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Axillary Reverse Mapping in Breast Cancer: Would We Need it in the Era of Surgical De-Escalation?

Introduction

In recent years, starting from the Veronesi revolution, breast surgery has undergone a notable de-escalation.^{1,2} Furthermore, improved treatment and the advent of genetic predictors added to the high rate of early cancer detection, owing to better screening and technologies which have led to a significant improvement in survival.³ Breast cancer is the most common cancer and, worldwide, there are approximately 8 million living women who have received this diagnosis in the past 5 years.⁴ Despite the improvement in survival, quality of life is often influenced by the sequelae of treatments, and the most frequent is certainly breast cancer-related lymphedema (BCRL).⁵ The role of axillary reverse mapping (ARM), which aims to reduce such sequelae, in the era of de-escalation of breast cancer surgery has not previously been re-evaluated. The purpose of this clinical commentary is to evaluate the potential benefit of ARM and its role in the era of de-escalation of breast cancer surgery.

Discussion

With the publication of data of Z0011, SINODAR-ONE and AMAROS clinical trials as well as the preliminary results of

SOUND study, the breast oncological community is moving toward “less is more” approach and breast surgery is experiencing a significant de-escalation.⁶⁻⁹ However, axillary lymph nodes dissection (ALND) still remains the standard for treatment in patients who are not eligible in the previously mentioned studies.⁹ Thanks to the advancements in sentinel lymph node biopsy and results of studies regarding de-escalation of axillary surgery; less than 20% of patients with breast cancer underwent ALND.¹⁰ The ALND technique has also experienced a significant de-escalation. In fact, less extensive ALND are currently performed; this is because the role of this procedure changed over the years, from a curative aim to a staging role.¹¹ Despite this reduction, ALND remains a procedure with relatively high morbidity for patients.¹² Lymphedema of the ipsilateral upper limb is the most common sequela following ALND with incidence reported in literature ranging from 7% to 58%.¹² Despite the reduction of absolute number of ALND, breast cancer related lymphedema BCRL affects about 3 to 5 million patients worldwide and strongly impair their quality of life.¹²

In 2007, Thompson introduced the Axillary reverse mapping ARM aiming to prevent BCRL.¹³ In this technique, based on the theory of 2 different pathways draining the breast and arm, a tracer is injected to identify and preserve arm nodes in order to reduce incidence of BCRL.¹³ Immediately after the first publication of ARM technique results and after the initial enthusiasm, the issue of oncological safety has been the major subject of debate. In addition, the feasibility of the technique and its effectiveness in preventing lymphedema have contributed to curb of the initial enthusiasm.

Feasibility, considered as the identification rate of nodes draining the upper limb during ALND, improved during the years.^{14,15} In

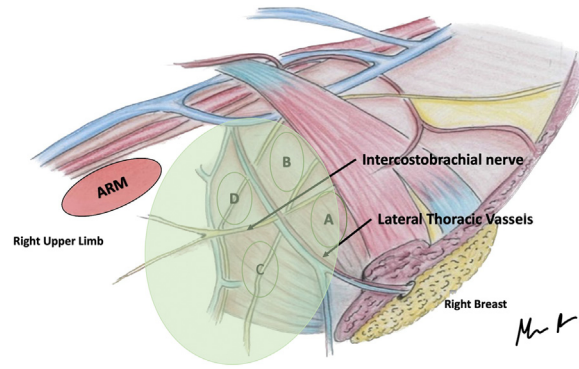
Abbreviations: ARM, axillary reverse mapping; ALND, axillary lymph nodes dissection; BCRL, breast cancer-related lymphedema; SNLB, sentinel lymph nodes biopsy.

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Figure 1 Estimated position of lymph nodes draining the upper limb that in the era of less extensive ALND could be preserved independent to axillary reverse mapping and green area standard extension of ALND. ALND = axillary lymph nodes dissection



a recent review considering 5 randomized clinical trials published by CO et al; the identification rate of arm lymph nodes ranged between 79% and 94%. The improvement of ARM feasibility could be attributed to increase of physician expertise and the use of double or triple tracer to identify arm lymph nodes, as reported in recent analysis. Number of ARM lymph nodes detected using more than 1 tracer increases significantly, permitting a more complete identification of upper limb lymphatic pathways and better outcomes in term of BCRL.¹⁶

ARM effectiveness in preventing lymphedema is nowadays confirmed in many randomized clinical trials.^{15,16} There was a lower postoperative incidence of lymphedema in patients subjected to ALND and ARM, and rate ranged from 3% to 25%. Differently, postoperative lymphedema post standard ALND ranged from 15% to 33% in a recent analysis.¹⁵⁻¹⁷ Older reports showed higher incidence of lymphedema also in patients subjected to axillary surgery. This could be attributed in changes of ALND in recent years; currently, less extensive ALND are being performed which could lead to greater preservation of lymph nodes of the upper limb and consequent reduction of lymphedema rate (Figure 1). Despite the increase in ARM technical expertise and the improvement of fluorescence camera technology, the incidence of lymphedema has not been completely resolved.¹¹ This incomplete result could be related to a possible crossover between lymph nodes and vessels draining the upper limb and the gland as reported in many studies considering lymphedema after SNLB.¹⁸⁻²⁰

Oncological safety remains the most debated issue regarding ARM. Majority of studies reported to demonstrate oncological safety of ARM included patients with preoperative axillary lymph nodes clinically negative (cN0), and subjected to ALND due to metastasis of sentinel lymph nodes.⁹ In this group of patients, possibility of ARM node metastasization was low considering that roughly 93% of patients with positive sentinel lymph nodes presented maximum 1 or 2 other metastasized lymph nodes and smaller than 2mm (pN1a).²¹ Probably, according to the novel results

and the de-escalation of the axillary surgical approach, in this patients ALND could be omitted.

Some studies included patients with clinically involved lymph nodes but data considering ARM in patients subjected to neoadjuvant chemotherapy or locally advanced breast cancer, especially in the axilla (cN3), are poor and retrospective.⁹⁻²² In an interesting study, published in 2021, authors affirm the potentiality of ARM to avoid unnecessary removal of palpable nodes.²³ In our opinion definition of palpable lymph nodes is not enough to establish the risk of metastatization nodes; consistency, extent of disease, and subtype must be considered.²⁰ Due to the lack of information, and data supporting the oncological safety of ARM nodes preservation in cN+ patients; in our opinion suspicious lymph nodes should be removed. In 2022, a Turkish group analyzed ARM in patients subjected to neoadjuvant chemotherapy.²⁴ In their analysis, using a triple tracer to map the draining system, researchers considered the neoadjuvant systemic treatments as factor to reduce the metastatic involvement of the ARM lymph nodes.²⁴ Authors did not report pathological response status of axillary lymph nodes after the treatment. Recently, in accordance with the “less is more” approach: in case of axillary complete radiological response indication for ALND is shifting towards less invasive surgery as sentinel lymph nodes or target axillary dissection reducing the incidence of lymphedema.²⁵ The Turkish group concluded that further studies are needed to confirm the oncological safety in patients subjected to neoadjuvant chemotherapy undergoing ARM.²⁵ In our opinion, the group of patients that must be investigated in order to analyze the oncological safety of ARM after neoadjuvant chemotherapy are partial or no responder cases, which are the patients that really could benefit from this conserving technique.

Conclusion

In the era of axillary surgical de-escalation and reduction in the extension of ALND, lymph nodes draining the ipsilateral arm could be preserved independent to ARM. The efficacy of ARM to reduce incidence of lymphedema is demonstrated and should be offered to

all patients undergoing ALND in order to reduce the sequela and improve the quality of life, although in the coming future absolute numbers of ALND will decrease. Oncological safety of ARM should be investigated with large randomized clinical trials, especially in partial or no responder patients to neoadjuvant chemotherapy and in cN3 patients subjected to upfront surgery, who are the patients subjected to more extensive ALND and which can benefit from this conserving technique.

Author Contributions

GV and MP Conceptualization, Methodology, Formal analysis, design of the study, and equally contributed to the manuscript. MP writing original draft. MM review of the literature and data collection. OCB supervision. All the authors review and approval of the final version to be published.

Disclosure

The authors have stated that they have no conflicts of interest.

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