NOTICE: This document contains comments from the reviewers and editors generated during peer review of the initial manuscript submission and sent to the author via email.

Questions about these materials may be directed to the Obstetrics & Gynecology editorial office: obgyn@greenjournal.org.
RE: Manuscript Number ONG-19-1005

Intraoperative capsule rupture, postoperative chemotherapy, and survival of women with stage I epithelial ovarian cancer: A JSOG-JSGO joint 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 Jul 16, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Thank you for this study evaluating an important clinical question of incidence of intraoperative rupture and prognostic implications for an otherwise stage I ovarian cancer. It is a good use of a large database, and I think the topic is appropriate for the Green Journal. I do think though there are some limitations that I recommend be addressed before considering for publication.

The methods seem for the most part sound, though I defer to the statisticians for those details. I do think there would be value in including other stage Ic categories for comparison of prognostic implications, especially regarding impact of chemotherapy.

It is a major limitation to the study that data were not included regarding surgical approach and comorbidities such as obesity and endometriosis, PID, etc. These are significant confounding variables to the conclusions, and the study would be best served by filling in these gaps. If truly not feasible to obtain these data from other sources, at the very least it should be specifically discussed in the methods section that the information is not included in the database and could not be included in your logistic regression modeling (in addition to mentioning it in the discussion).

Your conclusion on line 301 about decreased utilization of chemotherapy is an interesting and plausible hypothesis. Please be more clear that this is a proposed potential explanation (not a conclusion), as your study cannot link this cause and effect. Similarly, the proposition that observation is a reasonable option (line 305) is too much of a stretch. The data from the prospective study you describe is necessary to inform such a recommendation.

Some of the manuscript, especially in the introduction, would benefit from an edit for ease of reading and more clear and direct communication.

Reviewer #2: In this manuscript, the authors present a retrospective observational study based in Japan examining over 15,000 women with stage IA-IC1 epithelial ovarian cancer who underwent primary surgical treatment from 2002-2015. The study aim was to examine the impact of capsule rupture and the use of chemotherapy on cause-specific survival (CSS). These questions are relevant and incompletely understood and the studied database appears to offer improved understanding that could help in patient counseling. I have the following questions/comments:

1) Lines 118-122 could be dropped at the end of the introduction - it is not necessary to repeat the study aim in the methods.
2) Lines 84-86, “non-epithelial ovarian cancer or epithelial ovarian cancer other than these four types, borderline ovarian tumors, non-surgical management, and neoadjuvant therapy prior to the surgical treatment.” This sentence is confusing. I gather the "other than these four types" is referring to serous, mucinous, epidermoid and clear types that is cited earlier in the sentence but then you list borderline, non-surgical management etc., that could represent "other" categories that are included in your study cohort (yes, I know these add up to three but I had to stop and re-read this and that's my point).

3) If you’re going to use a CHAID model you have to include (usually in a box) your stopping rules and how the model was verified (K-fold, etc).

4) Can more be said about the database. Are the included data cross-checked for accuracy? Are there any data comparing the 50% of cases that are NOT included in the database w/ the ones that are? It seems odd that the kind of chemo used in a given cancer case wouldn't be included in the database.

Overall, the study has clear and worth aims, makes use on a sizable and apparently reliable database, and the analysis is appropriate with informative results.

Reviewer #3: Thank you for the opportunity to review a manuscript titled "Intraoperative capsule rupture, postoperative chemotherapy, and survival of women with stage I epithelial ovarian cancer: A JSOG-JSGO joint study". This is a retrospective study using a Japanese nationwide dataset from 2002-2015 at multiple institutions in Japan.

The objective of this study is to describe the significance of intraoperative capsule rupture in stage I ovarian cancer. This is not always clear or precisely stated in different parts of the manuscript. The questions I was looking for answers to were how many and which histology of stage I ovarian cancer had intraoperative rupture? If rupture occurred what was the CSS compared with those that did not rupture? And if rupture occurred then how did adjuvant chemotherapy change CSS?

The clinical value in these question is significant as this is a dilemma experienced by the gynecologic surgeon. One scenario is that attempts at en bloc resection often prevents patients from undergoing an attempted laparoscopic approach with subsequent increased morbidity and unclear impact.

The title seems wordy considering it does not describe any results or conclusive findings from the study. The precis/research highlight should state that only stage IA, IB, IC1 patient are included since IC2, IC3 were excluded.

This is not a unique or novel study but adds to the limited research surrounding this important question. It builds on prior publications in this journal such as Bakkum-Gamez et al. Influence of intraoperative capsule rupture on outcomes in stage I epithelial ovarian cancer. Obstet Gynecol 2009. And a few of this author's prior manuscripts such as Matsuo, K et al. survival outcome of stage I ovarian clear cell carcinoma with lymphovascular space invasion. Gynecol Oncol feb 2015.

Other specific questions for the authors:

1. Why did the authors decide to exclude IC2, IC3 cases but still include IA, IB, IC1 cases in which lymphadenectomy (staging) was not performed? Similarly, was cytology collected/available in all cases?

2. Do the authors believe that the difference in risk of intraoperative rupture between clear cell and mucinous histology is meaningful or clinically useful? i.e. regardless of histology there seems to be a 32-57% chance of intraoperative rupture.

3. Table 2: if possible, include n for columns because assuming column 1 whole cohort (15163) and ruptured cases (7227)

4. Line 20 abstract unclear what the comparisons groups are in cohort level analysis (?only ruptured 7,227)?

5. Line 25-27 only IA-IC1 and impact on survival if ruptured compared to not ruptured group?

6. Line 45 missing citation?

7. Line 55 seems to disagree with line 46, understanding the impact on survival in current literature; distinct survival in substages versus unknown.

8. Line 69 Are there any prior studies looking at the accuracy of this database. And does the database include grade among histologic subtypes

9. Line 82: how to reconcile the inclusion of cases without lymphadenectomy while excluding IC2, IC3. Would a portion of included stage I clear cell or serous tumors be "upstaged" if lymphadenectomy performed?

10. Line 114: was IC1. Or IC(b) data only collected after 2014? How was prior data clarified if FIGO staging only in 2014 provided separate substaging for intraoperative rupture?

(adhesions)? Surgeon? Do we know number of institutions? Volume per institution? More volume less rupture? Better survival?

12. Line 140: what were the intraoperative factors entered in the model?

13. Line 153: what does survival data were matured mean?

14. Line 164: which 2 groups? Rupture vs nonrupture, chemo vs no chemo?

15. Line 170: what were the adjuvant chemotherapy criteria? Did any IA, IB serous or clear cell histology receive adjuvant chemotherapy?

16. Line 170-172 seem better suited for background or discussion

17. Line 242: If possible, please reconcile that data in table 1 which seems to imply a temporal decrease in the use of adjuvant chemotherapy regardless of histologic subtype and why only for example 52% of serous ovarian cancer received adjuvant chemotherapy? For example, most endometrioid tumors were IA- grade 1?

18. Line 278: most likely due to histology or could it be type of surgeon or surgical approach (open vs MIS)? Factors not included in this study

19. Line 351: do the authors believe or have any data that rupture is less likely with an open approach than MIS? Even in stage IV disease?

20. Reference 14 is incomplete

In conclusion, since histology is not known preoperatively:
1. does rupture of ovarian capsule as suggested by FIGO staging result in decrease in survival? Yes, only if clear cell cancer found.
2. If ovarian capsule ruptured then is the patient likely to receive chemotherapy? Yes, but less likely than at the start of study in 2002
3. If chemotherapy given does that impact survival? Not in this analysis

STATISTICAL EDITOR’S COMMENTS:

1. lines 14-20 and later in text and Tables: Should round all aHR and CIs to the nearest 0.01, do not cite to nearest 0.001 precision.

2. Table 1: Need units for age.

3. lines 203,207, Table 2 footnote: risk is not the same as odds, ie, OR = 2.8 is not the same as ~3x the risk, since odds is a ratio of event occurring/event not occurring and odds ratio is a fraction of two such fractions, while risk is the ratio of an event occurring vs total of occurrence and non-occurrence of the event. So, need to change the language to odds rather than risks.

4. lines 217-223: Should point out to reader, either here or in Discussion, that the survival analysis method does not adjust for differences in age or other characteristics that could affect survival, while the adjusted HR or propensity matched models did include those other characteristics, hence while survival analysis showed significant differences for 3 histology types, after adjustment for baseline characteristics, the only histology type with a higher death rate was clear cell type.

5. lines 225-231: No need to give the order of numerical values for the aHRs of serous, mucinous or endometrioid. They were all NS different from their non-rupture cohorts and the numerical order has no importance. Simply state that only the clear cell had higher death rate.

6. Table 2: Need to cite, either in this Table or in another Table, the number of cases of intraoperative capsule rupture for each histology type. Should include both unadjusted and adjusted HRs and round all estimates and their CIs to nearest 0.01. Since CIs are given, no need to also cite the p-values. If needed, those which were statistically significant could be indicated by footnotes. Why were the referent histology type changed from the intraoperative ruptured cases to the post-op chemo ruptured cases. Should keep the same referent.

7. Table 3: Should not cite a p-value as 0.000, but rather as < 0.001

8. Fig 2: Need to include the "N" remaining at risk for each year interval along the x-axis for both cohorts (rupture and non-rupture)
9. Fig 3, legend: Should include concise summary of the stats analyses. For Fig 3A, only clear-cell had statistically higher aHR, while for Fig 3B, all histology types which received chemo had statistically equivalent aHRs.

10. Suggest that the supplemental figure 3 (based on propensity matching) is important corroboration and should be included in main text. Could consider putting both the adjusted model and propensity matched model results in the same figure, since the findings were so similar.

11. On the other hand, I suspect many readers will not find the results of Table 3 to be clinically useful, although they are interesting. I think the Table could be in Supplemental material and a brief summary included in the main text.

EDITORIAL OFFICE COMMENTS:

1. 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. 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:
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   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.

3. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

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 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, tables, boxes, figure legends, and print appendixes) but exclude references.

7. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not construct the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

8. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:
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* 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).

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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 Jul 16, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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