e-ISSN 2083–4640
ISSN 1507–1367

REVIEW ARTICLE

Reports of Practical Oncology and Radiotherapy
2022, Volume 27, Number 2, pages: 331–343
DOI: 10.5603/RPOR.a2022.0037
Submitted: 01.01.2022
Accepted: 02.03.2022

The role of radiotherapy in the management of nodal disease in breast cancer

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ABSTRACT

The management of nodal disease in breast cancer has evolved over the last two decades. With minimalist surgical approaches for early breast cancers becoming commonplace, the question of whether radiation can replace surgery to reduce morbidity is an important question in this population, as decision making has become more complex. In more advanced disease, and in patients with significant high-risk clinical and/or pathological features, the dilemma of who should receive regional nodal irradiation has been addressed in large studies but remains controversial. In this article, we summarise and discuss the recent trials which guide modern clinical practice, as well as some of the ongoing studies which aim to address outstanding questions within the field.

Key words: breast cancer; radiation oncology

Rep Pract Oncol Radiother 2022;27(2):331–343

Introduction

Breast cancer is the most common cancer and the most common cause of cancer death among women [1]. Some of the challenges faced in breast cancer stem from the heterogeneity of the disease and the differences in histological, prognostic and clinical features [2].

Nodal burden has traditionally been associated with worse outcomes [3–5]. Despite this knowledge, the management of nodal disease in breast cancer remains an ongoing question [6], particularly in early, low nodal-burden disease. With evidence for breast-conserving surgery (BCS) and adjuvant radiotherapy [7–9], appropriate, safe management of regional nodes has become topical and multiple randomised controlled trials have attempted to provide information to guide treatment.

The role of the sentinel lymph node biopsy (SLNB) has become particularly important in the surgical management of the axilla [10–12]. Historically, complete axillary lymph node dissection (ALND) alone has been associated with very low rates of local axillary failure, thought to be 0–2% [13], and similarly, the risk of axillary recurrence has been shown to relate to the extensiveness of ALND performed [14]. Furthermore, management of the axilla, either in the form of ALND or axillary radiation (AXR), in the clinically node-negative patient, has been shown to decrease axillary recurrence [15]. With a move towards ever-more minimalist surgical approaches, the question of whether morbid procedures such as ALND can be avoided completely or replaced by other therapeutic approaches, such as radiotherapy or systemic therapy, has become an important conundrum

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and generates much debate at multi-disciplinary meetings.

How best to manage patients with more extensive nodal involvement also remains a subject of controversy. Questions regarding the benefits of adjuvant regional nodal irradiation (RNI), to areas such as the supraclavicular fossa (SCF) and internal mammary nodes (IMN), are the topics of large clinical trials; however, as yet no universal consensus exists on the optimal utilisation of these therapies. Proposed benefits of RNI in locoregional control and survival must be weighed against the slightly increased risk of toxicity, such as cardiac toxicity [16], pneumonitis [17] and contralateral breast cancers [18]. Whilst hypofractionated whole breast irradiation (WBI) and chest wall irradiation (CWI) have become mainstream in the wake of large multicentre clinical trials [19], with subsequent validation internationally [20, 21], the small proportions of patients receiving RNI in these trials means that the ideal fractionation schedule for RNI remains unclear [22]. Although meta-analyses [12, 23, 24] have been helpful in defining the role of RNI, correct patient selection is a persistent challenge.

In this article, we review the most important studies in the management of nodal disease in breast cancer over the last 20 years.

Avoidance of axillary dissection in SLNB positive early breast cancer

Findings from several randomised trials showed that patients with a negative sentinel lymph node (SLN) can be spared the short-term and long-term morbidity of ALND, and this translates into a better quality of life. ALND is associated with harmful and often persistent side-effects including lymphoedema, shoulder mobility issues and discomfort. The need for ALND in patients with limited SLNB positive axillary nodes has recently been challenged and avoidance of surgical axillary dissection is an option for selected patients.

Z0011

The American College of Surgeons Oncology Group (ACOSOG) Z0011 randomised control trial compared BCS with sentinel lymph node dissection (SLND) alone versus ALND for patients with a positive SLN [25]. The study, carried out across 115 sites between 1999 and 2004, published its 10-year outcomes in 2017 [26].

Patients included had an invasive breast cancer less than 5 cm in size without palpable adenopathy and 1 or 2 SLN with metastases detected (not limited to micrometastases). Patients had a planned lumpectomy followed by opposing tangential-field WBI (third-field irradiation was prohibited), and adjuvant systemic therapy (type at the discretion of the treating physician). Four hundred and thirty-six patients and 420 patients were randomised to receive SLND alone or ALND, respectively. The trial under-recruited (target of 1900 patients) due to a lower than predicted mortality rate.

The primary endpoint was non-inferiority of overall survival (OS) and the secondary endpoint was disease-free survival (DFS). Results are outlined in Table 1. At 10-year median follow-up, OS for SLND alone was non-inferior compared to ALND, with no difference observed for DFS.

Twenty-seven percent of patients in the ALND group were found to have additional nodal involvement. However, at 5-year analysis, regional ipsilateral axillary recurrence was similarly rare for both intervention and control groups. Just 4 (0.9%) patients in the SLND alone compared with 2 (0.5%) in the ALND group had ipsilateral axillary failure. No difference was observed in the 10-year locoregional relapse-free survival for the SLND and ALND groups (83% *vs.* 81.2%).

Features associated with improved OS on multivariable analysis included age less than 50 ($p = 0.002$), any hormone receptor positivity ($p = 0.02$) and pathological tumour size ($p = 0.001$).

Of importance, there was no quality control reported for radiation therapy so it is difficult to know how patients were treated. For example, were lower axillary nodes included in radiation fields or not? Further evaluation of 605 patients included in the study showed that 89% of patients received WBI, of whom 15% received treatment to the SCF. Of the patients with sufficient tangent height records, high tangents were used in 51.4%. [27]. What is needed is more detailed information regarding radiation fields, outcomes by extent of nodal disease (beyond micrometastases) and further follow-up, since 75% had ER-positive disease and late recurrences are likely. At present, patients with early breast cancer with 2 or fewer positive SLN who are treated with BCS plus WBI can be considered for no additional

Table 1. Summary of trial results

Study design		Primary end-points	Secondary end-points
Management of the axilla			
IBCSG 23-01	BCS/mastectomy + SLNB (mi) + ALND *vs.* BCS/mastectomy + SLNB (mi) + SLN	**DFS** — no statistically significant difference at 5 years	**OS** — no statistically significant difference **Axillary failure** — < 2% for both groups **Surgical complications of AD** — more common for ALND **Lymphoedema** — more common for ALND (13% *vs.* 3%)
Z0011	BCS + SLNB + ALND *vs.* BCS + SLNB	**OS** — SLNB alone non-inferior at 10 years (83.6% *vs.* 86.3%)	**DFS** — no statistical difference at 10 years (80.2% and 78.2%) (**Regional recurrence** — < 1%)
AMAROS*	BCS/mastectomy + SLNB + ALND *vs.* BCS/mastectomy + SLNB + AXR	**Axillary recurrence** — underpowered for non-inferiority	**DFS** — no statistically significant difference **OS** — no statistically significant difference **Shoulder immobility** — no statistically significant difference **Lymphoedema** — more common for ALND (23% *vs.* 11% at 5 years post-treatment) **QoL** — no statistically significant difference
OTOASOR	BCS/mastectomy + SLNB + ALND *vs.* BCS/mastectomy + SLNB + AXR	**Axillary recurrence** — no statistically significant difference at 8 years	**OS** — no statistically significant difference at 8 years **DFS** — no statistically significant difference at 8 years
Management of IMNs			
MA.20	BCS + SLNB/ALND + RNI *vs.* BCS + SLNB/ALND	**OS** — no statistically significant difference at 10 years	**DFS** — favours RNI (82% vs 77%) **Locoregional DFS** — favours RNI (95.2% *vs.* 92.2%) **Distant DFS** — favours RNI (86.3% *vs.* 82.4%) **Toxicity** — favours no RNI
EORTC 22922	BCS/mastectomy + ALND/SLNB + IM-MS RT *vs.* BCS/mastectomy + ALND/SLNB	**OS** — no statistically significant difference at 15 years	**DFS** — no statistically significant difference **Cumulative incidence of breast cancer recurrence** — favours IM-MS (73.1% *vs.* 70.9%) **Cumulative incidence of breast cancer mortality** — favours IM-MS (24.5% *vs.* 27%)
Danish	BCS/mastectomy + ALND + IMNI *vs.* BCS/mastectomy + ALND	**OS** — favours IMNI at 8 years (75.9% *vs.* 73.3%)	**Breast cancer mortality** — favours IMNI (20.9% *vs.* 23.4%) **Distant recurrence** — no statistically significant difference
KROG 08-06	BCS/mastectomy + ALND + IMN/SCF RT *vs.* BCS/mastectomy + ALND + SCF RT	**DFS** — no statistically significant difference at 7 years	**OS** — no statistically significant difference **Breast cancer-specific survival** — no statistically significant difference **Toxicity** — no statistically significant difference

*initial published results as 10-year data not available in published form; BCS — breast-conserving surgery; SLNB — sentinel lymph node biopsy; ALND — axillary lymph node dissection; SLN — sentinel lymph node biopsy; AXR — axillary radiation; RNI — regional nodal irradiation; IM-MS — internal mammary and medial supraclavicular lymph node chain irradiation; IMNI — internal mammary node irradiation; IMN/SCF RT — internal mammary nodes and supraclavicular fossa irradiation; DFS — disease-free survival; OS — overall survival; QoL — quality of life

axillary treatment. This, however, does not extend to patients treated with mastectomy without adjuvant radiation therapy.

Do patients need additional axillary treatment for SLN-positive micrometastatic (< 2 mm) disease?

IBCSG 23-01

Initially published in 2013, the International Breast Cancer Study Group (IBCSG) 23-01 trial compared outcomes for patients randomised to receive either axillary dissection (AD) or no AD in breast cancers less than 5 cm in size with SLN micrometastatic (< 2 mm) disease without extranodal extension [28]. The study, performed across 27 institutions enrolling between 2001 and 2010, included patients undergoing surgical management of their primary breast malignancy without palpable axillary lymphadenopathy. The trial's 10-year outcomes were subsequently published in 2018 [29].

Four hundred and sixty-four patients in the AD group and 467 in the no AD group were included for analysis, with a median follow-up of 9.7 years (Tab. 2).

Table 2. Summary of sentinel lymph node biopsy (SLNB) studies' patient characteristics

	IBCSG 2301	Z0011	AMAROS	OTOASOR
Accrual	4/2001–2/2010	5/1999–12/2004	2/2001–4/2010	8/2002–6/2009
Number of centres	27	27	34	1
Follow-up [years]	9.7	9.3	6.1	8.1
Age	53–54	54–56	55–56	54.9
N	931	856	1425	474
Primary tumour size				
< 2 cm (T1)	638 (68.5%)	587 (68.6%)	1145 (80.4%)	243 (51.3%)
2–5 cm (T2)	281 (30.2%)	260 (30.4%)	275 (19.3%)	210 (44.3%)
> 5 cm (T3)	0 (0.0%)	0 (0.0%)	1 (0.1%)	21 (4.4%)
Unknown	12 (1.3%)	9 (1.1%)	4 (0.3%)	0 (0.0%)
Surgical management				
BCS	845 (90.8%)	856 (100.0%)	1166 (81.8%)	400 (84.4%)
Mastectomy	86 (9.2%)	-	248 (17.4%)	74 (15.6%)
ALND	461 (49.5%)	399 (46.6%)	744 (52.2%)	244 (51.5%)
Metastatic deposit size in sentinel nodes				
Micrometastases/ITC	909 (97.6%)	301 (35.2%)	564 (39.6%)	153 (66.5%)*
Macrometastases	21 (2.3%)	430 (50.2%)	861 (60.4%)	77 (33.5%)*
Unknown	1 (0.1%)	125 (14.6%)	0 (0.0%)	0 (0.0%)*
Number of involved sentinel nodes				
0	–	1†	–	1.3‡
1	890 (95.6%)		1093 (76.7%)	
2	40 (4.3%)		261 (18.3%)	
3	1 (0.1%)		56 (3.9%)	
4+	0 (0.0%)		15 (1.1%)	
Additional involved nodes in ALND	59/464 (13%)	97 (27.3%)	220/672 (32.7%)	94/244 (38.5%)
Hormone receptor status				
ER+	834 (89.6%)	641 (74.9%)	–	397 (83.8%)
PR+	702 (75.4%)	533 (62.3%)	–	346 (73.0%)
ER+/PR+	–	526 (61.4%)	–	–
HER2+	96 (10.3%)	–	–	58 (12.2%)
Systemic therapy				
Any	892 (95.8%)	826 (96.5%)	1278 (89.7%)	NS

*sentinel node metastatic deposit size only given for AXR group; †median number of involved sentinel nodes in SLND only group; ‡mean number of involved sentinel nodes; BCS — breast-conserving surgery; ALND — axillary lymph node dissection; ITC — isolated tumor cells

Eighty-seven percent of patients in the AD group had no further pathologically involved nodes following SN biopsy. Radiotherapy (intra-operatively, post-operatively, or in combination) was delivered to 98% in the AD group and 97% of the no AD group.

The primary end-point was DFS, with a 10-year DFS of 74.9% in the AD group and 76.8% in the no AD group (HR 0.85, log rank p = 0.024, p = 0.0024 for non-inferiority) (Tab. 1).

No difference was observed between the AD and no AD groups in 10-year OS (88.2% *vs.* 90.8), and local recurrence rates were similar between the two groups (3% *vs.* 3%). Regional events were more frequent in the no AD group (2% *vs.* 1%), as were ipsilateral axillary failures (2% *vs.* < 1%). There were fewer non-breast cancer events in the no AD group (6% *vs.* 9%). As expected, surgical complications of sensory neuropathy (19% *vs.* 13%), lymphoedema (13% *vs.* 4%) and motor

neuropathy (9% *vs.* 3%) were significantly more common in the AD group.

Subgroup analysis identified ER positivity, PR positivity, size of the largest metastatic SN < 1 mm, single involved SN only, HER2 negativity and invasive ductal histology as all being groups in which no AD was significantly non-inferior.

Overall, the study's data would support no additional axillary treatment being necessary for patients with breast cancers less than 5 cm with SLN micrometastatic (< 2 mm) disease without extranodal extension.

Axillary radiation (AXR) for early breast cancer with positive SLNB

Further involvement of the axillary lymph nodes can be predicted on the basis of factors such as tumour size, type, grade, vascular invasion, and extracapsular extension of cancer in the SNs. Patients with a high risk of axillary involvement still need axillary treatment. If AXR is to be prescribed, this typically excludes coverage of the dissected axilla in order to avoid an increased risk of morbidity associated with both radiation and surgery to the same axillary regions.(30)

AMAROS

The European Organisation for Research and Treatment of Cancer (EORTC) 10981-22023 AMAROS randomised, non-inferiority trial compared AXR with ALND following a positive SLNB in patients with early (T1–2) breast cancers and no associated palpable lymphadenopathy [31]. The study recruited patients between 2001 and 2010, comparing outcomes for 744 in the ALND group with 681 in the AXR group. AXR consisted of 50 Gy in 25 fractions delivered to levels I–III and the medial supraclavicular fossa. Adjuvant systemic treatment was left to the discretion of the treating physician. Patient characteristics are summarised in Table 2.

The primary endpoint was 5-year axillary recurrence, which was seen in 0.43% of the ALND group and 1.19% of the AXR group. No difference was observed between the ALND or AXR groups for DFS (5-year DFS 86.9% *vs.* 82.7%) or OS (5-year OS 93.3% *vs.* 92.5%). Axillary recurrence-free survival was analogous to OS as a result of the very low number of axillary recurrences. There was no difference in terms of shoulder mobility or quality of life (QoL) between the groups, however, lymphoedema was significantly more common in the ALND group at every measured time point (Tab. 1).

No individual features were felt to favour DFS towards either AXR or ALND on subgroup analysis.

Of note, 33% (220/672) of patients in the ALND group were found to have metastatic involvement of non-SN at pathological assessment, 8% (52/672) of whom had four or more (N2) metastatically involved nodes. Forty-one patients in this group went on to have combined (ALND and AXR) treatment to the axilla.

The 10-year follow-up results of AMAROS were presented at the San Antonio Breast Cancer Symposium in December 2018, and published in abstract form in early 2019 [32]. The results were broadly in keeping with those of the 5-year follow-up publication, strengthening the argument for long-term comparability of ALND and AXR in the SLN-positive early breast cancers. At the 10-year mark, no statistically significant difference was observed between ALND and AXR groups in terms of axillary recurrence (0.93% *vs.* 1.82%), OS (84.6% *vs.* 81.4%), distant metastases-free survival (DMFS) (81.7% *vs.* 78.2%), or cumulative locoregional recurrence (3.59% *vs.* 4.07%). Of note, second primary malignancies were significantly more commonly observed after AXR (11% *vs.* 7.7%, $p = 0.035$), however, the difference was felt to be low in absolute numbers.

OTOASOR

Published in 2017, the National Institute of Oncology, Budapest reported results of the single centre randomized clinical study, OTOASOR (Optimal Treatment Of the Axilla — Surgery Or Radiotherapy) [33]. The trial compared completion of axillary lymph node dissection (cALND) to regional nodal irradiation, in the form of AXR, in patients with SLN metastasis [pN1 (sn)] in stage I–II breast cancer.

Patients with primary invasive breast cancer (cN0 and cT ≤ 3 cm) were randomised before surgery to cALND (standard treatment) or AXR 50Gy. Between August 2002 and June 2009, 1,054 patients were randomised for cALND and 1052 patients for AXR. SLN were evaluated in 2,073 patients and was positive in 526 patients (25.4%). 474 cases were evaluable (244 in the cALND and 230 in the AXR arm). Of interest, and similar to in AMAROS

and Z0011, in the cALND group 94 of 244 patients (38.5%) who underwent completion axillary surgery had additional positive nodal metastases. Primary endpoint was axillary recurrence, with secondary endpoints of OS and DFS. The mean follow-up was 97 months.

Axillary recurrence was similar for both groups, at 2.0% in cALND arm *vs.* 1.7% in AXR arm (p = 1.00). OS at 8 years was 77.9% *vs.* 84.8% (p = 0.060), and DFS was 72.1% in cALND arm and 77.4% after AXR (p = 0.51). The study's results indicate that AXR is statistically not inferior to cALND in the selected population.

The long term follow-up results of OTOASOR and the AMAROS trials suggest that AXR instead of ALND does not increase the risk of axillary failure in selected patients with early-stage invasive breast cancer [cT ≤ 3 cm, cN0, pN1(sn)].

Axillary recurrence after 10 years in patients with positive SLNB treated with AXR is extremely rare and not significantly different from patients who were treated with ALND. OS, distant DFS and locoregional control are also comparable. Furthermore, AXR is less toxic than ALND, particularly with respect to less lymphoedema. It is reasonable to conclude that AXR is a safe treatment alternative to surgery for early-stage breast cancer patients with positive SLNB.

Management of the axilla in patients treated with neoadjuvant chemotherapy

For patients with clinically negative and radiologically negative axillary nodes at diagnosis, SLN biopsy can be performed before or after neoadjuvant systemic therapy. However, current St Gallen and European Society for Medical Oncology guidelines recommend carrying out SLNB after completion of neoadjuvant therapy in order to avoid a potential need for 2 separate surgeries [34]. In addition, post-neoadjuvant SLNB allows definitive assessment of complete pathological response (pCR) in the axilla to inform adjuvant treatment planning. For patients with positive axillary nodes at diagnosis, the SENTINA [35] and ACOSOG Z1071 [36] studies demonstrated feasibility for SLNB in patients who convert to clinically node-negative disease during neoadjuvant therapy. The procedure, however, has a lower detection rate and a higher false-negative rate (FNR) compared with SLNB performed before neoadjuvant chemotherapy, limitations which should be considered if biopsy is planned after neoadjuvant treatment.

Regarding axillary surgery, current guidelines recommend marking positive lymph nodes during biopsy, prior to initiating neoadjuvant systemic therapy. In the event that neoadjuvant therapy converts the patient to node-negative, the clips will allow confirmation that the original positive nodes were removed and examined. Guidelines also indicate removal of at least 3 total SLNs to reduce the FNR of SLN biopsy in these patients [34]. Results from the ACOSOG Z1071 trial showed that clip placement prior to neoadjuvant therapy and removal of the clipped node during SLNB reduces the FNR after neoadjuvant therapy from 13.4% to 6.8%. Patients who had no invasive disease in the breast had improved outcomes, while nodal involvement of any kind predicted a worse prognosis and the presence of residual in-situ disease was not prognostic. The evolving practice of targeted axillary dissection (TAD), whereby known upfront metastatic nodes are clipped prior to neoadjuvant treatment and subsequently excised even if not included in the SLNB sampling, may further refine surgical staging of the post-neoadjuvant axilla. The MD Anderson Group's findings from 2016 showed that addition of TAD to SLNB decreased FNR of axillary sampling to 1.4%, compared with 10% for SLNB alone [37]. These findings would reinforce the ACOSOG Z1071 results that inclusion of known upfront positive nodes improves accuracy of axillary staging. The current European Medicines Agency recommendations define pCR as no invasive disease in the breast and nodes (ypT0/is ypN0) as an appropriate endpoint in clinical trials of neoadjuvant therapy.

The AMAROS and OTOASOR trials demonstrated similar axillary control for AXR or ALND in patients with a positive SLN, but these data cannot be extrapolated to the neoadjuvant setting. Current guidelines recommend completion axillary dissection for women with residual nodal disease on SLN biopsy following neoadjuvant systemic therapy, including those with micrometastatic disease. Reported rates of non-SLN metastases in patients with a positive SLN after neoadjuvant treatment may range from 40% to 70%. Careful discussion on toxicity with the patient is warranted.

Multiple studies examining management of the axilla in the setting of neoadjuvant systemic treatment are currently ongoing. Regarding patients with persistent SN-positivity post-neoadjuvant treatment, the Alliance A011202 study [38] will compare ALND (levels I and II) followed by RNI (including the undissected axilla) versus no ALND and RNI to include full AXR in cT1–3 N1 patients. Similarly, the TAXIS [39] trial, will assess the role of targeted surgical excision of positive axillary nodes (TAS) followed by ALND and RNI (excluding the dissected axilla) versus TAS alone followed by RNI including full AXR. TAXIS will include patients who have received neoadjuvant systemic treatment but who still have residual axillary disease before surgery. It is hoped that these studies will further inform axillary treatment for breast cancer patients who have had an incomplete pathological response in the axilla following neoadjuvant treatment.

The National Surgical Adjuvant Breast and Bowel Project (NSABP)-B51 trial aims to shed light on how best to manage patients who convert from upfront node-positive to pathologically node-negative post-neoadjuvant treatment (ypN0) [40]. It is hoped that the role of adjuvant nodal radiotherapy (to include the undissected axilla, SCF and IMNs) versus no adjuvant nodal radiotherapy will be elucidated for this complex population.

Management of the post-neoadjuvant patient with pathologically regressed/responded SLN (ypN0), who were believed to be upfront node negative remains a controversial topic and data on best management is awaited. Whilst, as yet, no consensus exists for this specific population, a conservative approach would be to recommend nodal management of some sort on the basis of original node positivity.

Management of patients with more extensive nodal involvement

KROG 08-06

The Korean Radiation Oncology Group (KROG) recently published findings from their KROG 08-06 trial, in which they assessed the role of internal mammary node irradiation (IMNI) in node-positive breast cancer patients. The trial was performed across 13 centres in South Korea and included 735 patients who had undergone up-front surgical management of their disease (mastectomy or BCS) in combination with ALND. Patients received adjuvant radiation to the residual breast/chest wall as appropriate and were randomised to receive RNI with or without IMNI. Disease burden was relatively high, with 56% percent of patients having N2 or greater nodal burdens and nearly all patients received adjuvant systemic therapy.

The primary endpoint was 7-year DFS, with no statistically significant difference observed between IMNI and no IMNI (85.3% *vs.* 81.9%). Similarly, no significant difference was seen in terms of 7-year breast cancer mortality rates (8.4% *vs.* 10.8%), DMFS (85.8% *vs.* 83.2%) or OS (89.4% *vs.* 88.2%). Interestingly, there was no significant difference between the 2 groups from a toxicity perspective with similar amounts of arm oedema, brachial plexopathy, rib fracture, skin reaction and cardiac toxicity. Whilst there was a higher, but not significant (6.1% *vs.* 3.2%, $p = 0.06$), rate of pneumonitis in the IMNI group, there were no incidences of serious (grade 3 or greater) occurrences of radiation pneumonitis in either group.

On subgroup analysis, patients with medio-central primary tumours appeared to benefit most from the addition of IMNI. Within this group, 7-year DFS, breast cancer mortality and DMFS outcomes significantly favoured IMNI, an effect not seen in laterally located primary tumours. This may signal towards who could receive most benefit from IMNI.

EORTC 22922-10925

The EORTC 22922-10925 randomised trial published its 15-year results in 2020 [41]. This study examined the role of internal mammary and medial supraclavicular lymph node chain irradiation (IM-MS) in stage 1–3 breast cancer, comparing IM-MS with no IM-MS as a control, randomising 2002 patients to each group. The trial was conducted across 46 centres in 13 countries and included patients up to 75 years of age with involved axillary nodes or a central or medial primary tumour. Surgery consisted of mastectomy or BCS and ALND initially, however, from 2013, SLNB followed by ALND (if SN disease was identified) was allowed [42]. Adjuvant systemic treatment was offered to patients as per local institutional guidelines.

Of the 3049 patients who underwent BCS, 99.7% received adjuvant WBI. Of the remaining patients who underwent mastectomy, 73.3% underwent

chest wall irradiation (CWI). Fifty-five percent of patients in the study had some nodal involvement on pathological assessment, with 43% displaying N1 disease.

The primary endpoint was OS. At 15-year follow-up, OS in the IM-MS group was 73.1% and 70.9% in the control population, with no statistically significant difference between the groups.

Secondary endpoints were DFS, DMFS, cumulative incidence of breast cancer mortality, and cumulative incidence of any breast cancer recurrence. No difference was observed between IM-MS and control groups for 15-year DFS (60.8% *vs.* 59.9%) or DMFS (70.0% *vs.* 68.2%). However, the 15-year cumulative incidence of any type of breast cancer recurrence (24.5% *vs.* 27.1%, HR: 0.87, p = 0.024) and the 15-year cumulative incidence of breast cancer mortality (16.0% *vs.* 19.8%, HR: 0.81, p = 0.0055) significantly favoured the IM-MS group (Tab. 1).

Toxicity was evaluated for 3866 eligible patients, with side effects more common in the IM-MS group. Any grade of pulmonary fibrosis (5.1% *vs.* 2.3%) or cardiac fibrosis (2.0% *vs.* 1.1%), and any cardiac disease (8.6% *vs.* 7.2%) tended to be seen more in the IM-MS group but the difference was minimal.

MA.20

The MA.20 randomised trial assessed the effect of the addition of RNI to standard WBI and adjuvant systemic therapy (prior to RT) following BCS in patients with node-positive or high-risk node-negative breast cancer [43]. High-risk features in this latter group were defined as a tumour greater than 5 cm in size (T3), or a tumour greater than 2 cm in size with fewer than 10 axillary nodes removed and one or more of grade 3 histology, ER-negative disease, or lymphovascular invasion. One thousand eight hundred and thirty-two patients were randomised to RNI or control, with RNI including IM, SCF and axillary nodes. Median follow-up was 9.5 years. Patient characteristics are described in Table 3.

The primary endpoint was OS, with no significant difference in OS between RNI and no RNI groups (82.8% *vs.* 81.8%). Secondary endpoints were DFS, isolated locoregional DFS, distant DFS, and toxicity (Tab. 1).

Ten-year DFS (82.0% *vs.* 77.0%, HR: 0.76, p = 0.01), isolated locoregional DFS (95.2% *vs.* 92.2%, HR: 0.59, p = 0.009) and distant DFS (86.3% *vs.* 82.4%, HR: 0.76, p = 0.03) all statistically favoured the RNI group compared with the control arm. Subgroup analysis suggested ER/PR negative disease, although under-represented, benefitted from the addition of RNI in terms of survival.

Lymphoedema (8.4% *vs.* 4.5%, p = 0.001), late skin side effects including telangiectasia (6.9% *vs.* 4.3%, p = 0.02) and subcutaneous fibrosis of nodal irradiation fields (4.1% *vs.* 2.0%, p = 0.01) were all more common for RNI.

DBCG-IMN (Danish)

A Danish population-based cohort study assessing the effect of IMNI on early node-positive breast cancer was published in 2016 [44]. Patients were recruited between 2003 and 2007, with 3089 patients included, of whom 1492 received IMNI.

Patients with right-sided disease were allocated to the IMNI group, whereas those with left-sided disease were allocated to the no IMNI group. The reason for this was to control for the previously reported radiation-induced cardiac toxicity associated with IMNI, especially on the left. Median follow-up was 8.9 years.

Patients included had macrometastatic nodal disease. Surgery was in the form of mastectomy or BCS and ALND (level I and part of level II). Radiotherapy was to the breast/CW, scar, SCF nodes, IC nodes, and axillary levels II and III, as well as level I if 6 or more nodes contained macrometastatic disease. Right sided breast cancer in addition also included IMNI. Systemic therapy for hormone-receptor positive tumours was cyclophosphamide and fluorouracil, and methotrexate or epirubicin, with 5 years of tamoxifen for pre-menopausal women. Post-menopausal women with positive hormone receptor status received tamoxifen for 5 years, and from 2004, tamoxifen for 2.5 years followed by an aromatase inhibitor for 2.5 years. All hormone receptor-negative disease patients received adjuvant chemotherapy.

Eight-year OS was statistically longer for the IMNI group (75.9% *vs.* 73.3%). The cumulative incidence of breast cancer mortality at 8 years was lower for the IMN group. From a toxicity perspective, equal numbers of cardiac deaths occurred in the two groups (Tab. 1).

Subgroup analysis showed IMNI statistically improved 8-year OS in patients treated surgically

Table 3. Summary of regional nodal irradiation (RNI) studies' patient characteristics

	MA.20	EORTC 22922/10925	Danish	KROG 08-06
Accrual	3/2020–2/2007	7/1996–1/2004	1/2003–12/2007	11/2008–1/2013
Follow–up [years]	9.5	15.7	8.9	8.3
Age	53–54	54	56	48
N	1832	4004	3089	735
Regional nodal fields				
IMN	Yes	Yes	Yes	Yes
SCF	Yes	Yes	Yes	Yes
Axillary	Yes	No	Yes	Yes
Primary tumour size				
< 2 cm (T1)	960 (52.4%)	2408 (60.1%)	1281 (41.5%)	230 (31.3%)
2–5 cm (T2)	859 (46.5%)	1430 (35.7%)	1609 (52.1%)	412 (56.1%)
> 5 cm (T3/T4)	19 (1.0%)	141 (3.5%)	198 (6.4%)	83 (12.6%)
Unknown	–	–	6 (0.19%)	
Surgical management of breast				
BCS	1832 (100.0%)	3049 (76.1%)	1093 (35.4%)	367 (49.9%)
Mastectomy	–	955 (23.9%)	2016 (65.3%)	368 (50.1%)
Type of radiation				
RT with BCS	1820 (99.3%)	3039 (75.9%)	1093 (35.4%)	367 (49.9%)
No breast irradiation	12 (0.7%)	264 (6.6%)	–	–
RNI	893 (48.7%)	2002 (50.0%)	1492 (48.3%)	362 (49.3%)
Number of involved lymph nodes				
0	177 (9.7%)	1778 (44.4%)	0 (0.0%)	0 (0%)
1	907 (49.5%)	1727 (43.1%)*	1818 (58.9%)*	304 (41.4%)*
2	432 (23.6%)			
3	209 (11.4%)			
4+	97 (5.3%)	499 (12.5%)	1271 (41.1%)	431 (58.6%)
Hormone receptor status				
ER+	1367 (74.6%)	–	2486 (80.5%)†	524 (71.3%)
PR+	1102 (60.2%)	–		459 (62.4%)
Systemic therapy				
Any	–	3379 (84.4%)	–	–
Chemotherapy	1660 (90.6%)	994 (24.8%)	586 (19.0%)	727 (98.9%)
Hormonal therapy	1389 (75.8%)	1185 (29.6%)	1447 (46.8%)	494 (67.2%)
Combination therapy	–	1200 (30.0%)	1056 (34.2%)	–

*1–3 nodes (N1) involved; †hormone receptor status not subdivided by ER and PR; IMN — internal mammary nodes; SCF — supraclavicular fossa; BCS — breast-conserving therapy; RT — radiotherapy

with mastectomy (72.6% *vs.* 68%), with a tumour size of more than 5.1 cm (57.1% *vs.* 40.6%), 4 to 9 positive nodes (73.5% *vs.* 65.7%), more than 10 positive nodes (52.4% *vs.* 39.8%), grade 2 malignancy (76.6% *vs.* 72.2%) and premenopausal status (79.3% *vs.* 74.8%). Medial or central location approached significance (74.9% *vs.* 68.7%) favouring IMNI.

In an exploratory subgroup analysis of tumour location (lateral *vs.* medial/central) and number of macrometastatic nodes (1–3 *vs.* 4 or more), mortality outcomes favoured IMNI for patients who had a medial/central tumour and/or 4 or more positive nodes. For combination of these 3 subgroups (medial/central and 1–3 nodes, lateral and 4+ nodes, medial/central and 4+ nodes), the IMNI group

had a statistically better 8-year survival (72.2% *vs.* 64.8%, HR: 0.76, p = 0.001).

Summary of adjuvant IMNI radiation for axillary node-positive breast cancer

The main difference between the KROG 08-06, EORTC 22922/10925, MA.20 and the Danish studies concern the patient populations, with only axillary node-positive patients in the KROG and Danish studies, 90% node-positive patients in MA.20, and only 56% node-positive patients in the EORTC trial. To further compare the KROG and Danish trials, it is interesting to note that the benefit of IMNI was seen for mediocentral primary tumours in both studies, and for higher nodal burden in the Danish trial. The high nodal burden of the KROG population in general would align with these findings.

A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group, evaluating six studies that started after 1989, showed nodal irradiation significantly reduced breast cancer recurrence, breast cancer mortality, and any death, without any increase in non-breast cancer-related mortality (relative risk: 0.88, p = 0.002) [45]. Indeed, the absolute benefit was the largest in patients with a higher number of involved axillary lymph nodes. Technical developments over the past 20 years and moves to modern, volume-based radiotherapy are expected to result in continuing superior outcomes for this sub-group.

With specific reference to IMNI, a meta-analysis of 3 studies including 7170 patients (including MA.20 and EORTC 22922-10925), has shown improved OS, DFS and DMFS seen for patients who undergo RNI.(24) Whilst the individual studies failed to show a significant OS benefit to RNI, with absolute survival benefit ranging from 1–3% at 10-year follow-up, pooled results demonstrated statistically significant OS improvement. Indeed, the third study [46] in the analysis employed now rarely used 2-dimensional radiation planning techniques. As such, with the advent of modern conformal planning it is possible that the benefit from RNI may in fact be even greater. Inclusion of the recent KROG study in future meta-analysis will undoubtedly shed more light on the role of IMNI.

Conclusion

The management of nodal disease in breast cancer remains a complex issue. The fact that no difference was observed in the SN-only groups in Z0011 and IBSCG, despite additional nodal disease being identified in 27% and 13% of ALND groups, respectively, poses the question of why untreated residual nodal disease does not impact negatively on patient survival outcomes?

One potential explanation may be the axillary coverage provided by WBI. Prior to these studies being published, Reznik et al. retrospectively examined the radiation doses received by the axilla in a series of 35 patients who had undergone WBI, showing that with standard tangential fields axillary levels I, II, III, and Rotter's nodes received 66%, 44%, 31%, and 70% of the prescribed dose. When high tangential fields were applied the coverage of these areas increased to 86%, 71%, 73% and 94%, respectively [47]. Other possible reasons for the failure of residual disease to negatively impact survival outcomes may be the effect of systemic treatment (high hormone-receptor positivity in both studies) and/or that sub-clinical nodal disease may not progress to clinically significant disease.

As reported in the AMAROS trial, management of the axilla in some form is probably still required for patients who do not fall into the IBSCG or Z0011 treatment populations (i.e., patients undergoing mastectomy or non-BCS, with macrometastatic SN disease). Given the historic associated morbidity of ALND, particularly for lymphoedema, it seems reasonable that AR would be the approach of choice.

In node-positive breast cancer, the KROG, EORTC 22922/10925, MA.20 and Danish studies mentioned above would appear to support the benefit of regional nodal irradiation including IMNI in selected populations. In the MA.20 study, the addition of regional nodal irradiation to WBI significantly increased the relative disease-free survival by 24%, which was an absolute improvement of 5 percentage points at 10 years. In a recent meta-analysis by the Early Breast Cancer Trialists Collaborative Group of postmastectomy radiotherapy in node-positive patients, for every 1.5 recurrences (either locoregional or distant) that were prevented during the first 10 years after radiation, one breast-cancer death was prevented at 20 years. Although it is difficult to say

which nodal volumes are important to include as all areas are at risk for residual disease the EORTC trial suggests that irradiation of the internal mammary nodes is important. These study findings indicate the importance of basing treatment decisions on a careful discussion of the potential benefits and risks of adjuvant radiation.

Overall, radiotherapy plays a central role in the management of nodal disease in breast cancer patients. Areas of ongoing and future research include the role of radiotherapy in the setting of neoadjuvant chemotherapy, higher nodal disease burdens, as well as advances in radiotherapy techniques such as intensity modulated radiotherapy. Radiotherapy will likely continue to play an important part in the care of breast cancer patients.

Conflict of interests

None declared.

Funding

None declared.

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