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Review Article

Axillary Management after Neoadjuvant Chemotherapy; A Review of How and When?

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Abstract

Axillary management in breast cancer has multiple paradigm changes. From standard axillary dissection level 1 and level 2 to sentinel lymph node biopsy in early-stage breast cancer. Now sentinel lymph node biopsy trend to use after neoadjuvant treatment to reduce the morbidity from standard axillary dissection. This review is collecting information on axillary management after neoadjuvant chemotherapy. Such as how to improve the accuracy of SLN in initial clinical nodal negative and initial clinical nodal positive before receiving neoadjuvant treatment, the role of axillary dissection after SLN, and the role of radiation therapy and the factors that predict the pathological nodal negative after neoadjuvant treatment. This review can support surgeons who decide to do SLN after neoadjuvant treatment.

Keywords: Axillary surgery; Breast cancer; Neoadjuvant; Sentinel lymph node biopsy

Introduction

Neoadjuvant Chemotherapy (NAC) has been widely used in locally advanced breast cancer since 1970 [1]. In the past Sentinel Lymph Node Biopsy (SLN) after NAC was inadvisable as the NAC may alter lymphatic drainage decreasing accuracy and causing a high false negative rate. Therefore, Axillary Lymph Node Dissection (ALND) was recommended for axillary staging after NAC. Currently, because of the efficiency of predicting the response of disease and increasing the overall survival of a specific subtype if a pathological complete response can be achieved NAC has been extended further to early-stage breast cancer [2]. Sentinel lymph node biopsy surgery after NAC, a less invasive axillary procedure, has been controversial as it may decrease accuracy, has a high false negative rate (FNR), and prolong timing of surgery. In particular, the rate of conversion of an initial nodal from positive to negative identification rate (IR) was low (89%) and high FNR (13%) but some studies reported the way to decrease FNR to 8% when at least 3 nodes were removed [3] and decrease to <4% if the target node removed [3,4] This review aims to compile the current literature on axillary management in breast cancer patients treated with NAC.

Initial clinical node-negative before NAC (cN0)

Identification Rate & FNR

Previously, there were concerns about IR and FNR in SLN after NAC as chemotherapy uptake causes axillary fibrosis that alters the lymphatics. There are studies assessing these problems, including a study by Kelly K Hunt et al.;2009 [5] in the MD Anderson cancer center which enrolled 3746 stage T1-T3 breast cancer patients, cN0 that received SLN before adjuvant chemotherapy compared with 571 patients that had SLN after

NAC found that SLN identification rates were slightly lower in the NAC group 97.4% vs 98.7% in the surgery first group. There was no significant difference in FNR between the 2 groups (5.9 % in NAC, 4.1% in Surgery first, p=0.39) and they concluded that SLN after NAC was as accurate as SLN before chemotherapy. But the 2013 SENTINA trial, reported a detection rate of SLN before NAC was 99.1% in comparison with a detection rate of SLN after NAC of 80.1% and FNR 14.2 %. This study judged that SLN should be done before NAC. After this study, there have been numerous others which have debated the detection about this topic. Two large meta-analyses have been carried out, the first by Chong Geng et al.[6], in 2016, which collected data from 16 studies including initial node negative breast cancer patients who received NAC. The study reported an identification rate of SLN of 96%, FNR 6%, sensitivity 94%, NPV 98, and an accuracy of 99% which corresponds to the findings by Aliriza et al. [7], in 2019, a meta-analysis which included 23 studies in subgroup initial node negative breast cancer that received NAC before SLN and found an SLN IR of 94% and FNR 7%. From this evidence, at present, SLN after NAC in initial cN0 breast cancer patients is accepted as standard treatment.

When should SLN be done: before NAC vs post NAC to reduce the ALND rate

Since SLN has a primary goal of axillary staging by reducing ALND, then a discussion is essential as to the suitable timing for cN0 to do the SLN to decrease the rate of ALND. NSABP B18 and B27 [2,8] reported that SLN after receiving an AC regimen has a higher reduction rate of nodal positive than those who did not receive it and if the patients received a Docetaxel add on to AC the reduction rate of nodal positive is higher. In the study by MD Anderson [5], it is also noted that there is a significantly low incidence of positive SLN after NAC in T2 and T3, and there was a decreased trend in T1.Therefore, there is a likely recommendation that doing SLN after NAC can reduce ALND rate. But after the ACOZOG Z0011 [9] launch, the rate of ALND in pre chemotherapy decreased [10,11] due to the acceptance of 1-2 nodal positive breast conserving surgery in T1-T2 patients who will receive whole breast radiation. Whereas for NAC patients, even in the case of only one SLN positive there should be a progression to ALND. For this reason, there is a conflict as when is better to do SLN to decrease ALND. The studies found that the response to NAC was largely dependent on subtype. The highest response was in HER2 positive subtype (37-58%), followed by a triple negative subtype (TN) (33-37%) and the least response was the Hormonal (HM) positive subtype (6-13%) [12,13]. A study by Bi,Z Lui et al [13] in 2019 reported that the SLN positive rate after NAC in cN0 breast cancer varied by subtype. The highest rate of SLN positive was seen in the HM positive/HER2 negative which was 28.1 %, then TN 13.3% and HER2 enrich 10% and they proposed that it would be preferable to carry out SLN before NAC in the HM+/HER2- subtype but in TNBC or HER2+ the SLN should be done after NAC to decrease the rate of ALND. These findings were consistent with a previous study by Melissa et al, in the Memorial Slone Kettering Cancer Center in 2017 [14], which enrolled 1944 cT1-2 N0 breast cancer patients who underwent SLN in upfront surgery the outcomes being compared with surgery after NAC in case of ALND avoidance according to tumor subtype. That study divided patients into 3 groups: 1) upfront breast conserving surgery (followed by ACOZOG z0011, ALND was only done in the case of at least 3 positive SLN); 2) upfront mastectomy; and 3) an NAC group. The results showed that HM+/HER2- patients were significantly less likely to require ALND if treated with upfront BCS (15%) compare with the NAC group (34.2%). This difference was not found in TN or HER2 +.In upfront mastectomy group found that TN or HER2+ have a higher chance of ALND than the NAC group (TNBC 25.4 vs 7%, HER2+ 36.3% vs 8%). Furthermore, the multivariable analysis found ALND was decreased in the TNBC or HER2+ subtype in the NAC group compared with the upfront mastectomy group but this decreased rate not found in the HM + subtype. Therefore, it can be said that there is data to support SLN before NAC in the HM+ subtype if compatible with ACOZOG Z0011 which will benefit from a decreased rate of ALND. However, in TNBC or HER2 current data indicates a recommendation that SLN should be done after NAC to decrease the ALND rate.

Can axillary surgery be omitted

At present, there is a discussion about the de-escalation of axillary surgery, especially in the case of early stage breast cancer with initial clinical nodal negativity [15]. The abandoning of axillary surgery is also discussed in initial cN0 patients treated with NAC. To answer this problem, we need to know the nodal pCR rate after NAC. If there is high pCR rate the axillary surgery may be omitted. A study by Tadros et al, [16] described in MD Anderson Cancer Center report that cT1, cT2 breast cancer patients with HER2 positive or a triple negative subtype that initial cN0 has a breast pCR rate after NAC of 40% and in all cases when breast pCR has no evidence of nodal metastasis at the time of surgery. Therefore, doing SLN in this group of cases may be able to be omitted. The same was found in a study by Vender et al [17], which investigated factors predicting the likelihood of pathological nodal negative after NAC (ypN0) in cN0 patients. The study determined that breast pCR was a strong significant predictor of ypN0. In addition they discovered that the strongest predictors of ypN0 known before surgery were tumor biological subtype, tumor grade, breast pCR on MRI. This study also discovered a node positive rate <2% in the initial cN0 triple negative or HER2 enrich that underwent breast pCR and concluded omission of SLN may be considered in patients with TNBC or HER2+ or those who achieve

breast pCR on MRI. In 2018, subgroup analysis by Barron et al. [12] in cN0 patients who still have residual breast disease after NAC showed that ypN2, ypN3 rate in HM positive HER2 negative subtype was the highest (5.9%) followed by HER2 enrich (2%) and TNBC (1.7 %).

There are ongoing studies on the omission of axillary surgery after NAC, for example the ACIS trial [18], and the EUBREATS-01 trial [19]. The ACIS trial (Avoid sentinel lymph node biopsy in breast cancer patient after neoadjuvant chemo) is a prospective non-inferior cohort single arm registration study in HER2 positive or TN, cT1-3, initial cN0 breast cancer patient with a radiologic complete response on MRI after NAC.Clinical N0 is defined as no suspected node on axillary ultrasound, PET, or pathology negative in a suspected node.The primary outcome is axillary recurrence at 5 years.An axillary recurrence in 5 years < 6% is considered acceptable for the omission of axillary surgery. The EUBREAST-01 trial (Omission of SLNB in Triple negative and Her2 negative breast cancer patient with rCR and pCR in breast after NST) is a prospective randomized single arm surgical trial in cT1-3 HER2 positive or TN, cN0 patients (by sonographic and pathological prove in suspected node) who received standard NAC with anti HER2 if HER2 positive with a plan for BCS with whole breast radiation after NAC. Those who had radiologic complete response after NAC go on BCS to confirm breast pCR, and those who had breast pCR will be eligible for further axillary surgery. The primary outcome is 3 years axillary recurrence free survival. The success is 3 years axillary recurrence free survival > 98.5 %. Patients who did not have breast pCR after NAC, SLN will be performed with subsequent treatment guided by nodal pathologic results. Based on current data, patients with initial cN0 were able to received SLN and may even refrain from having an axillary procedure in HER2 enrich or TN subtypes in the case of breast pCR after NAC.

Initial clinical node positive (cN+) converted to cN0 after NAC

Identification rate and FNR

Since SLN in initially clinical nodal negative can be performed after NAC with acceptable IR and FNR, in cases of initially clinical nodal positive the decision for SLN can be considered in the case of conversion to clinical nodal negative after NAC. IR and FNR were investigated in the SENTINA trial, ACOSOG 2017 trial and SN FNAC trial. All three studies aimed at IR >90 % FNR < 10% because a previous meta-analysis [20] reported FNR in cN0 was 12% and IR was 90% while NSABP B27 [21] that included both cN0 and cN1 patients had FNR of 10.7%. An ACOSOG Z1071[4] study in cT0-T4, cN1-N2 M0 breast cancer patients that received NAC and SLN reported an IR of 92.9% and that FNR was decreased significantly when mapping was perform by dual technique with blue dye and radiocolloid (10.8% vs single 20.3%) and by exam at least 3 SLN (FNR 9.1% vs 21.1% for 2 SLN). These results corresponded to those reported by the SN FNAC trial [22], specifically that SLN after NAC in cT0-T3 N1-2 M0 breast cancer patients described an SLN IR of 87.6% and FNR of 11.5 % by using dual technique mapping. Presuming that SLN metastasis at any size was counted as positive by IHC to evaluate the SLN the FNR was 8.3% (if isolated tumor cell does not consider as positive the FNR was 13.3%). The SENTINA trial [23] was a four arm study that aimed to evaluate a specific algorithm for the timing of standard SLN procedures for patients treated with NAC. The primary end point was FNR of SLN after NAC in previously cN+. They found that IR was 80.1% and FNR 14.2%. A meta-analysis [3] in 2019 included 20 studies of cN+ breast cancer patient who received NAC to find the accuracy of different surgical axillary procedures compared with ALND reports the pool IR of SLN was 89 %, FNR was 17 % and pool IR of MARI (making axillary lymph node with radioactive iodine seed) was 97% FNR 7% but if the SLN and MARI were combined the IR was 100% and FNR 2-4%. So, the combination of SLN with excision of pre-NAC marked positive lymph nodes gave the highest level of accuracy in axillary staging in cN+ breast cancer patients receiving NAC. These findings correlated with a study by Kuemmel et al.[24] about targeted axillary dissection (TAD; SLN combines with excision target lymph node that marked before NAC biopsy) improved FNR to 4.3%. An updated meta analysis in 2021 by Siyang Caol et al [25] included 27 trials summarized pool IR 91%and FNR 15% and established that dual mapping can decrease FNR to 10%. They suggested removal of the targeted node in combination with SLN (TAD) to decrease FNR. However, the targeted node dissection is limited by technique to localized targeted LN and cost of the procedure.

From current data, it can be concluded that SLN after NAC in initial cN+ is possible. Even with high FNR it can be reduced by removal of at least 3 nodes, in combination with targeted node dissection and the use of IHC in pathology to get the best accuracy and the lowest FNR.

Factors that predicted ypN0 after NAC

Pathological complete response (pCR) in breast and axillary lymph nodes after NAC is associated with long term survival. It is known that pCR rate is related to tumor subtype [26]. The highest pCR rate was HM- HER2+ 38.9% then TNBC 31.1%, HM+, HER2+ 18.7% and the lowest pCR rate was HM+ HER2- 8.3%. In addition, nodal pCR rate is an important factor in the prediction of relapse free survival [27-29] and the association between nodal involvement after NAC and relapse free survival was also dependent on breast cancer subtype. The luminal subtype that has more than 4 nodal metastases after NAC will have impaired RFS when compared with no nodal metastasis after NAC. But in

the TNBC and HER2+ subtypes the RFS will reduce when there is only single nodal involvement [27]. The studies about factors associated with nodal pCR described breast cancer subtypes and clinical tumor response are the important factors predicting pathological nodal complete response [13,17,30-32].Other studies reported young age, high level KI 67 expression, high tumor grading are the factors related to ypN0 [31,33]. The highest ypN0 rate is in HM- HER2+ who receiving targeted therapy 60-74%, the second is TNBC 48-53.2% followed by HM+ HER2+ 36-49%. The lowest ypN0 rate is HM+ HER2- 13-21%.

Targeted node dissection: how to localize

As mentioned previously, targeted node dissection reduces FNR of SLN after NAC [3,24,25] but the localization technique is still limited by the accuracy and the cost of technology. There are multiple studies describing the accuracy of each technique to localize clinically positive lymph nodes before NAC. The SENTA trial [24] reported IR of clip localization was 77.8 % and FNR 4.3%. The RISAS trial [34] also reported an IR of 98% and FNR of 3.47% when localization is by radioactive iodine seed (I125) injected in the involved node before NAC. The TATTOO trial localization by highly purified carbon suspension injected in affected node before NAC report an IR of 93.6% and FNR of 9.10%.The technique to mark the affected node prior to NAC can be limited for some reason in clip localization may need a second stage. First, the clip is placed in the suspected node before NAC then the second stage is localization of the clip before surgery by wire or carbon tattoo at clipped node which makes the patient feel uncomfortable. The localization by radioactive seed has limited authorization in some countries, and the high cost and the radiologic signal can reduce over time especially in long term chemotherapy. Carbon tattoo localization is low cost, but it cannot localize without axillary exploration that may cut more lymphatics than other techniques and the ink may migrate after the chemotherapy because the injection is usually done into the fat around the node. The magnetic seed marking has a high IR rate (100%) but needs specific equipment and is high cost. In conclusion, the best method for target node biopsy is still controversial. There are many ongoing studies to find the most suitable technique and the outcome of de-escalating axillary surgery in cN+ patients treated by NAC [35,36].

Does RT should be done if ypN0

If the patient was nodal positive before NAC, it is debatable whether nodal pCR is still necessary for regional nodal irradiation (RNI). Which nodal status should be used to indicate the need for radiation, the nodal prior or after NAC is still being debated. Schiafstein A et al. compared outcomes between Whole Breast Radiation (WBRT) with or without RNI in cN+ converted to ypN0 treatment with BCS and SLN. Results showed that 10-year survival for WBRT alone is 83.6% and WBRT with RNI is 79.5% meaning that additional RNI may not provide long-term survival benefit [37]. That finding was in accordance with a previous retrospective study by a national cancer database study in 2016[38] on the impact of PMRT and RNI after NAC for cN+ breast cancer patients. This study included cT1-3 N1 M0 patients receiving NAC before surgery with 15315 patients divided into 4 cohorts according to breast surgery (mastectomy, BCS) and pathological nodal status (ypN0, ypN+) describe that, for all pathological nodal subgroup PMRT is independent associated with improve OS and no overall survival benefit when addition RNI to WBRT in BCS**.** NSABP B51[39] is an ongoing prospective randomized study to determine the role of RNI to reduce the rate of event for invasive breast cancer recurrent free interval in breast cancer patients which cN+ converted to ypN0. The results of this study should showed the role of radiation after NAC in cN+more clearly. Based on current information, there is no conclusion about the role of radiation after nodal conversion to pathological N0 after NAC. We recommend the use of other prognostic factors in local recurrence to be considered such as staging after NAC, pathological response of breast lesion, lympho-vascular invasion, and breast cancer subtype.

Pathological nodal positive after NAC: AXLN or RT

In early-stage breast cancer with no NAC if SLN positive and the criteria of ACOZOG Z0011 or AMAROS trial are met the axillary dissection can be omitted and RNI received instead. But in ypN+ after NAC the guidance is inconclusive. Tracy Ann Moo et al.[40], reported that in all ypN+ cases, 56% were non SLN positive which cannot be predicted by breast cancer subtype or size of SLN metastasis. Then they conclude that even cN0 or cN1 prior to NAC if ypN+ after NAC, ALND was recommend. Another study supporting this conclusion is one by Muyad et al [41] into 5year survival in cT1-3 N1 breast cancer patients that received NAC and converted to cN0. In this study SLN was done in all cases after NAC the ypN1 patients were divided to receive RT alone or receive ALND then RT. This study found a lower 5-year survival on RT alone (71%) compared with ALND plus RT (77%) which supports the practice of ALND in ypN+ after NAC. The Alliance A011202 trial [42] is an ongoing randomized study comparing ALND to axillar radiation in CT1-3N1 breast cancer patients with positive SLN after NAC. The primary outcome is invasive cancer recurrent free interval, the secondary outcome is overall survival and locoregional recurrence. While the results of this study have not been released yet the conclusion from current data suggest ALND in all positive SLN after NAC.

Conclusion

Axillary surgery for breast cancer has trended into a less invasive procedure. Axillary dissection is replaced by sentinel lymph node biopsy and targeted node dissection are in neoadjuvant

patients who initial clinical nodal negative or converted to clinical nodal negative after treatment. The identification rate and false negative rate were acceptable when using the dual technique, removing more than 2 nodes, and using IHC to investigation. The response of chemotherapy was dependent on breast cancer subtype. The HER2 enrich and triple negative cancer have high response rate than luminal subtype. The role of radiation therapy in ypN+ after NAC is in conclusion the result of an ongoing trial is necessary.

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