Reviewer's report

Title: Nitrous Oxide Does Not Increase the Risk of Cancer Recurrence after Colorectal Surgery: A Randomized, Blinded Study

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Reviewer: Peter Kranke

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General Comments:
The authors are to be congratulated for this important new information regarding the safety of anaesthesia. Although these data need to be confirmed in other analyses, until now they represent an important body of evidence as far as the outcome following general anaesthesia is concerned.

Anaesthesia affects clinical outcome. This is what the cited references in this research article do suggest. Not only by causing “anaesthesia-related” complications but also by causing subtle changes which are not visible at first glance. Case control design and other retrospective research are prone to underlying biases in the attempt to answer the important question which (immune) functions are altered by the anaesthetic technique. Therefore, it is a valuable piece of work to re-analyse data of randomized clinical trials and add the follow-up information on cancer recurrence, as the authors have done it.

Major Compulsory Revisions
1. Page 9, 2nd paragraph, 3rd sentence.

The authors stated in the methods section that “Using survivor function estimates from the control group (nitrogen), with 39/97 observed events in the nitrous oxide group and 38/107 observed events in the nitrogen group, we had an 80% power to detect a hazard ratios less than 0.44 or greater than 2.3 at the 0.05 significance level, if such hazard ratios indeed existed. Since more subtle effects of nitrous oxide are likely of clinical interest, our study should be considered exploratory.”

The last sentence is much more conservative as the title would suggest. Therefore, the authors may want to consider a non-declarative title or at least state that these are results that need further confirmation, e.g. “Nitrous oxide does not…. : A Follow-up of a randomized controlled trial.”

2. Page 14, 3rd paragraph.

This section covers how the authors deal with the patients that died without a histological diagnosis of cancer recurrence. The authors state that: “Of the 77 observed recurrences (per our definition), eight did not have a diagnosed recurrence; instead, their death certificates listed colorectal cancer as the cause of death.” They further speculate: “Though this assumption relies on the accuracy of death certificate information, we believe it is justifiable to assume they
It may be reasonable to perform and present a sensitivity analysis and explore how the outcome measure is affected by such a “worst-case” or “best-case” scenario. Such an analysis could further increase the reliability of the presented analysis.

Minor Essential Revisions
1. Page 24, Figure legends, figure 2.
   “Figure 2” instead of “Figuer 2”
2. Pages 26 and 27 as opposed to page 28 and 29:
The figures seem to be redundant in the received pdf.

Discretionary Revisions
1. Page 13, 1st paragraph, 2nd sentence.
The authors are quite optimistic regarding the therapeutic impact of cancer surgery and state: “Cancer surgery, usually the best hope for cure, is nearly always associated with minimal residual disease [1], and competence of host defense, especially natural killer cell function, appears to be a critical determinant of whether residual disease develops into clinical recurrence [4, 18]”. The authors may wish to attenuate or eliminate the statement “…usually the best hope for cure”, since that is applicable only to some entities of the disease.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
Do you have any non-financial competing interests in relation to this paper?
Reviewer has previously published scientific papers with the senior author of the manuscript under review