Reviewer's report

Title: Prognostic relevance of ALT-associated markers in liposarcomas: a comparative analysis

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Reviewer: Janice Royds

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Prognostic relevance of ALT-associated markers in liposarcoma: a comparative analysis

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Induction of a telomere maintenance mechanism (TMM) during tumourigenesis enables malignant cells to escape the normal constraints of telomere shortening and senescence during prolonged cell division. Mesenchymal cells appear to favour the alternative lengthening of telomeres (ALT) mechanism over the more common telomerase induction seen in carcinomas.

The study aims were to determine the prognostic significance of ALT in a mono-institutional cohort of 85 patients with liposarcoma, using two different methods for measuring ALT. Two methods have been described for measuring ALT, the direct estimate of the abnormally long and heterogeneous telomere fragment length by Southern blot and the in situ method of co-localisation of telomere components and PML protein in ALT associated PML bodies (APBs).

Irrespective of the method used, ALT showed prognostic significance indicative of a less favourable outcome for liposarcoma patients. There was 77.6% concordance between the two technologies used and when a tumour was defined as ALT by at least one method it was prognostic at 10 year follow up. APB presence proved to be a more sensitive indicator than telomere length, being an indicator of increased mortality at both ten and fifteen years. TRF length distribution as determined by Southern was only prognostic after 15 years' follow up.

The APB method appeared to be more sensitive than the Southern analyses in determining ALT and it was thought that this is probably due to the in situ nature of the APB assay enabling individual cells to be observed.

1. The aims of the study are well defined and clearly stated

2. The methods are appropriate. But more detail is needed for the APB assay. What probe was used? What antibody? What microscopy e.g. confocal or not?

3. The data obtained appear sound, reasonably well documented and adhere to accepted standards for reporting and data deposition. A table summarizing
clinical details and experimental data would be useful.

4. The limitations of the study could be more clearly stated. Only 3 samples were APB+ but ALT TRF-ve. The conclusions are perhaps a bit strong based on such low numbers. At 60 months the numbers are 36 : 12 vs 37 : 11 for ALT status based on APB or TRF analyses.

5 Acknowledgments are clearly stated.

6. The title and abstract reflect the work done and the findings

7. The paper is well written and well referenced.

Minor essential revisions:-

1. Abstract
The results section could be clearer. Which marker appears at 10 years and which at 15 years? This should be clearly stated instead of saying “respectively”.

2. Methods
More detail on the APB methodology should be included

3. Results
A table summarizing the results should be given. It is not easy picking out the results from the prose alone.

4. Discussion
Concordance was reported in glioblastoma for APB and TRF methodologies. The reason for the discrepancy with liposarcoma in this study is given as “time dependence of each assay to provide significant prognostic information”. This doesn’t make total sense as it is the assays themselves that were concordant not only their prognostic power. Further clarification here would be good. GBMs are possibly are more homogeneous group of tumours than the present cohort of liposarcomas which possibly included tumours of different grade.

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

Quality of written English: Acceptable

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