Author's response to reviews

Title: Preoperative serum CA125: A useful marker for surgical management of endometrial cancer

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Author's response to reviews: see over
Editor's comment:

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1. I do not understand the sentence from line 101-104 starting with “Omiting”. As it is written, this does not seem to be a true statement.

Response: It should be “Omitting lymphadenectomy in grade 1 or 2 tumors with less than 50% myometrial invasion, the incidence of undiagnosed lymph node metastasis is acceptable for patients with endometrial cancer.”

2. It seems that all patients did not undergo lymphadenectomy in this study and it should be clarified how many were completely staged.

How do you know that those patients did not have microscopic metastases. If all of them did not undergo lymph node staging then the entire model breaks down.

A prospective model was stated however approximately 25% were excluded with the majority of those excluded for “incomplete staging” however what constituted “complete” staging is not described.

Please discuss how this impacts your model and conclusions.

Response: In our inclusion criteria we only selected patients that had undergone complete staging including hysterectomy, bilateral salpingo-oophorectomy, pelvic ± periaortic lymphadenectomy and washing cytology. Therefore, all 995 patients in our study all had undergone lymph node staging.
In the Discussion, we mention that our study had selection bias. “Second, there was a selection bias, as 27% of 1,226 patients were excluded owing to a lack of preoperative serum CA125 levels, incomplete staging operation, or loss of follow up.”

3. Was the cutoff for Ca-125 levels the same for premenopausal and menopausal patients. If so, I do not think this is accurate. Premenopausal patients may have an elevated Ca-125 level depending on the timing with their cycle.

Response: The cutoff was different for premenopausal and menopausal patients. In Table 1, the mean rank of CA125 was higher in premenopausal patients than in menopausal patients. Accordingly, in the results, when using preoperative CA125 to predict lymph node metastasis, the best cutoff value of CA125 was 30 U/ml in premenopausal patients and 25 U/ml in menopausal patients.

4. Unfortunately after reading the manuscript, I am unsure of the criteria used in the prediction model of CA125. I am unsure if it was recurrence, metastasis or other criteria or all the above. Please clarify

Response: Our results indicate that preoperative serum CA125 is a good predictor of metastasis. The main purpose of this analysis was to evaluate if preoperative serum CA125 was helpful for gynecologic oncologists to determine the surgical management of endometrial cancer, particularly whether CA125 serum levels could indicate if a lymphadenectomy was required for clinical stage I patients. We found that preoperative CA125 was a good predictor of lymph node metastasis for patients with endometrial cancer, especially in patients with clinical stage I. In premenopausal
patients with clinical stage I, preoperative serum CA125 also was helpful for those patients who seek to preserve their ovaries. If preoperative serum CA125 was too high in patients with clinical stage I, complete cytoreduction should be recommended. Therefore, preoperative serum CA125 was an important predictor for patients with endometrial cancer and it should be taken into consideration when surgical management was determined, especially if lymphadenectomy should be undertaken in patients with clinical stage I.

5. It would be important to know how many patients had preoperative imaging and suspicion of metastatic disease prior to surgery.

Response: We have added clinical stage according to the 1971 FIGO staging. There were 864 (86.8%) patients with clinical stage I that had no preoperative imaging or suspicion of metastatic disease prior surgery. There were 131 (13.2%) patients with clinical stage II – IV that had preoperative imaging or suspicion of metastatic disease prior to surgery.

6. In your conclusion you state that this is a retrospective study, but in the purpose statement of the introduction you state it is prospective. Please correct.

Response: We had deleted the term “prospective”, and corrected it to “we designed the current study to evaluate the preoperative levels of CA125 in patients with endometrial cancer in relation to clinicopathological parameters, and whether these serum levels could provide additional information in determining the extent of surgical management.”

7. The conclusions made in this study are too definitive. Such definitive
conclusions cannot be made from a retrospective study.

The entire conclusion is overstated. At best this is an interesting finding that could be considered in a prediction model:

“In conclusion, preoperative serum CA125 is a good predictor for gynecologic oncologist to determine the surgical management in endometrial cancer. If the value of preoperative serum CA125 was >25 U/ml in patients with clinical stage I, lymphadenectomy should be undertaken. Young patients with endometrial cancer seeking to preserve their ovaries should be advised to remove them if the level of preoperative serum CA125 >30 U/ml, while complete cytoreduction should be recommended if preoperative serum CA125 >45 U/ml.”

Response: We have changed our Conclusion to read as follows: “The main purpose of this analysis was to evaluate if preoperative serum CA125 was helpful for gynecologic oncologists to determine the surgical management in endometrial cancer, particularly whether CA125 serum levels could indicate if a lymphadenectomy was required for clinical stage I patients. We found that preoperative serum CA125 was a good predictor of lymph node metastasis for patients with endometrial cancer, especially in patients with clinical stage I. In premenopausal patients with clinical stage I, preoperative serum CA125 also was helpful for those patients who seek to preserve their ovaries. If preoperative serum CA125 was too high in patients with clinical stage I, complete cytoreduction should be recommended. Therefore, preoperative serum CA125 was an important predictor for patients with endometrial cancer and it should be taken into consideration when surgical management is determined, especially if a lymphadenectomy should be
undertaken in patients with clinical stage I.”

8. I think that this study has a good concept, but needs to be more focused. The patient population studied needs to be more homogenous. I think that it should be focused on clinical Stage I patients where the decision for systemic lymphadenectomy and adnexectomy in premenopausal patients is not definitive. If there is evidence of extrauterine disease prior to surgery, then an elevated Ca-125 will not change surgical management.

Response: In the Results section, we focused on clinical stage I patients and added the subsection “The role of preoperative serum CA125 in patients with clinical stage I”

In 864 patients with clinical stage I, the patients with the FIGO stage I, II, III and IV were respectively 735, 59, 64 and 6. In patients with clinical stage I, the level of CA125 was also related to lymph node metastasis (P<0.01). When we evaluated the best cutoff level of lymph node metastasis factors using a ROC curve in patients with clinical stage I, the CA125 serum level of 25 U/ml was best, with 75.4% of sensitivity, 73.7% of specificity, 83.1% of false positive rate, 2.3% of false negative rate (Figure 2A). When we used preoperative serum CA125 to predict only lymph node metastasis without adnexal involvement, distant metastasis and positive peritoneal cytology, the CA125 serum level of 25 U/ml was best, with 71.7% of sensitivity, 77.6% of specificity, 83.3% of false positive rate, 2.2% of false negative rate (Figure 2B). The best cutoff to evaluate cervical stromal invasion in patients with clinical stage I was 22U/ml, with 69.7% sensitivity, and 70.4% specificity. The best cutoff value of serum CA125 level of 30 U/ml was with 81% of sensitivity, 78.4% of specificity in predicting adnexal involvement in patients with clinical stage I (Figure 3A). When we focused on
premenopausal patients, the best cutoff value of serum CA125 level of 30 U/ml was with 80% of sensitivity, 73.2% of specificity in predicting adnexal involvement (Figure 3B). When we used preoperative serum CA125 to predict extrauterine metastasis, 30 U/ml was the best with 74.3% of sensitivity and 81.9% of specificity.”

**Minor Essential Revisions**

1. In line 94-95 you state that peritoneal cytology is part of the standard treatment for endometrial cancer. This is no longer included in the staging system.

   Response: We had deleted the “peritoneal fluid sampling” from the line 98.

2. In line 99-101 you state, The disadvantage of systematic lymphadenectomy is a 7–10% risk of lymph cyst formation after surgery [2,3], along with increased anesthesia and operating time, and the need for a specialized surgical oncologist.” I would suggest including the risk of lymphedema, which is a much more symptomatic and long standing issue than lymph cyst formation.

   Response: We have changed the sentence to read “The disadvantage of systematic lymphadenectomy is a 13-22% risk of lower limb lymphedema after surgery[2,3], along with lymph cyst formation, increased anesthesia and operating time, and need for a specialized surgical oncologist.”

3. The second paragraph of the introduction needs to be shortened. There does not need to be as much information on the background of Ca-125 in ovarian
cancer. This weakens the purpose of the study.

Response: We have shortened the second paragraph and deleted the information on the background of CA-125 in ovarian cancer.

4. Need to include BMI information for the patient population.

Response: We have added, “The mean BMI of 995 patients was 26.32± 3.94kg/m².” in the Results. In addition, we also evaluated the preoperative levels of CA125 in patients with endometrial cancer in relation to BMI in Table 1.

5. Line 182-184 needs to be in the methods section.

Response: We had moved line 182-184 “The data on serum CA125 levels was not a standard normal distribution, so a nonparametric test was used to evaluate its relation with clinicopathological parameters.” into the Methods section.

6. Line 233-234 “… system, which determined grade 1 or 2 tumors with less than 50% myometrial invasion and no endometrioid cancer as low…” Suspect this is not worded correctly. Need to correct.

Response: We have changed it to read “In our study, using the Mayo clinic algorithm for omitting lymphadenectomy to include endometrioid histology, grade 1 or grade 2 tumors, myometrial invasion less than or equal to 50%, and no evidence of any metastatic disease at the time of surgery, the sensitivity, specificity, false positive and false negative rates are 71.8%, 80.2%, 76.7% and 2.8%, respectively.”

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