NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: 12/09/2022
To: "Michael Frumovitz" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-1933

RE: Manuscript Number ONG-22-1933

Secondary Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy for Advanced or Recurrent Mucinous Ovarian Cancer: Report of Two Cases

Dear Dr. Frumovitz:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by 12/30/2022, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Please note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* Figure 1: Please provide a letter of permission from the copyright holder to use this figure in print and online versions of the journal. Please upload as a figure file on Editorial Manager.

REVIEWER COMMENTS:

Reviewer #1: Re: ONG 22-1933

This is an intriguing manuscript, inasmuch as it reports two cases of long-term survival after unsuccessful primary therapy with chemotherapy in mucinous ovarian tumors. My main concern regarding this report of two cases is the lack of similarity between the two cases. Case 1 was a woman whose cancer arose in a benign cystic teratoma—in other words, in a germ cell-derived tumor. These are rare. Case 2 describes a tumor derived from Mullerian epithelium. Case 1 was treated primarily using the regimen of 5-fluorouracil (5-FU) and oxyplatin (OXP)—a regimen developed for GI malignancies; case 2 was first treated using the standard ovarian carcinoma regimen of carboplatin and paclitaxel, though there has been some interest in using 5-FU and OXP as primary chemotherapy against these tumors.

Be that as it may, after primary chemotherapy and recurrence, complete gross debulking was possible in both tumors. The ability to attain complete cytoreduction is unusual in recurrent ovarian carcinomas, since widespread miliary disease is the rule. So, a rare tumor and an unusual tumor were treated after recurrence using secondary reduction (which is not

possible more often than not) and HIPEC was given at the time of secondary cytoreduction. The results are gratifying, but it one wonders how many patients with epithelial mucinous ovarian carcinoma have completely resectable tumor after failure of primary chemotherapy due to persistence or recurrence.

Lumping the two mucinous carcinomas together as a clinical entity is misleading unless the authors can demonstrate that the natural history of a carcinoma arising from a benign germ cell tumor has the same relevant properties as a mucinous epithelial tumor. The manuscript should make this clear in the precis and the abstract.

Some specific points

* Lines 20-21: Change to "regimens developed for mucinous carcinoma as treatment for women…"

* Line 25: The article begins by discussing epithelial tumors, despite the fact that only one of the tumors treated was epithelial. They should consider removing the germ cell tumor from the case report or making it case 2 and adding a passage between the cases (or some other relevant place) saying that perhaps the histological features of the tumor rather than the tissue derivation is the germane factor. Of course, if there is comparability of tumor antigen expression between the tumors, the authors can describe this, and it would justify including both cases.

* Line 43: Change to "non-mucinous ovarian cancer."

* Line 48: Delete sentence beginning, "The pain persisted…"

* Line 62: Is the "index score" standard outside the authors' institution of the HIPEC community? The provenance of the index score should be cited here, and not just in the Figure. The citation should ideally be to a description in a journal article rather than to a book. The clinical significance, if any, and the validation of the index score should be described and cited.

* Lines 64-65: Delete "with mesh overlay and abdominal reconstruction," unless there is some importance to this.

* Line 65 and line 93: Change text to "complete gross cytoreduction."

* Line 66 ff.: The authors use higher cisplatin doses than are typical. If they can supply a citation for its safety and/or efficacy, they should.

* Line 68: Is any of the intraperitoneal therapy absorbed? If so, the text should be changed to "no further systemic therapy."

* Line 78: Spelling error: "Shen" should read "she."

* Line 81: Change to "At a 6-month…" It is not intuitive that there will be such a visit, so don't say "the."

* Line 97: Eliminate "At this writing." The sentence can still be rewritten to avoid the awkwardness of spelling out "twenty-seven."

* Line 101-103: Change "remarkably durable responses" to "continued absence of recurrence." By the time this manuscript sees publication in this or another journal it will be true that "both patients remain without clinical or radiological evidence of disease more than 2 years after complete operative cytoreduction and HIPEC."

* Lines 104-105: I don't think you can talk about significant improvement based on two cases, especially because 'significant' has statistical implications. Perhaps "These results far exceed the median…" would be a more reasonable claim.

* Lines 158-166: The Zivanovic trial cited as a basis for a previous dose of 100 mg/m2 was based on toxicity obtained at that dose, presumably deterring the investigators from pursuing a higher dose. The authors should be clear on this point.

* Lines 168-173: The authors then go on to describe their renal protective strategy. They do not cite the safety of this approach, and should do so, if they have published. Stating that 2 patients tolerated the procedure well (lines 174-175 does not constitute adequate supporting evidence for the safety of the approach. Even if they have unpublished data, they can describe this and cite to unpublished data if that is compatible with the publication policies of this journal. A description of a higher than typical dose given to two young patients may not be sufficient to persuade others to adopt this regimen, whether in the context of a trial or as off-label treatment.

Reviewer #2: In this case report, the authors describe 2 cases of primary mucinous ovarian cancer treated with cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC). They present existing data for HIPEC in advanced and recurrent ovarian cancer; prior data on mucinous cancers is limited and the 2 cases presented have done remarkably well with PFS of around 2 years in each case without additional treatments.

1. Case 1- The second sentence is unnecessary and could be deleted; suggest then adding the adjective "persistent" before "pain" in the first sentence.

2. Case 2-Was the described hysterectomy/oophorectomy a separate surgical procedure performed after the cystectomy? IF so, were any of the additional specimens removed positive for cancer?

3. Line 82 suggest deleting the word "abnormal".

4. Line 92 notes removal of "possible small bowel mesenteric implants". Since the authors have viewed the final pathology report, this sentence should not be ambiguous.

5. The authors administered double the previously reported and NCCN-recommended dose of cisplatin in their HIPEC regimen and report precautions taken to protect renal function. However, they should give more detailed information on the post-treatment renal function of their 2 cases.

--
Sincerely,
Jason D. Wright, MD
Editor-in-Chief

The Editors of Obstetrics & Gynecology

_____

Thank you for the allowing us to respond to the reviewers' comments. We would like to thank the editors and reviewers for reading our submission and for their thoughtful comments. We appreciate the opportunity to strengthen and resubmit our manuscript. Below are the comments, our responses, and the appropriate change to the manuscript. Please note we are happy to make additional edits/changes at the Editor's request.

EDITOR COMMENTS:

Please note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://urldefense.com/v3/__https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf__;!!PfbeBCCAmug!hk_ZlCT7VguwDIguujDFuOOpBM8e9y4oGIwwtLobMy3w1qHLbPlwo9rMvKtSsLYnbvmhHnzWoO1z9HpW-ndhog$ and making the applicable edits to your manuscript.

Response: We have reviewed the Revision Checklist and believe the manuscript is in compliance.

* Figure 1: Please provide a letter of permission from the copyright holder to use this figure in print and online versions of the journal. Please upload as a figure file on Editorial Manager.

Response: We have received permission from the author (Dr. Paul Sugarbaker) to utilize his figure. Please see attached email from Dr. Sugarbaker.

REVIEWER COMMENTS:

Reviewer #1: Re: ONG 22-1933

This is an intriguing manuscript, inasmuch as it reports two cases of long-term survival after unsuccessful primary therapy with chemotherapy in mucinous ovarian tumors. My main concern regarding this report of two cases is the lack of similarity between the two cases. Case 1 was a woman whose cancer arose in a benign cystic teratoma—in other words, in a germ cell-derived tumor. These are rare. Case 2 describes a tumor derived from Mullerian epithelium. Case 1 was treated primarily using the regimen of 5-fluorouracil (5-FU) and oxyplatin (OXP)—a regimen developed for GI malignancies; case 2 was first treated using the standard ovarian carcinoma regimen of carboplatin and paclitaxel, though there has been some interest in using 5-FU and OXP as primary chemotherapy against these tumors.

Be that as it may, after primary chemotherapy and recurrence, complete gross debulking was possible in both tumors. The ability to attain complete cytoreduction is unusual in recurrent ovarian carcinomas, since widespread miliary disease is the rule. So, a rare tumor and an unusual tumor were treated after recurrence using secondary reduction (which is not possible more often

than not) and HIPEC was given at the time of secondary cytoreduction. The results are gratifying, but it one wonders how many patients with epithelial mucinous ovarian carcinoma have completely resectable tumor after failure of primary chemotherapy due to persistence or recurrence.

Lumping the two mucinous carcinomas together as a clinical entity is misleading unless the authors can demonstrate that the natural history of a carcinoma arising from a benign germ cell tumor has the same relevant properties as a mucinous epithelial tumor. The manuscript should make this clear in the precis and the abstract.

Response: As mature cystic teratomas are benign lesions and as all pathology from the secondary cytoreduction surgery were invasive mucinous carcinoma we do not believe that the teratoma component had any bearing on the outcome of the case. We have clarified this in the manuscript by adding the following to the case in regards to the secondary cytoreduction: "All pathologic specimens returned invasive mucinous ovarian cancer with no teratoma components." (lines 66-67)

Some specific points

1. Lines 20-21: Change to "regimens developed for mucinous carcinoma as treatment for women…"

Response: Per the reviewer's suggestion, "utilized" has been changed to "developed" in the Teaching Points. (lines 20)

2. Line 25: The article begins by discussing epithelial tumors, despite the fact that only one of the tumors treated was epithelial. They should consider removing the germ cell tumor from the case report or making it case 2 and adding a passage between the cases (or some other relevant place) saying that perhaps the histological features of the tumor rather than the tissue derivation is the germane factor. Of course, if there is comparability of tumor antigen expression between the tumors, the authors can describe this, and it would justify including both cases.

Response: We believe the mature teratoma (which is not a malignant germ cell tumor) was an incidental finding and it is extremely unlikely that the invasive mucinous carcinoma arose from the mature teratoma. In addition, as described above, specimens from the secondary cytoreduction surgery revealed only invasive mucinous carcinoma with no evidence of mature teratoma element.

3. Line 43: Change to "non-mucinous ovarian cancer."

Response: Per the reviewer's suggestion, "ovarian cancer" has been changed to "non-mucinous ovarian cancer". (line 42)

4. Line 48: Delete sentence beginning, "The pain persisted…"

Response: Per the reviewer's suggestion, the sentence beginning, "The pain persisted…" has been deleted. (line 48)

5. Line 62: Is the "index score" standard outside the authors' institution of the HIPEC community? The provenance of the index score should be cited here, and not just in the Figure. The citation should ideally be to a description in a journal article rather than to a book. The clinical significance, if any, and the validation of the index score should be described and cited.

Response: The peritoneal carcinoma index is validated and reliable and used as standard of care in HIPEC surgery. The clinical development, validation, and reporting of its use in HIPEC surgery is beyond the scope of this manuscript. If the Editors would like us to add a paragraph or two discussing PCI we would be happy to do so but we are trying to be conscious of the Journal's word limit for case reports.

6. Lines 64-65: Delete "with mesh overlay and abdominal reconstruction," unless there is some importance to this.

Response: Per the reviewer's suggestion, "with mesh overlay and abdominal reconstruction," has been deleted. (lines 64-65)

7. Line 65 and line 93: Change text to "complete gross cytoreduction."

Response: Per the reviewer's suggestion, "complete cytoreduction" has been changed to "complete gross cytoreduction". (lines 65 and 95)

8. Line 66.: The authors use higher cisplatin doses than are typical. If they can supply a citation for its safety and/or efficacy, they should.

Response: The rationale for the cisplatin dose of 200 mg/m^2 is addressed in the final paragraph of the discussion (lines 173-188).

9. Line 68: Is any of the intraperitoneal therapy absorbed? If so, the text should be changed to "no further systemic therapy."

Response: Per the reviewer's suggestion, the text was revised to "no additional systemic therapy". (lines 69-70)

10. Line 78: Spelling error: "Shen" should read "she."

Response: The spelling error "shen" was corrected to "she". (line 80)

11. Line 81: Change to "At a 6-month…" It is not intuitive that there will be such a visit, so don't say "the."

Response: Per the reviewer's suggestion, "At the 6-month…" was changed to "At a 6-month" (line 83)

12. Line 97: Eliminate "At this writing." The sentence can still be rewritten to avoid the awkwardness of spelling out "twenty-seven."

Response: "At this writing" has been deleted and the sentence has been rewritten beginning with "More than…" (line 99)

13. Line 101-103: Change "remarkably durable responses" to "continued absence of recurrence." By the time this manuscript sees publication in this or another journal it will be true that "both patients remain without clinical or radiological evidence of disease more than 2 years after complete operative cytoreduction and HIPEC."

Response: We agree that by the time this is published both patients will likely have had > 2 years without recurrence however we cannot be certain that we will not detect a recurrence in either patient in the time between final submission and date of publication. Therefore we do not feel comfortable stating both patients will be > 2 years disease free.

14. Lines 104-105: I don't think you can talk about significant improvement based on two cases, especially because 'significant' has statistical implications. Perhaps "These results far exceed the median…" would be a more reasonable claim.

Response: Per the reviewer's suggestion, "represent significant improvement" has been deleted and replaced with "far exceed the reported median". (lines 107-108)

15. Lines 158-166: The Zivanovic trial cited as a basis for a previous dose of 100 mg/m2 was based on toxicity obtained at that dose, presumably deterring the investigators from pursuing a higher dose. The authors should be clear on this point.

Response: Per the reviewer's suggestion, we clarified that the investigators did not pursue additional dose levels above 100 mg/m^2. We have added the following to the Discussion: "Per their protocol, the investigators did not explore additional dose escalations above 100 mg/m^2." (line 171)

16. Lines 168-173: The authors then go on to describe their renal protective strategy. They do not cite the safety of this approach, and should do so, if they have published. Stating that 2 patients tolerated the procedure well (lines 174-175) does not constitute adequate supporting evidence for the safety of the approach. Even if they have unpublished data, they can describe this and cite to unpublished data if that is compatible with the publication policies of this journal. A description of a higher than typical dose given to two young patients may not be sufficient to persuade others to adopt this regimen, whether in the context of a trial or as off-label treatment.

Per the reviewer's suggestion, the following has been added to the Discussion: "At MD Anderson we have a long and safe experience utilizing cisplatin at a dose of 200 mg/m^2 with our CRS/HIPEC procedures. We have been using this dose for more than 10 years and have treated more than 150

patients with mesothelioma and recurrent appendiceal cancer without significant renal or non-renal toxicity compared with published data of 100 mg/m^2 (unpublished data)." (lines 173-179)

Reviewer #2: In this case report, the authors describe 2 cases of primary mucinous ovarian cancer treated with cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC). They present existing data for HIPEC in advanced and recurrent ovarian cancer; prior data on mucinous cancers is limited and the 2 cases presented have done remarkably well with PFS of around 2 years in each case without additional treatments.

1. Case 1- The second sentence is unnecessary and could be deleted; suggest then adding the adjective "persistent" before "pain" in the first sentence.'

Response: Per the reviewer's suggestion, the sentence beginning "The pain persisted" has been deleted (line 48)

2. Case 2-Was the described hysterectomy/oophorectomy a separate surgical procedure performed after the cystectomy? IF so, were any of the additional specimens removed positive for cancer?

Response: There were no other positive specimens which is reflected in the final stage assignment of IC. (line 77)

3. Line 82 suggest deleting the word "abnormal".

Response: Per the reviewer's suggestion, the word "abnormal" was deleted from the sentence beginning, "Computed tomography…" (line 84)

4. Line 92 notes removal of "possible small bowel mesenteric implants". Since the authors have viewed the final pathology report, this sentence should not be ambiguous.

Response: Following review of the final pathology report, and per the reviewer's suggestion, the word "possible" was deleted from "possible small bowel mesenteric implants…" (line 94)

5. The authors administered double the previously reported and NCCN-recommended dose of cisplatin in their HIPEC regimen and report precautions taken to protect renal function. However, they should give more detailed information on the post-treatment renal function of their 2 cases.

Response: Per the reviewer's suggestion, we have clarified that neither patient experienced renal toxicity (lines 69 and 98). Furthermore, we have discussed the high dose of cisplatin and renal protection in the Discussion (lines 173-188)