Reviewer's report

Title: Prognostic effect of preoperative Serum estradiol level in postmenopausal breast cancer

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Reviewer: Louk V Beex

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General:
Thanks for response to earlier comments. The paper gained much quality. The major problem remains its small robustness: Results are on the basis of possible selected and very small figures. This is already demonstrated by the (borderline) loss of significance in the multivariate analysis after inclusion of a small number of patients with local/regional relapse and contralateral breast cancer, as discussed by the authors in the responses to the questions of the reviewers. Besides that, inclusion of BMI in the multivariate analysis for the ER negative subgroup is missing. Nevertheless The results found in this well described particular group of women are of interest for the ongoing discussion and preclinical findings about non receptor mediated growth effects of estrogens in breast cancer.

Concrete remarks:
1. Abstract: fore-last sentence: add in the investigated ....... postmenopausal women...
2. Introduction: The referred study of James et al does not give information about ER levels and prognosis, but mainly discusses the relationship between hormone levels and development of breast cancer, which is a completely different subject.
3. Results: in the text 195 patients with HR positive disease are mentioned, in table 1 it is 190 patients. Furthermore, the percentage of women with HR positive disease and 1-3 nodes is not correct (table 1)
4. Results: As already said, BMI is not included in the multivariate analysis for ER negative women, although there is overall a nearly significant correlation between BMI and ER levels.
5. Discussion: To avoid clinical misinterpretation of the results, a more to the point discussion about the possible influence or lack of effect on prognosis of estrogen (lowering measures), as far as available, is welcome:

The present discussion suggests more influence of estradiol levels on prognosis, than given in the mentioned literature. This paper deals with prognosis of established ER positive or negative breast cancer, not with the role of estrogens as ethiologic factors for those diseases. From a clinical point of view, a possible role of higher estrogen levels in the prognosis of ER negative breast cancer is expectedly and obviously not counteracted by adjuvant tamoxifen therapy
(EBCTCG 2011: relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient level meta-analysis of randomized trials); But some data about the, for this paper important role of estrogen lowering treatments like aromatase inhibitors, also suggest that the effect for recurrence is neglectible. (i.e. for aminogluthethimide: Jones et al. J Clin Oncol 10:1547-1552. 1992); for small numbers of ER- patients treated with letrozole: Viale et al, BIG 1-98, J Clin Oncol 2007).

**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'