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Real de-escalation or escalation in disguise?

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ABSTRACT

The past two decades have seen an unprecedented trend towards de-escalation of surgical therapy in the setting of early BC, the most prominent examples being the reduction of re-excision rates for close surgical margins after breast-conserving surgery and replacing axillary lymph node dissection by less radical procedures such as sentinel lymph node biopsy (SLNB). Numerous studies confirmed that reducing the extent of surgery in the upfront surgery setting does not impact locoregional recurrences and overall outcome. In the setting of primary systemic treatment, there is an increased use of less invasive staging strategies reaching from SLNB and targeted lymph node biopsy (TLNB) to targeted axillary dissection (TAD). Omission of any axillary surgery in the presence of pathological complete response in the breast is currently being investigated in clinical trials. On the other hand, concerns have been raised that surgical de-escalation might induce an escalation of other treatment modalities such as radiation therapy. Since most trials on surgical de-escalation did not include standardized protocols for adjuvant radiotherapy, it remains unclear, whether the effect of surgical de-escalation was valid in itself or if radiotherapy compensated for the decreased surgical extent. Uncertainties in scientific evidence may therefore lead to escalation of radiotherapy in some settings of surgical de-escalation. Further, the increasing rate of mastectomies including contralateral procedures in patients without genetic risk is alarming. Future studies of locoregional treatment strategies need to include an interdisciplinary approach to integrate de-escalation approaches combining surgery and radiotherapy in a way that promotes optimal quality of life and shared decision-making.

1. Introduction

In the last two decades, breast surgical oncologists have increased their efforts to de-escalate breast surgery with the aim of reducing morbidity and improving life quality while preserving oncological outcomes of breast cancer (BC) patients. These de-escalation approaches include avoiding re-excisions for close surgical margins after breast-conserving surgery (BCS), introducing oncoplastic procedures to reduce mastectomy rates, decreasing the use of contralateral risk-reducing mastectomy (CRRM) in women with average risk of contralateral disease and omitting axillary lymph node dissection (ALND) in patients with low axillary tumor burden. In the setting of primary systemic treatment (PST), there is an increased use of less invasive procedures such as sentinel lymph node biopsy (SLNB) with or without targeted axillary dissection (TAD). Nowadays, SLNB remains the staging procedure of choice both in upfront surgery patients and post-PST patients with cN0 disease, while omission of any axillary surgery in both settings is under investigation. Further, several trials currently investigate omission of breast surgery in selected women with DCIS or in women who are excellent responders to PST.

This de-escalation has been made possible thanks to the effectiveness of systemic therapies but also to our efforts to continually adjust the treatment approach based on an individual patient's extent of disease, and by expanding our knowledge in aggressive tumors behavior. The idea that bigger surgery is better surgery has been replaced by careful selection of patients for the most appropriate surgical strategy. More

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precise surgery with improved imaging, modern localization techniques to guide surgery, standardization of SLNB and better evaluation of response after PST have improved locoregional recurrence rates as well as cosmetic outcomes.

Within the context of modern multidisciplinary management of BC, the impact of systemic therapy on surgical options and the impact of surgical options on postoperative treatment recommendations have been considered crucial in this surgical de-escalation. Breast surgeons have embraced the neoadjuvant approach as an ideal setting to de-escalate surgery. Nevertheless, the introduction of more effective systemic therapies should also create a space for de-escalation of other locoregional treatments. In view of the evidence, axillary irradiation may be re-considered in this setting to add value to the de-escalation, as well as ongoing studies on de-escalation of systemic therapy in HER2-positive tumors.

There is also an opportunity to strengthen the collaboration between multidisciplinary partners early in the design of studies. Some of the neoadjuvant trials include surgical endpoints, although surgical data are usually sub-optimally collected and results difficult to analyze. It is time for bringing the multidisciplinary team to the design of trials to reach a real impact in BC patients. Increasingly, the post-neoadjuvant setting is gaining importance, and therapy response can guide the escalation or de-escalation of other treatment strategies that have already demonstrated to improve survival in case of residual disease. The interplay between surgical de-escalation after PST and post-neoadjuvant treatment needs to follow the same strategy to gain its full potential for the benefit of patients.

De-escalation also requires an effort in the shared decision making as implementing de-escalation treatments might potentially result in lower disease control for a small minority of patients, while it may avoid overtreatment and morbidity in a large number of BC patients. On the other hand, some surgeons are concerned by a potential escalation of other treatment modalities (e.g., radiotherapy) following de-escalation of surgical extent. Standardization of the information given to patients to support them in their treatment choice and promote patient involvement in treatment decision-making is becoming imperative, much more so when omission of treatments is an option.

2. Local therapy of the breast

In the last two decades, an increasing body of evidence demonstrated equivalent clinical outcomes in women receiving less radical surgical treatment, allowing for a de-escalation becoming standard of care and an important goal to be achieved. In particular, current recommendations for surgical de-escalation include the avoidance of unnecessary re-excisions for tumor-free but supposedly “close” margins after BCS. Further, experimental approaches such as omitting breast surgery altogether e.g., in selected women with DCIS or in case of a clinical complete response to PST, are currently under investigation [1,2]. BCS is in general accompanied by radiotherapy. Concerns have been raised that reduction of surgical extent may lead to a potential escalation of radiotherapy.

An important milestone on the way towards surgical de-escalation was the release of the consensus statement defining an adequate surgical margin by the SSO/ASTRO [3]. The update was based on the observation that wide negative margins do not reduce local recurrence risk compared to a “no ink on tumor”-policy. Following this statement, national and international guideline committees gradually updated their recommendations as well [4–6] and this led to a marked reduction in secondary surgeries, either performed as local re-excisions or mastectomies [7]. Meanwhile, the increase in close margins without re-excision may lead to reflexive increases in the utilization of tumor bed boost irradiation. Although international guidelines recommend boost irradiation only in patients with an increased risk of local recurrence [8,9], boost irradiation was used in 76.7% of patients in 2012–2016 in a retrospective study from the National Cancer Database [10]. The use of boost irradiation declined overall, but an increased use was reported in patients receiving hypofractionated radiotherapy. This was true even for patients aged >70 years with negative margins. In a 2005 survey, >90% of radiation oncologists stated that they would recommend boost irradiation in case of close margins [11]. However, this practice is not supported by the current evidence and the SSO/SRO consensus did explicitly recommend against basing radiotherapy decisions on margin width [3]. The application of a boost in patients with close margins without additional risk factors can be thus considered as a real escalation of local treatment in the upfront surgery setting.

At the same time, the development of new targeted therapies significantly improved the efficacy of PST. In clinical trials, up to 80–90% of patients achieve pathological complete response (pCR) [12]. Although most guidelines clearly recommend the residual lesion identified on imaging or the center of the former tumor bed located by a marker prior or in the early course of chemotherapy as the target resection volume [4,5], some physicians are still concerned by data from the EBCTCG that showed a 5.5%-increase in recurrence rates after PST compared to upfront surgery [13]. Patients considered in this meta-analysis were, however, enrolled in 1980–2002 with a median follow-up of 9 years and last follow-up in 2013, and were not treated according to current standards. In addition, a small cohort of patients did not receive any surgery at all. Therefore, most clinicians agree that the higher recurrence rate found in the EBCTCG meta-analysis cannot be translated to the locoregional management of BC after PST today.

Several studies addressed the question, whether breast surgery could be replaced by minimally invasive biopsy in patients with a good response on imaging. The false-negative rates (FNRs) varied, however, between 18% and 50% [14–16]. Preliminary data from a small, highly selected cohort suggest that omission of surgery might not translate into higher local recurrence rates [15]. However, no data on patient-reported outcomes are available to assess whether omitting surgery is a real “de-escalation” also from patient perspective.

Given the improvements in systemic therapy and incorporation of the “no tumor on ink” definition of clear margins into guidelines, one could assume that the proportion of patients undergoing mastectomy would decrease over time. However, this is clearly not the case. More than one-third of all breast cancer patients receive mastectomy and this proportion has risen in the last decade [17,18]. Further, the rate of contralateral mastectomies in patients with but also without genetic risk are steadily increasing, especially in the Unites States, despite the fact that CRRM can improve prognosis only in cases with a proven pathogenic germline mutation in the BRCA1 gene [19], [18,20,21]. This evolution is alarming since it reflects a clear overtreatment. In the absence of high-risk mutations, BCS followed by RT is at least as effective as mastectomy with regard to disease-free (DFS) and overall survival (OS), and the risk of a contralateral BC remains low (0.3–0.6% per annum) [22,23]. Therefore, CRRM does not provide any survival benefit for most women and can be associated with worsened body image, reduced quality of life, and more complications and re-operations as compared to unilateral breast conservation. The decision to pursue CRRM in women who have a low-to-moderate risk of developing a contralateral BC should not be supported by the surgeon and be avoided as first line approach [24]. The patient asking for a CRRM deserves careful counseling and a shared decision-making process. In this context, in the sense of de-escalation, the patient should also be counseled about the effects of recommended adjuvant therapy (e.g., endocrine treatment) on risk reduction for contralateral disease. Concluding, the exact reasons for the unnecessary escalation of surgical treatment of the breast are not fully understood. An impact of patient counseling and the reimbursement systems should be considered.

3. Radiotherapy of the breast in early-stage low-risk BC

Adjuvant whole-breast irradiation (WBI) has represented the standard of care after BCS for the past decades due to the EBCTCG meta-

analysis demonstrating significant reductions in any first recurrence, BC mortality and overall mortality. However, even then it was demonstrated that although relative reductions in the recurrence risk were similar among subgroups, the absolute benefit varied largely. Omission of WBI after BCS in patients with low-risk BC has been studied in a variety of randomized trials. All studies showed a significant increase in local recurrence in the absence of WBI, however without a detriment on OS. In a meta-analysis of 5 trials, omission of radiotherapy led to a 6.8-fold increased local recurrence risk (HR 6.8, 95%-CI 4.23–10.93) [25]. The absolute benefit regarding local recurrence increased with follow-up beyond 5 years, suggesting that women with a life expectancy of >10 years may derive a greater benefit from radiotherapy [26–28]. In the most recent trial (PRIME-II) the local recurrence rates with and without radiotherapy changed from 1.3% vs. 4.3% at 5 years to 0.9% and 9.8% at 10 years [29]. The 2021 guidelines by EUSOMA/SIOG for elderly patients with BC states that "omission of radiotherapy in low-risk patients can be safe and reasonable" while WBI remains standard of care for most patients [30]. The German AGO guideline concludes that WBI may be omitted in patients with early-stage low-risk BC with a life expectancy <10 years receiving endocrine therapy, while accepting an increased local recurrence risk [5].

Most women that are candidates for radiotherapy omission also qualify for partial breast irradiation (PBI). In PBI, only the tumor bed with an additional safety margin is treated. PBI has been studied using a variety of techniques including intraoperative radiotherapy (IORT), multi-catheter brachytherapy and external-beam radiotherapy. Meta-analyses demonstrated comparable OS with an increased local recurrence risk compared to WBI [31–33]. This increase was due to recurrences outside of the original tumor bed and was driven by an increased risk of recurrence in trials of IORT. However, the pooled absolute differences in local recurrence between PBI and whole-breast radiotherapy were estimated to be <1.5% [33].

Escalation may occur in several ways: Patients that are candidates for radiotherapy omission may be treated with PBI instead. Some, but not all PBI-techniques have demonstrated reduced toxicity compared to WBI. Specifically, twice-daily PBI has been associated to inferior cosmetic results. Specific to IORT is the scenario of delivering PBI without knowledge of all information which may lead to patients receiving both WBI and IORT due to unanticipated risk factors. Currently, there are no data from randomized trials comparing PBI to no adjuvant radiotherapy. Due to the increasing convenience with ultra-hypofractionation given over just one week, physicians may also be more inclined to discuss WBI even in elderly frail patients with a limited life expectancy that qualify for radiotherapy omission.

4. Local therapy of the axilla

Scenario 1. cN0 and upfront surgery

The changes in the surgical management of the axilla in the recent decades are often hailed as the ultimate de-escalation in BC therapy. Indeed, after a long time of unselective use of ALND in all patients, the need for a more individualized approach became increasingly obvious with rising rates of early detection and improved adjuvant therapy options. Since lymphedema, loss of sensation, pain, and reduced mobility following ALND may affect patients' long-term life-quality, the search for less invasive means of axillary staging led to development of SLNB, which quickly became a widely accepted method of nodal staging in cN0 patients.

With regard to the increasing role of tumor biology and predictive factors for the selection of adjuvant treatment decisions, the role of prognostic factors such as the pN-status is steadily decreasing. Therefore, the routine use of SLNB is currently put into question taking into account a small but significant morbidity associated with the procedure [34]. The ASCO guidelines 2021 state that SLNB is not required in patients >70 years with ER+/HER2-negative early-stage BC [35]. This statement is supported by the Choosing Wisely statement updated in 2019. Two randomized (SOUND, INSEMA) trials will provide high-level evidence to define patient cohorts in whom SLNB can be omitted [34,36].

Scenario 2. Treatment of the axilla in cN0/pN1(sn)

In case of a positive SN, completion ALND remained standard practice for a long time. However, as nodal surgery has increasingly been regarded as a staging procedure without a survival benefit, the need for ALND in these patients became a matter of debate in the early 2000s. Several studies aimed at clarifying the benefit of ALND in this setting (Table 1). While the results were quickly incorporated into national and international guidelines [4,6,35], paving the way towards omitting ALND in patients with 1–2 positive SLNs, it is important to discuss participating patient populations and interventions performed in both studies to fully assess the clinical consequences arising from these findings.

The **ACOSOG Z0011** study was a randomized trial comparing outcomes in SLN-positive patients who did and did not undergo ALND [37,42]. The study was closed prematurely due to slow accrual after enrolling 891 patients. After a 10-year follow up, there was no difference in OS and DFS and the axillary recurrence rate was very low [37]. However, several issues concerning data quality and stratification have been raised. First, the number of patients harboring only micrometastatic foci in SNs was high (44.8% in the SLNB-only arm and 37.5% in the ALND-arm) and these patients would not have required completion ALND based on the lack of benefit of such showed in IBCSG 23–01 [43]. Second, 28 patients in the SLNB-only arm were documented as having no positive nodes at all [Table 1, [42]].

Nonetheless, the major criticism after the publication of the Z0011 results was the insufficient standardization of adjuvant irradiation. Although the protocol required that patients receive WBI using standard tangential fields and specified that a third-field of directed nodal treatment should not be used, the extent of RT coverage of regional nodes has been the subject of considerable speculation [44,45]. Since radiation oncologists were not blinded to patients' treatment arm, it has been hypothesized that patients in the SLNB-only arm might have received irradiation to level I/II more often than those in the ALND-arm. Therefore, data on administration of RT were reviewed in 605 patients and, in a second analysis, two independent radiation oncologists, blinded to the treatment arm, reviewed details on radiation fields in 228 available patients from the trial [45]. Interestingly, only 89% of all patients received WBI and the detailed analysis of RT fields showed that 19% of analyzed patients received directed regional nodal RT using ≥3 fields: 22 in the ALND-arm and 21 in the SLNB-only arm. Furthermore, >50% of patients in each arm received high tangential radiotherapy which leads to therapeutic irradiation of level I and II. Unsurprisingly, the highest rates of directed nodal irradiation were among those with multiple nodes involved. However, no significant differences were observed between surgical treatment arms regarding irradiation fields or tangential field height in this small and unplanned retrospective subset analysis. Most breast surgeons, however, stepwise abandoned ALND in patients who fulfilled the "ACOSOG criteria" since the body of evidence from cancer registries increased that ALND was of no benefit for patients undergoing BCS and WBI. The optimal radiation strategy remained, however, unclear in this cohort of patients leading to an escalation of target volumes in some but not all guidelines [5,6,35].

Recently, **SINODAR-ONE,** a trial with a similar design as Z0011, reached similar conclusions [39]. In contrast to Z0011, only patients with macrometastases were enrolled and mastectomy was not an exclusion criterion. The trial was closed prematurely after 889 of the planned 2000 patients were enrolled.

Another large study on surgical de-escalation in this setting was **AMAROS** [38,41,46]. In this study, patients with positive SNs were randomized between completion ALND and axillary RT. As in Z0011, 40% patients had no macrometastatic SNs (29% micrometastasis and

Table 1
Comparison of the available studies on ACOSOG Z0011 and AMAROS trials.

	ACOSOG Z0011 [37]	AMAROS [38]	SINODAR-ONE [39]	OTOASOR [40]
Patient number	891	1425	891	474
Patient population	T ≤ 5 cm, no palpable adenopathy, 1–2 metastatic SLNs, lumpectomy with no tumor on ink Excluded: Metastases identified initially or solely with immunohistochemistry; ≥3 positive SLNs, matted nodes, gross extranodal disease; PST	T1–2, no palpable lymphadenopathy, T ≤ 5 cm (before amendment: 3 cm), multifocality allowed after amendment Excluded: previous malignancy, PST, previous axillary surgery/radiotherapy; after amendment: SNs with only ITCs no longer regarded as positive	T ≤ 5 cm, cN0 on clinical examination and ultrasound, 1–2 SLNs with macrometastasis, age 40–75 years, BCS or mastectomy Excluded: inflammatory/bilateral BC, PST	T < 3 cm, cN0 (clinically/ ultrasound), pN1(sn), BCS or mastectomy
Phase	III	III	III	III
Arms	ALND vs. no ALND	ALND vs. axillary radiotherapy	ALND vs. no ALND	Axillary radiotherapy vs. ALND
Follow up	9.3 years	10 years [38]	2.8 years	8 years
Primary endpoint	OS	5-year axillary recurrence	OS	8-year axillary recurrence
Radiation therapy	Not clearly defined; recommended: tangential WBI and no third-field irradiation; 11% received no RT, 18.9% received prohibited supraclavicular irradiation, 52.6% received high tangential irradiation	RT arm: levels I-III and the medial part of the supraclavicular fossa; 25 fractions of 2 Gy ALND arm: RT allowed in pts. with ≥4 positive nodes	Recommended: tangential WBI	RT arm: level I-III and the medial part of the supraclavicular fossa; 25 fractions of 2 Gy ALND arm: RT allowed in pts. with ≥4 positive nodes and 1–3 with high risk-features
Results	SLNB-only vs. ALND arm: 10-year-OS: 86.3% vs. 83.6%, HR 0.85, 95%-CI 0–1.16, p = 0.02 10-year-DFS: 80.2% vs. 78.2%, HR 0.85, 95%-CI 0.62–1.17, p = 0.32	Axillary RT vs. ALND arm (10-year-data): Axillary recurrence: 1.82% vs. 0.93%, HR 1.71, 95%-CI 0.67–4.39, p = 0.37 OS: 81.4% vs. 84.5%, HR 1.17, 95%-CI 0.89–1.52, p = 0.26 DMFS: 78.2% vs. 81.7%, HR 1.18, 95%-CI 0.92–1.50, p = 0.19 [41] DFS: 70.1% vs. 75.0%, HR 1.19, 95%-CI 0.97–1.46, p = 0.11 10-year LRR: 4.1% vs. 3.6% [41] Second primary cancers: 12.1% vs. 8.3% (p = 0.035)	SLNB-only vs. ALND arm: 5-year-OS: 98.8% vs. 98.9%, p = 0.936 5-year RFS: 95.6% vs. 96.4%, p = 0.491	Axillary RT vs. ALND arm (8-year-data): Axillary recurrence: 1.7% vs. 2.0%, p = 1.00 OS: 84.8% vs. 77.9%, HR 0.59 (CI not reported), p = 0.06 DFS: 77.4% vs. 72.1%, HR not reported, p = 0.51

Abbreviations: DMFS – distant metastasis-free survival.

11% ITCs only, respectively). In contrast to Z0011, 17% of patients received a mastectomy. Until 2022, only the 5-year follow up was available as full publication [41]. Here, the 5-year axillary recurrence was 0.43% after ALND vs. 1.19% after axillary RT and the planned non-inferiority test was underpowered because of the low number of events. Lymphedema in the ipsilateral arm was reported significantly more often after ALND than after axillary RT at year 1, 3 and 5. At the SABCS 2018, 10-year follow up data were presented [41]. Somewhat unusual for a large randomized study, these results have not been published as full publication until November 2022 [38]. The axillary recurrence rate after 10 years was twice as high in the RT arm, compared to ALND group (1.82% vs. 0.93%). No significant differences between treatment arms regarding OS, DMFS and local recurrence rate were reported, but it is worth noting that survival intervals were numerically longer in the ALND arm (10-y-OS: 84.5% vs. 81.4%, 10-y-DFS: 75.0% vs. 70.1%), and that significantly more second primaries were observed after RT (12.1% vs. 8.3%), including contralateral BCs (3.1% vs. 1.5%). Of note, this unusually large difference in second primary cancers was not observed in other trials of regional nodal irradiation (RNI) including the internal mammary nodes which typically leads to higher exposure of the contralateral breast compared to axillary RT [47,48]. Quality of life data show that lymphedema was observed and treated significantly more often after ALND than after RT at every measured time point, with the highest incidence at 1 year. Overall, 44.2% of the patients reported lymphedema at least once after ALND compared with 28.6% of the patients after RT. Increase in arm circumference of ≥10% was observed more frequently after ALND. Shoulder mobility was similar and no significant differences were observed regarding QoL. Unfortunately, quality of life has not been assessed after 10 years, so that long-term comparison with regard to arm morbidity is lacking [38].

The single-center **OTOASOR trial** used a very similar design to the AMAROS trial [40]. Mastectomy was performed in 16% of patients and 29% of patients had micrometastases. There were no significant differences for DFS and OS, although OS was numerically better in the RT-arm. Clinical signs of lymphedema, paresthesia, swelling, and arm pain occurred in 15.3% in the ALND-arm and 4.7% in the RT-arm (p-value not reported) with the highest rates of morbidity seen in patients that underwent both ALND and RNI (23% in the ALND-arm with pN2-3 status). Quality of life was reported as similar between the arms, although data were not presented.

Based on the results from the Z0011 and AMAROS data and updated guidelines recommendations, most surgeons quickly adopted the "no completion ALND" policy into their clinical practice. Recently, an analysis of the SEER database showed that the percentage of patients undergoing SLNB alone increased from 22% in 2000 to 81% in 2016 for patients with 1–2 metastatic nodes [49]. Interestingly, surgical de-escalation is considered an option beyond patients fulfilling Z0011 criteria: in 2016, 21% of patients with 3–5 metastatic nodes did not undergo completion ALND. In this patient group, however, omitting ALND was reported to be associated with decreased survival [49].

While frequently described as an unprecedented example of treatment de-escalation, axillary management in patients with clinically unsuspicious but pathologically metastatic SNs may in fact represent a de-escalation of one treatment modality (surgery), and at the same time an escalation of another one (radiation therapy). This is on the one hand explained by the lower morbidity of axillary RT compared to ALND in the AMAROS and OTOASOR-trials and on the other hand by the coinciding publication of several trials that demonstrated improvements in DFS and BC-related mortality with RNI [48,50,51]. Currently, the AGO Breast Committee recommends that planned radiation target volume should include axilla level I and II with the cranial border located 5 mm below the axillary vein in all patients in whom completion ALND was omitted, if Z0011 inclusion criteria are fulfilled [4]. When Z0011 criteria are not fulfilled, RT should be performed as in the AMAROS trial, i.e., including level I-III and the supraclavicular fossa. According to current NCCN guidelines, use of comprehensive RNI with or without intentional inclusion of axilla should remain at the discretion of the radiation oncologist in patients fulfilling Z0011 criteria [6]. In those who do not, inclusion of any portion of the undissected axilla at risk is recommended and comprehensive RNI should be strongly considered. In the spirit of replacing surgery with irradiation, the ASCO recommends RT of the axilla instead of ALND in cN0 patients with positive SNs and tumors ≤5 cm restricted to one quadrant [35]. In patients who receive mastectomy and have 1–2 positive nodes, radiation to the axilla is recommended and ALND can be safely omitted.

Scenario 3. cN0 → ycN0

The appropriate timing of SLNB in cN0 patients undergoing PST was investigated in several large trials such as GANEA-2 [52], SENTINA [53], and the Swedish prospective multicenter trial [54,55]. All showed that it was feasible to perform SLNB after instead of before PST, and this new approach added the possibility to evaluate response to treatment not only in the primary tumor but in regional nodes as well, thus allowing an individualized post-neoadjuvant strategy for those with residual nodal metastasis [4,35].

In view of the very low rate of axillary involvement in some patient cohorts who achieve a complete response in the breast (triple-negative, HER2-positive), ongoing trials (e.g., EUBREAST-1) investigate whether axillary staging can be omitted entirely [56].

Scenario 4. cN0 → ypN1

The increasing use of PST opened new questions regarding optimal axillary management. While it is universally agreed that cN0 → ypN0 patients do not require any additional surgical interventions beyond SLNB, the optimal therapy for those harboring residual nodal metastasis remains to be clarified. Obviously, the answer to this question should not be searched for in the Z0011 and AMAROS trials, since patients receiving PST were excluded from both, and one needs to keep in mind that the biological significance of residual disease, persisting beyond systemic treatment, may be different from the one of nodal metastasis encountered in untreated patients undergoing upfront surgery.

Moo et al. reported on a large group of patients undergoing SLNB after PST [57]. All patients were ycN0 after PST, but the initial nodal status could be either clinically positive or negative. Patients with a positive SN were at high risk of harboring additional non-sentinel metastases. In case of macrometastatic SN, the probability of further positive nodes was 62%. Interestingly, the so-called low-volume residual disease was associated with additional positive nodes as well: 64% of patients with micrometastatic SN had positive non-sentinel nodes and 17% of those with isolated tumor cells (ITCs) harbored additional positive nodes. However, the patient number in the last group was very small (six). A recent retrospective analysis of the Dana Farber/Brigham and Women's Cancer Center and the NCDB reported inferior survival associated with ITC and micrometastasis in SNs compared with ypN0 status [58]. Based on these data, most guidelines (AGO, ASCO, ASBS) recommend ALND in case of macro- and micrometastasis in SNs after PST [4,35,59,60]. In the presence of ITCs, ALND may be discussed on an individual basis [35,59].

However, some of cN0→ypN1 patients would not have required an ALND if they had received upfront surgery (provided ≤2 SNs were positive and a BCS was performed), suggesting that surgical escalation may occur in the neoadjuvant setting. Indeed, the ASBS Consensus Guidelines on Axillary Management explicitly states that for cN0 patients with tumors not responding well to neoadjuvant chemotherapy (i.e., HR+/HER2-negative), the rates of ALND are expected to be lower in case of upfront surgery, in that most will have ≤2 positive SLNs and can avoid ALND. It remains to be seen if this escalation of axillary surgery in this setting is warranted and ultimately improves the oncological outcome. For those with responsive subtypes (HER2+/triple-negative), the rates of ALND can be reduced by a neoadjuvant approach, suggesting that tumor subtype should be taken into account when considering neoadjuvant therapy [59].

Scenario 5. cN + before PST

The clinically node-positive population receiving PST is currently the most controversially discussed clinical setting regarding management of the axilla. On the one hand, up to 60% of patients reach axillary pCR through PST and are potential candidates for surgical de-escalation, on the other hand leaving a metastatic node behind may result in increased recurrence rates and thus compromise oncological safety. Currently, in patients with clinically apparent nodal metastases who convert to clinically negative node status (cN+→ycN0), it is unclear which axillary surgical staging strategy should be preferred. This uncertainty is expressed in the heterogeneity of recommendations endorsed by different national and international societies, which range from SLNB to TAD or ALND [61,62]. Some guidelines do not recommend SLNB in this setting because of high FNRs reported in large trials (SENTINA and ACOSOG Z1071) and confirmed in a meta-analysis [52,53,63,64].

Independent of the technique chosen (SLNB or TAD), most guidelines recommend completion ALND in case of residual tumor burden found upon surgical staging procedure [4,35,59]. Whether ALND can be safely replaced by RT is currently being investigated in the ALLIANCE A011202 (NCT01901094) and TAXIS (NCT03513614) trials. In the setting of tumor-free nodes after SLNB or TAD (cN+→ypN0), it remains to be clarified which locoregional treatment should be offered. Current guidelines generally recommend that RT, which usually has been delivered just to the undissected portion of the axilla, should include the whole axilla in patients in whom surgical ALND was omitted. While the AGO Breast Committee does not recommend including axilla in the planning target volume in patients receiving ALND, the available evidence is not sufficient to decide whether it should be irradiated in case of negative SLNB or TAD in initially cN + patients (recommendation: +/−) [4]. Similarly, the ASCO guidelines recommend locoregional RT in selected patients if removed nodes are tumor-free and no ALND was performed [35]. In the largest cohort study of SLNB after PST, >80% of axillary recurrences occurred in patients who did not receive radiotherapy (10-year axillary recurrence rate 9.4% without vs. 2.3% with RT; p = 0.0002) [65].

Recently, the results of the international EUBREAST survey on surgical management of the axilla were reported [66]. 349 physicians from 45 countries completed a detailed online questionnaire on their approach to specific clinical scenarios. The survey revealed very heterogenous recommendations regarding type of surgery in cN+→ycN0 patients. In patients with a limited nodal burden, TAD was the most common surgical staging choice (54%), followed by ALND (30%), SLNB alone (21%), and TLNB (3%). In contrast, patients with a higher tumor load in the axilla (cN2) are more frequently offered upfront ALND (54%). Further, it is worth noting that up to one-third of respondents did recommend axillary RT and not an ALND in the presence of micro- or macrometastasis in the SLNB/TAD, suggesting that, yet again, de-escalation of surgical treatment may be accompanied by an escalation of radiation therapy. Similar results have recently been reported by a nation-wide survey conducted in Germany [67].

The optimal management of the axilla in cN + patients undergoing PST will hopefully be clarified in the ongoing trials. The **AXSANA** (Axillary Surgery After NeoAdjuvant Treatment) study is a prospective multi-center cohort study initiated by EUBREAST and evaluating different surgical staging techniques [61]. With a target accrual of 4500 patients (enrollment status as of January 2023: 3447 pts.), it is the largest study to address the currently opened issues such as the identification of patients who are suitable candidates for a surgical de-escalation, the oncological safety of SLNB, TAD and TLNB, the quality of life and arm morbidity after different procedures, the optimal radiation therapy after deescalated surgery, and the optimal marking and localization technique for TAD/TLNB. The **MINIMAX** (MINImal versus MAXimal Invasive Axillary Staging and Treatment After Neoadjuvant Systemic Therapy in Node Positive Breast Cancer) is a Dutch multicentre registry study with similar aims (target accrual ≈ 4000 pts.) [68]. In the **TAXIS** trial, an international, phase III randomized study, 1500 cN + patients will receive tailored axillary surgery (TAS = SLNB in combination with the selective removal of all palpable disease and documentation of the removal of the initially biopsy-proven and clipped node metastasis by specimen radiography) [69,70]. In case of histologically positive nodes, patients are randomized to ALND or no ALND. In the no-ALND arm the RT will include axilla. Further, in the phase III **ALLIANCE A011202**, 2918 cN + patients with positive SLN(s) after PST are randomized to ALND or RT. Finally, the randomized **ATNEC** study will compare ALND with axillary RT in node-positive patients achieving axillary pCR after PST. **NEONOD2** is currently the only trial addressing micrometastatic involvement of SN after PST [71]. cN+/ypN1mi patients will receive standard WBI without ALND or axillary RT. Their outcome will be compared to a control group of patients with ypN0 after SLNB alone.

Tailoring of adjuvant radiotherapy indication and volumes based on treatment response has long been postulated as a potential advantage of PST. The association between favorable treatment response and decreased recurrence risk has been consistently demonstrated. However, there are conflicting data regarding the benefit of RNI and postmastectomy radiotherapy (PMRT) in patients with early-stage node-positive BC (cT1/2cN1) and pCR/ypN0. Again, this may reflect escalation of radiotherapy for a subgroup of patients since both RNI and PMRT are only recommended in patients with high-risk features that receive upfront surgery and have a pT1-2 pN1-stage. Overall, locoregional recurrence rates in this group of patients have been declining over the past decades. However, patients treated with PST mostly represent a high-risk subgroup.

Recently, the prospective RAPCHEM trial has been published [72]. This trial from the Netherlands enrolled patients with cT1-2 cN1 (max. 3 suspicious nodes) BC. Although this was not a randomized trial, patients were grouped into three risk categories according to the nodal status after PST and radiotherapy volumes were prespecified for these risk groups. The majority of patients (81%) had ALND after PST while 11% had SLNB before PST and 8% of patients had SLNB or a MARI-procedure after PST. Low risk patients had ypN0 or pN1mi without risk factors (cT > 3 cm, G3, LVI). They were recommended only whole-breast radiotherapy after BCS and no PMRT. Intermediate risk patients had ypN1 after ALND, ypN1mi after SLNB without risk factors, pN1mi (SLNB) with at least one risk factor or pN1a (SLNB, ≤2 positive nodes) without risk factors. These patients were planned to receive whole-breast radiotherapy or PMRT with coverage of Level I/II in case of SLNB. Finally, high risk-patients had ypN2-3, ypN1(SLNB), ypN1mi with at least one risk factor, pN1a (≤2 positive SNs) with at least one risk factor or pN1a with 3 positive nodes. All of these patients were recommended whole-breast radiotherapy or PMRT with treatment of level III and the supraclavicular fossa. Level I/II were included in case of SLNB. Unfortunately, compliance with these recommendations was only 63.8% overall [73]. Protocol violations were more common in the low risk (compliance 62.0%) and intermediate risk (compliance 54.3%) groups which mostly received more radiotherapy than originally recommended – including PMRT in >30% of patients in the low risk-group. Overall, isolated locoregional recurrence rates were reassuringly low with 5-year rates of 2.1%, 2.2% and 2.3% for the three risk groups. Recurrence-free survival and OS were significantly worse for patients in the high risk-group compared to the intermediate- and low risk-group. Due to the high number of protocol-violations and ALND after PST, generalizability of these findings is limited. However, the locoregional recurrence rates provide important information for shared decision-making in this situation.

The NSABP B-51/RTOG1304-trial that has recently completed enrollment addresses the question of PMRT and RNI in cT1-3 cN1 that convert to ypN0 after PST. Patients were randomized to WBI with or without RNI and PMRT with RNI or no radiotherapy after mastectomy.

Is surgical de-escalation threatened by the election of (post-neo) adjuvant treatment depending on the number of positive nodes?

Several clinical trials showed a favorable effect from an additional post-neoadjuvant treatment with chemo- or targeted therapy on DFS/OS in patients with residual disease after PST (CREATE X, Katherine, OlympiaA, monarchE) [74–77]. OlympiA was a prospective double-blind trial with patients with germline pathogenic variants in BRCA1/2 and high-risk early BC randomly assigned to receive either a PARP-inhibitor olaparib or placebo for 1 year [76]. HR+/HER2--negative patients treated with upfront surgery were required to have ≥4 positive nodes. Those treated with PST were required to have residual tumor with a CPS + EG-score ≥3. It should be noted that the CPS + EG-score is heavily dependent on the number of affected nodes after PST. The monarchE trial evaluated the CDK4/6-inhibitor abemaciclib in the (post-neo)adjuvant setting for patients with high-risk early-stage HR+/HER2-negative disease [77]. High-risk was defined as ≥4 positive nodes or 1–3 nodes and another risk factor (T ≥ 5 cm, G3, or Ki-67 ≥ 20%).

Since the number of involved nodes was an important criterium for risk assessment in both trials, surgical escalation in the form of ALND may occur to allow eligibility of patients for additional (post-neo)adjuvant treatment. Although a minority of patients may risk under-staging by not having an ALND performed, the available evidence suggests that this does not mean they are undertreated [78].

5. Conclusions

In recent decades the extent of surgical procedures for the treatment of early BC decreased continuously from radical mastectomy to breast-conserving therapy and from routine ALND to lymph node (and axilla) sparing procedures. This process was on one hand achieved by the understanding of BC as a predominantly systemic disease whose cure is mainly based on the use of individualized, effective drugs, personalized optimal locoregional treatment and on the other hand by the increasing interdisciplinary cooperation between surgeons, radiation oncologists and medical oncologists that allowed de-escalation of one treatment modality by improving the therapeutic effect of another. The introduction of new targeted drugs and the increasing role of PST accelerated de-escalation strategies in BC surgery in recent years. There is some concern, however, that surgical de-escalation might induce an escalation of other treatment modalities (e.g., radiotherapy).

Numerous studies confirmed that reducing the extent of surgery in the upfront surgery setting does not impact locoregional recurrences and overall outcome. This relates to margin status and the widely accepted new standard of “no ink on tumor” but also to the omission of ALND in patients with limited, clinically occult nodal involvement. Since most of the trials that addressed the option of surgical de-escalation did not include standardized protocols for adjuvant radiotherapy, it remains unclear, whether the effect of surgical de-escalation was valid in itself or if radiotherapy compensated for the decreased surgical extent. The same holds true for surgical de-escalation strategies after PST especially with regard to the replacement of ALND by less invasive procedures (SLNB, TLNB, TAD). The impression that surgical de-escalation is often accompanied by an escalation of radiotherapy is therefore (at least in part) due to insufficiently defined study protocols with regard to the interdisciplinary approach for locoregional treatment. The increasing use of radiotherapy was further driven by the reduction of morbidity with axillary radiotherapy compared to ALND. In addition, deescalating both surgery and radiotherapy at the same time without a thorough assessment of their independent therapeutic effect may expose patients to an increased risk of recurrence. Uncertainties in scientific evidence may therefore lead to escalation of radiotherapy in some settings of surgical de-escalation. This process is boosted by reimbursement systems that in general promote more intensive treatment.

Even more alarming is the increasing rate of mastectomies including “risk reducing” contralateral procedures in patients without a clearly defined genetic risk. Although patients’ participation in decision making is crucial and (as first impulse) radical surgery appears an attractive option for many patients, it remains an important obligation of the treating physician to inform patients about the existing evidence and support them to overcome initial fears towards a long-term maintenance of quality of life. Again, however, the impact of reimbursement systems appears obvious.

Further, concerns have been raised that systemic escalation strategies in high-risk patients might lead to increased surgery in order to “qualify” patients for the respective treatment by increasing the harvest of positive nodes. Risk assessment by nodal status appears, however, phenomenon of the past and is increasingly being replaced by biological features.

Recent evolutions in the treatment of BC clearly confirm the importance of systemic treatment modalities on the outcome of the disease. This development induced the potential to de-escalate the extent of locoregional treatment and thus improve quality of life in many patients. Decisions in daily routine may increasingly be driven by reimbursement regulations leading to an escalation in disguise in some patients.

Future studies of locoregional treatment strategies need to include an interdisciplinary approach to integrate de-escalation combining surgery and radiotherapy in a way that promotes optimal quality of life and shared decision-making. The use of quality indicators and the certification of BC units as successfully carried out by EUSOMA and the German Cancer Society may contribute to detect and avoid over-as well as undertreatment in clinical routine. Informed consent and patient involvement become increasingly important in view of uncertainties with regard to some surgical de-escalation strategies.

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