Peer Review File

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Reviewer A

Chen and co-investigators aimed to identify the possible risk factors of tumor-specific deaths in EC patients 5-years after operation and to make a nomogram prediction model. Altogether, 482 EC patients were analyzed, subdivided into two groups. They reported that several risk factors, including tumor size, FIGO stage and the rate of vascular tumor thrombus were statistically significant factors between groups. The nomogram predictive model of EC patients with 5 years follow-up has also been presented. In the conclusion they suggested that "….The nomogram prediction model established in the present study was valuable in accurately predicting tumor-specific death in patients with EC 5 years after surgery…."

I would like to present below several point of controversy.

There are two EC patients subgroups but, unfortunately, the number of women in both groups are not even similar. For this reasoning, it is truly difficult to find the final conclusion/s/. The Reviewer did not know what is the positive rate for Ki67 /10%, 20% or even 50%/? The Authors stated that "…laparoscopic hysterectomy with double appendages and retroperitoneal lymph node resection.." was done. In general, the name of the procedure is: total laparoscopic hysterectomy with bilateral salpingo-oophorectomy and retroperitoneal lymph node resection. Is it true that this procedure was also applied in 42 EC patients with III FIGO stage of the disease? Vascular tumor thrombus, as a tumor marker, should be more precisely described. What was the cut-off level of CA125 /Table 1/? The Reviewer wonder did the patients' tumor-specific death was associated with the adjuvant therapy applied? How many patients received chemoradiotherapy after the primary surgery and what protocols were used?

Reply Reviewer A: We thanks very much for your feedback, which help to improve the quality of the present study. We have tried our best to revised the article. However, there were still some issues that we believed need further explanation.

⑴For example, you pointed out that the number of women in both groups are not even similar. However, the 5-year mortality rate of endometrial cancer is about 10%-20%. In this case, the number of cases between the two groups of the patients cannot be similar, unless we deleted a portion of the surviving cases, but we did not believe that this behavior was correct.

⑵The Reviewer did not know what is the positive rate for Ki67 /10%, 20% or even 50%/?

We thank for your reminder. The Ki67 positive standard should indeed be included in the article, and currently we have included the Ki67 positive standard in the article. Thank you again. See page 6, line 145-146.

(3) The Authors stated that "…laparoscopic hysterectomy with double appendages and retroperitoneal lymph node resection.." was done. In general, the name of the procedure is: total laparoscopic hysterectomy with bilateral salpingo-oophorectomy and retroperitoneal lymph node resection. Is it true that this procedure was also applied in 42 EC patients with III FIGO stage of the disease?

We thank for your help and we confirmed that the data in the present study was true. We have revised the name of the procedure. See page 5, line 133-136.

(4)Vascular tumor thrombus, as a tumor marker, should be more precisely described.

We thank for your recommendation. We have explained the vascular tumor thrombus in detail. See page 6, line 147-149.

(5)What was the cut-off level of CA125 /Table 1/?

As it can be seen from table 1. There was not significant differences between the two groups in CA125 (22.34±13.27 vs. 21.80±13.26 IU/L, P=0.767). So the predictive value of the CA125 for death was meaningless.

(6)The Reviewer wonder did the patients' tumor-specific death was associated with the adjuvant therapy applied? How many patients received chemoradiotherapy after the primary surgery and what protocols were used?

In Table 1, we supplemented the data on postoperative radiotherapy and chemotherapy. From the data, it can be seen that more patients in the death group received radiotherapy or chemotherapy due to their more severe condition, but there was no statistically significant difference between the two groups. See the table 1.

Reviewer B

Congratulation to the authors for a well conducted research. However the following points could be addressed:

1. General information: Line 122: what is the intraoperative histological diagnosis? Is the post operative biopsy or an intra op frozen section biopsy?

Reply 1: It was postoperative biopsy. We have revised the mistake. See page 5, line 119-120.

2.It would be better to put what stages of endometrial cancer were included in the study, rather than putting distant mets as an exclusion criteria.

Reply 2: We have revised it. Thanks. See page 5, line 119.

3. In line 124, presence of concomitant mets were an exclusion criteria, do the authors mean

the presence of synchronous / metachronous tumours? This could be specified

Reply 3: We have revised it. See page 5, line 124-125.

4.Was all the histologies were included? Some would be high risk histologies like serous/ clear cell which inherently have a higher mortality rate. Were all those excluded?

Reply 4: All the histologies were included.

5. As values of Ca 125 are mentioned in your table, want to clarify was Ca 125 done routinely for all your patients?

Reply 5: The CA125 of all patients enrolled in this study was routinely done.

6. The tables show FIGO stage but the figure (2) shows tumour grade. Whether it is both the stage or grade or any one needs to specify

Reply 6: We have revised the figure 3. Thanks. See the attached files.

7. Also can mention which version of FIGO staging was used as the staging has been updated in this year

Reply 7: 2018 version. We have added. See page 6, line 145.

8. How was the size 3.35 cm arrived at?

Reply 8: Tumor size was valuable for predicting tumor-specific death in patients with EC at 5 years after surgery with an area under the curve (AUC) of 0.754 [95% confidence interval (CI): 0.696–0.812, P=0.000]. The optimal diagnostic cut-off was 3.35 cm, for which the sensitivity and specificity were 0.694 and 0.621, respectively (see Figure 2).

9. Also retroperitoneal lymph node dissection has been mentioned. Pelvic/paraaortic nodes or both could be mentioned.

Reply 9: We have added it in the methods. See page 5, line 134-136.

10. In discussion, other studies were mentioned which has deduced normogram similar as the present one. Could the authors elaborate if those studies had similar parameters in their normograms or were different? Also how was the present study different from the other studies? One point is mentioned like this study focused on endometrial cancer patients receiving surgical management. This could be elaborated(like different modalities of management/ only surgery or surgery f/b adjuvant)as well as other points could be included as to how this study is novel from other studies?

Reply 10: We have added. Thanks for your help. See table 1.

11. Tables can have an extra row specifying the treatment modalities as the study focused on patients undergoing surgery for EC. Whether they received adjuvant/type of adjuvant etc.
Reply 11: The rate of patients received radiochemotherapy after surgery was added in table 1.

12. References should preferably not be put in conclusion
Reply 12: We have revised it. See page 9, line 244-248.

13. Conflict of interest statement needs to be added
Reply 13: We have added. See page 10, line 256-257.

Reviewer C

Endometrial cancer (EC) is the second most common gynecologic malignancy worldwide (1). Different risk groups stratification methods are discussed in the literature (2-3). In the current manuscript the authors describe a postoperative tumor-specific death prediction model for patients with EC.
After thorough analysis, my decision is to recommend that the article can be accepted for publication in Translational Cancer Research journal with revision! I have set out the reasons for this decision as follows:

1.Abstract section
Pg 2, line 54-57
"Previous studies 55 have confirmed…"
It is necessary to indicate exactly which studies these are or to revise the text.
Reply 1: We have deleted the sentence in the abstract. Thanks.

Introduction section
Pg 3, line 89
"…with a 5-year tumor-specific mortality rate of 12.57%"
The authors should give a range of data for the mortality rate (from…% to …%) and support it with different studies.
Reply 2: We have revised the sentence and added related refs. See page 4, line 86.

Pg 4, lines 107-108
"…and FIGO staging is more commonly used in patients with EC."
What do the authors mean with this statement!?
FIGO staging and WHO TNM classification are the most commonly used classification

systems that allow comparative analyses!

Reply 3: We have deleted it.

Pg 4, lines 110-112

It would be good to avoid the repetition of "…patients with EC…"

Reply 4: We have revised the sentences. Thanks.

Discussion section

Pg 7, line 229

Limitations

Authors should expand on this paragraph as "Limitations and strengths of the study" and to conduct a more in-depth analysis of both strengths and weaknesses.

Reply 5: We have revised it accordingly. We thank for your help. See page 9, line 231-240.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394–424

2. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, the ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group et al (2016) ESMO-ESGOESTRO consensus conference on endometrial cancer: diagnosis, treatment, and follow-up. Ann Oncol 27:16–41

3. Jørgensen SL, Mogensen O, Wu CS, Korsholm M, Lund K, Jensen PT (2019) Survival after a nationwide introduction of robotic surgery in women with early-stage endometrial cancer: a populationbased prospective cohort study. Eur J Cancer 109:1–11

Reviewer D

I read with great interest the Manuscript titled " Establishment and validation of a postoperative tumor-specific death prediction model for patients with endometrial cancer", topic interesting enough to attract readers' attention.

Although the manuscript can be considered already of good quality, I would suggest following recommendations:

- I suggest a round of language revision, in order to correct few typos and improve readability.

Reply 1: We have conducted a round of language revision accordingly. Thanks.

- The authors should discuss solid evidence on the use of new strategies for the early detection

of endometrial cancer. For example, you might consider using artificial intelligence, especially radiomic analysis of radiological images. I suggest this article to get deeper in the topic PMID: 36553988 and 37094971.

Reply 2: We have discussed the topic in the limitations section. See page 9, line 231-240.

Because of these reasons, the article should be revised and completed. Considering all these points, I think it could be of interest to the readers and, in my opinion, it deserves the priority to be published after minor revisions.

Reply 3: We thank for your positive feedback.