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Surgical Management of the Axilla in Breast Cancer: Evolving but Still Necessary

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The treatment of breast cancer continues to evolve at an exceptionally rapid rate.

Understanding of the importance of tumor biology and improvements in systemic therapy have greatly affected management. These improvements in systemic therapy, such as targeted therapy and immunotherapy, have resulted in improved locoregional control and de-escalation of locoregional therapy. Surgical treatment, as well, has developed to lessen side effects and improve quality of life. To understand the current role of axillary staging, the historical perspective of surgical management must be considered. The Halstedian view that breast cancer treatment must rely on maximum invasive locoregional therapy was disproven following modifications to the radical mastectomy and development of breast conserving therapy in the mid and late 20th century. The publication of the randomized trials by National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 and B-06 proved that less radical treatment of the breast is as effective as extensive alternatives.^{1,2} Although the extent of the operation on the breast itself decreased, the need for an axillary lymph node dissection (ALND) for staging and treatment remained unchanged for nearly the entire 20th century. Resection of involved nodes was considered essential for cure, and removal of uninvolved nodes essential for accurate staging. Despite the findings of NSABP B-04 showing no improvement in survival with axillary

dissection, the procedure remained necessary to identify patients with nodal involvement for whom adjuvant chemotherapy was recommended.

Surgeons then began to examine the extent of axillary surgery for accurate staging, and its role was finally challenged in the early 1990s with the development of sentinel lymph node biopsy (SLNB). The sentinel lymph node (SLN) hypothesis states there is a lymph node, or several nodes, to which a breast cancer spreads if it indeed metastasizes to the axilla. This hypothesis was proven by performing a SLNB and then, on the same patient, completing the ALND, thus illustrating that the status of the SLN accurately predicts the status of the entire axilla. The first major change utilizing SLNB resulted in the omission of traditional Level I and II ALND for the management of patients with early-stage breast cancer who had SLNs that were free of tumor. Axillary management was revolutionized by this simple procedure, which spared most node-negative patients an ALND. This was first shown in a pilot study³ and then in other prospective randomized multicenter trials.^{4,5} The largest of these trials was NSABP B-32, which randomized clinically node negative patients to SLNB alone or SLNB followed by ALND. All patients were pathologically node negative. Locoregional recurrence rates were less than 1% in both cohorts and overall survival (OS) and disease-free survival (DFS) were equivalent. The differences in patient-reported outcomes between SLNB alone and SLNB followed by ALND were quite remarkable. ALND was shown to have statistically significantly higher rates of lymphedema, sensory deficits, pain, and decreased range of motion than SLNB alone. Even before the publication of this trial, SLNB became the treatment of choice for axillary staging in the clinically node negative patient.^{5,6} This study and other randomized trials demonstrated that overall survival, breast cancer

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First Received: 1 August 2022

Accepted: 14 September 2022

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Published online: 04 October 2022

specific survival, and locoregional recurrence did not differ between women with tumor-free SLNs who undergo ALND or no completion axillary surgery. De-escalation of axillary surgical management with a SLNB in the node negative patient was shown to minimize morbidity without affecting oncologic outcomes.

SLNB alone without ALND for women with a tumor-free SLN was fairly rapidly accepted⁶ without results of randomized trials. However, patients whose SLN had even small deposits of tumor cells detected with immunohistochemistry (IHC)—now called isolated tumor cells (ITC), defined as a tumor deposit of ≤ 0.2 mm, or micrometastases, defined as a tumor deposit > 0.2 to ≤ 2 mm—were subjected to completion ALND. The prospective American College of Surgeons Oncology Group (ACOSOG) Z0010 trial evaluated the association between survival and metastases detected by IHC staining of SLNs and bone marrow biopsy specimens in patients with cT1–T2, cN0 breast cancer between 1999 and 2003. In the 3326 SLNs that were tumor-free on hematoxylin-eosin staining (H&E), 349 (10.5%) contained occult disease found with IHC. The findings of small metastases did not affect overall survival. Following publication of this study, IHC was no longer recommended for evaluation of SLNs by the College of American Pathologists.⁷

The prospective, randomized International Breast Cancer Study Group (IBCSG) more rigorously proved that micrometastases were not clinically significant and did not require treatment with ALND or alterations in systemic therapy.⁸ In IBCSG 23-01, 934 women undergoing lumpectomy or mastectomy with T1 or T2 tumors and micrometastatic disease in ≥ 1 SLN were randomized to ALND or no ALND between 2001 and 2010. Among the patients in the ALND cohort, additional involved axillary nodes were found in 13% of patients. After a median follow-up of over 5 years, there were no significant differences in axillary recurrence, OS or DFS between the two groups (axillary recurrence rates of 1% in the observation group versus $< 1\%$ in the ALND group; 87.8% in the observation group versus 84.4% 5-year DFS in the ALND group, $p = 0.16$). However, there were significantly higher rates of sensory neuropathy (18% versus 12%, $p = 0.012$), lymphedema (13% versus 3%, $p < 0.0001$), and motor neuropathy (8% versus 3%, $p = 0.0004$) in the ALND group compared with the group not treated with ALND. While many major centers abandoned ALND for patients with ITCs or micrometastases in the SLN, many treating physicians and even academic centers were reluctant to abandon ALND and accept the biologic concepts indicating that small metastases were not relevant for patients with modern treatment, illustrated by ACOSOG Z0010 and IBCSG 23-01.

The reluctance to accept omission of ALND for patients with micrometastases in the SLN was mild compared with the passion to complete ALND for patients with SLN macrometastases. Although the NSABP B-04 trial showed no survival advantage to removal or irradiating axillary lymph nodes, axillary management in this trial was largely ignored, primarily because of the use of adjuvant chemotherapy for node-positive women. With 25 years of follow-up, no improvement in survival could be demonstrated by treatment of the axilla in NSABP B-04 even without the use of adjuvant systemic therapy and even though most cancers were palpable and not screen-detected. Based on these results, ACOSOG Z0011 was designed and completed. This study included women with metastases detected with H&E who were treated with breast conserving surgery and SLNB. The study was designed specifically for patients undergoing breast conserving therapy for several reasons. NSABP B-04 was criticized because patients treated with mastectomy often had several lymph nodes included in the axillary tail. In addition, the reluctance to de-escalate axillary surgery exhibited by all specialties treating breast cancer was mitigated by the use of opposing tangential radiation fields, which were known to treat the low axilla.

ACOSOG Z0011 examined the effect of omission of ALND in women with SLN metastases treated with contemporary adjuvant systemic therapy. Patients with clinical T1 or T2 N0 breast cancer who underwent breast conserving surgery and were found to have one or two positive SLNs were randomized to ALND versus no further axillary surgery. Both micrometastases and macrometastases were allowed in this trial. In the SLNB alone cohort, 44.8% had micrometastases while 55.2% had macrometastases. All patients were to be treated with whole breast radiation and adjuvant systemic therapy.⁹ After 10 years of follow-up, this trial showed no significant difference in axillary recurrence (1.5% in observation only versus 0.5% in ALND, $p = 0.28$) or distant disease-free survival rates (80.2% in observation versus 78.2% in ALND, $p = 0.32$).¹⁰ ACOSOG Z0011 demonstrated that SLNB alone is as effective as ALND for selected patients with early node positive breast cancer undergoing breast conserving therapy and adjuvant systemic therapy.

ACOSOG Z0011 was not the only trial to demonstrate that ALND could be omitted for patients with involved SLNs. Equivalence in local control with axillary radiation, instead of ALND, in patients with ≤ 3 positive SLNs was later proven in the AMAROS (2001–2010) and OTOASOR (2002–2009) trials.^{11,12} In both trials, cN0 women who were found to have 1–3 positive SLNs were randomized to ALND or axillary radiation. Axillary radiation was not associated with a statistically significant higher risk of axillary recurrence than ALND in either study. ALND was,

however, shown to result in higher rates of lymphedema than axillary radiation in the AMAROS trial. All publications to date fail to show any association between axillary surgery and breast cancer-related outcomes. Although AMAROS showed decreased rates of lymphedema at 5 years, longer follow-up has not been published.

Complete omission of axillary staging in the elderly was examined in the Cancer and Leukemia Group B (CALGB) 9343 trial. In addition to evaluating the role of adjuvant radiation, it also allowed for evaluation of the role of ALND. From 1994 to 1999, CALGB 9343 enrolled patients 70 years of age and older who underwent a margin negative lumpectomy with cT1N0, hormone receptor (HR) positive breast cancer. While ALND was allowed, it was not encouraged. Patients were randomized to either tamoxifen plus whole breast irradiation or tamoxifen alone. Among the 62% of patients who did not undergo ALND, there were no axillary recurrences in the tamoxifen plus radiation group and 6 of 200 (3%) developed an axillary recurrence in the tamoxifen only group. Based on these results, the use of nodal staging in this population was questioned unless it would change systemic therapy recommendations.^{13,14} In IBCSG 10-93, postmenopausal women ≥ 60 years old with cT1–T3, cN0 breast cancer were randomized to breast surgery followed by tamoxifen with or without ALND. Of the 473 patients enrolled in this trial from 1993 to 2002, 45% underwent mastectomy, 33% underwent lumpectomy with radiation therapy, and 23% underwent lumpectomy without radiation. Locoregional recurrence was not significantly different among the groups—reported in 3% of the patients who did not undergo ALND and 1% of those who did. Like the findings of other trials, 28% of the patients who underwent ALND were found to be node positive. It is again safe to assume that 28% of the patients who did not have an ALND would have also been pathologically node positive, but a higher axillary failure rate was not identified.¹⁵

Due to the lack of survival benefit with nodal staging and the competing co-morbidities found in the older patient population with breast cancer, multiple other retrospective studies have shown that ALND can be safely deferred in clinically node negative women 70 years of age and older with HR-positive breast cancer.^{16–19} Axillary surgery may be omitted for selected patients, including women 70 years or older with early stage, clinically node negative, HR-positive breast cancer, women with severe co-morbidities for whom decisions for adjuvant therapy will not change despite axillary status, and perhaps those with histologic subtypes for whom the risk of nodal metastases is extremely low. The Society of Surgical Oncology Quality Committee subsequently initiated the Choosing Wisely Guidelines for breast cancer in 2016, in which routine use of SLNB in this group of women is discouraged.²⁰ As these

patients are unlikely to have chemotherapy recommended, regardless of nodal status, axillary surgery appears unnecessary. Since publication of these guidelines, it has been accepted that the benefit of nodal staging in this cohort is minimal and omission is deemed safe.

However, the recent publication of monarchE has challenged this, and may render the need for axillary staging in a group of women in whom its omission was accepted. The monarchE clinical trial randomized 5637 patients to adjuvant endocrine therapy for 5 years with or without abemaciclib for 2 years. Patients were eligible if they had four or more positive lymph nodes or 1–3 positive lymph nodes and high-risk features. The study demonstrated a 29% reduction in developing an invasive disease-free survival event for patients treated with abemaciclib. Notably, 57% of patients were post-menopausal.²¹ The results from monarchE align women with HR-positive breast cancer in a category similar to HER2-overexpressing tumors and triple negative breast cancer (TNBC), whereby understanding nodal status contributes to survival. Furthermore, the results of monarchE may prompt the need for ALND in more women with HR-positive breast cancer and a positive SLN to determine the need for abemaciclib. Additional studies may create additional dilemmas for surgical staging.

If there is pathologic nodal involvement, studies have demonstrated that axillary staging affects adjuvant radiation and systemic therapy decisions. Chapgar et al. utilized the NCDB to evaluate women 70 years of age and older with clinically node negative, HR-positive breast cancer.²² They found that 15% of patients had pathologically involved lymph nodes. These patients were more likely to receive chemotherapy, hormone therapy, and adjuvant radiation (post-lumpectomy and post-mastectomy). This was independent of tumor size, grade, patient age, and co-morbidities. The results support the continued use of axillary staging in elderly women in whom adjuvant treatment decisions, such as the use of whole breast radiation therapy, depend on its findings.

The status of the axillary lymph nodes historically played a significant role in determining need and extent of adjuvant systemic therapy. In recent years, however, genomic assays have been developed to predict prognosis and response to adjuvant systemic chemotherapy and the importance of anatomic staging appears to be diminished, with tumor biology now at the forefront.^{23,24} The results from the RxPONDER trial demonstrated no benefit for chemotherapy in post-menopausal women with HR-positive tumors and recurrence score (RS) of 25 or lower. However, all pre-menopausal women with nodal metastases in 1–3 SLNs were shown to benefit from chemotherapy.²⁴ Thus, nodal staging remains imperative in pre-menopausal women with HR-positive breast cancer,

but may not be necessary for clinically node negative postmenopausal women with low recurrence score or elderly women with small HR-positive tumors. Elderly women with larger tumors or palpable nodes still require axillary staging. In women with a clinically negative axilla, the axillary operation itself has no measurable impact on survival. However, nodal staging often influences systemic therapy decisions and provides information contributing to survival. Genomic assays provide useful information but cannot completely replace the knowledge gained from axillary staging. Nodal status is necessary to inform adjuvant treatment decision making, specifically when to escalate and de-escalate therapy. This can be seen across all biological subtypes of breast cancer.

In women with HER2-overexpressing tumors, the APT study demonstrated the safety of systemic therapy de-escalation. Between 2007 and 2010, 410 women with HER2-overexpressing tumors that were 3 cm or less and had pathologically uninvolved lymph nodes (though after 2009 a single micrometastases was permitted) who were administered adjuvant paclitaxel for 12 weeks and trastuzumab for 9 months had excellent results despite de-escalated therapy. With reported 7 years of follow-up, overall and disease-free survival were over 95%.²⁵ For women with HER2-overexpressing tumors that are 3 cm or smaller, axillary surgery permits de-escalation of systemic therapy if the SLN is pathologically tumor-free.

The presence of residual disease in the breast or axilla in patients with HER2-overexpressing tumors or triple negative breast cancer (TNBC) after neoadjuvant chemotherapy (NAC) prompts the need for escalated adjuvant therapy. The KATHERINE trial, conducted between 2013 and 2015, randomized 1486 women with HER2-overexpressing tumors and residual disease following NAC to trastuzumab or TDM-1. After 40-months of follow up, TDM-1 resulted in a 50% improvement in disease free survival.²⁶ The CREATE-X study (2007–2012) randomized 887 women with TNBC who had residual disease following NAC to capecitabine or no further therapy. Adjuvant capecitabine was found to prolong disease-free survival and overall survival in this cohort.²⁷ The benefit of adjuvant TDM-1 and capecitabine following NAC for women with HER2-overexpressing tumors and TNBC, respectively, mandates axillary staging to assess for residual nodal disease after NAC. No imaging modality has been shown to reliably identify residual disease after NAC.

Two areas for which there is no consensus for management warrant further attention: (1) the node positive patient after neoadjuvant chemotherapy and (2) observation versus SLNB in all clinically node negative patients. There are new data on the horizon that will hopefully shed some light on these conundrums. First and foremost, the results of the Alliance A11202 trial are long awaited. In

this phase III clinical trial, patients who are persistently node positive following NAC are randomized to regional nodal irradiation (RNI) plus axillary radiation or RNI plus ALND.²⁸ Expected trial completion is January 2024, and the findings will undoubtedly enhance understanding of the management of the node positive axilla after NAC. Until the results of this study are available, if a patient is node positive after NAC, ALND is recommended. Second, the ongoing SOUND (Sentinel node versus Observation after axillary UltraSouND), INSEMA (Intergroup-Sentinel-Mamma), and BOOG 2013-08 trials are comparing SLNB to observation in clinically node negative patients.^{29–31} The reported sensitivity and specificity of axillary ultrasound ranges from 26.4% to 94% and 53% to 98.1%, respectively.^{32,33} Without complete data from the trials mentioned above to guide treatment recommendations, axillary imaging cannot replace surgical nodal staging.

Therapy of breast cancer should change only after scientific trials demonstrate an improvement in outcome. This is a lesson previously learned when randomized studies dispelled the myth that high doses of chemotherapy followed by bone marrow autotransplantation was the preferred treatment for women with recurrent or advanced breast cancer.³⁴ Currently, there is no Level 1 evidence to support the routine omission of axillary surgery for most women with breast cancer. Genomic testing and randomized trials did not eliminate axillary surgery. They only refined its indications.

CONCLUSIONS

These dramatic changes in breast cancer management and our understanding have led some to suggest that axillary staging is obsolete. While it appears true that axillary operations themselves may not improve survival for most patients with early breast cancer, they remain necessary to select therapy that may be lifesaving or to permit de-escalation of treatment. There are no biologic predictors of nodal metastases, and no imaging modality is considered sensitive or specific enough to permit the omission of surgical axillary staging, which can lead to alterations in treatment. While prospective, randomized studies demonstrated that ALND is not necessary for some women with limited SLN metastases, these studies do not render axillary surgery obsolete. In these studies, all patients had a SLNB to determine axillary status. Furthermore, the impact of omission of ALND remains unproven in women with palpable lymph nodes, women undergoing operation with tumors greater than 5 cm or with three or more positive sentinel lymph nodes, women with gross extranodal extension, women for whom radiation is contraindicated, or women with residual nodal metastases following NAC.

In 2022, SLNB should be performed for nearly all clinically node negative patients. Axillary staging may be omitted for some patients, including those undergoing prophylactic mastectomy or those with ductal carcinoma in situ (DCIS) treated with breast conserving surgery. Axillary staging may also be omitted when axillary status is irrelevant and will not influence systemic therapy, such as patients 70 years or older with early stage, HR-positive breast cancer or patients with severe co-morbidities in whom adjuvant therapy will not be administered.

While ongoing studies may provide some answers to axillary management in different clinical scenarios, they may also lead to the possibility of omission of an axillary operation in certain groups of patients and to additional questions. Currently, axillary surgery is necessary for most women with breast cancer. There is no method to detect axillary metastases as effectively as axillary operation. SLNB remains the cornerstone of axillary management. It can only be omitted in a small number of selected patients. It is not outmoded or obsolete and cannot be discarded.

REFERENCES

- 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. <https://doi.org/10.1056/NEJMoa020128>.
- Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002;347(16):1233–41. <https://doi.org/10.1056/NEJMoa022152>.
- Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg.* 1994;220(3):391–401. <https://doi.org/10.1097/0000658-199409000-00015>.
- Giuliano AE, Haigh PI, Brennan MB, et al. Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer [published correction appears in *J Clin Oncol* 2000 Nov 15;18(22):3877]. *J Clin Oncol.* 2000;18(13):2553–9. <https://doi.org/10.1200/JCO.2000.18.13.2553>.
- Krag DN, Anderson SJ, Julian TB, 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. [https://doi.org/10.1016/S1470-2045\(10\)70207-2](https://doi.org/10.1016/S1470-2045(10)70207-2).
- Schwartz GF, Giuliano AE, Veronesi U. Proceedings of the consensus conference on the role of the sentinel lymph node biopsy in carcinoma of the breast April 19 to 22, 2001 Philadelphia Pennsylvania. *Hum Pathol.* 2002;33(6):579–89.
- Giuliano AE, Hawes D, Ballman KV, et al. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. *JAMA.* 2011;306(4):385–93.
- Galimberti V, Cole BF, Zurrada S, 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.
- Giuliano AE, Hunt KK, Ballman KV, 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):569–75. <https://doi.org/10.1001/jama.2011.90>.
- Giuliano AE, Ballman KV, McCall L, et al. 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;318(10):918–26. <https://doi.org/10.1001/jama.2017.11470>.
- Donker M, van Tienhoven G, Straver ME, 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. [https://doi.org/10.1016/S1470-2045\(14\)70460-7](https://doi.org/10.1016/S1470-2045(14)70460-7).
- Sávolt Á, Péley G, Polgár C, 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. <https://doi.org/10.1016/j.ejso.2016.12.011>.
- Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med.* 2004;351(10):971–7. <https://doi.org/10.1056/NEJMoa040587>.
- Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol.* 2013;31(19):2382–7. <https://doi.org/10.1200/JCO.2012.45.2615>.
- International Breast Cancer Study Group, Rudenstam CM, Zahrieh D, et al. Randomized trial comparing axillary clearance versus no 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. <https://doi.org/10.1200/JCO.2005.01.5784>.
- Chung A, Gangi A, Amersi F, Zhang X, Giuliano A. Not performing a sentinel node biopsy for older patients with early-stage invasive breast cancer. *JAMA Surg.* 2015;150(7):683–4. <https://doi.org/10.1001/jamasurg.2015.0647>.
- Boughey JC, Haffty BG, Habermann EB, Hoskin TL, Goetz MP. Has the time come to stop surgical staging of the axilla for all women age 70 years or older with hormone receptor-positive breast cancer? *Ann Surg Oncol.* 2017;24(3):614–7. <https://doi.org/10.1245/s10434-016-5740-z>.
- Welsh JL, Hoskin TL, Day CN, Habermann EB, Goetz MP, Boughey JC. Predicting nodal positivity in women 70 years of age and older with hormone receptor-positive breast cancer to aid incorporation of a Society of Surgical Oncology Choosing Wisely guideline into clinical practice. *Ann Surg Oncol.* 2017;24(10):2881–8. <https://doi.org/10.1245/s10434-017-5932-1>.
- McKevitt E, Cheifetz R, DeVries K, et al. Sentinel node biopsy should not be routine in older patients with ER-positive HER2-negative breast cancer who are willing and able to take hormone therapy. *Ann Surg Oncol.* 2021;28(11):5950–7. <https://doi.org/10.1245/s10434-021-09839-6>.
- Choosing Wisely, (2016). <https://www.choosingwisely.org/clinician-lists/sso-sentinel-node-biopsy-in-node-negative-women-70-and-over/>. Accessed Apr 14 2022.
- Harbeck N, Rastogi P, Martin M, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE

- study. *Ann Oncol.* 2021;32(12):1571–81. <https://doi.org/10.1016/j.annonc.2021.09.015>.
22. Chagpar AB, Horowitz N, Sanft T, et al. Does lymph node status influence adjuvant therapy decision-making in women 70 years of age or older with clinically node negative hormone receptor positive breast cancer? *Am J Surg.* 2017;214(6):1082–8. <https://doi.org/10.1016/j.amjsurg.2017.07.036>.
 23. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med.* 2018;379(2):111–21. <https://doi.org/10.1056/NEJMoa1804710>.
 24. Kalinsky K, Barlow WE, Gralow JR, et al. 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. *N Engl J Med.* 2021;385(25):2336–47. <https://doi.org/10.1056/NEJMoa2108873>.
 25. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer [published correction appears in *N Engl J Med.* 2015 Nov 12;373(20):1989]. *N Engl J Med.* 2015;372(2):134–41. <https://doi.org/10.1056/NEJMoa1406281>.
 26. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med.* 2019;380(7):617–28. <https://doi.org/10.1056/NEJMoa1814017>.
 27. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med.* 2017;376(22):2147–59. <https://doi.org/10.1056/NEJMoa1612645>.
 28. Comparison of axillary lymph node dissection with axillary radiation for patients with node-positive breast cancer treated with chemotherapy. Alliance A11202 Trial, NCT01872975. <https://clinicaltrials.gov/ct2/show/NCT01901094>. Accessed 2 May 2022.
 29. 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. <https://doi.org/10.1016/j.breast.2012.06.013>.
 30. Reimer T, Stachs A, Nekljudova V, 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. <https://doi.org/10.1055/s-0042-122853>.
 31. van Roozendaal LM, Vane MLG, van Dalen T, 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. <https://doi.org/10.1186/s12885-017-3443-x>.
 32. Alvarez S, Anorbe E, ALcorta P, et al. Role of sonography in the diagnosis of axillary lymph node metastases in breast cancer: a systematic review. *Am J Roentgenol.* 2006;186:1342–8.
 33. Abe H, Schmidt RA, Kulkarni K, et al. Axillary lymph nodes suspicious for breast cancer metastasis: sampling with US-guided 14-gauge core needle biopsy—clinical experience in 100 patients. *Radiology.* 2009;250:41–9.
 34. Gottlieb S. Bone marrow transplants do not help in breast cancer. *West J Med.* 1999;170(6):376.

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