Editorial

Axillary surgery in the case of limited involved axillary lymph nodes

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In the manuscript of *Gland Surgery*, Vernet-Tomás and colleagues are presenting the results of a pilot phase of the Multimodal Targeted Axillary Surgery (MUTAS) trial (1). All 25 patients with early breast cancer trial had biopsy-proven involvement of axillary lymph nodes and suspicious lymph nodes on axillary ultrasound. The maximum number of suspicious lymph nodes on axillary ultrasound was three. In 14 cases lymph nodes were also palpable. In the setting of upfront surgery, patients with biopsy-confirmed nodal involvement, usually receive axillary lymph node dissection (ALND). To investigate the accuracy of sentinel lymph node biopsy (SLNB) in this population, the authors performed both SLNB and ALND. The result of the SLNB in this situation was not reliably predicting the additional axillary tumor burden with a false negative rate (FNR) of 28%. Neither for the subgroup of patients with non-palpable axillary involvement (FNR 36%) nor for the subgroup of patients with palpable axillary nodes (FNR 21%) a benefit of SLNB in this situation could be demonstrated (1). In case of an acceptably low FNR this trial could have been hypothesis generating and would have paved the path for clinical trial deescalating axillary surgery by the use of SLNB also in case of upfront surgery and "clinically" involved lymph nodes.

The question is allowed why such a trial was necessary and even more why the authors of this editorial are convinced it is good these data are out now.

In case of one or two involved lymph nodes the recommendation of the National Comprehensive Cancer Network (NCCN) is to perform only SLNB based on the results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial (2). In the ACOSOG Z0011 trial the omission of ALND had no impact on the oncological outcome in cases of one or two involved sentinel lymph nodes (SLN) (3). The conclusion drawn by the NCCN to transfer these data to the situation of pretherapeutically involved lymph nodes is considered immature by some experts (4). We also believe that it is at least questionable to extrapolate the results of a trial demonstrating no harm from the omission of ALND in case of one or two involved SLN (i.e., clinically negative according to the definition used in the study protocol) to the setting of one or two clinically involved lymph nodes diagnosed prior to begin of therapy. According to a survey conducted in the United States half of the breast surgeons are still favoring ALND in case of any macrometastases in a sentinel node (5). This demonstrates that not even in the situation where the safety of de-escalation is proven with a 10-year follow-up it is common practice among breast surgeons to spare patients the side effects of ALND.

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In contrast to these data from the US survey, a statement of the European group of breast surgeons [European Breast Cancer Research Association of Surgical Trialists (EUBREAST)] describes the omission of ALND in cases of nodal involvement limited to the sentinel nodes as widely accepted (6). Although the authors of this editorial align with that standpoint and do recommend omission of ALND if the ACOSOG Z0011 criteria are fulfilled, we suggest caution when transferring the results of Z0011 to settings not investigated (or underrepresented) in the trial. The authors of the pilot phase of the MUTAS trial have demonstrated this caution to be justified.

The NCCN clearly defines who in their view should be treated by SLNB and that population is not simply the ACOSOG Z0011 population. In the ACOSOG Z0011 trial the patients were not allowed to have "*palpable adenopathy*" (3), whereas the population described in the NCCN guideline is "…*≤2 suspicious lymph nodes on imaging or ≤2 positive lymph nodes confirmed by needle biopsy*…" (2). This definition raises the question of how to define suspicious axillary lymph nodes prior to therapy. We strongly believe that with an FNR of up to 45% (7) palpation alone as performed in the ACOSOG Z0011 trial is inadequate. Axillary ultrasound can be an extremely helpful tool in the diagnostic work-up of the axilla before therapy (8) and yields negative predictive values up to 20% (9). However, even in adequately staged patients including ultrasound the rate of clinically occult sentinel node metastases is—depending on the tumor biology and the use of neoadjuvant treatment—up to 39.7% (10,11), there are even reports about gross nodal disease not detected before surgery and diagnosed by computed tomography for planning the radiation therapy (12). But if we perform preoperative staging examinations that do differ from the ACOSOG Z0011 trial and that are more accurately detecting patients with involved lymph nodes, we also have to ask ourselves if the NCCN approach may be immature but nonetheless a brilliant idea because there are also data that the high detection rate of preoperative ultrasound may convert more than 50% of the patients from clinically negative to clinically positive and in case of an axillary dissection performed because of these result may lead to an overtreatment of these patients if the ACOSOG Z0011 criteria are applied (13). It may be tempting to simply apply the criteria of the ACOSOG Z0011 trial to a population diagnosed by ultrasound. But we must not forget that the patients in the Z0011 trial received SLNB because they were considered clinically negative. It is far from clear that it is allowed to conclude from these data that SLNB is a safe option in a population that is considered clinically positive (although diagnosed by different means). The authors of the MUTAS trial have demonstrated that this may lead to a dangerous underestimation of the nodal extent and that the recommendation of the NCCN is not the solution to this dilemma. The only solution we do see is investigating the question of surgical de-escalation in patients with one or two involved lymph nodes diagnosed before upfront surgery (not SLN) in prospective clinical trials.

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