

Peer Review File

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Reviewer A

First, I understand the difficulty in finding and grouping cases in situations that are uncommon for early stages and less valued by researchers in general. The importance of this study with 27 cases is to give us experiences of alternatives on how to proceed in similar situations. That is why it is important to publicize it and I congratulate the authors' initiative.

Some points that I consider important in defining the results and not find, but could be partially solved by discriminating in Table 1 the 'Patients characteristics' by "Recurrence pattern" (study groups). In this way, it is possible to see other associations that could be influencing the results.

Comment 1: Residual disease: the definition needs to be clear. It seems to me that this is a residual disease not removed from surgery, to avoid further surgical morbidity. Part of it was thermally treated during surgery (L.123-124: "The residual tumor was electrically burned."). So 'Residual Disease' would be 'Possible residual disease' ? In Table 3 there are 4 cases in this situation.

We know that general knowledge in oncologic surgery guides us to avoid manipulating or sectioning tumors and to remove them entirely, with negative margins. On the other hand, salvage surgeries allow us to weigh advantages and disadvantages for a particular case and sometimes oncologic surgeries contaminate the operative field with tumor resection. For cervical carcinomas, there is no clear indication for debulking. Thus, I believe that the outcomes should also be cited according to the surgical margins involved or not, because the cases with compromised margins may have had a worse evolution, although it is possible that minimal residual disease or compromised margins can be controlled by adjuvant radiotherapy.

Reply 1: Thank you for the suggestion. Accurate definition of residual lesions is very important. During the operation, the unresectable tumors were electrically burned, but this did not guarantee that there were no residual tumors. In this situation, the margin was positive and should be defined as residual disease. The residual disease may also be a reason for the low PFS rate.

Changes in the text: We have defined residual tumor. See Page 6, Line 123-124.

Comment 2: How can you explain the OS of 65.7% for the pelvic-wall recurrence group, but with PFS=34.4%?

Reply 2: Thank you for this question. There was a big gap between OS and PFS at the 5th year (60th month), which may mainly because of the small sample number. The reduction of OS was observed after the 60th month according to the Kaplan-Meier survival curve. Another possible reason was the the development of supportive care, which may prolong the survival of patients after tumor progression.

Changes in the text: We have not changed the text.

Follow, there are some observations in the text:

Comment 3: Abstract

The conclusions do not match the results regarding the recurrence group. Although not statistically different for OS, the PFS do. Looking at the graphics seem that the non-central recurrence group and low radiotherapy dosage can be associated with a worse survival rate, but the number of the cases studied is low. Concluding, the results about non-central (pelvic wall) recurrences were better than the results previously reported, but they did not better than the central recurrence group. I suggest rewriting the conclusion, changing the word “especially” (L.58 and L.374).

Reply 3: Thank you for your advice on the accuracy of the conclusion.

Changes in the text: We have modified the conclusion. See Page 3, Line 56 and Page 17, Line 378-379.

Comment 4: Methods

Define which staging system and version were applied. Specify, if need, at the bottom of the tables.

Reply 4: Thank you for the suggestion.

Changes in the text: “The International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system” has been added to the bottom of table 1. See Page 21, Line 476.

Comment 5: Please, clarify: Lymph node+ was an exclusion criterion (L.104). Fig. 1 shows these exclusions after surgery, and in L.130-131 there is “radiotherapy done if iliac or para-aortic Lymph node+...”.

Reply 5: Thank you for the suggestion. Patients with positive lymph node were not been included in this study. The description of lymph node positive radiotherapy is a general rule of radiotherapy, which has caused misunderstanding.

Changes in the text: We delete “Inguinal of para-aortic radiation...respectively”. See Page 6, Line 129.

Comment 6: Results

L.161-162: the average time for the 1st relapse was 11 months (3-116 mo). Maybe this short time could be related to the initial staging. I would like to see a table: initial stage and place of relapse (by group).

Reply 6: Thank you for the suggestion. Most patients were stage IB1 and there was no significant difference in staging between the two groups.

Changes in the text: We add stage and pattern of relapse in table 1. See Page 21, Table 1.

Comment 7: How many cases performed radical pelvic lymphadenectomy? There are at least 21/27 would have done.

Reply 7: 24/27 patients received radical surgery including pelvic lymphadenectomy and the other 3 staged IA1 patients received total hysterectomy.

Changes in the text: The information of initial treatment has been added. See Page 7, Line 163-164.

Comment 8: In these cases, how long did the relapse occur and where? In the Discussion section L. 331-333, there is a phrase about laparoscopic surgery, but your finding must be in the Results section.

Reply 8: According to the results of LACC trial, compared with patients undergoing laparotomy, patients undergoing laparoscopy had an increased recurrence rate and multiple recurrent lesions. Usually, pelvic radiotherapy only includes pelvic lymph node drainage area, parametrial tissue and upper vagina. However, some multiple recurrent lesions were out of traditional pelvic radiotherapy volume. We discuss this topic because this situation will affect the target volume of radiotherapy. The median recurrent time of laparoscopy cases was 10 months(range 5-27 months) which was similar to that of laparotomy cases, so we didn't show this data. The location of multiple recurrent lesions was in mesentery and abdominal wall.

Changes in the text: We have added the information of multiple recurrent lesions. See Page 9, Line 195-197, Page 24, Table 3.

Comment 9: I didn't find the time gap between the 2nd surgery (for recurrence) and the RTCT starting. These data are important to correlate with the complication and possible delays in the treatment, as cited in L.235. There is something related to this issue reported in the L.353-355, but only for 3 cases.

Reply 9: Thank you for this question. The gap between surgery and RTCT is important. In this study, most patients started radiotherapy within 4 weeks. Only patients with delayed radiotherapy are mentioned in the article.

Changes in the text: We have added the information of gap between surgery and RTCT. See Page 23, Table 2.

Comment 10: Fig. 2

Add de cases number by the group. The '2A-2B-2C' needs to be placed out of the graphic.

Reply 10: Thank you for the suggestion.

Changes in the figure: We have modified the figure. See figure 2 and figure 3.

Comment 11: Fig. 2B

Interesting to note that the 61-month OS drops below 50% for the non-central group.

Reply 11: Thank you for your attention. This may be due to the small number of cases and the survival curve was calculated by SPSS.

Changes in the text: We have not changed the text.

Comment 12: Fig.3B/3E/3F

The curves are visually different, but the statistic fails due to the small 'n'. Non-central disease and lower RT dose seem to have worse survival.

Reply 12: There was statistical difference in figure 3B(P=0.047). There was a trend for worse survival of non-central disease and lower RT dose. The number is too small to draw a conclusion.

Changes in the text: We have not changed the text.

Comment 13: Table 4

I suggest reporting complications divided by Surgery and/or RTQT.

Reply 13: Thank you for the suggestion.

Changes in the text: We have modified table 4. See Page 25, Table 4.

Comment 14: Discussion

1st paragraph: I suggest highlighting the main results as described in the 2nd paragraph.

Reply 14: Thank you for the suggestion.

Changes in the text: We have described the main results in the 1st paragraph of Discussion. See Page 12, Line 264-266.

Comment 15: Lines 287-289

Beware, it seems to be different, but not statistically demonstrated by the small number of cases. I suggest rewriting this sentence.

Reply 15: Thank you for the suggestion. This sentence should be modified

appropriately.

Changes in the text: We have modified the sentence. See Page 13, Line 294-295.

Comment 16: Line 331-333

Laparoscopy and supplemental tab. Put this phrase in the Results.

Reply 16: Thank you for the suggestion.

Changes in the text: We have added the information. See Page 9, Line 195-197.

Comment 17: References

Only 4/15 are from the last 5 years. I suggest updating.

Reply 17: Thank you for the suggestion. In recent years, the progress of recurrent cervical cancer focuses on systemic treatment.

Changes in the text: We have updated some references. See Line 413, 416, 450.

Reviewer B

This study dealt with rare but unresolved issue about treatment of recurrent cervical cancer. Although the study was retrospective one, the result was relatively good by using both intensive salvage surgery and adjuvant radiochemotherapy. Therefore, this manuscript is meaningful in this field, I think. But, there are some issues and questions before acceptance.

Comment 1: Introduction section

“Traditionally, radiotherapy with or without chemotherapy is the preferred treatment for recurrent patients undergoing primary surgery without radiotherapy, both central and non-central pelvic recurrence.”

From NCCN guideline, when local/regional recurrence, there is a description of "consider surgical resection if feasible", then, "individualized EBRT ± systemic therapy ± brachytherapy". Were there any surgical results? Was surgery only outcomes was poor? Therefore, your study added adjuvant concurrent radiochemotherapy?

Reply 1: Thank you for this attention. Cervical cancer is infiltrating growth. There is usually no clear boundary for recurrence in the vaginal cuff or pelvic side wall. There is no safe margin for surgery at this site, except for radical surgery with serious complications, as described in Discussion, paragraph 4. Therefore, radiotherapy and chemotherapy are needed after surgery. In fact, NCCN did not cite any references when describing this part of treatment.

Therefore, your study added adjuvant concurrent radiochemotherapy?

The reason was that cervical cancer was infiltrating growth without clear boundary for recurrence in the vaginal cuff or pelvic side wall. There was no safe margin for surgery at this site. Therefore, surgery alone was not adequate for locally recurrent cervical cancer and radiotherapy with or without chemotherapy are needed after surgery.

Changes in the text: We have added an explanation to the description of NCCN guideline. See Page 4, Line 91-94.

Comment 2: Methods section

“Patients with lymph node recurrence were excluded.”

I think pelvic lymph node recurrences are regional recurrence. Regional recurrence is possible candidate for surgery from NCCN guideline. Then, why do you exclude the all the case of lymph node recurrence? Is this local recurrence analyses? If so, to avoid confusion, I prefer “Surgery followed by concurrent radiochemotherapy as treatment 1 for patients with ‘locally’ recurrent cervical cancer”.

Reply 2: Thank you for the suggestion. This study is focused on local recurrence.

Changes in the text: We have modified the title. See Page 1, Line 1.

Comment 3: From consort diagram, patients with distant metastases were also seemed to be excluded. Add the description, please.

Reply 3: Thank you for the suggestion.

Changes in the text: We have added “Patients with distant metastases and lymph node metastases were excluded”. See Page 5, Line 102-103.

Comment 4: Were there any patients who received salvage surgery but did not receive radiotherapy?

Reply 4: Thank you for your attention. In this study, all the patients received radiotherapy.

Changes in the text: We have described “All patients underwent pelvic radiotherapy”, so we have not changed the text. See Page 6, Line 128.

Comment 5: "Ureteral stent placement was applied for patients with partial cystectomy/ureterectomy or ureter/bladder injury"

Were there any cases such as ileal conduit or percutaneous cystostomy?

Reply 5: Thank you for your attention. In this study, there was not patient underwent ileal conduit or percutaneous cystostomy. Therefore, ileal conduit or percutaneous cystostomy did not mentioned in the manuscript.

Changes in the text: We have added “There was no patient undergoing ileal conduit

or percutaneous cystostomy”. See Page 8, Line 179.

Comment 6: Radiotherapy

“Inguinal or para-aortic radiation was performed if the lower third of the vagina was invaded or if there was common iliac lymph node metastasis and/or para-aortic lymph node metastasis, respectively.”

Why did the patients with lymph node cases include? Recurrence with lymph node were excluded, and initially lymph node involvement cases were staged 3C1 or 3C2 which did not fulfill the inclusion criteria and stage 3C was high risk factor and candidate for post operative radiotherapy after initial surgery.

Reply 6: Thank you for the suggestion. Patients with positive lymph node were not been included in this study. The description of lymph node positive radiotherapy is a general rule of radiotherapy, which has caused misunderstanding.

Change in the text: We have modified the description. See Page 6, Line 129.

Comment 7: Did EBRT use IGRT(image-guided radiation therapy)? 2-D? 3-D? IMRT? Add more information, please.

Reply 7: Thank you for the suggestion.

Change in the text: We have added “Weekly image-guided intensity modulated radiation therapy (IMRT) was used for EBRT.” See Page 8, Line 185-186.

Comment 8: “Progression-free survival(PFS) was defined as the time from diagnosis of recurrence to disease progression, death and disease progression were scored as events..” Modify the “..”.

Reply 8: Thank you for the suggestion.

Change in the text: We have deleted one “.”. See Page 7, Line 150.

Comment 9: Define the “progression”, please.

Reply 9: Thank you for the suggestion.

Change in the text: We have added the definition. See Page 5, Line 147-148.

Comment 10: Describe Grading scale of Complication such as CTCAE here, please.

Reply 10: Thank you for the suggestion.

Change in the text: We have added the CTCAE as grading of side effects. See Page 7, Line 154-155.

Comment 11: Results section

“All patients underwent postoperative radiotherapy with a median equivalent dose in 2 Gy fractions (EQD2) of 45.1 Gy (range, 44.3 Gy to 47.8 Gy). Twenty-six patients

underwent pelvic radiotherapy and one underwent pelvic, whole vagina, and inguinal radiotherapy”

One patient did not receive pelvic radiotherapy? Why?

Reply 11: Thank you for your attention. “Twenty-six patients underwent pelvic radiotherapy and one underwent PELVIC, whole vagina, and inguinal radiotherapy”, that means all the patients underwent radiotherapy.

Change in the text: We have not changed the text.

Comment 12: Weren't there any para-aortic node irradiation?

Reply 12: Thank you for your attention. There was not any patient undergoing para-aortic node irradiation for patients with positive lymph nodes were excluded.

Change in the text: We have not changed the text.

Comment 13: “Their median OS was 27 months (5 to 72 months) from the first recurrence.”

First recurrence is confusing. I think to use “after disease progression” is better.

Reply 13: Thank you for your suggestion.

Changes in the text: We have replaced “from the first recurrence” with “after disease progression”. See Page 8, Line 586 in “manuscript-TCR-R2-edit-revision-further-revision-revision.docx”.

Comment 14: Complications

“Grade 3 or higher complications, for example, neutropenia and anemia, were observed in 7 (25.9%) and 10 (37.0%) patients, respectively.”

Grade 3 or higher hematotoxicity?

Were there late adverse event after radiotherapy?

Reply 14: Thank you for the suggestion. The late adverse events were not remarkable due to the radiation dose was not high(compared to radical radiotherapy for cervical cancer), so we did not list the late adverse events.

Change in the text: We have replaced "complications" with "thermototoxicity". See Page 11. Line 251.

Comment 15: Discussion section

“Therefore, surgery for patients with recurrence, especially for patients undergoing previous laparoscopic radical surgery, is not only a treatment but also an assessment of how to perform effective radiotherapy.”

I think to describe “surgical and pathologic assessment” is easier to understand.

Reply 15: Thank you for your suggestion. According to the results of LACC trial, compared with patients undergoing laparotomy, patients undergoing laparoscopy as initial treatment have an increased recurrence rate and multiple recurrent lesions.

Usually, pelvic radiotherapy only includes pelvic lymph node drainage area, parametrial tissue and upper vagina. However, some multiple recurrent lesions were out of traditional pelvic radiotherapy volume, such as abdominal wall. We discuss this topic because this situation will affect the target volume of radiotherapy.

Change in the text: We have added "... radiotherapy according to surgical and pathologic factors". See Page 15, Line 340-341.

Comment 15: When salvage surgery, was open surgery recommended?

Reply 15: Thank you for your attention. The approach of surgery for recurrence is not the topic of this study. In this study, all the patients received open surgery. The approach of surgery for recurrence should be further studied.

Change in the text: We have not changed the text.