Nodal burden and nodal recurrence in patients with isolated tumor cells after neoadjuvant chemotherapy treated with axillary dissection or nodal radiation: the OPBC-06/EUBREAST-14R/ICARO study

1. Background

In the primary surgery setting, volume of disease in the sentinel lymph node (SLN) is an important predictor of the likelihood of additional non-SLN metastases.[1-5] Patients with low-volume SLN disease, defined as micrometastases or isolated tumor cells (ITCs), have a risk of additional non-SLN metastases of approximately 10–20%.[2,6-9]

However, after neoadjuvant chemotherapy (NAC), patients with residual nodal disease in the SLN have a higher nodal burden, with multiple studies showing additional positive lymph nodes at axillary lymph node dissection (ALND) in over 60% of cases.[10-12] Studies have also shown that, after NAC, the likelihood of finding additional positive lymph nodes is not affected by the size of the nodal metastasis found in the SLN or the tumor subtype.[10,13] In the SN-FNAC trial, which evaluated the feasibility of SLNB after NAC, additional positive lymph nodes (LNs) were found in 57% (4/7) patients with ITCs in the SLN, 37% (3/8) of those with micrometastases and 56% (34/61) of patients with macrometastases.[14] In ACOSOG Z1071, 36.4% (4/11) of patients with ITCs and 60.1% (164/273) of patients with micro- or macrometastases were found to have additional positive LNs. Similarly, in a study from Memorial Sloan Kettering Cancer Center, Moo et al. evaluated 171 patients with 1 positive SLN after NAC who had completion ALND and found that at least 1 additional positive non-SLN node was present in 17% (1/6) of patients with ITCs, 64% (28/44) of patients with micrometastases and 62% (75/121) of patients with macrometastases.[10] As the number of patients with ITCs in all these studies was very small (total n = 24), the nodal burden in this population is unknown.

In addition, as small deposits of cancer in the lymph nodes after NAC can potentially represent a population of tumor cells resistant to chemotherapy, management of ITCs is controversial.

Current guidelines recommend ALND for any viable tumor cells in the SLN after NAC, however in clinical practice many of these patients are managed without ALND and expert agreement is lacking. In a recent study from the National Cancer Database 37% of patients with ITCs, 24% with micrometastases and 13% with ypN1 disease after NAC were treated with SLNB alone.[15] During the last St. Gallen International Expert Consensus Conference, the panel was split when asked if the presence of metastases ≤ 2mm after neoadjuvant therapy in any SLN justifies complete dissection. While many panelists felt that axillary radiation could be an alternative to axillary dissection in such situations, others urged caution, and recommended awaiting the results of ongoing phase III trials that compare axillary radiation with axillary dissection in the setting of residual nodal disease.[16]

The prognostic impact of ITCs and micrometastases following NAC is also unclear. In a Netherlands Cancer Registry study, patients with residual ITC or micrometastatic nodal disease had a similar prognosis for disease free survival (DFS) and overall survival (OS) compared to patients with a nodal pCR.[17] In contrast, Wong et al. reported a greater risk for breast cancer recurrence associated with increasing residual nodal burden as well as a twofold increased risk of death associated with residual ITC or micrometastatic nodal disease as compared to nodal pCR.[18]

In summary, the residual nodal burden in patients with ITCs after NAC is unknown and currently there is no consensus to whether these patients should be treated with ALND. Real world data on oncologic outcomes in this population is sparse and to date no study has compared axillary recurrence rates after ALND or nodal RT in this population.

2. Purpose and Outcomes

The purposes of this multicenter retrospective cohort study is to determine the residual nodal burden in patients with isolated tumor cells detected in the SLN or the clipped node after NAC and to determine oncologic outcomes in this group of patients after ALND or nodal RT or observation.

Primary endpoints include:

- Patterns of treatment (ALND vs TAD/SLNB + axillary RT vs TAD/SLNB only) by geographic region and over time
- Incidence of additional micro- and macrometastases removed by ALND
- 3-year rate of axillary recurrence

Secondary endpoints include:

- 3-year rates of any regional, locoregional and any invasive recurrence
- To compare 3-year rate of axillary recurrence in ypN0(i+) with ypN0 (historic OPBC-04/EUBREAST-06/OMA control)

3. Data Source

Data will be collected from centers in the Oncoplastic Breast Consortium (OPBC) and EUBREAST networks. Patients with T1-4 biopsy-proven N0-3 BC who underwent NAC followed by axillary staging with either SLNB with dual tracer mapping or TAD and who were found to have isolated tumor cells in the SLN or clipped node .

4. Inclusion and Exclusion Criteria

Inclusion criteria

- Consecutive patients affected with T1-4 N0-3 breast cancer
- For cN+: Biopsy proven confirmation is required

- For cN0: any axillary staging technique including palpation is allowed
- Residual ITCs in the SLN or clipped node
- At least 1-year follow-up (12/2021 or later depending on the time of data collection)
- For cN0: SLNB with single or dual tracer mapping
- For cN+: SLNB with dual mapping or targeted axillary dissection (TAD: imaging-guided localization of sampled node in combination with SLN procedure with or without dual mapping)
- Underwent TAD/SLNB +/- ALND +/- axillary RT

Exclusion Criteria

- Male patients
- Patients with nodal pCR
- Patients with residual nodal micro- or macrometastases
- Stage IV disease at presentation
- Inflammatory breast cancer (T4d) at presentation

5. Material and Methods

6.1 Sample size

This is a retrospective cohort study. Consecutive patients will be included. There is no formal sample size calculation.

6.2 Variables of interest

- Patient characteristics (age at surgery, race/ethnicity)
- Tumor characteristics (cT, cN, Histology, Tumor grade, Receptor status)
- Neoadjuvant chemotherapy regimen and anti HER2 regimen
- Type of breast and axillary surgery and date of surgery
- Type of response

- Nodes: number of SLNs removed, number of SLNs with ITCs, number of lymph nodes removed at ALND, size of the largest metastases detected in the ALND specimen
- Method of detection: frozen section/final pathology? H&E or IHC?
- breast pCR (ypT0/is) y/n - if no, size of residual disease in the breast (cm)]

- Adjuvant systemic therapy:
  - Adjuvant capecitabine: yes/no
  - If HER2+: type of post surgical anti HER2 treatment (H/HP/TDM-1)
  - If HR+: type of endocrine therapy received
- Adjuvant radiation (dose and treatment field)
- Date of last follow up
- Type and date of recurrence:
  - Local/ regional/ locoregional/ synchronous (locoregional and distant)/ distant (site of distant disease)
  - Date of recurrence
  - Recurrence: yes/no
- Deceased: yes/no
  - Date of death
  - Cause of death

6.3. Statistics

Patterns of treatment will be reported descriptively. The rate of additional positive lymph nodes will be estimated in the group of patients who received ALND. Clinicopathological characteristics will be compared between patients treated with ALND and those treated with nodal RT only. 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. Competing risk analysis will be performed to assess the cumulative incidence rates of any axillary recurrence, locoregional recurrence, and any invasive (locoregional or distant) recurrence. Depending on

the median follow-up of both cohorts (ALND/nodal RT) the two-year (or three-year) cumulative incidence rates will be compared between ALND and nodal RT using the Gray's test. 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 copy all the health-related data, which define the patients, from the clinical information system into an excel chart and will encode the patients 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 dated XYZ and analyzed at Memorial Sloan Kettering Cancer Center. 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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