Author's response to reviews

Title: CT based three dimensional dose-volume evaluations for high-dose rate intracavitary brachytherapy for cervical cancer

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Author's response to reviews: see over
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Prof. Dafne Solera, M.D.
----- Executive Editor, BMC Cancer
Middlesex House 34-42 Cleveland Street
London, London W1T 4LB
United Kingdom

Dear Professor Solera

Thank you for taking our article into possible future publication for your journal. Please find revised version of our article and attached replies for reviewer’s comment. We hope you accept our revised version of our manuscript.

Sincerely yours,

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Reviewer’s Report

Major comments

Title pages: OK
Title name: OK
Abstract:
The number of applications (2-5 times) did not present in materials and methods.

Number of brachytherapy application is provided in ‘Methods’ in the abstract. … combined with 2-5 times of 6 Gy HDR-ICBT…..

Introduction: OK
Materials and Methods: adequate. However, the author didn’t explain some points to make this manuscript better.

For Concurrent chemotherapy, author should describe the cut-off level of “insufficient renal function” for clear definition.

According to reviewer’s comment, authors specified detailed criteria of renal function in the paragraph of ‘Treatment’.

In radio-therapeutic schedule, the author should describe the technique of EBRT whether that is conventional or 3D conformal whole pelvic irradiation. If the author used 3D-conformal RT with CT-based planning, the authors should add the technique of CT and target contouring into the manuscript. Moreover, the energy of machine should be defined too.

According to reviewer’s comment, authors described the technique of EBRT, CT protocol, and target contouring in the paragraph of ‘Radiotherapy’.

The size of central shielding should be reported into the text. If possible, how many patients who started central shielding after 20, 30 or 40 Gy? And which
criteria did the authors use for making decision of central shielding beginning? Who is suitable for 20, 30 or 40Gy?

According to reviewer´s comment, authors added the description about the size of central shielding and when to initiate CS in the paragraph of `Radiotherapy`.

For CT during ICBT, author should describe the technique of CT if possible (slice thickness and so on).

According to reviewer´s comment, authors added the description about the protocol of CT during ICBT in the paragraph of `Radiotherapy`.

For tandem/ovoid applicator, did author use ovoid with shielding or without shielding?

According to reviewer´s comment, shielding of the applicator was specified in the paragraph of `Radiotherapy`.

How the authors used bladder or rectal preparations? How much fluid did author fill into the bladder before CT?

According to reviewer´s comment, authors added the description about the preparation of bladder and rectum in the paragraph of `Radiotherapy`.

If possible, is it in-loading room CT or others? If other CT, the process of fixation and transportation is important, the author should describe this point.

According to reviewer´s comment, authors added the description about CT simulator situated used for brachytherapy in the paragraph of `Radiotherapy`. 
The author should explain more in cumulative dose calculations in EQD2. Does the cumulative dose in EQD2 in the authors’ manuscript mean the EQD2 of EBRT before Central shielding plus the EQD2 of ICBT?

According to reviewer’s comment, authors added the description about the calculation of EQD$_2$ in the paragraph of ‘Radiotherapy’.

**Results:** The data is in good quality. The statistics that the author used are very well. There are some points that authors should explain.

In case of sigmoid perforation, do authors use CT based plan for EBRT? (According to material and methods). If CT-based plan for EBRT was used, the author can identify the position of sigmoid that perforated situated outside or inside the central shielding. So this may effect to the dose calculation of sigmoid in EQD2 concepts and reveal that why patient has complication when the author concerned the maximal point of sigmoid.

Authors reviewed the CT image taken before colostomy, however it was difficult to detect the point of perforation nor to tell whether perforated point was within or outside of central shield.

**In table 1,** did ‘stage IV’ equal ‘stage IVA’ by FIGO?

According to reviewer’s comment, authors corrected the word in table 1.

**In table 2,** maximal diameters are Antero-posterior or right-left diameters?

Because maximum diameters were accessed by CT or MRI, it could be antero-posterior, cranio-caudal, or right-left. Therefore authors simply used the term ‘maximal diameter’.
Total treatment time should be reported in days, if possible.

According to reviewer’s comment, authors corrected the total treatment time in days.

How many patients received cisplatin plus s1 in authors’ study?

According to reviewer’s comment, authors added the description about the number of patients who received cisplatin plus S-1 in the section of ‘Results’.

How about treatment results in stage IV group (7 patients) or each group.

According to reviewer’s comment, authors added treatment results of stage IVA patients and each group divided by HR-CTV $D_{90}$ 60 Gy separately in the section of ‘Results’.

From 8/51 patients (15.7%) with recurrence or persistence after treatment, how many are in FIGO I/II/III/IVA?

According to reviewer’s comment, authors specified the number of patients who had disease recurrence or persistence according to FIGO stage in the section of ‘Results’.

How about the mean EQD2 in each stage group?

According to reviewer’s comment, authors specified the median EQD2 in each stage group in the section of ‘Results’.

OS, PFS and LCR should be Overall survival, Progression-free survival and local control rates.
According to reviewer’s comment, authors converted OS, PFS, and LCR into Overall survival, Progression-free survival and local control rates.

**How many patients who received the D90 ≤ 60Gy and >60Gy in this study. It is very important to evaluate the statistics. Moreover, the volume of HR-CTV at first application should be reported separately between D90 ≤ 60Gy and >60Gy (should be bigger in the group of <60Gy). It can help the author to predict the using of ISBT and discuss in the discussion. These should be added into the manuscript body.

According to reviewer’s comment, authors provided the number and volume of HR-CTV at the first application in each group in the section of ‘Results’.

**Figure** qualities are Ok,

The point of the length between uterine cavity and the upper margin of HR-CTV is very interesting. If possible, the author should present some images to show about measurement.

According to Viswanathan’s contouring guidelines [23], the upper margin of HR-CTV was set at the top of uterine cervix (level at which uterine vessels first abut cervical tissue or to point at which uterine cavity appears). Therefore authors considered that additional saggital image which showed uterine cavity and the upper margin of HR-CTV would not be so attractive as the reviewer intended and decided not to create additional figure.

**Discussion and Conclusions:** On the discussion, the authors work very well.

However the limitation did not correlate in conclusion. In conclusion, the sentence ‘Further improvement could be expected for cervical cancer with
insufficient response to EBRT by using IGBT’ was not supported by the discussion. The authors should add more details if possible.

According to reviewer’s comment, authors described about the inferior clinical results of patients with HR-CTV $D_{90} < 60$ Gy in the section of ‘Discussion’ and pointed out the necessity of future improvement for this population by using ISBT in the section of ‘Conclusion’.

If possible, the author should discuss more in future theme in their institute. From this study, the authors evaluated the dose of HR-CTV in the cases that were treated by point A. The authors can give more details that the authors will move to use HR-CTV as volume-base approach or stay at point-based treatment. Or In the future, if the authors find in some cases that the D90 of HR-CTV is not correlate to point A, the authors will optimize or not? These should be explain in discussion part.

According to reviewer’s comment, authors described about a future direction of IGBT in the section of ‘Discussion’.

The limitations are quite well. However, the discussion about how to solve limitation does not clear. If the author could not approach MRI at brachytherapy, how do the authors improve quality of treatment? This should be added more, if possible.

According to reviewer’s comment, authors described about a realistic future direction of IGBT in most institutions without having an access of MRI at the time of brachytherapy in the section of ‘Discussion’.

The acknowledgement and conflict of interests: OK

Minor revision
In the last sentences of introduction “in this study, we analyses correlations between clinical outcome and dose of HR-CTV contoured based on CT images” the grammar should be checked??

According to reviewer’s comment, authors corrected the tense of the sentence.

In Methods, ‘therefore current study consists of 51 patients’, this should be in past tense ??

According to reviewer’s comment, authors corrected the tense of the sentence.

Only reviewer interests, did the standard Manchester applicator has shielding? How about the artifact in CT and how did the authors correct it?

According to reviewer’s comment, shielding of the applicator was specified in the paragraph of ‘Radiotherapy’ in the section of ‘Methods’.

Only reviewer interests, how about the upper limit of D90 of HR-CTV in Japanese schedule. According to GEC-ESTRO recommendations, they limit at 85-90 Gy. For the Japanese schedule, How should be limit the maximally cumulative dose to D90 of HR-CTV in EQD2 concepts.

According to reviewer’s comment, authors described about target dose for HR-CTV D90 in the section of ‘Discussion’.

Only reviewer interests, the authors reported the data of cumulative EQD2 to the HR-CTV in image-guided brachytherapy (IGBT) for cervical cancer with CT-based planning. They reported the D90% of HR-CTV >60Gy was significantly favorable that related to Japanese data of adequate dose to point A in EQD2 as publications of Toita et al. In comparison, the standard of treatment for cervical cancer in IGBT from GEC-ESTRO and ABS described around the
80-90Gy in cumulative EQD2 (moreover, the study from Vienna series recommended the dose at least 87Gy for D90 of HR-CTV in EQD2 concepts). When we look at both concepts from Japanese and GEC-ESTRO, the Japanese schedule yield much lower than GEC-ESTRO concepts. Interestingly, treatment results from publications from both sides were nearly the same. So the adequate cumulative dose to HR-CTV are controversies between the two schools. So this manuscripts reach the standard of their publications from Japan. The point of difference in both school is central shielding application which differ in size and the time of beginning (Japanese schedule use 3 or 4 cm central shielding and apply them after 20-40Gy but GEC-ESTRO rarely used central shielding. So central shielding may affect the dose calculation in EQD2 concepts. The author should (if possible) report the details of central shielding (size, when beginning and the correlation between point A and shielding. it will make this manuscript more interesting.

According to reviewer´s comment, authors added the description about the size of central shielding and when to initiate CS in the paragraph of “Radiotherapy” in the section of “Methods”.

If possible, the authors should detail about the workload with using CT-based brachytherapy in their institute. This will guide the readers to consider to perform IGBT in their institutions.

According to reviewer´s comment, authors added the description about the workload with using CT-based brachytherapy in the section of “Method” in the paragraph of “Radiotherapy”.

How about the mean EQD2 in each stage group?

According to reviewer’s comment, authors specified the median EQD2 in each stage group in the section of ‘Results’. 
Sincerely yours
Reviewer