

December 12, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS manuscript number 6510 review.doc).

**Title:** Perioperative Care and Cancer Recurrence: Is There a Connection?

**Authors:** Khanna AK, Perez E R, Laudanski K, Moraska A, Cummings KC

**Name of Journal:** *World Journal of Anesthesiology*

**ESPS Manuscript NO:** 6510

The manuscript has been improved according to the suggestions of reviewers:

1 Format, author information and contribution, title page, core tip, keywords have been updated

2 Revision has been made according to the suggestions of the reviewers as enumerated below:

(Revisions are highlighted in red)

Reviewer 1:

It is well written review, that gives insight into the interesting theme of relation of anesthesia to cancer recurrence and makes a comprehensive summary. I agree with the authors that much is said on the field, but no really convincing data have emerged. The scope of the review is fulfilled, references are updated, language is appropriate and structure makes sense.

There are some minor comments that should be addressed: Minor comments

1. Page 7, 2nd paragraph: In anesthesia research a common problem encountered is to distinguish the effects of surgical stress from those of anesthesia, since they occur simultaneously. Don't the authors think that in the absence of large prospective studies, the role of anesthesia in determining the metastases is somewhat overemphasized? Please insert some comments

We refer the attention of the reviewer to the conclusion of the review where we have emphasized the fact that we do need more prospective randomized trials in this area, before we actually change our clinical practice. I quote from the review "Though much has been said and done about anesthetic technique and cancer recurrence, the question very much

remains unanswered. Multiple high quality, well-designed and validated studies are needed before a strong statement can be made one way or the other about the influence of an anesthetic technique on the recurrence and behavior of certain cancer types. The currently available data do favor regional anesthesia as a sole vehicle or in combination with general anesthesia, in addition to an increasing trend to autologous blood transfusion and attenuation of stress responses in the perioperative period. Areas of future interest could be related to some of the other anti-inflammatory and immunomodulatory drugs that we use in the perioperative period. These include a better categorization of various types of opioids, NSAIDS and other analgesics. A greater focus needs to be on longer follow-up of patients in these observational studies and long term outcomes related to the anesthetic technique and perioperative interventions.”

We have also added some comments as suggested by the reviewer under the section:

Rationale for Regional Anesthesia and effects of surgery and anesthesia

a. Effects of surgery and anesthesia on tumor cells

There is a large amount of data from anecdotal reports, observational and retrospective human studies and animal studies that emphasizes the so-called “deleterious” effects of general anesthesia and or surgical stress on cancer recurrence and outcomes. The authors would like to fore warn the reader that in the absence of large randomized prospective studies the clinician should not immediately change practices based on this data.

2. Page 11, line 4, correct “actors” to factors 3. Page 15, line 2, correct “hasn” to has  
Corrected and changes shown in red

4. Page 15, last paragraph: Please make some comments on the immunomodulatory effects of chronic pain and its psychological effects (e.g. depression) on cancer recurrence. Are there available data? How could this insert a bias in the studying of opioid effects on the cancer recurrence?

The role of the complex interplay between depression, immunotherapy, and advanced cancer, use of opioids and cancer pain has been highlighted in this additional paragraph included in the manuscript.

An additional potential confounder here would be psychological symptoms such as depression and its linkages with cancer pain and that those patients with depression are usually on a higher dose of opioids to treat this cancer pain. Cancer chemotherapy in more metastatic and advanced tumors (and those that potentially cause more pain and depression and need more opioids) with pharmacological agents that induce immunosuppression has depression as one of its side effects as well. <sup>[129]</sup> Specifically, IFN-alpha has been seen to decrease serum activity of prolyl endopeptidase (PEP). This enzyme is a cytosolic peptidase that is widely distributed in human tissues and body fluids. By playing an important role in intracellular protein turnover PEP is indirectly involved in the pathophysiology of psychiatric dysfunction in relation to mood disorder. High-risk melanoma patients receiving IFN-alpha were seen to have a clear decrease in PEP activity in the first four weeks of therapy. <sup>[130]</sup> Van Gool et al also investigated the levels of PEP in patients with metastatic renal cell carcinoma receiving immunotherapy and concluded that a role for PEP in the pathophysiology of IFN-alpha induced mood disturbance can neither be confirmed nor excluded.<sup>[131]</sup>

The complex interplay of opioids, cancer pain, immunotherapy, depression and immunomodulation means that clearly the effect of opioids themselves on cancer recurrence and metastases cannot be clearly elucidated and there is much more associated with this cause and effect relationship than what is plainly evident based on current literature.

5. Page 24, first paragraph: please delete or rephrase last sentence "Also, animals used...characteristic". This is actually an advantage of animal experiments, not a disadvantage, because comparison to control group occurs without intrasubject variation.

Not relevant and deleted: ~~Also, animals used for these experiments are inbred, leading to very similar genetic and immunological characteristics.~~

6. Page 29, Immunotherapy. The message of the authors is not clear. If immunotherapy helped NK cells to overcome the effects of anesthesia, but did not have any significant success on patient outcome, then why should the effect of anesthesia on NK cells be important?

The message here is that there is not enough human data to suggest a clear evidence of benefit of NK cell activation via immunotherapy and its beneficial role in prevention of cancer progression. This data clearly exists in animal (rat studies) and hence is a potential avenue for more research and a potential pathway of controlling cancer spread.

Reference 177 is a review article. Better literature support is needed.

177 **Houbiers JG, Brand A, van de Watering LM, Hermans J, Verwey PJ, Bijnen AB, Pahlplatz P, Eeftinck Schattenkerk M, Wobbles T, de Vries JE, et al.** Randomised controlled trial comparing transfusion of leucocyte-depleted or buffy-coat-depleted blood in surgery for colorectal cancer. *Lancet* 1994; **344**(8922): 573-578 [PMID: 7914960]

7. Page 31, 3rd sentence: "This may the reason...anesthesiologists". Syntactical error, please correct.

Changed to : This may be the reason for success with beta blocker therapy as highlighted in the section above and an area of interest for anesthesiologists.

8. Literature: Please check the references one by one and edit according to the style of the journal

We have changed our style of references in accordance with the journal's requirements. We used endnote to format our references and there is no tool in endnote to only bold the first author of each reference (this is a requirement per the journal). After contacting technical support at endnote they communicated with me that there is no formatting software that can do this.

I would ask the journal publishers to accept the references with changes that we have incorporated and to make bold the first author using a software tool that they might have.

Reviewer 2:

Thank you for submitting the review: Perioperative Care and Cancer Recurrence: Is There a Connection? These are the suggested

modifications: - It is preferable that the title would indicate to the reader that this is a review. -

Since this is an invited review and will be published as a review section in the journal it will be clear to reader. The question at the end of the title and interrogatory nature of the title are relevant because we want to focus on the fact that this is a burning question and one which as yet does not have an answer.

The Overview Section is very long and would better to make it more concise and more focused to the subject of the review. -

If possible we would prefer to keep the overview section to present length. On careful inspection of the contents of the overview it is reasonable to see that a topic of review as vast as this needs a strong overview for the reader to understand the magnitude of the issue in question. Also if we look at the size of the overview in relation to the whole article, it is certainly in perspective and size of the whole document.

Please remove the author's comments on yet unpublished studies and results. Please delete the last paragraph in section Clinical Trials on the Effect of Anesthesia on cancer Recurrence "it is unclear whether these clinical trials.."

Changed as under :~~It is unclear whether these clinical trials will definitively answer the question of whether we should modify our anesthesia plan considering the long term outcome for patients. Most of the studies are likely underpowered. The ones with planned large numbers of subjects based their power calculation on remote models with unclear clinical relevance. It is plausible that number of subjects will not be sufficient. It is also unclear how frequently data must be analyzed. One of the previously mentioned studies suggests that anesthesia has only transient effects.~~

These clinical trials and the planned studies going forward if properly powered and statistically robust will go a long way in answering the as yet unanswered question of modifying the anesthetic plan to provide a better cancer related outcome for the patient in question.

On behalf of all the authors, I thank the journal editors and reviewers for there valuable comments. These will go a long way in the betterment of our final manuscript.

I hope that the changes incorporated will satisfy the reviewers and journal editors.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Anesthesiology*.

Sincerely yours,

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