Reviewer's report

Title: Ki-67 is a valuable prognostic predictor of lymphoma but its utility varies in lymphoma subtypes: evidence from a systematic meta-analysis

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Reviewer: Ioannis Anagnostopoulos

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This meta-analysis deals with the value of Ki-67 immunostaining results in the prognosis of malignant lymphoma. The results of this analysis demonstrate a significant correlation between a high Ki-67 index and a poor survival outcome in non Hodgkin lymphomas particularly in diffuse large B cell lymphomas, mantle cell lymphomas and in NK/T cell lymphomas. The results of this study are interesting, there are however several points that need further clarification.

In their abstract the authors suggest that they analyzed the impact of Ki-67 expression on survival in various subtypes of lymphoma and after the introduction of rituximab. In the later parts of the manuscript it becomes clear (as expected by the fact that rituximab can only be used for therapy in the case of CD20-expressing B-cell lymphomas) that they could analyze the rituximal effect only in diffuse large B cell lymphomas and mantle cell lymphomas- and of course not in Hodgkin lymphoma and NK/T cell lymphoma which do not express CD20. This should be mentioned in the abstract, which should be modified accordingly.

The authors use the terms of „Ki-67 overexpression“ as well as the presence of „Ki-67- positive“ and „Ki-67-negative patients“. As the authors correctly state Ki-67 is expressed in all phases of the cell cycle. It is therefore hard to understand that there might be Ki-67 „overexpressing“ cells and malignant tumors like the lymphomas studied here, which are Ki-67 negative. As Ki-67 is constantly expressed in normal and in neoplastic cells it would be more fitting to use the terms of high and low Ki-67 index, or high/low proliferative activity respectively.

Another term that should be amended is the „subgroup of malignant lymphoma“. Actually the WHO lymphoma classification does not classify lymphomas into subgroups but into disease entities.

The authors state that they included in their study only publications dealing with the immunohistochemical detection of Ki-67. There are however some important informations missing:
- which Ki-67 antibody was used in the various studies?
- how was the percentage of Ki-67 positive cells evaluated (estimated or by image analysis)
- did the studies use tissue microarrays or whole tissue sections?
Another fact that is not sufficiently clarified for the readership is how the authors could extract reliable information from studies dealing with biologically different patient groups suffering from the same lymphoma entity. For example the two Hodgkin lymphoma studies selected are dealing either with only young patients (Barros et al.) or only with advanced disease stage (Morente et al.). This heterogeneity is also obvious in the diffuse large B-cell lymphoma group with studies including only young patients with good prognosis (Pfreundschuh et al.) and others with aggressive lymphoma and advanced stages (Jerkeman et al.)

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare that I have no competing interests.