OBSTETRICS & GYNECOLOGY

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- 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.*

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

Date: Apr 17, 2019
To: "Shaina F Bruce" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-467

RE: Manuscript Number ONG-19-467

Highlighting Disparities Among Cervical Cancer Patients Receiving Brachytherapy - A National Cancer Database Study

Dear Dr. Bruce:

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 May 08, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This is a retrospective cohort study using the National Cancer Database to identify women with the diagnosis of cervical cancer stage IB2 through IVA from 2004-2015. The objective was to look at the association of race/ethnicity and insurance to stage appropriate brachytherapy and survival. This is a very important study looking at disparities in treatment in a disease that already has a disparity in prevalence in the population. The authors should be applauded for their efforts in addressing this issue.

Abstract:

1. Line 31 I would recommend rewording the objective from sub optimal insurance to just stating the objective was looking at the association of race and type of insurance to stage appropriate brachytherapy and survival in women with cervical cancer.

2. Line 43 The Hispanic OR of .93 CI 0.86-0.99 and the p value = 0.115 seem at odds. It is not clear if this is in comparison to non Hispanic white women or to the Asian cohort.

Introduction:

3. Line 55-64 This is a concise overview of the problem and sets the stage for why brachytherapy is being evaluated.

Methods:

4. Line 101-103 Why was duration of radiation dichotomized into < or > 8 weeks? I assume this has to do with adequacy of primary radiation therapy. Could this also have been looked at as a continuous variable?

5. Line 109 Why were the 286 patients in other insurance excluded? If analyzed would this have made a difference in survival?

6. Line 111 Why was age < or > 65 chosen? This too could have been looked at as a continuous variable since most women are probably diagnosis much earlier vs. ovarian cancer. This is explained later in line 165.

Results:

7. Line 159-160 The difference in radiation recommended but not received and the disparities by insurance and race/ethnicity is interesting. It would be logical that these patients also did not receive brachytherapy and therefore are listed under < 8 weeks. In the introduction it was stated the cohort of 25,223 received radiation therapy. This needs to be clarified. Was received meaning recommended or at least initiated radiation?

8. The tables and figures are clear and stand alone.

Discussion:

9. Line 205 It is unclear how radiation therapy is being defined here "external beam and brachytherapy". Throughout the reading of the manuscript, although this is standard of care, it seems as though radiation treatment is looked at separately. I read this as some form of external beam +/- chemo radiation.

10. Line 233-234 The limitations of the study along with speculation for differences in OS are acknowledged. Related to biology of disease was there further assessment of whether these were all squamous vs. endocervical adnenocarcinoma or differed by race/ethnicity or insurance? Some discussion of whether this matters or is relevant would be helpful to the non gyn/onc reader.

Reviewer #2: Dr. Shaina F. Bruce et al conducted a National Cancer Database study investigating racial and insurance disparities amongst women with stage IB2 to IVA cervical cancer receiving brachytherapy as part of their primary treatment. Multiple studies have documented that racial and insurance disparities exist in the treatment and survival of cervical cancer. This study aimed to investigate if racial minorities and those with suboptimal insurance receive brachytherapy at the same rate as Non-Hispanic White patients with private insurance.

The results of this study suggest that there are racial disparities that exist in patients receiving brachytherapy. While Hispanic and Asian patients received brachytherapy at similar rates to Non-Hispanic Whites, Non-Hispanic Black patients received brachytherapy at significantly lower rates. When patients that did not receive brachytherapy were further divided into "recommended but not received" and "not planned or contraindicated" groups, Non-Hispanic Blacks and Asian patients were more likely to fall into the "recommended but not received group."

The results of this study suggest that there are also insurance related disparities that exist in patients' recipient of brachytherapy. Patients who are uninsured or covered by Medicaid or Medicare insurance receive brachytherapy at lower rates than patients with private insurance. Patients who are uninsured or covered by Medicaid or Medicare were more likely to fall into the "recommended but not received" group when compared to patients with private insurance.

Racial and insurance differences in overall survival were also noted. Across all stages, Asian and Hispanic patients had the best survival probabilities while Non-Hispanic White and Non-Hispanic Black patients had the worst survival probabilities. Patients who were unfunded or had private insurance had the best survival probabilities while those with Medicaid or Medicare insurance had the worst survival probabilities across all stages. However, survival differences by race and insurance groups were noted to be similar regardless of brachytherapy. This suggests that these survival differences are likely due to factors other than brachytherapy.

According to these results Non-Hispanic Blacks and patients with Medicaid or Medicare seem to be the groups most significantly affected by the disparities in brachytherapy. These groups received brachytherapy at significantly decreased rates despite recommendations for treatment and had the worst overall survival probabilities. Although this was a very strong study in terms of sample size, the information is limited by the fact that it was collected from a large National database. It would be difficult for Bruce et al to determine what barriers are opposing this patient populations' access to treatment.

Reviewer #3: Overall well done, and timely.

It is interesting that differences in brachytherapy treatment do not impact survival; perhaps this suggests that the benefit of brachytherapy (in this context) is primarily palliative?

"Patients who lived [in] metropolitan counties (the most populated) received significantly less brachytherapy than those in urban counties." I think you're trying to argue to say that patients in big cities got less radiation than people in small cities (so New Yorkers would get less radiation than people from Buffalo), but given that urban is usually taken to mean 'city' it might be best to clarify this. Or does 'urban' mean 'suburban' here?

Interesting that Hispanic patients had better survival despite not receiving more brachytherapy; are there any possible reasons for this?

The effects of race are relatively small (0.93-1.12) compared to the effects of insurance (0.72-1.01) or treatment facility region (0.89-1.57). Nonetheless they exist, are statistically significant, and are worth mentioning.

STATISTICAL EDITOR'S COMMENTS:

1. Abstract: See later comments. Need to clarify use of crude vs adjusted ORs and therefore whether the associations cited of receiving brachytherapy vs race or insurance were univariate or indeed independent associations.

2. General: The use of "determined" or "determinants" are too strong, the study was designed to evaluate associations and causal language or even language implying causation should be avoided.

3. Table 2: These all appear to be adjusted ORs (based on data from Table 1). Should include a separate column for crude ORs and label adjusted as aORs or adjusted ORs. Could also consolidate the OR with its CI into one column and eliminate the p-value column, since it is somewhat redundant, given the CIs. Should also cite in footnote the variables retained in the final regression model.

4. Table 5: Should cite how many women were included in the propensity score matching algorithm (Could be on-line supplemental). Also, given the large number of comparisons in this Table, should use a stricter inference threshold than 95% CIs or p< .05. P < .001 would be a more informative threshold, with less likelihood of spurious associations from multiple hypothesis testing. Again, should include a footnote citing the variables retained in the final model. I don't think it is clear to the reader that "differences in survival associated with race or insurance groups were independent of brachytherapy" as cited on lines 168-169. Should explain how Table 5 includes adjustment for brachytherapy.

5. Figs 1 and 2: Should include data showing how many women remained at risk for each time point along the x-axis. Since 4 groups are being compared, could include in Table format as supplemental, rather than incorporating within each graph.

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, 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.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. 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.

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, references, tables, boxes, figure legends, and print appendixes) but exclude references.

7. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure 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:

* 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).

9. 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.

10. 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.

11. 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.

12. 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.

13. The Journal's Production Editor had the following to say bout the figures in your manuscript:

"Author needs to upload all figures (1-2) as separate files in Editorial Manager
-Fig 2: text is very small and blurry, author should upload higher quality image or its original (editable file)"

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

14. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and 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.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

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If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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 May 08, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

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May 6, 2019

Re: Submission of revised manuscript, “Highlighting Disparities Among Cervical Cancer Patients Receiving Brachytherapy - A National Cancer Database Study”

The Editors
Obstetrics & Gynecology
409 12th Street, SW
Washington, DC 20024-2188

Dear Editors:

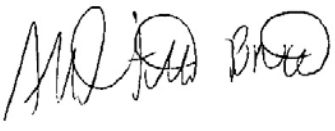
We are pleased to submit our revised manuscript entitled “Highlighting Disparities Among Cervical Cancer Patients Receiving Brachytherapy - A National Cancer Database Study” for exclusive consideration of publication as an original article in *Obstetrics & Gynecology.*

I affirm 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.

Please see below for an itemized list of all changes made in response to the reviewers’ comments. Please note that the line numbers included below refer to the final line numbers and not the line numbers when “tracked changes” are visible.

Thank you for your consideration of our work.

Sincerely,



Shaina F. Bruce, MD

Reviewer #1

Abstract

1. *Line 31 I would recommend rewording the objective from sub optimal insurance to just stating the objective was looking at the association of race and type of insurance to stage appropriate brachytherapy and survival in women with cervical cancer.*

Response: We have modified the abstract as recommended. Please refer to lines 30-31.

2. *Line 43 The Hispanic OR of .93 CI 0.86-0.99 and the p value = 0.115 seem at odds. It is not clear if this is in comparison to non Hispanic white women or to the Asian cohort.*

Response: We have corrected the confidence interval for Hispanic patients. Please refer to lines 42 and 146.

Introduction

3. *Line 55-64 This is a concise overview of the problem and sets the stage for why brachytherapy is being evaluated.*

Response: We appreciate this comment.

Methods

4. *Line 101-103 Why was duration of radiation dichotomized into < or > 8 weeks? I assume this has to do with adequacy of primary radiation therapy. Could this also have been looked at as a continuous variable?*

Response: Yes, the duration of radiation was dichotomized into less than or greater than 8 weeks because both SGO and ASTRO recommend completion of all radiation therapy for cervical cancer in less than 8 weeks. This could have been evaluated as a continuous variable, but we believe the disparity can be interpreted more directly if dichotomized.

5. *Line 109 Why were the 286 patients in other insurance excluded? If analyzed would this have made a difference in survival?*

Response: We excluded these patients because the "other insurance" group was very small compared to the overall number of patients in the cohort. Our statisticians do not believe that excluding these patients has any impact on the results, and we did not feel that we could draw meaningful conclusions about this group given its size.

6. *Line 111 Why was age < or > 65 chosen? This too could have been looked at as a continuous variable since most women are probably diagnosis much earlier vs. ovarian cancer. This is explained later in line 165.*

Response: Brachytherapy, age, and their interaction all violated the proportional hazard assumptions in each stage model, so brachytherapy effect was evaluated separately in patients < 65 years old and in patients ≥ 65 years old (lines 169-173). We dichotomized age at 65 years old as that is the typical age of Medicare eligibility.

Results

7. *Line 159-160 The difference in radiation recommended but not received and the disparities by insurance and race/ethnicity is interesting. It would be logical that these patients also did not receive brachytherapy and therefore are listed under < 8 weeks. In the introduction it was stated the cohort of 25,223 received radiation therapy. This needs to be clarified. Was received meaning recommended or at least initiated radiation?*

Response: All patients in the cohort of 25,223, as stated in the Methods section, did receive radiation therapy during their primary treatment (either external beam and vaginal brachytherapy or external beam only). However, the patients in the "recommended but not received" or "not planned or contraindicated" analysis included only those patients who *did not* start or receive any radiation therapy as part of their primary treatment. This is specified in lines 168-170. In an effort to distinguish this subset of patients (3,012 patients were included in the "reason for no radiation" analysis), we have added an explanation to the Methods section, please refer to lines 96-97.

8. *The tables and figures are clear and stand alone.*

Response: We appreciate this comment.

Discussion

9. *Line 205 It is unclear how radiation therapy is being defined here "external beam and brachytherapy". Throughout the reading of the manuscript, although this is standard of care, it seems as though radiation treatment is looked at separately. I read this as some form of external beam +/- chemo radiation.*

Response: Although our primary objective was to determine disparities in brachytherapy treatment among patients in minority race and insurance groups, we were limited by the information provided by the NCDB. We were able to clearly discern which patients received brachytherapy and which patients did not. However, many patients who did not receive brachytherapy did undergo external beam radiation, presumably chemo/radiation as the Reviewer suggested. For certain analyses such as "duration of radiation therapy" and "reason for no radiation," it was not possible to distinguish between brachytherapy and external beam. This is because the NCDB does not distinguish between brachytherapy and external beam in those data categories. Therefore, these analyses were performed for those that received radiation during their primary treatment, regardless of whether it was brachytherapy, external beam, or both.

10. *Line 233-234 The limitations of the study along with speculation for differences in OS are acknowledged. Related to biology of disease was there further assessment of whether these were all squamous vs. endocervical adnenocarcinoma or differed by race/ethnicity or insurance? Some discussion of whether this matters or is relevant would be helpful to the non gyn/onc reader.*

Response: We chose not to include histology in the analysis because histologic type does not direct or change management per NCCN guidelines. As our primary objective was to determine disparities among race and insurance groups with respect to brachytherapy, we did not believe histology to be pertinent. Existing literature suggests that incidence of the more aggressive adenocarcinoma is actually higher in non-Hispanic white patients compared to non-Hispanic black patients. Additionally, rates of squamous cell carcinoma have

decreased over the past few decades across all racial groups, although this decline was noted to have stabilized in non-Hispanic white patients around 2010. Therefore, it does not seem that variations in histology significantly affect the survival differences recognized among racial minorities. The medical community continues to learn more about differences in tumor biology and how those differences impact aggressiveness of tumors and responses to treatment. This goes beyond histology, for example, in ovarian cancer.

Rauh-Hain JA, Clemmer JT, Bradford LS, Clark RM, Growdon WB. Racial disparities in cervical cancer over time. Cancer. 2013; 119(20): 3644-3652.

Reviewer #2:

Dr. Shaina F. Bruce et al conducted a National Cancer Database study investigating racial and insurance disparities amongst women with stage IB2 to IVA cervical cancer receiving brachytherapy as part of their primary treatment. Multiple studies have documented that racial and insurance disparities exist in the treatment and survival of cervical cancer. This study aimed to investigate if racial minorities and those with suboptimal insurance receive brachytherapy at the same rate as Non-Hispanic White patients with private insurance.

The results of this study suggest that there are racial disparities that exist in patients receiving brachytherapy. While Hispanic and Asian patients received brachytherapy at similar rates to Non-Hispanic Whites, Non-Hispanic Black patients received brachytherapy at significantly lower rates. When patients that did not receive brachytherapy were further divided into "recommended but not received" and "not planned or contraindicated" groups, Non-Hispanic Blacks and Asian patients were more likely to fall into the "recommended but not received group."

The results of this study suggest that there are also insurance related disparities that exist in patients' recipient of brachytherapy. Patients who are uninsured or covered by Medicaid or Medicare insurance receive brachytherapy at lower rates than patients with private insurance. Patients who are uninsured or covered by Medicaid or Medicare were more likely to fall into the "recommended but not received" group when compared to patients with private insurance.

Racial and insurance differences in overall survival were also noted. Across all stages, Asian and Hispanic patients had the best survival probabilities while Non-Hispanic White and Non-Hispanic Black patients had the worst survival probabilities. Patients who were unfunded or had private insurance had the best survival probabilities while those with Medicaid or Medicare insurance had the worst survival probabilities across all stages. However, survival differences by race and insurance groups were noted to be similar regardless of brachytherapy. This suggests that these survival differences are likely due to factors other than brachytherapy.

According to these results Non-Hispanic Blacks and patients with Medicaid or Medicare seem to be the groups most significantly affected by the disparities in brachytherapy. These groups received brachytherapy at significantly decreased rates despite recommendations for treatment and had the worst overall survival probabilities. Although this was a very strong study in terms of sample size, the information is limited by the fact that it was collected from a large National database. It would be difficult for Bruce et al to determine what barriers are opposing this patient populations' access to treatment.

Response: We appreciate these positive comments. To address the Reviewer's last sentence, please refer to lines 228-231 where we have listed some possible barriers to treatment.

Reviewer #3:

1. *It is interesting that differences in brachytherapy treatment do not impact survival; perhaps this suggests that the benefit of brachytherapy (in this context) is primarily palliative?*

Response: In general, brachytherapy is not intended for palliation but rather for curative purposes. However, we cannot discern intent of treatment from this database.

2. *"Patients who lived [in] metropolitan counties (the most populated) received significantly less brachytherapy than those in urban counties." I think you're trying to argue to say that patients in big cities got less radiation than people in small cities (so New Yorkers would get less radiation than people from Buffalo), but given that urban is usually taken to mean 'city' it might be best to clarify this. Or does 'urban' mean 'suburban' here?*

Response: We have modified the definitions of "metropolitan," "urban," and "rural" to include the population ranges per the NCDB (please refer to lines 155-159). Our data suggests that those in the most populated (metropolitan) and least populated (rural) counties receive less brachytherapy then those in urban counties (urban being generally less populous cities or suburbs of large cities).

3. *Interesting that Hispanic patients had better survival despite not receiving more brachytherapy; are there any possible reasons for this?*

Response: A cancer survival advantage among Hispanic women has been noted in the literature for the past three decades. This is an interesting paradox because Hispanic women tend to have similar socioeconomic status as non-Hispanic black women, yet Hispanic women have a survival advantage. Our study found that Hispanic women receive brachytherapy at similar rates to non-Hispanic white women, but survival probabilities for Hispanic women were better. This could be attributed to differences in social support, religion, faith, or other cultural influences that cannot be accounted for in our study. We have added this discussion to the manuscript, please refer to lines 249-254.

4. *The effects of race are relatively small (0.93-1.12) compared to the effects of insurance (0.72-1.01) or treatment facility region (0.89-1.57). Nonetheless they exist, are statistically significant, and are worth mentioning.*

Response: We have included the effects of race and insurance status in the Results section of the manuscript, please refer to lines 146-153. Moreover, these results are further discussed in lines 202-217. We do not believe that discussing the degree of significance is within the scope of our study.

STATISTICAL EDITOR'S COMMENTS:

1. *Abstract: See later comments. Need to clarify use of crude vs adjusted ORs and therefore whether the associations cited of receiving brachytherapy vs race or insurance were univariate or indeed independent associations.*

Response: All ORs reported in the manuscript are adjusted ORs. These are estimated from the final multivariable logistic regression model, which included covariates listed in Table 2. Please refer to lines 145-146.

2. *General: The use of "determined" or "determinants" are too strong, the study was designed to evaluate associations and causal language or even language implying causation should be avoided.*

Response: We have eliminated all variations of the word "determine" as requested.

3. *Table 2: These all appear to be adjusted ORs (based on data from Table 1). Should include a separate column for crude ORs and label adjusted as aORs or adjusted ORs. Could also consolidate the OR with its CI into one column and eliminate the p-value column, since it is somewhat redundant, given the CIs. Should also cite in footnote the variables retained in the final regression model.*

Response: The ORs reported in Table 1 are adjusted ORs estimated from the final multivariable logistic regression model. Respectively, the covariates listed in Table 2 are retained in the final regression model. That is, Table 2 is devoted to the final multivariable logistic regression model results. Reporting "crude" ORs in this or any other table is not statistically appropriate because the significance of univariate associations between brachytherapy receipt and every other covariate is already tested using the chi-squared test as presented in Table 1. This table is devoted to presenting the univariate associations between brachytherapy receipt and every other covariate. In the footnote of Table 2, we have specified which variables from the univariate analysis (Table 1) were not included in the final multivariate analysis (Table 2).

4. *Table 5: Should cite how many women were included in the propensity score matching algorithm (Could be on-line supplemental). Also, given the large number of comparisons in this Table, should use a stricter inference threshold than 95% CIs or p< .05. P < .001 would be a*

more informative threshold, with less likelihood of spurious associations from multiple hypothesis testing. Again, should include a footnote citing the variables retained in the final model. I don't think it is clear to the reader that "differences in survival associated with race or insurance groups were independent of brachytherapy" as cited on lines 168-169.

Response: The propensity adjustment was implemented using the inverse probability weighting rather than matching, as described in the methods, please refer to lines 124-126). As recommended by the Editor, we have revised the analyses reported in Table 5 to use alpha=0.001. Respectively, 99.9% confidence intervals are now reported instead of the original 95% confidence intervals. Since Table 5 reports the results of the final multivariable multiplicative hazard regression models (extension of the Cox model), the covariates listed in Table 5 are exactly the ones retained in these models. Since brachytherapy was included (and significant) in all models reported in Table 5, the "differences in survival associated with race or insurance groups" are adjusted for brachytherapy receipt and other significant predictors of the overall survival. We have revised the manuscript to better explain how the results reported in Table 5 imply that the differences in survival associated with race or insurance groups were significant with adjustment for brachytherapy receipt and other significant predictors of the overall survival. Please refer to lines 181-183.

5. *Figs 1 and 2: Should include data showing how many women remained at risk for each time point along the x-axis. Since 4 groups are being compared, could include in Table format as supplemental, rather than incorporating within each graph.*

Response: We have included the supplementary tables (Supplementary Table 1 and Supplementary Table 2) with the number of patients at twelve month intervals for all survival plots included in Figures 1 and 2.

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, 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.*

2. *OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.*

Response: Opt-in.

2. *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.

Response: Noted, thank you.

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.*

Response: The data used in this study is from the National Cancer Database (NCDB). The NCDB is a program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. It is a nationwide oncology outcomes database for approximately 1,500 Commission accredited cancer programs in the United States. It is

estimated that 70% of all newly diagnosed cancer cases are captured and reported to the NCDB. Data is collected and submitted using nationally standardized data item and coding definitions as defined in the CoC's *Facility Oncology Registry Data Standards.* Data reported from CoC-approved hospitals are abstracted from patient charts by Certified Tumor Registrars (CTR) who undergo training specific to the cancer registry. All data submitted to the NCDB undergoes many integrity checks, and each year the NCDB undergoes internal quality monitoring and validity reviews. Additionally, every few years surveyors from the CoC evaluate each hospital's data collection processes. We have added this information to the Methods section of the manuscript, please refer to lines 81-89.

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* [link intentionally omitted]

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.

Response: We have completed a STROBE checklist and included it with our resubmission.

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* [link intentionally omitted]

If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

Response: We have noted the ReVITALize definitions, but none of these terms are used in our manuscript.

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, references, tables, boxes, figure legends, and print appendixes) but exclude references.*

Response: Our revised manuscript is 15 pages without references (includes title page, précis, abstract, text, figure legends) and 22 pages including tables. The manuscript is also less than the maximum 5,500 words.

7. *Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure 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.*

Response: Our title “Highlighting Disparities among Cervical Cancer Patients Receiving Brachytherapy” is 79 characters with spaces. “A National Cancer Database Study” will serve as a subtitle.

8. *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).*

Response: We do not have any acknowledgements for this manuscript. The study was presented as a poster at the 2019 Society of Gynecology Oncology Winter Meeting, which is listed on Page 2.

9. *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.

Response: The abstract length is 300 words (not including section titles).

10. *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.*

Response: All abbreviations and acronyms are spelled out the first time they are used in the abstract and again in the body of the manuscript.

11. *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.*

Response: We have eliminated all virgule symbols.

12. *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.

Response: We have ensured all tables conform to the journal's style requirements.

13. *The Journal's Production Editor had the following to say about the figures in your manuscript:*

"Author needs to upload all figures (1-2) as separate files in Editorial Manager

-Fig 2: text is very small and blurry, author should upload higher quality image or its original (editable file)"

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

Response: We have revised Figure 2 as requested.

14. *Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at* [link intentionally omitted]

The cost for publishing an article as open access can be found at

http://edmgr.ovid.com/acd/accounts/ifauth.htm

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

Response: Noted, thank you.