Author's response to reviews

Title: Serum HE4 as a Biomarker to Detect Recurrent Endometrial Cancer in Patients Undergoing Routine Clinical Surveillance

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Author's response to reviews: see over
Editor in Chief
BMC Cancer

Dear DR

Please find enclosed a revised version of our manuscript “Serum HE4 as a Biomarker to Detect Recurrent Endometrial Cancer in Patients Undergoing Routine Clinical Surveillance” We have addressed reviewers comments as outlined below

Reviewer's report 1
Title: Serum HE4 as a Biomarker to Detect Recurrent Endometrial Cancer in Patients Undergoing Routine Clinical Surveillance Version: 2 Date: 25 November 2014
Reviewer: Giuseppe Vizzielli

Reviewer's report:

Discretionary Revisions
Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer's report 2
Title: Serum HE4 as a Biomarker to Detect Recurrent Endometrial Cancer in Patients Undergoing Routine Clinical Surveillance Version: 2 Date: 17 December 2014
Reviewer: Michael Frumovitz

Reviewer's report:

Thank you for the opportunity to read your manuscript entitled “Serum HE4 Detects Recurrent Endometrial Cancer in Patients Undergoing Routine Clinical Surveillance.” This manuscript retrospectively analyzed 98 patients with endometrial cancer of which 26 (27%) recurred. The authors found HE4 to be a better biomarker for recurrence than CA125 although the sensitivity was still only 84%. The authors conclude that HE4 may be a useful marker for following patients with uterine cancer, particularly endometrioid histologies.

Prior to consideration for publication, the following concerns should be addressed:

1. Page 3, lines 89-90. The authors state “With more than 300,000 cases occurring annually worldwide, endometrial adenocarcinoma (EAC) is the
most common gynecological cancer.” This is not true. Cervical cancer, with almost 500,000 annual cases worldwide, is the most common gynecological cancer.

Thank you this line has been edited and now states:

“With more than 300,000 cases occurring annually worldwide, endometrial adenocarcinoma (EAC) is the second most common gynecological cancer”


Thank you this has not been added to page 3 2nd paragraph the sentence reads

“The Society of Gynecologic Oncologists recommend a thorough clinical history, clinical examination and patient education of worrying symptoms as the most effective methods of detecting recurrent EAC and state that at present there is a lack of evidence to support diagnostic interventions such as vault cytology or routine imaging to monitor endometrial cancer patients for recurrent disease”

3. Page 4, line 128: Please remove extra period.

Thank you, this has been removed

4. Page 8, line 192: Please change “diagnostic” to “diagnosis”.

Thank you, this has been changed

4. Page 8, lines 203-205: The authors write: “While increased HE4 levels at diagnosis have been shown to be prognostic by many groups [9, 11, 13, 16], this study focuses on HE4 and CA125 levels at the interval and recurrence/final time points.” This statement does not belong in the Results but rather in the Introduction just prior to the objectives of the study.

Thank you this sentence has been removed and paragraph 2, page 4 lines 127-128 have been edited as requested

5. Page 8, line 209: Please capitalize the “T” in “table”.

Thank you, this has been corrected
6. Page 10-11, final paragraph: The authors are quick to give full sets of numbers for sensitivity, specificity and NPV for all patients and the subset with endometrioid histology. For CA125, they only give the full percentages for all cancers and ask us to assume that there was no “significant” change for those with endometrioid. Please provide all the numbers and let the reader decide.

Thank you, this has been added and the data are presented in Table 4.

7. Page 14, line 336: The authors state that HE4 is elevated in 88% of patients with recurrent endometrioid endometrial cancer. I believe this should be 84%.

Thank you, this should be 81% - 21/26 cases. It has been changed.

8. Do the authors have any comparator group of recurrent patients who did not get HE4? In other words, did following HE4 make a difference in survival? They write in the Conclusion that their numbers approach those for CA125 in ovarian cancer yet we know that following CA125 in ovarian cancer patients does not change survival so why should we follow HE4 in women with endometrial cancer especially when only 20% or so will recur?

Unfortunately we do not had such a cohort, however this study did not focus on survival. The next logical step would be to examine whether HE4 would impact on clinical decision making and whether that would have an impact on survival. We have added this to the conclusion.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests

COMMENTS FOR AUTHORS

I really appreciate the manuscript by Brennan et al. summarizing the role of serum HE4 detecting recurrent endometrial cancer in patients undergoing routine clinical surveillance. Maybe in the next future we will face on a wider diffusion of novel follow up strategies based on new biomarkers. In this context, the proposed manuscript, although requires other confirmative prospective studies, suggests that HE4 may be used to triage and monitor EAC patients at high risk of recurrence, particularly in patients with low-grade endometrioid histology who would generally be considered at low risk of developing recurrent disease. Finally, only one small revision is required in order to improve the quality of the manuscript.

Specific points:
Material and methods
- Page 5 line 145: authors should delete this sentence since it is a result.

Thank you, this has been deleted

Kind regards

Prof. Andreas Obermair