

## Peer Review File

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### Reviewer A

This study is a big study based on information on breast cancer patients from 17 cancer registries from 2000 to 2017 using SEER\*Stat 92 (version 8.4.0).

First, the authors created a nomogram. They then studied the role of axillary treatment, particularly the importance of AX clearance, based on recurrence risk. Endpoints were BCCS and OS and long-term prognostic results have been reported.

There are several points of concern.

- As the authors also point out in the text, Z11 was introduced into clinical practice during the study period. The indications for axillary dissection have changed considerably. This especially happened with the BCT. How did the authors assess its impact? This raises a question of whether results should be considered separately for post- and pre-guideline implementation of the Z11.

**Response:** Thank you very much for your suggestion. We have added the impact of the Z0011 trial on axillary surgeries before and after the implementation of the guideline.

**Changes in the text:** Lines 255-265, Paragraph 19, Page 13.

- Another important difference in clinical practice would be the HER2-positive and HER2-negative subgroups. Clinical practice, especially preoperative treatment, varies widely. What is the impact?

**Response:** Thank you very much for your advice. HER2 is also an important factor affecting the prognosis of breast cancer, which is associated with a poor prognosis. HER2-positive patients can be treated with targeted therapy before or after surgery. Although the positive significance of HER2 was not found in our prediction models, it is undeniable that HER2 is of great significance for the prognosis of breast cancer patients. In the revised manuscript, we elaborated on the significance of HER2.

**Changes in the text:** Lines 297-305, Paragraph 20, Page 15.

- What about the effectiveness of adjuvant chemotherapy? Low-risk cases often include those who do not receive chemotherapy. The opposite trend would be real for high-risk cases. How did the authors assess this issue?

**Response:** Thank you very much for your question. This study provided nomograms to predict the 3-year and 5-year OS and BCSS of breast cancer patients, and then established two risk-stratified prediction models to quickly determine which patients

had no statistically significant differences in survival outcomes between SLNB alone and ALND. The prognostic factors affecting the survival of patients in each GMTRL score group included grade, marital status, T stage, radiotherapy and lymph node metastasis. We did not find a positive contribution of chemotherapy to our prediction models. However, chemotherapy is indeed a very important factor affecting the prognoses of patients in clinical practice, and future researches can focus more on exploring the significances of chemotherapy in the prediction models of axillary surgeries.

This study found that low-risk cases usually included patients who had received radiotherapy, while medium-high risk cases often included patients who had not received radiotherapy. The reason for the results may be that radiotherapy can reduce the recurrence and metastasis of breast cancer, prolong the survival time, and improve the prognoses of patients. Radiotherapy can replace the positive effects of ALND to some extent, so that low-risk patients who have been treated with radiotherapy can avoid ALND without affecting survival. However, patients not received radiotherapy have a high risk of recurrence and metastasis, with poor prognoses, because of which, they cannot avoid ALND and they are usually classified as medium- and high-risk groups.

**Changes in the text:** Lines 303-305, Paragraph 20, Page 15.

- What methods were used to assess the condition of the axilla? Questions arise regarding clinical and histopathological methods.

**Response:** Thanks for your question. In clinical practice, the methods used to evaluate the status of axillary lymph nodes in breast cancer patients mainly include axillary examination, ultrasound, MRI and mammography. If an enlarged lymph node can be touched in the axilla, with a hard texture and unclear boundary, the axilla may be considered for existing metastatic lymph nodes, in which case further imaging examination should be recommended.

If the radiographic findings report enlarged axillary lymph nodes with unclear boundaries between the cortices and medullas, the patient may have metastatic axillary lymph nodes.

Of course, the gold standard for detecting axillary lymph node metastasis is pathological method. Ultrasound-guided needle biopsy of the axillary lymph node is one of the most commonly used methods to determine the presence of metastatic lymph nodes. Patients with clinically negative axillary lymph nodes can be treated by sentinel lymph node biopsy, and frozen pathological examination can be performed during the operation. If we find the metastatic lymph nodes, axillary lymph node dissection can be further performed, and the excised specimens can be examined by paraffin pathological examination. Paraffin pathology is the most accurate method.

## **Reviewer B**

The authors propose a risk stratification model to predict endpoints in patients with N+ breast cancer, seeking to de-escalate axillary treatment. To do this, they used a well-known database (SEER) and deserve congratulations for the idea. Here are my suggestions:

**Grammar and spelling:** apparently, they are good (article reviewed by professionals in English).

**Response:** Thank you very much for your compliment.

**Title** – I don't like titles that "conclude" the research. I think the title has to encourage the reader to read the article and look for the answer. Authors can keep the title as it is, or make any changes to it. This is a personal opinion.

**Response:** Thanks. According to your suggestion, we have revised the title of the article as shown below: An exploratory study of whether axillary lymph node dissection can be avoided in breast cancer patients with positive lymph nodes.

**Changes in the text:** Lines 2-3, Page 1.

**Abstract** – well written and concise. Highlights of the study are included accordingly.

**Response:** Thank you very much for your compliment.

### **Introduction:**

Page 2 # 75: the authors mention the Z11 trial, but it is important to mention a drawback of such study, which was the presence of around 30% of patients who received lymph node irradiation, and this was an exclusion criterion for the study. This point is very important to be reinforced here, as it will imply the final interpretation of the study. Did the patients benefit from lymph node irradiation (this is understood as formal irradiation of the supraclavicular fossa with/without inclusion of the axilla, or by "incidental" irradiation of axillary levels I and II through the tangent fields of breast irradiation), and could this be "Making up" the data and security of the nomogram? One "clue" to this is that radiotherapy was one of the independent predictors of OS and BCSS.

**Response:** Thank you very much for your question, and we quite agree with you. As you mentioned, the irradiation of axillary lymph nodes in patients with breast cancer does reduce the risk of recurrence, and there is no doubt that patients can benefit from irradiation of the lymph nodes.

However, the data in this study were downloaded from the SEER database, which only

provided information on whether patients were treated with radiotherapy, not the site of radiotherapy. Therefore, the radiotherapy received by the patients mentioned in this study was a general concept. We only knew whether the patients received radiotherapy, but not which parts were treated. This study concluded that radiotherapy was an important factor affecting the prognosis of breast cancer, and it also affected the risk stratification. The “radiotherapy” mentioned could be the irradiations of the whole breast, the axilla or the supraclavicular fossa, but we did not know which part of the radiotherapy played a crucial role.

The question you raised is worth our thinking. This is also a disadvantage of our study. In future studies, we should incorporate more detailed data about the specific sites of radiotherapy and explore whether the effects of irradiations on different sites are consistent.

**Changes in the text:** Lines 316-318, Paragraph 21, Page 16.

#### **Material and methods:**

Page 3 # 96: the authors could search (for this study, or at least encourage this gap for future studies) among the variables analyzed by SEER\*Stat, aspects of radiotherapy (only in the breast, or breast + lymph nodes, etc.).

**Response:** Thanks for your suggestion, which is very meaningful for our research.

Unfortunately, the SEER database only provides information on whether patients with breast cancer are treated with radiotherapy, not the specific site of radiotherapy (irradiations of the whole breast, axilla, or supraclavicular fossa). This is also a weakness of this study. In future studies, we will incorporate more information about the specific irradiation sites of radiotherapy to explore whether the effects of irradiations on different sites are consistent, which is also of great significance for our clinical work.

**Changes in the text:** Lines 316-318, Paragraph 21, Page 16.

**Results:** well described and organized

**Response:** Thanks for your compliment.

#### **Discussion:**

# 233: the authors could take advantage of the mention of the AMAROS and OTOASOR studies, which proposed “elective irradiation” of lymph node sites in their study arm. As is known, the complication rates of irradiated patients were lower than those who underwent surgery. Previously (Page 5 #203), the authors cite the Louis-Sylvestre study, however, this study was conducted in the pre-SNB era.

**Response:** Thank you very much for your advice. Indeed, we should add elective irradiation to this study, subdivide radiotherapy into the irradiations of the whole breast,

axilla or supraclavicular fossa, and investigate the effects of irradiations on different sites separately. However, due to the limitations of the SEER database, we currently do not have the means to achieve such a goal. In future studies, we can select the data from other databases or from our own hospital to include more information about the radiotherapy sites.

**Changes in the text:** Lines 316-318, Paragraph 21, Page 16.

**Data interpretation:** Why did patients with intermediate and high GMTRL scores have a significant benefit from ALND? Was it because there was “an extra local treatment”? Or did these patients receive irradiation in the lymph nodes? This is a pertinent point that must be raised by the authors.

**Response:** Thank you very much for your suggestion. Patients with intermediate and high GMTRL scores are often accompanied with larger tumors, advanced stages and poor grades, so that they have high risks of recurrence and metastasis, with poor prognoses. If these patients have metastatic axillary lymph nodes, not performing ALND will increase the risks of recurrence and distant metastasis, ultimately affecting their survival. For these patients, ALND plays a crucial role and cannot be replaced by any other treatment modalities. Therefore, patients with intermediate and high GMTRL scores can significantly benefit from ALND.

**Changes in the text:** Lines 291-297, Paragraph 20, Page 15.

**Table 1:** in the “breast Surgery” section, there is “no Surgery/BCS” in the same line. Is this correct? Was it a formatting error?

**Response:** Thanks for your question. “No Surgery” means that the breasts of the patients were not operated on, probably because the primary tumors on the breasts were not found, and these people only underwent SLNB or ALND, which were surgical methods for the axilla. Patients who did not undergo breast surgeries and those who underwent breast-conserving surgeries were divided into the same group, comparing with those who underwent mastectomy.