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Reviewer A

Comment: This is a retrospective review of 116 patients with uterine cervical cancer treated with radical hysterectomy and lymphadenectomy, including 59 who received preoperative high-dose-rate vaginal brachytherapy and 57 who received traditional vaginal gauze packing to stop vaginal bleeding. The results showed that the time required for hemostasis was significantly shorter in the brachytherapy group than in the gauze packing group. In addition, there were no significant differences in complications and survival between the two groups. From these results, the authors concluded that preoperative high-dose-rate brachytherapy brings the better hemostatic effect to patients than vaginal gauze packing. This report is interesting and well written. However, it has some major flaws. First, postoperative radiation therapy to the pelvis more likely causes complications, but it was not evaluated at all. Secondly, patients in this study were treated with various treatment methods, including with or without pelvic irradiation and several chemotherapy regimens. It is inherently difficult to draw firm conclusions from their dataset with retrospective selection bias. Finally, the time required to stop vaginal bleeding was shorter in the brachytherapy group, but the total bleeding volume was similar in the two groups. Considering postoperative radiation therapy to the pelvis is usually applied to patients with high risk for recurrence, preoperative irradiation might not be recommended for such patients from a concern about overdose. Besides, there are some problems that the authors need to clarify and revise as mentioned in the specific comments below.

Reply: Thanks for pointing out this problem. First, of 39 patients with high-risk

factors, 35 (30.2%) patients received postoperative radiation therapy to the pelvis. Among these patients, 19 patients received preoperative HDR-VOBT and 16 patients received gauze packing. As shown in Tables 4, 11 patients (31.4%) experienced grade 3 or higher acute hematological toxicity. The incidences were similar between preoperative HDR-VOBT (36.8%) and gauze packing (25%). There were 7 patients (20%) developed acute grade 3 or greater gastrointestinal toxicity. The incidences were similar between preoperative HDR-VOBT (21.1%) and gauze packing (18.8%). Four patients (11.4%) experienced grade 3 or greater acute urinary toxicity. The incidences in patients treated with preoperative HDR-VOBT and gauze packing were 15.8 % and 6.3 %, respectively (p=0.608). The incidences of grade 3 or greater chronic gastrointestinal and genitourinary toxicity were 5.7% and 2.9%, respectively. The chronic gastrointestinal and genitourinary toxicity of HDR-VOBT was not significantly higher than gauze packing. Three patients (8.6%) developed grade 3–4 chronic toxicity, including 2 patients with proctitis and 1 patient with vesicovaginal fistula. The patient with vesicovaginal fistula received surgery repair. The complications caused by postoperative radiation therapy to the pelvis were summarized in the Table 4. We have modified our text as advised. Secondly, we are sorry for our mistake. The mean volume of bleeding before treatment was similar in the two groups. The mean volume of bleeding after treatment was decreased in the brachytherapy group. The mean volume of vaginal bleeding after treatment was 83.4 mL (range 30-150 mL)for the whole group: 56.8 mL (range 30-80 mL) bleeding in the preoperative HDR-VOBT group and 111.1 mL (range 80-150 mL) in the gauze packing group ($p < 0.001$). The mean time to achieve hemostasis was 3.5 h in the preoperative HDR-VOBT group and 8.1 h in the vaginal packing with gauze group ($p < 0.001$) (Table 2). Finally, this is a small-sample retrospective study with certain

inherent bias, and the conclusion should be validated in further prospective studies.We will expand the case samples and design prospective studies.

Changes in the text: we have modified our text as advised (see Results, Page11-12, line232-247; Table 4; Results, Page 8, line167-171; Discussion, Page 14, line303-307) with yellow color.

Specific comments:

Comment: 1. Methods, page 3, lines 83 to page 4, line 84

A total of 116 patients received preoperative high-dose-rate brachytherapy or traditional vaginal gauze packing. How was it decided which treatment was applied to each patient? Was it only preference of gynecological oncologists?

Reply: Thanks for pointing out this problem. It was not only preference of gynecological oncologists. We explaned the pros and cons of the different treatments between preoperative HDR-VOBT and traditional vaginal packing with gauze alone. We had respect for patient autonomy. All patients provided written informed consent.

Changes in the text: we have modified our text as advised (see Methods, Page 5, line79-81) with yellow color.

Comment: 2. Methods, page 4, lines 109–111

In this study, a dose of 8 Gy was delivered to a point of 0.5 cm posterior to the surface of the tumor. What is the rationale of this radiation dose and prescribed point? Please give the information.

Reply: Thanks for pointing out this problem. Radiotherapy is effective for the treatment of vaginal bleeding in cervical cancer. Brachytherapy plays an important role in controlling the bleeding caused by cervical tumors. North American guidelines recommend two regimens of 5 Gy via a vaginal cuff, which have been proven to reduce the need for additional transfusion in 93% of the patients without acute or long-term grade 3–5 complications [17]. The conformal dose distribution can minimize the dose delivered to the rectum and the bladder, without changing the definitive

treatment plan. The symptomatic bleeding from a cervical tumor can be reduced by vaginal cuff brachytherapy before the initiation of the definitive treatment [18].
In our center, one regimen of 8 Gy at 0.5 cm from the surface of the tumor is used to control persistent vaginal bleeding, which has the same biological equivalent dose (BED) with two regimens of 5 Gy [19].

Changes in the text: we have modified our text as advised (see Discussion, Page 13, line272-283) with yellow color.

Comment: 3. Methods, page 5, lines 130 and 131

The complications were evaluated with the Chassagne glossary. Generally, more authorized toxicity criteria, e.g. CTCAE and RTOG/EORTC scale, might be preferably used for toxicity evaluation.

Reply: Thanks for pointing out this problem. As for the postoperative radiation therapy to the pelvis, acute and chronic toxicity assessment was performed according to the Radiation Therapy Oncology Group acute and late toxicity criteria.

Changes in the text: we have modified our text as advised (see Methods, Page 7, line136-138) with yellow color.

Comment: 4. Results, page 6, line 157

The authors wrote "glandular carcinoma". Is this correct as an official term? It should be adenocarcinoma, shouldn't it?

Reply: Thanks for pointing out this problem. We have modified our text as advised.

Changes in the text: we have modified our text as advised (see Methods, Page 5, line 84; Results, Page 8, line157) with yellow color.

Comment: 5. Results, page 6, lines 178–182

Of 39 patients with high-risk factors, 15 received additional external beam radiation therapy. Why didn't the remaining 24 patients receive adjuvant irradiation? Was it due to a concern about an excessive radiation dose?

Reply: Thanks for pointing out this problem. We are sorry for the misunderstanding. Of 39 patients with high-risk factors, 15(12.9%) only received additional external

beam radiation therapy without postoperative chemotherapy, 4(3.4%) only received postoperative chemotherapy without radiotherapy, and 20(17.2%) received chemoradiotherapy. We have modified our text as advised.

Changes in the text: we have modified our text as advised (see Results, Page 9, line185-188) with yellow color.

Comment: 6. Results, page 7, line 183

A total dose of 45 Gy was delivered to the pelvis. Please describe radiation therapy method in further detail, particularly a fraction dose and the radiation field.

Reply: Thanks for pointing out this problem. We have modified our text as advised. Three-dimensional conformal radiation therapy (3D-CRT) was delivered using 6-MV photons with a four-field box technique. Patients underwent CT (16-slice Philips Brilliance Big Bore CT) simulation with oral contrast agents; Rectum and bladder preparation were performed before CT simulation. The clinical target volume (CTV) were contoured on the individual axial CT slices for each patient. The CTV covered the vaginal fragment and regional lymph nodes (common iliac, internal iliac, external iliac, obturator, presacral, and/or para-aortic lymph nodes). The planning target volume (PTV) was defined as the CTV plus an 7 mm margin. A total dose of 45Gy (1.8Gy per fraction) was prescribed to the PTV.

Changes in the text: we have modified our text as advised (see Results, Page 9-10, line188-197) with yellow color.

Comment: 7. Results, page 7, lines 191–193

Eight patients developed local recurrence. Did these patients receive postoperative radiation therapy? Was there the relationship between postoperative radiation therapy and the incidence of local recurrence?

Reply: Thanks for pointing out this problem. These patients with high-risk factors had received postoperative radiation therapy. There was no relationship between postoperative radiation therapy and the incidence of local recurrence. We have

modified our text as advised.

Changes in the text: we have modified our text as advised (see Results, Page 10, line203-206) with yellow color.

Comment: 8. Figures 1 and 2

Reply: Thanks for pointing out this problem. We have modified our text as advised.

Changes in the text: we have modified our figures (see figure 1 and 2) .

Comment: 9. Table 1

Was no relationship between postoperative radiation therapy and the incidence of complications observed?

Indeed the time to stop vaginal bleeding was shortened by brachytherapy, but the bleeding volume was not decreased. Do the authors really recommend brachytherapy to shorten only by 4.6 hours at the median time?

Reply: Thanks for pointing out this problem. Of 39 patients with high-risk factors, 35 (30.2%) patients received postoperative radiation therapy to the pelvis. Among these patients, 19 patients received preoperative HDR-VOBT and 16 patients received gauze packing. As shown in Tables 4, 11 patients (31.4%) experienced grade 3 or higher acute hematological toxicity. The incidences were similar between preoperative HDR-VOBT (36.8%) and gauze packing (25%). There were 7 patients (20%) developed acute grade 3 or greater gastrointestinal toxicity. The incidences were similar between preoperative HDR-VOBT (21.1%) and gauze packing (18.8%). Four patients (11.4%) experienced grade 3 or greater acute urinary toxicity. The incidences in patients treated with preoperative HDR-VOBT and gauze packing were 15.8 % and 6.3 %, respectively (p=0.608). The incidences of grade 3 or greater chronic gastrointestinal and genitourinary toxicity were 5.7% and 2.9%, respectively. The chronic gastrointestinal and genitourinary toxicity of HDR-VOBT was not significantly higher than gauze packing. Three patients (8.6%) developed grade 3–4 chronic toxicity, including 2 patients with proctitis and 1 patient with vesicovaginal fistula. The patient with vesicovaginal fistula received surgery repair. The

complications caused by postoperative radiation therapy to the pelvis were summarized in the Table 4. We are sorry for our mistake. The mean volume of bleeding before treatment was similar in the two groups. The mean volume of bleeding after treatment was decreased in the brachytherapy group. The mean volume of vaginal bleeding after treatment was 83.4 mL (range 30-150 mL) for the whole group: 56.8 mL (range 30-80 mL) bleeding in the preoperative HDR-VOBT group and 111.1 mL (range 80-150 mL) in the gauze packing group ($p < 0.001$).

Changes in the text: we have modified our text as advised (see Results, Page11-12, line232-247; Results, Page 8, line167-172) with yellow color.

Reviewer B

The authors analyzed patients with vaginal bleeding and early-stage cervical carcinoma, treated in one institution during 4 years. The study population was good, all together 116 patients, treated with high-dose-rate vaginal ovoid brachytherapy or vaginal packing with gauze. The size of the two groups was balanced. The Vaginal brachytherapy has been studied in bleeding of advanced cervical cancer, but no in early stage cervical cancer. So, the point of the study has thus been interesting. However, the manuscript has several shortcomings.

Reply: Thanks for pointing out the shortcomings. We have modified our text as advised.

Abstract

Comment 1: the main goal and the research results are not congruent:

Line 28. "...to assess the efficacy and safety of preoperative high-dose-rate vaginal ovoid brachytherapy (HDR-VOBT) for the treatment of vaginal bleeding"

Line 40 to 44. "Three-year overall survival (OS) and disease-free survival (DFS) 41 were 92.2% and 81.9%, respectively. Five-year OS and DFS were 91.4% and

81%, 42 respectively. Furthermore, 40.5%, 15.5%, and 2.6% of the patients had grade 1, 2, and 43 3 complications, respectively. In multivariate analysis, the presence of positive lymph 44 nodes significantly affected OS (RR 8.822 [3.604–21.597]) and DFS (RR 26.217 CI 45 [13.307–51.654])"

Reply: Thanks for pointing out this problem. We have modified our text as advised. No differences were observed regarding the five-year OS (91.5% vs. 91.2%) and DFS (76.3% vs. 86%) between the preoperative HDR-VOBT group and the vaginal packing with gauze group. The mean volume of vaginal bleeding after treatment was 83.4 mL (range 30-150 mL) for the whole group: 56.8 mL (range 30-80 mL) bleeding in the preoperative HDR-VOBT group and 111.1 mL (range 80-150 mL) in the gauze packing group ($p < 0.001$). The mean time to achieve hemostasis was 3.5 h in the preoperative HDR-VOBT group and 8.1 h in vaginal packing with gauze group ($p < 0.001$). There was no significant difference in postoperative risk factors, complications, and survival between the two groups.

Changes in the text: we have modified our abstract as advised (see Abstract, Page 2, line37-44) with yellow color.

Introduction

Comment 2:

Line 55. Cervical cancer is not third, but 4th most common cancer among women world-wide (see the manuscript's reference no.2)

Reply: Thanks for pointing out this problem. We have modified our text as advised. Cervical cancer is the 4th most common cancer among women world-wide[1, 2].

Changes in the text: we have modified our text as advised (see Introduction, Page 4, line52) with yellow color.

Comment 3:

Line 56-57. The authors write the numbers like these are about the world, but this is statistics from the United States. Both incidence and deaths are much higher in the world.

Also, the facts are old (2018). There are in the referred 'National Cancer Institute. Surveillance, Epidemiology and End Results 313 Program. Cancer stat facts: cervical cancer'could find now estimated numbers for the year 2021.

Reply: Thanks for pointing out this problem. We have modified our text as advised. More than 14480 new cases and 4,290 cervical cancer deaths were estimated to occur in 2021.

Changes in the text: we have modified our text as advised (see Introduction, Page 4, line52-55) with yellow color.

Comment 4:

Line 57-58. The fact about vaginal bleeding as a cause of death (6%) is taken from the article about advanced cervical cancer, which have totally different bleeding intensity than in the case of the early cervical cancer.

Reply: Thanks for pointing out this problem. We have modified our text as advised. Vaginal bleeding is the immediate cause of death in 6% of the women with advanced cervical cancer.

Changes in the text: we have modified our text as advised (see Introduction, Page 4, line54-55) with yellow color.

Comment 5:

Line 60 and 66. Reference no.6 - The authors use an inadequate reference what leads to the ACOG "frequently asked questions", the patients' section.

Reply: Thanks for pointing out this problem. We have removed the Reference no.6 as advised.

Changes in the text: we have removed the Reference no.6 as advised.

Comment 6:

Line 62-66 Treatment options are described inaccurately (with definitive radiation is used with brachytherapy, and usually with concurrent chemotherapy) (see reference no.8 National Comprehensive Cancer Network, Clinical Practice

Guideline in Oncology.)

Reply: Thanks for pointing out this problem. We have modified our text as advised. The current National Comprehensive Cancer Network guideline recommends two initial treatment options for the 2018 International Federation of Gynecology and Obstetrics (2018 FIGO) preoperative early-stage cervical cancers (IB1/IB2 /IIA1): radical hysterectomy and lymphadenectomy, or with definitive radiation is used with brachytherapy, and usually with concurrent chemotherapy.

Changes in the text: we have modified our text as advised (see Introduction, Page 4, line59-63) with yellow color.

Comment 7:

Line 66-75 The literature review should cover more broadly the incidence of bleeding in early cervical cancer, the effect on treatment results, possible anaemia. Why is the subject being investigated?

Reply: Thanks for pointing out this problem. There is a lack of relevant research reports on the he incidence of bleeding in early cervical cancer, the effect on treatment results, possible anaemia. In our clinical work, we have noticed that about 11% of the patients with early cervical cancers had different degrees of vaginal bleeding, which required a preoperative intervention. So we investigated the subject.

Changes in the text: we have modified our text as advised (see Introduction, Page 4, line63-66; Introduction, Page 4, line70-72) with yellow color.

Comment 8:

Methods

Line 80. "Five patients who needed crossover treatment including emergency interventions (like surgery or arterial embolization), preoperative HDR-VOBT and traditional vaginal packing with gauze were excluded from this study." Why? Possibly these patients with greater bleeding would add interest of the manuscript?

Reply: Thanks for pointing out this problem. These patients with greater bleeding

were treated with surgery or arterial embolization. This part will be reported in other research of our center.

Comment 9:

Line 87-91. Are the volume of the bleeding and the time to achieve hemostasis the inclusion criteria?

Reply: Thanks for pointing out this problem. The volume of the bleeding is the inclusion criteria(<200ml).

Changes in the text: we have modified our text as advised (see Methods, Page 5, line82-86) with yellow color.

Comment 10:

Line 92 and line 87 and 103. The inclusion criteria and the exclusion criteria are in different places in the manuscript. Not logical.

Reply: Thanks for pointing out this problem. We have modified our text as advised. The inclusion criteria were age (range, 18–70), preoperative cervical biopsy in cases of squamous carcinoma or adenocarcinoma, treatment involving radical hysterectomy and lymphadenectomy (by laparotomy or laparoscopy) with preoperative HDR-VOBT or traditional vaginal packing with gauze, the volume of the bleeding before treatment (<200ml). The exclusion criteria were primary cone biopsy, the need for crossover treatment and an interval between the end of treatment and the beginning of the study lower than 6 months.

Changes in the text: we have modified our text as advised (see Methods, Page 5, line82-89) with yellow color.

Comment 11:

Line 86 and Table 1. ”We re-staged all patients following the FIGO 2018 staging system”. According to the FIGO 2018 staging, a patient with positive lymph nodes at least stage III. But in the text and in the Table 1 all patients are st.I to st.II. In the Table 1 the positive pelvic lymph nodes are found in 19 cases. Maybe

it would be better to use the older FIGO system?

Reply: Thanks for pointing out this problem. We have modified our text and Table 1 and 2. as advised. For this research, we staged all patients following the FIGO 2009 staging system.

Changes in the text: we have modified our text and Table 1 as advised (see Methods, Page 5, line95-96; Table 1) with yellow color.

Comment 12:

Line 108. In the cases of brachytherapy, vaginal packing with gauze was used for the applicator, like in the normal brachytherapy cases. How long did the applicator with the packing stayed in the vagina? How big is the importance of the radiation or the packing to achieving haemostasis in these cases?

Reply: Thanks for pointing out this problem. According to the attenuation of the Iridium-192 source, the different irradiation time was calculated to reach the same prescribed dose (8 Gy was applied to a point 0.5 cm posterior to the surface of the tumor). It was about 5 minutes. During each brachytherapy, gauze was only used to fix the applicator in the vagina in a short time. So the radiation played the major role to achieve hemostasis in these cases.

Changes in the text: we have modified our text as advised (see Methods, Page 6, line110-111) with yellow color

Results

Comment 13:

Line 162. The mean volume of vaginal bleeding was 148 mL (range 50-200 mL). Bleeding 200 mL or less is clinically insignificant. So, both methods (VOBT or packing) for achieving haemostasis are sufficient.

Reply: Thanks for pointing out this problem. We are sorry for our mistake. As for our inclusion criteria, the mean volume of vaginal bleeding before treatment was 148 mL (range 50-200 mL). The mean volume of vaginal bleeding after treatment was 83.4 mL (range 30-150 mL) for the whole group: 56.8 mL (range 30-80 mL) bleeding in

the preoperative HDR-VOBT group and 111.1 mL (range 80-150 mL) in the gauze packing group ($p < 0.001$). The volume of the vaginal bleeding and the time needed to achieve hemostasis were significantly less in the preoperative HDR-VOBT group than in the vaginal packing with gauze group, indicating that preoperative HDR-VOBT might be more effective in controlling vaginal bleeding than the vaginal packing with gauze alone. Vaginal packing with simple gauze rolls is a simple first-aid measure to control the bleeding. To perform an effective vaginal packing, it is ideal to expose the upper part of the vagina in the lithotomy position (with the legs in stirrups) by using instruments (speculum). The patients might need sedation or short-term general anesthesia. The vaginal vault is tightly packed in order to keep even pressure in the vagina. In this situation, catheterization is often required. Because of the urethral pressure, it is difficult for patients to pass urine. To enhance the effectiveness of the vaginal packing, patients' mobility is often restricted, in the bed with limb elevation. Hemostatic agents (with local, per-oral or parenteral administration) might be helpful for treating persistent vaginal bleeding. During the vaginal packing, the underlying infection (often occurring in necrotic tumors) can also cause bleeding. The preoperative HDR-VOBT could ease the patients' sufferings, improve the curative effect, shorten the time of treatment, and reduce the risk of infection.

Changes in the text: we have modified our text as advised (see Results, Page 8, line161-162; Results, Page 8-9, line167-172; Discussion, Page13-14, line283-287; Discussion, Page12-13, line261-271; Discussion, Page13-14, line287-289) with yellow color.

Discussion

Comment 14:

The packing is more accessible and affordable. There is emphasized in the manuscript the negative sides of the packing (the lithotomy position, sedation or short-term general anesthesia). Still, the insertion of the applicator has partly the same requirements. Without the opinion of the patients, it is not possible to decide whether one of the procedures is more uncomfortable.

Reply: Thanks for pointing out this problem. The volume of the vaginal bleeding and the time needed to achieve hemostasis was significantly less in the preoperative HDR-VOBT group than in the vaginal packing with gauze group, indicating that preoperative HDR-VOBT might be more effective in controlling vaginal bleeding than the vaginal packing with gauze alone. The preoperative HDR-VOBT could ease the patients' sufferings, improve the curative effect, shorten the time of treatment, and reduce the risk of infection. We explained the pros and cons of the different treatments between preoperative HDR-VOBT and traditional vaginal packing with gauze alone. We had respect for patient autonomy. All patients provided written informed consent before treatment.

Changes in the text: we have modified our text as advised (see Discussion, Page13-14, line283-289; Methods, Page 5, line79-81) with yellow color

Comment 15:

In both, Results and Discussion is lot of information, that is irrelevant in connection with the main goal of this study.

Reply: Thanks for pointing out this problem. We have modified our text as advised. We deleted the irrelevant text in the Results and Discussion parts as following: We analyzed the clinical, pathology, and surgery features of the study population in Table 1. For the whole group, the survival rates were significantly decreased in the cases with high 2018 FIGO stage of the disease, positive lymph nodes and lymphovascular invasion ($p < 0.001$) in univariate analysis. The covariates with p-values lower than 0.05 from univariate analysis were further analyzed in the multivariate Cox proportional hazards analysis. The factor of positive lymph node significantly affected the overall survival (RR 8.822 [3.604–21.597]) as well as disease-free survival (RR 26.217 CI [13.307–51.654]) (Results part).

For advanced cervical cancer with palliative treatment, the choice of interventions includes vaginal packing; interventional radiology techniques (embolization of the uterine artery); uterine artery resection; uterine artery ligation; and ionizing radiation/radiotherapy (Discussion part).

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

Comment 16:

Table 1

Percentages (e.g. complications) have been calculated in both groups (VOBT and gauze packing) from the total amount of patients (n=116). It would be more informative if percentages were calculated from the patients of the group.

Reply: Thanks for pointing out this problem. We have modified our Table 3 as advised.

Changes in the text: we have modified Table 3 as advised (see Table 3).

Comment 17:

There is also very much different information in the one table. It would be easier to read, if there was one table for background characteristics of the patients, and the other one for the results of the treatment.

Reply: Thanks for pointing out this problem. We have modified our Table 1 and 2 as advised.

Changes in the text: we have modified Table 1 and 2 as advised (see Table 1 and 2).

Summary

Comment 18:

The idea to compare different methods (VOBT and vaginal packing) to achieve haemostasis in early cervical cancer is good and this has not been previously studied.

By the results, in both methods the haemostasis is good and the bleeding is not clinically significant (max 200 ml). Still, the time to achieve the haemostasis is significantly shorter in the cases of the VOBT. In some situation, it could be important.

It is good that the effect of previous bleeding treatment on surgery and complications has been analyzed. Information on the hemostatic drugs used in both methods, as well as information on changes in patients' hemoglobin levels,

would been increased interest of the study. Unfortunately, the price and availability of the VOBT do not explored in this study. Presumably, gauze package is cheaper, even if it requires a longer stay in the hospital.

The text is not logical and fluent, readability suffers from time to time. Also, all results are not relevant for the aim of the study (example, it has not been hypothesized that OS would depend on the mode of initial hemostasis, or fact that positive lymph nodes affected the overall survival is not connected to the vaginal bleeding treatment before surgery).

Several references are not the original studies, some of the statistics in the Introduction are outdated.

The manuscript is a retrospective study. However, on line 150 "...informed consent was taken from all the patients." (when?) And estimating the amount of bleeding in the cases of the gauze packing (line 92 to lie 102) is not ordinary clinical work but referring to the prospective design of the study.

The manuscript would require major corrections before possible publication. In its current form, the manuscript does not meet the requirements for original scientific research.

Reply: Thanks for pointing out this problem. We are sorry for our mistake. The mean volume of vaginal bleeding before treatment was 148 mL (range 50-200 mL). The mean volume of vaginal bleeding after treatment was 83.4 mL (range 30-150 mL) for the whole group: 56.8 mL (range 30-80 mL) bleeding in the preoperative HDR-VOBT group and 111.1 mL (range 80-150 mL) in the gauze packing group ($p < 0.001$). The volume of the vaginal bleeding and the time needed to achieve hemostasis were significantly less in the preoperative HDR-VOBT group than in the vaginal packing with gauze group, indicating that preoperative HDR-VOBT might be more effective in controlling vaginal bleeding than the vaginal packing with gauze alone.

The cost of the HDR-VOBT treatment is about ＄234: 90% of the cost was payed by national health insurance, and 10% of the cost was payed by patient.

We deleted the irrelevant text in the Results and Discussion parts as following: We analyzed the clinical, pathology, and surgery features of the study population in Table

1. For the whole group, the survival rates were significantly decreased in the cases with high 2018 FIGO stage of the disease, positive lymph nodes and lymphovascular invasion ($p < 0.001$) in univariate analysis. The covariates with p-values lower than 0.05 from univariate analysis were further analyzed in the multivariate Cox proportional hazards analysis. The factor of positive lymph node significantly affected the overall survival (RR 8.822 [3.604–21.597]) as well as disease-free survival (RR 26.217 CI [13.307–51.654]) (Results part). For advanced cervical cancer with palliative treatment, the choice of interventions includes vaginal packing; interventional radiology techniques (embolization of the uterine artery); uterine artery resection; uterine artery ligation; and ionizing radiation/radiotherapy (Discussion part).

Thanks for pointing out this problem. We have modified the references and updated the statistics in the Introduction as advised.

We explained the pros and cons of the different treatments between preoperative HDR-VOBT and traditional vaginal packing with gauze alone to the patients. We had the respect for patient autonomy. All patients provided written informed consent before treatment.

Changes in the text: we have modified our text as advised (see Results, Page 8, line161-162; Results, Page 8-9, line167-172; Discussion, Page13-14, line283-287; Methods, Page 5, line79-81) with yellow color.