in Mean+SD instead of median

Reply: we have modified our text as advised (see Page 9, line185)

Changes in the text: Page 9, line185 with yellow color

Comment 12: Page 8, line 171: No significant difference was found between two methods, does that mean DIR based dose composite did not offer better estimation on Target DVH compared to straight addition? The purpose of this study needs to be

clarified.

Reply: The purpose of this study is to verify the accuracy of cumulative dose distributions at the targets in the combined EBRT and ICBT which is still a challenge for clinicians, especially for patients with uncontrolled or recurrent tumors who need secondary radiotherapy. Although it showed no significance in all DVH parameters between DIR and straight addition, DIR-based dose accumulation was significantly helpful to visually show the cumulative dose distribution in the target area to clinicians in combined radiotherapy for cervical cancer in routine clinical settings. Therefore, we recommended the DIR dose composite.

(see Page 4, line64-67; Page 5, line90-92; Page 14, line293-296)

Changes in the text: Page 4, line64-67; Page 5, line90-92; Page 14, line293-296 with yellow color

Comment 13: Page 8, line 174: Not sure it is true that DIR is routine for clinical application. The quality of DIR is dependent of image quality, user skills and software algorithm. Several centers use Excel sheet based EQD2 dose composite recommended by ABS. https://www.americanbrachytherapy.org/resources/for-professionals/physics-corner/

Reply: we have modified our text as advised: DIR is now accepted as a plan evaluation tool for clinical purposes at several radiation oncology centers not only for automatic contouring but also for diagnostic image registration and dose accumulation. The quality of DIR is dependent on image quality, user skills, and software algorithm. Several centers also use an Excel sheet-based EQD2 dose composite recommended by the American Brachytherapy Society. In these applications, these registrations must be characterized in phantom studies and also checked on a per-patient basis around regions in which deformable registration guided the clinical decisions (12). (see Page 10, line194-201)

Changes in the text: Page 10, line194-201 with yellow color

Comment 14: Page 9, line 200. Since miscalculation can be 4%-6% per mm, would 5mm CT slice thickness used in this study resulted in high calculation and fusion uncertainty?

Reply: 5mm CT slice thickness used in our study could result in high calculation and

fusion uncertainty which is the main limitation of our study. (see Page 14, line 283,284)

Changes in the text: Page14, line 283,284 with yellow color

Comment 15: Page 12, line 263. Why do you think this is the limitation of this study? Under coverage was due to OAR dose sparing and this was a clinical judgement. This study is about DIR dose composite.

Reply: we have deleted this part as advised.

Changes in the text: we have deleted this part as advised.