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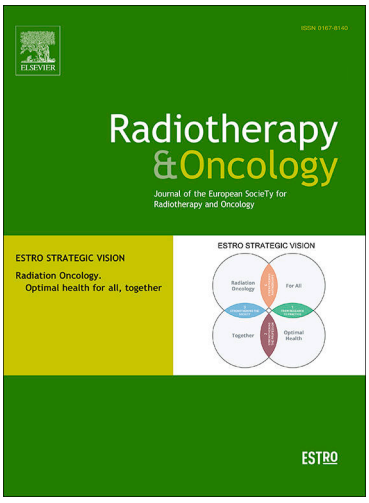

Review Article

The impact of radiotherapy on trials of axillary management in early breast cancer

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Subject: Title page

The impact of radiotherapy on trials of axillary management in early breast cancer

July 2025

Subject: Highlights

Title: The impact of radiotherapy (RT) on trials of axillary management in early breast cancer.

- ALND should no longer be routine in patients with cN0 and SLNB+ (1-2 nodes)
- Axillary RT is equivalent to ALND in SLNB+ (1-2 nodes) but less morbid
- SLNB could potentially be avoided in low-risk ER+/Her2 negative disease
- Trials of the de-escalation of local treatment must reflect the complex interdependence of surgery, radiotherapy and systemic therapy.
- De-escalation of multiple treatments without evidential support should be avoided

The impact of radiotherapy on trials of axillary management in early breast cancer

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Abstract

The presence of metastatic disease in the axillary lymph nodes is one of the most important prognostic factors in early breast cancer[1-3] but the management of the clinically and radiologically negative axilla (cN0) with positive nodes following sentinel lymph node biopsy (SLNB) is still a matter of debate. The presence of nodal macrometastases (>2mm) is often regarded as an indication for axillary lymph node dissection (ALND)[4] but randomised studies have reported no benefit for ALND in terms of locoregional recurrence (LRR) or survival with a significant risk of long term arm lymphoedema[5]. As a consequence, many centres offer axillary radiotherapy (ART) but as to whether this is required in patient with low burden axillary disease (1-2 involved nodes) is still debatable.

Surgery and radiotherapy (RT) have both demonstrated effectiveness as loco-regional therapies in breast cancer but without accurate assessment of radiation doses and targets in surgical trials of the axilla, results from randomised controlled trials (RCTs) become ambiguous. A lack of robust Radiotherapy Quality Assurance (RTQA) has contributed to variable practice and the oncology community has waited for over a decade for confirmatory trials delaying implementation of potentially clinically relevant results.

This review article discusses the main RCTs conducted to determine the oncological safety of reduced axillary surgery with an emphasis on the influence of RT on trial conduct, endpoints and conclusions.

Introduction

Surgery has been the main treatment modality for the management of axillary metastases in breast cancer. However, there is significant morbidity associated with axillary lymph node dissection (ALND). Although ALND is still recommended in patients with 3 or more nodes involved, surgical de-escalation in patients with 1-2 positive nodes has been studied with the aim to minimise long term toxicity. Irradiation to the axilla offers equivalence in terms of oncological outcomes with reduced toxicity, as demonstrated in the EORTC 10981-22023 AMAROS (*After Mapping of the Axilla: Radiotherapy or Surgery?*)[6] and OTOASOR (Optimal Treatment Of the Axilla-Surgery Or Radiotherapy)[7] trials, but whether irradiating the axilla could also be safely avoided in patients with low axillary burden remains unclear. Axillary radiotherapy (ART) can also contribute to lymphoedema, so it is important to understand if ART is necessary in patients with 1-2 axillary positive nodes. The emphasis in this narrative review article is on the Radiotherapy Quality Assurance (RTQA) of axillary treatment in randomised controlled trials (RCTs) of early breast cancer.

Methods

This review article aimed to characterise the use of radiotherapy (RT) in relevant trials of the axilla in different clinical settings. Authors focused on trials previously identified in systematic reviews/meta-analysis but carried out expanded search for RT related publications for each of those individual trials using keywords RT, radiation fields, RTQA and RT quality assessment using MEDLINE.

Trials were categorised into three main groups

1- Trials in patients with clinically and radiologically negative axilla (cN0) but with 1-2 positive sentinel lymph nodes randomised to ALND versus not. Trials were updated to include the SINODAR and SENOMAC trials (table 1). RT related publications were identified for each trial and presented in table 2.

2- Trials of patients with cN0/+SLNB with a randomisation between ALND versus ART (table 3).

3- Trials in patients with cN0 with a randomisation of SLNB versus not. Four trials were identified[8] (table 4).

Results

1. Surgical clinical trials in patients with cN0/+SLNB - randomisation between ALND versus not.

Surgical procedures have evolved from ALND to axillary sampling and subsequent implementation of SLNB to stage the cN0 axilla[9,10] However, the identification of positive nodes after SLNB was generally accepted as an indication for ALND, despite 50-65% of patients subsequently not found to have further nodal involvement[11,12].

Substantive RCTs have been conducted to assess the oncological safety of ALND avoidance in patients with a positive SLNB and are summarised in Table 1.

The first of these trials was the **American College of Surgeons Oncology Group Z0011 (ACOSOG, now Alliance)**[13]. This pivotal trial challenged the indication for ALND after a positive SLNB. It has now reported 10-year update showing no difference in its primary endpoint of overall survival (OS) among women with T1-T2 invasive breast cancer and cN0 but 1-2 positive nodes in SLNB, treated with breast conserving surgery (BCS) and adjuvant breast radiotherapy. 27% of participants in this trial were found to have additional nodal involvement in the ALND arm. Because this was a randomised trial, it is expected that the same proportion of nodal involvement would have been present in the control arm (SLNB alone) and yet the incidence of axillary recurrence was very low (0.9%), suggesting that most axillary metastases at diagnosis do not progress to clinically significant axillary recurrences. At 10 years, only one regional recurrence was seen in the SLNB alone group and none were seen in the ALND group[13].

Shortly after, two trials were conducted to investigate if refraining from ALND was safe when the SLNB was involved with micrometastatic disease (with a randomisation of ALND versus not). These trials were the AATRM 048/13/2000[14] and the IBCSG 23-01[15].

The **AATRM 048/13/2000** trial[14] started in 2000. In the ALND group, 13% of patients had further nodal involvement of only one additional node, and in 6% the node showed micrometastatic involvement. The nodal recurrence rate was 1.7%, slightly higher than in other trials, but there was no difference in disease free survival (DFS).

The **IBCSG 23-01** trial[15] had a similar design and also reported no significant difference in DFS at 5 years but there was less surgical morbidity comprising sensory neuropathy, arm lymphoedema and infective complications in the SLNB only arm. The locoregional recurrence rate (LRR) was 0.9% in both arms. Following the results of AATRM 048/12/2000 and IBCSG 23-01 trials, ALND has been generally avoided when the SLNB shows micrometastasis only[14,16].

The **SINODAR One** trial[17], was a non-inferiority multicentre RCT which also assessed ALND avoidance and included patients after BCS (75%) or mastectomy. It reported after a median follow-up of 34 months, that the 3-year OS in the no axillary treatment arm was not inferior to ALND, with only one axillary nodal recurrence in each group. Similar to the Z0011 trial, this trial did not reach the pre-specified sample size or number of events.

The recently published **SENOMAC** trial[18] was the largest and most recent trial in this category and enrolled 2766 patients with T1-T3 disease, treated with BCS or mastectomy, and 1-2 macrometastatic positive nodes[19], but it allowed additional nodes with micrometastasis. It also included patients with a confirmatory fine needle aspiration (FNA) cytology of involved nodes (but not palpable axillary disease) and extranodal extension (ENE). 87.3% had ER positive/HER-2 negative disease. With a median follow-up of 46.8 months, the estimated 5-year recurrence free survival (RFS) was 89.7% (95% confidence interval [CI], 87.5 to 91.9) in the SLNB group and 88.7% (95% CI, 86.3 to 91.1) in the ALND group demonstrating that the omission of completion of ALND was not inferior to more extensive surgery[18].

The **POSNOC** (POsitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus ALND or axillary radiotherapy) trial started in 2014 in the UK, Australia and New Zealand[20,21]. The main randomisation was between axillary treatment (accepting either ALND or ART as decided by local team) versus no further axillary treatment. It has completed recruitment and is due to report in summer 2026, 5 years after randomisation of the last patient.

1.1 RTQA of surgical trials of cN0/+SLNB - randomisation between ALND versus not.

Since the publication of the Z0011 trial, several concerns have been expressed which question the applicability of this trial to clinical practice. These included poor recruitment rates (<50% of original target), fewer than anticipated events, a high proportion of cases with micrometastasis only (approximately 44.8% in the SLNB alone arm), a high proportion of patients lost to follow-up (21% in the ALND group and 17% in the SLN group) and a lack of prospective RTQA[22,23].

Given the likely burden of subclinical axillary disease but the very low axillary recurrence rate, clinical oncologists raised the question if incidental ART delivered through the tangential breast fields, or non-protocol direct axillary irradiation, may have played a role in reducing axillary recurrences. The possibility that clinicians modified the tangential field height to cover a higher proportion of the axilla was raised.

Although this trial lacked formal RTQA, a retrospective review has been published[24]. From 228 patients with available RT records, only 142 had sufficient data to evaluate field height. Authors considered high tangential fields (HTF) as those with a cranial border of the medial tangential field within 2 cm of the humeral head and using this criterion, HTF were used in 50% of cases in the ALND arm and 52.6% in the SLNB only arm. As this study aimed to demonstrate ALND versus SLNB alone, direct nodal irradiation was against trial protocol. Retrospective review however confirmed 18.9% did receive nodal RT, although this and other protocol deviations were similar between both arms[24].

Despite the uncertainties in the Z0011 trial validity, mainly due to the lack of RTQA to answer the question about the role of incidental ART, there have never been RTQA analyses published for the IBCSG 23-01, AATRM 048/13/2000 or the SINODAR-One trials. A summary of the RTQA for surgical axillary trials is shown in Table 2.

Detailed analysis of the RTQA in the SENOMAC trial has been published[25]. Since 93% of the per protocol population recruited in the trial originated from Sweden and Denmark, the authors focused in these two countries for the RT analysis and correlation with case report forms (CRF). The report included 1176 patients (874 from Sweden and 302 from Denmark) which accounted for 46% of the recruited trial population.

As per trial protocol, RT was mandatory to the preserved breast. However, RT to nodal regions was prescribed according to guidelines of the recruiting country[26,27], and target regions differed. As an example, in Sweden 40% of participants in the SLNB arm and 37% of patients in the ALND arm

received level I axillary RT. In Denmark, nearly all cases (97%) in the SLNB group received RT to level I axilla and the proportion of level I axilla irradiated after ALND group was 14%.

For the entire cohort, RTQA demonstrated that 55% of patients in the SLNB only arm and 31% of the ALND arm had level I as an intended target (defined as >50% of the delineated target volume). However, given tangential fields was the technique most used, a high coverage of level I was found even when it was not intended. This incidental dose to level I brought the level I median V90% dose to 83%. It appears that in effect, this trial partly compared axillary irradiation to ALND and partly compared ALND with ART to ART with SLNB, the former comparison more similar to AMAROS than Z00011, as recognised by the authors[18]

This publication highlighted that a significant proportion of patients in the ALND arm also received intended RT to the operated level I axilla[25]. Although unlikely to affect the primary study outcome of OS, this may potentially increase arm lymphoedema rates and it is not intended routine practice in other parts of the world. Patient reported outcomes (PROMs) for the SENOMAC study have also been reported[28] but did not focus on prevalence of lymphoedema but rather used adapted scales to measure arm related function. This analysis concluded that one year after surgery, arm mobility was significantly affected by ALND. The additional impact of ART on arm mobility over that found after ALND alone in this study is unclear.

The POSNOC trial has in-built RTQA in the trial protocol. The pre-trial QA (prior to site activation) included a questionnaire detailing immobilisation technique, treatment delivery and dosimetry. In addition, on-trial QA performed retrospective individual case reviews of at least three plans including RT to nodal regions and recommended collection of RT data for all participants[20]. It is expected the RTQA for POSNOC will be reported to complement interpretation of trial results.

2. Trials of cN0/+SLNB - randomisation between ALND versus ART

The role of ART instead of ALND in the node positive axilla has been studied in some older randomised clinical trials including NSABP-B04 and the Institute Curie and Edinburgh studies[7,29,30] but the main two trials comparing ALND versus ART following the introduction of SLNB were the AMAROS and OTOASOR trials.

The **EORTC 10981-22023 AMAROS** trial enrolled over 4800 patients with T1-T2 cN0 disease and published its findings in 2014[31]. 1425 patients were found to have a positive SLNB and were randomised to either ALND or ART. In the ALND group, 220 patient (33%) had additional positive nodes. The primary endpoint was 5-year axillary recurrence with an expectation of a no more than 4% incidence of axillary recurrence in the RT arm compared with an expected 2% in the ALND arm. However, the number of events was lower than anticipated. Axillary recurrence occurred in 0.5% (4/744) patients in the ALND group and 1% (7/681) in the ART group resulting in the trial being underpowered to confirm non-inferiority[31].

The 10-year update of these results confirmed a low axillary recurrence rate (ARR) of 0.93% (7 events) after ALND and 1.82% (11 events) after RT with similar DFS and OS[6]. Given the very low numbers of axillary recurrences, the trialists concluded that both ALND and RT offer comparable axillary control, but RT causes less morbidity in terms of arm lymphoedema and avoids complications of further surgery.

In the AMAROS trial, lymphoedema was reported at 1, 3 and 5 years with an incidence of clinical lymphoedema of 28%, 23% and 23% in the surgery arm and 15%, 14% and 11% in the RT arm respectively. Overall, 44.2% of the patients in the ALND arm reported lymphoedema at any point in the trial compared with 28.6% of the patients in the ART group[6]. Fewer patients in the ALND group

reported shoulder mobility issues at 1 year, but the difference disappeared at 5 years and did not lead to differences in quality of life (QOL).

The **OTOASOR** trial was published in 2017[7]. This single centre study was conducted by the National Institute of Oncology in Budapest and recruited patients with ≤3 cm tumours and cN0. Patients were randomised to ALND or regional nodal irradiation (RNI), defined as all 3 levels of the axilla and the supraclavicular fossa, after BCS or mastectomy with positive SLNB. Most patients had BCS (82-84%). A total of 474 patients had a positive SLNB. 244 patients were randomised to ALND and 230 patients to RNI. Axillary recurrence occurred in 5/244 patients (2%) in the ALND group and 4/230 (1.7%) in the RNI group. Most recurrences occurred in the context of other sites of metastatic disease. RNI without ALND was concluded not to increase axillary recurrence and was reported to be an alternative treatment for patients with sentinel node metastases.

In the OTOASOR trial, the rate of lymphoedema, paraesthesia, swelling, arm pain and shoulder mobility issues were 15.3% in the ALND group and 4.7% in the RNI group. The authors reported that combining ALND with ART further increased arm morbidity to 31.5%[7]

2.1 RTQA of trials of cN0/+SLNB - randomisation between ALND versus ART

ART in the AMAROS trial included all three levels of the axilla and the medial part of the supraclavicular fossa (SCF) as defined in the protocol. Patients received 50Gy in 25 fractions[31]. The AMAROS trial RTQA has been published[32]. The RTQA team performed dummy cases evaluating protocol compliance for RT plans for all centres intending to participate in the trial. This identified that a significant number of plans had protocol deviations including different dose prescriptions, dose heterogeneity or lack of techniques to produce non-overlapping match planes. Individual recommendations per centre led to adaptations and considerable improvements towards protocol compliance and consistency among participants. This highlights once more the role of RTQA in standardising techniques, potentially reducing long term toxicity and enhancing reliability of trial results[32].

There has been no further publication of RTQA from the AMAROS trial with regards to protocol compliance and dosimetry. Authors found 77% of patients in this trial had pN1 (1-3 nodes involved) in the ALND arm, pN2 (4-9) was 9.5% and pN3 (≥10 nodes) 3.4%. The exact pathological number of nodes involved would not be known if patients have ART but is expected to be comparable to those found in the ALND arm. As ART as described included all levels of the axilla and the medial SCF (levels I-IV in modern nomenclature) then the number of involved nodes is less relevant for clinicians to make a decision on what to include in the RT target. 9.5 % of patients received IMC RT[6].

In the OTOASOR trial, RNI also involved irradiation of all 3 levels of the axilla and SCF and the dose used in this trial was 50Gy/25 fractions. There has not been a separate RTQA publication of the OTOASOR trial but some RT details were included in the study protocol.

3. Trials of cN0 with randomisation of SLNB versus not

Some investigators have already questioned the relevance of the SLNB procedure given its known morbidity[33]. Avoidance of SLNB could prevent wound infection (1%), seroma (7.1%), bleeding/haematoma (1.4%), axillary paraesthesia (8.6%) and lymphoedema (6.9%)[34]. There are also marked operational advantages with reductions in radiology time, theatre capacity and pathology resources[35]

Four RCTs have been designed to investigate the safety of SLNB omission in patients with low-risk cN0 early breast cancer including the SOUND[36], INSEMA[37] , BOOG 2013-08[38] and NAUTILUS trials[39], (Table 4).

The **SOUND (Sentinel Node vs Observation After Axillary Ultra-Sound)** trial[36] included patients with unifocal ≤2cm cN0 disease and a negative axillary ultrasound (US) who were treated with BCS and whole breast RT (WBRT), with some patients receiving partial breast irradiation (PBI) within the ELIOT study[40]. A high proportion of patients had ER positive/HER-2 negative cancers (87.8%). 13.7% in the SLNB arm had positive nodes (8.6% macrometastases, 5.1% micrometastases) and only 0.6% had ≥4 positive nodes.

After a median follow-up of 5.7 years, 1.7% locoregional relapses occurred in the SLNB group versus 1.6 % in the no axillary surgery group confirming non-inferiority (HR 0.84; 90% CI, 0.45-1.54) with similar DFS and OS[36]. Despite a 13.7% incidence of positive SLNB in the axillary surgery arm, the incidence of axillary nodal recurrence was only 0.4% in the absence of SLNB.

Recommendations for adjuvant systemic therapy were similar in both groups and made regardless of the information provided by SLNB, supporting the use of biological characteristics and genomic profile in the decision for adjuvant chemotherapy[41,42]. Authors acknowledged the lack of pathological nodal status information still creates a challenge for oncologists[43]. Nodal status is commonly used to inform decisions concerning endocrine therapy and RT, with some parts of the world choosing to offer RNI in all patients with a positive SLNB.

The **INSEMA (Intergroup-Sentinel-Mamma study)** trial commenced in 2015[37,44]. The first phase of the trial recruited 4858 patients who were randomised to SLNB versus not. This trial had a second randomisation so patients with 1-2 positive nodes at SLNB were then randomised to ALND versus not, similar to the Z0011 trial. However, this second randomisation recruited fewer patients than expected because of a low (13%) rate of 1-2 macrometastases and patient refusal to continue trial participation with a ALND arm. Most patients had ER positive (96.9%) and HER-2 negative (91.5%) tumours demonstrating the increasing tendency to recommend primary systemic therapy (PST) for patients with triple negative or HER-2 positive disease, a population excluded in this trial.

The INSEMA trial has now published its primary results showing omission of SLNB was non-inferior to SLNB in terms of axillary recurrence (0.3% in SLNB arm and 1% in the SLNB omission arm) after a median follow-up of 6 years[45]. Both the SOUND and the INSEMA trials have confirmed the non-inferiority of omitting standard SLNB in patients reflecting their eligibility criteria.

Patients in the SLNB-omission group had a lower incidence of lymphoedema (1.8% vs. 5.7%), restriction in arm mobility (2.0% vs. 3.5%), and less pain with arm or shoulder movement (2.0% vs. 4.2%) than patients who underwent SLNB. QOL data have also confirmed patients who did not have SLNB experienced less arm morbidity[44].

The proportion of patients with clinical T1 N0 disease was 90%. 83% had pN0 after SLNB, which was higher than the 70% predicted at study design, and 3% pN1mi.

The **BOOG 2013-08[38]** trial is a non-inferiority trial which recruited across many centres in the Netherlands. The primary endpoint is regional recurrence (RR) rate and results are expected this year.

The NAUTILUS (No Axillary Surgical Treatment for Lymph Node-Negative Patients after Ultra-Sonography) [39] trial recruitment is ongoing. The eligibility criteria include patients with T1–2 and cN0

disease, treated with BCS and whole-breast RT. Axillary ultrasound is mandatory before surgery. 1734 patients need to be randomized and the primary endpoint of this trial is the 5-year invasive DFS.

3.1 RTQA of trials of cN0 with randomisation of SLNB versus observation

There has been no RTQA published for the SOUND trial and therefore it is not possible to understand the effect of any incidental ART.

The INSEMA trial had RTQA embedded in the protocol with assessment of the actual RT dose delivered to specific axillary nodal levels and it was a secondary endpoint for the trial[46]. The protocol required patients to receive "standard" tangential fields and acknowledged partial low axillary irradiation is inevitable and not considered a protocol deviation. Contouring of the ipsilateral axilla (levels I-III) was mandatory for all patients using RTOG consensus definitions[47]. Internal mammary nodal area (IMNs) was not routinely contoured in the INSEMA trial[46].

From a total of 4858 patients randomised in the trial, 235 patients with protocol-compliant records were reviewed for RTQA, accounting for the first three cases per institution after excluding cases with major contouring deviations. The WBRT dose was 50Gy/25 fractions, 50.4Gy/28 fractions or 40Gy/15 fractions with a tumour bed boost, indicated for all except for selected cases with a very low risk of recurrence[46]. HTF in this trial were defined as inclusion of level I and middle to upper-level II axilla. Comprehensive nodal irradiation (high tangents plus SCF) was not allowed except for patients with ≥4 positive nodes.

At least 25% of patients were unintentionally treated with a mean dose to level I axilla of ≥95% of the prescribed breast dose and 50% of reviewed patients received ≥85%. However, the range was wide (0.8% to 110.5%). A few factors were associated with incidental axillary RT, but high body mass index (BMI >30 kg/m2) was the main factor in subgroup analysis[46].

The mean doses to level 2 axilla were significantly lower. However, 25% of patients still received a mean dose of >75% of prescription breast dose (approximately 37.8Gy with normo-fractionation and 30Gy with the hypofractionated regimen). There was no difference in axillary radiation doses between arms which excluded intentional use of HTF, as demonstrated in previous trials[46].

The BOOG trial RTQA was recently published[48]. 91.1% of patients received hypofractionated regimens (15-16 fractions of 2.67Gy) with a tumour bed boost given in 39.6% and either forward or Inverse IMRT. Delineation according to ESTRO guidelines was mandatory[49]. Acceptable Planning Target Volume (PTV) coverage was between 95-107% of the prescribed dose (including RNI if applicable), also maximum, minimum mean doses were recorded. Patients with a positive SLNB were allowed nodal RT according to an expert consensus[50] whereas patients in the no-SLNB arm were not.

RT plans were analysed in the first 25% of cases from each centre. PTVs, mean (incidental) dose, and the volume (as percentage of total volume) receiving at least 50%, 95% and 107% were recorded. For nodal regions V95% ≥95, ≥80 and V50% values were recorded. Arbitrarily, an incidental nodal dose of V95% ≥80% (at least 80% of the PTV of interest received at least 95% of the prescribed dose) was considered therapeutic[48].

The mean incidental PTV dose to level I axilla was approximately 60% of the prescribed breast RT dose and comparable in both arms whereas only 1.5% of patients received an incidental dose to level I axilla V95≥80%, which was the threshold considered by the authors as therapeutic, and none of the nodal areas were unintentionally treated with V95%≥95%. The quality of nodal contouring

was not evaluated in this trial. 8.9% of patients received Fast-forward trial fractionation (26Gy in five fractions) potentially resulting in a different biological equivalent dose to breast and incidentally treated axilla[48].

There are no RT details available in NAUTILUS study protocol publication[39] and this trial is currently ongoing.

DISCUSSION

Strategies for the identification and treatment of axillary metastases in early breast cancer have evolved over recent decades. Breast surgeons pioneered axillary management optimisation with emphasis in avoiding "low value axillary procedures" and reducing long term morbidity. The concept of avoiding ALND in the SLNB positive axilla started with the Z0011 trial but it has since been addressed by other trials. While this strategy provided some evidence to support a reduction in ALND for patients with 1-2 nodal metastases, it has facilitated a shift towards increasing use of ART instead, as seen in the recently published SENOMAC trial. This has certainly been the case in Europe, also influenced by the results of the AMAROS and OTOASAR trials.

Those trials with a SLNB arm reported an incidence of positive SLNB of between 27-40%[13,51] and yet demonstrated a very low incidence (<2%) of ARR. Isolated axillary recurrences were rare and most occurred in the context of wider metastatic disease. This confirmed most nodal metastases do not progress to clinically relevant axillary recurrences and aggressive local therapy is unlikely to change oncological outcomes in patients with limited axillary nodal burden, particularly in the presence of modern systemic therapies.

The proportion of patients with a positive SLNB is even lower in trials of SLNB avoidance of around 13-17%. Both the SOUND and INSEMA trials reported oncological outcomes and confirmed a very low axillary recurrence rate. The incidence of N2 (≥4 nodes) disease was 0.6% in the SOUND trial and 0% in the BOOG 2013-08 trial[48] confirming that patients within the eligibility criteria are unlikely to have high axillary disease burden potentially requiring more intensive local treatment, such as ALND or ART.

The exclusion of patients having PST, has resulted in trials of mainly ER positive/HER-2 negative disease. Most of these patients have a favourable hormonal profile and will be recommended adjuvant endocrine therapy, a factor also contributing to falling locoregional recurrence and improvements in long term survival[52-54].

Another factor implicated in the lack of progression of occult nodal axillary metastases is incidental ART. There is anatomical overlap between the breast tissue in the axillary tail and level I and low-level II axilla. The incidental ART doses through adjuvant breast tangential fields becomes more relevant when assessing axillary treatment avoidance. However, some authors have highlighted that a reduction in incidental axillary dose could eliminate the potential benefit this radiation has on axillary recurrence[55]. Other authors emphasised that including the level I axilla, intentionally or unintentionally, increases the dose to the humeral head and may increase late effects on arm and shoulder mobility[25]

One study estimated the proportion of level I receiving 95% of the prescribed dose increased from 51% when standard tangents were used to 79% with high tangents[56]. Others have reported the percent volumes of levels I and II covered by 95% of the prescribed dose (in a 50 Gy/25 fraction schedule) to have received 17-29Gy for level I and around 11Gy for level II axillary nodes and therefore below usual breast RT prescription doses[57,58].

The first indication of the possible impact of breast irradiation on axillary recurrence was published in 2008 within a study carried out to assess risk factors for axillary recurrence after a negative SLNB[59]. Axillary recurrence was seen in 2.8% and most patients who experienced recurrence had not received breast irradiation[59]. A subsequent systematic review confirmed a disproportionately high number of axillary recurrences in patients who did not receive WBRT concluding that breast RT does reduce axillary recurrences[55].

Many trials have specifically investigated incidental ART[60-64] and several factors including high BMI, field versus volume-based planning, radiation technique (three-dimensional conformal RT -3D-CRT versus IMRT) and tumour bed boost among others, affected incidental ART doses.

Another systematic literature review investigated incidental ART by different RT techniques[65]. The average dose delivered using 3D-CRT and standard fields were 22-43.5Gy for level I, 3-35.6Gy for level II and 1- 20.5Gy for level III. Using 3D-CRT with HTF all axillary doses were higher with average doses for level I 38-49.7Gy for level I, 11-47.1 for level II and 5-44.7Gy for level III. The use of tangential fields undoubtedly increases incidental ART doses while more modern techniques such as Volumetric Modulated Arc Therapy (VMAT) increases conformality to PTV breast/Chest wall and are likely to reduce unintentional incidental ART. However, this will need to be balanced against the low-dose bath to other organs at risk (OARs) including lung and contralateral breast, often seen as a trade-off for volumetric techniques.

The definition of HTF itself varies between publications with some defining HTF when the superior border reaches the humeral head[56,66] but others when the superior border was within 2 cm[24,64]. More recent trials have used international contouring guidelines[47,49] and were able to more accurately assess incidental ART. In the BOOG trial[48] the mean incidental PTV dose to level I axilla was approximately 60% of prescribed dose in both arms with a small proportion of patients (1.5%) receiving what was considered a therapeutic dose (V95%>80%).

However, what seems consistent among most of the RTQA publications of axillary treatment optimisation is that, despite trials showing a significant proportion of HTF used in clinical practice, radiation oncologists did not appear to have intentionally modified field placement and incidental ART was comparable between arms[24,46,48].

It is becoming clear that ALND should be reserved for patients with a significant axillary disease burden (≥3 nodes involved). A more relevant and recent question is whether one could also avoid ART in patients with 1-2 positive nodes. The POSNOC trial is likely to inform practice, as included a randomisation arm with no axillary treatment. Of note the T-REX trial[67] is randomising between no further axillary treatment and RNI patients with cN0 but 1-2 positive sentinel node macrometastases. The primary endpoint for T-REX is RFS at 5 years. RNI is given over 15 fractions but patients receiving whole breast RT only, >50 years old without indications for tumour bed boost could also be treated with 26Gy/5 fractions, as per Fast Forward trial fractionation[68]. RTQA is integrated in the protocol. T-REX trial recruitment is ongoing and is anticipated to be completed by the end of 2028[67].

ENE is also a predictor for non-sentinel node tumour burden and some groups have advocated ALND for those with ENE detected in the SLNB. ENE is also associated with increased breast cancer recurrence and mortality[69]. However, the definition and classification of ENE varies significantly among publications and many of the trials discussed only excluded patients with gross ENE (eg: SENOMAC trial) and still demonstrated no benefit from ALND[18].

A shift towards consideration of omitting SLNB in selected low-risk populations has already started. Approximately 90% of patients in the INSEMA trial were 50 years of age or older and 95% had ER

positive/Her-2 negative cancers. The authors considered it reasonable to apply trial results to this population, although there were few patients with cancers over 2 cm[45].

In April 2025, the American Society of Clinical Oncology (ASCO) published updated recommendations for sentinel lymph node biopsy in early breast cancer[70]. It states clinicians should not recommend routine SLNB in selected patients who are postmenopausal and ≥50 years of age and with negative findings on preoperative axillary ultrasound for grade 1-2, small (≤2cm), ER+/HER2- breast cancer and who undergo BCS. This guideline has been endorsed by the American Society for Radiation Oncology (ASTRO).

All these factors undoubtedly inform the decision to spare surgical interventions but at present leave oncologists in the sometimes-difficult position of making treatment decisions without nodal staging. Pathological information of the number of nodes is often necessary to access some adjuvant drugs. A recently published post-hoc analysis of the SENOMAC trial discouraged ALND for the sole purpose of identifying pN2-N3 disease to allow patients to gain access to CDK 4/6 inhibitors. It was estimated that to avoid one invasive disease free survival (IDFS) event at 5 years, ALND would need to be performed in 104 patients, and would result in nine patients having severe arm function impairment[71]. Future clinical trials in early ER positive/HER-2 negative patients should not be designed based on the number of pathological nodes involved, as it is likely this information will become increasingly unavailable.

The increasing role of clinico-genomic tools to guide radiotherapy decisions, rather than relying on the number of nodes involved, is also promising. Some of these signatures have been specifically developed to assess RT benefit and identify those patients at high risk of LRR in whom local therapy intensification may be justified[72,73]. They may also help identifying those patients with N1 disease and low risk pathological/genomic features who may not benefit from RNI[74]. The Taylor RT trial is a RCT investigating if regional RT could be avoided in patients with low risk node positive or T3N0 with low Oncotype DX recurrence score (<18) (CCTG MA.39)[75]. This trial recruitment is ongoing.

There are also online nomograms prediction tools to estimate the likelihood on SLNB involvement[76] or, if the cancer has already spread to the SLNB, what is the likelihood that the cancer has also spread to additional axillary nodes[77]. These nomograms are useful to help clinicians to make decisions in a more standardised and consistent manner and may have an increasing role in clinical practice.

Radiation oncologists have also focused in RT optimisation with particular interest in breast RT avoidance[78-81] or the use of PBI aiming to reduce long term radiation toxicity[82,83]. There is significant overlap in patient selection for RT avoidance, PBI and SLNB avoidance trials. This may create a conflict for multidisciplinary teams, as current RT optimisation strategies required pathological confirmation of negative axillary node status. Patients who do not undergo SLNB are likely to require adjuvant WBRT so a tension between breast versus axillary 'de-escalation' both in clinical trials and routine care may be problematic.[84] It is also highly likely that radiological axillary staging will play a bigger role in the future as the sensitivity of modern imaging continues to increase[85].

So, what would the loco-regional recurrence rate be in a low-risk population in the absence of SLNB and whole breast RT? In the CALBG 9343 trial[81], a trial of Tamoxifen, Tam+RT and RT alone, the management of the axilla was left to the clinician discretion. Patients in the Tamoxifen only arm, who did not undergo axillary surgery (ALND or SLNB) and did not have WBRT had an axillary recurrence rate of 3%. Authors questioned over a decade ago whether SLNB was warranted in this population.

The decision to offer SLNB, RT or none takes place early in these patients' cancer pathway when tolerability to endocrine therapy (ET) is unknown. Some guidelines[4,41] recommend RT optimisation strategies in patients "likely to adhere" to ET but in clinical practice ET adherence is difficult to predict and in some cohorts is low[86,87]. The de-escalation of multiple treatments without evidential support should not be recommended.

It remains a challenge for clinicians how to apply these data to complex clinical decisions in individual patients. The highest possible level of evidence for RNI comes from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of 14324 women in 16 clinical trials reported in 2023[88]. This reported an absolute gain in terms of 15-year risk of any recurrence and breast cancer mortality of 2.9% from regional RT patients with 1-3 nodes involved.

The DBCG-IMN2[89] trial has also recently confirmed the benefit of nodal RT, including internal mammary irradiation, in patients 1-3 positive nodes. The survival benefit was seen despite of contemporary systemic therapy and there was no subgroup identified for safe omission of RNI.

Paradoxically, although it seems that de-escalation of surgical axillary procedures may be possible in some patients with cN0/N1 disease, it has not yet been demonstrated that RNI could also be spared.

It is important to highlight that the EBCTCG meta-analysis reported benefit according to categories of nodal involvement (N1=1-3 nodes involved). However, trials of axillary treatment avoidance have mainly selected patients with cN0 and 1-2 pathological nodes and axillary de-escalation is moving towards patients with tumours <2cm and ER+/Her2 negative receptor profile. It seems reasonable to assume that the risk of loco-regional recurrence, and therefore the benefit of locoregional treatment, would be lower for this good prognosis population. In addition, trials avoiding axillary treatment in patients with 1-2 nodes involved have reported up to 10-year results and longer-term follow-up is needed, particularly for patients with ER+/HER2 negative cancers.

Finally, breast cancer axillary management has been complex and dynamic over the last decades. Heterogeneity and lack of RTQA in many instances has undoubtedly hampered implementation of surgical axillary trials results. ESTRO international consensus reporting guidelines aiming to standardise essential and optimal RT requirements in breast cancer trials have been published[90]. Locoregional treatment reporting is also poor in systemic therapy trials. The PRECEDENT project also aims to identify a core outcome set (COS) and reporting guidelines in locoregional therapies (surgery and RT) in neoadjuvant systemic therapy trials[91]. These efforts are expected to improve the robustness and reproducibility of the results produced. Efforts to unify practice should also aim to achieve international consensus of RT targets depending on extent of axillary surgery, if well conducted trials are expected to change clinical practice worldwide.

Conclusion

ALND is no longer indicated in patients with limited axillary disease. ART offers equivalent oncological outcomes compared with ALND with less morbidity, particularly lymphoedema. If the POSNOC and T-REX trials confirm that patients with limited axillary involvement do not need the axilla treated at all, it is likely that SLNB will no longer be justified for increasing numbers of patients with cN0 and tumour related low-risk features.

Breast cancer mortality has fallen in recent years and locoregional recurrence has become increasingly uncommon. Surgery and RT are highly effective but interdependent therapies which have played a major part in these improvements. This interdependence means that neither should be utilised in routine care, nor investigated within trials, in isolation. Without careful QA for both

modalities uncertainty will persist concerning their respective contributions to outcomes and the pathway to successful de-escalation of locoregional therapy will be compromised.

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