Reviewer's report

Title: Ki-67 is a Strong Prognostic Marker of Non-Small Cell Lung Cancer When Tissue Heterogeneity is considered.

Version: 2  Date: 24 February 2014

Reviewer: Aurelie Fabre

Reviewer's report:

This is an interesting study looking at Ki67 in tumour heterogeneity in lung cancer on surgically resected tissue using an interesting novel methodology- Spiral array- that appears to cover larger areas of tumour than tissue microarray and included various areas of a same tumour.

However the authors need to be more up-to-date with current subclassification of lung adenocarcinomas and include this to make the paper more appealing to current lung cancer diagnosis and management.

Major Compulsory Revisions

The study could be strengthened if the recent classification of pulmonary adenocarcinoma could be applied (Travis WD, Brambilla E, Noguchi M, et al. The new IASLC/ATS/ERS international multidisciplinary lung adenocarcinoma classification. J Thorac Oncol 2011;6:244 –285) and a breakdown of Ki67 reading depending on the subtype (lepidic vs acinar vs solid, vs papillary/micropapillary) as well as Ki67 in mucinous vs non mucinous adenocarcinoma would be of great value.

Also a comparison of the Spiral Array to a conventional tissue section in displaying various subtypes of adenocarcinoma on the reels would be helpful in a pilot group.

Similarly did Ki67 correlate with differentiation of squamous cell carcinomas?

p15: It is unclear how Ki67 HS showed 21 score 0- please explain

p16: HeS is a differential between HS and LS- how was this correlated with poor survival? Did high HeS vs low HeS show any differences?

In clinical practice a cut off value for Ki67 is easier to apply that the one proposed in this paper- did you find any cut-off value for Ki67 that correlated with survival- it appears that <10% is a good cut off? how does this apply to lepidic adenocarcinomas?

Discretionary revisions:

- The small cell carcinomas, albeit of limited stage, should be excluded from this study as tumour heterogeneity is rarely an issue in this tumour.

- TTF-1 is a marker of lung differentiation- Was there any correlation with Ki67 scores and expression of TTF-1 on tumour? Any association with molecular
changes (EGFR/KRAS/ALK)

**Level of interest:** An article of importance in its field

**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' below.