

# Axillary lymph node dissection in breast cancer patients: obsolete or still necessary?

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Given the decreased prognostic value of axillary staging, over the last decades, the role of axillary surgical staging has evolved considerably.<sup>1</sup> Several randomized clinical trials demonstrated that local control of the disease can be achieved without axillary lymph node dissection, even in the presence of minimal to moderate nodal involvement.<sup>2,3</sup> Despite systemic therapy is tailored to tumor intrinsic subtype, in some clinical conditions the decision of adding adjuvant treatments is still influenced by nodal status (Table 1).<sup>4</sup>

The RxPONDER trial demonstrated no benefit for chemotherapy in post-menopausal women with HR + breast cancer, 1 to 3 positive lymph nodes, and a low recurrence score ( $\leq 25$ ).<sup>4</sup> According to this result a surgical axillary staging plays a fundamental role on the identification of low-risk patients who may benefit from chemotherapy de-escalation. A recent long-term trial, monarchE, confirms the benefits of adjuvant abemaciclib added to endocrine therapy in patients with HR + breast cancer and  $\geq 4$  positive lymph nodes or 1–3 lymph nodes with histologic grade 3 disease or tumor size  $\geq 5$  cm.<sup>5</sup> Based on these findings, omission of axillary lymph node dissection in patients with HR + HER2-breast cancer could lead to under-staging and consequent undertreatments.

In this Issue of *The Lancet Regional Health – Europe*, Tove and colleagues evaluated the impact of axillary lymph node dissection omission on adjuvant chemotherapy in cN0 HR + HER2-breast cancer patients with positive sentinel lymph nodes in their secondary analysis of data from the SENOMAC trial.<sup>6</sup> Authors reported, in their double arm randomized clinical trial, no significant difference in the overall portion of patients receiving adjuvant chemotherapy with no impact on the five years recurrence free survival, despite the significantly higher rate of positive lymph nodes identified in patients subjected to axillary lymph node dissection considering a sample size of 2168 patients.<sup>6</sup> In this secondary analysis, Tove and colleagues subdivided the

cases according to menopausal status.<sup>6</sup> In premenopausal patients, axillary clearance did not impact adjuvant chemotherapy, probably due to the influence of breast cancer intrinsic subtype.<sup>6</sup> Differently, when the authors considered age of 50 years as the cut-off for menopausal status, they reported, in the post-menopausal sample, a significantly higher incidence of chemotherapy in patients subjected to axillary lymph node dissection, highlighting a possible under-staging and under-treatment for this category of breast cancer women if axillary lymph node dissection is omitted.<sup>6</sup>

Therefore, considering axillary lymph node dissection mandatory after a metastatic sentinel lymph node in women with HR + HER2-breast cancer could be an overtreatment due to the low probability of finding pN2 axillary staging in cN0 patients (ranging from 3.5% to 16% in published trials).<sup>2,3,7</sup> In fact, most patients who are at risk of having four or more positive lymph nodes usually have locally advanced breast cancer and clinically positive lymph nodes.<sup>7</sup> On the other hand, in patients who are candidates to abemaciclib, a second surgery for axillary clearance will delay adjuvant systemic therapy and therefore impair oncological outcome.<sup>7</sup> This controversy is not yet resolved, and it could be partly resolved by the use of ribociclib.<sup>8</sup> In fact, preliminary results of NATALEE trial support ribociclib added to endocrine therapy in patients with HR + HER2-, including pN0 patients, overcoming the need to perform axillary lymph node dissection to determine the need for CDK4/6 inhibitors. Axillary surgery, due to its related sequel, should be de-escalated; in concordance with Tove and colleagues, the development of new predictive tools and imaging technologies to determine axillary stage is needed.<sup>6</sup>

In the secondary analysis of SENOMAC trial data, authors reported a significant variation between countries and regions in the proportion of adjuvant chemotherapy due to the gradual implementation of de-escalating guidelines.<sup>6</sup> Although these results, of safe omission of axillary lymph nodes clearance after metastatic lymph node have been well demonstrated,<sup>2,3</sup> adherence to this de-escalation, out of the study trial, is believed to remain very low in routine clinical practice. These recommendations should be added to the guidelines as soon as possible, in order to achieve large-scale results and homogeneity in the treatments for breast cancer patients.

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Indication to adding chemotherapy to hormone treatment in luminal-like B breast cancer
Indication for regional node irradiation
Indication for abemaciclib in patients fulfilling monarchE criteria
Indication for dual anti-HER2 therapy
Indication to Olaparib in post-NeOCHT in patients BRCA+
Indication to type and duration of endocrine treatment in ER+ breast cancer

**Table 1: Clinical conditions where adjuvant treatments are influenced by nodal status.**

Despite oncological safety of axillary lymph nodes clearance, omission was reported in many trials. In order to obtain results that truly allow for safely avoidance of axillary lymph-node clearance with no risk of under-treatment, multidisciplinary randomized clinical trials involving surgeons, oncologists and radiation physicians should be performed. Furthermore, longer follow-ups are needed, considering that events occur gradually over 10–15 years in patients with HR + HER2-breast cancer.

#### Contributors

GV conceptualized and wrote the commentary and direct literature data discussion. MP performed literature revision and discussed the literature data and contributed to the final manuscript. OCB supervision, discussed the literature data and contributed to the final manuscript. All the authors review and approved the final version.

#### Declaration of interests

All the authors declare that they have no potential conflict of interest.

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