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Viewpoints and debate

Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: **S**entinel node vs **O**bservation after axillary **U**ltraSou**ND**)

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VIEWPOINTS AND DEBATES

Sentinel lymph node biopsy (SLNB) is the standard approach for axillary staging in patients with early breast cancer. Recent data showed no outcome difference in patients with positive sentinel node between axillary dissection vs no further axillary surgery, raising doubts on the role of SLNB itself. Therefore, a new trial was designed comparing SLNB vs observation when axillary ultra-sound is negative in patients with small breast cancer candidates to breast conserving surgery.

The Z0011's bomb

Sentinel lymph node biopsy (SLNB) is the standard approach for axillary staging in patients with breast cancer worldwide[1] and the clear trend of breast cancer treatment is tending towards minimizing axillary surgery, even in the presence of sentinel lymph node (SLN) involvement.

Giuliano et al.[2,3] recently reported the results of the Z0011 Trial designed by the American College of Surgeons Oncology Group (ACOSOG) which randomized patients with 1-2 positive SLNs to receive either axillary lymph node dissection (ALND) or no further axillary surgery. The publication of these data exploded like a bomb over the surgical community. Even though the early interruption of accrual made this study theoretically underpowered to completely fulfil the primary endpoint (Overall Survival), the clinical relevance of these data is in no way diminished by statistical evaluations. They confirm that removal of lymph nodes does not have curative intent as previously pointed out by prospective randomized clinical trials carried out in the pre-SLNB era.[4–6] Furthermore, the results showed that excellent local control can be achieved foregoing ALND in the presence of SLN involvement (1% axillary relapse after 6.3 years of median follow up).

However, our interpretation of these data is that the concept itself of the SLNB lost much of its importance. In fact, SLNB was developed as a method to obtain information on axillary lymph node status allowing surgeons on the one hand to spare the morbidity of axillary clearance in patients with negative nodes, and on the other hand to identify patients with positive nodes as candidates for a wider surgical extent. The Z0011 trial showed that there is no outcome advantage in dissecting the axilla in the presence of positive SLN, meaning not only that wider surgery in the axilla is not improving outcome but also that the information achieved by removing lymph nodes does not change the prognosis of the disease.

Moreover, to date the impact of prognostic information of axillary lymph node status on the decision-making process is less important than it was in the past as the adjuvant treatment is more and more tailored towards the biological features of the disease rather than on the risk of recurrence.[7] In the AMAROS trial which randomized patients with positive SLNs to receive either axillary clearance or axillary radiotherapy, the type of adjuvant treatment did not change between the two groups[8] suggesting that detailed information on axillary status is not going to change treatment recommendations.

So, if axillary reappearance is lower than expected in patients with negative SLNBs,[9] if an excellent local control can be achieved without dissecting the axilla even in patients with positive SLNs,[2] and if the information on extent of nodal involvement does not change type of treatment[8] and mostly nor does it change prognosis,[3] the following questions immediately arise: do we really

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need to look for a SLN? Do we really need the information obtained by identifying and examining the SLN?

Biological and clinical meaning of minimal SLN involvement

Another important point is the clinical meaning of SLN micrometastases. In fact, after SLNB entered into routine clinical practice, diagnoses of micrometastases markedly increased[10] due to an extensive evaluation of the SLN. However, the prognostic impact of micrometastases in the SLN seems to be reduced if compared to the role of micrometastases diagnosed in the pre-SLN era. In fact, data from our institute[11] has shown that the presence of a single micrometastatic lymph node is associated with a higher risk of distant recurrence as compared to node-negative disease only for patients undergoing ALND for staging purposes but not for patients staged with SLNB. These data led the authors to conclude that treatment recommendations for systemic therapy should not take into account the presence of a single micrometastatic lymph node identified during complete serial sectioning of sentinel node. Similar data were published by Hansen et al[12] reporting the outcome of patients with micrometastases in the SLN being similar to node negative patients.

Recently the accrual was completed of a trial launched by the International Breast Cancer Study Group (IBCSG) which explored the significance and the biological impact of micro-metastases in the SLN. Patients with micro-metastases in the SLN were randomized to receive either ALND or no further axillary treatment (neither surgery nor radiotherapy). Meanwhile, results from our institute[13] proved excellent OS (97% at 5 years) and low axillary relapse cumulative incidence (1.6% at 5 years) foregoing axillary dissection in the presence of SLN micrometastases.

Therefore, if the presence of micrometastases in the SLN need not be considered when deciding recommendations for systemic treatment[11] and if in the presence of limited involvement of the SLN[2,3,13] axillary dissection can be spared, the following questions arise: do we really need to look for minimal SLN involvement? If not, should we try to switch from a surgical staging method to an imaging method of staging the axilla capable of diagnosing relevant nodal involvement?

The next step

Therefore, at the European Institute of Oncology of Milan we designed the SOUND trial (**S**entinel node vs **O**bservation after axillary **U**ltra-Sou**ND**) which is a prospective randomized controlled multicentric study representing a further step forward in the conservative approach to breast cancer aimed at improving patients' quality of life.

Eligibility and exclusion criteria are listed in Tables 1 and 2. In this trial (Fig. 1) patients with breast cancer smaller or equal to 2 cm, who are candidates for breast-conserving surgery and with a clinically negative axilla will undergo an axillary ultra-sound in order to rule out an evident or suspicious nodal involvement.

Table 1
SOUND trial: Eligibility criteria.

- Breast cancer $\leq$2 cm, and a clinically negative axilla
- Any age
- Candidates to receive breast conserving surgery + radiotherapy
- Negative preoperative assessment of the axilla (ultrasound with or without FNAC in case one doubtful node is found)
- Written informed consent must be signed and dated by the patient and the investigator prior to inclusion.
- Patients must be accessible for follow-up.

Table 2
SOUND trial: exclusion criteria.

- Synchronous distant metastases
- Previous malignancy
- Bilateral breast cancer
- Multicentric or multifocal breast cancer
- Previous primary systemic therapy
- Pregnancy or breastfeeding
- Pre-operative diagnosis (cytology or histology) of axillary lymph node metastases
- Pre-operative radiological evidence of multiple involved or suspicious nodes
- Patients with psychiatric, addictive, or any disorder, which compromises ability to give informed consent for participation in this study.

Patients showing a single doubtful (not suspicious) lymph node will undergo an ultrasound-guided fine needle aspiration cytology. Patients with either negative cytology of the single doubtful lymph node or with negative ultrasound of the axilla will be eligible for randomization into two groups:

1. SLNB $\pm$ axillary dissection
2. No axillary surgical staging

In arm 1, no axillary dissection will be performed in the case of either negative SLN or in the presence of isolated tumour cells or micrometastases. SLNB will be completed by axillary dissection in the presence of macrometastases diagnosed in the SLN.

Primary endpoint of the trial is distant disease-free survival. This endpoint, a proxy of overall survival, will allow reliable results to be obtained in a shorter period of time compared to overall survival. Secondary endpoints will be the cumulative incidence of distant recurrences, the cumulative incidence of axillary recurrences, the disease-free survival (DFS) and the overall survival (OS). Other secondary endpoints are quality of life and evaluation of type of adjuvant treatment administered.

Overall, 1560 women (780 per arm) will be enrolled to decide whether the group without treatment of the axilla is no worse than the reference group, given a margin Δ of non-inferiority of 2.5% (maximum tolerable 5-years DDFS = 94%).

There are several concepts behind this study. First the acknowledgement that imaging may play a role in axillary staging. Secondly, we are convinced that decisions on adjuvant systemic treatment should be taken considering the prediction of response rather than prognosis as this attitude reflects a higher probability for the patient to benefit from a certain type of treatment. Finally, a less invasive surgery associated with a more tailored medical approach is aimed at improving patients' quality of life.

Therefore, the hypotheses of this trial are that:

1. Avoiding axillary surgery is not worsening the outcome of patients with small breast cancer
2. The absence of pathological information regarding the risk of recurrence given by nodal status is not leading to a worse outcome of these patients
3. Pre-operative imaging of the axilla can identify patients with a clinically relevant nodal burden.

Closing observations

Ultrasound is a simple method of preoperative assessment which to date has never been routinely and prospectively used to address this issue. However, the presence of adipose tissue in the axillary cavity may represent an intrinsic limitation to this type of imaging method. Nevertheless, increasing expertise on this specific topic, low costs, absence of radiation exposure and easy

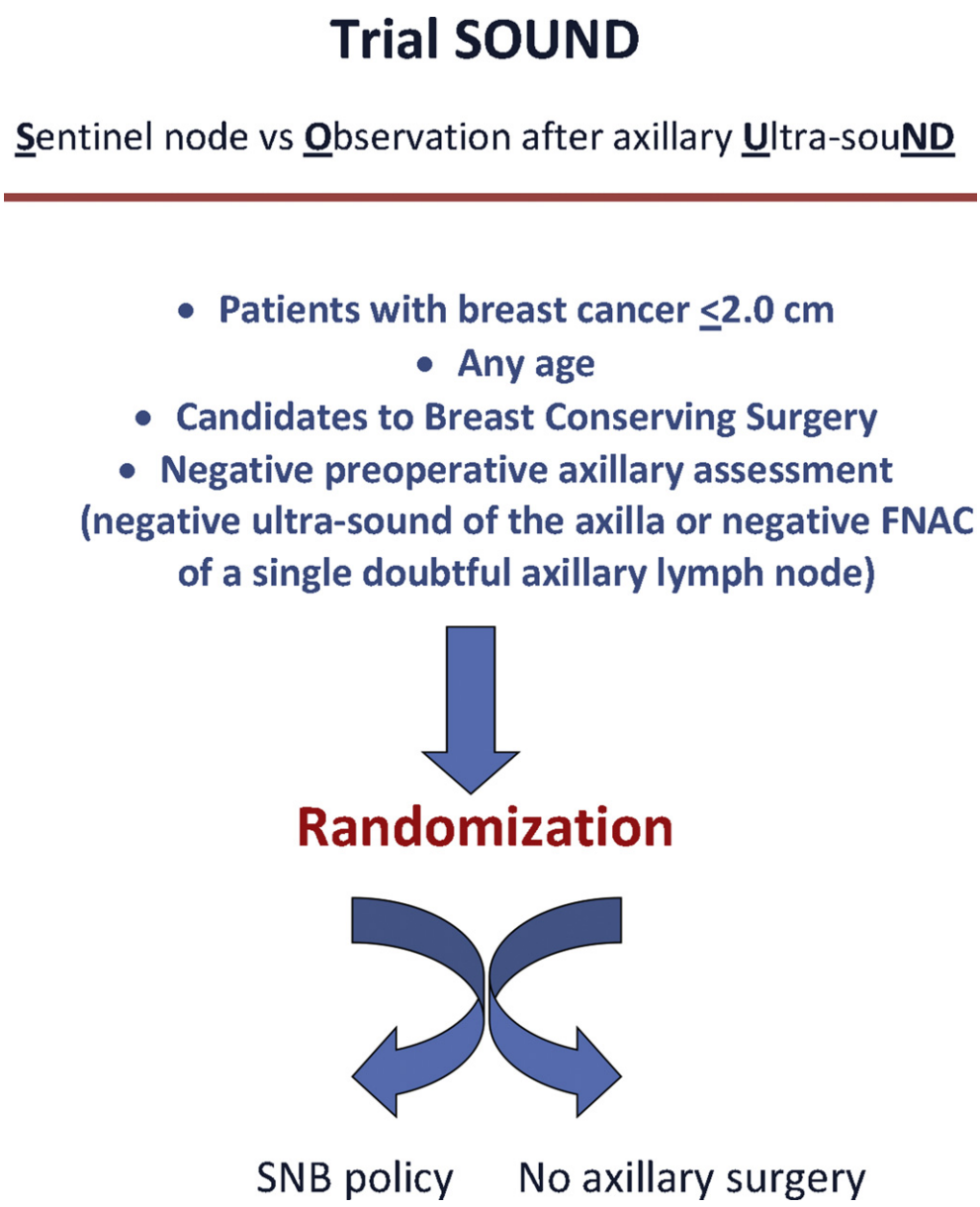

Fig. 1. SOUND trial: study design.

applicability also in conjunction with Fine Needle Aspiration and Cytology (FNAC) make ultrasound an interesting method of readily assessing the axilla prior to surgery. Obviously it is not possible to compare the staging power of extensive histological analysis of the SLN with this imaging modality, but in our opinion this trial will yield important information regarding the possibility of screening patients for sub-clinical axillary relevant disease.

This prospective randomized trial also represents an excellent opportunity to explore the importance and role of stem cells. In fact, cancer samples from patients entering the trial are being stored for future analysis in order to evaluate whether the expression of a stemness signature in cancer cells might be relevant in cancer progression and recurrence.

The European Institute of Oncology of Milan, Italy is leader and promoter of the SOUND trial which was launched within a collaborative group named SOLE (Senologia Oncologica Lombarda di Eccellenza – "Oncological Senology Excellence in Lombardy"). After the study launch of February 2012, a number of other Italian centres have voiced their intention to join this trial soon, and we are available to extend the frontiers of co-operation.

Conflict of interest statement

We declare no conflicts of interest.

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