International Journal of Cancer Management
Volume 15 · Issue 8 · e119065

OPEN PEER REVIEW

Prevalence of DNA Mismatch Repair Deficiency in Endometrial Cancer Using Immunohistochemistry

Behnoush Mehdizadeh, Masomeh Gharib, Amir Hossein Jafarian, Monavvar Afzal Aghaee, Fatemeh Homaei Shandiz, Amirhosein Irajpour

SUBMITTED	REVISED	ACCEPTED	DOI
27 Aug 2021	2 Apr 2022	30 Aug 2022	10.5812/ijcm-119065

About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

1 comment · 21 Oct 2021

Referee 1 Reviewer

ACCEPT 21 Oct 2021

Dear authors

Thank you for submitting the article entitled "Immunohistochemistry to determine the prevalence of mismatch repair-deficiency in 2 endometrial cancer". Though grammar and typing errors are understandable to some extent (especially with language barriers) and not necessarily the point of peer review, a handful of errors in this article affect the readers' ability to understand the material. Please recheck the whole text.

Regards,

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear editor and reviewers

Thank you for your consideration.

The manuscript entitled “Prevalence of DNA Mismatch Repair Deficiency in Endometrial Cancer Using Immunohistochemistry” was revised based on comments raised by your team. The changes are highlighted in yellow. Also, a point-by-point reply is available here:

1. The whole text was checked for grammatical issues.

2 Revision 1

0 comments

No public comments in this round.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear editor and reviewers

Thank you for your consideration.

The manuscript entitled “Prevalence of DNA Mismatch Repair Deficiency in Endometrial Cancer Using Immunohistochemistry” was revised based on comments raised by your team. The changes are highlighted in yellow. Also, a point-by-point reply is available here:

Comments:
1. Please correct the remaining typographical and grammatical errors. For example, in the Abstract "IHC expression of the MMR proteins (viz. MLH1, MSH2, MSH6, and PMS2) was 12%", what does "vis." mean? Also in line 134.
Thank you for your comment. We correct these mistakes.

The prevalence of LS based on the IHC expression of the MMR proteins (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) was 12% in the patients with EC.
2. Line 28-29: "Endometrial cancer (EC) is known as the most common malignancy of the female reproductive system (1)." However, based on ref. #1 it is the 2nd most common GYN cancer after cervical cancer.
Thank you for your comment. We correct these mistakes

Endometrial cancer (EC) is known as one of the most common malignancy of the female reproductive system
3. Lines 33-35: "The lifetime cumulative incidence risk of this condition in people harboring inactivating mutations in the DNA MMR genes, resulting subsequently in MMR deficiency, is thus 42-71% (4, 7)." This sentence requires correction. It would be hard to understand for readers.
Thank you for your comment. We revise this sentence.

The inactivating mutations in the DNA MMR genes result in a significant increase in the risk of endometrial cancer in the affected population
4. Lines 40-41: "IHC for a four-antibody panel of the MMR proteins is also a highly sensitive and specific method to evaluate LS (13)." Please add the sensitivity and specificity rates.
Thank you for your comment. We revise this sentence and add the requested data.

with a sensitivity between 85% and 100% and specificity between 85% and 92% and overall concordance rate of 98% between MMR IHC and MSI molecular testing (1, 2).

5. Lines 43-44: "this condition more effectively (14,18), the data regarding the presence of mutations. Please cite references in the main text in order. It seems ref. # 15,16, and 17 are missed.

Thank you for your comment. We design the references by Endnote to overcome this problem.

6. Line 85: Please designate the reason for excluding patients with metastatic disease. It is suggested to include them.

Thank you for your comment. We include “being metastatic at the presentation” as one of the exclusion criteria considering the rarity of this clinical scenario for patients with endometrial cancer.

being metastatic at the presentation [considering the rarity of condition for patients with endometrial cancer],

7. Table 3. Tumor site/The lack of … MMR proteins: two patients are missed. Also, Tumor site/The expression of … proteins: twenty patients are missed. If their data are unavailable, please mention them in the table.

Thank you for your comment. We have added this footnote to the table.

* Data of two patients in column “The lack of ... MMR proteins” and data 20 patients in in column “The expression of ... proteins” are missing.

8. Table 3. What does "tumor density" mean? if it means tumor grade or differentiation, please use the common term. Please also correct it in the main text.

Thank you for your comment. We have changed it to tumor grade in the whole text.

9. Lines 116-118: "On the other hand, previous studies have thus far shown a good correlation between IHC results (as an available and relatively cheaper method) and polymerase chain reaction (PCR) test ones in the evaluation of LS (22)." Please add information delineating the extent of correlations.

Thank you for your comment. We have added the highlighted sentence in response to your query.

On the other hand, previous studies have thus far shown a good correlation between IHC results (as an available and relatively cheaper method) and polymerase chain reaction (PCR) test ones in the evaluation of LS with a overall concordance rate of 98% between MMR IHC and MSI molecular testing (1-3).

10. Discussion: Please add more information on similar studies evaluating the association between MMR mutation and demographic/tumor characteristics.

Thank you for your comment. We have added more details.

11. Discussion: Recent evidence has delineated the functional role of mitochondria in repairing the DNA mutations as well as its crucial role in cancer pathogenesis (https://www.preprints.org/manuscript/202201.0171/v1). It is suggested authors mention this important issue and discuss this article.

Thank you for your comment. We try to cite this article “DOI: 10.1016/j.mito.2021.12.001” instead of this preprint.

Beside MSI, recent evidence has delineated the functional role of mitochondria in repairing the DNA mutations as well as its crucial role in cancer pathogenesis and their responses to treatments (4).

12. References: Please cite at least three relevant articles from IJCM.

Thank you for your comment. We have considered this comment.

Moreover, alteration of the K-Ras gene and other tumor suppressor genes are among the other important pathways (5, 6).

Reference

1. Boland CR, Goel A. Microsatellite instability in colorectal cancer. *Gastroenterology*. 2010;**138**(6):2073-87.e3. doi:10.1053/j.gastro.2009.12.064. [PubMed:20420947].
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4. Akbari H, Taghizadeh-Hesary F, Bahadori M. Mitochondria determine response to anti-programmed cell death protein-1 (anti-PD-1) immunotherapy: An evidence-based hypothesis. *Mitochondrion*. 2022;**62**:151-8. doi:10.1016/j.mito.2021.12.001. [PubMed:34890822].
5. Jabbara N, Asaadi Tehrani G, Lalooha F, Farzam SA, Elmizadeh K. Promoter Hypermethylation Analysis of the Tumor Suppressor Genes RASSF1A and RASSF2A in Iranian Endometrial Carcinoma Patients. 2017;**10**(4):e8629. doi:10.5812/ijcm.8629.
6. Izadi-Mood N, Sarmadi S, Rostamnasl B. Alteration of the K-Ras Gene Expression in Atypical and Nonatypical Hyperplastic Endometrium. 2013;**6**(4):e80474.

3 Revision 2

0 comments

No public comments in this round.