Title: Targeting and Limiting Surgery for Patients with Node-Positive Breast Cancer

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Author's response to reviews: see over
Dear Editors of *BMC Medicine,*

Thank you for the opportunity to revise our review of the latest literature regarding sentinel lymph node dissection in breast cancer which we have entitled, “Targeting and Limiting Surgery for Patients with Node-Positive Breast Cancer.” We appreciate the helpful suggestions from our reviewers and have incorporated their revisions into the manuscript. We have listed each point made by the reviewers below with the revisions that we made. These changes have also been highlighted in the manuscript. As suggested, we have added 2 tables: one describing the trials in clinically node negative patients (ACOSOG Z0011, AMAROS, and IBCSG 23-01) and another describing the trials in clinically node positive patients (ACOSOG Z1071, SENTINA, and SN FNAC). All figures and tables have been made exclusively for this publication and do not require copyright permission.

Please let us know if there are any other changes that you feel would be helpful. Thank you again for allowing us to submit this review for consideration in your journal.

Sincerely,
Abigail S. Caudle, MD, MS
Henry M. Kuerer, MD PhD

**REVIEWER 1**

*Discretionary Revisions:*

1. Page 3, 2nd paragraph, 1st line should include references 10,11 unless reference 6 gives all of the info later provided on those 2 trials.

The references have been added as follows:
“Several phase III, multicenter trials showing that ALND can be omitted in selected SLN positive women have recently been reported with resulting changes in clinical practice.[6-9]”

2. Page 5, 2nd paragraph, 2nd line needs word-smithing. Perhaps “NCT has the benefit of allowing for individualized patient monitoring of in situ tumor response, with a complete pathologic response (pCR) recognized by many as a surrogate for improved long term outcomes.”

This has been changed to the following:

“Giving chemotherapy preoperatively allows for assessment of *in situ* tumor response, thus identifying agents with no efficacy early so that the patients can be spared unnecessary toxicity. In addition, complete pathologic response (pCR) is now
recognized as a surrogate for long term outcomes which has made the neoadjuvant approach a valuable research platform. [12, 13]"

3. Page 6, 1st paragraph, 3rd line also needs word-smithing. “Furthermore, women found to have small volume occult nodal disease that would have been easily eradicated with chemotherapy would still require ALND.”

We have revised the text to read:

“Furthermore, it commits women with clinically occult nodal disease to ALND even though the nodal metastases would have been easily eradicated with chemotherapy”

**Minor/Major Essential Revisions:**

1. Define small or low volume nodal disease, such as N1

Because this definition varies depending on the context, we have clarified or omitted this terminology throughout the manuscript as follows:

“they all reflect the same notion that patients with small volume clinically occult nodal metastases found by SLND can safely avoid completion ALND with equivalent oncologic outcomes.” (Page 5, last paragraph)

“Furthermore, it commits women with small volume clinically occult nodal disease to ALND even though the nodal metastases would have been easily eradicated with chemotherapy.” (Page 6, 1st paragraph)

“The omission of ALND in clinically node negative patients with small volume nodal metastases discovered by SLND…” (Page 13, 2nd paragraph)

2. Define FNR more precisely as it seems it can be used in 2 ways. (1) The sentinel node has no cancer (never did or previously did) but there is metastases present in the non-sentinel node at the time of the SLNB. This definition can be used pre or post NCT. (2) The metastatic node clipped prior to chemotherapy is not the sln (and the sln has cancer) or the clipped node was not found in the alnd specimen and thus left in situ (1071 trial). Am I understanding this correctly based on the fnr you report throughout the paper?

We have defined False Negative Rate as described in (1), or:

\[
\text{False Negative Rate} = \frac{\text{Number of pts with node of question (whether sln or clipped node depending on the context) even though other nodes were positive}}{\text{Total number of patients who have any positive node.}}
\]

We have attempted to make this more clear in our introduction (1st paragraph) by saying: “...false negative rate (i.e. number of patients in whom no cancer is seen in
When we talk about a FNR for the clipped node, we use the same definition and calculation, i.e. the number of patients in which the clipped node had no disease yet other nodes did contain disease divided by the total number of node positive patients.

Our description of the situations described in (2) are described in the manuscript as follows:

“In 25% of cases evaluated, the clipped node could not be identified as a sentinel node using dual mapping agents or palpation. That is, if the SLND procedure was performed alone, the node that had been proven to have metastases prior to NCT would have been left in the patient and not tested in a quarter of cases.” (Page 10, 2nd paragraph)

3. It would be very helpful to know the clinical N stage prior to NCT for all of these studies. For Z011 we know they are clinically N0. But in the studies where the patient had known nodal disease pre-NCT was there a documented N-stage. One would imagine that believed N1 disease has a better chance of converting to N0 post NCT and thus more likely to be adequately addressed by post NCT SLNB especially when 3 SLNs are removed.

We have added Table 2 to show the differences in the ACOSOG Z1071, SENTINA, and SN FNAC trial.

4. If available please provide similar information for each clinical trial. For example in Z0011 what was the % of patients with additional nodal disease found at ALND. That information has been published.

This was included for the AMAROS trial (“In the ALND group, 33% (220/672) had additional positive non-SLN identified” -Page 4, 2nd paragraph). We have added this information for the ACOSOG Z0011 trial and IBCSG 23-01 trial as follows:

In patients randomized to ALND, additional positive non-SLN were identified in the axillary specimen in 27% of cases. (Page 4, 1st paragraph)

Possibly reflecting the fact that only patients with micrometastases were eligible for enrollment, only 13% of patients in the ALND group had additional positive non-SLN. (Page 5, 2nd paragraph)

5. In the AMAROS trial, how many patients had mastectomy? They randomized pts to ALND vs Axillary RT. Is this both the BCT and mastectomy cohorts? Did the mastectomy cohort randomized to axillary XRT also have chest wall XRT?

We have added information about breast surgery in each group to the text as below (page 4, 2nd paragraph):
Unlike the Z0011 trial, the type of breast surgery was not dictated by the protocol so patients undergoing mastectomy were eligible for enrollment [17% of the ALND cohort and 18% of the axillary radiotherapy group].

Chest wall coverage was not required in the protocol if patients were randomized to the axillary radiotherapy arm. In patients undergoing mastectomy who were randomized to axillary radiotherapy, about 40% received chest wall radiation and 60% did not.

6. The trials quoted report a low false negative rate post NCT if the SLNB no longer contains metastatic disease. No mention was given to your institution’s original retrospective study (Breslin- first author) citing a 38% FNR. What’s changed? Is it that larger and more prospective studies no longer support that finding or is it that the study included N2 pts with more recent studies limiting eligibility to clinically N1 disease?

The Breslin et al. paper reported on patients treated from 1994-1999, which was early in the SLN experience as evidenced by the fact that the SLN identification rate improved dramatically during the study from 64.7% at the beginning of the study to 94% by the end of the study. The study is also limited by a small sample size of only 14 patients who started as clinically node positive. We feel that that papers we cited by Shen et al. (Cancer 2007) which showed a FNR of 25% and Alvarado et al. (Ann Surg Oncol 2012) which showed a FNR of 20% are a better reflection of contemporary experience with the procedure.

7. Many of the studies contained within your manuscript support identifying more than 1 sln. Yet the definition of a sentinel lymph node is 1 (the first) lymph node. Do the authors recommend more than 1 sln be retrieved post NCT? If so, should we adjust our rule book as to the definition of a sln (5% of the first node or 5% of the tumor bed, X times the background count?)

While there may be one “true” sentinel node, we defined sentinel nodes as those identified during a sentinel node dissection which contain blue dye, have increased radioisotope counts or are palpable. The ACOSOG Z1071, SENTINA, and SN FNAC trials show that removing more than 1 node as a part of the SLND improves the false negative rate. This has prompted a lot of controversy surrounding the optimal SLND technique in clinically node positive patients who complete NCT and may be candidates for omission of ALND. Some groups have felt comfortable omitting SLND if at least 3 nodes were removed and all were negative. We feel that removal of the clipped node as a component of SLND is more important than an absolute number of nodes to be removed.

8. In the ACOSOG Z1071 trial the clipped node was in the ALND specimen or not identified in 37% of the patients. This seems like a high number. For centers
where a radioactive seed cannot be placed in the clipped node, what procedure should be offered in addition to slnb? Wire loc the clipped node? What do the authors recommend if the sln does not contain the clipped node? If the clipped node cannot be identified intraoperatively, should the surgeon default to an ALND?

We recommend default to complete ALND if the clipped node is not identified as a component of SLND. This is the reason that targeted axillary dissection is attractive as a way to offer all patients the opportunity for omission of ALND, even if the clipped node is no longer identified as a SLN. We have included the following text in the manuscript to describe these efforts (Page 11):

Marking of the nodes with documented metastases using India ink at diagnosis has also been proposed but many surgeons are concerned that this might require more dissection of healthy lymphatics to identify and retrieve these nodes after NCT compared with more targeted methods.[37] Efforts are now underway to identify alternative approaches to localize nodes with proven metastases using novel localizing methods.

9. What was the low FNR with the TAD study and is that referring to identifying the clipped/seeded node and not that the node converted to negative but additional nodal disease was identified.

We defined the FNR of TAD as:
[The number of patients in whom the clipped node and SLNs were negative but other positive nodes were identified] / [The number of node positive patients]

The data on TAD has not been published, which is why we did not include it in this publication. The FNR that we presented at the SSO Annual Meeting was 2%, but we do not want to include this unpublished data at this time. We hope that the manuscript describing this technique will be published soon.

10. In the Netherlands study, how is the seed still radioactive 3-4 months post NCT that it could be identified at surgery and doesn’t that concern anyone that it is emitting low dose radiation for such a long time?

The half-life of the seeds is 60 days, so it still emits a signal at 3-4 months. Because of radioactivity regulations in the US, leaving a seed in place for this amount of time would lead to considerable issues. However, there is precedence for leaving them in place in prostate cancer, where the seeds are often placed for therapeutic reasons and left in place forever.

**REVIEWER 2**

1. Page 6, P1. “In one study from our institution, the SLN identification rate...” I would recommend referring to the institution by name.
We have revised this to say “In one study from MD Anderson Cancer Center”

2. Page 7, P1. “While only 21.1% (67/317) of patients with hormone-positive patients achieved a nodal pCR, 49.4% (84/170) of triple negative patients and 64.7% (134/207) HER2 positive patients had nodal conversion. I would recommend changing the wording to patients with hormone receptor positive disease... patients with triple negative disease...and those with HER2 amplified disease.

We have made this revision. The new text states: “While only 21.1% (67/317) of patients with hormone-positive disease achieved a nodal pCR, 49.4% (84/170) of patients with triple negative disease and 64.7% (134/207) of those with HER2 amplified disease had nodal conversion.”

3. Page 8. The description of the SENTINA study is difficult to follow. It would be helpful if the study group names (A, B, C, D) were used throughout this section to indicate which subset is being discussed. In three separate sentences, the authors note that biopsy confirmation of nodal metastases was not required for study participation. In a separate sentence, the authors describe sentinel node biopsy findings for 142 patients with biopsy confirmed nodal metastasis. Presumably, pretreatment axillary lymph node biopsy was allowed but not required for study participation. A figure might be helpful to organize the schema and findings from this complex trial.

Figure 3 now reflects the different arms of the trial. In addition, we have revised the text as follows: “The authors showed that SLNs could be detected in 99.1% before NCT (Arm A), however among patients who had nodal metastases identified by a SLND prior to NCT; a second SLND procedure (Arm B) was only successful in 60.8% demonstrating that patients should only undergo one SLN procedure for staging. Arm C focused on the possibility of accurately restaging the axillary nodes after NCT in clinically node positive patients. The authors report an overall false negative rate for SLND in these patients of 14.2%, with findings similar to the Z1071 trial that the false negative rate was lower when more SLNs were retrieved and dual tracers were used. One important aspect of the trial to note is that they did not require pathologic confirmation of lymph node involvement. The FNR for SLND in the 149 patients who had biopsy confirmed metastases was 19% compared to 12.3% in the 443 patients who were classified as node positive without pathologic confirmation.”

4. Page 10. “in order to localize the clipped node, patients have a I125 seed placed in the clipped node under ultrasound guidance 1-5 days before surgery, similar to our technique for breast primary tumor localization using I125 seeds.” I would recommend changing the sentence to read “…similarly to the technique described by XXX author et al for breast primary tumor localization…”

We have made the following revisions:
“Similar to the techniques for breast tumor localization,[37, 38] an $^{125}$ seed is placed in the clipped node under ultrasound guidance 1-5 days before surgery.”

5. Page 11, at the end of the page. “One such trial, NSABP-51/RTOG 1304 is currently enrolling biopsy proven node positive (N1) patients who undergo NCT and have no residual nodal...” I would recommend changing the sentence to “...enrolling patients with biopsy proven N1 disease who undergo...” There are multiple examples of this terminology throughout the paper, and the manuscript should be reviewed thoroughly to standardize descriptions of patients and their disease states.

We have reviewed the manuscript and made the following revisions:

“NSABP-51/RTOG 1304, is currently enrolling patients with biopsy proven node positive (N1) disease who undergo NCT” (Page 12, 2nd paragraph)

“Another cooperative group trial is enrolling patients with biopsy proven node positive (N1) disease who do not achieve a nodal pCR with NCT.” (Page 12, 3rd paragraph)

“elimination of axillary surgery in patients with node positive breast cancer after NCT...” (Page 13, 2nd paragraph)