Reviewer's report

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

Version: 4
Date: 18 March 2014
Reviewer: Niamh Conlon

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MAJOR COMPULSORY REVISIONS

1. This is an excellent study yielding important information on the prognostic value of the assessment of LBVI by immunohistochemistry in early breast carcinoma. However, a major limitation to this study is the decision not to centrally review the original H&E slides of the cases, but instead to simply extract the data from the original pathology report. In my opinion, the fact that the presence of LBVI has not been assessed by the same investigators on H&E as well as on immunohistochemistry undermines all the comparisons between the relative strengths (in terms of prognostic power) of H&E and the immunohistochemical markers in the assessment of LBVI. I would strongly advise that every effort be made to review the H&E slides centrally before proceeding with publication of this study. An alternative approach would be to cut, stain and review a new H&E on the same block used for IHC in each case. If this is not possible, then this study limitation should be clearly outlined in the Discussion section and I would consider changing the emphasis of the paper title and the conclusions to reflect this shortcoming ie remove the comparison to H&E and just state that IHC for LBVI has prognostic value.

DISCRETIONARY REVISIONS

1. Results, paragraph 2, sentence 1: the authors may like to clarify this statement. It seems to suggest that H&Es were reviewed in the study, whereas everywhere else in the paper it is stated that the LVBIH&E status was based on the pathology report only. Were H&Es actually reviewed or is this just a general statement based on experience?

2. Discussion, paragraphs 8 and 9: I would suggest moving these useful paragraphs to earlier in the discussion and adding a paragraph at the end summing up the impact of the results of this study and giving the authors’ opinion on what further investigations are needed to further establish the prognostic power of immunohistochemical assessment of LVBI.

3. The Discussion section would benefit from some rewriting generally, in my opinion. Several topics briefly outlined in the introduction (the prognostic role of LVI in the routine reporting of breast carcinoma, the current understanding of the relative importance of blood vessel invasion vs lymphovascular invasion, the lack of a standardized, agreed method of assessment for LBVI etc) need to be
discussed in more detail here, including a more extensive literature review. This would help in placing the findings of this study in the context of current clinical practice, and our evolving understanding of the prognostic factors in early breast carcinoma. Further issues that I would like to see discussed include:

a) the lack of consistency between the diagnostic frequency rate of BVI in studies in this field (16% in this study, 27-29% in Kato et al (ref 19, 20) and 0.7% in Mohammed et al (ref 18)) and whether the authors consider that this inconsistency undermines any argument that this data should influence current pathologic reporting guidelines

b) the advisability of extrapolating the results of this study to the general population of breast carcinoma patients in light of the fact that this patient cohort does not appear entirely representative of this population (53% of patients ER-negative). Additionally, further information in the Methods section on how the patient cohort was selected initially would also be welcome.

MINOR ESSENTIAL REVISIONS

Minor issues not for publication:
1. There are grammatical or typographic errors in the following sentences:
   - Abstract, paragraph 1, sentence 1 “BVI is a critical step…”
   - Abstract, paragraph 3, sentence 4 “associated”
   - Introduction, paragraph 1 sentence 2 “accounts for approximately one tenth…”
   - Introduction, paragraph 2, sentence 1: add hyphen to “endothelial lined” and remove following semi-colon
   - Introduction, paragraph 2, sentence 3 “Since then, a number…”
   - Methods, paragraph 3, sentence 8: remove second “were” and replace with a comma
   - Results, paragraph 2, sentence 1 “accompanied by adjacent…”
   - Results, paragraph 2, sentence 3 “morphological characteristics…”
   - Results, paragraph 3, sentence 3: should this figure be 150 patients (rather than 152)?
   - Results, paragraph 5, sentence 4 “older age (P=0.043)
   - Discussion, paragraph 1, sentence 1: move “using” to before “LBVI H&E”
   - Discussion, paragraph 4, sentence 1: remove both semi-colons. Replace with parentheses or rewrite sentence.
   - Discussion, paragraph 4, sentence 2: remove semi-colon.
   - Discussion, paragraph 8, sentence 1: “D2-40 is a…”
   - Discussion, paragraph 8, sentence 1: remove “s” in “cells”
   - Discussion, paragraph 8, sentence 2: “although the D2-40 antibody also binds to the myoepithelium”
2. Suggestions for stylistic changes:
- Introduction, paragraph 2, sentence 1: suggest changing “Lymphovascular invasion” to “Lymphatic and blood vessel invasion (LBVI)”, removing “which”, adding a period after “blood vessels” and starting a new sentence with “It…”
- Introduction, paragraph 2, sentence 3: suggest adding references after this statement.
- Introduction, paragraph 4, sentence 1: suggest adding references after this statement.
- Introduction, paragraph 4, sentence 2: spell out “immunohistochemistry” before abbreviating it.
- Methods, paragraph 2, sentence 2: sentence is unnecessary and can be deleted, in my opinion.
- Methods, paragraph 6, sentence 1: spell out “ICC” beforeabbreviating it.
- Results, paragraph 1, sentences 1 and 2: sentence needs rewriting and addition of punctuation.
- Discussion, paragraph 2, sentence 2: this sentence needs to be rewritten eg start with “Likewise, our findings in terms of the association between LBVIH&E and other well established high risk factors such as…. are in keeping with previous studies”
- Table 1: suggest re-formatting table as I have difficulty reading the Patient column in the present format

**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.