Author's response to reviews

Title: Neutrophil count is associated with survival in localized prostate cancer

Authors:

Houda Bahig (houdabahig@gmail.com)
Daniel Taussky (daniel.taussky.chum@ssss.gouv.qc.ca)
Guila Delouya (g.delouya@gmail.com)
Amal Nadiri (amalnadiri@gmail.com)
Ariane Gagnon-Jacques (arianegagnonjacques@msn.com)
Paule Bodson-Clermont (Paule.Bodson-Clermont.chum@ssss.gouv.qc.ca)
Denis Soulières (Denis.Soulieres.chum@ssss.gouv.qc.ca)

Version: 4 Date: 29 April 2015

Author's response to reviews: see over
Dear Editor,

Re: MS: 5083623791636646 - "Neutrophil count is associated with survival in localized prostate cancer"

We thank you for favorably considering our article and for the constructive feedback received on our manuscript. Please find enclosed point-by-point answers to the reviewers’ questions, as well as the revised manuscript.

We thank you for re-considering this work for publication and hope to have satisfactorily completed the revisions requested by the reviewers.

Best regards,

Drs. Houda Bahig and Daniel Taussky for the authors

Reviewer 1:

1. The authors state that neutrophil count is an independent prognostic factor for OS, however, the author do not provide a cut-off values therefore limiting the value of their observation.

   In the context of our retrospective study, we decided not to use cut-off values. This, because we believe that the determination of a cut-off value based on ROC curve has little statistical value by the fact that we didn’t use a validation sample. In order to be statistically valid, our cohort should have to be divided in 2 samples: a test sample and a validation sample. Because neutrophil information was only available in 950 patients in our study, this would have significantly reduced the sample size for the analysis. In addition, use of cut-off values determined a priori was not privileged as cut-off values vary significantly among existing studies in the literature. However, we do agree on the importance of cut-off values for clinical application. Whereas the aim of this study was to identify predictive factors, the next step, in a future work, would be the development of a predictive nomogram with determination of cut-off values. We added a commentary discussion these points briefly in the discussion section.

2. The authors conclude that neutrophil counts represent systemic inflammation, however the NLR ration was not associated with mortality. The authors should discuss the in more detail. The authors should also include other known markers of inflammation for their analysis.
The pathogenesis underlying the change in leukocyte counts in the context of cancer remains unclear. There are currently it is currently hypothesized that the presence of tumor cells may stimulate a local inflammation ultimately leading to a systemic inflammatory response (1). Several studies have reported a high NLR to be associated with prognosis and the hypothesized explanations are the following: a) the high NLR reflects an increased neutrophil response to the tumor and which consequently favors angiogenesis and tumor progression (2), b) the high NLR reflects lower lymphocytes, and therefore a decreased anti-tumor immune response (3), c) the combination of 1 and 2. Results from our study favor the prognostic role of neutrophils, however, the results of our study are limited by its retrospective nature and potential bias. In addition, as leukocyte data was not available for all patients, our study may have been underpowered to detect a statistically significant difference in NLR or lymphocyte counts.

Other known factors of inflammation such as C-reactive protein or albumin levels are not routinely included in laboratory investigations of localized prostate cancer patients and therefore could not be included in our study.

We discussed these above mentioned points more briefly in the discussion section.

3. The authors need to include WBC.

Total WBC was not included in the initial data collection and analysis because of the strong collinearity between WBC and lymphocytes/neutrophils. As monocytes represent only a minimal portion of total WBC, we added lymphocyte+neutrophil count in the univariate OS analysis model as best estimate of total WBC. This was added to the survival analysis in table 2. A trend for increased mortality in patients with increased lymphocyte+neutrophil count was noted, but this was not statistically significant.

Reviewer 2:

Several comments,

1) They showed that 5 years OS and BFRS for the patients were 93%, and 95%, respectively. Are these results reflect that few patients died in prostate cancer?

In fact, only a minority of patients died from prostate cancer and the total number of deaths was small. This is however not surprising as 90% of our cohort had low to intermediate risk prostate cancer. In a previous study by d’Amico, only between 0-6% of patients with low and intermediate risk prostate cancer were estimated to die from prostate cancer at 10 years whereas numbers reached 45% in high-risk disease (4). As specified in the manuscript (line 199), the number of deaths was too small to stratify according to cause of death and therefore we cannot determine whether the lower survival in patients with a high neutrophil count was caused by more aggressive disease or a systemic inflammation from another cause (ex: cardiac disease).
2) Page3, Line 13, “BFRS” is firstly used, needs to explain the abbreviation.

_This was corrected in the manuscript._

3) Figure 1 and 2, please explain the 3 lines.

_The 3 lines represent the Kaplan Meier survival curve and the associated lower and upper 95% confidence interval. An explanation was added to the figure caption._

4) Table 1, write down the unit on Lymphocytes and Neutrophils.

_This was added to table 1._

**References:**


