Reviewer’s report

Title: Immunohistochemical detection improves the prognostic value of lymphatic and blood vessel invasion in primary ductal breast cancer

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Reviewer: Tim Dekker

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Major compulsory revisions:

1- The authors state that the data regarding LVSI foci detected on H&E slides was recovered from archival pathology reports. Unfortunately, this might threaten the applicability of the data. These LBVSI-H&E lesions were likely scored over a longer period of time by multiple observers (presumably pathologists during routine practice), which might lead to significant interobserver differences. This is the case since not all observers have the same interest in LVSI (by which I mean the energy for scanning the entire slide for LVSI) or have different opinions of what really constitutes LVSI. On the other hand, all LVSI foci detected with the aid of IHC were detected by one/two observers with the specific goal of detecting these foci. I would therefore suggest a blinded review of all H&E-stained slides by the same observers to prevent this problem. I would also suggest adding what criteria were used for what exactly constitutes LVSI (especially for the H&E-based detection), as this is not provided in the manuscript but is of vital importance in order to reach high interobserver correlation.

2- The authors refer to the 11th St Gallen guidelines as one of the consensus reports regarding lymph vascular space invasion (LVSI). However, these guidelines recommend the detection of peritumoral LVSI. The intra- and peritumoral LVSI foci were not separately analysed in the present study (although briefly mentioned in the methods section). This is important, considering that a previous report by Yamauchi et al (Human Pathology 2007) already demonstrated that H&E-stained slides are more reliable for detecting peritumoral LVSI foci (as compared to intratumoral LVSI foci). I would therefore recommend scoring intra- and peritumoral LVSI analyses separately as well as separate analyses concerning the concordance with LVSI-H&E and cancer-specific survival.

3- The positive expression of D2-40 in normal myoepithelial cells seems to be the major problem for accurate use of this marker. This might be especially true in some cases of DCIS (D2-40 is positive in 77% of all DCIS cases, Rabban, Chen Human Pathology 2008), where the morphology of both the D2-40-positive cells as well as the neoplastic cells might not be enough to identify whether a lesion is indeed LVSI or DCIS. p63 staining should be performed in these cases, yet this was not performed in the current study which relied on morphological distinction alone (as stated in the results section). Please provide more information on what...
morphological characteristics were used and whether p63 stainings were performed.

Minor essential revisions:

4- The p-value for the correlations between cancer-specific survival in node-negative patients and triple-negative patients and LBVI-H&E seems discordant between the text and the tables (either P=0.006 or P=0.005 for triple-negative patients and either P=0.168 or P=0.163 for the node-negative patients).

5- It would be of interest to know whether the patients included in the study were treated with hormonal therapy and adjuvant chemotherapy or radiotherapy after primary surgical therapy. As far as I can tell, this information is not provided in the manuscript, but is important for interpreting survival analyses.

Discretionary revisions:

6- In line with the St Gallen guidelines and recent publications, it seems that only tumors with extensive LVSI seem to warrant specific attention (in the sense of additional therapies). However, the distinction between limited and extensive LVSI presence (by whatever measure) is not made in in this study. This is important for assessing the relationship between LVSI and prognosis and might also influence the concordance between the LBVSI-H&E and LVSI-IHC detections.

7- The manuscript refers to 84 patients that were found to have LVI or BVI that were not identified on H&E stains. It would be of interest to review these 84 slides and identify what the reason was for not reporting H&E in these cases (poor morphology, retraction artefacts etc).

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