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Lessons from the SOUND trial and future perspectives on axillary staging in breast cancer

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The SOUND (Sentinel node *versus* Observation after axillary ultra-soUND) randomized trial[1] was conceived right after the ground-breaking data of the Z-0011 trial[2] had demonstrated that there was no oncological benefit to performing axillary lymph node dissection (ALND) after breast-conserving therapy when the sentinel lymph node was involved. Because there was some initial reluctance to accept the results, several confirmatory trials[3–5] were launched across Europe. In contrast, pursuing a spark lit by Professor Umberto Veronesi, this author designed the SOUND trial[6,7] as a natural continuation of Z-0011 to determine whether it might be possible to avoid axillary surgery entirely, and whether imaging might eventually replace surgery as the axillary staging procedure. Although the first question had already been raised[8,9], interest in obtaining the answer had waned owing to the introduction of sentinel lymph node biopsy (SLNB), an elegant, minimally invasive procedure that provides the same staging power as ALND[10].

The results from the SOUND trial clearly confirmed that axillary surgery, and even SLNB, can be omitted entirely for patients with small breast cancers, without any detrimental effect in terms of distant disease-free survival at 5 years[1]. This is exactly what the authors expected to find when the trial was initiated. It was not, however, expected that the data would be this excellent in terms of number and distribution of events. The cumulative incidence of isolated axillary recurrences at 5 years was 0.4% in the no-axillary surgery arm. In the whole cohort, only 2% of patients developed distant relapse, 1% developed a local breast relapse, and 1% developed contralateral breast cancer. No patients died from breast cancer as a first event. It is interesting to note that the most frequent oncological event found during this trial was the diagnosis of other malignancies unrelated to breast cancer (approximately 3%)[1].

These findings imply that axillary surgery can be avoided without harming patients, but raise another question. How do we decide which individuals could avoid this procedure without missing relevant information? Multidisciplinary efforts must be made to define which patients' postoperative treatment plans would not be affected by omitting the SLNB procedure. The data from the SOUND trial are in line with the Choosing Wisely campaign[11]; therefore, patients aged over 70 years with small oestrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer, at the very least, should be spared SLNB. With some variation according to country, 20–25% of women with breast cancer could safely avoid this procedure with minimal risk of medical or radiation therapy undertreatment. Moreover, patients presenting with SOUND-like features can be reassured that, for the first 5–6 years after surgery, the risk of recurrence is extremely low with proper interdisciplinary management. These data reinforce the importance of undergoing screening programmes to achieve early diagnosis and save lives. Finally, the excellent outcome data mentioned above provide evidence that the number of follow-up examinations can be reduced, which in turn implies reduced psychological distress for the patients as well as lower costs for national health systems.

Another important finding is how an inexpensive diagnostic procedure like ultrasound imaging performed during the preoperative evaluation was able to rule out substantial nodal burden in the axilla. Only 13.7% had positive nodes in the SLNB arm. Of these patients, 11.7% had just one positive node and only 0.6% had four or more positive nodes. This latter finding appears to be critical for determining whether to extend axillary surgery for a potential prescription of abemaciclib or olaparib[12,13]. Patients with SOUND-like criteria have a less than 1% likelihood of having four or more positive nodes, and therefore should not be treated with ALND in case a positive SLNB is found.

This leads to the point, bringing us back to what we have known for decades[14], that lymph node surgery is just a staging procedure. In the SOUND trial, adjuvant treatment recommendations did not differ between the two study groups. A similar rate of patients received chemotherapy as well as all other medical and radiation therapy treatments. Things have however changed greatly over the past few years; a greater variety of treatment options are now available compared with the situation a decade ago, and there will be newer treatments in the near future. Therefore, the next challenge is to better understand what level of information is required to provide the best treatment option for each patient. It seems a bit anachronistic in this era of biological and genomic characterization of the tumour, with an increasing role of liquid biopsies, to still be relying on nodal status to tailor postoperative treatments. For this reason, it appears likely that the impact of surgical staging will be reduced progressively until it eventually disappears. The role of axillary surgery, although perhaps not the immediate future, will

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probably be restricted to a limited number of clinical scenarios, such as in the infrequent occurrence of a bulky nodal relapse or where primary medical treatment does not provide a complete response.

The final lesson concerns the present and future of clinical research in the field of breast cancer surgery. The SOUND trial was managed with extremely limited funds, which would not even be sufficient to start a clinical study today. It took the authors more than 5 years to recruit 1463 patients in 18 centres, some at high-volume institutions. Additional projects with a similar study design were later launched in other European countries, such as the INSEMA trial[15] in Germany or BOOG 13-08[16] in the Netherlands, confirming the need to plan and coordinate the next generation of trials at an international level in the hopes of avoiding duplication, sparing resources, and reducing the time required to complete accrual and eventually collect data.

In fact, these are the very reasons why EUBREAST (EUropean Breast cancer REsearch Association of Surgical Trialists) was founded[17]. EUBREAST currently has several international trials actively recruiting under its umbrella (http://www.eubreast.org). For example, the AXSANA trial[18] was designed to understand what should be considered the proper axillary surgical management of patients with positive nodes converting to node-negative after primary systemic therapy. Over 4500 patients were enrolled in less than 3 years with 288 centres actively recruiting around the world. These figures confirm that coordinated planning and international cooperation are the key elements to move forward.

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Data availability

No new data were generated or analysed in support of this research.

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