

## Peer Review File

Article information: <http://dx.doi.org/10.21037/abs-21-20>

### Reviewer A

**Comment 1:** Astronomical is too strong a word to describe the health burden of breast cancer.

**Reply 1:** We have modified the word “astronomical”.

**Changes in the text:** In Page 5, line 3, the word “astronomical” has been changed to “great”.

**Comment 2:** I suggest that the statements around Z11 have some caveats, possibly mentioning that the results of follow-up studies such as POSNOC are awaited. This is important, as if Z11 is accepted, then the need for completion surgery, and model such as the MDACC one, is limited. This also means that the second paragraph of the Discussion should be modified to reflect the concern in many parts of the world regarding the results of Z11 (mainly that RT QA was poor and many SN+ve patients received axillary RT).

**Reply 2:** The second paragraph in discussion has been modified to address concerns with the Z0011 trial and to include ongoing studies such as the POSNOC trial.

**Changes to text:** Text has been added to the discussion section in page 11, lines 9-18

**Comment 3:** Were all the positive SNs identified on frozen section - this is suggested in the inclusion criteria?

**Reply 3:** Yes, all the positive SNs were identified on frozen section as stated in the inclusion criteria.

### Reviewer B

**Comment 1:** Can the authors comment on how they will or might use this information to guide future clinical practice?

**Reply 1:** The applications in clinical practice has been added to discussion.

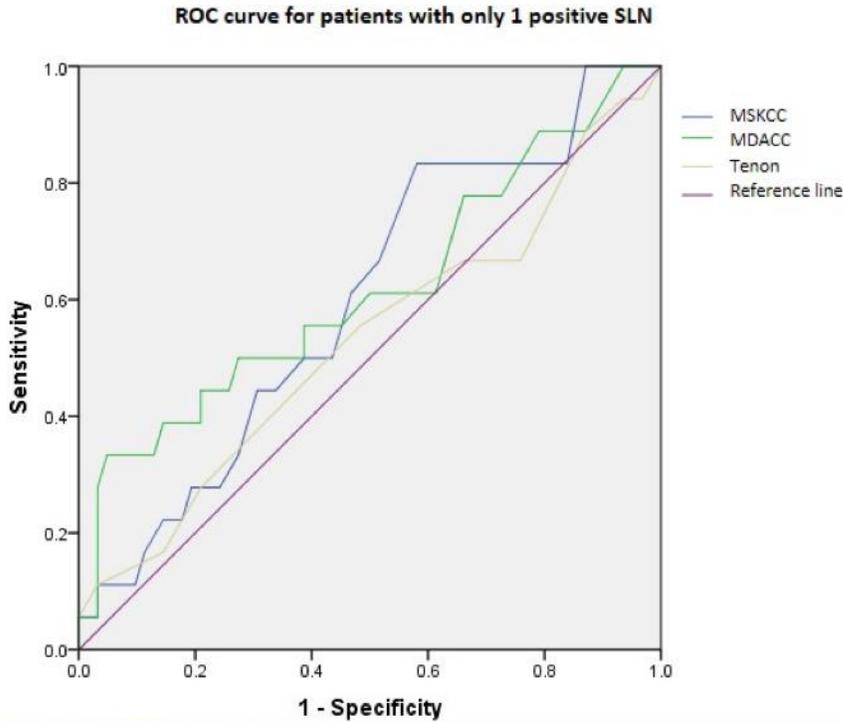
**Changes to text:** Text regarding clinical implications has been added to Discussion section in page 13, lines 1-8.

**Comment 2:** Can they comment further on specific prediction characteristics of the model, for example, is one better than the others for patients with only 1 positive SLN?

**Reply 2:** Further subgroup analysis has been performed on patients with only one positive SLN. In this patient group, all three nomograms showed poorer performance for predicting non-SLN metastases. The AUROC of MDACC (0.618, 95% CI 0.457-0.779,  $p = 0.21$ ) was still the highest, compared with MSKCC (0.597, 95% CI 0.453-0.741,  $p = 0.21$ ) and Tenon score (0.529, 95% CI 0.368 – 0.690,  $p = 0.71$ ). This reflects that these predictive nomograms are less accurate when the nodal metastatic burden is low. Results are shown in the figure below.

**Changes to text 2:** Further analysis and their results are added to the text in Results section in page 9, line 18-21, and also to the Discussion section in page 12, lines 13-15 and Conclusion

section in page 13, lines 20-21. A brief summary has been added to supplement the Abstract section in page 4, lines 2-3. The figure shown below was not added to the manuscript text to avoid confusion.



Area under the ROC curve (AUROC)		
	Area	95% confidence interval
MSKCC	0.597	0.453 - 0.741 (p = 0.21)
MDACC	0.618	0.457 - 0.779 (p = 0.13)
Tenon	0.529	0.368 - 0.690 (p = 0.71)

**Comment 3:** Can you provide either in text or as a flow chart the total number of patients treated with surgery at the same time period, the proportion who had SLN surgery, the total number who were SLN+ (on frozen section examination) and of these the number SLN+ who had a cALND and are reported on in your study? It would be helpful to perhaps compare the tumor characteristics of the SLN+ patients who did and did not have a cALND in a table.

**Reply 3:** The relevant flow chart of patient recruitment has been attached to the manuscript. Analysis of the tumour characteristics of the SLN + patients who did and did not have ALND has been performed and there are no statistically significant differences, except regarding the lymphovascular permeation (LVI), SLN characteristics and N staging. The patients who did not receive completion axillary dissection all only had micrometastases in their positive SLN with no extranodal extension. As a result, all of them are N1mi. The majority of them had no LVI. This is in line with the current practice in my hospital. Though Z0011 is generally followed, the consensus with the oncology department dictates that those with macrometastases should receive a completion axillary dissection regardless of whether they fulfill the Z0011 criteria or not. The table of this comparison is shown below, but has not been added to the manuscript to avoid confusion as the study focuses only on patients who has received ALND.

**Changes to text:** A new flow chart of patient recruitment named “Figure 1” has been added to the manuscript. A short description of patient recruitment was added to the Results section in page 9, lines 2-3.

<b>Tumour characteristics</b>			
<b>Characteristics</b>	<b>Completion ALND (%)</b>	<b>No Completion ALND (%)</b>	<b>P value</b>
<b>Type of operation</b>			
Mastectomy	90 (68.2%)	9 (52.9%)	0.210
BCT	42 (31.8%)	8 (47.1%)	
<b>T stage</b>			
T1	54 (40.9%)	7 (41.2%)	0.052
T2	69 (42.3%)	9 (52.9%)	
T3	9 (6.8%)	1 (5.9%)	
<b>Grade (Modified Bloom and Richardson)</b>			
1	27 (20.5%)	7 (41.2%)	0.109
2	63 (47.7%)	5 (29.4%)	
3	42 (31.8%)	4 (23.5%)	
<b>Lymphovascular invasion</b>			
Present	71 (53.8%)	5 (29.4%)	0.047
Absent	61 (46.2%)	12 (70.6%)	
<b>Multifocal</b>			
Yes	25 (18.9%)	3 (17.6%)	0.898
No	107 (81.1%)	14 (82.4%)	
<b>Type of tumour</b>			
Invasive ductal	118 (89.4%)	15 (88.2%)	0.506
Invasive lobular	3 (2.3%)	0 (0%)	
Others	11 (8.3%)	2 (11.8%)	
<b>ER status</b>			
Positive	104 (78.8%)	16 (94.1%)	0.133
Negative	28 (21.2%)	1 (5.9%)	
<b>PR status</b>			
Positive	93 (70.5%)	15 (88.2%)	0.122
Negative	39 (29.5%)	2 (11.8%)	
<b>HER 2 status</b>			
Positive	21 (15.9%)	5 (29.4%)	0.368
Negative	110 (83.3%)	12 (70.6%)	
Equivocal	1 (0.8%)	0 (0%)	
Number of SLN (median)	3	4	0.547
Number of positive SLN (median)	1	1	0.204
<b>Type of positive SLN</b>			
Macrometastases	96 (72.7%)	0 (0%)	0.001
Micrometastases	36 (27.3%)	17 (100%)	
<b>N stage</b>			
1mi	29 (22.0%)	1 (100%)	0.001
1	88 (66.7%)	0 (0%)	
2	14 (10.6%)	0 (0%)	
3	1 (0.8%)	0 (0%)	
<b>Extranodal spread</b>			
Present	38 (30.4%)	0 (0%)	0.012
Absent	87 (69.6%)	15 (100%)	

**Comment 4:** Please comment specifically on how you handled patients who had a negative SLN on frozen section analysis but had a positive SLN on permanent section pathology. Were these patients excluded from analysis?

**Reply 4:** The study was designed to only include patients with positive SLNs (defined as micrometastases or macrometastases) on frozen section, hence those whose SLNs frozen section was falsely negative (total 6 patients) were excluded from analysis.

**Changes to text:** none.

**Comment 5:** Introduction – the authors point out these NSLN prediction models have been validated among other cohorts of Asian breast cancer patients = can the authors clarify for the reader what is special about their patient cohort that supplements the existing literature? It would also be helpful to the reader to share what these other studies found specifically validating these nomograms in Asian populations but I do not see that mentioned in this work. If others have validated maybe a summary table showing number of patients and years and specific population and C statistic including all SLN+ and SLN metastasis >2 mm would be helpful and a valuable contribution from this work. That might be a nice citable addition to the literature.

**Reply 5:** Hong Kong breast cancer patients have been shown to have an earlier age of onset compared with Caucasians, with the highest 5-year relative survival rate amongst Asian countries. This study is the first validation study in Hong Kong and one of the few validation studies with subgroup analysis on patients with minimal axillary disease (micrometastases, only 1 involved LN) on the accuracy of MSKCC, MDACC and Tenon scores. A table summarizing the validation studies performed in Asian countries has been added to the manuscript. Out of all studies included, only the one done by Tanaka et al (2013) included subgroup analysis on patients with micrometastases only, which showed poor accuracy of MSKCC on prediction of non-SLN metastases, similar to what we found in this study.

**Changes to text:** A new comparison table “Table 1” and two extra countries and three references have been added to the manuscript in the Introduction section in page 6, lines 3-5; also reference section in page 17, references 16-18. Text clarifying the aims of this study and characteristics of the patient cohort has been added to Introduction section in Page 6, lines 6-11.

**Comment 6:** Table – can you report number of SLNs removed and number positive as median please? Can you report N subcategory – were any N0i+ patients included? What proportion of the N1 were N1mi – think would be good to report N1mi separately from N1.

**Reply 6:** The table has been modified as suggested. All N0i+ patients were excluded from analysis.

**Changes to text 6:** The section on “no. of SLNs (median)” and “no. of positive SLNs” and “number of NSLN (median)” and “N stage” has been modified in table 2.

**Comment 7:** Please clearly describe your criteria for post-mastectomy radiation and regional nodal radiation for patients treated with breast conserving surgery. While both chemotherapy and surgical treatments appear to be de-escalating, in many places it appears that a greater number of patients are being recommended for radiation after mastectomy and for regional nodal radiation in addition to whole breast radiation follow breast-conserving surgery.

**Reply 7:** In my hospital, local radiotherapy (to breast or chest wall) is recommended for patients with tumour size  $\geq 4$ cm, inadequate margins, extensive lymphovascular permeation, breast

conserving surgery (BCT) or whenever regional RT is required. Regional RT to the axilla is recommended for T3/T4 tumours, inadequate axillary dissection (less than level II dissection or less than 10 LNs removed) and certain SLN positive cases without completion AD. For pT1N1mi patients who did not receive a completion axillary dissection, axillary RT is only given when the MSKCC nomogram predicts  $\geq 20\%$  risk of additional LN involvement.

**Changes to text:** none.

**Comment 8:** Suggest omitting/revising final paragraph before discussion. Not sure what it adds to the work. Might consider substituting your recommendations for incorporating this into clinical practice

**Reply 8:** The last discussion paragraph has been deleted as suggested.

**Changes to text 8:** The last discussion paragraph has been deleted as suggested in Discussion section page 13.

**Comment 9:** Minor comments: please spell out abbreviations prior to first use (e.g. AUROC in abstract, etc.)

**Reply 9:** The sentence with AUROC in the abstract section has been modified as suggested.

**Changes in text 9:** “area under the receiver operating characteristic” has been added in front of the abbreviation “AUROC” in page 2, line 14-15. “Receiver operating characteristic” has been added to the Abstract section in page 2, line 11.

**Comment 10:** edit for English language/style – suggest substitute “Patients” for they in the first few sentences in Methods section, consider removing “our” in front of patients in the results section, consider revising single sentence paragraphs; consider modify first sentence of discussion adding “for breast cancer” since SLN surgery has been described for other epithelial cancers since the 1950’s; consider rewriting “Yet despite their limitations, we still believe that these nomograms have a role in the era of Z0011 – mainly in adjuvant planning, when they can be used to assess risk of residual lymph node metastases in patients with positive SLN but did not receive completion axillary dissection (or incomplete axillary dissection) to decide who would benefit from radiotherapy to the axilla.” for clarity and correct grammar.

**Reply 10:** The relevant modifications have been made

**Changes to text:**

1. “patients” have been substituted for “they” in the methods section (page 7, line 2 and 7)
2. The inclusion and exclusion criteria has been combined into one paragraph (page 7, line 2-10)
3. “Our” has been removed in the results section. (page 9, line 5)
4. Modification in paragraph format in the introduction section (page 7, lines 14-19)
5. “for breast cancer” has been added to the discussion section (page 11, line 3)
6. The confusing sentence as stated above in the discussion section has been deleted.