Author's response to reviews

Title: Survival of patients with operable breast cancer (Stages I-III) at a Brazilian public hospital - a closer look into cause-specific mortality

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Author's response to reviews: see over
Author's response to reviewers

Survival of patients with operable breast cancer (Stages I-III) at a Brazilian public hospital - a closer look into cause-specific mortality

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Thank you for consideration of our manuscript for publication in BMC Cancer. We have reviewed the above manuscript according to your reviewer’s comments.
Reviewer #1 (Dr. Byington)

MINOR ESSENTIAL REVISIONS

Background Section:
1 - “whereas the age-adjusted mortality for the world population in the country…”.
The correct expression should be “whereas the age-adjusted mortality to the world population in the country…”

We have rewritten the sentence as “whereas the age-adjusted mortality was…”.

2 – “In Goiania, located in the Central-West Region of Brazil, the survival rate was 65.4%.” A reference is needed for this survival rate!

We have added a reference for the survival rate.

3 – “The Breast Pathology Laboratory of the UFMG School of Medicine is responsible for all breast pathology exams and it keeps records of diagnostic and surgical specimens from the HC-UFMG since 1989 [20].” I understand that this all refers to the exams performed in specimens from patients assisted at this hospital but the way the sentence is written it makes us think of a “more comprehensive all”. I suggest the authors to rephrase the sentence to clarify this issue.

We have rewritten the sentence as: “The Breast Pathology Laboratory of the UFMG School of Medicine is responsible for all breast pathology exams from the HC-UFMG and it has kept records of diagnostic and surgical specimens from it since 1989.”

4 – “The goal of our study is to evaluate cause-specific survival”. Although currently used by some authors I personally dislike this expression. I would rather say that the goal is to “estimate survival and cause-specific mortality.” This is because how can one say that “the cause of survival was breast cancer”?

We agree the term can be confusing. We have rewritten the last paragraph of the background section. We have added a definition of cause-specific survival and a reference to avoid any misinterpretations.

5 – “to compare our findings to the prognosis of patients treated in other Brazilian institutions, as well as to survival in developed countries”. Here, “prognosis” and “survival” are being improperly used as synonyms. The authors should change both to “survival”.

Following the recommendations of the second reviewer, we have rewritten the last paragraph of the background section and dropped these sentences. Therefore, the use of these two words as synonyms is no longer an issue.

Methods Section:
Information on life status and death causes
1 – “To identify patients from the study’s cohorts…” Should be corrected to “To identify patients from the study cohort…”
We have rewritten the sentence as suggested.

2 – “to estimate breast cancer-specific survival…” Here I make the same comment as above: one can be very specific about a cause of death but hardly about a cause of survival… But it is a matter of preference as authors are using this term. When analyzing a survival curve we look at the survival of patients with some health condition, not at the condition itself.

Although this term may be confusing, we have decided to keep it along the paper, following the literature. We hope the definition we added in the background section will avoid some of the potential misunderstandings.

Data analysis
1 – “We estimated Kaplan-Meier curves to describe the cause-specific survival of patients over 5 and 10-year periods…”. I would rather say “We estimated Kaplan-Meier curves to describe the survival of this cohort over 5 and 10-year periods…”.

We have rewritten the sentence as suggested.

Results
1 – “…The mean age of patients was 55.32 years (SD=13.97, range 20-97 years). Only 47 patients (5.24%) were 35 years old or younger; most patients (677, 75.47%) were between 36 and 69 years, and 173 patients (19.29%) were 70 and older.”
I’d like to know the median age of patients. As described, almost 20% of them were 70 and older. This illustrates a skewed distribution so the mean is not the best description.

We have also added the median age of patients (53 years of age).

2 – “…where treated in the private health system.”
The “where” ought to be corrected to “were”

We have rewritten the sentence as suggested.

3 – “…The most frequent tumor size was T2 (2 to 5 cm), with 348 cases (38.8%).”
The term “most” should be used only when more than 50% is implicated.

We have changed the use of term “most” across the paper as suggested by the reviewer.

4 – “…Most patients where in stage III at diagnosis (359 cases, 40.02%).”
If 40.02% were in stage III at diagnosis it is not correct to say “most patients”. It does not apply. I would suggest “a great number of patients were in stage III at diagnosis (359 cases, 40.02%)”

We have rewritten the sentence as suggested.
5 – “…Five-year breast cancer-specific survival for the entire cohort was 78.5%,” I insist that it is not correct to say “breast cancer-specific survival”. I think a better way to express the findings of survival analysis should be “Five-year survival of breast cancer patients”. Patients’ survival is not “caused” by breast cancer! The same is valid for the rest of the paper, every time “cancer-specific survival” is referred.

As we stated before, we have decided to keep this term along the paper, following the literature. We hope the definition we added in the background section will avoid some of the potential misunderstandings.

6 – “…Being treated by the SUS was associated with a worse survival,”
The use of the term worse is inadequate for it refers to a qualitative aspect that is not possible to infer from the data. It should be changed to “shorter”.

We have made the changes throughout the paper as suggested.

7 – “…In terms of therapy, being submitted to neoadjuvant systemic therapy, undergoing mastectomy and undergoing axillary node dissection were associated with worse overall survivals.”
Again, this paper is not about quality of life. The data shown do not allow to say if the survival was better or worse. It is only possible to say “longer” or “shorter”. The authors should have a closer look at this issue for it is repeated all through the paper.

Whenever the term “worse survival” was used, we have replaced it with “shorter survival”.

Discussion
1 – “Since survival analyses methods vary among studies, it is difficult to compare breast cancer survival rates among cancer facilities and mostly among countries.”
I would disagree on that. Survival analyses methods used in this study – Kaplan-Meier estimates and Cox proportional hazards model – are amongst the most widely used for such studies. Yet, the rest of the same paragraph points to the real reasons of the different findings. I would suggest the authors to suppress this affirmative.

We have suppressed this affirmative as suggested.

• MAJOR COMPULSORY REVISIONS (WHICH THE AUTHOR MUST RESPOND TO BEFORE A DECISION ON PUBLICATION CAN BE REACHED)

Methods Section
Data analysis
1 – “Survival interval was calculated in months from date of surgery in patients not submitted to neoadjuvant chemo or hormone therapy and from biopsy date in patients who underwent such therapies”.
Why did you use the date of biopsy and not the beginning of neoadjuvant therapy as the starting point for this group of patients? Shouldn’t the clock begin to tick for both groups at the start of treatment, be it surgery or chemo/hormone therapy? I suppose the group submitted to surgery had also undergone a biopsy and waited for some time until surgery. Being so, why didn’t you use also the date of biopsy as the starting point? Please, clarify this point.

Unfortunately, the date of the first biopsy for patients who had surgery as the primary treatment was not available for all patients in the HC-UFGM data, since some of them were diagnosed outside the Hospital and then referred to it. To make this issue explicit, we have added the following phrase in the statistical analysis section: “Since the date of the first biopsy was not available for all patients who had surgery as the primary treatment, survival interval was calculated in months from date of surgery in patients who did not undergo neoadjuvant chemo- or hormone therapy and from biopsy date in patients who underwent such therapies. Also, we tried to keep the staging as accurate as possible by using the clinical stage in the date of biopsy or the pathological stage in the date of surgery.”

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
'I declare that I have no competing interests'

We would like to thank the language corrections and report that the editing firm Blue Pencil Science has revised the new version of the article.
Reviewer #2 (Dr. Dorsi)

The abstract should be improved according to the following comments.

We have changed the abstract according to the comments.

The terminology about the standard of development of countries has recently changed and the terms “developed country” is no longer used, it has been substituted for “high-income country”, “middle-income” and “low-income”, reference number one (Harford, 2011). I recommend the authors use this terminology in throughout the manuscript.

We have changed the terminology as suggested.

In the background section, in the end of the first paragraph there are some statements about the survival rate in Goiania, the authors should provide a reference for them.

We have added a reference for the survival rate in Goiania.

In the end of the background section (page 4, last paragraph), the main goal of this study seems to be “to evaluate cause-specific survival of female patients with operable breast carcinoma (stages I-III) treated at HC-UFMG from 2001 to 2008”. The rest of this phrase “and to compare our findings…” is not part of the main objective, it is more a part of the discussion of the results, as well as the last statement “We will also discuss how different approaches to survival studies can change the results”. I recommend summarizing the main objective according to the above.

We agree and have rewritten the end of the background section.

The background is well supported by the literature review, but there are lots of old references (before 2000) and an excess of references (50). I recommend selecting the most important and newer references, and using only those.

We have removed eight references (original numbers 6, 7, 11, 24, 32, 42, 49, and 50) from the paper and kept only the newer ones.

In the methods section, the authors should provide the number and date of approval of the study protocol in the UFMG Ethics Committee.

We have added the number and date of approval of the study protocol.

The authors should also provide the sample size calculation to address the main objectives of the study.

We did not sample the cases. All breast cancer cases surgically treated at HC-UFMG from 2001 to 2008 were initially included in the study. The exclusion criteria (for example, in situ carcinomas) are described in the study’s population section. To make this point clearer, we have changed the following phrase in the study’s
population section: “Among the 1119 patients selected for this study…” to “Among the 1119 patients who underwent surgery for breast cancer treatment at HC-UFMG from 2001 to 2008, we excluded…”. Also, to avoid further misunderstandings, we have replaced the word “sample” throughout the paper whenever the term was not appropriate.

The methods section should be better organized starting with the study's design, population, sample size, methods, data collection, variables, and statistical analysis.

We agree the organization of the methods section needs to be improved. Therefore, we have reorganized it as study's design, study's population, variables, information on survival status, and statistical analysis. We have not separated population from sample size in two different subsections, as suggested by the reviewer, because we are not sampling the cases, but using all breast cancer cases surgically treated at HC-UFMG from 2001 to 2008. With respect to the data collection subsection, there is a sentence about this topic in the subsection study's population, and therefore, we have not created a specific subsection to it. Finally, instead of methods, as suggested by the reviewer, we have a subsection called information on survival status and death causes, to present in a very direct and clear way how we determined the survival status and causes of death of our patients – a key issue in our study.

In the 6th and 7th page, the second paragraph starting with “Data from the Surveillance Epidemiology and End Results (SEER from the United States…” is not part of the methods of this study, the authors did not analyze and present results of the SEER, so I recommend suppressing this part of the methods section.

In fact, we tried to use SEER data to produce comparable estimates to our own results. However, we agree this approach is confusing since it is not part of our main goal. Therefore, we have decided to take the analysis of SEER data out of the article, and compare our estimates only to international results already published in the literature.

In the statistical analysis the authors should provide the p-value for entry and the p-value for getting out the variables of the multivariable Cox model.

We have added the p-values as suggested.

The authors say that they used the chi-square test for linear trend to compare the frequencies of T and N over the study. I recommend not using such abbreviations (T and N). They did not show the results of these comparisons using the chi-square, only the log-rank test of the comparisons of rates of survival (Table 1), so I recommend excluding the chi-square and including the p-value of the log-rank also in the Kaplan-Meier curves.

We have removed the abbreviations T and N from the text. We have added the p-value of the log-rank test in the legend of figure 1. Finally with respect to the chi-
square test for a trend, we used it to compare the frequency of the stages over the years and ages and the use of neoadjuvant systemic therapies for different age groups. These results are reported on the paragraphs #4 and #5 of the results section. We also added a phrase about this test in the statistical analysis section: “The chi-square test for a linear trend was used to compare the frequencies of tumor stage over the years of the study, as well as tumor stage in each age category.”

In the end of the methods section (page 9), there is a phrase about the databases where the literature review was done, I suggest changing this to the background section as well as to give more details on the literature search (key-words, languages, date of the search, criteria of inclusion and exclusion of studies etc).

We agree and we have moved the following phrase to the background section: “Studies from Brazil and other countries were retrieved from the PubMed and LILACS databases in February 14, 2013, using the search terms breast cancer, survival, and Brazil. Seven hospital cohort studies that separated patients by stage and were not aiming to evaluate specific prognostic markers or new treatments were selected. For PubMed, English language was used, and for LILACS, both English and Portuguese languages were used.”

The Results section should be better organized. I recommend starting with the main results of the study, the 5-year global survival and the 5-year survival according to stages. They are at page 11, second paragraph.

We have reorganized the results section as suggested.

In page 10 there are some abbreviations (IDC and ILC) that should be written out.

We have written out these abbreviations.

In the end of the Discussion, page 13 third paragraph, the statement about SEER should be in the Discussion section.

We have decided to take the analysis of SEER data out of the article, and compare our estimates only to international results already published in the literature.

In the Discussion, I recommend starting with the discussion of the main results that are presented at page 16, 1st and 2nd paragraphs).

We have started the discussion with the main results as suggested.

Page 14, 1st paragraph, they state that “In our study, the tumor stage was the strongest predictor of survival” but they present in the multivariate model three separate variables: tumor size, lymph node status and histologic grade”. I recommend changing the statement according to the results.

We have made the changes as suggested.
One important limitation of this study is the lack of measures of socioeconomic position, like schooling or income. The authors state that they are important predictors of survival but do not present any of them, only the SUS/Private insurance as a surrogate. Why didn’t they collect and present other measures, like schooling? If they did not have access to them, they should include this in the limitations of the study. If is possible to access them, I recommend including in the analysis.

Socioeconomic information, such as family income and education level, are not available on medical records from HC-UFMG. We have added this in the limitations of the study.

In Table one, I recommend including first the age of participants that is presented only in the end of the table.

We have made the changes as suggested.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests