OXYGENATE

(nO aXillarY surGEry iN early breAsT cancEr international prospective registry study)

Prospective multicenter registry specifically for patients who have undergone surgery for primary breast cancer without undergoing sentinel lymph node biopsy. The main objective of this registry is to collect detailed, real-world data on the outcomes of this therapeutic approach, providing information on its clinical effectiveness when sentinel lymph node biopsy is omitted.

Study protocol

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Version 2.0
20.06.2025
12 pages

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1. Background

For many decades, sentinel lymph node biopsy (SLN) has been the standard of care in early breast cancer. In recent years the publication of the ACOSOG Z0011, (1, 2) showed that there was no advantage in performing axillary lymph node dissection (ALND) compared with not performing ALND, even when up to 2 sentinel nodes are positive, for patients receiving breast-conserving surgery, adjuvant radiotherapy, and medical treatment, In the study, 23.7% of the control group (ALND) patients had additional metastatic lymph nodes other than sentinel nodes. However, the axillary recurrence rate or DFS did not differ in the SLN only and control groups. (1)These findings raise questions about the need to remove sentinel lymph nodes, especially in patients who undergo breast-conserving surgery and whole-breast radiation.

The Sentinel Node versus Observation after Axillary Ultrasound (SOUND) trial was a prospective, multi-national noninferiority phase 3 study, which randomized patients with a negative preoperative axillary ultrasound (US) to SLN or no axillary surgery, prior to breast conserving surgery (BCS). (3) The primary focus of the study was to determine the oncological outcomes in patients with negative ultrasound results who avoided SLN. The results showed that there were no significant differences in survival or axillary recurrences. 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 a distant relapse, 1% developed a local breast relapse, and 1% developed contralateral breast cancer. Interestingly, the diagnosis of other malignancies unrelated to breast cancer (approximately 3%) was the most frequent oncological outcome. (3)

Furthermore, only 13.7% of the patients treated with SLN had positive lymph nodes, with 11.7% having just one. Patients have only a likelihood of 0.6% of having four or more positive nodes, and therefore should not be treated with ALND in case a positive SLN is found.

Other international trials have backed up these findings. Both the NAUTILUS (4) trial and the INSEMA (5) trial confirmed that management of patients with N0 on ultrasound can be carried out without axillary surgery, leading to improved survival outcomes and fewer complications. Likewise, omission of axillary surgery was reported to be both safe and improve health-related quality of life in the IIT 2015-06 Chung-SNBO trial(6) in South Korea and the BOOG 2013-08 study (7) in the Netherlands. The totality of the evidence from these studies suggests that in early-stage breast cancer, the minimally invasive approach with omission of sentinel lymph node biopsy can be a suitable solution that improves postoperative outcomes for patients.

Axillary ultrasound (AUS) is the method of choice worldwide to assess lymph node involvement in patients with known or suspected breast cancer.(8) With advances in imaging techniques, the accuracy of AUS to predict axillary status with or without node biopsy has increased significantly. According to the literature, US can be highly specific if morphologic characteristics are used, with a sensitivity ranging from 26% to 76% and a specificity of 88%–98% for nonpalpable metastatic lymph nodes. (9) The accuracy of AUS can be improved with image guided biopsy.

With the publication of the SOUND and the INSEMA trial, several questions have been raised related to the selection of adjuvant treatment in those patients with omitted SLN.
The changing in clinical practice after the publication of these trials are being implemented and, in some Institutions, patients with a negative clinical exam and negative axillary ultrasound, postmenopausal, age ≥ 50 years, with grade 1–2, ER positive > 10%, T1, non-lobular invasive breast cancers and a Ki-67 < 20% , no longer require SLNB. (10)
This group of patients are the ones who most benefit from PBI, so the dilemma is whether patients who comply with the selection criteria for these trials can be treated with PBI considering that the SOUND trial included only 10% of patients treated with PBI.

Looking at the data in the SOUND trial, adjuvant radiotherapy and hormonal treatment are administered for most of the patients. Precisely, about 98% took hormone therapy, and 98% of patients underwent postoperative radiotherapy. Among these, 10% underwent partial breast irradiation (PBI), while the remaining portion got whole breast irradiation (WBI). (3)
For early-stage breast cancer, it has been repeatedly observed that most ipsilateral breast tumor recurrence occur in the original tumor bed.(11) The highest benefits of whole breast irradiation (WBI) seems to result from the dose delivered in the tissue surrounding the tumor bed. Nonetheless, the challenge is to reduce treatment morbidity while maintaining the ability to decrease local recurrences. As a result, techniques such as breathing-adapted image-guided RT and partial-breast irradiation (PBI) have been developed to reduce toxicity without compromising the oncologic outcomes. (12)

PBI can be delivered through different techniques that include both external beam RT (EBRT), intraoperative RDT and brachytherapy. PBI has become widely used in the treatment of early-stage, low-risk breast cancer, as it has shown equivalencies in terms of local control and overall good cosmetic outcomes. (13)

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This group of patients are the ones who most benefit from PBI, so the dilemma is whether patients who comply with the selection criteria for these trials can be treated with PBI considering that only the SOUND trial has 10% of patients treated with PBI.
These findings are particularly timely in the context of results from the IMPORT LOW study that have been reported, showing the non-inferiority of PBI compared to WBI after breast-conserving surgery in cohorts similar to those enrolled in the SOUND study. (14) Data from the PBI group in the IMPORT LOW study show that at 5 and 10 years, the cumulative incidences of local recurrence were 0.5%[8] and 2.8%[10], respectively, indicating long-term effectiveness of PBI in preventing local recurrences, as also confirmed by the ASTRO guidelines. (14, 15)

In oncology, real-world data (RWD) and real-world evidence (RWE) are rapidly emerging as common sources of information for patients, clinicians, and regulators. Randomized controlled trials (RCTs) reduce bias and confounding through the randomization process and provide the highest quality of evidence regarding efficacy. But given the inherent differences between observational data and clinical trial results, RWD may still have independent value as complementary tools to trial results. (16) Once that there is robust evidence that the omission of SLN in early stage breast in selected patients works, the question is whether it does work in real world practice within the different practices and policies.

Our study will establish a prospective cohort study as an international registry of all those patients who undergo BCS for primary breast cancer without SLN to assess outcomes in real world. The next challenge is to better understand which patients with no axillary surgery and early-stage breast cancer have similar outcomes focusing on the radiation therapy and the systemic treatment option for each patient.

This will be a very large dataset of value to clinicians and researchers worldwide. From this information, we hope to be able to refine breast cancer management practices, improve the care of

patients, and assess whether the less-invasive approach can be recommended for more patients without compromising oncologic outcomes. This registry will serve to help further the precision in the management of breast cancer patients, affording them ideal care and minimizing the encumbrance of undue invasive procedures.

2. Purpose and Outcomes

Our prospective study will establish a comprehensive international registry specifically for patients who have undergone surgery for primary breast cancer without SLNB. The main objective of this registry is to gather detailed, real-world data on the outcomes of this particular treatment approach, providing insights into the clinical efficacy and quality of life of patients when SLNB is omitted.

3. Study aims

Primary endpoint

Evaluation of the 3-year axillary recurrence rate

Evaluation of the 5-year invasive disease-free survival (iDFS)

Secondary endpoints

Evaluation of different type of radiation therapy

Evaluation of different type of systemic treatment

Evaluation of outcomes based on histologic stage and subtype

4. Inclusion and Exclusion Criteria

4.1 Inclusion criteria

- Any age
- cT1-2
- cN0 Negative preoperative assessment of the axilla (ultrasound with or without FNAC /Core biopsy in case one doubtful node is found)
- Breast surgery as first treatment
- **No axillary surgery**
- Multifocal/ multicentric breast cancer
- Candidates to receive breast conserving surgery
- Written informed consent must be signed and dated by the patient and the investigator prior to inclusion.
- Patients must be accessible for follow-up.

4.2 Exclusion Criteria

- Synchronous distant metastases
- **Any axillary surgery**
- Neoadjuvant treatment
- Previous malignancy
- Bilateral 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 their ability to give informed consent for participation in this study.

Statistical analysis

A sample size calculation was performed to determine the number of participants required for a non-inferiority study comparing the experimental group to the general population. The reference axillary recurrence rate was set at 0.3% based on population data, while the expected recurrence rate in the experimental group was 1.0%, as reported in published studies. A significance level of 5% and a statistical power of 80% were used. The analysis determined that 744 participants were required. To account for potential dropouts and exclusions, the sample size was increased by 10%, resulting in a final adjusted sample size of 827 participants.

5. Material and Methods

This is an international prospective cohort study. Consecutive patients will be included.

Variables of interest

- Center ID
- Patient ID
- Age (at surgery)
- Premenopausal/Postmenopausal
- Genetic risk factors (BRCA1, BRCA2, ATM, CHECK2, PALB2, PTEN, TP53, etc.)
- Personal risk factors (tobacco smoke, alcohol, physical inactivity, substance abuse, Obesity, etc.)

- Comorbidity (high blood pressure, DM, chronic lung disease, deficiency anemias, kidney disease and failure, weight, height, BMI, etc.)
- Side (Right-Left)
- Objective examination axillary (palpable/not palpable)
- Mammography (date, nodule or microcalcifications, size in mm)
- Ultrasound breast (date, size in mm)
- Ultrasound axillary lymph nodes (negative/doubtful)
- Cytology or histology of doubtful axillary lymph node (yes/no)
- MRI (YES/NO)
  Date, size in mm
- Unicentric/multifocal/multicentric
  By mammogram, US, MRI
- Breast core biopsy Histological:
  - Date
  - Histotype (NST, lobular, other type)
  - Grade (1,2,3)
  - ER: %
  - PgR: %
  - Her2 0, 1+, 2+(FISH/SISH/ISH no amplified), 2+(FISH/SISH/ISH amplified) 3+
  - Ki67: %
- Date of surgery
- Type of breast surgery (Lumpectomy, oncoplastic surgery (round block, mammoplasty)
- Definitive histological result:
  - pT (mm)
  - Foci (u, m)
  - Histotype (NST, lobular, invasive + DCIS, other type)
  - Grade (1,2,3)
  - ER: %
  - PgR: %
  - Her2 0, 1+, 2+(FISH/SISH/ISH no amplified), 2+(FISH/SISH/ISH amplified) 3+
  - Ki67: %

- RT (yes/no)
    - PBI (yes/no)
        - Date (start/end)
        - If yes, type (intracavitary brachytherapy, interstitial brachytherapy, external beam radiation treatment (EBRT), single fraction intraoperative radiation (IORT))
        - Gy
        - number of fractions

    - WBI (yes/no)

    If yes:
        - Date (start/end)
        - Type (VMAT, breasth holding, IMRT)
        - Gy
        - Number of fractions
    - Boost dose (yes/no)
        - If yes, Gy
        - If yes, how many fractions
- Adjuvant endocrine therapy (yes/no)
    - Type of endocrine therapy (tamoxifen, Letrozole, exemestane, anastrozole, other SERD)
- Adjuvant CT (yes/no)

Follow-up

- Date of last follow-up
- Recurrence: yes/no
- Type of recurrence: local/regional/locoregional/synchronous (regional + distant, local + distant, locoregional + distant)
- Date of recurrence
- Deceased: yes/no
- Date of death
- Cause of death

6. Registration and therapy

All patients with histologically confirmed invasive breast cancer and a negative axillary US who are candidates for omitting SLN biopsy or any axillary surgery will be informed about the possible participation in the study. The inclusion and exclusion criteria are verified by the investigator and written informed consent is obtained from the patient. Surgical treatment, pathological assessment and postoperative locoregional and systemic therapy should be conducted according to institutional and national standards. Since the OXYGENATE study in a non-interventional trial, the study sites do not deviate from their own institutional protocol at any timepoint. The follow up on patient status is conducted yearly during the first 5 years after surgery.

7. Data management and analysis

CUN conducts data management and analysis. All patients who fulfill inclusion criteria should be recorded in the study identification list that remains at the study site.

For further analysis pseudonymized data are either filled in the CRF by the study site and transmitted directly by the study site via eCRF. The eCRF platform that will be used for data management in the study is the institutional REDCap platform of the Clínica Universidad de Navarra, and a formal request for its use has already been submitted. REDCap (Research Electronic Data Capture) is a secure and standardized platform for collecting and managing clinical research data. This tool complies with data protection requirements and allows for the collection of pseudonymized information, ensuring that participants' data is not directly identifiable and that their confidentiality is properly protected.

Regarding the subsequent utilization of health-related data, it will be performed encrypted, and according to Article 26 HRO on data protection, the data will be transferred to the PI as established in the Data Transfer Agreement and analyzed at the Clínica Universidad de Navarra in Madrid. The data will be used exclusively for this project, and all confidential data will be securely protected.

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