Reviewer's report

Title: Preoperative neutrophil-to-lymphocyte ratio is an independent prognostic marker in patients with laryngeal squamous cell carcinoma

Version: 2
Date: 8 February 2015
Reviewer: Han Zhang

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MAJOR REVISIONS REQUIRED

Introduction
72 – Please rephrase line to a combination of surgery, radio-, and chemotherapy.
73 to 74 – What epidemiological study? Please cite source. What does the authors mean by “improved little”? Are they referring to survival outcomes?
77 to 84 – Unclear what the background behind neutrophil to lymphocyte ratio; what kind of history does it have in head and neck cancer? What are previous findings? It’s not made clear what the reasoning for this particular study is.
83 to 84 – Grammatical mistakes

Methods
94 – Grammatical Error
95 to 97 – Were patients who had palliative treatment included? Please specify whether treatment with curative intent was an inclusion factor.
97 – Clarify what is meant by “chronic infectious diseases”
100 – Specify what is meant by no preoperative steroids. Does the authors mean to say no steroids ever or within what time frame does there need to be from steroid administration to inclusion. If there is a time frame, what is the justification for that time frame?
102 – Unclear as to why NLR is calculated this way; where is the precedent or previous study that showed this to the way to be calculated?
103 to 105 – Procedural breakdown belongs in the results section
107 to 109 – Please change “date of surgery” for DFS and OS calculations to “date of treatment” as not all patients had surgery upfront as the primary modality for their tumors. Also If patients received RT or Chemotherapy; what doses were used for RT and which chemotherapy agents were used? Most patients will not tolerate the full course of chemotherapy, what did the author use as a “cutoff” for acceptance that the patients received chemotherapy?

Statistical Analysis
118 to 120 – It’s unclear what variables was included in the cox-regression analysis; in this particular study, matters of TNM staging, age, gender,
combordities as well as treatment status should all play a part in effecting the survival status.

Results
Demographic Data
136 to 137 – The authors need to more clear about “Smoking” and “drinking” histories. Pack years? Amount of alcoholic drinks per day? Last time they smoked or drank?

DFS and OS
155 – Please provide SD as well as range and median for follow-up
171 – the authors likely means histological grade instead of “historical grade”
173 – It’s unclear what the authors meant by “clinical grade” do they mean the TNM staging done clinically? If so does that meant he TNM staging system otherwise used in the paper is pathological? It’s also unclear as to why the clinical grade was no included in the multivariate analysis
176 to 182 – It’s interesting that T staging was not prognostic of DFS but was in OS. This bring back to the question of why treatment modalities was no included in the cox-regression analysis, given that early and late stage laryngeal cancer was included in this study, it’s pivotal that treatment modalities are included. Without this valuable piece of information, it is in my opinion that the analysis is flawed and yields a confounded result.

Tables – It’s confusing why 60 is used as the cutoff for age differentiation within this study? Where is the supporting evidence/literature to show that this has effect on survival?

Discussion
206 to 210 – As the author states that optimal cut-off value for NLR is not accepted; it’s certainly not established within the head and neck cancer literature. Perhaps a study to first establish evidence of optimal cut-off for head and neck cancer in general and in particular as a prognostic factor in a disease site where treatment and prognosis is well established (i.e. Oral Cavity) before an undertaking in this study would be justified.
215 to 220 – The study by Kim et al, has a much different goal as compared to this study, as such it is unclear what kind of comparisons the authors are trying to establish between the two papers.
221 to 223 – What studies?

Comments:
A very interesting paper in a possibly exciting new prognostic marker for head and neck cancer. There are however several limitations and issues with this paper that precludes suggestion for publication.
1) It is unclear the role of NLR in head and neck cancer or any cancer in general. The literature surrounding this possible prognostic maker is still controversial and
is yet to be established. The role of NLR in particular in head and neck cancer has not been looked at in any large scale study in relation to prognosis. Therefore, a initial study to look at the possibility of NLR’s role in head and neck cancer in general as a prognostic factor needs to be established before any further studies can be undertaken. This study in particular does not address the issues of how NLR is optimally calculated? When is the preoperative values taken? The cut-off value is not clearly proven and the authors themselves state that there is no universally accepted value. Therefore, without that, one cannot ascertain as to the applicability of a cut-off value within this cohort of patients compared to another.

2) One of the main flaws of the methods of this study is the lack of treatment modalities. Because the study encompasses a wide TNM stage of laryngeal cancer, the lack of treatment modalities within the cox-regression analysis is a major confounder that renders the analysis and the conclusions of the study flawed in drawing it’s conclusions

3) There is also a lack of comorbidity and performance scores which need to be included in the multivariate analysis as they are another source of major confounder within the analysis. This is especially true given that NLR is proposed as an “inflammatory marker” that has a role in patient immunity and overall well-being status.

4) There is also serious doubt that even if NLR is a true prognostic marker for head and neck cancer, what the utility of it’s clinical value is. There is currently so many prognostic values including TNM staging system. What utility does NLR add on top of these factors? How does it affect the treatments and effects on patients from a clinical stand-point.

Overall a ambitious study exploring an interesting point that needs a lot of clarification and background work to be done before any valid conclusions can be made.

Level of interest: An article of limited interest

Quality of written English: Not suitable for publication unless extensively edited

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