Reviewer's report

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

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Reviewer: Ekkasit Tharavichitkul

Reviewer's report:

This manuscript report the cumulative dose for D90 HR-CTV in EQD2 concepts. The authors used CT-based during treatment by brachytherapy, prescribed dose to point A with treatment and evaluated the cumulative dose to HR-CTV/bladder/rectum/sigmoid later. The results showed favorable results in EQD2 >60Gy for D90 of HR-CTV. This is good quality manuscript. The research question of authors is very well. However, they need some revisions before publications as followings;

Major comments
Title pages: OK
Title name: OK

Abstract:
The number of applications (2-5times) did not present in materials and methods.
Introduction: no suggestion for this part appear

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.

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.

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

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

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

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

The author should explain more in cumulative dose calculations in EQD2. Does the cumulative dose in EQD2 in the authors’ manuscript means the EQD2 of EBRT before Central shielding plus the EQD2 of ICBT?

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.

In table 1, did ‘stage IV’ equal ‘stage IVA’ by FIGO?
In table 2, maximal diameters are Antero-posterior or right- left diameters?
Total treatment time should be reported in days, if possible.
How many patients received cisplatin plus s1 in authors’ study?
How about treatment results in stage IV group (7 patients) or each group.
From 8/51 patients (15.7%) with recurrence or persistence after treatment, How many are in FIGO I/II/III/IVA ?
OS, PFS and LCR should be 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.

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.

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.

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 explaind in discussion part.

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.

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??

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

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

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.

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. The 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 more 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 publicaitons 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 effect 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.

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.

How about the mean EQD2 in each stage group?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.