OBSTETRICS & GYNECOLOGY

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

Date: Jan 24, 2019
To: "Jason D. Wright" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-2381

RE: Manuscript Number ONG-18-2381

CHEMOTHERAPY VERSUS CHEMOTHERAPY AND RADIATION FOR STAGE III UTERINE CANCER

Dear Dr. Wright:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Feb 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Abstract -

Objective - Recent data shows that chemotherapy alone has a similar survival with decreased toxicity compared to chemotherapy and external beam radiation in comparing outcomes of patients with Stage III uterine cancer

Methods - Stage III endometrial, serous, clear cell uterine cancer with chemotherapy +/- vaginal brachytherapy and chemo/ XRT +/- vaginal brachytherapy was compared

Results - 18,456 women - 51% chemo alon, 48.8% chemo with XRT - decreased mortality shown across all subtypes

Conclusion - Combination chemo / XRT showed decreased mortality as compared to chemotherapy alone

Introduction - Endometrial cancer is reviewed. Stage III and IV tumors make up a small percentage but have low 5 year survivals and the optimal management is uncertain based on recent prospective trials which have not shown a survival advantage for combination chemo and XRT

Methods - National Cancer Database was used

Patient selection - Stage III Uterine cancer patients between 2004-2015, primary aim to determine with external beam XRT improved survival over chemotherapy alone - chemo alone could include vaginal brachytherapy
Statistical analysis - described

Results - 18.456 women - 51.2% received chemotherapy alone and 48.8% received chemotherapy and XRT

combo - 39.6% of St IIIA, 51% St IIIB, 51.2% St IIIC

Patients receiving chemo alone were more likely to die than those receiving combo therapy - Stage IIIA had a 21% decrease in mortality and Stage IIIC had a 23% decrease

Discussion - Stage III uterine cancer survival was improved with chemotherapy and XRT across all histologic subtypes and for individual substages

combination therapy decreased mortality by 24%

findings differing between population based study versus clinical trial - no details on number of cycles/ chemotherapeutic agents and it doesn't factor in increased toxicity and decrease in quality fo life

Comments -
This is overall an excellent population based study showing pretty convincing benefit of combination therapy treatment vs chemotherapy alone

Obviously treatment needs to be individualized, but the findings are significant and the study is overall well done.
It is unfortunate that more information is not available about chemo type.

I do think it is important to address the issue of vaginal brachytherapy. This could have had a significant impact on local/ regional recurrence of disease.

I think it would be important to separate the data to see if there was a difference in survival between the subgroups that either did or did not receive vaginal brachytherapy in both treatment groups and see how this impacts survival. Is the beneft truly due to external beam radiation or is there a significant benefit just from vaginal brachytherapy. I feel like this piece of information is a very important addition.

Reviewer #2: The best way to treat stage III endometrial carcinoma remains controversial despite the recent presentation of findings from several cooperative group studies and it is unclear whether adjuvant radiation therapy, chemotherapy or a combination of both provides patients with the best oncologic outcomes.

The authors of this study attempt to determine whether stage III endometrial cancer patients receiving a combination of chemotherapy and external beam radiation therapy have better survival than patients receiving chemotherapy alone using the National Cancer Database (NCDB). The NCDB is a large national database that compiles information on cancer patients from over 1,500 hospitals in the United States, capturing more than 70% of new cancer diagnoses. The authors identified 18,456 women who underwent a hysterectomy between 2004 and 2015 with a pathologic diagnosis of stage III endometrial carcinoma and received adjuvant chemotherapy with (9,456 patients) or without (9,000 patients) external beam radiation therapy. They then performed statistical analyses to compare these groups including adjusted survival curves and log-rank test to compare all-cause mortality. Sensitivity analyses were performed to examine the role of pathologic factors in treatment choices and outcomes and chemotherapy variations in outcomes. In this study, combination therapy increased with stage at diagnosis and was used more commonly to treat endometrioid histology. Table 1 shows that the cohorts were well-balanced when comparing clinical and pathologic characteristics. The major finding of this study is that women who received chemotherapy alone had worse all-cause mortality than women who received combination therapy with a hazard ratio of 0.76 (CI 0.72-0.81). These findings were confirmed in sensitivity analyses examining stage and use of multi-agent chemotherapy. From this study, the authors conclude that adjuvant treatment of stage III endometrial cancer patients with combination chemotherapy and external beam radiation leads to better oncologic outcomes when compared to treatment with chemotherapy alone.

Major points:
-I think the question that the authors are trying to answer is clinically important and I do not think this paper suggests that we should abandon the use of combination therapy in favor of chemotherapy alone in the treatment of Stage III endometrial cancer.

-The study is large with over 18,000 patients diagnosed and treated over a 12-year time frame. The cooperative group studies that this paper refers to enrolled 20X fewer patients. It would be impossible to enroll this number of patients into a randomized trial and thus a database study is a good option for looking at outcomes in a large cohort of patients. However, as the authors note in their discussion, there are limits to such studies.

-As stated in their discussion (lines 291-295), the combination treatment group is a widely diverse group of patients that includes patients who received chemotherapy for radiation sensitization purposes only and patients who received multi-agent chemotherapy and radiation either concurrently or sequentially. These two patient populations, and the intentions of treatments, are very different and grouping them together likely confounds the study. The authors attempt to tease apart these groups by performing a subgroup analysis looking at only patients who received multi-agent chemotherapy and radiation; they did not find that outcomes of this group differed from those of all patients in the chemo-radiation group. Providing more information about the number of patients that received multi-agent chemotherapy as opposed to single agent chemotherapy would have helped illustrate to the reader the diversity (or lack thereof) within this group.

-I am curious as to why the authors excluded patients receiving radiation alone from their study. This may have allowed for a good comparison group and provided insight into the degree to which radiation therapy contributes to the survival benefit seen with combination therapy. I think the authors should have at least rationalized why they excluded this population especially since PORTEC3 compared radiation alone to combination therapy.

Minor Points:
-Figure 3, a Kaplan-Meier of overall survival, shows overlapping confidence intervals and converging curves after 5 years, likely due to small numbers.

-Formatting of the tables could be improved so that categories and subgroups are on the same page.

-The study provides some information regarding treatment practices and changes in practices over this time frame.

Reviewer #3:

Specific questions:

Line 126: "recent prospective clinical trials" - please provide references

Line 140: Although NCDB captures 70% of newly diagnosed cancer cases, can we assume that the number is this high for GYN as well?

Line 149: Why were patients who had radiation alone excluded?

Line 165: What, specifically, is site-specific Factor 1?

General comments:
This is a well written paper, but is limited by the nature of database driven studies (i.e. the authors can only use the variables provided in the NCDB). As NCCN guidelines for stage III disease recommend systemic therapy AND/OR external beam radiation (+/- vaginal brachytherapy), further explanation is needed as to why patients who had radiation alone were excluded. This omission severely limits the paper (unless the authors can provide a robust justification).

Reviewer #4:

ONG-18-2381
Chemotherapy vs Chemotherapy and Radiation for Stage III Uterine Cancer

The authors present a retrospective evaluation of data from the National Cancer Database focused on surgical Stage III uterine cancers who received either chemotherapy or chemoradiation in the adjuvant setting. The primary purpose of the analysis was to determine if use of radiation along with chemotherapy was associated with improved survival compared to the use of chemotherapy alone. The authors sought to overcome the inherent limitations of a database analysis by strictly defining the types of cases to be included and by employing statistical testing (propensity score analysis) to adjust for bias due to confounding variables.

The authors found 18,456 patients that met their inclusion criteria, slightly more (51.2%) receiving chemotherapy alone. More women with endometroid tumors received chemoradiation, compared to those with serous and clear cell histologies who were more likely to receive chemotherapy alone. In the survival analysis, the authors observed that women who were treated with chemoradiation were less likely to die compared to women treated with chemotherapy alone. This finding remained consistent across different sub-types of uterine cancer. Additionally, this finding remained consistent in sensitivity analyses.

The manuscript is well-written, straightforward, and topical. I think it is a meaningful contribution to the ongoing discussion/debate about the best treatment for women with Stage III uterine cancers. Despite recent prospective, randomized data, important questions remain. The data presented here are in line with the outcome of Stage III patients in PORTEC 3. The abstract of GOG 258 shows us the importance of radiation in achieving local control of advanced uterine cancers. The data here would argue that there is, in fact, a survival advantage as well. I have the following comments, thoughts, and suggestions for the authors.

Methods
144-150 During the timeframe under study (2004-2015), there was a change in the staging system for uterine cancer (FIGO 2009). Many patients who were Stage IIIA due to positive washings prior to 2009, would no longer be included after 2009. This group has an otherwise favorable outcome, compared to the remaining Stage III patients. I would suggest that women who were Stage III by positive washings alone should be excluded from this analysis as they do not contribute to our contemporary understanding of the treatment of advanced uterine cancer.

Conclusion

245 I would recommend stating, "These results suggest…. "
257-258 Use of chemotherapy alone was more common, according to the data presented.
266-267 It is worth noting that the overall survival data of GOG 258 is not mature
387 Double check the reference of the GOG 258 abstract for accuracy

Figures
While interesting, Figure 2 does not add to the overall thrust of the paper and is adequately described in the text. On the other hand, the Supplemental Figure is quite interesting and should be brought into the main portion of the manuscript.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

lines 149-150: Should comment on the reasons for excluding the group with radiation treatment alone. Were those inherently a different population that could not be compared to the other cohorts? Seems like a logical extension of comparing chemo vs chemo + radiation to have also compared with radiation alone.

lines 180-181: If the model were cubic, then why would it be anything but degree = 3?

lines 194-198: Were the survival data examined to determine if the losses conformed to the proportional hazards rate assumption?

Table 1: Should briefly explain for the reader how the method resulted in expansion of the sample from a total of 18,456 to an adjusted sample total of 19,304.

Fig 1: Should elaborate on the Excluded = 8,177 to identify the subsets.

Table 2: Need units for age.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

- Not clear to at least this non Oncologist how including chemo with brachytherapy could be considered chemo alone. Why would that not be considered chemoradiation? As several reviewers note, and I agree with them, it would make sense to include a radiation group alone as well.

- The Journal style doesn't not use the virgule (/) except in numeric expressions. Please edit here and in all instances.

- What is the mortality of the cohort? Please add this information to the Abstract and body text.

2. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
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3. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email

from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

4. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 26 typed, double-spaced pages (6,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

7. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

8. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

9. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

10. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

11. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

12. Figures

Figure 1: This figure may be resubmitted as-is.

Figures 2–3 and Appendix 1: Are high res versions of these figures available (preferably in the original file type [eps, tiff, jpeg])? Items pasted into other programs often lose resolution.

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publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

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If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Feb 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

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