Peer Review File

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Reviewer A: This comprehensive review aims to update on the role of RNI following SNB in invasive breast cancer. It is very informative but there there are just a few comments.

Comment 1: Importantly, it should always be clear when the authors refer to primary surgery (and RNI after that) versus neoadjuvant treatment –Could you please clarify that in your manuscript.
Response 1: We have clarified this in the text. Thank you for this observation.

Comment 2: Line 116-117: Please clarify if tangential RT includes any of the axilla in the treatment field.
Response 2: Thank you for this comment. The following changes have been made.
In text edits, line 117: "WBI typically consists of tangent fields which include level I axillary lymph nodes in the treatment field."

Comment 3: Line 153-156: Please clarify that the SENOMAC trial does not re-assess Z0011 since in many cases, RNI is added as according to national guidelines, which was not the case in Z0011.
Response 3: Thank you for this comment. We have amended the text according to your recommendation.
In text edits, line 154: The SENOMAC trial is underway comparing ALND versus no ALND in cN0 patients with up to 2 nodes on SLNB that are positive for macrometastatic disease. The inclusion criteria was expanded to those with T3 disease and those treated with mastectomy (NCT02240472).

Comment 4: Line 172 etc: I think it would be interesting to hear your thoughts about why some studies show cancer-specific survival benefits but no improved overall survival. Increased mortality due to RNI?
Response 4: We thank you for this comment and have added possible reasons in this paragraph.
In text edits, line 172: "This may be due to several reasons; namely, effective systemic therapy agents utilized contemporaneously were not widely administered during the study period between 2000 and 2007. Furthermore, the median number of axillary nodes examined in the study was 12, thus the benefit seen with RNI may be due to the limited axillary dissection."

Comment 5: Line 186: as far as I know, the BOOG 2013-07 trial is proceeding without randomisation due to under-recruitment.

Response 5: Unfortunately, we have not been able to verify this information in our search, including on clinicaltrials.gov.

Comment 6: Line 195: I do not agree with the use of the word "should" undergo ALND. Please develop more clearly. "Should" is an opinion.
Response 6: Thank you for your comments. We agree that the vocabulary used reflected an opinion and was inappropriate to use in this manuscript. We have updated the text accordingly.
In text edits, line 197: "Patients with SLNB positive disease who do not require any radiation following mastectomy have the option to undergo ALND, however, the question arises as to whether these patients can undergo SLNB alone."

Comment 7: Line 196: do you mean "undergo" instead of "under"?
Response 7: Thank you for pointing out this spelling error. We have corrected this in the text.
In text edits, line 197: "Patients with SLNB positive disease who do not require any radiation following mastectomy have the option to undergo ALND, however, the question arises as to whether these patients can undergo SLNB alone."

Comment 8: Line 218: pCR in axillary lymph nodes is rather up to 60% in specific subtypes. Please amend with modern data.
Response 8: Thank you for this observation. We have updated the text with more modern statistics.
In text edits, line 218: "For those with clinically node positive disease, NAC has been associated with pCR in the axillary lymph nodes in 40%-75% of patients with higher rates observed in patients with HER2 positive and triple negative disease, high- grade tumors, and lower T stages."

Comment 9: Line 220: please add more detail about the potential adjustment of RT in the face of pCR.
In text edits, line 223: "Per NCCN guidelines, pCR in the axilla can allow for less extensive surgical exploration of the area as well as lead to reduced radiation to this site by decreasing radiation fields due to exclusion of the axilla."

Comment 10: Line 229-246: the description of the arms in the SENTINA trial is not correct. Arm d did not have a second SNB after NAC (line 236-237). In line 237, did you mean "ypN0" or rather "ycN0". In line 241, please be clear with that the detection rate you report is the first SNB, not the second. In line 242, the FNR actually decreased to 8.6% when a combination of dye and radioactive tracer were used. Could you please specify what you mean by "radiotracer dye"? Please specify "worse outcomes" in line 244. I suspect you refer to a increased FNR and lower DR in comparison with cN0? Line

246, it is the combination of radioactive tracer and dye that is suggested to improve FNR.

Response 10: Thank you for these suggestions. We have updated the text to reflect the suggestions

In the text edits, line 234-257: "The following prospective studies sought to further investigate this topic. The SENTINA study was a multicenter cohort with the primary endpoint of identifying the FNR of SLNB in patients with clinically node positive disease who converted to clinically node negative (ycN0) following NAC. 1,737 patients were randomized to 4 arms. Arm A included patients with clinically node negative disease (cN0) who underwent SLNB before NAC and received no further axillary management due to negative SLNB ($pN0_{sn}$). Arm B included patients with cN0 disease with a positive SLNB before NAC ($pN1_{sn}$) who then underwent a second SLNB and subsequent ALND following NAC. Arms C and D contain patients who were cN1-2 who underwent NAC. For patients who had conversion to clinically node negative disease (ycN0), they subsequently received SLNB and ALND (Arm C). For patients who continued to have clinically node positive disease after NAC (ycN1), ALND was performed (Arm D). The detection rate of the 1,022 women who underwent first SLNB before NAC was 99.1% (95% CI 98.3–99.6) (Arms A and B). The detection rate did not differ among the detection techniques of using combined radiocolloid and blue dye versus radiocolloid alone. In Arm C, the detection rate was 80.1% (95% CI 76.6–83.2) and the overall FNR was 14.2% (95% CI 9.9–19.4). Of note, the FNR was 16.0% using radiocolloid alone and decreased to 8.6% with the addition of blue dye. Also, the removal of 3 or more lymph nodes reduced the FNR below 10%. These results suggest that SLNB has worse detection rates and FNR following NAC in previously clinically node positive patients who convert to ycN0 compared to patients who undergo SLNB first. The results also suggest that the use of a combined radiotracer may improve the FNR (26)."

Comment 11: Line 263: please remember that the cut-off of 10% for an "acceptable" FNR stems from primary surgery, not NAC. There is no consensus to that threshold also being valid after NAC.

Response 11: Thank you for this comment. The authors of the ACOSOG Z1071 used the FNR threshold of 10% based of those reported from the metanalysis by Xing et al that evaluated studies of SLNB following NAC in cN0 patients. We have updated the text to provide clarification for the readers.

In text edits, line 265: "Of note, this threshold was acquired from those reported in studies of SLNB following NAC in cN0 participants."

Comment 12: Line 268: Please add more description of TAD/TLNB.

Response 12: We have provide a brief overview of these topics in the text.

In text edits, line 279: "The use of targeted staging procedures are used more frequently in this setting. During neoadjuvant SLNB, positive nodes are marked with a

clip or other marker. A targeted SLNB (TLNB) or targeted axillary dissection (TAD) requires the removal of these marked nodes for evaluation of treatment response. The SenTa study was a prospective registry study that aimed to identify the accuracy of TLNB and TAD after neoadjuvant systemic therapy. 548 were included in the study. After NST (n = 473), the clipped TLN was intraoperatively resected in 77.8% of the patients. (95% CI 74.0 to 82.0). TAD had a DR of 86.9% (95% CI 81.8 to 91.0) while the DR of SLN and TLN were both 64.8%. FNRs were 7.2% (95% CI 3.1 to 13.6) for TLNB followed by and 4.3% (95% CI: 0.5 to 14.8) for TAD followed by ALND."

Reviewer B: Thank you for the opportunity to review this article. It offers a very comprehensive review on the role of axillary nodal management in the setting of SLNB when there is node positive disease.

Comment 1: Treatment of nodes, especially the incorporation of the IMNs often leads to challenging anatomies with the potential need to use IMRT or VMAT to plan cases in case the standard dose constraints are not met. Could the authors please comment on if there are any studies underway to look at the long term effects of using complex treatment planning techniques on toxicities especially when it comes to low dose to the heart and lungs? Is there an effort to consolidate data from all these trials with respect to some of these low dose parameters such as the lung V10 Gy, V5 Gy as well as lower doses to the heart.
Response 1: We thank the reviewer for this suggestion as there is ongoing investigation into different radiation techniques to decrease dose to normal structures, particularly to the heart when comprehensive nodal irradiation is required. We include a paragraph about these studies in the end of the 'Future Directions' section.
In text edits, line 374: "There are efforts to further reduce dose to the heart when treating with RNI as cardiac dose has been linked to increased risk of cardiovascular events in women treated for breast cancer (35). Intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) has shown to be dosimetrically superior to 3-dimensional conformal radiation therapy with respect to coverage but can be at the cost of increasing integral dose to normal structures (36). An improvement upon this has been pencil beam scanning with proton therapy, which offers excellent target coverage and lower dose to normal structures (36). Currently, a randomized study of proton versus photon therapy for patients with breast cancer is ongoing (RADCOMP; NCT02603341) with a primary endpoint of reduction in major cardiovascular events."