ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

DOTTORATO DI RICERCA IN

SCIENZE CHIRURGICHE

Ciclo 36

Settore Concorsuale: 06/C1 – CHIRURGIA GENERALE

Settore Scientifico Disciplinare: MED/18 – CHIRURGIA GENERALE

TITOLO TESI

OMISSION OF AXILLARY CLEARANCE IN PATIENTS WITH EARLY BREAST CANCER AND POSITIVE SENTINEL NODE BIOPSY TREATED WITH CONSERVATIVE SURGERY: APPLICATION OF THE ACOSOG Z0011 TRIAL IN CLINICAL PRACTICE

Presentata da: Giovanni Cisternino

Coordinatore Dottorato

Prof. Bianca Maria Piraccini

Supervisore

Prof. Mario Taffurelli

Co-supervisiore

Prof. Gilberto Poggioli

Esame finale anno 2024

ABSTRACT

Background: Axillary lymph node dissection (ALND) in presence of sentinel lymph node metastases has been the surgical standard in breast cancer (BC) patients for many years. Today, after the publication of the American College of Surgeon Oncology Group (ACOSOG) Z0011 trial and considering the increasing knowledge of BC biology, axillary clearance is a procedure restricted to a dwindling group of patients with a clearly metastatic axilla.

Objective: To evaluate, as evidenced in literature by Z0011 study, that the omission of ALND in patients with cT1-2 cN0 BC undergoing breast conserving surgery (BCS) and histological finding of metastases in 1 or 2 sentinel lymph nodes is not associated with a worse prognostic outcome.

End point: Primary endpoint of the study was overall survival (OS). Secondary endpoints were disease free survival (DFS) and locoregional recurrence.

Patients and methods: This research project is a prospective observational trial involving two Italian high-volume Breast Surgery Units: IRCCS Policlinico di Sant'Orsola and IRCCS San Raffaele Research hospital. All patients undergoing up-front BCS for BC between the 1st of November 2020 and 31st of July 2023, were screened and those with cT1-2 cN0 BC with preoperative negative axillary ultrasound with 1 or 2 metastatic sentinel lymph nodes treated with sentinel node biopsy (SLNB) alone entered the study. All procedure followed standard clinical practice. After surgery all patients' final pathology were discussed in the multidisciplinary breast meeting.

Results: A population of 795 cT1-2 cN0 BC patients underwent BCS and SLNB during the study period. 705 women fulfilled exclusion criteria (672 negative sentinel node biopsy, 33 ALND) and were excluded. Ninety patients were included. Median age was 60 (52-68) years. Seventy-five patients (83%) had a clinical T1 tumor and 15 (17%) a clinical T2. Median tumor size at final pathology was 16 mm (11-19). Tumor receptor status was: 94% luminal A or B tumors, 2% were HER2 positive tumors and 4% were triple negative. The median number of nodes removed was 2 (1-3). Eighty-one patients had 1 positive lymph node (90%), while 9 had 2 sentinel node metastasis (10%). Micrometastases were identified in 39 patients (43%) and 51 patients (57%) had lymph node macrometastasis. All patients underwent adjuvant radiotherapy. Thirty-tree Oncotype Dx testing (37%) were performed: 29 resulted in a low recurrence score ($\leqslant$25), 4 high recurrence score (>26). Seventeen patients (19%) performed adjuvant chemotherapy. Two patients received immunotherapy with trastuzumab and pertuzumab. Endocrine therapy was given to 84 patients (93%). In 2 patients CDK 4/6 inhibitor, abemaciclib, was added to endocrine therapy. At a median follow-up of 19 months (IQR 13-23) OS and DFS were 100%. No loco-regional recurrence was seen.

Conclusion: The preliminary results of our study confirm that omitting ALND in patients meeting Z011 criteria is oncologically safe and should be the standard of care in all breast units. However, in the modern context of personalization of BC treatment, each decision should be based on a multidisciplinary discussion.

INDEX

1) BACKGROUND

2) AXILLARY SURGERY HISTORY

3) PATIENTS AND METHODS

4) RESULTS

5) DISCUSSION

6) FUTURE PERSPECTIVES

7) CONCLUSION

8) BIBLIOGRAPHY

BACKGROUND

Axillary lymph node dissection (ALND) in presence of sentinel lymph node metastases has been the surgical standard in breast cancer (BC) patients for many years. Today, considering the increasing knowledge of BC biology, the current trend is to avoid axillary dissection even in presence of metastatic sentinel lymph node involvement.

The American College of Surgeons (ACOSOG) randomized clinical trial Z0011, published in 2011, demonstrated that among women undergoing breast conserving surgery (BCS) for tumors smaller than 5 cm (cT1/2), no palpable lymph nodes (cN0) and having 1 or 2 metastatic sentinel lymph nodes, 5- and 10-year overall survival (OS), disease-free survival (DFS) and loco-regional recurrences for patients treated with sentinel lymph node biopsy (SLNB) alone are non-inferior to OS, DFS and recurrences of patients who underwent ALND. As a result, the rate of comorbidities related to axillary surgery was reduced. [1-2] To date, lymphedema, loss of sensitivity and functional limitation of the upper limb remain relevant axillary surgery complications, which are no further acceptable if not associated with any prognostic advantage.

Considering these, international guidelines started to [3-4] propose no ALND in case of BC with metastatic sentinel lymph node detection in patients who meet the Z0011 study criteria. Several multicenter, prospective, randomized international studies started to confirm these results. [5-6] Among these, the SINODAR-ONE, a randomized national multicenter study closed the accrual in April 2020 and results have been recently published. [7]

Furthermore, compared to the past, the presence of axillary lymph node metastases has no longer the same prognostic value: in multidisciplinary teams, adjuvant therapy is now proposed based on the bio-molecular parameters of each neoplasm, with respect to the different bioprofiles of the breast tumor, regardless of lymph node involvement, obtaining the same outcome in terms of survival. [8] Moreover, in ER+/HER2- early breast cancer, the21-gene recurrence score (RS) assay (Oncotype Dx) has been prospectively validated as a tool providing both prognostic and predictive information useful for tailoring adjuvant chemotherapy administration. [9-10]

With this in mind, we decided in November 2020 to start this research project to introduce the Z0011 study criteria in clinical practice.

AXILLARY SURGERY HISTORY

In 1757, the French physician Henri F. Le Dran was one of the first surgeons to support the concept of axillary dissection as an integral part of the surgical treatment of breast cancer. [11] In 1866, the German pathologist Rudolph Virchow, supported by robust autopsy studies, postulated that the axillary lymph nodes represented the point of spread via the lymphatics to distant sites. [12] Following this hypothesis, William Halsted proposed the principle that the surgical approach to BC should comprise extirpation of the breast and adjacent lymph nodes and promoted radical mastectomy, whereby the breast, pectoralis muscles, and ipsilateral axillary nodes were removed en-bloc [13-14]. In the early years of the 20th century, the anatomical extension of the Halsted technique was debunked to reduce the disfigurement patients who underwent surgery experienced, gave way to modified radical mastectomy—the approach that became the gold standard of "current best practice" in BC treatment until the mid- 1980s.
After, during the 1970s, Umberto Veronesi in Milan, described the technique of preserving breast anatomy, which became known as 'quadrantectomy' and defined the ablation of the neoplastic tissue with an ample portion of healthy surrounding parenchyma with a macroscopic margin varying from 2 to 3 cm. The National Cancer Institute in Milan started recruiting patients in 1973. A median follow-up of 20 years showed the overall and BC-specific survival rates to be alike in the two groups; these outcomes without doubt confirmed that in a great number of patients affected by BC the conservative approach is, in terms of oncological safety, non-inferior to radical mastectomy. [15]
Breast conservation is now the gold standard for the treatment of early BC.
Also in the 1970s, 2 large trials, the Kings/Cambridge and NSABP-04 trials, questioned the modified radical mastectomy axiom. They randomized patients with a clinically node-negative axilla to either early or delayed axillary treatment. And in the mid-1980s, we saw the beginning of a gradual de-escalation in axillary surgery. [16]

Axillary nodal status is one of the most important prognostic factors in BC. It mainly has a staging role helping define patients who are candidates to adjuvant treatments. Historically, axillary staging was obtained through ALND, which in the past also included level III (and in some cases also supraclavicular and internal mammary nodes) apart from level I and II of axillary nodes that now define axillary dissection instead. [17]
Even if ALND is now more conservative than before, it is an invasive surgical procedure that may cause many complications, such as pain and numbness (39%), lymphedema (25%), reduced arm mobility (16%) and infection (11%). [18] This vision imposes the necessity to minimize the indication of complete axillary dissection as much as possible. [19]
The concept of SLNB was firstly proposed in 1993 by Krag et al. who undertook a pilot study of 22 patients with clinically node negative BC involving radio-localization of the sentinel lymph node. This study concluded that SLNB was a predictor of the status of nonsentinel axillary nodes but acknowledged the need for a larger clinical trial to verify the value of the technique [20]. After this, notorious surgeons like Armando E. Giuliano started to ameliorate and routinarily use SLNB technique. Giuliano in fact reported in 1995 an identification rate over 90%, and an accuracy in predicting the axillary nodal status by examining the SLN of 100%, among 107 patients who received both a SLNB with blue dye alone followed by completion ALND [21, 22].
Different practice-changing trials have been then carried out, starting from the Milan trial, that between 1998 and 1999 demonstrated better quality of life and reduced morbidity in the SLNB group compared to the standard ALND arm [23]. Another important trial was Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) that, consistently with the previous one, showed reduced arm morbidity and better quality of life [24].

Different trials showed the non-inferiority of sentinel node biopsy alone versus axillary dissection. Giuliano et. al in 2000 concluded after a prospective observational study that among 133 selected women, complication rates were negligible after SLNB alone and that the absence of axillary recurrences supported SLNB as an accurate staging alternative for BC and that routine ALND could be eliminated for patients with histopathological negative sentinel nodes [25].
Veronesi et al. in 2003 on NEJM reported the results of the first prospective randomized trial in which patients who were histopathological sentinel node tumor-free were randomized to ALND or no further axillary treatment. In over 500 patients, he showed no difference in axillary recurrence and in overall survival (OS). The only measurable difference reported was decreased morbidity in patients treated with a SLNB alone compared to those treated with ALND [26].
NSABP B-32 trial carried out between 1999 and 2004 was the largest of several phase III, randomized controlled trials comparing SLNB to conventional axillary dissection, and showed no statistically significant differences for the endpoints of OS, progression- free survival (PFS) and regional control [27].
SLNB has been considered feasible and safe, with an axillary recurrence rate of less than 1%, ensuring excellent regional nodal control, with a reported false-negative rate (FNR) of 6%-8% [28, 29]. The introduction of SLNB represented a revolution and one of the latest innovations on the path of minimizing the surgical approach to breast cancer patients, strongly reducing postsurgical morbidity and improving early and long-term quality of life.
Practice guidelines recommend no further axillary surgery in breast cancer with pathologically negative (pN0) axilla. [30]
The role of SLNB as standard of care to stage clinically node negative, non- T4 invasive breast cancer is currently undiscussed [31]. Much differently there is an abundance of controversy on how to handle the axilla when the sentinel node turns out to be metastatic [32].
Prior to 2011 in fact, SLNB was the standard of care for staging the clinically negative axilla in breast cancer patients, with ALND reserved for patients with clinical axillary metastases or metastases found on SLNB [33]. However, results obtained from different trials, among which ACOSOG Z0010 [34] and NSABP-32 [27], and even the much older NSABP B-04 [35], started to make the rationale of doing completion ALND even in patients with positive sentinel lymph nodes questionable and opened the way to a new approach studied for the first time in ACOSOG Z0011 study.

ACOSOG Z0011 TRIAL
The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial was designed to compare the OS of patients who had hematoxylin and eosin (H&E) detected metastases in their sentinel lymph node and were treated with completion ALND compared to patients managed without completion ALND or third field axillary radiation. The primary endpoint of the study was OS. However, locoregional control was assessed to determine the effect of ALND and SLNB on this endpoint for women managed with BCS, adjuvant systemic therapy, and opposing tangential field whole breast irradiation [1-2].
This study had the design of a randomized prospective trial.

Its inclusion criteria were:

- Women ≥18 years
- T1 or T2, N0, M0
- SLNB demonstrating with nodal metastatic breast cancer per frozen section, touch preparation, or hematoxylin-eosin staining
- SLNB within 60 days of invasive breast cancer diagnosis
- Treatment with lumpectomy to negative margins

- Eastern Cooperative Oncology Group/Zubrod status ≤2

Exclusion criteria on the other hand were:

- Metastasis identified by immunohistochemical staining
- Mastectomy
- Partial or no radiation treatment
- Palpable adenopathy or gross extra nodal disease: preoperative axillary evaluation was only clinical and did not forecast ultrasound evaluation
- ≥3 positive nodes on SLNB
- Matted nodes
- Neoadjuvant hormonal/chemotherapy treatment
- Third field axillary nodal irradiation
- ALND defined as an anatomic Level I and II dissection with at least 10 nodes removed
- Pregnant or lactating patients.

Although target enrolment was 1900 patients, this trial was closed early due to lower-than-expected accrual and event rates. Patients were randomized either to completion ALND (n=445) or observation (n=446). All patients were supposed to receive adjuvant radiation through tangential fields. Almost all patients received systemic chemotherapy with or without hormone therapy.

At a median follow-up of 6.2 years axillary recurrence rate was 0.5% among patients treated with ALND compared to 0.9% treated with SLNB only (P:0.45). DFS was 82.2% after SLNB and ALND compared to 83.8% after SLNB alone (P:0.13), whereas OS was 91.9% versus 92.5%, respectively.
The update at a median follow-up of 9.25 years showed no statistically significant difference in OS (P:0.02) and DFS (P:0.13) between the two study arms. The cumulative incidence of nodal recurrences at 10 years was 0.5% in the ALND arm and 1.5% in the SLNB alone arm (P:0.28). Ten-year cumulative locoregional recurrence was 6.2% with ALND and 5.3% with SLNB alone (P: 0.36). These findings do not support routine use of axillary lymph node dissection in this patient population based on 5- and 10-year outcomes [2].

Most criticism was initially due to the short follow-up of six years. Although it was a sufficient time to see most axillary recurrences, many argued that longer follow-up was necessary. However, ten-year results have been published which again showed no advantage to ALND for clinically node-negative women whose SLNs were positive and who were managed with BCS, adjuvant system therapy, and whole breast RT.
In addition, owing to low accrual and event rate, the study did not reach the prespecified sample size of 1900 participants or 500 deaths and this was considered an important weakness of the study. Like most large randomized trials in BC management, not all biological subtypes were represented in large numbers (in the treatment received sample 66.8% were ER+/PgR+; 15.2% were ER+/PgR-; 0.8% ER-/PgR+; 17.2% ER-/PgR- in the ALND group, while 68.9% were ER+/PgR+; 13.6% were ER+/PgR-; 1% ER-/PgR+; 16.5% ER- /PgR- in the SLNB only group). Differences in outcomes may be seen for patients with different individual circumstances. However, the authors argued that not all biological subtypes can be analyzed for small variations in locoregional treatment.
Another significant criticism was that the axillary radiation fields were not planned and some patients had nodal irradiation. Subsequent evaluation of the radiation fields showed that 11% of patients did not receive any radiation at all, some had nodal irradiation (18.9%), but most had whole breast only albeit with high tangents (89.6% in the SLNB group and 88.9% in the ALND group). These differences in radiation technique were considered to impact the observed outcomes [2].

ACOSOG Z0011 trial has been a bomb dropped in the surgical oncology community being not only a practice-changing trial but also leading to a change in the way of thinking as well. After its results the American Society of Clinical Oncology (ASCO) stated that clinicians should not recommend ALND for women with early-stage breast cancer who have one or two SLN metastases and will receive BCS with conventionally fractionated whole-breast RT [36, 37]. According to ASCO this concept is evidence-based and the strength of this recommendation is strong as benefits outweigh harms. Patients with larger tumors, more than two positive sentinel lymph nodes, inflammatory breast cancer, undergoing mastectomy or planned to receive unconventional radiation treatments are excluded from this recommendation. However, despite the ten-year results, many surgeons have not yet fully accepted the omission of ALND for node-positive women. While surgeons at most major cancer centers have abandoned ALND, many practicing surgeons have not. Acceptance of a less radical procedure is always slow [38].

BEYOND ACOSOG Z0011 TRIAL

Study	Design	Inclusion criteria	Arm	End point
IBCSG 23-01 trial 2001-2010 [41]	multicentre, randomised, non-inferiority, phase 3 trial	any age BC ≤5 cm one or more micrometastases (≤2 mm) in sentinel node (no macrometastates) (isolated tumor cells were included as micrometastates)	931 (1:1) BC 464 standard arm (ALND) 467 experimental arm (No ALND) 91% BCS, 9% mastetctomy	primary endpoint: DFS Secondary endpoints: OS, site of recurrence, and surgical complications of AD (axillary dissection)
AMAROS trial 2001-2010 [54]	Randomised, multicentre, open-label, phase 3 non-inferiority	Any age T1–2 BC, unifocal, invasive breast cancer, with no palpable lymphadenopathy Randomization (1:1) to receive either axillary lymph node dissection or axillary radiotherapy in case of a positive sentinel node	4806 BC (1:1) 2402 axillary lymph node dissection 744 sentinel node positive (ALND group) 2404 axillary radiotherapy 681 sentinel node positive (axillary RT group) 82% BCS, 17% mastectomy	primary endpoint: 5-year axillary recurrence Secondary endpoints: axillary recurrence-free survival, DFS, OS, shoulder mobility, lymphoedema, and Quality of life
SINODAR-ONE trial 2015-2020 [7]	Prospective, multicenter, non inferiority, phase 3 randomized trial	Age ≥40 e ≤75 BC ≤5 cm cN0 (ultrasound assessment) 1 or 2 macromestases in sentinel lymph nodes	822 (1:1) BC 403 standard arm (ALND) 419 experimental arm (no ALND) 75.2% BCS, 24.8%mastectomy	Primary end point: OS Secondary end points: RFS
SOUND trial 2012-2017 [42]	Prospective, multicenter, non inferiority, phase 3 randomized trial	Women of any age BC ≤2 cm cN0 negative pre-perative axillary US BCS and RT Axillary lymph node with micro and macro metastases were defined positive	1405 (1:1) BC 708 standard arm (SLNB group) 697 experimental arm (no axillary surgery)	Primary end point: DDFS Secondary end points: cumulative incidence of distant recurrences, the cumulative incidence of axillary recurrences, DFS, OS, and the adjuvant treat- ment recommendations.

Study	Results	Conclusions
IBCSG 23-01 trial 2001-2010 [41]	Median follow-up 5.0 years -5-year DFS was 84·4% AD group and 87·8% no AD group (log-rank p=0·16) -5-year OS 97·6% AD group and 97·5% no AD group (log-rank p=0·7) -5-year cumulative incidence of breast cancer events was 10·8% AD group and 10·6% no AD group (p=0·90)	no difference between the AD and no AD arms for the primary endpoint of DFS. OS also did not differ between the two arms.
AMAROS trial 2001-2010 [54]	Median follow-up: 6.1 years -5-year axillary recurrence was 0·43% in ALND and 1·19% in axillary RT (radiotherapy) -5-year DFS was 86·9% in ALND and 82·7% in axillary RT p=0·18 -5-year OS was 93·3% in ALND group and 92·5% in axillary RT p=0·34	No significant differences between the two groups in 5-year axillary recurrence, DFS, and OS Significant difference in the incidence and severity of lymphoedema in favor of the axillary radiotherapy group
SINODAR-ONE trial 2015-2020 [7]	Median follow-up 34.0 months -5-year OS rates were 98.9% and 98.8% in the ALND and SNLB-only arm of treatment, respectively (p = 0.936). -5-year RFS rates were 96.3% and 95.6%, in the ALND and SNLB-only arm of treatment, respectively (p = 0.511). -5-year cumulative incidence of recurrence of 6.9% and 3.3% in the standard and experimental treatment arm, respectively (p = 0.444) Only one axillary lymph node recurrence was observed in each group of treatment	The 3-year survival, regional, and distant relapse rates of patients with T1–2 BC and one or two macrometastatic SLNs treated with BCS, SLNB only, and adjuvant therapy were not inferior to those of patients treated with ALND
SOUND trial 2012-2017 [42]	Median follow-up 5.7 years -5-year DDFS was 97.7% in the SLNB group and 98.0% in the no axillary surgery group (log- rank P = .67) -5-year DFS was 94.7% in the SLNB group and 93.9% in the no axillary surgery group (log-rank P = .30) -5-year OS was 98.2% in the SLNB group and 98.4% in the no axillary surgery group (log-rank P = .72) -5-year cumulative incidence of distant metastases was 2.3% in the SLNB group and 1.9% in the no axillary surgery group (Gray P = .69) -5-year cumulative incidence of axillary recurrences was 0.4% in both groups (Gray P = .91)	Omission of axillary surgery was non- inferior to surgical staging performed by SLNB when evaluating DDFS at 5 years in patients with BC up to 2 cm and a negative result on preoperative ultrasonography of axillary lymph nodes

PATIENTS AND METHODS

This research project is a prospective observational trial evaluating the results of omitting ALND in patients, that meeting the Z0011 criteria, who underwent BCS and SLNB in two high-volume centers. The study involved two Italian Breast Surgery Units: IRCCS Policlinico di Sant'Orsola and IRCCS San Raffaele Research hospital.
Purpose of the study is to evaluate, as evidenced in literature by Z0011 study [1,2], that the omission of ALND in patients with cT1-2 cN0 BC undergoing BCS and histological finding of metastases in 1 or 2 sentinel lymph nodes is not associated with a worse prognostic outcome (overall survival, disease-free survival, locoregional recurrence).
Primary endpoint of the study was overall survival (OS), defined by the time between the date of surgery and the date of death for any cause.
Secondary endpoints were disease free survival (DFS), defined as the time since the date of surgery and the first date of local and/or distant breast cancer recurrence, and locoregional recurrence, defined as disease recurrence in the same operated breast or in the ipsilateral axillary lymph nodes, internal mammary chain, subclavicular or supraclavicular.
Patients who underwent BC surgery between the 1st of November 2020 and 31st of July 2023 at IRCCS Policlinico di Sant'Orsola and San Raffaele University Hospital were screened to be included in this study.

Inclusion criteria were:

- age>=18
- biopsy proven BC
- cT1-2
- Clinically negative axillary (cN0)
- Negative preoperative ultrasound
- BCS followed by radiotherapy
- M0
- No neoadjuvant systemic therapy
- Presence of 1 or 2 micro (≤2mm) or macrometastases (>2mm) in the sentinel lymph nodes on definitive histological examination

Exclusion criteria were:

- pregnancy and breastfeeding status
- Inflammatory breast cancer
- Presence of 3 or more metastases on histological examination
- Negative SLNB
- ALND performed

Differently from Z0011 trial, we didn't exclude patients with bilateral or multicentric disease, patients with previous history of breast cancer or other tumors neither patient with positive margins at lumpectomy.
Patients were evaluated by a surgical oncologist at diagnosis. They underwent mammography, breast and axillary ultrasound, together with core needle biopsy of the lesion to confirm the diagnosis and have histological and molecular characterization of the tumor. In case of suspicious node at axillary ultrasound examination, patients were sent to axillary fine-needle aspiration and in case of positivity underwent ALND or primary systemic therapy, in case of multiple suspicious nodes,

and were excluded from the study. Other exams were required if necessary, based on clinical evaluation.
As per observational study, BCS and SLNB were carried out following routine clinical practice. However, the sentinel lymph node was analyzed by hematoxylin-eosin frozen section and immunohistochemical analysis in San Raffaele Breast Unit, whilst in Sant'Orsola Breast Unit the OSNA technique (One Step Nucleic acid Amplification) was applied. This is an automated molecular diagnostic assay quantifying Cytokeratin 19 (CK19) mRNA expression, an epithelial cell marker that is normally absent in lymph node tissue. The expression rate of CK19 mRNA correlates with the size of the metastatic foci. [39]
All patients signed a regular informed consent.
After surgery all cases were discussed in the multidisciplinary breast meeting to decide the appropriate adjuvant therapy.
Data were prospectively collected from a maintained database of electronic medical records and recorded in Databreast and Microsoft Excel (Microsoft Cor., Redmond, Wash.) on an "ad hoc" spreadsheet where data on patients, tumor characteristics, surgery, pathology, radiotherapy, medical therapy regimen and follow-up have been reported.
Discrete variables were described as number and percentage or median and interquartile range (IQR), which reports the range between the 25th and 75th percentile.

RESULTS

During the study period, 1798 patients underwent surgery for BC, 1158 of these had BCS. Two hundred and seventeen patients were candidate to neoadjuvant chemotherapy, whereas 941 were candidates to up front surgery.
A population of 795 patients with cT1-2 cN0 BC underwent BCS and SLNB. Among these women 716 fulfilled exclusion criteria (664 have a negative sentinel lymph node at final pathology, 41 underwent ALND) and were excluded. Ninety women were included in the study. (Figure 1)
Patients' clinical and pathological characteristics are showed in table 1.
Median age of the included patients was 60 (52-68) years. 75 patients (83%) had a clinical T1 tumor and 15 (17%) a clinical T2.
Median tumor size at final pathology was 16 mm (11-19), most were pT1c tumors (57%), invasive ductal carcinoma (87%), G2 (51%) with no lymph vascular invasion (54%).
Eleven patients had a multiple tumor that was radically excised with breast conservation. One patient presented positive margins for intraductal carcinoma but no radicalization was performed.
Two patients had a previous breast cancer and 9 had a history of previous cancer elsewhere. Six patients had bilateral disease. For the outcome analysis only the side with the positive sentinel lymph node at final pathology was considered. One patient had metastasis in both sentinel lymph node and was considered twice.
Most tumors were luminal A-like (55%) and luminal B-like (39%). 3 cases were triple negative and 2 tumors had HER2 overexpression (1 Luminal-HER2 positive, 1 HER2 positive-ER/PR receptor negative).

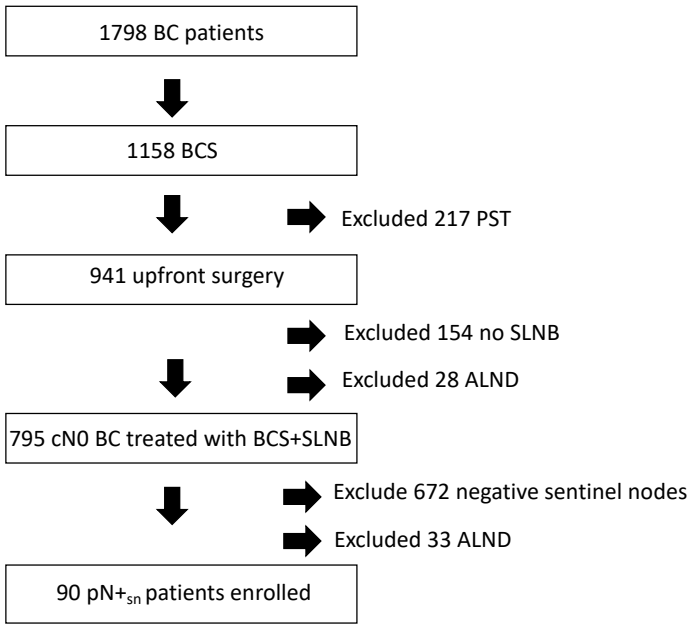

Figure 1 Flow Diagram
PST: primary systemic therapy;

Population, n	90
Age (years), median (IQR), n (%)	60 (52-68)
≤50y	19 (21%)
>50y	71 (79%)
Clinical stage, n (%)	
T1	75 (83%)
T2	15 (17%)
Histological type, n (%)	
Ductal	78 (87%)
Lobular	5 (5%)
Other	7 (8%)
Grade, n (%)	
G1	30 (33%)
G2	46 (51%)
G3	14 (16%)
Lymphovascular Invasion, n (%)	
absent	49 (54%)
focal	25 (28%)
extended	16 (18%)
Pathological stage, n (%)	
T1a	2 (2%)
T1b	18 (20%)
T1c	51 (57%)
T2	19 (21%)
Tumor size, median (IQR), mm	16 (11-19)
Receptor status, n (%)*	
Luminal A	50 (55%)
Luminal B	35 (39%)
Luminal Her2 +	1 (1%)
Her 2+	1 (1%)
TN	3 (4%)
Multiple tumor, n (%)	11 (12%)
Bilateral tumor, n (%)	6 (7%)
Previuos controlateral breast cancer, n (%)	2 (2%)
History of other cancer, n (%)	9 (10%)

*Luminal A: Ki 67≤22% and/or PgR>20%

Table 1. Clinical and pathological characteristics

The number of lymph nodes removed and the extent of metastatic involvement are presented in Table 2. The median total number of nodes removed was 2 (1-3). 81 patients had 1 positive lymph node (90%), while 9 had 2 sentinel node metastasis (10%).
Micrometastases were identified in 39 patients (43%), while the remaining 51 (57%) had lymph node macrometastasis.

Number of histologically positive nodes, n (%)	
1	81 (90%)
2	9 (10%)
Total number of lymph node s removed, Median (IQR)	2 (1-3)
Size of sentinel lymph node metastasis, n (%)	
Micro (≤2 mm)	39 (43%)
Macro (>2 mm)	51 (57%)

Table 2. Lymph node histopathological characteristics

Table 3 shows the details of adjuvant therapy administered.
All patients underwent post operative radiotherapy according to standard clinical practice.
The multidisciplinary team decided to perform 33 Oncotype Dx testing (37%), to better define the chemotherapy benefit. Twenty-nine patients had low recurrence score (≤25), while 4 patients had a recurrence score high (>26). In total, 17 patients (19%) performed adjuvant chemotherapy according to standard clinical practice. 2 patients received immunotherapy with Trastuzumab and Pertuzumab. Endocrine therapy was given to 84 patients (93%). In 2 patients CDK 4/6 inhibitors Abemaciclib was added to endocrine therapy. Four patients stopped endocrine therapy for intolerance to side effects.

Radiotherapy, n (%)	
No	0
Yes	90 (100%)
Adjuvant Chemotherapy, n (%)	
No	73 (81%)
Yes	17 (19%)
Oncotype DX, n (%)	33 (37%)
RS Low (0-25), n	29
RS High (26-100), n	4
Type of Chemotherapy, n	
AC (adriamycin/cyclophosphamide)+ Taxane	4
EC (Epirubicin/cyclophosphamide)+Taxane	10
Carboplatin/taxane	2
TC(cyclophosphamide+taxane)	1
Pertuzumab+Trastuzumab*	2
Endocrine Therapy	
No	6 (7%)
Yes	84 (93%)
Type of Endocrine Therapy	
Anastrozole	26
Letrozole	40
Exemestane	13
Tamoxifen	3
Exemestane+Abemaciclib	2
LHRH analogue*	18

*In addition to standard therapy

Table 3. Adjuvant therapy characteristics

Follow up data are shown on Table 4.
At the end of the third years of enrollment among patients who had a minimum follow-up time of six months, median follow-up was 19 months. (IQR 13-23). All patients are alive and in good general condition. One patient developed a bone metastasis from squamous cell carcinoma of the cervix. At this time no loco-regional recurrence was seen.
No major intraoperative complications occurred in the study cohort.

Overall survival	
No. of events/No. of patients (%)	0/90 (100%)
Median OS FUP time, in patients with a ≥6 months follow up (IQR), month	19 (13-23)
Disease Free survival	
No. of events/No. of patients (%)	0/90 (100%)
Median OS FUP time, in patients with a ≥6 months follow up (IQR), months	19 (13-23)
Locoregional recurrence	
No. of events/No. of patients	0/90

Table 4. Follow-up

DISCUSSION

During the years the surgical management of the axilla has changed radically. SLNB was first described in 1993 [20] and it progressively acquired the role of a new method of axillary staging with less morbidity. SLNB alone is now the standard staging procedure among all clinically node-negative (cN0) BC patients. The last ten years have increasingly seen SLNB as the sole axillary surgical procedure among selected patients with low-volume axillary metastases based on the results of the ACOSOG Z0011 trial [1].
The modern trend of de-escalating surgery to treat BC follows the evidence of better outcomes after less invasive surgery [36]. In this context SLNB has evolved from being the main procedure to stage the axilla, to become the only therapeutic procedure in early BC when sentinel node is positive, thus reducing post-surgical morbidity and improving quality of life [40]. ALND is associated with considerable morbidity, and the results of ACOSOG Z0011 trial showed that its related complications can be avoided without decreasing cancer control. The results of 10-year follow-up provided additional support to the concept that axillary dissection is not necessary for long-term disease control and survival for patients with early BC and positive sentinel lymph node undergoing breast conservation [2].
Although the initial outcomes of the ACOSOG Z0011 study gave rise to controversy [46], the management of women with positive sentinel lymph node changed radically. Many international studies started to strengthen and extend the indications coming from the Z0011 trial. [5-6] One of these, the SINODAR-ONE trial, an Italian randomized multicenter study closed the accrual in April 2020 and recently published the first follow up data. [7]

We thought and started this research project at the end of SINODAR-ONE trial enrollment, in which the Sant'Orsola breast surgery unit participated. Our study aimed to translate into clinical practice the results obtained from Z0011 trials, allowing patients to reduce the complication rate related to ALND.

Our preliminary results showed that at a median follow up time of 19 months OS and DFS was 100%. We reported only one distant relapse, not related to BC, but a bone metastasis from squamous cell carcinoma of the cervix. Compared to Z0011 study, patients with a previous history of cancer (both breast and other sites) patients with multicentric or bilateral tumors, patients with positive margins at lumpectomy were included. Considering these characteristics, almost one third of the study population (27 patients) would have been excluded from the Z0011 study. This could be considered a strength of our study, as our population mirrors a real-life translation application the Z011 study criteria into daily clinical practice.
Due to the short median follow-up, despite being excellent, our OS and DFS are not comparable with literature data yet. In the Z0011 trial [1] at a median follow-up of 6.2 years the 5-year OS was 92.5% in the SLNB-alone group, while the 5-year DFS was 83.9%. In the IBCSG 23-01 [41], also including tumors with micrometastases in the SLNB after BCS or mastectomy, the 5-year OS was 97.5% in the group without ALND whereas the 5-years DFS was 87·8%. In the SINODAR-ONE trial [7], including patients undergoing either BCS or mastectomy for T1–2 breast cancer and presenting one or two macrometastatic sentinel lymph nodes, at a median follow up of 34 months 5-year OS rate was 98.8% in SLNB-only arm of treatment, while the 5-years recurrence free survival rate was 95.6%. In the SOUND trial [42], where patients with breast cancer $\leqslant$2 cm and a negative preoperative axillary ultrasound were randomized to SLNB (plus standard surgery) versus

observation (no axillary surgery), at a median follow up of 5.7 years the 5-year OS rate was 98.4% in the no axillary surgery group, while the 5-year DFS rate was 93.9%.

No locoregional recurrence were seen during the study period. In the Z0011 trial [1] the 5-years rate of local recurrence was 1.6% in the SLNB group. In the IBCSG 23-01 [41] the rate of axillary recurrence was very low at 5 years: 1% in the SLNB group. In the SINODAR-ONE trial [7] the 5-year cumulative incidence of recurrence was 3.3% in the experimental treatment arm but only one axillary lymph node recurrence was observed in each group of treatment. In the SOUND trial [42] the 5-year cumulative incidence of axillary recurrence was 0.4% in both groups. Notably, although in these trials a certain burden of nodal disease was left behind in the experimental group (anticipated to be 27% in Z0011 trial, 44% in SINODAR trial and 14% in the SOUND trial on the basis of nodal positivity rates in the standard treatment arms), there was no difference between groups in terms of locoregional recurrence. In our population the short follow-up refrained us from finding potential locoregional recurrence. However, axillary recurrences are known to occur relatively early after surgical treatment. In fact, in the NSABP B-04 [35], the median time to axillary recurrence was 14.8 months, 19.1 months in the ACOSOG Z0010 [34] trial and 48 months reported a median time to axillary recurrence of in the ACOSOG Z0011[1].

In our cohort, the rate of micrometastases ($\leqslant$2 mm) was 43% and the rate of macrometastases was 57%. Our percentage of micrometastases is similarly to 44.6% of the Z0011 trial [1] in the SLNB-only arm. In the SINODAR-ONE trial [7] micrometastastatic lymph nodes were excluded and at final pathology 0.7% patients showed micrometastases in the SLNB-only group. In the SOUND trial [42] 97 patients (13.7%) of the in the SLNB group had positive axillary nodes, 36 (37%) with micrometastases and 61 (63%) with macrometastases. Patients with a sentinel lymph node micrometastasis notoriously have a very low risk of recurrence as reported in well-known trials like IBCSG 23-01 [41] and guidelines recommend no axillary clearance in these cases [30]. Nevertheless, since our study referred to the application of the Z0011 study criteria in clinical practice, we also included patients with micrometastatic sentinel nodes in our analysis.

When considering the tumor receptor status, our population exhibited 94% were luminal like A or B tumors, 2% were HER2 positive tumors and 4% were triple negative. This distribution differs from Z0011 trial [1] where ER-/PR- tumors were 16,3% in the SLNB-group while ER+/PR+, ER+/PR-, ER-, PR+ tumors accounted for 83,7%. HER2 expression was not reported. In the SINODAR-ONE trial [7] luminal like A or B tumors accounted for 82,6%, the HER2 positive for 11% and the triple negative for 3%. In the SOUND trial [42] in the no-axillary surgery group the luminal HER2 negative tumors were the 88,5%, the HER2 positive were 6,7% and the triple negative were 4,7%, whereas in the axillary surgery group the luminal HER2 negative tumors were the 87,1%, the HER2 positive were 6,8% and the triple negative were 6,1%. Our study started in November 2020 and the distribution of tumor receptor status reflects the actual trend of patients undergoing upfront surgery who generally present luminal breast cancer whilst women with HER2 positive and triple negative BC usually undergo neoadjuvant chemotherapy in relation to the possibility of tailoring the post-operative treatment based on the presence of residual disease after treatment.

All patients received adjuvant whole-breast radiotherapy, 93% endocrine therapy and 19% adjuvant chemotherapy. Two patients also received anti-HER2-agents. In the SLNB only arm of Z0011 [1] 46.6% of patients received endocrine therapy, 58% adjuvant chemotherapy and 89,6% received a whole-breast radiation therapy. In the SINODAR-ONE trial [7] adjuvant endocrine therapy was administered to most of the enrolled patients (90,2%), adjuvant chemotherapy was delivered to

44.6% in the experimental treatment arm, adjuvant HER2 targeted immunotherapy was administered to 82 patients (9,3%). Most enrolled patients (71%) underwent adjuvant whole breast radiotherapy following BCS. In the SOUND trial [42] in the no axillary surgery group, 653 patients (93,7%) had ER-positive BC; of those, 646 (98.9%) received endocrine therapy, 47 patients (6,7%) had HER2-positive BC and almost all of these (46 patients) received trastuzumab. Overall, 142 women (20.1%) in the SLNB group and 122 women (17.5%) in the no axillary surgery group received chemotherapy, while 694 women (98.0%) in the SLNB group and 680 women (97.6%) in the no axillary surgery group received radiotherapy.

This thesis shows some strengths such as the prospective data, the detailed data collection and the availability of data from two high-volume breast units among the greatest in Italy. Another strength of our study is that we also reported the Oncotype Dx recurrence score data. This was indicated by the multidisciplinary team for 33 patients (37%). Results showed 29 low recurrence scores ($\leqslant$25), whereas 4 patients had a high recurrence score (>26) and underwent adjuvant chemotherapy. Today, in luminal BC, the Oncotype DX is an additional asset which is useful for tailoring the adjuvant treatment in patients at intermediate risk of relapse. Our adjuvant chemotherapy rate is lower than Z0011 trail, and closer to the percentage shown in the SOUND population. This could be explained by the fact that most of our patients were diagnosed with an early BC with a good prognosis: 83% had a T1 stage, 94% were luminal tumors and the performance of pre-operative axillary ultrasound allowed to exclude patients with a high axillary disease burden. Moreover, compared to the past, BC is increasingly diagnosed through core-biopsy, which allows to obtain more information and a pre-operative bio-molecular characterization of the lesion. These data identify patients at low risk versus patients at higher risk of relapse (such as HER2 positive or triple negative breast cancers) for whom a neoadjuvant chemotherapy approach is desirable.

In our clinical practice we support the value of ultrasound as an extremely important tool for obtaining a reliable preoperative axillary staging, as shown in previous literature [43]. Sensitivity of ultrasound scan in detection of axillary nodal metastasis is reported to be in literature around 74% with a specificity of 89%, positive predictive value of 87%, negative predictive value of 84% and overall accuracy of 83% [44-45]. Previous studies looking at pathologic nodal disease burden by axillary ultrasound results have shown rates of pN2-3 disease ranging from 0%-3% for patients with negative axillary ultrasound versus 8%-31% for patients with suspicious ultrasound findings. [46] Z0011 patient selection was only based on clinical examination and preoperative ultrasound was not mandatory. Today axillary ultrasound is usually part of the work-up exams of BC patient. Although our pre-operative axillary ultrasound data are not reported, as they were not an objective of the study, it is worth to note that our study population derives from a previous patient selection based on preoperative axillary ultrasound results. However, axillary ultrasound itself does have a few limitations: it is an operator-dependent exam with great inter-observer variability and its role could be limited in obese patients due to the presence of adipose tissue in the axillary cavity. [47] Similarly, after a negative preoperative axillary ultrasound the SLNB group of the SOUND trial [42] revealed a limited number of micro- and macromestastatic sentinel nodes (13,7%) which was absolutely lower than the rate reported in Z0011 trial, likely due to the screening effect of preoperative ultrasound. In fact, SOUND trialists concluded that given the limited number of patients with macrometastases, the very low number of patients with extensive nodal involvement (0.6% with 4 or more positive nodes) in the axillary surgery group, and the extremely low cumulative incidence of axillary lymph node recurrence in the no axillary surgery group (0.4% at 5 years), the performance of ultrasonography should be routinely applied in the preoperative workup of all patients with BC.

Finally, this thesis has some important limitations. The first being the relatively small number of patients included, as the inclusion criteria selected a limited number of patients. Secondly, the short median follow-up makes it difficult to find potential recurrences. This limitation was discussed during the initial presentation of the research project, which required to be developed over 3 years with preliminary results at the end of the third year of enrollment. However, the follow up is ongoing, and our goal is to achieve a minimum follow up of 5 years. In the meantime, the routine application of the Z0011 study criteria continues in the daily clinical practice of both centers. Furthermore, our study population include early BC with a good prognosis and at low risk of recurrence, thus we cannot exclude the possibility that breast events might appear over a longer follow-up period than 5 years follow-up.

FUTURE PERSPECTIVES

Today, BC management is mainly driven by tumor biology which impact diagnosis and staging, as well as surgical and medical treatment personalization. Moreover, thanks to the screening program and the increased awareness, most of breast malignancies are diagnosed at an early stage. As a result, the SLNB-positive rate is falling below 20%, as reported in specialized European breast centers, an encouraging result when compared to the 29% reported in the NSABP B-32 trial [27]. Since the publication of the Z0011 study, the meaning of sentinel lymph node biopsy has changed. This study showed that there is no outcome advantage in dissecting the axilla in the presence of positive sentinel lymph node, meaning that the information achieved by removing lymph nodes does not change the prognosis of the disease. This started the modern era of axillary surgery.
However, some questions still remain open in different fields: what will be the role of preoperative axillary imaging? Is sentinel lymph node biopsy still necessary in early breast cancer? In which cases ALND is still required to determine nodal burden and to tailor adjuvant treatments?

Firstly, axillary surgery de-escalation goes hand in hand with the improvement in imaging techniques. This has paved the way to the hypothesis that prognostic information on nodal status could be obtained with an accurate diagnostic exam rather than surgery. In this context, positron emission tomography/magnetic resonance imaging (PET/MRI) is a relatively new and promising imaging tool that could overcome some of the limitations of the axillary ultrasound. [48] A prospective comparative trial between axillary surgery and PET/MRI is ongoing in IRCCS San Raffaele research hospital. The SNB vs. PET/MRI 2 trial compares PET/MRI and SLNB in staging the axilla of early BC patients who are candidates to up front surgery. This trial could add further information in the way to a further de-escalation of surgical treatment of BC.

Secondly, prospective European studies are underway with the challenging assumption of verifying the utility of the SLNB itself, especially in specific subgroups of women with early BC, that are less likely to metastasize regionally. The SOUND trial was recently published. [42] The ongoing INSEMA and BOOG 2013-08 are studying the safety of omitting SLNB in BCS in the presence of clinically negative axillary nodes. [49-50] The results of these trials will help to evaluate whether the lack of pathologic lymph-node status information could be adequate in the adjuvant treatment decision-making process. Other studies involve BC patients either with a conservative or radical (mastectomy) surgical plan, which could contribute to further scientific growth in axillary management, better defining the role of axillary treatment. [51]

Thirdly, the modern trend of de-escalating axillary surgery must face with results of novel oncological trials that highlights the possibility to tailor oncological therapy selecting patients on the basis of nodal disease burden. In this context, the total number of positive lymph nodes could still be useful to define high-risk patients and to tailor the adjuvant treatment.
In particular, the RxPONDER study [10] randomly assigned patients undergoing up-front surgery with 1-3 positive nodes and a RS of ≤25 to chemotherapy plus endocrine therapy or endocrine therapy alone. Based on the findings from RxPONDER, chemotherapy is not indicated in postmenopausal women with 1-3 positive node HR+/HER2- breast cancer and a RS of ≤25. Whilst, for premenopausal women, chemotherapy should be advised for patients with 1-3 positive nodes regardless of the RS. Additionally, the OlympiA trial, [52] a phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after neo- or adjuvant chemotherapy in patients with germline BRCA 1-2 mutations and high-risk HER2 negative breast cancer showed a 3-years invasive DFS of 85.9% in the olaparib group vs 77.1% in the placebo group (P<0.001) and 3-years distant

disease–free survival of 87.5% in the olaparib group vs 80.4% in the placebo group (P<0.001). Patients with triple negative BC who were treated with adjuvant chemotherapy were required to have axillary node–positive disease or an invasive primary tumor measuring at least 2 cm on pathological analysis, whereas patients who were treated with adjuvant chemotherapy for hormone-receptor–positive, HER2- negative breast cancer were required to have at least four pathologically confirmed positive lymph nodes. The results showed that adjuvant Olaparib was associated with longer survival free of invasive or distant disease than was placebo. Finally, in the monarchE trial [53], an open-label, phase 3, multicenter, randomized study hormone receptor positive HER2 negative node positive breast cancer at high risk of recurrence were randomly assigned (1:1) to receive standard-of-care endocrine therapy with or without abemaciclib 150 mg orally twice a day for 2 years (treatment period). High-risk disease was defined as either four or more positive axillary lymph nodes, or between one and three positive axillary lymph nodes and at least one of the following: grade 3 disease, tumor size ≥5 cm, or Ki-67 ≥20%. At 4 years, the absolute difference in invasive disease-free survival between the groups was 6.4% (85.8% [95% CI 84.2 – 87.3] in the abemaciclib plus endocrine therapy group vs 79.4% [77.5–81·1] in the endocrine therapy alone group). The authors concluded that adjuvant abemaciclib reduces the risk of recurrence and support the use of abemaciclib in patients with high-risk hormone receptor-positive, HER2-negative early breast cancer.

Hence, these modern trials define high risk patients also on the basis of the number of metastatic lymph nodes which is usually higher than those one or two sentinel nodes removed by standard SLNB. As a result, this raises the doubt whether in some cases ALND is still necessary to quantify the exact number of positive nodes to appropriately tailor systemic therapy recommendations. In fact, in our study population, someone of the ALND performed after positive SLNB were planned after the multidisciplinary discussion to have more information on the axillary status. This confirms the importance of the case-by-case discussion within a multidisciplinary team.

CONCLUSIONS

The common thread from the past that weaves its way through the present and stretches toward the future is the progressive tendency to tailor the single patient treatment and whenever possible, to reduce the extension of axillary lymph-node surgery, in BC management.
The advent of sentinel lymph node biopsy has led to a progressive de-escalation of surgical methods for axillary staging in early BC. ALND is in fact now restricted to a group of patients with a clearly metastatic axilla or to those patients for whom information coming from this surgery could impact adjuvant treatment.

The preliminary results of our study confirm that omitting ALND in patients meeting Z011 criteria is oncologically safe and should be the standard of care in all breast units. However, in the modern context of personalization of breast cancer treatment, the one-size-fits-all approach is not advisable and each surgical decision should be based on a multidisciplinary discussion.

BIBLIOGRAFIA

1. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall LM, Morrow M. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA. 2011 Feb 9;305(6):569-75. doi: 10.1001/jama.2011.90. PMID: 21304082; PMCID: PMC5389857
2. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, Ollila DW, Hansen NM, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, Hunt KK, Morrow M. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA. 2017 Sep 12;318(10):918-926. doi: 10.1001/jama.2017.11470. PMID: 28898379; PMCID: PMC5672806.
3. Burstein HJ, Curigliano G, Loibl S, Dubsky P, Gnant M, Poortmans P, Colleoni M, Denkert C, Piccart-Gebhart M, Regan M, Senn HJ, Winer EP, Thurlimann B; Members of the St. Gallen International Consensus Panel on the Primary Therapy of Early Breast Cancer 2019. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Ann Oncol. 2019 Oct 1;30(10):1541-1557. doi: 10.1093/annonc/mdz235. PMID: 31373601
4. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S, Senkus E; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2019 Aug 1;30(8):1194-1220. doi: 10.1093/annonc/mdz173. Erratum in: Ann Oncol. 2019 Oct 1;30(10):1674. Erratum in: Ann Oncol. 2021 Feb;32(2):284. PMID: 31161190.
5. Reimer T, Hartmann S, Stachs A, Gerber B. Local treatment of the axilla in early breast cancer: concepts from the national surgical adjuvant breast and bowel project B-04 to the planned intergroup sentinel mamma trial. Breast Care (Basel). 2014 May;9(2):87-95. doi: 10.1159/000360411. PMID: 24944550; PMCID: PMC4038316
6. Goyal A, Dodwell D. POSNOC: A Randomised Trial Looking at Axillary Treatment in Women with One or Two Sentinel Nodes with Macrometastases. Clin Oncol (R Coll Radiol). 2015 Dec;27(12):692-5. doi: 10.1016/j.clon.2015.07.005. Epub 2015 Aug 5. PMID: 26254841
7. Tinterri C, Gentile D, Gatzemeier W, Sagona A, Barbieri E, Testori A, Errico V, Bottini A, Marrazzo E, Dani C, Dozin B, Boni L, Bruzzi P, Fernandes B, Franceschini D, Spoto R, Torrisi R, Scorsetti M, Santoro A, Canavese G; SINODAR-ONE Collaborative Group. Preservation of Axillary Lymph Nodes Compared with Complete Dissection in T1-2 Breast Cancer Patients Presenting One or Two Metastatic Sentinel Lymph Nodes: The SINODAR-ONE Multicenter Randomized Clinical Trial. Ann Surg Oncol. 2022 Sep;29(9):5732-5744. doi: 10.1245/s10434-022-11866-w. Epub 2022 May 12. PMID: 35552930.
8. Burstein HJ, Curigliano G, Thürlimann B, Weber WP, Poortmans P, Regan MM, Senn HJ, Winer EP, Gnant M; Panelists of the St Gallen Consensus Conference. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann Oncol. 2021 Oct;32(10):1216-1235. doi: 10.1016/j.annonc.2021.06.023. Epub 2021 Jul 6. PMID: 34242744; PMCID: PMC9906308
9. Sparano JA, Gray RJ, Ravdin PM, Makower DF, Pritchard KI, Albain KS, Hayes DF, Geyer CE Jr, Dees EC, Goetz MP, Olson JA Jr, Lively T, Badve SS, Saphner TJ, Wagner LI, Whelan TJ, Ellis

MJ, Paik S, Wood WC, Keane MM, Gomez Moreno HL, Reddy PS, Goggins TF, Mayer IA, Brufsky AM, Toppmeyer DL, Kaklamani VG, Berenberg JL, Abrams J, Sledge GW Jr. Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer. N Engl J Med. 2019 Jun 20;380(25):2395-2405. doi: 10.1056/NEJMoa1904819. Epub 2019 Jun 3. PMID: 31157962; PMCID: PMC6709671

10. Kalinsky K, Barlow WE, Gralow JR, Meric-Bernstam F, Albain KS, Hayes DF, Lin NU, Perez EA, Goldstein LJ, Chia SKL, Dhesy-Thind S, Rastogi P, Alba E, Delaloge S, Martin M, Kelly CM, Ruiz-Borrego M, Gil-Gil M, Arce-Salinas CH, Brain EGC, Lee ES, Pierga JY, Bermejo B, Ramos-Vazquez M, Jung KH, Ferrero JM, Schott AF, Shak S, Sharma P, Lew DL, Miao J, Tripathy D, Pusztai L, Hortobagyi GN. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer. N Engl J Med. 2021 Dec 16;385(25):2336-2347. doi: 10.1056/NEJMoa2108873. Epub 2021 Dec 1. PMID: 34914339; PMCID: PMC9096864
11. Le Dran HF. Memoires avec un precis de plusieurs observations sur le cancer. Mem Acad R Chir 1757;3:1–54.
12. Virchow R. Cellular pathology. Philadelphia, PA: Lippincott; 1863.
13. Halsted WS. I. The Results of Operations for the Cure of Cancer of the Breast Performed at the Johns Hopkins Hospital from June, 1889, to January, 1894. Ann Surg. 1894 Nov;20(5):497-555. doi: 10.1097/00000658-189407000-00075. PMID: 17860107; PMCID: PMC1493925
14. Halsted WS. I. The Results of Radical Operations for the Cure of Carcinoma of the Breast. Ann Surg. 1907 Jul;46(1):1-19. doi: 10.1097/00000658-190707000-00001. PMID: 17861990; PMCID: PMC1414357
15. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, Aguilar M, Marubini E. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002 Oct 17;347(16):1227-32. doi: 10.1056/NEJMoa020989. PMID: 12393819
16. Bromham N, Schmidt-Hansen M, Astin M, Hasler E, Reed MW. Axillary treatment for operable primary breast cancer. Cochrane Database Syst Rev. 2017 Jan 4;1(1):CD004561. doi: 10.1002/14651858.CD004561.pub3. PMID: 28052186; PMCID: PMC6464919
17. Dumitru D, Khan A, Catanuto G, Rocco N, Nava MB, Benson JR. Axillary surgery in breast cancer: the beginning of the end. Minerva Chir. 2018 Jun;73(3):314-321. doi: 10.23736/S0026-4733.18.07728-3. Epub 2018 Mar 28. PMID: 29589679
18. Brar P, Jain S, Singh I. Complications of Axillary Lymph Node Dissection in Treatment of Early Breast Cancer: A Comparison of MRM and BCS. Indian J Surg Oncol. 2011 Jun;2(2):126-32. doi: 10.1007/s13193-011-0078-2. Epub 2011 Jul 22. PMID: 22693405; PMCID: PMC3244199
19. Gentilini O, Veronesi U. Staging the Axilla in Early Breast Cancer: Will Imaging Replace Surgery? JAMA Oncol. 2015 Nov;1(8):1031-2. doi: 10.1001/jamaoncol.2015.2337. PMID: 26291922
20. Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surg Oncol. 1993 Dec;2(6):335-9; discussion 340. doi: 10.1016/0960-7404(93)90064-6. PMID: 8130940
21. Giuliano AE. Mapping a pathway for axillary staging: a personal perspective on the current status of sentinel lymph node dissection for breast cancer. Arch Surg. 1999 Feb;134(2):195-9. doi: 10.1001/archsurg.134.2.195. PMID: 10025463
22. Giuliano AE. The evolution of sentinel node biopsy for breast cancer: Personal experience. Breast J. 2020 Jan;26(1):17-21. doi: 10.1111/tbj.13729. Epub 2019 Dec 26. PMID: 31876042
23. Veronesi U, Viale G, Paganelli G, Zurrida S, Luini A, Galimberti V, Veronesi P, Intra M, Maisonneuve P, Zucca F, Gatti G, Mazzarol G, De Cicco C, Vezzoli D. Sentinel lymph node

biopsy in breast cancer: ten-year results of a randomized controlled study. Ann Surg. 2010 Apr;251(4):595-600. doi: 10.1097/SLA.0b013e3181c0e92a. PMID: 20195151
24. Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, Yiangou C, Horgan K, Bundred N, Monypenny I, England D, Sibbering M, Abdullah TI, Barr L, Chetty U, Sinnett DH, Fleissig A, Clarke D, Ell PJ. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst. 2006 May 3;98(9):599-609. doi: 10.1093/jnci/djj158. Erratum in: J Natl Cancer Inst. 2006 Jun 21;98(12):876. PMID: 16670385
25. Giuliano AE, Haigh PI, Brennan MB, Hansen NM, Kelley MC, Ye W, Glass EC, Turner RR. Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer. J Clin Oncol. 2000 Jul;18(13):2553-9. doi: 10.1200/JCO.2000.18.13.2553. Erratum in: J Clin Oncol 2000 Nov 15;18(22):3877. PMID: 10893286
26. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, Intra M, Veronesi P, Robertson C, Maisonneuve P, Renne G, De Cicco C, De Lucia F, Gennari R. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med. 2003 Aug 7;349(6):546-53. doi: 10.1056/NEJMoa012782. PMID: 12904519
27. Krag DN, Julian TB, Harlow SP, Weaver DL, Ashikaga T, Bryant J, Single RM, Wolmark N. NSABP-32: Phase III, randomized trial comparing axillary resection with sentinal lymph node dissection: a description of the trial. Ann Surg Oncol. 2004 Mar;11(3 Suppl):208S-10S. doi: 10.1007/BF02523630. PMID: 15023753
28. Lyman GH, Giuliano AE, Somerfield MR, Benson AB 3rd, Bodurka DC, Burstein HJ, Cochran AJ, Cody HS 3rd, Edge SB, Galper S, Hayman JA, Kim TY, Perkins CL, Podoloff DA, Sivasubramaniam VH, Turner RR, Wahl R, Weaver DL, Wolff AC, Winer EP; American Society of Clinical Oncology. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol. 2005 Oct 20;23(30):7703-20. doi: 10.1200/JCO.2005.08.001. Epub 2005 Sep 12. PMID: 16157938
29. Giuliano AE, Han SH. Local and regional control in breast cancer: role of sentinel node biopsy. Adv Surg. 2011;45:101-16. doi: 10.1016/j.yasu.2011.03.015. PMID: 21954681
30. Telli ML, Gradishar WJ, Ward JH. NCCN Guidelines Updates: Breast Cancer. J Natl Compr Canc Netw. 2019 May 1;17(5.5):552-555. doi: 10.6004/jnccn.2019.5006. PMID: 31117035
31. Esposito E, Di Micco R, Gentilini OD. Sentinel node biopsy in early breast cancer. A review on recent and ongoing randomized trials. Breast. 2017 Dec;36:14-19. doi: 10.1016/j.breast.2017.08.006. Epub 2017 Aug 29. PMID: 28854395
32. Veronesi P, Corso G. Standard and controversies in sentinel node in breast cancer patients. Breast. 2019 Nov;48 Suppl 1:S53-S56. doi: 10.1016/S0960-9776(19)31124-5. PMID: 31839161
33. Malik AA, Urooj N, Shamim R, Salim M, Bano R, Chaudhry Z, Khan HM, Khan AI. Managing the Axilla in Early Breast Cancer. Impact of ACOSOG Z0011 Trial in Changing Practices in a Low Middle Income Country. Asian Pac J Cancer Prev. 2017 Aug 27;18(8):2079-2082. doi: 10.22034/APJCP.2017.18.8.2079. PMID: 28843225; PMCID: PMC5697463
34. Giuliano AE, Hawes D, Ballman KV, Whitworth PW, Blumencranz PW, Reintgen DS, Morrow M, Leitch AM, Hunt KK, McCall LM, Abati A, Cote R. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. JAMA. 2011 Jul 27;306(4):385-93. doi: 10.1001/jama.2011.1034. PMID: 21791687; PMCID: PMC5389856
35. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total

mastectomy followed by irradiation. N Engl J Med. 2002 Aug 22;347(8):567-75. doi: 10.1056/NEJMoa020128. PMID: 12192016
36. Gentilini OD, Cardoso MJ, Poortmans P. Less is more. Breast conservation might be even better than mastectomy in early breast cancer patients. Breast. 2017 Oct;35:32-33. doi: 10.1016/j.breast.2017.06.004. Epub 2017 Jun 20. PMID: 28644995
37. Di Micco R, Zuber V, Fiacco E, Carriero F, Gattuso MI, Nazzaro L, Panizza P, Gianolli L, Canevari C, Di Muzio N, Pasetti M, Sassi I, Zambetti M, Gentilini OD. Sentinel node biopsy after primary systemic therapy in node positive breast cancer patients: Time trend, imaging staging power and nodal downstaging according to molecular subtype. Eur J Surg Oncol. 2019 Jun;45(6):969-975. doi: 10.1016/j.ejso.2019.01.219. Epub 2019 Jan 31. Erratum in: Eur J Surg Oncol. 2019 Sep;45(9):1754. PMID: 30744944
38. Giuliano AE, Hawes D, Ballman KV, Whitworth PW, Blumencranz PW, Reintgen DS, Morrow M, Leitch AM, Hunt KK, McCall LM, Abati A, Cote R. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. JAMA. 2011 Jul 27;306(4):385-93. doi: 10.1001/jama.2011.1034. PMID: 21791687; PMCID: PMC5389856
39. Tamaki Y. One-step nucleic acid amplification assay (OSNA) for sentinel lymph node biopsy. Breast Cancer. 2015 May;22(3):230-4. doi: 10.1007/s12282-012-0390-x. Epub 2012 Aug 9. PMID: 22875641
40. Güth U, Myrick ME, Viehl CT, Schmid SM, Obermann EC, Weber WP. The post ACOSOG Z0011 era: does our new understanding of breast cancer really change clinical practice? Eur J Surg Oncol. 2012 Aug;38(8):645-50. doi: 10.1016/j.ejso.2012.04.018. Epub 2012 May 19. PMID: 22608851
41. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, Baratella P, Chifu C, Sargenti M, Intra M, Gentilini O, Mastropasqua MG, Mazzarol G, Massarut S, Garbay JR, Zgajnar J, Galatius H, Recalcati A, Littlejohn D, Bamert M, Colleoni M, Price KN, Regan MM, Goldhirsch A, Coates AS, Gelber RD, Veronesi U; International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013 Apr;14(4):297-305. doi: 10.1016/S1470-2045(13)70035-4. Epub 2013 Mar 11. Erratum in: Lancet Oncol. 2013 Jun;14(7):e254. PMID: 23491275; PMCID: PMC3935346
42. Gentilini OD, Botteri E, Sangalli C, Galimberti V, Porpiglia M, Agresti R, Luini A, Viale G, Cassano E, Peradze N, Toesca A, Massari G, Sacchini V, Munzone E, Leonardi MC, Cattadori F, Di Micco R, Esposito E, Sgarella A, Cattaneo S, Busani M, Dessena M, Bianchi A, Cretella E, Ripoll Orts F, Mueller M, Tinterri C, Chahuan Manzur BJ, Benedetto C, Veronesi P; SOUND Trial Group. Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial. JAMA Oncol. 2023 Sep 21:e233759. doi: 10.1001/jamaoncol.2023.3759. Epub ahead of print. PMID: 37733364; PMCID: PMC10514873
43. Gentilini O, Veronesi U. Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: Sentinel node vs Observation after axillary UltraSouND). Breast. 2012 Oct;21(5):678-81. doi: 10.1016/j.breast.2012.06.013. Epub 2012 Jul 25. PMID: 22835916
44. Rajesh YS, Ellenbogen S, Banerjee B. Preoperative axillary ultrasound scan: its accuracy in assessing the axillary nodal status in carcinoma breast. Breast. 2002 Feb;11(1):49-52. doi: 10.1054/brst.2001.0352. PMID: 14965645

45. Ahmed M, Jozsa F, Baker R, Rubio IT, Benson J, Douek M. Meta-analysis of tumour burden in pre-operative axillary ultrasound positive and negative breast cancer patients. Breast Cancer Res Treat. 2017 Nov;166(2):329-336. doi: 10.1007/s10549-017-4405-3. Epub 2017 Jul 28. Erratum in: Breast Cancer Res Treat. 2017 Nov;166(2):337. PMID: 28755147; PMCID: PMC5668351
46. Hinson JL, McGrath P, Moore A, Davis JT, Brill YM, Samoilova E, Cibull M, Hester M, Romond E, Weisinger K, Samayoa LM. The critical role of axillary ultrasound and aspiration biopsy in the management of breast cancer patients with clinically negative axilla. Ann Surg Oncol. 2008 Jan;15(1):250-5. doi: 10.1245/s10434-007-9524-3. Epub 2007 Aug 7. PMID: 17680314
47. McCartan D, Stempel M, Eaton A, Morrow M, Pilewskie M. Impact of Body Mass Index on Clinical Axillary Nodal Assessment in Breast Cancer Patients. Ann Surg Oncol. 2016 Oct;23(10):3324-9. doi: 10.1245/s10434-016-5330-0. Epub 2016 Jun 23. PMID: 27338746; PMCID: PMC5070647
48. Di Micco R, Santurro L, Gasparri ML, Zuber V, Cisternino G, Baleri S, Morgante M, Rotmensz N, Canevari C, Gallivanone F, Scifo P, Savi A, Magnani P, Neri I, Ferjani N, Venturini E, Losio C, Sassi I, Bianchini G, Panizza P, Gianolli L, Gentilini OD. PET/MRI for Staging the Axilla in Breast Cancer: Current Evidence and the Rationale for SNB vs. PET/MRI Trials. Cancers (Basel). 2021 Jul 16;13(14):3571. doi: 10.3390/cancers13143571. PMID: 34298781; PMCID: PMC8303241
49. Goyal A, Dodwell D. POSNOC: A Randomised Trial Looking at Axillary Treatment in Women with One or Two Sentinel Nodes with Macrometastases. Clin Oncol (R Coll Radiol). 2015 Dec;27(12):692-5. doi: 10.1016/j.clon.2015.07.005. Epub 2015 Aug 5. PMID: 26254841
50. van Roozendaal LM, Vane MLG, van Dalen T, van der Hage JA, Strobbe LJA, Boersma LJ, Linn SC, Lobbes MBI, Poortmans PMP, Tjan-Heijnen VCG, Van de Vijver KKBT, de Vries J, Westenberg AH, Kessels AGH, de Wilt JHW, Smidt ML. Clinically node negative breast cancer patients undergoing breast conserving therapy, sentinel lymph node procedure versus follow-up: a Dutch randomized controlled multicentre trial (BOOG 2013-08). BMC Cancer. 2017 Jul 1;17(1):459. doi: 10.1186/s12885-017-3443-x. PMID: 28668073; PMCID: PMC5494134
51. de Boniface J, Frisell J, Andersson Y, Bergkvist L, Ahlgren J, Rydén L, Olofsson Bagge R, Sund M, Johansson H, Lundstedt D; SENOMAC Trialists' Group. Survival and axillary recurrence following sentinel node-positive breast cancer without completion axillary lymph node dissection: the randomized controlled SENOMAC trial. BMC Cancer. 2017 May 26;17(1):379. doi: 10.1186/s12885-017-3361-y. PMID: 28549453; PMCID: PMC5446737
52. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, Gelber RD, de Azambuja E, Fielding A, Balmaña J, Domchek SM, Gelmon KA, Hollingsworth SJ, Korde LA, Linderholm B, Bandos H, Senkus E, Suga JM, Shao Z, Pippas AW, Nowecki Z, Huzarski T, Ganz PA, Lucas PC, Baker N, Loibl S, McConnell R, Piccart M, Schmutzler R, Steger GG, Costantino JP, Arahmani A, Wolmark N, McFadden E, Karantza V, Lakhani SR, Yothers G, Campbell C, Geyer CE Jr; OlympiA Clinical Trial Steering Committee and Investigators. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021 Jun 24;384(25):2394-2405. doi: 10.1056/NEJMoa2105215. Epub 2021 Jun 3. PMID: 34081848; PMCID: PMC9126186.
53. Johnston SRD, Toi M, O'Shaughnessy J, Rastogi P, Campone M, Neven P, Huang CS, Huober J, Jaliffe GG, Cicin I, Tolaney SM, Goetz MP, Rugo HS, Senkus E, Testa L, Del Mastro L, Shimizu C, Wei R, Shahir A, Munoz M, San Antonio B, André V, Harbeck N, Martin M; monarchE Committee Members. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a

preplanned interim analysis of a randomised, open-label, phase 3 trial. Lancet Oncol. 2023 Jan;24(1):77-90. doi: 10.1016/S1470-2045(22)00694-5. Epub 2022 Dec 6. PMID: 36493792

54. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, Cataliotti L, Westenberg AH, Klinkenbijl JH, Orzalesi L, Bouma WH, van der Mijle HC, Nieuwenhuijzen GA, Veltkamp SC, Slaets L, Duez NJ, de Graaf PW, van Dalen T, Marinelli A, Rijna H, Snoj M, Bundred NJ, Merkus JW, Belkacemi Y, Petignat P, Schinagl DA, Coens C, Messina CG, Bogaerts J, Rutgers EJ. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol. 2014 Nov;15(12):1303-10. doi: 10.1016/S1470-2045(14)70460-7. Epub 2014 Oct 15. PMID: 25439688; PMCID: PMC4291166.