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Breast and axillary surgery in malignant breast disease: a review focused on literature of 2018 and 2019

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Purpose of review

There have been fundamental changes in the surgical approach to breast cancer management over the last decades. The primary objective of achieving locoregional control, however, remains unchanged.

Recent findings

In addition to strategies optimizing systemic treatment and radiotherapy, current discussions focus on improving the surgical approach to breast cancer. Especially in view of the increasingly pivotal role of neoadjuvant chemotherapy NAT/NAC (NACT), gauging the extent of tissue removal in the breast and the width of resection margins in breast-conserving surgery is highly important, as is the extent of axillary surgery. Although sentinel lymph node (SLN)-positive patients always underwent axillary lymph node dissection in the past, this paradigm has been challenged in recent years. Targeted axillary dissection (TAD) has emerged as a new staging option in biopsy-proven node-positive patients who convert to clinical node negativity (cN0) after NACT. TAD combines the removal of the SLN and of the target lymph node marked prior to NACT. The accuracy of axillary staging both before and after NACT plays an important role for prognostication and multidisciplinary treatment plans, while its extent has significant effects on patients' arm morbidity and quality of life.

Summary

The current review focuses on recent evidence regarding surgical management of the breast and axilla in patients with primary breast cancer based on a PubMed and EMBASE literature search for publication years 2018 and 2019.

Keywords

breast-conserving surgery, mastectomy, neoadjuvant chemotherapy, sentinel lymph node, targeted axillary dissection

INTRODUCTION

Surgery is a crucial part of the multimodal therapy concept. Current surgical strategies in breast cancer management primarily focus on reducing the extent of tissue removal in breast and axilla to improve patients' quality of life as well as the esthetic outcome while maintaining high oncological safety. With the introduction of the sentinel lymph node biopsy (SLNB) for patients with clinically node-negative breast cancer, axillary lymph node dissection (ALND) was replaced as a staging procedure for patients undergoing primary surgery. Based on affirmative data regarding detection and false negative rates, the removal of the SLN is now also recommended after neoadjuvant chemotherapy NAT/NAC (NACT) in patients with initially clinical negative nodes [1–5]. There has been an increase in detection of

isolated tumor cells [pN0(i+)] and micrometastases (pN1mi) on axillary staging after NACT [6]. The prognostic impact of low-volume nodal involvement and the role of locoregional therapy in this situation,

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KEY POINTS

- Margin status is still the most important prognostic factor for local control after primary surgery.
- SLN biopsy (SLNB) is the standard of care staging procedure in cN0 patients with invasive disease.
- Axillary lymph node dissection after a positive SLNB may be avoided in cN0 patients with micrometastasis or macrometastasis in up to two SLNs.
- Combined methods of SLNB and removal of axillary metastases marked pre-NACT (TAD) achieve considerably better FNRs than SLNB alone.
- TAD is considered as the preferred procedure in patients who convert from cN1 to ycN0.

however, are still unclear. An additional unanswered question concerns those patients with an initially clinically positive axilla (cN+) who show a complete remission after NACT: how far can de-escalation of axillary surgery proceed, and when can ALND be avoided? In view of new strategies for post-NACT treatment options for patients with residual disease [7,8], the diagnostic accuracy of surgical breast (ypT) and lymph node (ypN) staging has gained even more significance even in minimal residual disease.

The current review summarizes recently published evidence (focusing on the last 2 years) on the extent of surgery to the breast and the axilla both in primary surgery and after NACT, with special regard to tumor biology, locoregional radiotherapy, and systemic therapy.

REVIEW

Surgery of the breast: as primary therapeutic approach

Margin status is still the most important prognostic factor for local control after primary surgery. No ink on tumor for invasive carcinomas and a 2 mm margin for ductal carcinoma in situ are considered sufficient if combined with whole-breast irradiation [9]. For both breast-conserving surgery (BCS) and mastectomy, a main objective remains the best possible aesthetic-reconstructive outcome in combination with highest oncological safety. Studies on patient satisfaction report rates above 80% for all reconstructive procedures [10] which could possibly be increased with improved methods (e.g. fat supplementation). There is uncertainty regarding the preferred method but a clear relation between the surgical outcome and the education and skills of the physician and different breast cancer centers has been shown [11].

Surgery of the breast: after neoadjuvant chemotherapy

Recent Early Breast Cancer Trialists Collaborative Group data showed a 15 year local recurrence rate higher for patients who underwent NACT (21.4%) than for those receiving systemic therapy after primary surgery (15.9%) [12]. Despite this, no prognostic relevance for disease-free survival (DFS) and overall survival was observed. Importantly, a large number of patients did not undergo any breast surgery but only radiotherapy after NACT; for those patients, the increase in local recurrence rates was 11.3% compared with patients not receiving NACT, while local recurrence rates in patients who were operated after NACT were only increased by 3.2. In the meantime, imaging modalities and radiotherapy approaches have significantly improved. Therefore, these data can hardly be used to adequately define the necessary extent of surgery to the tumor bed. Instead, a recently published retrospective analysis including 382 patients treated with NACT between 2002 and 2014 reported an overall local recurrence rate of only 3.9% after 5 years. Even in patients with a negative margin width of 1 mm or less ($n = 65/382$, 17.0%), no local recurrence was observed. The authors concluded that a policy of 'no tumor on ink' was sufficiently effective for the resection of the tumor after NACT [13].

In the Responder trial, the role of vacuum-assisted biopsy (VAB) to predict a pathological complete response (pCR) was compared with excisional biopsy. Although the trial was based on the hypothesis that breast surgery might be omitted in patients with a good response to chemotherapy, it had to be discontinued due to an excessively high false negative rate (FNR) [17.8%, 95% confidence interval (CI): 12.8–23.7%] in the VAB group.

Surgery of the breast: reconstruction methods

When mastectomy is indicated, skin-and nipple-sparing techniques with immediate reconstruction in selected patients are associated with no increase in recurrence rates yet a better quality of life compared with conventional mastectomy and delayed reconstruction. Depending on the location of the tumor, the nipple-areola complex can be preserved. Following a mastectomy, reconstruction can be carried out using implants or autologous tissue or a combination of both [14]. For single use of implants combinations with acellular dermal matrices (ADM) or meshes are the current standard of care. One-stage implant-based breast reconstruction with ADM does not yield superior results in terms of patient-reported quality of life compared with two-stage reconstruction [15] but current data (with 6-months follow-up) showed an

association with more adverse outcomes requiring surgical intervention in contrast to conventional implant-based reconstruction without ADM [16].

Surgery of the axilla: as first therapeutic approach

The surgical approach toward the axilla has been a controversial issue over the last decades. Data from recently published trials have provided practice-changing recommendations for this scenario. However, further controversies have been triggered in the surgical community, resulting in widely differing recommendations [17].

SLN biopsy has replaced ALND in clinically node-negative breast cancer patients who undergo primary surgery, with false negative rates below 10%. Since adjuvant systemic treatment decisions are mainly based on tumor biology, the question whether axillary staging can be omitted altogether has become a subject of discussion. Two trials addressing this issue have recently finished accrual (INSEMA, SOUND). The AMAROS [18], The American College of Surgeons Oncology Group (ACOSOG) Z0011 [19] and IBCSG 23–01 studies provided evidence that ALND can be omitted in patients with occult SLN involvement or be replaced by locoregional radiotherapy. As a result of these trials, whose methodological limitations are well known, ALND is being increasingly abandoned in clinical routine: A big data analysis of 1131363 women with clinical stage I–III breast cancer in the US National Cancer Data Base (255306 with ALND and 876057 without ALND) showed declining ALND rates from 2004 (32%) to 2014 (16%; $P < 0.001$) in both BCS and mastectomy patients [20]. After adjustment, this effect was maintained, with ALND rates decreasing with each additional year (odds ratio = 0.90, 95% CI 0.89–0.90). Resident procedure volumes similarly declined from 1999 to 2017 ($P < 0.001$), indicating that less experienced junior residents who are predominantly performing ALND do so with very low absolute numbers. Similarly, a Dutch study observed a reduction of the ALND rate from 75% in 2011 to 17% in 2015 [21]. Important contributing factors to performing an ALND were unfavorable tumor morphology or biology. The extent of axillary surgery correlates with the surgeon's experience: Those with more experience perform less radical procedures than less experienced surgeons [22]. Furthermore, ALND rates vary considerably between different institutions [23,24]. A German study group analyzed 188909 data records and identified 13741 patients with cT1/2N0M0 cancers with one to two positive SLNs, treated with BCS and tangential field irradiation. In 2008, an ALND was performed in 94.6% of these cases, while in 2015,

this figure had decreased to only 46.9%. Similar trends were reported by the EUSOMA working group [24]: Analyzing 671 patients fulfilling the criteria of the Z0011 trial, rates of ALND showed a statistically significant decrease from 2010 (89%) to 2011 (73%), reaching 46% in 2016 ($P < 0.001$).

Surgery of the axilla: after neoadjuvant chemotherapy

SLN detection rates are very high (97.6%) after NACT in patients who initially present with a clinically negative lymph node status, and the omission of ALND after a negative SLN biopsy is associated with a negligibly small number of axillary recurrences as shown in the GANEA-2 (GANgion sentinelle après chimiothérapie NéoadjuvanteMARI - axillary lymph node marking with radioactive iodine seeds) trial, which was first to address the safety of SLN biopsy in this setting. In 419 enrolled patients, only one axillary recurrence (0.2%) was reported after a median follow-up of 3 years, along with a 3-year event-free survival of 97.8% [25]. This is similar to retrospective data from the MD Anderson Cancer Center, which reported a 1.2% regional recurrence rate after a median follow-up of 47 months in patients having a negative SLN biopsy after NACT compared with 0.9% for those having a negative SLN biopsy upfront [1].

In the case of cN1, the prospective SENTINA (SENTinel NeoAdjuvant) and ACOSOG Z1071 trials showed FNRs higher than 10%. In the Canadian SN FNAC trial, the FNR was 8.4% in ypN0, but increased to 13.3% if ITCs were classified as node negative. FNR was reduced when immuno-histochemical was performed or ultrasound was added. In case of post-NACT axillary ultrasound FNR decreased from 8.4 to 2.7% [26]. Little data are currently available to determine the necessity of ALND in cN+ and histopathological complete remission of SLN (ypN0). Only two retrospective studies are available that show no benefit of an additional ALND in cN+ypN0 patients compared with SLN biopsy alone [27,28]. Importantly, post-NACT ultrasound assessment of the axilla has a very low sensitivity and cannot replace SLN biopsy as a staging procedure [29].

A hypothesis-generating finding from ACOSOG Z1071 suggested that the marker localization of a preoperatively positive lymph node by clip or radioactive seed and its targeted removal after NACT (TLNB-targeted lymph node biopsy) could reduce the FNR to 10.1% (Fig. 1). For the localization of the targeted lymph node (TLN), several techniques such as placement of clips, coils, radioactive seeds, and carbon tattooing have been described [30–32, 33,34,35]. In a retrospective analysis of a prospective database, the FNR could be further reduced to 2% if

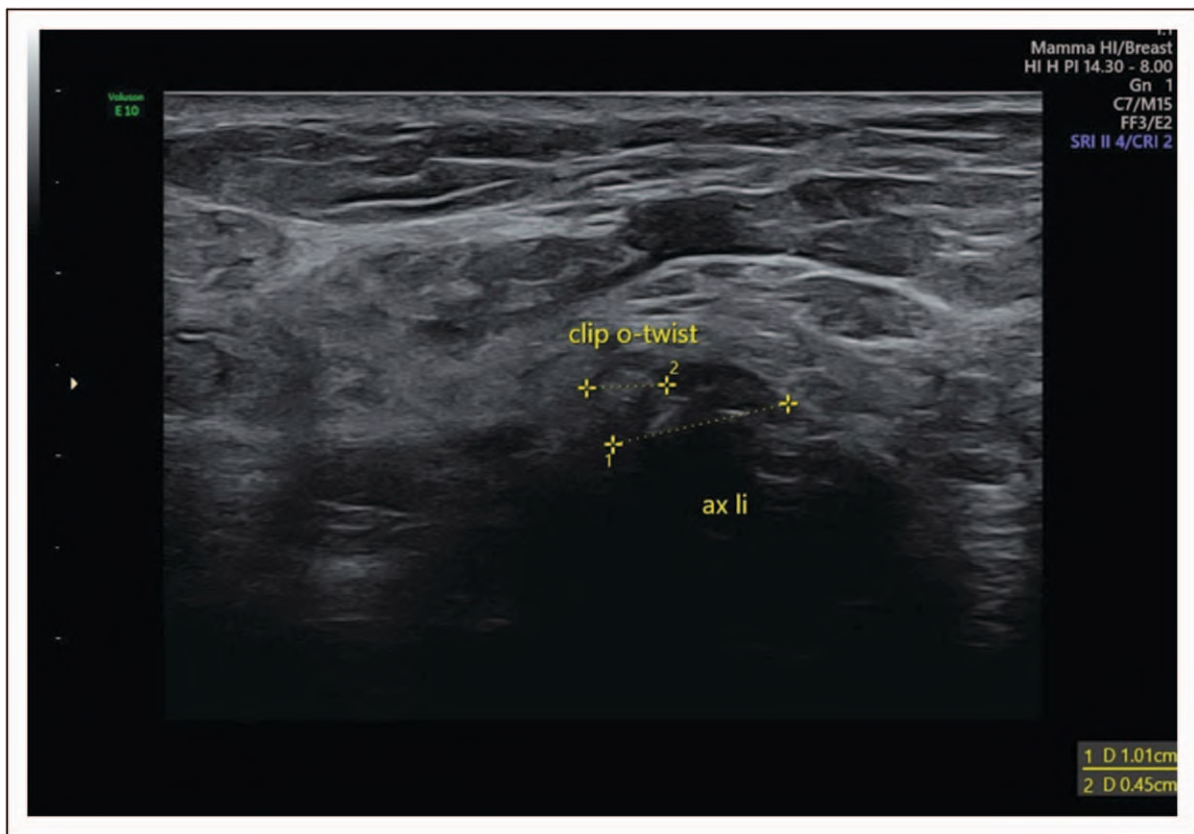


FIGURE 1. Sonographic-guided marker localization of a preoperatively positive axillary lymph node by clip.

both SLN and TLN were removed [36]. This combination procedure, named targeted axillary dissection (TAD), was confirmed to achieve the lowest FNRs in a recent meta-analysis [37^{***}] including 20 studies with 2217 patients: 17 studies on SLN biopsy, one on MARI (marking of the tumor-positive lymph node with a radioactive iodine seed) and two on combination procedures. Overall, the axillary pCR rate was 37%. For SLN biopsy alone, pooled rates of detection rate and FNR were 89 and 17%, respectively, and the negative predictive value (NPV) ranged from 57 to 86%. For MARI, the detection rate was 97%, FNR 7%, and the NPV 83%: In the MARI procedure, predominantly used in The Netherlands, a radioactive seed is placed in the affected lymph node at biopsy and left in place throughout NACT. The combination of MARI with a SLN biopsy is assessed in the ongoing RISAS trial, thus implementing TAD [38]. For combination procedures, detection rate was 100%, FNRs ranged from 2 to 4% and the NPV from 92 to 97%. Table 1 gives an overview on recently published trials that compare different minimally invasive staging procedures and their combination with regard to feasibility (detection rate) and accuracy to predict the axillary status (FNR). These studies show clear advantages for the combination procedures (TAD) as compared with SLN biopsy or TLNB alone.

The TAD identification rate still needs improvement since the optimal localization technique is not yet clear. The most common method, that is clip localization of the TLN, is not yet a reproducible procedure for clinical routine. High failure rates of up to 30% have been reported in combination with preoperative wire localization [53^{*}]. A significantly lower failure rate of 17% was achieved with ultrasound-guided TLN detection [54]. TAD seems best suited to reduce the extent of axillary surgery with good clinical response of NACT, even though prospective data on significantly larger collectives will yet have to confirm this. Results from ongoing trials are expected in the near future (SENTA, PreATNEC, GANEA 3, TATTOO). So far, however, no data regarding oncologic safety (recurrence rates) and morbidity are available that compare ALND, SLNB, TLNB, and TAD. A Europe-wide prospective register (AXSANA) is currently planned by the EUBREAST study group to address these issues.

Surgery of the axilla: individual subgroup analyses

A study from the American National Cancer Data Base (NCDB) included 30 821 patients with cT1/cT2

Table 1. Selection of the most important and current studies on sentinel lymph node biopsy, single removal of marked LN and combination methods (targeted axillary dissection) of preneoadjuvant chemotherapy histopathologically confirmed axillary lymph nodes

| Author | Method | n | Markers | Identification rate (%) | FNR (%) |
|---|---|----------------------|---|---|--|
| Alvarado <i>et al.</i> [39] | SLNB | 150 | Tc and/or blue | 92.7 | 21 (12–32) |
| Boileau <i>et al.</i> [40] | SLNB | 153 | Tc and/or blue | 87.8 | 8 (3–17) |
| Boughley <i>et al.</i> [41] | SLNB (ACOSOG Z1071) | 689 | Tc and/or blue | 92.7 | 15 (11–19) |
| Enokido <i>et al.</i> [42] | SLNB | 143 | Tc and/or blue | 90.9 | 21 (12–33) |
| Kuehn <i>et al.</i> [43] | SLNB | 1.022 592 (Arm C) | Tc with/without blue | 82.6 | 19 (10–31) |
| Park <i>et al.</i> [35] | SLNB | 169 | Single radioactive | 94.9 | 22 (14–31) |
| Pinero-Madrona <i>et al.</i> [44] | SLNB | 94 | Tc with/without blue | 84.0 | 40 (21–61) |
| Yu <i>et al.</i> [45] | SLNB | 122 | Single blue | 95.8 | 36 (17–59) |
| Zetterlund <i>et al.</i> [46] | SLNB | 195 | Tc and/or blue | 77.9 | 14 (8–23) |
| Donker <i>et al.</i> [47] | Marking of +LN (with radioactive Iodine seed; MARI) | 100 | Preiodine seed Post-NA | 97.0 | 7 (2–16) |
| Dashevsky <i>et al.</i> [48] | Marked +LN | 28 | Preclip postultrasound guided wire localization | – | n.d. |
| Kim <i>et al.</i> [49 [■]] | Marked +LN, SLN | | Preimage-guided clip Postultrasound | 95.8 | – |
| Nguyen <i>et al.</i> [50] | Marked LN+, SLN | 56 | 125I Radioactive seed | 72 (with only ultrasound); 91 in combination with CT, palpation and SLNB | – |
| Park <i>et al.</i> [31] | Marked LN+; SLNB, ALN | 20 | Charcoal tattooing | 80.0 | 20 (combined 0) |
| Hartmann <i>et al.</i> [34] | TLN, SLNB, ALND | 30 | Preclip Postultrasound-guided wire localization | 70.8 Clipped node identification rate | – |
| Plecha <i>et al.</i> [51] (retrospective) | Marked LN+, SLNB, ALND | 73 | Clip | 97 | – |
| Caudle <i>et al.</i> [36] | TAD SLNB + 125I seed placement in clipped node after NACT completion | | Preclip Postiodine seed (SLN: Tc and/or blue) | 100.0 | 2 (0–11) |
| Siso <i>et al.</i> [33 [■]] | Intraoperative ultrasound- guided excision of axillary clip | 46 | Preclip Post-NA (SLN: Tc and/or blue) | n.d. | 4.1 (0–21) |
| Boughley <i>et al.</i> [52] | Marked LN+, SLNB, ALND | 203 | Clip | 83 | 6.8 (1.9–16.5) clipped node within SLN; 19 (5.4–41.9) clipped node in ALND |
| Van Nijntjen <i>et al.</i> [38] | SLNB + 125I seed placement before NAC (RISAS) | 225 | Iodine-125 seed | – | – |

Patient numbers for only SLNB under $n = 100$ were excluded in SLNB-focused studies. Studies for TLN, MARI and TAD included lower patient numbers because of the absence of statistical valid data. ALN, axillary lymph node; ALND, axillary lymph node dissection; CT, computed tomography; FNR, false negative rate; NACT, neoadjuvant chemotherapy; SLN, sentinel lymph node; Tc, technetium; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection; TLN, target lymph node.

cN0/N1 breast cancer treated with NACT. Post-NACT surgical staging of the axilla demonstrated a 1.6% rate of axillary node positivity in initially cN0 patients with HER2-positive or triple-negative breast cancer who achieved a breast pCR [55[■]]. This is in clear contrast to the rate of axillary involvement in the initially cN0 group not achieving breast pCR with 16.9% in HER2-positive and 12.6% in triple-negative cases, and for the initially cN1 group (Table 2). The authors hypothesize that axillary surgery could be entirely avoided in these selected cases. In the group of hormone receptor-positive

HER2-negative breast carcinomas, a correlation between breast pCR and ypN0 status was found to a lesser degree: For initially cN0 patients with a breast pCR, the ypN1 rate was 4%. These results confirm previous studies with smaller patient numbers which showed a correlation between breast and axillary pCR and their association with intrinsic subtypes [56,57[■]]. In contrast to triple-negative and HER2-positive tumors conversion from cN1 to ypN0 was significantly lower for estrogen receptor+/Her2 (ERBB2)– tumors (50 versus 31.9%) (Table 3; [57[■]]).

Table 2. Relationship between pathological complete response and axillary lymph node involvement after neoadjuvant chemotherapy

| Clinical node status | No of pts | No. (%) of patients | | |
|---------------------------------|-----------|---------------------|-------------|-------------|
| | | ypN0 | ypN1 | ypN2/ypN3 |
| Breast pCR | | | | |
| Biologic subtype of cN0 disease | | | | |
| HR-positive/Her2-positive | 1732 | 1696 (97.9) | NR(<3) | NR (<1) |
| vHR-negative/Her2-positive | 1330 | 1317 (99.0) | 13 (1.0) | 0 |
| TNBC | | | | |
| HR-positive/Her2-negative | 646 | 620 (96.0) | 26 (4.0) | 0 |
| Biologic subtype of cN1 disease | | | | |
| HR-positive/Her2-positive | 959 | 831 (86.7) | 110 (11.5) | 18 (1.9) |
| HR-negative/Her2-positive | 842 | 747 (88.7) | NR (<11) | NR (<2) |
| TNBC | | | | |
| HR-positive/Her2-negative | 711 | 494 (69.5) | 187 (26.3) | 30 (4.2) |
| Residual breast disease | | | | |
| Biologic subtype of cN0 disease | | | | |
| HR-positive/Her2-positive | 2870 | 2336 (81.4) | 475 (16.6) | 59 (2.1) |
| HR-negative/Her2-positive | 870 | 772 (88.7) | 82 (9.4) | 16 (1.8) |
| TNBC | | | | |
| HR-positive/Her2-negative | 4423 | 2959 (66.9) | 1203 (27.2) | 261 (5.9) |
| Biologic subtype of cN1 disease | | | | |
| HR-positive/Her2-positive | 1672 | 581 (34.7) | 858 (51.3) | 233 (13.9) |
| HR-negative/Her2-positive | 691 | 308 (44.6) | 299 (43.3) | 84 (12.2) |
| TNBC | | | | |
| HR-positive/Her2-negative | 4560 | 785 (17.2) | 2487 (54.5) | 1288 (28.2) |

Extent of nodal disease at surgery by pathologic nodal category. HR, hormone receptor; pCR, pathological complete response. TNBC, triple negative breast cancer. Adapted from [55^{***}].

Table 3. Comparison of different types of breast cancer with respect to response to neoadjuvant chemotherapy in case of ypN0

| | Breast pCR and ypN0 | No breast pCR and ypN0 | P value* |
|--------------------------------------|---------------------|------------------------|----------|
| cT1-3 N0 ER+ Her2+ n=277 | 98.4 (122/124) | 85.0 (130/153) | P<0.001 |
| cT1-3 N1 ER+ Her2+ n=308 | 51.8 (58/112) | 19.9 (39/196) | P<0.001 |
| cT1-3 N0 ER- Her2+ n=128 | 100 (97/97) | 90.3 (28/31) | P=0.013 |
| cT1-3 N1 ER- Her2+ n=233 | 46.7 (70/150) | 30.1 (25/83) | P=0.014 |
| cT1-3 N0 ER+ Her2- n=932 | 93.3 (83/89) | 64.7 (545/843) | P<0.001 |
| cT1-3 N1 ER+ Her2- n=1,404 | 31.9 (38/119) | 5.1 (65/1285) | P<0.001 |
| cT1-3 N0 triple negative n=337 | 98.5 (139/132) | 87.3 (179/205) | P<0.001 |
| cT1-3 N1 triple negative n=465 | 48.5 (79/163) | 15.6 (47/302) | P<0.001 |

Data are presented as percentages with the numbers in parentheses. χ^2 test and Fisher exact test between pts with breast pCR and ypN0 versus pts without breast pCR and ypN0. Er indicates estrogen receptor, triple negative: negative for ER, PR and Her2. Overview of ypN0 in the case of breast pCR and without breast pCR after NACT for the different breast cancer subtypes. ER, estrogen receptor; NACT, neoadjuvant chemotherapy; pCR, pathological complete response. Adapted from [57^{**}]. *P<0.05 value with significance.

CONCLUSION

The development of clinical guidelines for the management of the axilla in breast cancer is a work in progress. Despite the known methodological shortcomings of the ACOSOG Z0011 trial which explains the cautious implementation of its results in current guidelines, ALND is increasingly being abandoned in daily routine for patients with clinically occult involvement of the SLN even if the criteria of the underlying trials (ACOSOG Z0011, IBCSG 23–01, AMAROS) are not fulfilled.

After NACT, TAD has been proposed to replace conventional ALND with its concomitant morbidity for patients who convert from a cN1 to a ycN0 status.

Based on the existing data, there are still no uniform guidelines for axillary surgery in Europe and worldwide. The observed correlation of breast and axillary pCR after NACT and its association with the intrinsic subtype may further de-escalate surgical management in the axilla.

Taking into account the data reported in this article, the following points are regarded as trend-setting for the current surgical treatment of breast and axilla.

- (1) No ink on tumor is the accepted standard for invasive resection margins for patients who undergo primary BCS.
- (2) After NACT, there is no reason to aim for wider resection margins than in primary surgery.
- (3) SLN biopsy is the standard of care staging procedure in cN0 patients with invasive disease.
- (4) ALND after a positive SLN biopsy may be avoided in cN0 patients with micrometastasis or macrometastasis in up to two SLNs,
- (5) For the following statement no evidence is available, but after discussion the German Guidelines state that patients fulfilling the above criteria who undergo mastectomy, may also avoid axillary dissection after multidisciplinary discussion of individual cases and consideration of axillary irradiation.
- (6) Suspicious lymph nodes should be assessed by core needle biopsy.
- (7) Combined methods of SLN biopsy and removal of axillary metastases marked pre-NACT (TAD) achieve considerably better FNRs than SLN biopsy alone, and are therefore considered as the preferred procedure in patients who convert from cN1 to ycN0.
- (8) The ideal localization method for TAD has yet to be defined.
- (9) Further studies are needed to assess the prognostic significance of axillary surgery on DFS and overall survival, and provide information on the

need for radiotherapy after NACT in case of axillary pCR.

Results from large, confirmatory randomized trials that assess the omission of ALND in case of a positive SLN biopsy are expected in the near future (INSEMA, POSNOC, SENOMAC, SINODAR-ONE).

In view of the ongoing reduction of the extent of surgery in the axilla, the question arises whether radiotherapy of the axilla needs to be performed, and if yes, what target volume should be irradiated. Further trials will show whether a good response to NACT may further de-escalate locoregional treatment (Alliance 011202 and NSABP-51/RTOG 1304).

In summary, this review is limited by the heterogeneity of included studies with small patient numbers and different patient populations. Thus, results and consequences should be interpreted with caution and could be subject to change in the near future.

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- of special interest
- of outstanding interest

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