

OBSTETRICS & GYNECOLOGY



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obgyn@greenjournal.org.

Date: Sep 10, 2021
To: "John K. Chan" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-1673

RE: Manuscript Number ONG-21-1673

Symptoms of Women with High-Risk Early Stage Ovarian Cancer:

An NRG Oncology Group Study

Dear Dr. Chan:

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).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

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 Oct 01, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Thank you very much for the opportunity to review this manuscript. Despite major advancement in treatment of ovarian cancer, as the authors of this manuscript clearly outlined, we still don't have a reliable screening method to detect ovarian cancer at its earliest stage. As a result, only 20% of ovarian cancers are found at its earliest stage and most women discover their cancer at advance stages mostly stage III and IV. Early diagnosis is the key to optimal prognosis. I commend the authors of this manuscript for tackling such an important topic and trying to distinguish symptoms related to early stage ovarian cancer. Please see my comments and questions below.

Introduction:

1) Line 33: Please consider rewording the second part of this sentence. "resistant disease"? do you mean chemo resistant or resistant to all therapies? It is incomplete for a non-oncologist reader.

2) Line 48: Did you have access to evaluate the characteristics of symptoms presented in this study? The symptoms are described but the severity, frequency or characteristics of these symptoms are not mentioned. It mentioned as part of your aim yet it is clearly not addressed throughout the manuscript.

Material and methods:

3) Did all the presenting symptoms get included and the most common symptoms were analyzed?

4) Please explain why the RFS and OS survival were evaluated in relation to presenting symptoms. We know that patients included in this study had early stage ovarian cancer after surgical staging and the final pathology evaluation. It is also known that women with early stage ovarian cancer have close to 94% 5 year OS. Why not focus on symptoms as it pertains to early presentation of ovarian cancer since presenting symptoms in early stage doesn't impact overall survival nor recurrence free interval.

Results:

5) The symptoms presented in this manuscript although are among the most common presenting symptoms in women suspected of ovarian cancer but are extremely vague and non-specific. Were there any specific characteristic related to these symptoms in this subgroup of patients? One can always argue there are plethora of differential diagnosis in women with pelvic and abdominal pain. Even when there is a large adnexal mass found, the possibility of benign vs malignancy

can't be excluded without imaging and other supporting evidence.

6) Are you able to exclude the past medical/surgical history or past abdominal or pelvic pain related to other disease process like endometriosis in these patients?

7) My other issue is that this retrospective study only look at the presenting symptoms recorded by the provider. No standard set of symptoms, characteristic, severity of all symptoms were recorded. Relying on medical record can be misleading and it assumes that all providers asked similar questions and recorded everything similarly and in details. Additionally, as you mentioned in your study limitation, it relies on patients' memory of the symptoms as well.

8) Majority of symptomatic women have tumor size greater than 10 cm. One can argue that peritoneal sign and abdominal pain, as it is supported in this manuscript, can be only related to tumor size and not type of tumor (benign or malignant). It is hard to argue the association of high risk ovarian cancer to vague symptoms when a large mass is present in the abdomen. As you already know, often time even small ovarian masses may be most potent and women may present with advance disease and distant metastasis. How would this impact clinical practice?

9) Lines 129-133: In this manuscript earlier in line 94-95 of your result section, no significant difference in presenting symptoms was observed based on age, stage or histologic subtype. However, in the lines (129-133), you argue that lower number of patients with symptoms are due to early stage cancer contradicting your own result. As symptoms are related to size of the mass and not the tumor histology. Please clarify.

10) Did you also closely look at patients presenting with urinary symptoms? Based on parity and other factors such POP or neurologic issues, women may present with ongoing urinary symptoms. I think one way to demonstrate pre-existing symptoms in these women were not counted as sign of ovarian cancer is to look at new onset of symptoms mentioned in this study.

11) As patients' demographics such as weight or other pre-existing conditions are not mentioned, it is hard to extrapolate that all patients were asymptomatic before developing large tumors. Do you think sharing more detail of your patient population clarifying some of questions regarding BMI or preexisting symptoms?

12) In clinical implications section, what does this manuscript add to the already known common symptoms related to large pelvic mass? How does this help recognize early symptoms of high risk ovarian cancer?

13) Under strengths and limitation: I noted that you started with limitation and then mention the strengths of this study. I suggest swapping as the reader is looking for strengths and then limitations based on the heading of this section

14) Again I am not convinced adjuvant chemotherapy or treatment plans beside knowing that all patients were surgically staged add anything to the strength of this study since we are talking about early stage with lower recurrence rates and higher 5 year OS.

Reviewer #2:

1. Authors can draft a questionnaire for screening, early ovarian cancer risk assessment based on their finding which will add strength to the current manuscript.
2. Authors should report the comorbidities and their medication at the time of study enroll. This will highly interfere with the outcome of the participants symptoms.
3. Table 1. Total number participants enrolled in the study with symptoms (n=301) does not correlate with the number of participants listed in the table (n=362). Figure 1 distribution of characteristics of symptoms total percentage is 96%, please include is there any other symptoms are missing or eliminated from the presentation.
4. Provide details of tumor size and symptom analysis made, tumor size 11-15 and >15 cm columns sum-up more than 100%. Please provide detailed analysis method and the data as supplementary.
5. Figure 4 advanced stage data is not clear. Since early stage data are distributed as per symptoms and represented in percentage, but advanced stage data doesn't present well. Advanced stage data are from previous study, please acknowledge the approval from respective journal/authors in the text.
6. The current manuscript needs to be structured, example discussion part contains subtitle of results.

Reviewer #3: The authors present a secondary analysis of GOG 157 on signs/symptoms of ovarian cancer in early stage patients. This is a very important and novel topic given that much has been written about women with ovarian cancer that are advanced stage with regards to symptoms. Overall I found this to be a reasonably well written work which answers important and a novel clinical question of symptoms of women with early, non metastatic disease.

Specific points

- 1) Line 46- this should be reworded as this implies this is a new study, when in fact it is a secondary analysis.
- 2) Line 64--> How did you account for patients that had multiple symptoms; did these patients fare worse?
- 3) Line 88- please round significant figures similarly throughout your work
- 4) Line 109- you use the term silent disease yet your data speaks otherwise. I would use the discussion to talk about how even early ovarian cancer is not a "Silent disease" and in fact does have presenting signs.
- 5) Line 174-175--> IS there an appreciable difference in outcomes between stage 1 and stage 2 disease? I don't really think there is so you could group these into one cohort.
- 6) Figures--> It is interesting in your KM curves that having one or multiple symptoms did not seem to affect survival; i.e. even having one symptom could be used to prevent death; this could be expounded upon more in the conclusion for the reader.

STATISTICAL EDITOR COMMENTS:

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

Table 1: The %s should each include 95% CIs.

Table 2: Again, need to include CIs. The stats test employed (Chi-square) evaluates whether the counts among the three columns (no, single, or multiple symptoms) conforms to a random distribution. One cannot ascribe the p-value results to a particular stratum (row characteristic). If one were to apply a chi-square test to the tumor size ≤ 10 vs 11-15 cm, the distribution is NS.

Fig 1: Again, need to include CIs.

Fig 2, Table 2 and lines 85-88: The stats test used in Table 2 is misquoted in text. The test evaluated distributions among all three strata of tumor size and all three conditions (no, 1 or multiple symptoms). The question posed in text is ≥ 1 symptom frequency among the three strata of tumor sizes. Thus, 1 and multiple symptoms are aggregated into one category vs no symptoms. The overall chi-square for that comparison has $p = 0.07$, while the chi-square trend has $p = 0.02$. Need to include CIs for each %.

lines 89-92: This is simply the converse of the question posed by one or more symptoms, since the complementary count (and %) would be those with no symptoms. The stats are the same. Pair-wise, there is no difference between the 34% (tumors ≤ 10 cm) vs the 29% with tumors 11-15 cm.

lines 93-99: There is also the issue of statistical power. Can report the proportions, but cannot generalize the results to a larger population.

Figs 3a and 3b: Need to include the number of patients in each cohort remaining at each time point along the x-axes.

Fig 4: Need to provide CIs of some statistical comparison of the two cohorts.

EDITOR COMMENTS:

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- * Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
- * Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
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6. 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 data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions> and the gynecology data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

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17. Figures

Figure 1: Please add tick marks along the y-axis.

Figure 2: Please replace the pattered bars with a solid color.

Figure 3: The current figure file can be resubmitted.

Figure 4: Please replace the pattered bars with a solid color.

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* A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

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 Oct 01, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Dwight J. Rouse, MD, MSPH
Editor-in-Chief

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