European Journal of Surgical Oncology 50 (2024) 107954

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Review Article

Is routine axillary lymph node dissection needed to tailor systemic treatments for breast cancer patients in the era of molecular oncology? A position paper of the Italian National Association of Breast Surgeons (ANISC)

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A B S T R A C T

Background: De-escalation of axillary surgery in breast cancer (BC) management began when sentinel lymph node biopsy (SLNB) replaced axillary lymph node dissection (ALND) as standard of care in patients with node-negative BC. The second step consolidated ALND omission in selected subgroups of BC patients with up to two macrometastases and recognized BC molecular and genomic implication in predicting prognosis and planning adjuvant treatment.

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https://doi.org/10.1016/j.ejso.2024.107954
Received 3 December 2023; Received in revised form 17 December 2023; Accepted 5 January 2024
Available online 6 January 2024
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Outcomes from the recent RxPONDER and monarchE trials have come to challenge the previous cut-off of two SLN in order to inform decisions on systemic therapies for hormone receptor-positive (HR+), human epidermal growth factor receptor type-2 (HER2) negative BC, as the criteria included a cut-off of respectively three and four SLNs.

In view of the controversy that this may lift in surgical practice, the Italian National Association of Breast Surgeons (Associazione Nazionale Italiana Senologi Chirurghi, ANISC) reviewed data regarding the latest trials on this topic and proposes an implementation in clinical practice.

Material and methods: We reviewed the available literature offering data on the pathological nodal status of cN0 breast cancer patients.

Results: The rates of pN2 status in cN0 patients ranges from 3.5 % to 16 %; pre-surgical diagnostic definition of axillary lymph node status in cN0 patients by ultrasound could be useful to inform about a possible involvement of ≥4 lymph nodes in this specific sub-groups of women.

Conclusions: The Italian National Association of Breast Surgeons (ANISC) considers that for HR + HER2-/cN0-pN1(sn) BC patients undergoing breast conserving treatment the preoperative workup should be optimized for a more detailed assessment of the axilla and the technique of SLNB should be optimized, if considered appropriate by the surgeon, not considering routine ALND always indicated to determine treatment recommendations according to criteria of eligibility to RxPONDER and monarch-E trials.

1. Background

The role of axillary surgery in the management of breast cancer (BC) has evolved considerably over the last three decades, due to multimodality strategies and the decreasing value of axillary surgery as a staging procedure, evolving from axillary lymph-node dissection (ALND) to sentinel lymph node biopsy (SLNB) [1,2]. The latter has become standard practice in clinically node-negative patients, minimising morbidity such as lymphedema and sensory loss, without affecting oncological outcomes [3–5], whereas recent research demonstrates even the safe omission of SLNB in selected cases [6].

Moreover, surgical management of minimal to moderate disease burden in the axillary lymph-nodes has dramatically changed, following landmark randomized trials, like the IBCSG 23-01, ACOSOG Z0011, SINODAR ONE and AMAROS [7–10]. In these trials, long-term follow-up confirmed the safety of omitting ALND, resulting in reduced morbidity and better quality of life.

Outcomes from the recent RxPONDER and monarchE trials [11,12] have come to challenge the previous cut-off of "metastasis in up to two SLNs" in order to inform decisions on systemic therapies for hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2–) BC, as the criteria included a cut-off of respectively three and four SLNs.

In view of the controversy that this may lift in surgical practice, the Italian National Association of Breast Surgeons (ANISC) reviews data regarding the latest trials on this topic and proposes an approach in clinical practice.

2. Material and methods

We reviewed the available literature offering data on the pathological nodal status of cN0 breast cancer patients. PubMed, Cochrane Library and Google Scholar were searched from January 2010 to September 2023. All the authors of the paper independently reviewed retrieved articles and the studies offering useful data for our review were considered for inclusion.

3. Results

Several studies offering data on the rates of pN2 status in cN0 patients and on the role of pre-operative ultrasound in the assessment of the axilla are available in literature.

In the ALND arm of the ACOSOG Z0011 trial, 13.7 % of patients had a total of ≥4 positive nodes [3]. A study on a population of 5,142 clinically negative BC patients, reported that 16 % of 1,314 patients submitted to ALND with a positive SLN had ≥4 positive nodes [13]. Further data underlined the impact of molecular subtype in the likelihood of extensive node involvement [14]. A recent report from Memorial Sloan Kettering Cancer Center on 3363 cN0 postmenopausal women identified only 3.5 % pN2 patients in the HR+/HER2- setting, and, on multivariable analysis age <65 years, lymphovascular invasion, multicentric/multifocal tumors and tumor size >2 cm were significantly associated with pN2-3 disease [15]. Another recent study on 2532 postmenopausal women with early stage cN0 HR-positive, HER 2-negative breast cancer with a single positive SLN reported on a very low risk (5 %) of having four or more positive nodes on final pathology, concluding for the reliability of a limited staging with SLNB only to guide therapeutic decisions in this subset of patients [16]. Additionally, a recent SEER study has also reported good long-term outcome data for cN0 BC presenting ≥4 positive nodes at ALND and low RS, regardless CT treatment [17]. In conclusion, the presence of pN2-3 disease in patients that are cN0 at presentation seems to be an uncommon scenario, provided that meticulous preoperative work-up has been performed.

On the other hand, the role of pre-surgical diagnostic definition of axillary lymph node status in cN0 patients by ultrasound could be useful to inform about a possible involvement of ≥4 lymph nodes in this specific sub-groups of women, as reported by several studies [18–20]. In addition, role of US in predicting the extension of axillary lymph-node involvement in clinically node negative BC is ongoing, with several randomized trials (INSEMA, BOOG2013-8, and NAUTILUS trials) [21–24] comparing observation to SLNB in selected cN0 BC women. The SOUND trial has been recently published confirming the non-inferiority of omitting axillary surgery for T1 patients and a negative result on ultrasonography of the axillary lymph nodes (6).

Moreover, data deriving from two meta-analyses also showed how there are some patients with limited nodal burden at the US who could still benefit from a de-escalation of axillary surgery, but at the same time, that advanced pN stage is extremely uncommon in the presence of a negative preoperative axillary ultrasound [25,26]. Man and coll. concluded that more than half of the patients with pre-operative positive axillary ultrasound and biopsy proven axillary nodal metastases were over-treated by ALND. The authors suggested a quantification of suspicious nodes and extent of cortical morphological changes in axillary ultrasound to help identifying suitable patients for sentinel lymph node biopsy, sparing unnecessary ALND (26).

4. Discussion

Several randomized clinical trials have shown that local disease control can be achieved without ALND, even in the presence of limited metastatic SLNs involvement, and information on axillary lymph node status does not change either the type of adjuvant treatment or the prognosis, and therefore the role of axillary surgical staging in clinically node-negative early BC patients has been questioned.

The status of the axillary lymph nodes historically played a crucial part in defining need and extent of adjuvant systemic therapy [5,27]. The number of nodes *per se* has been used to define the N stage, but numerical differences have not demonstrated any differences in outcomes or treatment decisions, as long as N stage does not change.

In recent years, genomic assays and molecular features have been developed to predict prognosis and response to adjuvant systemic chemotherapy, revealing greater value in tailoring systemic therapy

based on intrinsic subtypes, limiting the role of anatomical staging [28].

Therefore, adjuvant therapies can be predominantly defined according to biologic features of the primary tumor in addition to nodal involvement in the majority of patients where this question is relevant [6]. Some clinical conditions are still influenced by nodal status, such as the decision of adding chemotherapy to endocrine treatment in luminal-like B tumors, or the indication for olaparib in the post-neoadjuvant setting for high-risk patients with BRCA mutation [6].

However, data from the RxPONDER and the monarchE trials (11,12), have recently lifted a real-world debate regarding the need of completion ALND in planning adjuvant therapies, following the results of studies aimed at defining systemic therapy in patients with HR+, HER2– BC.

The RxPONDER trial demonstrated no benefit for chemotherapy in post-menopausal women with HR-positive BC, 1–3 positive SLNs and recurrence score (RS) of 25 or lower. However, chemotherapy (CT) was reported beneficial for all pre-menopausal women with nodal metastases in 1–3 SLNs, regardless of the RS [11].

Recent long-term monarchE trial data has confirmed the persisting benefit of adjuvant abemaciclib added to endocrine therapy for HR + HER2- high-risk BC patients, with an increase in absolute invasive disease-free survival and distant relapse-free survival benefit at 4 years [12]. The study randomized 5637 patients, defined at high risk according to specific clinical criteria: high-risk was defined as ≥4 pathologically positive axillary nodes (reflecting the pN2 population that is, by definition, high-risk) or 1-3 positive nodes and at least one of the following characteristics: tumor size ≥5 cm, histologic grade 3 disease, or Ki-67 ≥ 20 %. However, Ki-67 index was not required for enrollment, given that abemaciclib benefit was reported consistent regardless of Ki-67 index [29].

It becomes clear from the aforementioned that RxPONDER intended to identify a low-risk population, where omission of chemotherapy would be feasible and safe, whereas monarchE intended to identify a high-risk population, with the rationale that it would be easier to demonstrate a benefit by addition of abemaciclib. However, these trials were not designed to challenge the need for ALND in a group of patients that the safety of its omission has already been established.

Therefore, the question is not whether ALND is mandatory in HR + HER2- BC women with a metastatic SLN to determine the need for abemaciclib. While such an approach seemingly addresses the question, it is important to consider that, especially in this group of high-risk patients, a return to the operating theatre for completion ALND will delay adjuvant systemic therapy, even if it is performed without any complications. This is a critical factor that needs to be weighed in before lightheartedly considering return to theatre, as any delay has been well documented to yield a detrimental effect on oncological outcomes (28). Moreover, the higher morbidity of all the unnecessary ALNDs has to be seriously considered. This could also impact on the waiting lists of breast surgical units, with a further load on the operating theaters.

Therefore, the question that arises is to understand what is the probability that further lymph nodes are metastatic after ALND with 1–3 positive SLNs, to possibly justify the indication for ALND in such clinical scenarios.

The results of our review that the probability of finding a pN2 axilla in a cN0 breast cancer patient is very low, ranging form 3.5 %–16 %, and that ultrasound is a realiable diagnostic tool to pre-operatively assess the status of the axilla, since its sensitivity in patients proved to be pN2 is very high.

Moreover, according to the data of the monarchE trial, most patients who are at risk of having four or more positive lymph nodes where T2 or T3. In modern practice, these patients are usually candidates for more detailed workup (tomosynthesis, MRI, staging) and are all more commonly considered for neoadjuvant systemic therapy rather than upfront surgery (12). It is also important to consider the fact that an optimal SLNB is expected to harvest more than one lymph node and that randomised controlled trials have earlier suggested that a yield of three SLNs is standard practice to reduce false negative rates [30]. Finally, it needs to be highlighted that the need for four or more lymph nodes addresses only one of the inclusion criteria for administration of abemaciclib or de-escalation of chemotherapy in the postmenopausal with a low RS score. In the light of this evidence, this practically means that any "dilemma" would refer to a very limited subgroup of patients.

Recently, Mittendorf and colleagues offered a commentary view on the matter, reflecting a pragmatic perspective from the point of view of breast surgeons [31]. They mainly underlined how monarchE trial was likely concepted without specific purposes aimed at evaluating the role of ALND in women with HR + HER2- BC. They highlighted the lack of information on how many SLNBs were performed compared to ALNDs, as well as the lack of data on the clinical nodal status of the 36 % patients undergoing neoadjuvant CT. The authors also suggested the choice of discussing the option of ALND possibly in cases with 1–3 positive SLNs but in the absence of other risk factors (high tumor size or grade) [20]. The authors emphasized how the results of both RxPONDER and monarch-E trials should be duly interpreted in the context of the evidence deriving from trials investigating the surgical management of the axilla with up to two macrometastatic sentinel lymph nodes [17].

However the preliminary results of the phase III NATALEE trial, recently presented at the American Society of Clinical Oncology Meeting, support Ribociclib + ET as the treatment of choice in a broad population of patients with stage II or III HR+/HER2− BC, including patients with N0 disease [32]. These findings will overcome the need of performing ALND in patients with HR+/HER2− BC and up to two macro metastatic SLNs with the only aim of determining the need for CDK4/6 inhibitors.

5. Conclusions

In conclusion, in the specific context described, ANISC considers that for HR + HER2-/cN0-pN1(sn) BC patients undergoing breast conserving treatment:

- the preoperative workup should be optimized for a more detailed assessment of the axilla;
- in patients at high risk for a more relevant nodal burden, the technique of SLNB should be optimized, if considered appropriate by the surgeon, not considering routine ALND always indicated to determine treatment recommendations according to criteria of eligibility to RxPONDER and monarch-E trials;
- given the advances in the field of systemic therapies to inform optimal treatment decisions our challenge is dual: on one hand giving the optimal diagnostic information according to present trial criteria but, as importantly, on the other hand not to condemn patients to possible unnecessary dissections that could have a very clear detrimental effect on QoL without any advantage terms of oncological outcomes.

Therefore ANISC considers mandatory to discuss any surgical option for BC patients in a multidisciplinary setting, personalizing the decision and taking in account all the available recent scientific evidence and each woman clinical variables.

The same multisciplinary approach should be applied to the design of any clinical trial investigating new therapeutic approaches for BC management, and multidisciplinary scientific boards should share inclusion criteria and consider all available evidence in any discipline related to BC treatment.

ANISC recognizes the unquestionable value of cited studies on de-escalation of axillary surgery with limited positive SLNs [7–9].

In agreement with these scientific considerations [20], the Italian National Association of Breast Surgeons (ANISC) believes that the omission of ALND in HER+/HER2-BC patients who satisfy the RxPONDER and monarch-E criteria might represent understaging, but very rarely undertreatment [20].

Table 1
Indications for axillary lymph node dissection in breast cancer treatment.

Indications for ALND in BC treatment
Clinically node-positive axilla, confirmed by fine needle aspiration or core biopsy in a patient for whom neoadjuvant chemotherapy is not planned
SLN positive patients who fall outside the Z0011/SINODAR ONE selection criteria (i.e. >2 macrometastatic SLN, matted nodes, gross extra nodal extension, mastectomy or breast conservation without whole-breast RT)
Inflammatory Breast Cancer (cT4d)
Sentinel or axillary nodes which remain positive after neoadjuvant chemotherapy outside clinical trials
Positive SLN after a previous SLN biopsy in breast recurrence
Axillary recurrence after SLN biopsy

In such specific contest, extrapolating data on the basis of pragmatism and everyday clinical practice, ANISC considers routine ALND not indicated to evaluate eligibility to RxPONDER and monarch-E trials and determine treatment recommendations of these systemic trials for HR + HER2- selected BC patients.

However, at the same time, ANISC considers axillary surgery not obsolete, endorsing the recommendation to ALND in all the clinical conditions listed in Table 1.

Moreover, the issue of the residual nodal burden after SLNB in cN0 invasive lobular BC patients should be considered. In this peculiar type, the risk of clinical and radiological understaging is reportedly to be higher [33], due to the absence of morphological anatomical changes and often little desmoplastic reaction, which hinder macroscopic detection and imaging findings of pathological nodes. Therefore, decision-making in this specific setting might consider this issue, to establish correct surgical and oncological treatment plans.

The future might look to technological advances in imaging staging of the axilla, as well as in precision medicine, with the possible development of predictive models through machine and deep learning, which might be useful in predicting the exact extent of the axillary disease burden.

Sources of funding

The authors received no funding for this work.

CRediT authorship contribution statement

Nicola Rocco: Conceptualization, Methodology, Data curation, Writing – original draft. **Matteo Ghilli:** Conceptualization, Methodology, Data curation, Writing – original draft. **Annalisa Curcio:** Conceptualization, Methodology, Data curation, Writing – original draft. **Marina Bortul:** Writing – review & editing. **Stefano Burlizzi:** Visualization, Investigation, Supervision, Validation. **Carlo Cabula:** Visualization, Investigation, Supervision, Validation. **Roberta Cabula:** Writing – review & editing. **Alberta Ferrari:** Visualization, Investigation, Supervision, Validation. **Secondo Folli:** Visualization, Investigation, Supervision, Validation. **Lucio Fortunato:** Visualization, Investigation, Supervision, Validation. **Patrizia Frittelli:** Writing – review & editing. **Oreste Gentilini:** Writing – review & editing. **Sara Grendele:** Visualization, Investigation, Supervision, Validation. **Massimo Maria Grassi:** Visualization, Investigation, Supervision, Validation. **Simona Grossi:** Visualization, Investigation, Supervision, Validation. **Francesca Magnoni:** Data curation, Writing – original draft. **Roberto Murgo:** Visualization, Investigation, Supervision, Validation. **Dante Palli:** Visualization, Investigation, Supervision, Validation. **Francesca Rovera:** Writing – review & editing. **Alessandro Sanguinetti:** Visualization, Investigation, Supervision, Validation. **Mario Taffurelli:** Writing – review & editing. **Giovanni Tazzioli:** Visualization, Investigation, Supervision, Validation. **Daniela Andreina Terribile:** Writing – review & editing. **Francesco Caruso:** Conceptualization, Methodology. **Viviana Galimberti:** Conceptualization, Methodology, Data curation, Writing – original draft.

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