Author's response to reviews

Title: Relative mortality in soft tissue sarcoma patients: a Danish population-based cohort study

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Dear Editorial board of BMC Cancer,

Please find enclosed the manuscript, “Relative mortality in soft tissue sarcoma patients: a Danish population-based cohort study”, by Katja Maretty-Nielsen et al., to be submitted as an original research article to BMC Cancer. All authors have seen and approved the contents of the manuscript. There is no conflict of interest. We certify that the submission is original work and is not under review in any other publication.

The manuscript has previously been submitted to the BMC Cancer (Manuscript ID: 6088363451146165). The reviewers raised a number of criticisms and after careful assessment of these, the manuscript has been thoroughly revised and we believe that we have adequately addressed all of the criticisms:

Reviewer 1:

Major Compulsory Revisions:

1. Let us please know about the differences between the sarcoma types, relative survival after metastasis and recurrence. Please do not restrict to the most common only.

   Answer: We have added a table (Table 3) showing the 5-year relative mortality according to the histological subtypes. It is not possible to estimate the relative survival after relapses (local recurrence or metastases) using the comparison cohort in this study. The comparison cohort was selected at the time of sarcoma diagnosis and thus all individuals from the selected cohort were alive at this time; however, this might not be the case at the time of relapse of the sarcoma patient and thus using the selected comparison cohort will lead to biased results. In order to investigate the relative survival after relapse a new comparison cohort should be selected at the time of relapse; however, this was not feasible in the current study.

2. Can you also provide data about the influence of different treatments or is that not in the database?
**Reviewer 2:**

Major Compulsory Revisions:

1. I do have a methodological issues however, which is the following: the purpose of relative survival and cause-specific survival analysis is to estimate net-survival, i.e. the (hypothetical) survival which might occur if all risks of dying of other causes than the cancer of interest were removed thus studying the proportion of patients dying directly from cancer or indirectly from its consequences. Competing risks theory allows to calculate “real world” probabilities where a patient is not only at risk of dying from their cancer but also from any other cause of death using cumulative incidence functions. The cumulative incidence function will always be lower than cause specific mortality (1 minus the Kaplan-Meier survival estimate) in the presence of competing risks. In this paper Maretty-Nielsen et al. estimate relative mortality, which attempts to estimate net-survival and does not account for competing risks, and compare this to a “cancer-specific” mortality estimate. However for this latter estimate deaths due to other causes were treated as competing events. This alone may fully explain their finding that the “cancer-specific” mortality estimates are lower than the relative mortality estimates. I therefore do not agree with the conclusion of the abstract and the paper. I (strongly) suggest not to estimate “cancer-specific” mortality as a cumulative incidence function.

**Answer:** The statistical analysis of disease-specific mortality has been changed according to the suggestion from the reviewer, and is now analyzed using Kaplan-Meier failure estimates. When analyzing disease-specific mortality using Kaplan-Meier, no difference between disease-specific and relative mortality was observed. The result, discussion and conclusion sections have therefore been changed according to this.
Discretionary Revisions:

2. Table 3 presents mortality rates and crude/adjusted MRR. The second part of the table actually presents MRR conditional on surviving up to 5 years. However, the mortality rates are cumulative mortality rates and have no direct relation with the MMR shown in the left columns. I would suggest to present the cumulative mortality from 5 years of follow-up (i.e. for age-group 0-39 this conditional mortality would be 6.0% and the expected mortality 0.7%, the ratio of which (8.6)much better reflects the MMR shown in the column to the right than is currently the case).

   Answer: This is a very good point raised by the reviewer and the cumulative mortalities in the second part of table 3 have thus been changed appropriately, so that they reflect the conditioning of surviving the first five years.

Minor comments:


   Answer: This was corrected in the abstract.

4. Statistical analysis page 9: line 13 should read either “… and the observed survival in the age- and sex matched…” OR “and the expected survival based on the observed survival in the age- and sex matched ….”

   Answer: The sentence has been changed to “… and the observed survival in the age- and sex matched…”

5. Statistical analysis page 10: line 3 “violation of” instead of “contradiction to”

   Answer: This was corrected.
6. Discussion, page 16: with regard to using life tables. Although I agree that technically life tables are indeed rarely free of deaths due to the disease of interest, in case of a rare cause of death, such as death due to STS, the bias this may introduce will be negligible. And as life tables are derived from mortality in the total population there is no sampling bias (so no confidence interval needs to be estimated for the expected survival) which needs to be accounted for in the design chosen in this study. The benefit of good internal comparability in this study may be fully countered by the sampling variability introduced. This is worth mentioning.

Answer: The following has been added to the discussion section:“However, since soft tissue sarcoma is a very rare disease, the issue of soft tissue sarcoma patients being included in the data on which the life tables are derived is considered minor.” and “However, when using a matched general comparison cohort to assess the mortality in the general population there is a potential sampling bias, which is not present when using life tables.”

To our knowledge this is the first study of relative mortality in soft tissue sarcoma patients using an individual age- and gender-matched comparison cohort from the general population. The cancer-specific mortality, using death certificates, among soft tissue sarcoma patients has been studied numerous times. However, using cancer-specific measures entails two potential problems; misclassification of the underlying cause of death, and no consensus on which causes of death are related to the cancer. Previous studies have concluded that causes of death are associated with issues of inaccuracy and substantial variability of coding according to cancer type, age at death, and time period. Furthermore, while some deaths are directly related to cancer, others are more complex, with cancer merely contributing to the death. In these cases assigning death as either cancer-specific or not can be problematic and ambiguous.

In this study we found an overall 5- and 10-year relative mortality of 33% and 36%, respectively. The relative mortality varied according to age, grade, stage of diagnosis, and level of comorbidity, being highest in younger patients and in patients without comorbidity. No statistical significant difference between the relative and the cancer-specific mortality was found. The relative mortality provides an unbiased and accurate method to differentiate between cancer-specific and non-cancer-specific deaths. However, when data on the cause of death is of a sufficient quality, there is no difference between relative mortality and disease-specific mortality based on death certificates.
We hope that the editorial board and the reviewers will find our comments sufficient and the study as important and interesting as we do.

Yours sincerely,

Katja Maretty-Nielsen, on behalf of the authors.