

# OBSTETRICS & GYNECOLOGY



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**Date:** Jan 29, 2019  
**To:** "Koji Matsuo" [REDACTED]  
**From:** "The Green Journal" em@greenjournal.org  
**Subject:** Your Submission ONG-18-2268

RE: Manuscript Number ONG-18-2268

Association of surgical volume for radical hysterectomy and survival of women with early-stage cervical cancer: A Japanese Gynecologic Oncology Group study

Dear Dr. Matsuo:

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 19, 2019, we will assume you wish to withdraw the manuscript from further consideration.

#### REVIEWER COMMENTS:

Reviewer #1: The purpose of this manuscript was to "examine the association between surgical volume and survival of women with early-stage cervical cancer who underwent radical hysterectomy." This was a retrospective cohort study of subjects who underwent radical hysterectomy between 1/2004 to 12/2008 at JGOG sites.

1. The authors note that they used "a universal data entry form for collecting clinical, tumor, treatment, and survival information from archived medical records." Who extracted the archived medical records, reviewed the records and recorded the information on the universal data entry form? Did one or more than one person review the records and record the data? What was done to ensure accuracy of data entry on the form? What was done if there was missing data?
- 2.. Did one or more than one member of the research staff review the data on the universal data entry form and record it in the master excel data sheet? The authors note that the principal investigator "reviewed the accuracy, consistency, and quality of the dataset". Please expand on what the principal investigator did to ensure accuracy, consistency and quality? What was the accuracy, consistency and quality of the data in the dataset?
3. How many JGOG designated institutions are there in Japan? How were the 116 institutions who participated chosen to be involved in this study? In Japan do all JGOG-designated member institutions have fellowship-trained physicians?
4. The authors note that "among 6,003 cases in the dataset, 5,964" were included in this study. Why were the other 39 cases excluded?
5. Line 82: "a surgical volume". Should it be "surgical volume"?
6. Line 204: "were more likely to be young whereas those in the low-volume group were old." Please re-write this sentence.
7. Line 213-214: "low-volume centers were more likely to receive neoadjuvant chemotherapy prior to RH whereas those in the high-volume centers". Please re-write.
8. Lines 283-285: "volume was somehow consistent to what observed in this study ( $\geq 21$  cases a year), and similar trends have also been observed in endometrial cancer surgery." Please re-write.
9. Please carefully review references and make sure they conform to Green Journal's instructions for authors, esp et al.

Reviewer #2: Matsuo et al present there manuscript looking at the association of surgical volume for radical hysterectomy and survival of women with stage I and II cervical cancer.

Given the current state of research in regards to open vs minimal invasive radical hysterectomy, a question regarding surgical volume is timely.

However, There is too much bias in this paper to state that surgery at high volume centers is the reason for improved survival.

Low/Moderate sites demonstrated a stark difference from what would be seen in academic/high volume centers. The low and moderate sites were more likely to give neoadjuvant chemotherapy and perform surgery on bulky disease. Neoadjuvant chemotherapy has shown lack of benefit in multiple RCT trials both nationally and internationally. Also surgery for bulky disease is not supported by clinical trials and the NCCN guidelines. Therefore, what may really be being seen in this study is not a questions of surgical skill, but a question of quality of care at low/moderate vs high volume centers.

Instead of focusing on surgical outcomes, a better question may be to look at outcomes in general. Other studies published on cancer outcomes by volume centers, including uterine and ovarian, have focused on outcomes in general, rather than any one factor.

Rigorous inclusion/exclusion criteria may be able to improve the ability to look at just surgery.

Reviewer #3: Matsuo et al. have submitted the analysis of JGOG institutions with the intent of investigating the role of surgical volume in radical hysterectomy outcomes.

Overall, the manuscript is well written, and the analysis is appropriate. Moreover, the manuscript is timely, given the recent literature highlighting the differences in minimally invasive hysterectomy and open approaches.

I have a few suggestions and questions for authors to address:

1. The inclusion of Stage II patients makes the applicability of this data in the United States limited, given that all these patients would have received primary chemoradiation. Authors should address this issue in the limitations.
2. The cases were from 2004-2008, which provides a challenge for this manuscript. In this time frame, several surgical innovations have happened and could undermine the results of this study. However, the core message of high-volume = better oncologic outcomes might not have changed. Nevertheless, authors should discuss this in the limitations of this study.
3. Methods: p-value minimization technique utilized by this paper is something I had not personally heard of before. However, based on their explanation, I am not very convinced that it is the right technique. Authors defined the volume cut-offs using the primary outcome (overall survival), then they analyzed the data and concluded that high-volume is associated with improved survival. There are two possible ways to address the problem:
  - a) Make arbitrary cut-offs (e.g <10 cases/yr, 10-20 cases/year etc.)
  - b) Use volume as a continuous variable. Then perform the analysis to define optimal cut-offs where adjusted survival changes. For example, if adjusted survival is statistically improved after 60 cases/year, then that becomes a better way to define the cut-off.

Once these issues are addressed, I think this manuscript is very timely. Given that we are now doing open radical hysterectomy and falling volume of radical hysterectomy in the US (PMID 30424895), centralization of radical hysterectomy should be advocated.

#### STATISTICAL EDITOR'S COMMENTS:

1. lines 136-144: The method used to stratify surgical volume used the DFS by Cox PH regression to identify the three outcomes, which would essentially identify optimal cutpoints to highlight the differences. Authors should also include: not just how many subjects, but how many centers were identified as high, medium or low volume centers. Also, what were the results of analysis if another method were used to stratify, such as division into quartiles, or simply above/below the median. In other words, a method that does not use the outcome data (DFS) to determine the group boundaries.
2. Table 1: To what extent could the differential rates of sampled lymph nodes have led to incorrect ascertainment of Clinical stage which in turn could have affected DFS etc?
3. General and Table 2: Were the outcomes of DFS, overall survival etc tested as to whether the distributions conformed to the assumptions of proportional hazards vs another distribution, e.g, Weibull?

4. Table 3: This Table is in an important format, but for the purposes of our readers, would be better to show with p-values how well matched the two data sets were after propensity score matching. Could either include another column with p-values or include this Table (with SD) as supplemental table and main text Table 3 with p-values.

5. Fig 1: Were these categories stable over the 5 years or did some centers initially in low volume category have enough cases in later years to become mid-volume (line 204-205). Seems clear from this figure that there were many more mid-volume than high-volume centers and that the variability in low-volume centers is likely due to their low volume (ie, small sample sizes), hence wider CIs. Again, should identify how many centers were in each category.

#### ASSOCIATE EDITOR - GYN:

Please insert a sentence at beginning of Abstract Results to orient the reader by stating either PFS or OS in the IB1-IIB or IB1 alone group

#### EDITORIAL OFFICE COMMENTS:

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4. 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.

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Figure 3: Please upload each of these graphs as a high res image (jpeg, tif, eps). Items pasted into other programs often lose resolutions and appear poorly in print.

Appendices: Note that appendices should be named per the order in which they appear in the manuscript (ie, Appendix 1, Appendix 2, etc.). Please update the appendix file and the manuscript to reflect this."

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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 19, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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