Reviewer's report

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

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Reviewer: Adri C Voogd

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The authors were able to collect a large cohort of patients with breast-conserving treatment and long-term, complete follow-up, which is an achievement in itself. Figures 1 and 2 are very useful for reasons of follow-up and patient counseling. Still, they are not the result of the frailty model but of a straightforward Cox regression analysis for each end-point separately. The main advantage of the frailty models (or random -effects survival models) seems to lay in the fact that statistical power is increased by allowing each patient to have more than one outcome. However, this seems only true when similar types of events are considered. The advantage is not very obvious when different clinical entities, such as loco-regional recurrence, contralateral breast cancer and other second malignancies are analyzed simultaneously. Though it is demonstrated by the authors in Table 4 that risk estimates became more precise, these estimates are very difficult to interpret. For example, is grade a prognostic factor for all outcomes or only for loco-regional and distant recurrence and for breast cancer death, as was indicated by the Cox regression analysis. What is the clinical usefulness of these RR’s if they do not relate to a specific outcome but only to the aggregate of very heterogeneous clinical entities. And what does including type of prior event (i.e., locoregional recurrence, contralateral breast cancer, distant metastases and 2nd primary cancer other than breast) in this frailty model add to including these events as a time-dependent covariate in a Cox regression model and relate it to each of the other outcomes. For example, what is the hazard ratio for subsequent distant disease in patients with a loco-regional recurrence? This is what you want to know when you have to decide about the need for systemic treatment.

The question thus remains what frailty models add to the standard techniques used to analyze treatment outcomes following breast cancer treatment (in this case breast-conserving treatment).

Other comments:

Introduction:

The sentence “The main concern…absence of hormonal receptors [2,3]” is not correct grammatically.

Introduction could be more straightforward. The phrase “..different prognostic factors ….after BCS [4,5]” could be omitted, and also the prase “In most
applications …irrespective of whether a local recurrence occurred before.” And then start with: “The most straightforward approach in these settings of recurrent events is simply…”

Please specify the principles and baseline assumptions underlying the frailty model more clearly. Here it is suggested that it is possible to control for the correlation of recurrent events of different types. However, in the analyses all outcomes were analyzed together, not taking into account their different clinical etiology and prognostic impact. This seems to be a contradiction.

Results

Results could be more concise.

Table 1 could be restricted to the first column and the absolute number of the different events (LRR, metastases, death, contralateral breast cancer) could be mentioned in the text.

Discussion

The explanation for the protective effect of lympho-vascular invasion on the risk of contralateral breast cancer is too difficult to grasp.

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

**Quality of written English:** Not suitable for publication unless extensively edited

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