ONCOPLASTIC
BREAST CONSORTIUM

Role of Axillary Lymph Node Dissection for Residual MACROMETASTASES After NEOADJUVANT Chemotherapy in Patients With HER2+ and Triple Negative Breast Cancer: The OPBC-11/MACRONAC study

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1. Background

Indications for neoadjuvant chemotherapy (NAC) have changed over the last three decades and its use has increased particularly in patients with aggressive tumor subtypes that have high response rate to chemotherapy/immunotherapy/targeted therapy, such as triple negative breast cancer (TNBC) and HER2+ tumors.[1,2] Surgical downstaging to avoid mastectomy in patients who present with an unfavorable tumor-to-breast size ratio and axillary lymph node dissection (ALND) in node-positive patients is a major advantage of NAC.[3,4]

Although a breast pathological complete response (pCR) is not necessary to downstage patients to breast conserving surgery, nodal pCR is currently considered necessary to avoid ALND.[5,6] Nonetheless, real-world studies show that surgeons are currently omitting ALND in a significant proportion of patients with residual micro- and macrometastases. In a study from the National Cancer Database (NCDB), which included over 6000 women diagnosed from 2012 to 2021 with cT1-3N1M0 tumors who underwent NAC and had residual nodal disease (ypN1mi-2), ALND was omitted in 28-42% of patients with residual macrometastases and in 40-69% of patients with residual micrometastases.[7] Similarly, Boughey and colleagues reported axillary management patterns in the prospective ISPY2 trial. Omission of ALND for ypN+ patients increased from 6.9% in 2011 to 39.2% in 2021.[8] Retrospective studies have shown that omission of ALND in patients with low volume residual nodal disease does not result in an increased risk of axillary or distant recurrence with limited short term follow up.[9] However, in the microNAC study, which retrospectively evaluated oncological outcomes in patients with residual micrometastases treated with and without ALND in a real-world cohort of nearly 1600 patients treated in 84 countries, patients with TNBC treated without ALND were at increased risk of axillary recurrence.[10] This finding raises concerns that although ALND omission may be safe in patients with tumors for which highly effective systemic treatment options exist, it may not be the case for TNBC patients for whom options are limited in case of residual disease after NAC. There are currently three ongoing

randomized controlled trials (RTCs) evaluating omission of ALND in favor of nodal radiation in patients with residual nodal disease after NAC. The ALLIANCE A011202 in the United States and the TAXIS and ADARNAT trials in Europe.[11-13] While these trials will provide level I evidence to guide clinical practice, patients need to be followed for several years until the trials' primary endpoints can be evaluated and their results can be published. Importantly, all these three trials enrolled patients with residual nodal disease after systemic therapy, hence, patients enrolled have predominantly HR+HER2- tumors (this is the case for 68.9% of patients enrolled in the ALLIANCE 011202 and for 80% of the first 500 patients enrolled in the TAXIS trial). Therefore, they will have limited statistical power to guide management for patients with HER2+ and TNBC.[14,15]

In addition, data regarding the safety of breast conserving surgery (BCS) in patients with multiple ipsilateral breast cancers (MIBC) treated with NAC is limited. Patients treated with NAC were excluded from the ACOSOG Z11102 trial which showed that BCS with adjuvant radiation with lumpectomy site boosts yields acceptably low 5-year local recurrence rate.[16] In a single center retrospective study from the Dana Farber Cancer Institute, that evaluated 73 patients with MIBC treated with NAC followed by BCS, local recurrence was low (1.4%) at a median follow-up of 3 years.[17] However, no studies have evaluated LR rates in patients with HER2+ and TNBC MIBC with residual nodal disease after NAC.

In summary, despite pending level I evidence, an increasing number of surgeons are omitting ALND in patients with residual nodal disease after NAC. Results from the ongoing RTCs are not expected soon, and they only included a small number of patients with ER negative tumors. Real world data on oncologic outcomes in this population may be helpful to inform management in this clinical scenario since prospective data will remain limited. Furthermore, additional data can guide the use of breast conservation in patients with MIBC with residual nodal disease after NAC.

2. Purpose and Outcomes

The purpose of this multicenter retrospective cohort study is to determine the safety of omission of axillary lymph node dissection in patients with TNBC and HER2+ tumors with residual macrometastases (in the SLN/TAD/TAS or MARI node) after NAC. A secondary objective is to determine the safety of breast conservation in patients with multiple ipsilateral breast tumors treated with breast conservation after NAC.

Aims:

- **To assess the risk of axillary recurrence in patients with residual macrometastases after NAC overall and by use of axillary dissection**
- **To compare local recurrence rates in patients with single vs multiple ipsilateral breast cancer (MIBC) according to the type of breast surgery (lumpectomy or mastectomy)**

Primary endpoint:

- 3-year rate of any axillary recurrence (defined as isolated or combined with local or distant recurrence)

Secondary endpoints:

- 3-year rate of isolated axillary recurrence
- 3-year rate of local recurrence
- 3-year rate of locoregional recurrence
- 3-year rate of any invasive recurrence
- Proportion of patients with additional ITCs, micro- and macrometastases removed by ALND
- Factors associated with the presence of additional positive lymph nodes at ALND

- Factors associated with axillary and invasive recurrence
- To compare 3-year rate of any axillary, isolated axillary, local, locoregional and any invasive recurrence in patients treated with and without ALND

3. Data Source

A call for participation will be made within the Oncoplastic Breast Consortium (OPBC) and other international networks. Patients who presented with cT1-4 N0-3 TNBC (including ER-low tumors) or HER2+ BC who underwent NAC followed by axillary staging with either SLN surgery, TAD, TAS or the MARI procedure and were found to have residual macrometastases will be included.

4. Inclusion and Exclusion Criteria

Inclusion criteria

- **Women and men with a diagnosis of stage I-III TNBC or HER2+ breast cancer at diagnosis.** HER2+ is defined as an IHC score of 3+ or positive FISH. TNBC is defined as ER and PR IHC expression of 0 and HER2 negativity defined as either IHC expression of 0–1+ or lack of gene amplification (FISH < 2.0). **Patients with ER low (1-10%) and/or PR low (1-10%) tumors are allowed.**
- Any histological subtype
- For cN0 at presentation: any axillary staging technique including palpation with or without imaging is allowed. Dual tracer mapping is not required for SLN surgery.
- For cN+ at presentation: Percutaneous biopsy proven confirmation is required at diagnosis. Staging techniques after NAC include: SLN surgery with dual mapping or Targeted Axillary Dissection (TAD: imaging-guided localization of sampled node in combination with SLN procedure with or without dual mapping) or Tailored Axillary Surgery (TAS: removal of the sentinel lymph nodes as well as selective removal of all palpable disease and documentation of the removal of the initially biopsy-proven and

clipped lymph node metastasis by specimen radiography) or the MARI procedure (Marking Axillary Lymph Nodes with Iodine Seeds).

- Received neoadjuvant chemotherapy
- Residual macrometastases (metastasis greater than 2 mm in diameter) detected on SLN surgery or TAD ot TAS or MARI (on frozen section or final pathology)
- Concomitant presence of ITCs and micrometastases in other sentinel lymph nodes is allowed
- Following SLN surgery/TAD/TAS/MARI patients underwent completion ALND, nodal RT, both or no further axillary treatment
- At least 1-year follow-up (had surgery at any time point until October 2024 at the latest)
- Prior history of ductal carcinoma in situ (DCIS) is allowed

Exclusion Criteria

- Did not undergo SLN surgery/TAD/TAS/MARI (e.g., went straight to ALND)
- Presence of ITCs or micrometastases alone in the sentinel nodes (or TAD nodes or MARI node or TAS nodes) without macrometastases
- HR+HER2- tumors (except ER low and or PR-low)
- Stage IV disease at presentation
- Inflammatory breast cancer at presentation
- Neoadjuvant endocrine therapy
- Macrometastases detected by OSNA

5. Minimum number of cases per institution

The minimum number of cases included per institution is 5

Authorship criteria by number of included patients:

<3% of the entire cohort: one study-group position

3-5% of the entire cohort: two author positions (1 as lead author and 1 as study-group)

>5% of the entire cohort: three author positions (1 as lead author and 2 as study group)

In case of total author count limitations on abstracts for scientific meetings, authors will be selected by number of included patients. Sites unable to provide data related to the presence of MIBC will be included in the main manuscript reporting the association of axillary surgery and oncological outcomes but will not be included in the manuscript analyzing the rate of local recurrence in patients with single vs multiple ipsilateral tumors.

6. Material and Methods

6.1 Sample size

This is a retrospective cohort study. All participating sites are encouraged to contribute consecutive patients. Pragmatic sample size determination depends on the number of patients included by the participating sites.

6.2 Variables of interest

- Center
- Age (at surgery)
- Race (Asian, Black, Caucasian, other/unknown)
- Ethnicity (Hispanic, non-hispanic)
- BMI at surgery
- Any pathogenic or likely pathogenic mutations (BRCA1, BRCA2, PALB2, ATM, CDH1 etc) y/n/not tested
- cT at presentation
- cN at presentation
- pre-NAC MRI y/n
- Single breast tumor

- Multiple ipsilateral breast cancer (MIBC, defined as ≥2 areas of biopsy proven cancer with ≥2 cm of normal breast tissue between them)

  In case of MIBC: ER/PR/HER2 status of each cancer, size of each cancer, histology of each cancer

  In case of MIBC: same quadrant, >one quadrant, missing
- cN0 or cN+ (biopsy-proven) at presentation
- Date of surgery
- Type of breast surgery: BCS/therapeutic reduction mammoplasty/mastectomy
- Type of axillary surgery

  -SLN surgery
- with single mapping (only allowed in cN- cases)
- with dual mapping (mandatory in cN+ cases)

  -TAD (in cN+ cases - both single or dual mapping allowed)

  -MARI (in cN+ cases)

  -TAS (in cN+ cases)
- Number of SLNs removed
- Number of SLNs with macrometastases
- Number of concomitant SLNs, TAD, or MARI nodes with micrometastases or ITCs
- Detection on frozen section? y/n/ frozen section not performed
- Method of detection? H&E or IHC?
- ALND y/n
- Number of additional LNs removed
- Number of additional positive lymph nodes
- Size of the largest nodal metastasis found in the ALND specimen:

  ITCs/micrometastasis/macrometastasis
- Histology (NST/lobular/other)

- Breast pCR: yes/no
- Residual tumor size in the breast: size (cm)
- For patients with multiple ipsilateral tumors please describe the size the residual disease at each disease site: size (cm)
- Tumor grade
- Receptor status (at presentation)

  - ER+ and/or PR+/HER2+;

  - ER-/PR- HER2+;

  - ER-/PR-/HER2-;
- Type of NAC regimen for HER2- (AC-T/AC-T + Carbo/AC-T +Carbo + pembrolizumab/AC-free regimen/other)
- Type of NAC regimen for HER2+ (AC-TH/AC-THP/TCH/TCHP/other)
- Adjuvant capecitabine: yes/no
- If HER2+: type of post-surgical anti-HER2 treatment (H/HP/TDM-1)
- If HR+HER2+: received adjuvant endocrine therapy: yes/no,

  - if yes: type of endocrine therapy
- Adjuvant Abemaciclib yes/no
- Adjuvant Olaparib yes/no

Radiotherapy: yes/no

- Target Volume:

  Whole breast irradiation: y/no

  Chest wall irradiation: y/no

  Regional nodal irradiation:y/n

Follow-up

Date of last follow up

- Recurrence: yes/no

- Type of recurrence: local/regional/locoregional/synchronous (regional and distant, local and distant, locoregional and distant)
- Type of regional recurrence: axillary only, axillary and supraclavicular or internal mammary, supraclavicular or internal mammary without axillary
- Date of recurrence
- Deceased: yes/no
- Date of death
- Cause of death

6.3. Statistics

Clinicopathological characteristics will be compared between patients treated with and without ALND. Wilcoxon rank sum test or t-test will be used for continuous variables, and the Chi-square or Fisher's exact test will be used for categorical variables. The rate of additional positive lymph nodes will be estimated in the group of patients who underwent ALND. Factors associates with additional positive lymph nodes will be assessed using logistic regression. Competing risk analysis will be performed to assess the cumulative incidence rates of any axillary recurrence, local recurrence, locoregional recurrence, and any invasive (locoregional or distant) recurrence. Depending on the median follow-up of both cohorts (ALND, no ALND) the 3-year (or 5-year) cumulative incidence rates will be compared between ALND and no ALND using the Gray's test. Factors associated with axillary and any invasive recurrence will be evaluated with univariable a multivariable logistic regression. Type I error rate will be set to 0.05 (α). All statistical analyses will be conducted using R 3.5.3 (R Core Development Team, Vienna, Austria).

7. Procedure for unencrypted data

The subinvestigators will collect all the health-related data, which define the patients, from the clinical information system. Data will be transferred to the OPBC coordinating site (University

Hospital Basel) or to the Memorial Sloan Kettering Cancer Center (MSKCC). All patients will be encoded with a neutral number (letters, or numbers). At the same time, they will have a key document containing all the neutral numbers and the patient IDs and health related data in order to assign health related data to patients. The project leader will administer the key document. The following usage of health-related data will be performed in encrypted form and in compliance with data protection according to article 26 of the Human research Ordinance HRO. Data will be transferred to the PI, Giacomo Montagna MD MPH, as outlined in the Data Transfer Agreement and analyzed at MSKCC. All persons involved in the project will carefully handle the confidential data and will not disclose any data use beyond this project.

8. References

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