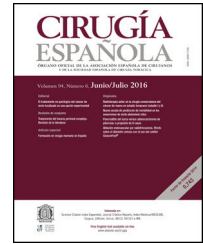




CIRUGÍA ESPAÑOLA

www.elsevier.es/cirugia


Special article

Reducing axillary surgery in breast cancer



L. Tejedor*, S. Gómez-Modet

Hospital Universitario Punta de Europa, Universidad de Cádiz, Spain

ARTICLE INFO

Article history:

Received 5 January 2023

Accepted 23 May 2023

Keywords:

Axillary lymph node dissection
Sentinel lymph node biopsy
Neoadjuvant systemic therapy
Targeted axillary dissection
De-escalating axillary surgery

A B S T R A C T

This article provides a brief account of the recent evolution of the highly controversial surgical management of the positive axilla in patients with breast cancer, an issue still open to disparate surgical procedures. This short review highlights the reports that supply the rationale for current trends in reducing the aggressiveness of this surgery and discusses the course of the trials still in progress pointing in the same direction, thus supporting the principle of not performing axillary lymph node dissection for staging purposes alone.

© 2023 AEC. Published by Elsevier España, S.L.U. All rights reserved.

Reduciendo la cirugía axilar en el cáncer de mama

R E S U M E N

Este artículo es un breve resumen de la reciente evolución del controvertido tratamiento quirúrgico de la axila en pacientes con cáncer de mama, que sigue estando abierto a procedimientos quirúrgicos demasiado dispares. Esta corta revisión destaca las publicaciones que constituyen la base lógica de las tendencias actuales hacia la reducción de la agresividad quirúrgica y recalca los ensayos clínicos aún en progreso apuntando en esta misma dirección, apoyando así el principio de evitar la linfadenectomía axilar solo por razones de estadía.

© 2023 AEC. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Palabras clave:

Linfadenectomía axilar
Biopsia de ganglio centinela
Tratamiento sistémico
neoadyuvante
Disección axilar dirigida
Desescalando la cirugía axilar

For more than a century, axillary lymph node dissection (ALND) associated with breast cancer has caused high morbidity (overall, 70%).¹ Pain, reduced arm motion, lymphedema, paresthesia (ranges: 27.5%–40%, 24%–29.8%, 3.5%–42% and 10.9%–63.2%, respectively), etc., have plagued thousands

of patients, motivating healthcare professionals involved in the treatment of this disease to explore their mitigation.^{2–6} Since the 1990s, publications about the endoscopic axillary approach (with or without liposuction) have described advantages over the open technique (mainly, less postope-

* Corresponding author.

E-mail address: tejedor@comcadiz.es (L. Tejedor).
<https://doi.org/10.1016/j.ciresp.2023.05.014>

0009-739X/© 2023 AEC. Published by Elsevier España, S.L.U. All rights reserved.

rative pain) as well as certain drawbacks (e.g., a small number of port-site recurrences); as a result, the technique has not yet gained wide acceptance.⁷⁻⁹ ALND based on breast lymphatics level, called axillary reversed mapping, is a more recent technique also aimed at reducing the extent and morbidity of the procedure.^{10,11}

Several assays including low-risk patient groups with absent palpable lymph nodes (i.e., low axillary nodal burden) have provided insight on axillary management by comparing ALND versus no axillary surgery. The NSABP-04, INT09/98, IBCSG 10-93 and AXIL95 Group trials, as well as other essays,¹²⁻¹⁷ have found no difference in disease-free or overall survival between these treatments, while also proving that axillary disease is clinically inconsequential in around half of these patients, even without adjuvant treatment. Adding systemic therapy and axillary radiotherapy was even able to further reduce the axillary recurrence rate to 1%.^{12,14,17}

Sentinel lymph node biopsy (SLNB), although not free of morbidity,² was the first of these great steps in the de-escalation of surgical aggressiveness. The NSABP B-32 trial showed that SLNB minimized the side effects of ALND, offering equivalent overall and disease-free survival rates and regional control.¹⁸ Initially, SLNB was indicated for cT1-3 N0 disease and ductal carcinoma in situ (DCIS) with suspicion of invasion or requiring mastectomy, but these indications rapidly expanded. SLNB may be considered in cases of multifocal or multicentric disease, prior breast or axillary surgery and pregnancy. The ACOSOG-Z0001 trial proved that ALND could be safely omitted in patients with fewer than 3 positive sentinel lymph nodes (SLN) (given a clinically negative axilla), breast tumor smaller than 5 cm, breast-conserving surgery (BCS) with whole-breast radiotherapy, and adjuvant treatment with hormone therapy or chemotherapy.¹⁹ These conditions for omitting ALND were later extended to SLN with micrometastases or isolated tumor cells,²⁰ mastectomy for infiltrating cancer (including T4a-c), if axillary radiation is to be administered,²¹⁻²⁴ and to the microscopic extracapsular extension of the SLN.¹⁵ SLNB is also feasible for patients with invasive local recurrence after BCS presenting with cN0, although the clinical significance of its results are not clear.²¹ In cases of positive axilla and ER+/PR+/HER2- tumor subtype (which have a low probability of response after neoadjuvant systemic therapy [NST]), primary surgery and SLNB with 1-2 positive nodes may avoid ALND. Furthermore, there seems to be no significant differences in outcome between patients with fewer than 3 positive macrometastases in SLNB receiving axillary radiotherapy compared to those with ALND, regardless of their immunohistochemical subtype or menopausal status.²⁵⁻²⁷

Currently, certain conditions have been accepted by several guidelines to omit axillary staging, including: cases in which staging will not change adjuvant therapy, pure DCIS with breast-conserving surgery, patients over the age of 70 years with hormone receptor positive T1-2 N0 tumors, prophylactic mastectomy, malignant phyllodes tumor and primary breast sarcoma.²⁰

More recently, one more step has been provided by the increased use of NST, which can convert pN1 patients to clinically negative axillary disease (ycN0) in 41%-74% of patients.²⁸⁻³⁰ In these ypN0 patients, avoidance of ALND has

been accepted by using SLNB with dual tracer and the retrieval of more than 2 negative SLN, by the retrieval of the pre-NST marked node alone (target lymph node biopsy or TLNB), or by the retrieval of the TLN with at least 2 SLN (targeted axillary dissection [TAD]). The false negative rates (FNR) of these techniques are below the consensus threshold of 10%, with TAD showing the lowest figures.^{31,32} Again, micrometastases and isolated tumor cells in these nodes, even after NST, do not lead to ALND whenever axillary radiotherapy is to be administered.²⁴ To complicate matters, the need for adjuvant axillary radiotherapy for patients with a pathological complete response on SLNB or TAD is still debatable. Since the marked node is almost systematically affected in all patients who remain N positive after NST,³³ the biopsy only of this node could be enough for axillary staging, with a higher FNR than TAD but still less than 10%.³⁴

Nevertheless, even these 2 latter techniques aimed at reducing axillary aggressiveness in initially N1 patients remain controversial, since SLNB alone could lead to the same clinical results of low regional recurrence.³⁵⁻³⁷ Thus, reducing the FNR may have minimal clinical significance as the axillary recurrence rates of N1 patients undergoing SLNB are less than 2% in some long-term follow-up reports of randomized trials, observing no significant differences compared to N0 patients.³⁸⁻⁴⁰ In other words, false-negative SLNB does not result in regional recurrence for most patients, as occurs in patients with initial surgery.

In addition, the role of the axillary status to define disease treatment has been further limited by using information provided by the biological and genetic characteristics of the tumor cells from immunohistochemistry staining and genomics platforms in the management of invasive breast cancer. HER2-positive and triple-negative patients with tumors of a certain size are treated with neoadjuvant chemotherapy and biological therapies, regardless of their axillary extension, as adjuvant treatment is administered to patients showing a high risk of recurrence in the genetic profile of their tumors, not according to the axillary involvement.⁴¹

Notwithstanding these advances, indications for ALND, though less extensive, are still significant: patients with cN2-3 at presentation (although treatment of the negative axilla is unclear), cN0 patients with 3 or more positive SLNB,^{19,22,23} failed SLNB detection in high-risk patients (high grade, lymphovascular invasion, cT3-4, HER2 positive or triple negative tumors, multifocal/multicenter disease, premenopausal), N-positive patients unfit for NST or those who remain positive after the treatment (including occult breast cancer), inflammatory breast cancer, axillary recurrence and positive axilla in invasive local recurrence.

In the pursuit of further reduction of axillary dissection, many trials are underway. The A011202/MAC19 trial randomizes patients who are SLNB positive after NAC to ALND vs no further axillary surgery, then administering axillary radiotherapy to all patients.⁴² The SOUND (Sentinel Node versus Observation after Axillary Ultrasound), NAUTILUS, INSEMA (Intergroup-Sentinel-Mamma) and the BOOG 2013-08 trials⁴³⁻⁴⁶ seek to determine whether SLNB can be avoided in cN0 patients. The TAXIS trial (Tailored Axillary Surgery with or without ALND Followed by Radiation Therapy in Patients with Clinically Node-positive Breast Cancer), SENOMAC trial (Sen-

tinell Node Biopsy in Breast Cancer: Omission of Axillary Clearance after Macrometastases) and AXSANA study⁴⁷⁻⁴⁹ search for further advances in the surgical de-escalation of the positive axilla.

We already know that the information about the axillary involvement of breast cancer only carries staging value, good local control can be obtained without ALND even in patients with positive SLNB, and prognostic information of the axillary status has lost importance due to the role of the biological characteristics of the disease (molecular subtypes and genetic platforms) in the treatment decision-making process. Consequently, the current guiding principle for most breast surgeons is not to perform ALND for staging reasons alone.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

- Kakuda JT, Stuntz M, Trivedi V, Klein SR, Vargas HI. Objective assessment of axillary morbidity in breast cancer treatment. *Am Surg*. 1999;65(10):995-8. <http://dx.doi.org/10.1177/000313489906501021>.
- Che Bakri NA, Kwasnicki RM, Naairah K, Omar G, Lee A, Grant Y, et al. Impact of axillary lymph node dissection and sentinel lymph node biopsy on upper limb morbidity in breast cancer patients: a systematic review and meta-analysis. *Ann Surg*. 2023;277(4):572-80. <https://doi.org/10.1097%2FSLA.0000000000005671>.
- Togawa K, Ma H, Sullivan-Halley J, Neuhaus ML, Imayama I, Baumgartner KB, et al. Risk factors for self-reported arm lymphedema among female breast cancer survivors: a prospective cohort study. *Breast Cancer Res*. 2014;16(4):414. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4189147/>.
- Soares EWS, Nagai HM, Bredt LC, da Cunha AD, Andrade RJ, Soares GVS. Morbidity after conventional dissection of axillary lymph nodes in breast cancer patients. *World J Surg Oncol*. 2014;12:67. <http://dx.doi.org/10.1186/1477-7819-12-67>.
- Sagen A, Karsen R, Sandvik L, Risberg MA. Changes in arm morbidities and health-related quality of life after breast cancer surgery — a five-year follow-up study. *Acta Oncologica*. 2009;48:8. <http://dx.doi.org/10.3109/02841860903061691>.
- Langer I, Guller U, Berclaz G, Koechli O, Schaer G, Fehr M, et al. Morbidity of Sentinel Lymph Node biopsy (SLN) alone versus SLN and completion axillary lymph node dissection after breast cancer surgery: a prospective Swiss multicenter study on 659 patients. *Ann Surg*. 2007;245(3):452-61. <http://dx.doi.org/10.1097/01.sla.0000245472.47748.ec>.
- Luo C, Guo W, Yang J, Sun Q, Wei W, Wu S, et al. Comparison of mastoscopic and conventional axillary lymph node dissection in breast cancer: long-term results from a randomized, multicenter trial. *Mayo Clin Proc*. 2012;87(12):1153-61. <http://dx.doi.org/10.1016/j.mayocp.2012.07.022>.
- National Institute for Clinical Excellence. Interventional Procedures Programme. Interventional procedures overview of endoscopic axillary node retrieval for breast cancer; 2004. <https://www.nice.org.uk/guidance/ipg147/evidence/overview-pdf-304302061>.
- Tang P, Hu Y, Wang Z, Gao G, Qu X, Jiang J, et al. Clinical practice guidelines for endoscopic breast surgery in patients with early-stage breast cancer: Chinese Society of Breast Surgery (CSBrS) practice guidelines 2021. *Chin Med J*. 2021;134(21). Published online. <https://mednexus.org/doi/full/10.1097/CM9.0000000000001592>
- Thompson M, Korourian S, Henry-Tillman R, Adkins L, Mumford S, Westbrook KC, et al. Axillary reverse mapping (ARM): a new concept to identify and enhance lymphatic preservation. *Ann Surg Oncol*. 2007;14(6):1890-5. <http://dx.doi.org/10.1245/s10434-007-9412-x>.
- Nos C, Lesieur B, Clough KB, Lecuru F. Blue dye injection in the arm in order to conserve the lymphatic drainage of the arm in breast cancer patients requiring an axillary dissection. *Ann Surg Oncol*. 2007;14(9):2490-6. <http://dx.doi.org/10.1245/s10434-007-9450-4>.
- 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;347(8):567-75. <http://dx.doi.org/10.1056/NEJMoa020128>.
- Agresti R, Martelli G, Sandri M, Tagliabue E, Carcangiu ML, Maugeri I, et al. Axillary lymph node dissection versus no dissection in patients with T1N0 breast cancer: a randomized clinical trial (INT09/98). *Cancer*. 2014;120(6):885-93. <http://dx.doi.org/10.1002/cncr.28499>.
- International Breast Cancer Study Group. Randomized trial comparing axillary clearance in older patients with breast cancer: first results of international breast cancer study group trial 10-93. *J Clin Oncol*. 2006;24(3):337-44.
- Avril A, Le Bouedec G, Lorimier E, Classe JM, Tunon-de-Lara C, Giard S, et al. Phase III randomized equivalence trial of early breast cancer treatments with or without axillary clearance in post-menopausal patients results after 5 years of follow-up. *Eur J Surg Oncol*. 2011;37(7):563-70. <http://dx.doi.org/10.1016/j.ejso.2011.04.008>.
- Martelli G, Boracchi P, Ardoino I, Lozza L, Bohm S, Vetralla G, et al. Axillary dissection versus no axillary dissection in older patients with T1N0 breast cancer: 15-year results of a randomized controlled trial. *Ann Surg*. 2012;256(6):920-4. <http://dx.doi.org/10.1097/SLA.0b013e31827660a8>.
- Veronesi U, Orecchia R, Zurrada S, Galimberti V, Luini A, Veronesi P, et al. Avoiding axillary dissection in breast cancer surgery: a randomized trial to assess the role of axillary radiotherapy. *Ann Oncol*. 2005;16(3):383-8. <http://dx.doi.org/10.1093/annonc/mdl089>.
- Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol*. 2010;11(10):927-33.
- Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *Jama*. 2011;305(6):569e75. <http://dx.doi.org/10.1001/jama.2011.90>.
- Galimberti V, Cole BF, Zurrada S, Viale G, Luini A, for the International Breast Cancer Study Group Trial 23-01 investigators. et al. IBCSG 23-01 randomised controlled trial comparing axillary dissection versus no axillary dissection in patients with sentinel node micrometastases. *Lancet Oncol*. 2013;14(4):297-305. [http://dx.doi.org/10.1016/S1470-2045\(13\)70035-4](http://dx.doi.org/10.1016/S1470-2045(13)70035-4).
- Cody HS III, Snider H, Schwartz T, Rosenkranz KM, James TA, The Society's ALND Working Group. Consensus guideline on axillary management for patients with in-situ and invasive breast cancer: a concise overview. The American Society of Breast Surgeons. Official statement; 2022. <https://www.breastsurgeons.org/docs/statements/>

Consensus-Guideline-on-the-Management-of-the-Axilla-Concise-Overview.pdf.

22. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJH, et al. 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;15(12):1303-10. [http://dx.doi.org/10.1016/s1470-2045\(14\)70460-7](http://dx.doi.org/10.1016/s1470-2045(14)70460-7).
23. Savolt A, Peley G, Polgar C, Udvarherlyi N, Rubovszky G, Kovacs E, et al. Eight-year follow up result of the OTOASOR trial: the Optimal Treatment of the Axilla – Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: a randomized, single centre, phase III, non-inferiority trial. *Eur J Surg Oncol.* 2017;43(4):672-9. <http://dx.doi.org/10.1016/j.ejso.2016.12.011>.
24. Burstein HJ, Curigliano G, Loibl S, Winer EP, Thurlimann B, Members of the St. Gallen Consensus Panel on the Primary Therapy of Early Breast Cancer. 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;30(10):1541-57. <http://dx.doi.org/10.1093/annonc/mdz235>.
25. Bilimoria KY, Bentrem DJ, Hansen NM, Bethke KP, Rademaker AW, Ko CY, et al. Comparison of sentinel lymph node biopsy alone and completion axillary lymph node dissection for node-positive breast cancer. *J Clin Oncol.* 2009;27(18):2946-53. <http://dx.doi.org/10.1200/jco.2008.19.5750>.
26. Li CZ, Zhang P, Li RW, Wu CT, Zhang XP, Hu HC. Axillary lymph node dissection versus sentinel lymph node biopsy alone for early breast cancer with sentinel node metastasis: a meta-analysis. *Eur J Surg Oncol.* 2015;41(8):958-66. <http://dx.doi.org/10.1016/j.ejso.2015.05.007>.
27. Lee J, Choi JE, Kim SJ, Lee SB, Seong M, Jeong J, et al. Comparative study between sentinel lymph node biopsy and axillary dissection in patients with one or two lymph node metastases. *J Breast Cancer.* 2018;21(3):306-14. <http://dx.doi.org/10.4048/jbc.2018.21.e44>.
28. Diego EJ, McAuliffe PF, Soran A, McGuire KP, Jhonson RR, Bonaventura M, et al. Axillary staging after neoadjuvant chemotherapy for breast cancer: a pilot study combining sentinel lymph node biopsy with radioactive seed localization of pre-treatment positive axillary lymph nodes. *Ann Surg Oncol.* 2016;23:1549-53. <https://link.springer.com/article/10.1245/s10434-015-5052-8>.
29. Dominici LS, Negron Gonzalez VM, Buzdar AU, Lucci A, Mittendorf EA, Le-Petross HT, et al. Cytologically proven axillary lymph node metastases are eradicated in patients receiving preoperative chemotherapy with concurrent trastuzumab for HER2-positive breast cancer. *Cancer.* 2010;116(12):2884-9. <http://dx.doi.org/10.1002/cncr.25152>.
30. Boughey JC, McCall LM, Ballman KV, Mittendorf EA, Ahrendt GM, Wilke LG, et al. Tumor biology correlates with rates of breast-conserving surgery and pathologic complete response after neoadjuvant chemotherapy for breast cancer: findings from the ACOSOG Z1071 (Alliance) Prospective Multicenter Clinical Trial. *Ann Surg.* 2014;260(4):608-16. <https://doi.org/10.1097%2FSLA.0000000000000924>.
31. Montagna G, Lee MK, Sevilimedu V, Barrio EV, Morrow M. Is nodal clipping beneficial for node-positive breast cancer patients receiving neoadjuvant chemotherapy? *Ann Surg Oncol.* 2022;29:6133-9. <http://dx.doi.org/10.1245/s10434-022-12240-6>.
32. Kuemmel S, Heil J, Rueland A, Seiberling C, Harrach H, Schindowski D, et al. A prospective, multicenter registry study to evaluate the clinical feasibility of targeted axillary dissection (TAD) in node-positive breast cancer patients. *Ann Surg.* 2022;276(5):e553-62. <http://dx.doi.org/10.1097/sla.0000000000004572>.
33. García-Novoa A, Acea-Nebri B, Díaz Carballada C, Bouzón Alejandro A, Conde C, Cereijo Gareia C, et al. Combining wire localization of clipped nodes with sentinel lymph node biopsy after neoadjuvant chemotherapy in node-positive breast cancer: preliminary results from a prospective study. *Ann Surg Oncol.* 2021;28(2):958-67. <http://dx.doi.org/10.1245/s10434-020-08925-5>.
34. de-Wild SR, Simons JM, Vranken Peeters MJTFD, Smidt ML, Koppert LB. De-escalating axillary surgery in node-positive breast cancer treated with neoadjuvant systemic therapy. *Breast Care.* 2021;16:584-9. <http://dx.doi.org/10.1159/000518376>.
35. Kahler-Ribeiro-Fontana S, Pagan E, Magnoni F, Vicini E, Morigi C, Corso G, et al. Long-term standard sentinel node biopsy after neoadjuvant treatment in breast cancer: a single institution ten-year follow-up. *Eur J Surg Oncol.* 2020;47(4):804-12. <http://dx.doi.org/10.1016/j.ejso.2020.10.014>.
36. Galimberti V, Ribeiro Fontana SK, Maisonneuve P, Steccanella F, Vento AR, Intra M, et al. Sentinel node biopsy after neoadjuvant treatment in breast cancer: five-year follow-up of patients with clinically node-negative or node positive disease before treatment. *Eur J Surg Oncol.* 2016;42(3):361-8. <http://dx.doi.org/10.1016/j.ejso.2015.11.019>.
37. Tee SR, Devane LA, Evov D, Rothwell J, Geraghty J, Prichard RS, et al. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. *Br J Surg.* 2018;105:1541-52. <http://dx.doi.org/10.1002/bjs.10986>.
38. Hunt KK, Yi M, Mittendorf EA, Guerrero CBA, Babiera GV, Bedrosian I, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy is accurate and reduces the need for axillary dissection in breast cancer patients. *Ann Surg.* 2009;250(4):558-66. <http://dx.doi.org/10.1097/SLA.0b013e3181b8fd5e>.
39. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomized controlled trial. *Lancet Oncol.* 2013;14(4):297-305. [http://dx.doi.org/10.1016/S1470-2045\(13\)70035-4](http://dx.doi.org/10.1016/S1470-2045(13)70035-4).
40. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJH, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomized, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol.* 2014;15(12):1303e10. [http://dx.doi.org/10.1016/s1470-2045\(14\)70460-7](http://dx.doi.org/10.1016/s1470-2045(14)70460-7).
41. National Comprehensive Cancer Network (NCCN). Guidelines version 3. 2023 Invasive Breast Cancer. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
42. Boughey J, Haffty B, Buchholz T, Symmans WF, Hunt K, Armer J, et al. Alliance A011202: a randomized phase III trial comparing axillary lymph node dissection to axillary radiation in breast cancer patients (cT1-3 N1) who have positive sentinel lymph node disease after receiving neoadjuvant chemotherapy. *ClinicalTrials.gov*. National Institute of Health. US National Library of Medicine; 2013. <https://clinicaltrials.gov/ct2/show/NCT01901094>.
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;21(5):678-81. <http://dx.doi.org/10.1016/j.breast.2012.06.013>.
44. Jung JG, Ahn SH, Lee S, Kim E, Ryu JM, Park S, et al. No axillary surgical treatment for lymph node-negative patients after ultra-sonography [NAUTILUS]: protocol of a prospective randomized clinical trial. *BMC Cancer.* 2022;22:189. <http://dx.doi.org/10.1186/s12885-022-09273-1>.

45. Reimer T, Stachs A, Nekljudova V, Loibl S, Hartmann S, Wolter K, et al. Restricted axillary staging in clinically and sonographically node-negative early invasive breast cancer (c/it1-2) in the context of breast conserving therapy: first results following commencement of the intergroup-sentinel-mamma (INSEMA) trial. *Geburtshilfe Frauenheilkd.* 2017;77(2):149–57. <http://dx.doi.org/10.1055/s-0042-122853>.
46. van Roozendaal LM, Vane MLG, van Dalen T, van der Hage JA, Strobbe LJA, Boersma LJ, et al. 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;17(1):459. <http://dx.doi.org/10.1186/s12885-017-3443-x>.
47. Henke G, Knauer M, Ribi K, Hayoz S, Gérard MA, Ruhstaller T, et al. Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS): study protocol for a multicenter, randomized phase-III trial. *BMC Trials.* 2018;19(1):667. <http://dx.doi.org/10.1186/s13063-018-3021-9>.
48. de Boniface J, Frisell J, Andersson Y, Bergkvist L, Ahlgren J, Rydén L, et al. Survival and axillary recurrence following sentinel node-positive breast cancer without completion axillary lymph node dissection: the randomized controlled SENOMAC trial. *BMC Cancer.* 2017;17(1):379. <http://dx.doi.org/10.1186/s12885-017-3361-y>.
49. Banys-Paluchowski M, Gasparri ML, de Boniface J, Gentilini O, Stickeler E, The AXSANA Study Group. et al. Surgical management of the axilla in clinically node-positive breast cancer patients converting to clinical node negativity through neoadjuvant chemotherapy: current status, knowledge gaps, and rationale for the EUBREAST-03 AXSANA study. *Cancers.* 2012;13:1565. <http://dx.doi.org/10.3390/cancers13071565>.