Cancer Treatment Reviews 101 (2021) 102297

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

De-escalation of axillary irradiation for early breast cancer – Has the time come?

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ARTICLE INFO

Keywords:
Breast cancer
Primary systemic therapy
Axillary de-escalation
Sentinel lymph node biopsy
Radiation therapy

ABSTRACT

Introduction of sentinel lymph node biopsy, initially in clinically node-negative and subsequently in patients presenting with involved axilla and downstaged by primary systemic therapy, allowed for significant decrease in morbidity compared to axillary lymph node dissection. Concurrently, regional nodal irradiation was demonstrated to improve outcomes in most node-positive patients. Additionally, over the last decades, introduction of more effective systemic therapies has resulted in improvements not only at distant sites, but also in locoregional control, creating space for de-escalation of locoregional treatments. We discuss the data on de-escalation in axillary surgery and irradiation, both in patients undergoing upfront surgery and primary systemic therapy, with special emphasis on the feasibility of omission of nodal irradiation in patients undergoing primary systemic therapy. In view of the accumulating evidence, omission of axillary irradiation may be considered in clinically node-positive patients converting after primary systemic therapy to pathologically negative nodes on sentinel lymph node biopsy (preferably also with in-breast pCR), presenting with lower initial nodal stage, older age and were treated with breast-conserving surgery followed by whole breast irradiation. Omission of regional nodal irradiation in patients with aggressive tumor phenotypes achieving a pCR is under investigation. In patients undergoing preoperative endocrine therapy the adoption of axillary management strategies utilized in case of upfront surgery seems more suitable than those used in post chemotherapy-based primary systemic therapy setting.

Abbreviations: ACOSOG, American College of Surgeons Oncology Group; ALND, axillary lymph node dissection; BC, breast cancer; BCS, breast conserving surgery; BCT, breast conserving therapy; cN0, clinically node-negative; cN+, clinically node-positive; DBCG, Danish Breast Cancer Cooperative Group; DFS, disease-free survival; DMFS, distant metastasis-free survival; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; EORTC, European Organisation for Research and Treatment of Cancer; ER, estrogen receptor; IBCSG, International Breast Cancer Study Group; IMN, internal mammary nodes; ITC, isolated tumor cells; LN, lymph node; LRR, locoregional recurrence; MSKCC, Memorial Sloan Kettering Cancer Center; NCDB, National Cancer Database; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; pCR, pathological complete response; PMRT, postmastectomy radiation therapy; PS(E)T, primary systemic endocrine therapy; PST, primary systemic therapy; RNI, regional nodal irradiation; RS, Oncotype DX Breast Recurrence Score; RT, radiation therapy; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; WBI, whole breast irradiation.

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https://doi.org/10.1016/j.ctrv.2021.102297
Received 8 August 2021; Received in revised form 24 September 2021; Accepted 26 September 2021
Available online 8 October 2021

Introduction

Decades of progress in early breast cancer (BC) treatment, in particular advances in early detection and tumor-biology-driven systemic therapy have resulted in improvements in both local/distant control and overall survival (OS) [1]. Resultant improved disease control together with the morbidity associated with locoregional treatments have led to locoregional treatment (surgery and radiation) de-escalation attempts, aiming to decrease treatment-related sequelae and – as a result – improve patients' quality-of-life.

In regional lymph node (LN) management the first steps were made in axillary surgery. Already at the turn of the centuries sentinel lymph node biopsy (SLNB) in clinically node-negative (cN0) patients with omission of axillary lymph node dissection (ALND) in sentinel lymph node (SLN)-negative patients became a standard of care [2]. Almost twenty years later, the American College of Surgeons Oncology Group (ACOSOG) Z0011 randomized trial demonstrated the feasibility of ALND omission in patients with limited axillary nodal involvement (<3 positive nodes), treated with tangential breast irradiation and adjuvant systemic therapy (Table 1) [3].

Additionally, the randomized International Breast Cancer Study Group (IBCSG) 23–01 and AATRM 048/13/2000 trials and the single arm SENOMIC study confirmed the safety of ALND omission in patients with one or more micrometastatic (≤2 mm) SLN [4,5,9]. More recently the SINODAR One trial assessed the feasibility of ALND omission following SLNB in a relatively higher risk population with clinically T1-T2N0 tumors and 1–2 SLN macrometastases, irrespective of surgery to the primary tumor (breast-conserving surgery (BCS) vs mastectomy) [6]. At a median follow-up of 30 months, no axillary recurrences were observed. Of note, around 20% of patients in the SLNB arm underwent mastectomy, and the use of radiation therapy (RT) was left to treating physician's discretion (no details were reported). Several ongoing trials addressing similar unmet needs are still ongoing (SENOMAC - NCT02240472, POSNOC - NCT02401685, INSEMA - NCT02466737) [10–12]. Finally, the AMAROS (European Organisation for Research and Treatment of Cancer (EORTC) 0981–22023) and OTOASOR trials confirmed comparable axillary control and a decrease in lymphoedema (AMAROS) in cT1–2 N0 SLN-positive patients treated with axillary RT, as compared with ALND [8,13].

Interestingly, the largely forgotten National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial conducted in the early 1970s, in patients having only clinical evaluation of preoperative nodal status and no adjuvant systemic treatments, demonstrated no significant difference at 25-year follow-up in terms of disease-free survival (DFS), relapse-free survival, distant-disease-free survival, or OS in cN0 patients who have been randomly assigned to conventional radical mastectomy, total mastectomy with postoperative regional nodal irradiation (RNI) or total mastectomy followed by ALND at axillary recurrence [14]. Similarly, there was no difference in outcomes between patients with clinically positive nodes (cN+) treated by radical mastectomy or by total mastectomy and RT. However, all outcomes were dramatically worse compared to more recent findings, which makes the translation to current practice impossible.

Genomic profiling for locoregional treatment decisions

Another approach to de-escalate axillary treatment is to select patients according to genomic profile. In the NSABP B-28 trial, which randomized node-positive patients to more versus less aggressive postoperative chemotherapy (AC-T vs AC) and in which no RNI was allowed, a strong relationship between the Oncotype DX Breast Recurrence Score® (RS) and locoregional recurrence (LRR) risk was demonstrated, with 11.2 years risk of LRR of 3.3%. 7.2% and 12.2% for patients with low, intermediate and high scores, respectively [15]. Similarly, among the 316 estrogen receptor (ER)-positive, node-positive patients from the Southwest Oncology Group trial S8814, who underwent mastectomy without postmastectomy radiation therapy (PMRT) (252 patients) or breast-conserving therapy (BCT) including whole breast irradiation (WBI) (64 patients) followed by tamoxifen alone, chemotherapy followed by tamoxifen, or concurrent tamoxifen and chemotherapy, estimated 10-year cumulative LRR rates were 9.7% for low and 16.5% for intermediate or high RS (p = .02) [16]. This difference remained significant among postmastectomy patients, with 10-year actuarial LRR rates of 7.7% for low vs 16.8% for intermediate or high RS (p = .03). Importantly, in a subset of postmastectomy patients with 1–3 involved nodes, the low RS group had only 1.5% LRR rate, suggesting a possibility of omitting RT. It is important to remember, though, that these patients routinely underwent ALND.

The ongoing NCIC MA.39 trial is assessing the role of RNI in ER-positive, low genomic risk (RS <18) patients with 1–3 involved LN, treated with modern systemic therapies (NCT03488693) [17]. However, as the trial includes patients both after SLNB and ALND, the feasibility of

Table 1
Published/presented trials on de-escalation of axillary surgery in patients undergoing *de novo* surgery.

Trial	Patient number	SLN involvement	Breast surgery	RT details	Median follow-up (years)	DFS
ACOSOG Z0011 [3]	891 (target accrual 1900)	≤2 SLN, without gross extranodal disease, 45% micrometastases	100% BCT	tangential fields obligatory, 51%* "high tangents", 19%* "on purpose" third regional nodal irradiation field; irrespective of SLNB or ALND arm	10	SLNB 80,2% ALND 78,2%
IBCSG 23-01 [4]	934 (target accrual 1960)	micrometastases only	90% BCT	97% of BCT patients had RT (19% intraoperative only)	10	SLNB 76,8% ALND 74,9%
AATRM 048/13/2000 [5]	247 (target accrual 352)	micrometastases only	92% BCT	RT (breast only) in all BCT patients; high tangents or axillary field not allowed	5	SLNB/ALND 98,2%
Sinodar One [6]	889 (target accrual 2000)	1–2 macrometastases	78% BCT	RT indication independent of the omission of ALDN, no details reported	2.5	SLNB 95.15% (projected 5-y) ALND 93.5% (projected 5-y)
AMAROS [7]	4823 (1425 randomized)	60% macrometastases, 29% micrometastases, 11% ITC	82% BCT	no ALND arm: 4 levels of the axilla	10	SLNB + RT 78,2% (DMFS) SLNB + ALND 81,7% (DMFS)
OTOASOR [8]	2106 (526 randomized, 474 analyzed)	60% macrometastases, 36% micrometastases, 6% ITC	84% BCT	no ALND arm: 4 levels of the axilla	8	SLNB + RT 77,4% SLNB + ALND 72,1%

ALND – axillary lymph node dissection, BCT – breast conserving therapy, ITC – isolated tumor cells, RT – radiation therapy, SLN – sentinel lymph node
* applies to patients with known RT field details (calculations extrapolated among patients with known and unknown tangent height).

axillary de-escalation in the SLNB subgroup may be difficult to demonstrate.

Role of axillary radiation therapy in patients undergoing upfront surgery

A number of RT trials and population registry series have demonstrated the benefit of RNI (Table 2).

In the Canadian MA.20 trial the addition of RNI (including internal mammary, supraclavicular, and axillary LN) in 1832 women with node-positive or high-risk node-negative BC treated with BCS and adjuvant systemic therapy resulted in 10-year DFS improvement (82.0% for RNI vs 77.0% for the control; HR 0.76; 95 %CI 0.61–0.94; p = .01), albeit without OS difference [18]. The EORTC 22922/10925 "Internal mammary" trial, which randomized 4004 patients with involved axillary nodes and/or a medially located primary to irradiate or not the internal mammary and medial supraclavicular LN, at a median FU of 15.7 years showed significant reduction of BC mortality (HR 0.81; 95 %CI 0.69–0.94; p = .005) and BC recurrence (HR 0.87; 95 %CI 0.77–0.98; p = .024), also without OS improvement (HR 0.95; 95 %CI 0.84–1.06; p = .358) [19]. A smaller French trial randomized 1407 patients with positive axillary nodes or central/medial tumors to receive postoperative chest wall and supraclavicular nodes irradiation with or without internal mammary nodes (IMN). The study failed to demonstrate a statistically significant survival benefit, although a numerical, potentially clinically meaningful >3% difference in 10-year OS in favor of IMN irradiation was observed and the negative interpretation of this trial may have resulted from insufficient sample size [20]. Additionally, in a series of 3089 patients from the Danish Breast Cancer Cooperative Group (DBCG) registry managed by a uniform policy of IMN irradiation only in patients with right-sided tumors, a reduction in BC mortality (adjusted HR 0.85; 95 %CI 0.73–0.98; p = .03) and OS improvement in favor of IMN irradiation (adjusted HR 0.82; 95 %CI, 0.72–0.94; p = .005) without increased risk of death from ischemic heart disease was observed [21]. However, the role of irradiation of particular nodal sub-volumes cannot be evaluated based on the outcomes of these studies because of the differences in target volumes. It is also important to remember that all the "old" trials demonstrating BC mortality benefit from PMRT involved RNI [22]. However, taking into account the consistent improvements in locoregional control, resulting from modern systemic therapies, these results might not be fully applicable to currently treated patients [23–25].

Importantly, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis evaluating 13,404 patients in 14 RNI trials found no effect on BC recurrence or BC mortality and increased non–BC related mortality leading to increased overall mortality in 8 studies starting between 1961 and 1978. In sharp contrast, RNI significantly reduced BC recurrence, BC mortality and any death, without increased non-BC related mortality in six studies initiated after 1989 [24].

The ACOSOG Z0011 trial demonstrated that ALND may be safely omitted in in patients with limited axillary nodal involvement treated with tangential field irradiation and adjuvant systemic therapy [3]. However, the trial protocol did not specify the details of postoperative RT. In an analysis of the ACOSOG Z0011 radiation field design, 18.9% of patients received directed RNI using ≥3 fields and among >80% patients irradiated with tangential beams only, approximately 50% were treated with so-called "high tangents" (cranial border ≤2 cm from humeral head), leaving only approximately 40% treated with "classical" tangential beams technique [26].

According to a study comparing dose coverage of regional LN areas following the Z0011, AMAROS, EORTC 10981–22023 and MA-20 field design, high tangent irradiation resulted in a similar dose distribution in levels I and II of the axilla, as compared to the field design in the AMAROS trial, which included intentional axillary irradiation [27]. It also needs to be remembered that both ACOSOG Z0011 and IBCSG 23–01 enrolled relatively low-risk node-positive patients. ACOSOG Z0011 allowed for inclusion of patients with ≤2 positive SLN, without gross extranodal disease and no primary systemic therapy (PST). >70% of patients in the SLNB arm had only one involved SLN and in 45% only micrometastatic disease was present [3]. An even lower risk population was enrolled in the IBCSG 23–01 study, which allowed for only micrometastatic disease and no PST. In this study 95% had involvement of only one SLN and approximately 90% of patients underwent BCT, including breast irradiation [4]. Importantly, although tangential-field WBI does not assure reliable dose coverage of levels I and II of the axilla, therapeutic irradiation dose is delivered to at least part of this volume in a significant percentage of patients [28–30].

More supportive data on omission of axillary LN irradiation comes from a prospective series from the Memorial Sloan Kettering Cancer Center (MSKCC – New York, United States), validating the ACOSOG Z0011 results in real-world setting [31]. Among the 484 patients treated with SLNB alone with a minimum follow-up of 12 months, 103 cases received WBI using a prone technique (which practically excludes axillary irradiation) and only one nodal relapse (1%) was observed [31].

De-escalation of axillary treatment in patients undergoing primary systemic therapy

Surgical trials have demonstrated that in patients without clinical nodal involvement at baseline sensitivity and long-term outcomes of SLNB performed after PST are identical to those undergoing upfront surgery [32,33]. However, nodal involvement was a classical indication for ALND before the era of PST. Yet, PST allows for conversion from limited nodal involvement (cN1) to negative nodal status (ypN0) in approximately 40% of patients [34]. Trials attempting to define the role of SLNB in patients presenting with nodal involvement and treated with modern PST have demonstrated satisfactory sensitivity in the post-PST setting, provided dual tracer is used or at least 3 SLN are identified (Table 3) [34–39].

However, because all patients in these studies underwent ALND, long term outcomes including the axillary recurrences after SLNB alone are unknown. Such information was provided by a prospective MSKCC cohort of cN1 patients receiving PST followed by a negative SLNB and no further axillary surgery [40]. Among the 610 patients included, 234

Table 2
Published data on regional nodal irradiation (randomized trials + Danish cohort).

Trial	Patient number	median follow-up	Irradiated LN groups (difference between arms)	DFS	OS	Comment
MA.20 [18]	1832	9.5 years	IM, SC, AX	↑ (82.0% vs 77.0%, HR 0.76; p = .01)	NS	RT to operated axilla in case of <10 LN examined or >3 LN involved
EORTC 22922/ 10925 [19]	4004	15.7 years	IM, medial SC	NS	NS	RT to operated axilla only if inadequate surgery DMFS NS, ↓ BC recurrence and BC mortality
French [20]	1334	11.3 years	IM	NS	NS	
DBCG [21]	3089	8.9 years	IM	–	↑ (75.9% vs 72.2%, HR 0.82, p = .005)	DMFS NS, ↓ BC mortality

AX – axilla, BC – breast cancer, DMFS – distant metastasis-free survival, HR – hazard ratio, IM – internal mammary, LN – lymph nodes, NS – not significant, RT – radiation therapy, SC – supraclavicular.

Table 3
Published trials on de-escalation of axillary surgery in cN+ patients converting to ycN0 after primary systemic therapy (studies >100 patients).

Trial	Patient number	SLN identification rate	False negative rate
ACOSOG Z1071 [35]	689	92.7%	12.6% (9.1% in patients with >2 SLN identified, 10.8% with dual tracer)
SENTINA [36]	592 (Arm C)	80.1%	14.2% (4.9% in patients with >2 SLN identified, 8.6% with dual tracer)
SN FNAC [37]	153	87.6%	8.4% (4.9% in patients with >2 SLN identified, 5.2% with dual tracer)
GANEA 2 [38]	307	79.5%	11.9%
Swedish [39]	195	77.9% (80.7% with dual tracer)	14.1% (4% in patients with ≥2 SLN identified)
MD Anderson Cancer Center [34]	150	93%	16.1%

SLN – sentinel lymph node.

(42%) had ≥3 negative SLNs and underwent SLNB alone. Of those, 205 (88%) received postoperative RT, with 164 (80%) receiving RNI. At a median follow-up of 35 months, there was only 1 (0.4%) axillary recurrence, synchronous with a breast recurrence, in a patient who refused RT. In another series of 688 consecutive cT1-3 cN0-2 patients operated at the European Institute of Oncology (Milan, Italy) (2000–2015), who became or remained cN0 after PST and underwent SLNB with at least one SLN found, ALND was not performed even if a single SLN was negative and nodal RT was not mandatory [41]. Despite less strict axillary management, including RNI only in 10.9% of cN+ BCT patients and 37.9% of cN+ postmastectomy patients, after 9.2-year median follow-up axillary failures occurred in only 1.8% of initially cN1-2 and in 1.5% of initially cN0 patients.

The LRR risk in PST treated patients is related to intrinsic tumor phenotype. In the ACOSOG Z1071 the highest LRR risk was observed among triple-negative tumors (HR 5.91 comparing to hormone-receptor-positive BC) [42]. In the EORTC 10,994 (p53) trial the highest rate of LRR as first event was seen among HER2-positive tumors treated without trastuzumab (10.4%) and triple-negative tumors (8.9%) [43]. However, this phenomenon seems to be balanced by a good response to PST. In the series of 751 patients treated with PST and BCT at MD Anderson Cancer Center (Houston, United States), 5-year LRR-free survival rate in patients with 4 main phenotypes (ER+/HER2-, ER+/HER2+, ER-/HER2-, ER-/HER2+), who achieved pathological complete response (pCR) ranged from 97.4% to 100% [44]. Among similarly treated group of 335 patients from a single Korean institution, after median 7.2 years follow-up, there were no LRRs among triple-negative patients, who achieved a pCR [45]. Similar, 100% 5-year locoregional control in the pCR subgroup was observed among 233 patients treated with PST, mastectomy and postoperative RT at MSKCC [46]. Additionally, in the National Cancer Database (NCDB) series of triple-negative and HER2-positive cN+ patients, who achieved a breast pCR, the rate of node positivity at surgery was as low as 1.6% [47]. Based on these data, EUBREAST initiated a trial evaluating omission of SLNB in triple-negative and HER2-positive BC patients with in-breast pCR after PST (NCT04101851).

In patients with residual axillary nodal involvement ALND remains standard, as even in micrometastatic disease LRR seems high even in patients achieving breast pCR [48]. Indeed, among the 1617 patients from the NCDB (2006–2014) and matched for patient, tumor, and treatment characteristics, SLNB (+ RNI) was associated with significantly lower survival, compared to ALND (+ RNI) (HR 1.7, 95 %CI 1.3–2.2, p < .001), with estimated 5-year OS of 71% and 77%, respectively [49]. Exploratory subgroup analyses showed that SLNB was comparable with ALND in patients with luminal A or B tumors with single metastatic LN (HR 1.03, 95 %CI 0.59–1.8, p = .91). However, in another, more recent NCDB series (2012–2015) of 1411 cT1-3 N1 ypN1 patients, OS of these treated with SLNB with RNI (206 patients) and ALND + RNI (1205 patients) did not differ (5-year OS: 76% vs. 73%, p = .39; after propensity score matching: 79% vs. 69%, p = .33, respectively) [50].

Another approach towards de-escalation of axillary treatment, although with limited application outside The Netherlands due to regulatory issues, includes the combined use of PET/CT before PST and the MARI (removal of axillary LN marked with radioactive iodine seeds) procedure after PST [51]. According to this protocol, patients showing 1–3 FDG-avid axillary LN (cN <4) and a tumor-negative MARI node (MARI-) receive no further axillary treatment. All cN <4 patients with a tumor-positive MARI node (MARI+), as well as patients with ≥4 FDG-avid LNs [cN(4+)] and MARI- receive locoregional RT. An ALND is performed only for cN(4+) patients with MARI+. After 16 months of follow-up no LRR were seen in 39 patients (24.5%) in whom no RNI was used and only 1 - among 71 patients (44.7%) in whom ALND was replaced by RNI, in spite of residual axillary disease at surgery.

The 2021 the St. Gallen Consensus Guidelines support the recommendation for ALND in case of residual nodal macrometastases after PST. RNI may be a potentially acceptable alternative to ALND in patients with micrometastatic disease or isolated tumor cells. Importantly, systemic treatment options such as capecitabine or trastuzumab emtansine for residual invasive cancer are not considered equivalent alternatives to ALND [52].

Radiation management of axilla after PST is less straightforward. As far, as there is general agreement on no need of RNI in cN0 patients remaining pathologically node-negative (ypN0) after PST and on avoidance of axillary irradiation in the post-ALND setting. However, the role of axillary irradiation in patients who convert from cN+ to ypN0 after PST and are spared ALND is much less clear, and many guidelines urge caution concerning RT tailored by response to PST [53,54]. Also, the recently published policy review on local management following PST for early BC does not provide much guidance on the details of RNI [55].

High-level evidence data from prospective, optimally randomized studies on the role of axillary irradiation in this patient subgroup are lacking. In this framework, recommendations have to be made from less direct evidence. The pooled analysis of NSABP B-18 and NSABP B-27 trials provided prospective data on locoregional control in a homogenous population of PST-treated patients [56]. Both trials strictly defined the locoregional management: lumpectomy patients received breast RT alone; mastectomy patients were not allowed RT. Axillary surgery routinely employed ALND. Independent predictors of LRR in lumpectomy patients were age, baseline clinical nodal status, and pathologic breast tumor and nodal status; in mastectomy patients, these were baseline clinical tumor size and nodal status, and pathologic nodal status/breast tumor response (Fig. 1). 10-year LRR probability in mastectomy patients remained <10%, irrespective of primary tumor size in pCR patients and in clinically (pre-PST) and pathologically node-negative patients, who failed to achieve in-breast pCR. In the lumpectomy + WBI group the LRR risk was strongly age-related and the only subgroup which LRR risk remained <10% for all age groups were cN0 patients, who achieved a pCR; slightly worse outcomes were seen in clinically and pathologically node-negative patients, who failed to achieve pCR in the breast and in cN+ patients who achieved a pCR. The highest LRR risk in both subgroups was observed among pathologically node-positive patients (HR 2.71). Interestingly, relatively lower nodal recurrence risk was observed among BCT, as compared to mastectomy patients, despite numerically higher recurrence rate in the ipsilateral breast. One of the possible explanations could be that in the BCT subgroup at least part of the nodal areas received therapeutic irradiation doses from the tangential fields.

Finally, in the unpublished CTNeoBC metanalysis, LRR rates in postmastectomy patients were lower in the subgroup with (3.8%) vs.

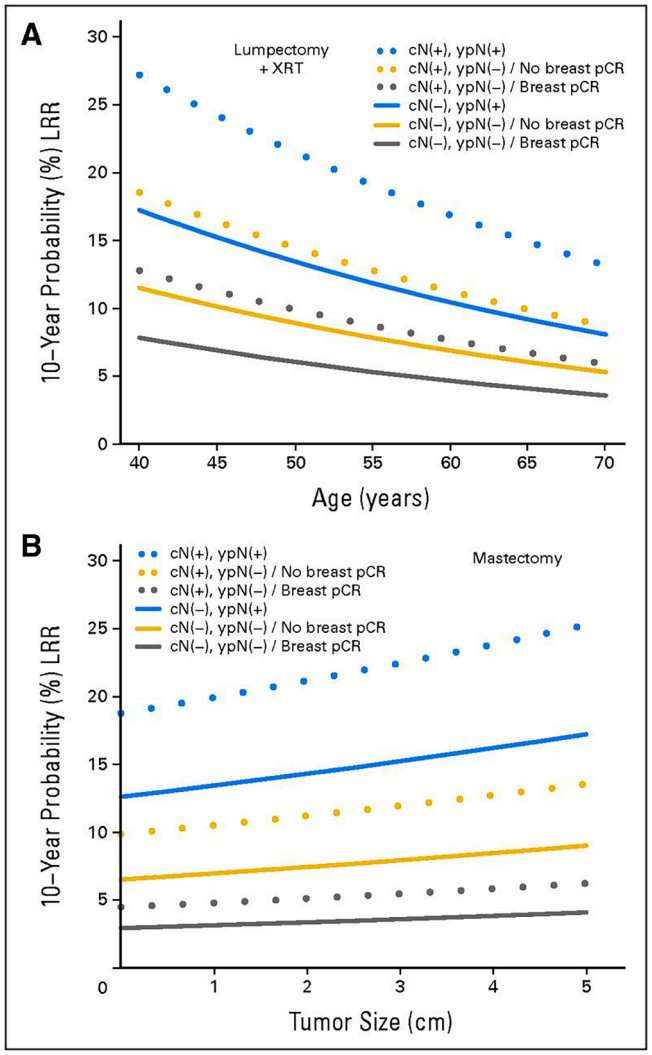

Fig. 1. 10-year risk of locoregional recurrence for breast conserving therapy (A) and mastectomy (B) following preoperative chemotherapy in pooled analysis of NSABP B-18 and NSABP B-27 trials [56]. cN – clinical nodal status (before preoperative chemotherapy), pCR – pathological complete response, XRT – radiation therapy; ypN – pathologic nodal status (after preoperative chemotherapy).

without (8.1%) pCR, irrespective of RT use, whereas in lumpectomy patients, LRR rates were similar in patients with (6.0%) and without (6.3%) pCR [57]. Interestingly, in hormone receptor–positive, HER2-negative patients with a pCR low recurrence rates, regardless of grade and type of breast surgery, were observed. Among ypN+ patients, grade 3 tumors were associated with significantly higher LRR rate than grade 1 or 2 cancers, suggesting a place for omission of RT in the latter group. [57]. Unfortunately, information on the use and details of postoperative RT was lacking.

Indirect information on postoperative RT efficacy in post-PST patients may be derived from population-based registries such as NCDB, *post hoc* analyses of clinical trials or retrospective patient series (Table 4) [58].

Among 10,283 cT1-3 N1 postmastectomy patients from NCDB (2003–2011), 3040 (29.6%) converted to ypN0. The use of postoperative RT was associated with improved OS independently of nodal response (ypN+, HR 0.795; $p < .001$ and ypN0, HR 0.743; $p = 0.19$) [59]. However, in another NCDB (1998–2009) series of 1560 postmastectomy, stage II (node-positive) or III patients who converted to ypN0, no OS benefit was observed from postoperative RT. Although the

Table 4
Effect of radiation therapy in cN+ patients converting to ypN0 after primary systemic therapy.

	Type of breast surgery	Patient number	Effect of postoperative RT (RNI for BCS patients)
NCDB (2003–2011) [59]	mastectomy	3040	↑ OS
NCDB (1998–2009) [60]		1560	OS NS ↑ OS in clinical stage IIIB/ IIIC, T3/T4, no pCR (breast)
NCDB (2010–2015) [61]		7499	OS NS
NCDB (2004–2008) [62]		1937	OS NS ↑ OS in HR- patients
Gepar Trials [63]		158	borderline ↓ LRR
ACOSOG Z1071 [35]		157	LRR, DFS, BCSS, OS NS
Chinese [64]		185	↓ LRR, ↓ DM, ↑ DFS, OS NS
KROG 12–05 [65]		151	LRR, DFS, OS NS
Institut Curie [66]		92	LRR, DFS, OS NS
MD Anderson [67]		106	Stage I and II LRR – NS, Stage III ↓ LRR
NCDB (2003–2011) [59]	breast conserving surgery	2070	OS NS
ACOSOG Z1071 [35]		125	LRR, DFS, BCSS, OS NS
NCDB (2010–2015) [61]		4842	OS NS
Centre René Huguenin [68]		84	DFS, OS NS
KROG 12–05 [65]		251	LRR, DFS, OS NS

BSC – breast conserving surgery, BCSS – breast cancer-specific survival, DFS – disease-free survival, DM – distant metastases, HR – hormone-receptor, LRR – locoregional recurrence, NS – non-significant, OS – overall survival, pCR – pathological complete response, RNI – regional nodal irradiation.

RT group patients had more advanced disease, PMRT showed no association with OS on multivariate analysis [60]. Significant improvement was seen, however, in higher-risk subgroups, such as clinical stage IIIB/ IIIC disease ($p = .027$), T3/T4 tumors ($p = 0.25$) or residual invasive disease after PST ($p = .041$). In a series of 16,535 postmastectomy patients (2010–2015) improvement in adjusted OS with the use of PMRT was seen among ypN1, but not ypN0 patients [61]. In another NCDB series (2004–2008) of 8321 cN1-2 patients who underwent PST followed by mastectomy and were unselected for pathological nodal status, PMRT was associated with an OS benefit in both cN1 (5-year OS 75.8% vs. 71.9%, $p < .01$) and cN2 (5-year OS 69.2% vs. 58.6%, $p < .01$) subgroups [62]. In the subgroup of ypN0 patients, PMRT improved OS for hormone-receptor negative patients but not hormone-receptor positive patients.

In a combined analysis of three German Breast Group trials (GeparTrio, GeparQuattro, GeparQuinto), in 817 postmastectomy, non-inflammatory BC patients, among whom RT was administered to 676 (82.7%), in the multivariate analysis RT was associated with borderline lower risk of LRR (HR 0.51, 95 %CI 0.27–1.0; $p = .05$). This effect was mostly expressed in cT3/4 and cN+ patients, including those who converted to ypN0 [63]. Additional risk factors for LRR included lack of ER and progesterone receptor, and baseline nodal status. In the ACOSOG Z1071 trial, where patients treated with mastectomy and ALND underwent RT at physician's discretion, omission of PMRT was associated with higher LRR risk (HR 4.84; 95 %CI 1.50–15.61; $p = .008$) [42]. Further subset analysis demonstrated that the RT omission detriment was limited to patients with residual node-positive disease (HR 4.14; 95 %CI 1.15–14.92; $p = .030$). This detrimental effect on LRR did not, however, translate into other long-term outcomes, such as DFS, BCSS or OS. In another series of 185 cT1-3 N1 BC patients, who converted to

ypN0, treated in a single Chinese institution (Beijing, China) between 1999 and 2013, for patients with and without PMRT, the 5-year LRR, distant metastasis, DFS and OS rates were 1.1% and 7.5% (p = .071), 5.1% and 15.0% (p = 0.023), 95.0% and 79.0% (p = 0.008), and 100.0% and 94.5% (p = 0.089), respectively [64]. In patients with stage III disease, the 5-year LRR and DFS rates were 1.9% and 14.4% (p = 0.041) and 91.9% and 67.4% (p = 0.022), respectively, whereas in stage II patients the 5-year distant metastasis and DFS rates were 0 and 11.5% (p = 0.044), and 100.0% and 84.9% (p = 0.023), respectively. In contrast, in a similar multicenter retrospective study from Korea (KROG 12–05) the 5-year DFS, LRRFS, and OS rates, although numerically in favor of PMRT (91.2, 98.1, 93.3% with PMRT vs 83.0%, 92.3%, and 89.9% without PMRT), weren't statistically different [65]. No effect from PMRT on LRR, DFS and OS was also seen in a series from Institut Curie (Paris, France) [66]. In a series of 226 patients from MD Anderson, who achieved a pCR, no benefit from PMRT was seen for stage I and II patients, however, the 10-year LRR rate was significantly improved with PMRT for Stage III patients (7.3% for PMRT vs. 33.3% without PMRT; p = .040) [67].

In a systematic review on the use of PMRT in post-PST patients clinical stage II (T1-2 N0-1), age >40 years, estrogen receptor-positivity, pCR or 0–3 positive nodes without lymphovascular invasion or extracapsular extension, were identified as associated with ≤10% risk of LRR without radiation [69]. No detailed information on the PMRT benefit was provided, however, in relation to the pathological nodal status.

In BCT patients, among 5032 cT1-3 N1 undergoing PST (NCDB 2003–2011), no benefit from the addition of RNI to WBI was seen, both in ypN0 and ypN+ patients [59]. Also, in the ACOSOG Z1071, the BCT subgroup of the KROG 12–05 and among 9474 patients from another NCDB series (2010–2015), no benefit from RNI was observed, irrespective of pathological nodal status [42,61,70]. In a series of 248 ypN0 patients from Centre René Huguenin (Saint-Cloud, France) no difference in DFS and OS in relation to the RNI use was seen both among cN0 (164 patients) and cN+ (84 patients) subgroups [68]. In another Korean study (KROG 16–06) of 261 ypN0 patients (41% cN+), ALND was found to be the only favorable factor for locoregional control and RNI had no effect on LRR, DFS, or OS, irrespective of the response to PST [71]. The lack of RNI benefit in BCT patients may be explained that in many of these trials and series the routinely used tangential breast irradiation often involved also a large part of the axilla.

Finally, a recent systematic review attempting to assess the role of RNI in cN2 patients converting to ypN0, based on 4 retrospective studies of 1107 patients (3 studies – postmastectomy, 1 study – BCT) demonstrated numerical, although not statistically different improvements in DFS (91.2% vs 83%) and LRR-free survival (98.1% vs 92.3%) from locoregional RT [72]. Additionally, loco-regional RT was associated with an OS benefit among patients with stage IIIB-C (79.3% vs 71.2%, p = .027) and T3-T4 tumors (82.6% vs 76.6%, p = .025).

The current major guidelines in most cases strongly recommend RNI (with avoidance of operated axilla) for both clinical and pathological (yp) nodal involvement [53,54]. The only exception was the 2019 St. Gallen Consensus, in which RNI in case of cN1 patients converting to ypN0 was recommended only in the presence of additional adverse factors [73]. This, however, is being changed back in the 2021 edition to a strong recommendation against omitting RNI for patients whose presented with a clinically positive axillary node(s), even when pCR is achieved [52].

More light on the feasibility of axillary de-escalation will be shed by ongoing phase III randomized trials in baseline cN+ patients undergoing PST followed by surgery including SLNB. The NSABP B-51/RTOG 1304 randomizes cT1-3pN1 patients who converted to ypN0 into RNI vs no RNI (NCT01872975) [74]. In the higher risk ypN+ population the ALLIANCE A011202 trial is evaluating omission of completion ALND in patients undergoing RNI (NCT01901094) [75]. The main objective of the SAKK 23–16/IBCSG 57–18/ABCSG-53/GBG 101 (TAXIS) trial is to test the hypothesis that in mixed population of cN+ patients undergoing PST or upfront surgery including tailored axillary surgery, axillary RT in pathologically node-positive patients is non-inferior to ALND in terms of DFS (NCT03513614) [76]. The feasibility of omission of ALND and RNI in patients with micrometastatic SLN will be assessed by the NEONOD2 trial (NCT040196780) [77]. Additionally, a Dutch Prospective Registration Study (RAPCHEM/BOOG 2010–03) (NCT01279304) evaluated the outcome of risk-adapted irradiation policy based on the ypN status: (1) ypN0 (low-risk): WBI and no PMRT; (2) ypN1 (intermediate-risk): RT to breast or chest wall, in case of no ALND: RT to level I and II of the axilla; (3) ypN2 (high-risk): RT to breast or chest wall and regional LN (excluding operated axilla) [78]. The assessment of the chosen policy in this study may, however, be hampered by many deviations from the RT protocol observed, especially in intermediate-risk patients.

In view of the accumulating evidence, omission of axillary RT in cN+, post-PST patients undergoing SLNB may be considered in patients with ypN0 (preferably also with in-breast pCR), lower initial N stage, older age and treated with BCS followed by WBI. RNI may probably also be omitted in patients with aggressive tumor phenotypes achieving a pCR (Table 5).

A practice of selecting patients for RNI based on ypN status after PST is, however, already existing, as demonstrated among 26,009 patients from the NCDB (2010–2015) [61]. Over the observed time-period, the use of RNI among ypN1 patients increased from 49% to 59%, whereas it remained stable at approximately 44% among ypN0 patients.

Finally, it should be stressed, that axillary RT, if indicated, should routinely be applied only to the unoperated part of the axilla, given that most failures occur in the unoperated part of the nodal drainage area and that adding RT to surgery increases lymphoedema rates [18,19].

Axillary de-escalation after primary (neoadjuvant) endocrine therapy (PS(E)T)

Chemotherapy-based PST in ER-positive, HER2-negative patients is related to lowest pCR rates among all BC phenotypes [79]. Also, the nodal pCR rate in this subgroup remains the lowest [80]. The pCR rates after PS(E)T are even lower, differing from 4.1 to <10% after PS(E)T vs. 15.6% after chemotherapy [81,82].

No standards exist regarding axillary management following residual disease after PS(E)T and it is often assumed that it should mirror that after chemotherapy-based PST. As the probability of conversion of cN+ to ypN0 after PS(E)T is very low, the recommendations applying to situation after chemotherapy-based PST may not be applicable here. Additionally, it needs to be remembered that patients undergoing surgery after chemotherapy-based PST have in most cases already completed all planned treatment of this particular modality (i.e., no further improvement in outcome from this treatment can be expected), whereas in case of PS(E)T the patients usually have finished only few months out of 5–10 years of endocrine treatment planned and the pathological status at surgery does not reflect the efficacy of fully completed treatment. Furthermore, patients with gross nodal involvement are likely to additionally receive adjuvant chemotherapy.

Unfortunately, none of the PS(E)T trials have evaluated the type and outcomes of axillary management. A hypothesis generated by the group from Dana Farber/Brigham and Women's Cancer Center (Boston, United States), that minimal residual nodal burden after PS(E)T would not have a detrimental impact on long-term outcomes, because patients selected for PS(E)T have not received their full systemic therapy at the time of surgery resulted in a comparative analysis of patients undergoing upfront vs post-PS(E)T surgery in relation to pathological nodal status [83]. In a series of 3406 PS(E)T-treated patients, matched in a propensity score analysis for clinical characteristics of age, race, clinical tumor and nodal stage, histology, grade, type of surgery, and presence of lymphovascular invasion with same number of patients undergoing upfront surgery, 5-year OS between patients from both cohorts was similar for all analyzed nodal stages. Another analysis from the same group demonstrated that in the NCDB cohort of PS(E)T patients there was no difference in 5-year estimated OS by type of axillary surgery (SLNB vs ALND) in any residual nodal disease burden subgroup (ypN0;

Table 5
Recommendations for axillary lymph node dissection and irradiation of axillary nodal volumes in relation to pathological nodal status in cN+ patients converting to ycN0 after primary systemic therapy and sentinel lymph node biopsy /targeted axillary dissection.

	Risk group	ypN0	ypN0(i+), ypN1mi	ypN1 ≤2	ypN1 >3
PST (ChT or ET)	Low	Axillary RT: level I and II; consider RNI omission if WBI or chest wall RT	Axillary RT: level I and II	ALND, if not: axillary RT: level I and II	ALND + axillary RT: non-resected part up to level IV
	High	Axillary RT: level I-IV	Axillary RT: level I-IV	ALND + axillary RT: non-resected part up to level IV	ALND + axillary RT: non-resected part up to level IV

ALND – axillary lymph node dissection; PST – primary systemic therapy; SLNB – sentinel lymph node biopsy; TAD – targeted axillary dissection; ChT – chemotherapy; ET – endocrine therapy; RNI – regional nodal irradiation; RT – radiation therapy; WBI – whole breast irradiation.
Note: Lymph node levels covered should be according to the lymph node levels involved, extent of surgery, and lymph node levels at risk for residual subclinical disease. The absolute number of nodes excised is not a true indicator of the axillary lymph node level reached at time of surgery (e.g., 10 lymph nodes excised does not mean that all level 1 and 2 lymph nodes were dissected). The radiation therapy volumes should be defined based on evaluation of the pre-treatment and post-treatment imaging, changes seen on radiation planning CT and if in doubt, after consulting the surgeon. If medially/centrally located tumor with indication for axillary radiation therapy up to level IV, strongly consider internal mammary nodes irradiation
Risk group definition:
- Low Risk: ≤2 cN+ before PST AND complete response in the breast AND age >40
- High Risk: >2 cN+ before PST AND/OR TNBC AND/OR incomplete response in the breast AND/OR age <40.

1–2 positive nodes; ≥3 positive nodes) [84]. It needs to be remembered, however, that due to pattern of relapse of luminal tumors characterized by late recurrences, 5-year OS may be not the optimal end point.

Thus, as survival outcomes for PS(E)T patients are more resembling patients undergoing upfront surgery rather than patients treated with chemotherapy-based PST and the prognostic significance of residual nodal disease after PS(E)T mirrors that after upfront surgery, in this patient population the adoption of axillary management strategies utilized in case of upfront surgery may be more appropriate than those used in post chemotherapy-based PST setting.

Conclusions

One of the goals in treating BC patients should be to tailor the trimodality treatment according to the risk of recurrence, this will allow to reduce morbidity associated with therapy and costs without compromising outcomes. Decreasing the intensity of regional management of the axilla started with trials of SLNB in patients undergoing upfront surgery and significantly progressed with the wide diffusion of PST. Conversion of cN+ disease into ypN0 allows for reduction in the extent of axillary dissection, and – in some cases – probably also in the use and extent of postoperative RT. It needs to be remembered, however, that, as reported by the EBCTCG metanalysis, the introduction of PST initially resulted in increased LRR rates, most probably resulting from reducing extent of locoregional treatments following disease downstaging [85]. Another pitfall of available data suggesting possible further de-escalation of axillary management is that most come from retrospective analyses, which are statistically underpowered and no final conclusions can be made before results from ongoing prospective randomized trials become available. Another possible approach towards therapeutic de-escalation while maintaining very low LRR rates in patients at low risk of distant relapses, is the reduction of systemic therapy utilization combined with optimal locoregional control by RT.

Extreme caution should be taken, however, when deciding about omission of particular therapeutic components. We encourage strongly to conduct this de-escalation process in a stepwise manner, carefully monitoring for increased LRR rates. This should be accompanied by collecting relevant patient-, tumor- and treatment-related data to allow for fully informed evaluation of treatment de-escalation outcomes. For this, enrollment of patients preferably into prospective controlled randomized studies or, if not feasible, into high-quality registries is of utmost importance.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Elżbieta Senkus: Conceptualization, Methodology, Project administration, Writing – original draft. **Maria Joao Cardoso:** Investigation, Writing – review & editing. **Orit Kaidar-Person:** Investigation, Writing – review & editing. **Aleksandra Łacko:** Investigation, Writing – original draft. **Icro Meattini:** Investigation, Writing – review & editing. **Philip Poortmans:** Investigation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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