Reviewer’s report

Title: Separate and combined analysis of successive dependent outcomes after breast-conservation surgery: recurrence, metastases, second cancer and death

Version: 1 Date: 17 February 2010

Reviewer: Jean-Yves Pierga

Reviewer’s report:

This is a very interesting study on outcome of breast cancer and relation between various events: locoregional relapse, distant metastasis, controlateral cancer, second cancer and death. This is a work on statistical analysis methodology which should be reviewed by an expert in biostatistics. The authors explain that the events are non independent and it is clearly of interest to look at the correlation between local relapse, distant metastasis and controlateral or second cancer. The results given in figure 2 a and b are very informative and original. They confirm the correlation between LR and DM. However, I do not understand how the authors can integrate in their model breast cancer related death. This event is obviously associated with DM and I wonder if in this series it was possible to observe a BCRD without DM. This event is in any case the last one, excluding the others. It is not clear for me how this parameter is pondered in the frailty model. They explain page 14 that death from breast cancer did not importantly bias their finding but this deserve more explanation.

As the prognostic significance of the five events is very different, I do not see the interest of figure 1

Page 11: one can guess that after developing DM, the risk is very high of having a second event which will be at least breast cancer death except for the older patients who can die from other causes. I would be more interested by a chronological analysis of the relation between LR, DM, controlateral cancer and death than by a simultaneous analysis including death which for me has no clinical relevance.

The authors hypothesized in the introduction and that this model analysis can generate adapted therapeutic interventions but nothing in their results substantiate this assertion.

HER2 data on the series would have been of great interest and would allow the analysis of the correlation between LR, DM and death in various breast cancer subtype (HR+, HER2+, and triple negative).

In conclusion, this is a large series of breast cancer patients with long follow-up giving chronological information on the incidence of events after surgery. This series can represent a new reference. However, I recommend a biostatistical review of this work because I am not able to evaluate and appreciate the clinical
interest of the combined analysis developed in this work.

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

**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