The Breast 67 (2023) 21–25

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

"This house believes that: Sentinel node biopsy alone is better than TAD after NACT for cN+ patients"

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ARTICLE INFO

Keywords:
Neoadjuvant chemotherapy
Pathologic response
Sentinel node biopsy
Target axillary dissection

ABSTRACT

The increased use of neoadjuvant chemotherapy (NACT) has changed the approach to breast surgery. NACT allows de-escalation of surgery by both increasing breast conservation rates (up to 40%), the initial goal of this chemotherapy, and in particular it permits reduces axillary surgery. Furthermore, in relation to the molecular characteristics of the tumor we can have a pathological complete response (pCR) ranging from 20 to 80%.

In clinically node positive (cN+) patients who converted to clinically node-negative (cN0) various prospective studies have demonstrated that the false negative rate (FNR) of the sentinel node biopsy (SNB) were higher than the acceptable 10% and strategies to reduce the FNR in cN + patients are being investigated.

But all the effort to reduce the FNR does not have clinical prognostic significance. This has already been demonstrated in the literature in different randomized trials with long term follow up.

The 10-year follow-up of our study confirmed our preliminary data that the use of standard SNB without the use of clip is acceptable in cN1/2 patients who become cN0 after NAT and will not translate into a worse outcome.

In fact, the axillary recurrences were less than 2%. Similar positive data with different follow up were also confirmed by other studies that used SNB alone without TAD. All these studies, with encouraging results on the follow up, confirm that SN surgery alone for selected patients who have an excellent response to NACT is rationale and not oncologically inferior to AD during a short- and long-term follow-up.

1. Introduction

Since 2000 sentinel node biopsy (SNB) has become standard practice in breast surgery, particularly for clinically negative axilla cases [1–3]. Subsequently, thanks to randomized studies such as IBCSG 23–01, Z0011 and Amaros, axillary dissection (AD) was abandoned also for patients with a positive sentinel node. But clinically positive axillary nodes were widely considered a contraindication to SNB in breast cancer in upfront surgery [2,4,5].

Only if image-guided fine needle aspiration (FNAC) or fine needle ago-biopsy (FNAB) are negative, then SNB deserves wider consideration as an alternative to routine AD, but what about the axilla with a positive FNAC or FNAB? Increased rationale for neoadjuvant chemotherapy (NACT) has changed the approach to breast surgery (BS) in recent years.

NACT allows de-escalation of surgery with a relative increase of breast conserving treatment (BCT) by up to 40% which was the initial goal of this chemotherapy, and in particular it permits a reduction in axillary surgery [6–10]. Furthermore, NACT have the power to achieve a pathological complete response (pCR) ranging from 20 to 80% according to the molecular characteristics of the tumors [7,11–14]. The axillary pCR rates reach more than 50% in triple-negative breast cancer tumors (TNBC) and 80% in Human Epidermal Growth Factor Receptor Type 2 Positive (HER-2 positive) patients receiving trastuzumab plus pertuzumab [13–15]. Therefore, those who may reach axillary pCR are unlikely to benefit from AD.

Another important element in de-escalation of axillary surgery is the reduced arm morbidity which has always been a major objective to improve quality of life in all axillary upfront surgery trials.

The role of SNB and the data supporting its use is different for those with clinically negative and clinically positive nodes prior to chemotherapy. For clinically node-negative patients, SNB after NACT may be suitable if the identification rate of SNB and the FNR is similar to those in

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https://doi.org/10.1016/j.breast.2022.12.010
Received 21 November 2022; Received in revised form 15 December 2022; Accepted 19 December 2022
Available online 20 December 2022
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upfront surgery and a clinically negative axilla [16–19].

However, for those node-positive patients who converted to cN0, small retrospective studies reported FNR approaching 10% [10,20,21].

In 2015, the accuracy of SNB in cN + patients was evaluated in a systematic review of the literature with different studies that included cN + patients prior to neoadjuvant therapy. The authors found SN identification rates of 92.3% and FNR of 15.1% [22]. In a recent meta-analysis by Simons et al., 2217 patients were analyzed and similarly, identification rates of SN and FNR were respectively 89% and 17% [23].

Different prospective studies such ACOSOG Z1071, SENTINA, SN FNAC and GANEA 2 demonstrated that the FNR of the SNB was higher than the acceptable 10% [7–10]. Among the studies that demonstrated the feasibility of SNB in positive initial axillary disease there is a variation in the techniques used to minimize the FNR. One of these strategies, as suggested by the San Gallen 2021 Consensus, is to remove more than three negative axillary lymph nodes [24]. The 2022 NCCN guidelines are similarly cautious and suggest marking of positive axillary nodes with a tattoo or clip, the so-called target axillary dissection (TAD) as an alternative to reducing FNR using dual tracer and by removing more than 2 negative sentinel nodes [25]. Therefore, TAD was certainly a very clever idea with a well-defined purpose and with these two procedures we can surely achieve an acceptable FNR.

There are several different methods for labeling the positive lymph node for TAD and also different ways of recovering them during surgery. Localization methods include placement of titanium clips, radioactive or magnetic seeds, or carbon particles, which are usually inserted or injected into the biopsy-proven positive lymph node prior to therapy. However, these methods have advantages and disadvantages. radioactive seeds, for example, cannot be used in all countries due to radiation regulations, and as for clips, these may move and thus may not be detected after therapy [26–28].

The oncological consequences of different axillary staging methods are still unclear. Of note, none of these procedures refers to the analysis of the outcome, which is our fundamental goal [29].

Although all of these techniques have been shown to reduce the FNR [30,31], we have seen, since SNB was introduced, that we have false negative rates which didn't correspond to an increase in axillary recurrences or a worsening of disease-free survival (DFS) or overall survival (OS) [3,32].

Based on this, we thought that even in the case of surgery after neoadjuvant therapy it would be possible to use the same technique of SNB, which, in house, consisted in identifying the lymph node only with a radioactive tracer.

1.1. Studies using SNB alone

Our first study, published in 2016 with a follow up of only 5 years, was criticized precisely in the light of the results of the prospective studies which showed an unacceptable FNR. However, these studies focused only on this data without survival results [33].

After a median follow up of 61 months, we analyzed 396 patients, of which 249 started as cN0 and 147 cN+. We found that axillary failure occurred in only 1 case (0.7%) in a cN + patient who became cN0. The 5-year distant disease-free survival (DDFS) was 81.1% in initially cN0 and 73.4% in initially cN1/2 ($p = 0.33$) and the 5-year OS was 93.3% in initially cN0 and 86,3% in initially cN1/2 ($p = 0.12$).

Our first conclusion was that the data despite the limited follow-up, were reassuring. Also, as we presumed, the FNR was not to be considered as an impossibility to perform the SNB even with a single tracer with an identification rate of 99% [33]. In the other 1% we could identify the SN by re-injecting the radiotracer.

Thanks to these results, we continued our policy and were able to analyze the data after 10 years of follow-up with more patients [34]. In this last retrospective single-institution study we recruited 688 patients: 466 started cN0 and 222 patients started as cN1/2 (Table 1).

Table 1
Clinic-pathologic characteristics and treatment according to cN status prior NAT.

	cN0 (N = 466)		cN1/2 (N = 222)		*P*-value
	N	%	N	%	
Age					0.033
≤40 years	119	25.5	74	33.3	
>40 years	347	74.5	148	66.7	
Median (IQR)	47 (40–55)		45 (38–53)		
Menopausal status					0.311
Premenopausal	258	55.4	132	59.5	
Postmenopausal	208	44.6	90	40.5	
cT					<0.001
cT1	42	9.0	11	5.0	
cT2	367	78.8	136	61.3	
cT3	57	12.2	75	33.8	
Grade at biopsy					0.015^
Low	22	4.7	4	1.8	
Intermediate	176	37.8	69	31.1	
High	187	40.1	110	49.5	
Unknown	80	17.2	39	17.6	
Not performed	1	0.2	0	–	
Subtype at biopsy					<0.001^
Luminal A	113	24.2	20	9.0	
Luminal B (Ki67 ≥ 20%)	136	29.2	79	35.6	
Luminal B (HER2 positive)	53	11.4	31	14.0	
HER2 positive (non-luminal)	33	7.1	37	16.7	
Triple negative	87	18.7	41	18.5	
Unknown	44	9.4	14	6.3	
Systemic neoadjuvant treatment					<0.001
Endocrine therapy alone	84	18.0	18	8.1	
Anthracycline	65	13.9	26	11.7	
Anthracycline + endocrine therapy	23	4.9	14	6.3	
Anthracycline + taxane	116	24.9	61	27.5	
Anthracycline + taxane + endocrine therapy	29	6.2	14	6.3	
Trastuzumab + chemotherapy	54	11.6	55	24.8	
Trastuzumab + chemotherapy + endocrine therapy	24	5.2	13	5.9	
Other chemotherapy	20	4.3	4	1.8	
Other chemotherapy + endocrine therapy	51	10.9	17	7.7	
Number of SN removed					0.117
1	213	45.7	111	50.0	
2	149	32.0	54	24.3	
3+	104	22.3	57	25.7	
Median (min-max range)	2 (1–8)		2 (1–6)		
Local treatment					<0.001
Quadrantectomy	278	59.7	119	53.6	
Breast radiotherapy	267	96.0	106	89.1	
Loco-regional radiotherapy	11	4.0	13	10.9	
Mastectomy	188	40.3	103	46.4	
No radiotherapy	154	81.9	64	62.1	
Loco-regional radiotherapy	34	18.1	39	37.9	
Systemic adjuvant treatment					<0.001^
No adjuvant therapy	19	4.1	15	6.8	
Endocrine therapy alone	249	53.4	81	36.5	
Trastuzumab	24	5.2	31	14.0	
Trastuzumab + endocrine therapy	45	9.7	32	14.4	
Trastuzumab + chemotherapy	13	2.8	3	1.4	
Trastuzumab + chemotherapy + endocrine therapy	5	1.1	6	2.7	
Other chemotherapy	64	13.7	36	16.2	
Other chemotherapy + endocrine therapy	34	7.3	14	6.3	
Unknown	13	2.8	4	1.8	
ypT					<0.001
ypTx/is	40	8.6	34	15.3	
ypT0	55	11.8	46	20.7	
ypT1	165	35.4	75	33.8	
ypT2	171	36.7	50	22.5	
ypT3	35	7.5	17	7.7	
ypN					<0.001
ypN0	305	65.5	123	55.4	
ypN0 (+itc)	9	1.9	2	0.9	
ypN1	76	16.3	41	18.5	

(*continued on next page*)

Table 1 (*continued*)

	cN0 (N = 466)		cN1/2 (N = 222)		*P*-value
	N	%	N	%	
ypN1 (mic)	44	9.4	16	7.2	
ypN2	23	4.9	25	11.3	
ypN3	9	1.9	15	6.8	

^ Unknown category was not considered in the p-value calculation.

The results obtained met our expectations, in fact the axillary recurrences found were less than 2% in particular in the group that started from a positive axilla were 1.8%, if we considered that 2 of them had a micrometastatic SN and refused the AD. If we considered only those with a negative SN the percentage drops to 1.6%. What characterized the uniqueness of this study is that there were no requirements for number of SNs retrieved, in fact 74% had ≤2 SNs removed. Not only that, but what we wanted to show was that the 10-year cumulative incidence of distant events was slightly higher for cN1/2 patients (16.6%) compared to cN0 (13.1%), although this difference was not statistically significant ($p = 0.148$) [34]. So, our data confirm that the use of SNB, even with our only standard procedure, is acceptable in cN1/2 patients who become cN0 after NACT and will not translate into a particularly worse outcome in those with high pCR seen in patients with HER2 positive disease and TNBC who are those women who most deserve from de-escalation of axillary surgery [34].

Similar positive data with different follow up were also confirmed by other studies that used SNB alone without TAD (Table 2). One of these is the Barrio's study at Memorial Sloan Kettering Cancer Center which enrolled 234 patients with positive axilla before chemotherapy who had 3 or more negative SNs and had SNB alone [35]. After a median follow-up of 40 months, they found only 1 axillary nodal recurrence synchronous with local recurrence in a patient who refused RT, while among patients who received RT (n = 205), there were no nodal recurrences [35].

Also, Pitlin et al. found that during the median 34-month follow-up period 159 (52.5%) of these patients were spared AD. This included 139 with a negative SN and 20 SN + patients who did not undergo AD [36]. Only 1 patient (of 159 patients) who was treated with SNB only and had two negative SNs at the time of the initial surgery developed axillary recurrence after 2 yrs of follow-up. Patients with ypN0 who underwent SN surgery only did not have worse oncologic outcomes from omission of AD and importantly sentinel node surgery for node-positive patients after neoadjuvant chemotherapy was not oncologically inferior to axillary lymph node dissection with respect to locoregional recurrence [36].

The Wong et al. retrospectively identified 244 consecutive patients with cT1-3cN0-2 breast cancer who underwent NAT followed by SNB: 112 were cN0 at presentation, whereas 132 had biopsy-proven cN1-2 disease and converted to cN0 after treatment [37]. Overall, 211 patients were treated with SNB alone and had a median follow-up period of 36 months. For 58 cN1-2/ypN0 patients who underwent SNB alone, the 5-year local and regional recurrence rates were respectively 4.1% and 0%, with no axillary recurrences noted. For the cN0/ypN0 group, the 5-year axillary recurrence rate was 1.0% similar to the cN1–2/ypN0 group, for which no axillary recurrences were reported ($p = 0.44$) [37].

Table 2
Retrospective studies that used SNB alone without TAD.

Author	N. of pts	Axillary recurrence	Follow up
Kahler Ribeiro Fontana S	123	1.6%	10 yrs
Martelli G	81	0%	7 yrs
Wong SM	58	0%	5 yrs
Barrio A	234	1.6%	3 yrs
Piltin MA	139	0.7%	2 yrs

The last study by Martelli et al. who prospectively recruited 353 consecutive cT2 cN0/1 breast cancer patients, who underwent primary chemotherapy followed by surgery at the National Cancer Institute of Milan. If the SNs were pN0, patients generally received no further axillary treatment (SNB only); if the SNs were pN1, completion axillary dissection (AD) (SNB + AD) was usually performed. 10-year OS 89% [95% confidence interval (CI): 81%–99%] in SNB only patients versus 86% (95%CI: 78%–95%) in SNB + AD patients; 10-year DFS 79% (95% CI: 68%–92%) versus 69% (95%CI: 58%–81%) [38].

Of the 216 patients who were cN1 before chemotherapy, the axilla was disease-free in 121 on histological examination: 81 of these received SNB only, and 40 received SNB + AD (with no positive nodes found on pathological examination). After a median follow-up of 87 months in the group SNB only no patient developed axillary failure [38].

2. Discussion

The role of the SNB and the data that support its practice are very consistent, also in the scenario involving neoadjuvant therapy. Currently it's uses in cN + patients who converted to cN0 patients after NACT is being widely debated. However, the reassuring results at follow-up, confirm that SN surgery alone for selected patients who have an excellent response to NACT is not oncologically lower than the AD during short-term and long-term follow-up.

There are ongoing studies that aim to demonstrate which is the best method of axillary surgery after NAT in cases that start with a positive axilla. One of these, AXSANA, initiated by EUBREAST, is a large, prospective, non-interventional cohort study evaluating the best axillary strategy in the cN + that down-staged to cN0 after NACT. This study intends to collect all the staging methods adopted by the various individual institutions with primary endpoints invasive disease-free survival (IDFS), axillary recurrence rate and quality of life and arm morbidity [28].

Studies with different methods of TAD localization and in particular studies with the SN alone biopsy, all aim to reduce axillary surgery and therefore de-escalate to improve women's quality of life.

We must consider the drawbacks of both methods. The costs of TAD, depending on the method used, can be more or less high and certainly higher than the SN alone, in particular if we consider the use of the single tracer.

The procedure before and after TAD surgery requires more time and additional costs, and there are several doubts about how many lymph nodes to tag. Another problem is the inability to find the clip, that occurs in up to 30% of cases [39,40]. In this case the question arises whether to proceed directly to the AD. On the other hand, the biopsy of the SN alone does not affect the costs which are the same as the upfront surgery, it is not time consuming and above all what is reassuring is that the follow-up data show that it is a safe procedure.

A possible criticism of SNB alone with respect to the FNR may relate to the lack of information on residual disease that is important for adjuvant therapy, but it is true that residual disease can also be assessed on the complete lack of response in the tumor.

The critical issue that both methods have is the role of regional node irradiation (RNI), which was not standardized in different studies. The administration of adjuvant locoregional radiotherapy (RT) after NACT, either to the chest wall after mastectomy or to the breast after breast-conserving surgery, is generally based on the initial clinical stage and the final pathological stage. However, the need for RT in patients with cN1/2 axillary status, who became negative cN0 after therapy is still being discussed, especially including cases with pCR [41].

We also expect a de-escalation of radiotherapy for those patients who have a nodal pCR, but we probably have wait for the results of the randomized clinical trial NSABP B-51/RTOG1304 [42]. This trial aims to determine whether RNI in lymph node-positive patients that down-staged to ypN0 after NACT could reduce the recurrence-free interval rate. However, until we have convincing data, we cannot abstain

from radiotherapy in these cases [42].

Even the randomized Alliance trial will provide appropriate data on the elimination of the axillary surgery in cases with positive SN after NACT that are randomized to AD plus RNI versus RNI with no additional axillary surgery. Effectively, RT has been studied as an alternative to AD, especially in the group of patients undergoing NACT, in which the clinically positive axilla (cN1/2) became negative (cN0) following therapy [43].

We are definitely moving towards a de-escalation of axillary surgery, which is considered a staging procedure that does not seem to influence breast cancer mortality, since the risk of developing metastasis mainly depends on the biological characteristics of the tumor. However, surgical management remains uncertain in cases of low residual volume disease, such as isolated tumor cells (ypN0i+; <0.2 mm) and micrometastatic disease (ypN1mi; 0.2–2.0 mm) after NACT because there is a probability of not finding more disease after AD and further studies should be considered [44,45].

The developments in NACT and research towards a more personalized therapy will be able to identify those patients who really do not need overtreatment. In the future, post-surgical therapy should be considered based on the biological characteristics of the tumor and not on nodal status. Furthermore, the exceptional pathological response after NACT in breast and axillary surgery may decrease or even eliminate the need for surgery in selected cases of breast cancer, however additional prospective clinical trials evaluating this approach are needed [46].

3. Conclusion

Certainly, TAD brought excellent results in reduction terms of FNR, but SNB alone, even it is not necessarily the lymph node biopsied before chemotherapy, it demonstrates that does not appear to affect survival rate.

Support

No financial support was received for this study.

Declaration of competing interest

All the authors have no conflicts of interest in regards to the conflict of this manuscript.

Acknowledgements

The authors thanks Dr. Linda Cairns for English revision, and Maria Grazia Villardita for help with manuscript preparation.

References

[1] Lyman GH, Temin S, Edge SB, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2014;32(13):1365–83. https://doi.org/10.1200/JCO.2013.54.1177.

[2] 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.

[3] Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med Aug 07 2003;349(6):546–53. https://doi.org/10.1056/NEJMoa012782.

[4] Galimberti V, Cole BF, Viale G, et al. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol Oct 2018;19(10):1385–93. https://doi.org/10.1016/s1470-2045(18)30380-2.

[5] Bartels SAL, Donker M, Poncet C, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer: 10-year results of the randomized controlled EORTC 10981-22023 AMAROS trial. *J Clin Oncol*. 2022:Jco2201565. https://doi.org/10.1200/jco.22.01565.

[6] Tee SR, Devane LA, Evoy D, 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*. Nov 2018;105(12):1541–52. https://doi.org/10.1002/bjs.10986.

[7] Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA*. 2013;310(14):1455–61. https://doi.org/10.1001/jama.2013.278932.

[8] Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol*. 2013;14(7):609–18. https://doi.org/10.1016/S1470-2045(13)70166-9.

[9] Classe JM, Loaec C, Gimbergues P, et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. *Breast Cancer Res Treat*. 2019;173(2):343–52. https://doi.org/10.1007/s10549-018-5004-7.

[10] Boileau JF, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. *J Clin Oncol*. 2015;33(3):258–64. https://doi.org/10.1200/JCO.2014.55.7827.

[11] Tadros AB, Yang WT, Krishnamurthy S, et al. Identification of patients with documented pathologic complete response in the breast after neoadjuvant chemotherapy for omission of axillary surgery. JAMA Surg Jul 1 2017;152(7):665–70. https://doi.org/10.1001/jamasurg.2017.0562.

[12] Caudle AS, Bedrosian I, Milton DR, et al. Use of sentinel lymph node dissection after neoadjuvant chemotherapy in patients with node-positive breast cancer at diagnosis: practice patterns of American society of breast surgeons members. Ann Surg Oncol Oct 2017;24(10):2925–34. https://doi.org/10.1245/s10434-017-5958-4.

[13] Pilewskie M, Morrow M. Axillary nodal management following neoadjuvant chemotherapy: a review. *JAMA Oncol*. 2017;3(4):549–55. https://doi.org/10.1001/jamaoncol.2016.4163.

[14] Murphy BL, Day CN, Hoskin TL, Habermann EB, Boughey JC. Neoadjuvant chemotherapy use in breast cancer is greatest in excellent responders: triple-negative and HER2+ subtypes. *Ann Surg Oncol*. 2018;25(8):2241–8. https://doi.org/10.1245/s10434-018-6531-5.

[15] Fisher CS, Margenthaler JA, Hunt KK, Schwartz T. The landmark series: axillary management in breast cancer. Ann Surg Oncol Dec 20 2019. https://doi.org/10.1245/s10434-019-08154-5.

[16] Mamounas EP, Brown A, Anderson S, et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from national surgical adjuvant breast and bowel project protocol B-27. J Clin Oncol 2005/04/20 2005;23(12):2694–702. https://doi.org/10.1200/JCO.2005.05.188.

[17] Xing Y, Foy M, Cox DD, Kuerer HM, Hunt KK, Cormier JN. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. *Br J Surg*. 2006;93(5):539–46. https://doi.org/10.1002/bjs.5209.

[18] Hunt KK, Yi M, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy is accurate and reduces the need for axillary dissection in breast cancer patients. Ann Surg Oct 2009;250(4):558–66. https://doi.org/10.1097/SLA.0b013e3181b8fd5e.

[19] Tan VK, Goh BK, Fook-Chong S, Khin LW, Wong WK, Yong WS. The feasibility and accuracy of sentinel lymph node biopsy in clinically node-negative patients after neoadjuvant chemotherapy for breast cancer–a systematic review and meta-analysis. J Surg Oncol Jul 1 2011;104(1):97–103. https://doi.org/10.1002/jso.21911.

[20] Newman EA, Sabel MS, Nees AV, et al. Sentinel lymph node biopsy performed after neoadjuvant chemotherapy is accurate in patients with documented node-positive breast cancer at presentation. Ann Surg Oncol 2007//2007;14(10):2946. https://doi.org/10.1245/s10434-007-9403-y.

[21] Canavese G, Dozin B, Vecchio C, et al. Accuracy of sentinel lymph node biopsy after neo-adjuvant chemotherapy in patients with locally advanced breast cancer and clinically positive axillary nodes. *Eur J Surg Oncol*. 2011;37(8):688–94. https://doi.org/10.1016/j.ejso.2011.05.012.

[22] van Nijnatten TJ, Schipper RJ, Lobbes MB, Nelemans PJ, Beets-Tan RG, Smidt ML. The diagnostic performance of sentinel lymph node biopsy in pathologically confirmed node positive breast cancer patients after neoadjuvant systemic therapy: a systematic review and meta-analysis. *Eur J Surg Oncol*. 2015;41(10):1278–87. https://doi.org/10.1016/j.ejso.2015.07.020.

[23] Simons JM, van Nijnatten TJA, van der Pol CC, Ejt Luiten, Koppert LB, Smidt ML. Diagnostic accuracy of different surgical procedures for axillary staging after neoadjuvant systemic therapy in node-positive breast cancer: a systematic review and meta-analysis. *Ann Surg*. Mar 2019;269(3):432–42. https://doi.org/10.1097/sla.0000000000003075.

[24] Burstein HJ, Curigliano G, Thürlimann B, et al. 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 Oct 2021;32(10):1216–35. https://doi.org/10.1016/j.annonc.2021.06.023.

[25] www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed November 2022.

[26] Caudle AS, Yang WT, Krishnamurthy S, et al. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. J Clin Oncol Apr 1 2016;34(10):1072–8. https://doi.org/10.1200/jco.2015.64.0094.

[27] Donker M, Straver ME, Wesseling J, et al. Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients: the MARI procedure. *Ann Surg*. 2015;261(2):378–82. https://doi.org/10.1097/sla.0000000000000558.

[28] Banys-Paluchowski M, Gasparri ML, de Boniface J, 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 (basel) 29 2021;(7):13. https://doi.org/10.3390/cancers13071565.
[29] Patel R, MacKerricher W, Tsai J, et al. Pretreatment tattoo marking of suspicious axillary lymph nodes: reliability and correlation with sentinel lymph node. *Ann Surg Oncol*. 2019;26(8):2452–8. https://doi.org/10.1245/s10434-019-07419-3.
[30] Boughey JC, Ballman KV, Le-Petross HT, et al. Identification and resection of clipped node decreases the false-negative rate of sentinel lymph node surgery in patients presenting with node-positive breast cancer (T0-T4, N1-N2) who receive neoadjuvant chemotherapy: results from ACOSOG Z1071 (alliance). *Ann Surg*. 2016;263(4):802–7. https://doi.org/10.1097/SLA.0000000000001375.
[31] Mittendorf EA, Caudle AS, Yang W, et al. Implementation of the American college of surgeons oncology group Z1071 trial data in clinical practice: is there a way forward for sentinel lymph node dissection in clinically node-positive breast cancer patients treated with neoadjuvant chemotherapy? Ann Surg Oncol 2014//2014;21(8):2468–73. https://doi.org/10.1245/s10434-014-3775-6.
[32] 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 Oct 2010;11(10):927–33. https://doi.org/10.1016/s1470-2045(10)70207-2.
[33] Galimberti V, Ribeiro Fontana SK, Maisonneuve P, 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. https://doi.org/10.1016/j.ejso.2015.11.019.
[34] Kahler-Ribeiro-Fontana S, Pagan E, Magnoni F, 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 Oct 15 2020. https://doi.org/10.1016/j.ejso.2020.10.014.
[35] Barrio AV, Montagna G, Mamtani A, et al. Nodal recurrence in patients with node-positive breast cancer treated with sentinel node biopsy alone after neoadjuvant chemotherapy-A rare event. JAMA Oncol Dec 1 2021;7(12):1851–5. https://doi.org/10.1001/jamaoncol.2021.4394.
[36] Piltin MA, Hoskin TL, Day CN, Davis Jr J, Boughey JC. Oncologic outcomes of sentinel lymph node surgery after neoadjuvant chemotherapy for node-positive breast cancer. Ann Surg Oncol Aug 10 2020. https://doi.org/10.1245/s10434-020-08900-0.
[37] Wong SM, Basik M, Florianova L, et al. Oncologic safety of sentinel lymph node biopsy alone after neoadjuvant chemotherapy for breast cancer. Ann Surg Oncol May 2021;28(5):2621–9. https://doi.org/10.1245/s10434-020-09211-0.
[38] Martelli G, Barretta F, Miceli R, et al. Sentinel node biopsy alone or with axillary dissection in breast cancer patients after primary chemotherapy: long-term results of a prospective interventional study. Ann Surg Nov 1 2022;276(5):e544–52. https://doi.org/10.1097/sla.0000000000004562.
[39] Hartmann S, Reimer T, Gerber B, Stubert J, Stengel B, Stachs A. Wire localization of clip-marked axillary lymph nodes in breast cancer patients treated with primary systemic therapy. *Eur J Surg Oncol*. 2018;44(9):1307–11. https://doi.org/10.1016/j.ejso.2018.05.035.
[40] Nguyen TT, Hieken TJ, Glazebrook KN, Boughey JC. Localizing the clipped node in patients with node-positive breast cancer treated with neoadjuvant chemotherapy: early learning experience and challenges. Ann Surg Oncol Oct 2017;24(10):3011–6. https://doi.org/10.1245/s10434-017-6023-z.
[41] Buchholz TA, Lehman CD, Harris JR, et al. Statement of the science concerning locoregional treatments after preoperative chemotherapy for breast cancer: a National Cancer Institute conference. *J Clin Oncol*. 2008;26(5):791–7. https://doi.org/10.1200/jco.2007.15.0326.
[42] https://clinicaltrials.gov/ct2/show/NCT01872975 - Accessed November 2022.
[43] https://clinicaltrials.gov/ct2/show/NCT01901094 - Accessed November 2022.
[44] King TA, Morrow M. Surgical issues in patients with breast cancer receiving neoadjuvant chemotherapy. Nat Rev Clin Oncol Jun 2015;12(6):335–43. https://doi.org/10.1038/nrclinonc.2015.63.
[45] Tinterri C, Canavese G, Bruzzi P, Dozin B. Neonod 2: rationale and design of a multicenter non-inferiority trial to assess the effect of axillary surgery omission on the outcome of breast cancer patients presenting only micrometastasis in the sentinel lymph node after neoadjuvant chemotherapy. *Contemp Clin Trials Commun*. 2020;17:100496. https://doi.org/10.1016/j.conctc.2019.100496.
[46] Kuerer HM, Smith BD, Krishnamurthy S, et al. Eliminating breast surgery for invasive breast cancer in exceptional responders to neoadjuvant systemic therapy: a multicentre, single-arm, phase 2 trial. Lancet Oncol Oct 25 2022. https://doi.org/10.1016/s1470-2045(22)00613-1.