Reviewer's report

Title: Prognostic significance of lymphangiogenesis in laryngeal carcinoma patients

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Reviewer: Panayiotis Kyzas

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Peer Review on the BMC Article: Prognostic significance of lymphangiogenesis in laryngeal carcinoma patients, by Garcia-Carracedo et al.

General Comments

In the current study the authors have examined lymphangiogenesis and its prognostic significance in samples from patients with laryngeal/pharyngeal cancer. They found that the detection of tumour emboli and increased lymphatic vessel density were associated with poor prognosis.

The findings of the current study cannot be characterized as novel, since lymphangiogenesis has been examined in the past in HNSCC (Cancer research 2003, 63(8):1920-1926, Am J Surg Pathol. 2006 Feb;30(2):185-93, Cancer research 2002, 62(5):1315-1320). Some of these references (but not all) are cited by the authors. However, this study is important for 2 reasons: First, it enrolls quite a large patients' population (104 patients) and second, the results confirm previous observations.

Molecular prognostic factors' literature faces threats from potential biases including lack of registration and protocols, lack of power calculations, selection of cut-offs and outcomes and variability of the assessment method for the postulated prognostic factor (J Natl Cancer Inst. 2005;97:1043-55, Eur J Cancer. 2007 Nov;43(17):2559-79, BMJ. 2009 Dec 30;339:b4184. doi: 10.1136/bmj.b4184). These problems have led to the development of recommendations for the reporting of prognostic marker studies, the REMARK criteria (J Natl Cancer Inst. 2005;97:1180-4). Obviously, these criteria were not followed in the current study. I strongly recommend rephrasing of the relative sections of the manuscript in a way that fits the REMARK criteria, and discuss the limitations of their work, citing the proper articles referred above.

Major Compulsory Revisions

1. Title: Please add “pharyngeal” in the Title, since the population was not entirely homogeneous of laryngeal cancer patients.

2. In the Abstract/Results: What was the outcome for which poor prognosis was recorded? (Death/recurrence/response to treatment/other?).

3. Page 4/Introduction: Podoplanin is indeed a very specific lymphatic endothelial marker. Its specificity has been recently quantified; therefore the proper
reference should be cited (Mod Pathol. 2005 Nov;18(11):1490-7.)

4. Page 5/Methods: Has the study been registered prior to commence? Was there any formal protocol submitted?

5. Page 5/Methods: How many assessors have evaluated the staining? Were they blinded to the outcome?

6. Page 6/Statistical analysis: I cannot understand the dichotomization of the stage to I vs. II-IV. A more appropriate one would be I-II vs. III-IV. I suspect this may have introduced significant bias in the analyses and I suggest re-doing the analyses with the proposed clustering.

7. Pages 6-7/ Statistical analyses: Using only disease specific deaths is hazardous – Overall survival has been shown to be the safest outcome as being the least amenable to biases.

8. Discussion, page 10: This is not the first report on the impact of the presence of tumour emboli; references that the authors cite have already examined this issue.

9. The conclusion may be too bold – there is still a long way until re-validation and replication will allow implication of lymphangiogenesis into clinical practice.

10. The authors are to be congratulated for the quality of their figures.

11. In the KM figures, I would like to see the number of patients for each group in every time point (i.e. every 10 months).

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests'