EDITORIAL
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Peritumoral infiltration of local anesthetic before surgery in early breast cancer: a comment

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ABSTRACT

This is a comment on a study recently published about peritumoral infiltration of local anesthetic before surgery in early breast cancer. Previously, animal models and a randomized study for stage IV breast cancer patients inferred that the removal of the primary tumor resulted in increased growth factors and worse distant disease control. Therefore, breast cancer surgery might not be a strictly local intervention. In this new randomized study, the intervention was a peritumoral infiltration of local anesthetic — lidocaine 0.5% in the six tumor margins, as an attempt to limit the systemic repercussions of surgery. Although the adjuvant treatment available for the study seems outdated, leading us to question the external validation, limited resources may have increased the power of surgery. Unknown mechanisms during surgery can change the patient's journey, and it is our duty to look at surgical studies with due seriousness.

KEYWORDS: breast neoplasms; mastectomy; mastectomy, segmental; lidocaine.

EDITORIAL

This is a comment on a study recently published in the *Journal of Clinical Oncology* (JCO) about peritumoral infiltration of local anesthetic before surgery in early breast cancer[1]. The Indian group led by Dr. Rajendra Badwe is the same group that published, in 2014, a randomized study on primary site surgery for stage IV breast cancer[2]. In that study, patients in the upfront surgery group had worse distant disease-free survival (DFS). Similarly, in animal models, the removal of the primary tumor resulted in increased growth factors and worse distant disease control. It was then hypothesized that breast cancer surgery is not a strictly local intervention but has systemic consequences. This study, as well as studies on animal and experimental models, reinforces the need and interest in further well-designed studies to clarify the mechanism of lidocaine as a protective factor.

Badwe et al.[1] considered an intervention that could limit the systemic repercussions of surgery. The proposed intervention was a peritumoral infiltration of local anesthetic — lidocaine 0.5% in the six tumor margins. A total of 1,600 breast cancer patients with axillary staging N0 or N1 and eligible for upfront surgery were randomized 1:1 for peritumoral infiltration or conventional surgery.

The primary outcome was 5-year DFS. In the experimental and control groups, the 5-year DFS was 86.6% and 82.6%, respectively (hazard ratio (HR)=0.74, 95%CI 0.58–0.95, p=0.017). The secondary outcome was overall survival, with 90% in the lidocaine group and 86.4% in the control group (HR=0.71, 95%CI 0.53–0.94, p=0.019).

The absolute DFS difference found (4%) is below the minimum expected difference (7%) that was used for statistical design. The relative difference (HR) was also overestimated in the original protocol (estimated HR=0.68 and real HR=0.74). However, the number of events was also lower than expected (538 expected and 225 events found). Recruitment was slow and the protocol was amended to allow for an interim review. In any case, the DFS finding was positive with a significance below p=0.024, the alpha level established after the interim analysis.

By correspondence, Dr. Badwe stated that they did not systematically use ultrasound to guide the infiltration, as most of the tumors were palpable (mean size, 3 cm). The criterion for determining whether the infiltration was correct was the inability to use diathermy due to excess water content.

The study was open-label. The group did not consider the possibility of saline injection in the control group, for blinding

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purposes. Data on margins and weight of the specimens were not collected. Despite being defined as open-label, Dr. Badwe also stated that the team maintaining follow-up was not aware of the randomization.

Factors such as age, menopausal status, staging, molecular subtype, type of surgery, and adjuvant treatments were well balanced between groups. Approximately 36% of the patients underwent mastectomy, and 80% underwent adjuvant radiotherapy. Approximately 67% of patients underwent axillary dissection. Only 35% of all patients with overexpressed HER-2 received targeted therapy. This treatment seems outdated, leading us to question the external validation of the study for our population. However, limited adjuvant therapies may have increased the power of surgery.

A recent literature review by Zhang et al. summarizes clinical evidence and data from randomized trials that suggest the role of local anesthetics in inhibiting tumor progression[3]. This study by Badwe, as well as studies on animal and experimental models, reinforces the need and interest in further well-designed studies to clarify the mechanism of lidocaine as a protective factor.

It is too early to assess whether these findings will change our practice. Three factors can hinder surgeon adherence: infiltration impairs thermal dissection, infiltration has to be associated with intraoperative ultrasound for non-palpable tumors, and finally it was not tested after neoadjuvant therapy.

The JCO editorial that accompanied the article brings a reflection: "The administration of peritumoral lidocaine before surgery resulted in a 4% DFS benefit at 5 years which is not that dissimilar from benefit we see from many systemic therapies that carry potential toxicity risk"[4]. The editorial concludes by saying that "it seems reasonable to introduce this intervention as an easy, cost-effective intervention" and that "additional investigation will be required to elucidate the mechanism of this benefit."

Therefore, unknown mechanisms during surgery can change the patient's journey, and it is our duty to look at surgical studies with due seriousness. Finally, two lessons remain: surgery has power and the slightest thing can make a difference.

AUTHORS' CONTRIBUTION

JFB: Conceptualization, Methodoloy, Project administration, Writing – original draft. MMM: Conceptualization, Supervision, Validation, Writing – review & editing. JLBB: Conceptualization, Supervision, Validation, Writing – review & editing.

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