Until the early 90's, axillary lymph node dissection (ALND) was part of standard care for all breast cancer patients. ALND mainly served as a staging method, since lymph node involvement is an important prognostic factor, but also served to guide adjuvant treatment options and to provide regional control. From clinically node negative (cN0) patients included in the B04 trial, it became clear that although 40% had involved lymph nodes in the ALND specimens, only 19% of patients in whom ALND was omitted developed clinically relevant axillary disease (1,2). These patients underwent a “delayed” ALND without impacting long-term prognosis. In the 90's, the sentinel lymph node biopsy (SLNB) was introduced for axillary staging in breast cancer. In case of a negative SLNB, the risk of metastases in the remaining lymph nodes appeared to be negligible. Hence, cN0 patients without any involvement in the SLN(s) can be spared the morbidity of an ALND. Following results from three landmark trials (ACOSOG Z0011 (3), IBCSG 23-01 (4) and AMAROS (5)), indications for an SLNB-only approach extended to patients with only limited involvement of the SLN(s). These trials included large numbers of patients (ranging from 891 to 4806 patients). The main drawbacks of these trials are that mastectomy patients were not well represented and T3 tumors were not included as were patients treated with neoadjuvant systemic treatment. The vast majority of patients in these trials had only 1 positive SLN. In the Z0011 trial, 50% had micrometastatic SLN-involvement and in the IBCSG 23-01 (which only included micrometastases) 70% had SLN-involvement with metastases smaller than 1 mm. 

Chauhan et al. also focus on patients with limited SLN-involvement (6). A total of 1152 cN0 breast cancer patients that underwent SLNB were retrospectively identified from a single institution. Approximately 20% of these patients had SLN-involvement, of whom the majority (67%) had macrometastatic involvement and 32% had micrometastatic involvement (the remainder had isolated tumor cells only). In 62 of 72 patients with micrometastatic SLN-involvement, an ALND was performed. Only 9 of these patients (14.5%) had additional positive lymph nodes in the ALND specimen. On univariate analysis, no factors could be identified that significantly predicted the presence of additional positive non-SLN(s) in the case of micrometastatic SLN-involvement. In case of macrometastatic SLN-involvement, a significantly higher number of patients had additional positive lymph nodes in the ALND specimen (27.7% vs. 14.5%, P=0.029). These findings are consistent with reports from previous studies. The study by Chauhan et al. is mainly limited by the small number of included patients with a positive (micrometastatic) SLNB. Furthermore, it is unknown if axillary ultrasound was always part of the diagnostic work-up. In practices where axillary ultrasound is routinely performed, it is known that pathologic axillary disease is limited to the SLN(s) in the majority of cN0 patients.

In light of the results from trials like Z0011, missing positive non-SLN(s) seems clinically irrelevant in patients with only limited (micrometastatic) SLN-involvement. Several guidelines mention that adjuvant regional...
treatment (ALND and/or radiotherapy) is not indicated in case of micrometastatic SLN involvement in patients treated with breast conserving surgery followed by whole breast irradiation and adjuvant systemic treatment (7-9). Importantly, the presence of extensive axillary lymph node involvement is likely related to aggressive tumor biology and therefore may rather indicate the need for additional systemic treatment than the need for more extensive axillary surgery (since extensive surgery may not compensate for adverse tumor biology). Several trials are currently further addressing the clinical relevance of adjuvant surgery in cN0 patients with SLN-involvement (see Table 1). The authors already mentioned the POSNOC trial, in which cT1cN0 patients with macrometastatic SLN-involvement in 1 to 2 nodes are randomized between adjuvant treatment alone versus adjuvant treatment with ALND or radiotherapy (10). Patients undergoing neoadjuvant systemic treatment are also included, in which case the SLNB has to be performed prior to systemic treatment. In the Italian SINODAR ONE trial (11), cT1-2cN0 patients, again with macrometastatic SLN-involvement in up to 2 nodes, are randomized between ALND or no ALND. In the Swedish SENOMAC trial (12), the same patient group is included (including T3 tumors), and again randomized between ALND or no ALND. In all trials, patients undergoing mastectomy are included. These trials are expected to address shortcomings of trials like Z0011 and will hopefully provide us with definite answers. Depending on these results, the presence of non-SLN involvement may no longer be relevant in case of limited SLN-involvement, but even in the case of macrometastases.

Another very interesting and relevant question is, whether SLNB itself may be redundant in selected cN0 patients. Several trials are currently investigating a “no axillary surgery” approach in cN0 patients (see Table 1). In the Dutch BOOG 2013-08 trial (13), cT1-2cN0 patients undergoing breast conserving surgery are randomized in a 1:4 ratio between no SLNB or SLNB. In this trial, patients in the SLNB-group undergo a second randomization to ALND or no ALND in case of 1 to 3 macrometastatic SLN(s). The SOUND trial (15) includes cT1cN0 patients scheduled for breast conserving surgery with whole breast irradiation and randomizes patients (with a negative axillary ultrasound or negative FNA) between

<table>
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<tr>
<th>Study</th>
<th>Inclusion criteria</th>
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<th>Primary endpoint</th>
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<tr>
<td>INSEMA</td>
<td>cT1–2, breast conserving surgery with whole breast irradiation</td>
<td>SLNB vs. observation [in patients with a positive SLNB a second randomization follows (ALND vs. no ALND)]</td>
<td>Adjuvant</td>
<td>Invasive disease-free survival at 5 years</td>
<td>Recently finished accruing (≥6,000)</td>
<td>≥60</td>
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<tr>
<td>SOUND</td>
<td>cT1, breast conserving surgery with whole breast irradiation</td>
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<td>Distant disease-free survival</td>
<td>Finished accruing (1,464)</td>
<td>60</td>
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<tr>
<td>BOOG 2013-08</td>
<td>cT1–2, planned for breast conserving surgery</td>
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<td>1,160/1,644</td>
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<tr>
<td>POSNOC</td>
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<td>Axillary treatment (ALND or RTx) or no axillary treatment</td>
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<td>Target 1,900</td>
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<tr>
<td>SINODAR ONE</td>
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<tr>
<td>SENOMAC</td>
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<td>Adjuvant or neoadjuvant</td>
<td>Breast cancer specific survival at 5 years</td>
<td>Target 3,500</td>
<td>≥60</td>
</tr>
</tbody>
</table>

* all are multicenter randomized controlled trials. SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.
SLNB or no SLNB. In patients with macrometastatic SLN-involvement, an ALND is mandated. In these last two trials, patients treated with neoadjuvant systemic treatment are not included. With the increasing use of neoadjuvant systemic treatment, also in patients with early stage breast cancer, we should keep in mind that trials like Z0011 did not include patients treated with neoadjuvant systemic treatment. Results of these trials should therefore not be extrapolated to the neoadjuvant setting, as positive SLNs detected after systemic treatment indicate resistant disease that likely requires further adjuvant treatment.

In conclusion, axillary management is continuously evolving. Which patients may benefit from an ALND and which patients may even safely avoid any axillary surgery needs further clarification. Chauhan et al. emphasize that patients should be informed adequately by their treating physicians concerning pros and cons of limiting axillary surgery. This remains pivotal to warrant a legitimate process of shared decision making, whilst awaiting results of ongoing trials.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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