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The Evolving and Multidisciplinary Considerations in Nodal Radiation in Breast Cancer

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The therapeutic management of regional lymph nodes in breast cancer has seen a remarkable change in the past 2 decades. Clinical trials have refined our knowledge regarding the biology of the disease including the prognostic significance of disease in the regional lymph nodes. The contemporary management of lymph nodes is also influenced by advances in surgical technique, radiation oncology delivery systems, and effective systemic therapy regimens. This paper describes the role of regional nodal irradiation in the context of the de-escalation of axillary surgery, improved understanding of the molecular and pathologic features, and increasing use of neoadjuvant chemotherapy.
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Introduction

Axillary lymph node dissection (ALND) was the standard of care in the management of invasive breast cancer for most of the 20th century. The accepted indications for the procedure were to confirm the pathologic status of axillary lymph nodes, to guide subsequent adjuvant therapy, and also to provide therapeutic benefit for local control. In our contemporary practice, sentinel lymphadenectomy (SLN) has supplanted ALND in node-negative and select node-positive patients. Several studies that extended the role of SLN in patients with axillary lymph node metastases have contributed to the evolving role of regional node radiation in breast cancer.

Sentinel Lymphadenctomy in Node-Negative Breast Cancer

With progress in lymphatic mapping techniques, the success of SLN in clinically node-negative patients has been extensively studied in randomized trials,[1-5] meta-analyses, and retrospective reviews. Accrued clinical experience notes high success rate with accurate pathologic information and low false-negative rates. The NSABP B32 Trial[1] compared SLN plus ALND to SLN alone. The results showed no difference with regard to overall survival (OS), disease free survival (DFS), and loco-regional recurrence free survival. Similarly, the 10-year update by Veronesi et al[3] also revealed extremely low rates of axillary recurrence with SLN alone Table 1. Data from various randomized trials have also established lower morbidity with SLN procedure compared to ALND. Table 2 summarizes the incidence of observed morbidity based on extent of axillary surgery.[1-4]

Sentinel Lymphadenectomy in Node-Positive Breast Cancer—Implications for Regional Nodal Radiation

The metastatic burden in the axillary lymph node is variable and may be reported as isolated tumor cells (≤0.2 mm and/or <200 cells), micrometastasis (>0.2 mm but ≤2 mm and/or >200 cells) and macrometastasis (>2 mm). The frequency of IHC detected occult node metastasis ranges from 10%-15 %.[1,5] Results from both studies conclude that clinically significant metastases are those detected by H&E alone.

Recent trials have extended the use of SLN to patients with a low burden of metastatic disease found on examination of the sentinel lymph nodes. Table 3 lists trials that included clinically node-negative patients who have pathologically confirmed metastases in the SLN. The IBCSG 23-01 trial[6] and AATRM trial[7] compared SLN to ALND in patients

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Table 1 Outcomes by Type of Axillary Surgery in Node-Negative Patients

Study	Axillary Surgery	No. of Patients	Axillary Recurrence	Overall Survival
B-32 8-y f/u	ALND	1975	8 (0.4%)	91.8%
Krag Lancet Oncol 11:927 2010[1]	SNB	2011	14 (0.7%)	90.3%
Veronesi 10 y f/u	ALND	259	0	89.7%
Veronesi Ann Surg 251:595 2010[3]	SNB	257	2 (0.8%)	93.5%

Abbreviation: ALND, Axillary lymph node dissection.

Table 2 Morbidity of the Axilla is Based on Extent of Surgery

	Follow-up Months	Surgery Type	No. of Patients	Edema Mild	Edema Mod+	Range of Motion	Numbness
NSABP B-32[1]	36	SNB	2008	16.7%	7-9%	13.2%	7.5%
		ALND	1975	27.6%	13%-14%	19.0%	30.5%
ALMANAC[2]	12	SNB	478	4%	1%	–	11%
		ALND	476	11%	2%	–	31%
Veronesi[3]	24	SNB	100	1%	0	0	1%
		ALND	100	25%	12%	21%	68%
SNAC[4]	12	SNB	544	–	4.2%	2.5%	–
		ALND	544	–	6.9%	4.4%	–

Abbreviation: ALND, Axillary lymph node dissection.

with nodal micrometastases. IBCSG 23-01[6] primarily included breast cancers with T-size <3 cm (92%) undergoing breast conserving surgery (91%) and whole breast radiation (WBI),and adjuvant systemic therapy was administered in 96% of patients. The observed additional risk of positive nodes in the completion ALND group was 13%. The study reported similar 5-year DFS between the SLN group and completion ALND group (P = 0.16). With regards to the effect of micrometastatic disease burden on outcomes, univariate analysis noted no significant difference in disease-free survival for patients with metastases in the SLN nodes of 1 mm or smaller in size (n = 643) and the patients with SLN metastases measuring 1·1-2·0 mm (n = 266) in size, P = 0·59.

The AATRM 048/13/2000[7] trial included a total of 247 early-stage breast cancer patients randomly assigned to completion axillary surgery or SLN alone. Patient eligibility included breast cancers with T size <3.5 cm, clinical N0 with micrometastatic disease in the SLN. Most patients underwent BCS and received radiation. At a median follow-up of 5 years, there were no differences in disease-free survival, or recurrence rate between the 2 arms (P = 0.325). Additional risk of lymph node metastases in the completion ALND group was 13%.

The ACOSOG Z0011 trial[8] also randomized patients with positive sentinel lymph nodes to SLN alone or ALND, but unlike the prior 2 trials included patients with macroscopic nodal metastases. Eligible breast cancer patients underwent breast conserving surgery, had tumors <5 cm in size (clinical T1-2N0), and had microscopic and/or macroscopic metastases in up to 2 SLN nodes. Approximately 50% of the patients enrolled had macrometastases. The 10-year update of this trial[9] reported 1 regional recurrence in the SLN alone group vs none in the ALND group between years 5 and 10. Ten-year regional recurrence did not differ significantly between the 2 groups. The 10-year survival was 86.3% and 83.6% in the SLN alone group and in the completion ALND group, respectively. The 10-year DFS was 80.2% in the SLN alone group and 78.2% in the completion ALND group (P = 0.32).

In the ACOSOG Z 11 study, the risk of additional non-sentinel positive lymph nodes was noted to be 27% in the ALND arm and yet the nodal relapse observed in the SLN arm was only 0.9%. Many factors are suggested to have contributed to the low nodal failure rate including a largely favorable study population, estrogen-receptor (ER) positive postmenopausal patients, 65% with only 1 SLN positive for metastases, and the fact that almost all (97%) received systemic therapy.

Most patients in the IBCSG 23-01 and AATRM trials and all patients in the ACOSOG Z11 trial had breast conserving surgery. Only a small percentage of patients in the IBCSG 23-01 and AATRM trials underwent mastectomy and SLN without radiation. Hence, the question of whether postmastectomy radiation (PMRT) can be safely omitted in patients with micrometastatic disease who undergo mastectomy and SLN without a completion dissection is not reliably addressed in these randomized trials. However, there are single institution experiences that do suggest no detriment in recurrence rates with mastectomy and N1mic with SLN alone.[10,11]

The 3 randomized trials[6,7,8] described above mandated WBI for patients who had breast conserving surgery. However, the details on the radiation fields used are not well described in the published results. This raises the question of whether variability in the radiation field design may have

Table 3 Axillary Management in Node-Positive Patients

	# of Patients	Surgery Type for Breast	Nodal Burden	Randomization	Additional Nodes+ve in ALND Arm	Ax Recurrence	Follow-up	Disease-Free Survival	P Value
IBCSG 23-01[6]	931	BCS + RT (80%)	Micromets	SLN vs ALND	13%	1% vs <1%	5-year	87.8% vs 84.4%	0.16
AATRM 048/13/2000[7]	247	BCS + RT	Micromets	SLN vs ALND	13%	NR	*5-year	100% vs ~98%	0.325
ACOSOG Z11[8]	856	BCS + RT	Micro/macro	SLN vs ALND	27%	0.9% vs 0.5% (5-year)	10 years	80.2% vs 78.2%	0.32

Abbreviations: ALND, axillary dissection; SLN, sentinel lymphadenctomy.
* Estimated from KM curve.

contributed to the low axillary recurrence rates. In an effort to study the radiation fields used in the ACOSOG Z11 trial, Jagsi et al[12] identified 228 patients enrolled in the study for whom complete radiation therapy (RT) data were known. Review of the RT records revealed that 18.9% of patients received regional nodal irradiation with a third field directed to the supraclavicular and axillary region. In a further subset (n = 142), high tangents (defined as a cranial tangent border ≤2 cm from humeral head) were delivered to 50% of patients. The inclusion of nodal radiation was not insignificant and should be kept in context when considering the excellent outcomes at 10 years.

A study from Memorial Sloan Kettering Cancer Center also sought to determine the relationship between nodal irradiation and outcomes in patients with a low burden of axillary disease who undergo SLN alone. Among 484 patients with disease in up to 2 LN with SLN alone, 103 were treated prone (21%), 280 (58%) were treated supine, and 101 (21%) received RT to the breast and regional nodes. The 5-year cumulative nodal recurrence rate was <1.4% in all groups and did not differ significantly by RT fields.[13] The number of patients included in this retrospective study is too small to draw any firm conclusions on the impact of RNI in this population. Taken together, these 2 studies support the need to further study the question of optimal RT target and field design in node-positive patients undergoing SLN only.

Ongoing studies are exploring the omission of axillary sampling altogether in clinically node-negative patients. The SOUND trial (NCT02167490) is enrolling patients with tumors <2 cm with a negative axilla on ultrasound to either undergo SLN or observation. The INSEMA trial (NCT02466737) has a similar randomization but it includes patients with tumors up to 5 cm in size.

Regional Nodal Radiation After Axillary Surgery in Node-Positive Breast Cancer

In the setting of mastectomy, The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported that PMRT to chest wall and regional nodes significantly reduced breast cancer mortality ($P = 0.04$) in 1772 patients having ≥4 positive lymph nodes. There was also a significant decrease in LRR ($P < 0{\cdot}00001$), and overall recurrence ($P = 0{\cdot}0003$). Among the 1314 women with one to three positive nodes, PMRT also reduced LRR ($P < 0{\cdot}00001$), overall recurrence ($P = 0{\cdot}00006$), and breast cancer mortality ($P = 0{\cdot}01$).[14]

The Canadian Trial[15] also examined the role of PMRT in node-positive premenopausal patients with randomization to CMF alone vs CMF plus loco regional irradiation. Updated results at 20 years note benefit of RNI in addition to chemotherapy with statistically significant improvements observed in event-free survival ($P = 0.009$), survival free of isolated local failure ($P = 0.002$), breast-cancer-free survival ($P = 0.004$), and OS ($P = 0.03$). The French trial[16] evaluated the role of chest wall and supraclavicular nodes with/without

internal mammary nodes (IMN) irradiation post mastectomy. The 10-year results reported an OS of 59.3% in the IMN non-irradiated group and 62.6% in the IMN-irradiated group ($P = 0.8$).

An update combining Danish 82b and 82c postmastectomy trials[17] that compared menopausal status-specific systemic therapy alone to RT+ same systemic therapy showed that with 18-year follow-up, the risk of any breast cancer event was 73% and 59% ($P < 0.001$), LRR was 49% and 14% ($P < 0.001$), and risk of any distant metastasis was 64% and 53% ($P < 0.001$) without PMRT and with PMRT, respectively. Further, a subset analysis of the Danish 82b and 82c trials[18] suggest that hormone receptor and HER2-neu status, in addition to nodal status, may guide the benefit of postoperative local regional RT.

In the setting of breast conserving surgery, the MA20 study[19] compared WBI alone to WBI with the addition of RNI that included the IMN. Patients included in this study were node-positive or high-risk node-negative breast cancer. The trial accrued 1832 patients of whom 10% were node negative and 85% had 1-3 positive nodes. With the exception of 35 patients in the WBI group and 33 patients in the WBI+RNI group all patients had ALND. Almost all patients (99%) had tumors <5 cm in size, 75% were ER positive, 90% received chemotherapy, and 76% received endocrine therapy. The results note that with the addition of RNI to WBI there is a reduction in the rate of breast-cancer recurrence. With 10-year follow-up, there was no difference in OS ($P = 0.38$) but an improvement in DFS ($P = 0.01$) and isolated loco regional DFS ($P = 0.009$) favored the RNI arm. This reduction was primarily in regional recurrence events. In a prespecified subgroup analysis, the benefits on disease outcomes were greater in patients with ER-negative cancer. ER negative patients receiving RNI had significantly better 10-year rate of OS as compared with the control group ($P = 0.05$). However, in patients receiving RNI there was increased risk of grade 2 or higher pneumonitis ($P = 0.01$) and lymphedema ($P = 0.001$) observed.

The EORTC 22,922 study[20] also investigated the benefit of RNI (including the IMN) in patients with high-risk node-negative and node-positive disease. This trial included 4004 patients who underwent mastectomy (24%) or breast conserving surgery (76%) with ALND. The 24% of patients who underwent a mastectomy were randomized to chest wall RT vs chest wall RT and RNI. Approximately 44% of patients in this study were node negative and met study eligibility because of centrally or medially located primary tumors, and 96.5% of study patients had a primary T-size <5 cm. The majority of patients in the study had N1a nodal stage, and 94% patients received chemotherapy, hormonal therapy, or both. The results noted no benefit of RNI on OS ($P = 0.06$), but there was a significant improvement in DFS ($P = 0.04$), distant disease-free survival, and breast cancer mortality ($P = 0.02$) reported.

A prospective population-based cohort study[21] from Europe investigated the benefit of including the IMN in the RNI fields among early-stage node-positive breast cancer patients. In this study population, patients with right-sided breast cancer had the IMNs included whereas patients with left-sided breast cancer received RNI without including the IMNs due to concern for cardiac toxicity. A total of 3089 patients in the study had a median follow-up time of 8.9 years. Patients with right breast cancer in whom IMNs were treated had a better outcome as compared to the patients with left breast cancer who did not receive radiation to the IMN, with 8-year OS rates of 75.9% and 72.2% ($P = 0.005$), respectively.

In summary, the trials summarized in Table 4 include patients who were high-risk node negative or lymph node positive for metastases detected by ALND/ axillary clearance. In this category of early-stage breast cancer patients, RNI has a marginal effect on OS. The MA20 study results showed a possible benefit of RNI in the triple negative subgroup but neither the MA20 nor EORTC 22,922 trials were powered to determine which subsets of patients most benefit from RNI. Thus, other disease factors such as T-stage, the burden of axillary disease, grade, lymphovascular invasion, patient age, ER status, and the receipt of chemotherapy must also be considered when deciding which patients are most likely to benefit from RNI.

There is increasing interest in the use of biomarkers to better stratify patients by risk of regional recurrence. Recent reports note a significant association between the 21-gene OncotypeDX recurrence score (RS) assay and the risk of LRR in node-negative[22] and node-positive patients[23]. The use of genomic assays to guide decision-making regarding RNI is an area of active study. The MA39 trial (NCTNCT00005957) is randomizing patients with low-risk node-positive breast cancer to RNI vs no RNI, Eligible patients will include those with 1-3 positive axillary lymph nodes and an RS <18. The primary outcome is breast cancer recurrence-free interval. This and other similar trials will help us better refine which patients most benefit from RNI.

Regional Node Radiation in Lieu of Axillary Surgery

Whether or not axillary radiation (Ax RT) can substitute for ALND in patients with positive sentinel lymph nodes has been explicitly studied in multiple trials. Table 5 is a summary of the 3 trials that evaluated Ax RT in place of ALND. The AMAROS trial[24] enrolled 4806 clinically node-negative patients with Stage T1-2 breast cancer. Patients were treated with lumpectomy and SLN or mastectomy and SLN. Among them, the SLN positive patients (n = 1425) were randomized to completion ALND or Ax RT. The patients had a median tumor size of <2 cm, 29% of them had micrometastases on pathology, and 90% of patients received systemic treatment. In the Ax RT arm 50 Gy was delivered to the level I-III axilla and the medial supraclavicular fossa. In the group of patients undergoing completion ALND the incidence of additional lymph nodes with metastases was 33%. The 5-year rate of axillary recurrence was 0.43% in the ALND arm and 1.19% in the radiation arm ($P = 0.34$). The 5-year DFS was 86·9% and 82·7% ($P = 0.18$) in the ALND group and Ax RT group,

Table 4 Regional Node Irradiation (RNI)

Study # of Patients	Breast Surgery	Node Status	RNI Study	Overall Survival	*P* Value
Canadian Trial [Ragaz JNCI 2005][15]	Mastectomy	Node positive	Mastectomy + chemotherapy vs Mast. + Chest wall/RNI + chemotherapy	37% 47%	0.03
DBCG Trial 82b and 82c[17]	Mastectomy	Node positive Or high risk node negative (T size > 5 cm high risk)	82b Mastectomy + CMF vs Mastectomy + CMF + RT	45% 54%	<0.001
			82c Mastectomy + tamoxifen vs Mastectomy + tamoxifen + RT	45% 36%	0.03
French Trial[16] n = 1334	Mastectomy	Node positive Or node-negative medial central ca	Chest wall + SCV vs Chest wall + SCV/IMN	59.3% 62.6%	0.8
MA 20 n = 1832[19]	BCS	Node positive Or node negative high risk	WBI + boost vs WBI + boost + SCV/IMN	81.8% 82.8%	0.38
EORTC 22922 n = 4004[20]	BCS (75%) Mastect (25%)	Node positive Or node-negative medial central ca	WBI + boost or chest wall vs WBI + boost + SCV/IMN or chest wall + SCV/IMN	80.7% 82.3%	0.06
DBCG-IMN[21] n = 3089	BCS mastectomy	Node positive	WBI/CW + boost + SCV (left breast) vs WBI/CW + boost + SCV/IMN (right breast)	72.2% 75.9%	0.005

Abbreviation: IMN, internal mammary nodes.

respectively. The 5-year OS was 93·3% and 92·5% ($P = 0.34$) in the ALND group and Ax RT group, respectively. Patients treated with ALND were at significantly higher risk of lymphedema compared to Ax RT at every measured follow-up time point (23.2% vs 10.8%; $P < 0.0001$).

The Optimal Treatment of the Axilla—Surgery or Radiotherapy trial[25] also investigated the role of Ax RT in lieu of completion ALND. This study randomized patients to completion ALND or RNI. Patients with T-size <3 cm and evidence of SLN metastasis were eligible. The 474 evaluable patients had a mean follow-up of 97 months; the rate of axillary recurrence was 2% in the ALND group and 1.7% in the RT arm ($P = 1.00$) with no differences in DFS or OS.

The Institut Curie trial[26] enrolled 658 clinically node-negative patients with T-size <3 cm. All patients underwent BCS and received whole breast RT. The randomization was again between ALND and Ax RT; however, unlike the AMAROS and Optimal Treatment of the Axilla—Surgery or Radiotherapy trial, patients in the radiation group did not have a SLN and were not proven to have pathologically positive nodal disease. Among the patients randomized to the ALND the incidence of lymph node metastases noted was 21%. At 10 and 15 years, however, survival rates were identical in both groups (73.8% vs 75.5% at 15 years). Axillary recurrence were less frequent in the ALND group at 15 years ($P = 0.04$). There was no difference in rates of recurrence in the breast or supraclavicular and distant metastases between the 2 groups.

In summary, for appropriately selected patients with nodal metastases Ax RT in lieu of ALND provides excellent outcomes in patients with early stage breast cancer with significantly less morbidity.

Regional Node Radiation After Neoadjuvant (NAC) Chemotherapy and Surgery

The optimal management of the regional lymph nodes following NAC is an evolving area of study, specifically regarding the feasibility of SLN after NAC, the timing of axillary surgery in relation to NAC, and the role of regional nodal irradiation in relation to clinical and pathologic stage of disease.

The timing of SLN is variable and may be performed prior to NAC or after completion of NAC at the time of definitive breast surgery. SLN after NAC in patients with clinically-node-negative disease at presentation provides accurate pathologic information and low false-negative rates.[27,28] Following NAC in clinically node-positive disease patients, studies including the prospective SENTINA study[29] and ACOSOG Z1071[30] have reported on the accuracy of pathologic status and false-negative rate (FNR). Taken together, these studies demonstrated a FNR > 10% but a reduction in the FNR to an acceptable level below 10% with the removal of 3 or more SLN and the use of dual tracer. Additional techniques employed to optimize SLN after NAC include

Table 5 Regional Node Irradiation in Lieu of Axillary Surgery

Study	No. of Patients	Randomization	Positive Nodes in ALND Arm	Follow-up	Axillary Recurrence	Disease-Free Survival	Clinical Lymphedema
AMAROS Trial[24]	1425	Axillary dissection vs axillary radiation	33%	5 years	0.43% vs 1.19%	86.9% vs 82.7%	23% vs 11%
OTOASAR Trial[25]	474	Axillary dissection vs axillary radiation	38.5%	97 months mean	2% vs 1.7%	72.1% vs 77.4%	15.3% vs 4.7% (1 year)
Institute Curie Trial[26]	658	Axillary dissection vs axillary radiation	21%	15 years	1% vs 3%	64.3% vs 65.5%	Not reported

Abbreviation: ALND, axillary lymph node dissection.

marking the abnormal axillary lymph node prior to NAC with a clip and/or the observation of pathologic treatment effect in the nodes removed with SLN to indicate prior involvement with disease. An advantage of the earlier timing is accurate axillary staging prior to any down staging by chemotherapy which allows identification of accurate lymph node status at presentation. This approach however entails an additional surgical procedure and such a practice requires having an evidence base for improved outcomes.

RNI is generally indicated in patients who remain pathologically node positive after NAC. Results of NASBP B-18 and NSABP B-27 show low rates of loco-regional recurrence in clinically node-negative patients who were pathologically node positive; however, the number of patients in these subset analyses are small with rates of regional recurrence of 7.5%-8.7% among the lumpectomy patients (n = 276) and 4.8%-6.4% among the mastectomy patients (n = 271).[31] The ongoing ALLIANCE A011202 trial (NCT01901094) is investigating the need for ALND among patients who remain ypN+ after NAC. In this trial, patients are randomized to ALND and RNI vs RNI alone among patients who have a positive SLN after NAC.

For those patients who become pathologically node negative, the role of RNI is more controversial. Among lumpectomy patients, rates of regional recurrence ranged from 0% to 1.8% in patients with a breast pathologic complete response (pCR) (n = 84) and 0%-2.4% in patients without a breast pCR (n = 142). Among mastectomy patients, there were no regional recurrences in patients with tumors <5 cm who had a breast pCR (n = 21) or in patients with tumors >5 cm regardless of breast pCR (n = 94). There was an 8.1% rate of regional recurrence in mastectomy patients with tumors <5 cm with no breast pCR (n = 37).[31] The numbers from these subset analyses are small and thus practice-defining conclusions based on this data cannot be made. Toward this end, the ongoing NSAPB B-51 trial (NCT01872975) is exploring whether clinically node-positive patients who achieve a pCR in the nodes require RNI. Lumpectomy patients are randomized to whole breast RT vs RT to the breast and nodes. Mastectomy patients are randomized to no PMRT vs RT to the chest wall and regional nodes. In order to meet eligibility criteria, patients must have T1-3N1 breast cancer with pathologically proven node-positive disease prior to chemotherapy. SLN is allowed provided that at least 2 axillary nodes are removed. Patients with ypN0i+ disease are eligible. As of April 2018, the trial has accrued 926 patients out of a target of 1636 patients.

While we await the results of NSABP B-51 (NCT01872975) the management of patients who are clinically node positive prior to NAC, and who become ypN0 remains controversial. Other factors, such as prechemotherapy and postchemotherapy T-stage, response in the breast, disease biology including ER, PR, and HER2 status, type of chemotherapy received, presence of lymphovascular invasion or other high-risk features, patient age, and pathologic nodal burden are considered and may influence recommendations. Generally patients with prechemotherapy node-positive disease in the setting of a ypN0 status for whom RNI may not be recommended would have favorable features (eg,

Table 6 Trials Which Aim to Address Management of Regional Nodes

	Randomization	Eligibility
Omission of axillary surgery		
SOUND trial (NCT02167490)	SLN vs No axillary surgery	cN0 T < 2.0 cm
INSEMA trial (NCT02466737)	SLN vs No axillary surgery	cN0 T < 5.0 cm
POSNOC (ISRCTN54765244)	Systemic therapy vs systemic therapy + ALND or axilla XRT	T1-T2, 1-2 SLN macromets
SENOMAC trial (NCT 02240472)	Completion axillary dissection vs No further surgery	T1-T3 primary and with macro metastasis in not more than 2 lymph nodes
After neoadjuvant chemotherapy		
SN FNAC (NCT00909441)	SLN vs ALND	IIA, IIB, IIIA (T1-3 and N1-2) breast cancer that present with US guided FNA positive axillary nodes
NSABP 51 (NCT01872975)	RNI vs No RNI	cT1-T3N1M0 postneoadjuvant SLN negative for metastases
ALLIANCE A011202 (NCT01901094)	ALND + nodal XRT (excluding dissected axilla) vs Nodal XRT	c T1-3N1M0 postneoadjuvant SLN positive for metastases
Regional nodal irradiation		
TAILOR RT low-risk node positive MA 39 (NCTNCT00005957)	RNI vs No RNI (lump. + WBI or mastectomy − RT)	1-3 positive nodes and oncotype DX score <18

Abbreviations: ALND, axillary dissection; RNI, regional nodal irradiation; SLN, sentinel lymphadenctomy; WBI, whole breast radiation.

postmenopausal with a cT1, strongly ER positive, low-intermediate grade with no high-risk features). While patients with isolated tumor cells are considered to have a pCR in the nodes, clinically node-positive patients who have pathologic micrometastases (ypN1mi) are generally grouped with the pathologically node-positive disease and are indeed eligible for enrollment on ALLIANCE A011202 (NCT01901094).

Radiation Field and Technique

The RNI target volume may include some or all of the regional nodal basins that is, axilla, supraclavicular nodes, and IMN chain. In several trials evaluating the role of RNI, it is noted that the nodal basins included in the RNI target varied. Both the MA20 and EORTC trials specified inclusion of the IMNs whereas the AMAROS trial did not include the IMNs. Though no randomized trials have explicitly compared RNI with and without inclusion of the IMN, the DBCG-IMN study discussed previously showed a benefit of inclusion of the IMNs.

With regard to technique, the contemporary radiation delivery aims to reduce exposure to organs at risk. Patients are routinely treated using 3-dimensional treatment planning techniques, either field-in-field forward plan or inverse plan intensity modulated RT. The use of voluntary or gated deep-inspiration breath hold has become more widely utilized to further reduce cardiac and pulmonary dose. This technique has enabled inclusion of the IMN while still limiting the dose to the heart and lungs to acceptable low exposure thresholds.

Most of the experience accrued in clinical trials addressing RNI has used 1.8 Gy/fraction to 2 Gy/fraction and total dose delivered is in the range of 45-50 Gy. More recent data have established the efficacy of hypo-fractionation in breast cancer. However, this dose fractionation is generally not used for treating RNI, and is an area of ongoing study.

Summary and Future Directions

In recent years, there have been major advances in the multidisciplinary management of regional lymph nodes in breast cancer. These include the use of SLN as opposed to ALND or the use of Ax RT in lieu of ALND for patients with a low burden of axillary disease. Recent data have also supported the use of RNI in patients with a low axillary burden or even high-risk node-negative disease who have undergone breast

conservation or PMRT. Following NAC, the use of SLN is gaining acceptance and the role of radiation in the setting of a pCR in the nodes is an area of active research. Table 6 summarizes other key ongoing clinical trials aimed at optimizing the management of regional lymph nodes. The improved outcomes with RNI reported in clinical trials are gaining wide applicability in no small part due to the increasing sophistication of radiation technique with 3D-based planning. More recently, the use of deep-inspiration breath hold has further advanced the ability to deliver RNI while sparing the heart and lungs. Which patients with a low burden of axillary disease or with high-risk node-negative disease are most likely to benefit from RNI is still an area of ongoing research, and current studies such as MA39 (NCTNCT00005957) incorporating biomarkers will help to better risk-stratify patients. The ultimate aim is to assess each individual patient's risk for recurrence thereby individualizing multidisciplinary management, and furthering improvements in overall clinical outcomes of breast cancer patients.

References

1. Krag DN, Anderson SJ, Julian TB, et al: Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: Overall survival findings from the NSABP B-32 randomized phase 3 trial. Lancet Oncol 11:927-933, 2010
2. Mansel RE, Fallow L, Kissin M, et al: Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: The ALMANAC trial. JNCI 98:599-609, 2006
3. Veronesi U, Viale G, Paganelli G, et al: Sentinel lymph node biopsy in breast cancer: Ten-year results of a randomized controlled study. Ann Surg 251:595-600, 2010
4. Sentinel lymph node biopsy versus axillary clearance in operable breast cancer: The RACS SNAC trial, a multicenter randomized trial of the Royal Australian College of Surgeons (RACS) Section of Breast Surgery, in collaboration with the National Health and Medical Research Council Clinical Trials Center. Ann Surg Oncol 11(3 Suppl). 216S-21S
5. Cote R, Giuliano AE, Hawes D, et al: ACOSOG Z0010: A multicenter prognostic study of sentinel node (SN) and bone marrow (BM) micrometastases in women with clinical T1/T2 N0 M0 breast cancer. JCO 28
6. Galimberti V, Cole BF, Zurrida S, et al: Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): A phase 3 randomised controlled trial. Lancet Oncol 14:297-305, 2013
7. Solá M, Alberro JA, Fraile M, et al: Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastasis: final results from the multicenter clinical trial AATRM 048/13/2000. Ann Surg Oncol 20:120-127, 2013
8. Giuliano AE, Hunt KK, Ballman KV, et al: Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: A randomized clinical trial. JAMA 305:569-575, 2011
9. Giuliano AE, Ballman KV, McCall L, et al: Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis. JAMA 318:918-926, 2017
10. Mamtani A, Patil S, Stempel M, et al: Axillary micrometastases and isolated tumor cells are not an indication for post-mastectomy radiotherapy in stage 1 and 2 breast cancer. Ann Surg Oncol 2017: 1-7
11. FitzSullivan E, Bassett RL, Kuerer HM, et al: Outcomes of sentinel lymph node-positive breast cancer patients treated with mastectomy without axillary therapy. Ann Surg Oncol 24:652-659, 2017
12. Jagsi R, Chadha M, Moni J, et al: Radiation field design in the ACOSOG Z0011 (Alliance) trial. JCO 32:3600-3606, 2014
13. Morrow M, Van Zee KJ, Patil S, et al: Axillary dissection and nodal irradiation can be avoided for most node-positive Z0011-eligible breast cancers: A prospective validation study of 793 patients. Ann Surg 266:457-462, 2017
14. EBCTCGMcGale P, Taylor C, et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: Meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 383:2127-2135, 2014
15. Ragaz J, Olivotto IA, Spinelli JJ, et al: Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst 97:116-126, 2005
16. Hennequin C, Bossard N, Servagi-Vernat S, et al: Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. Int J Radiat Oncol Biol Phys 86:860-866, 2013
17. Nielsen HM, Overgaard M, Grau C, et al: Study of failure pattern among high-risk breast cancer patients with or without post mastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the danish breast cancer cooperative group DBCG 82 b and c randomized studies. J Clin Oncol 24:2268-2275, 2006
18. Kyndi M, Sorensen FB, Knudsen H, et al: Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: The Danish Breast Cancer Cooperative Group. J Clin Oncol 26:1419-1426, 2008
19. Whelan TJ, Olivotto IA, Parulekar WR, et al: Regional nodal irradiation in early-stage breast cancer. N Engl J Med 373:307-316, 2015
20. Poortmans PM, Collette S, Kirkove C, et al: Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med 373:317-327, 2015
21. Thorsen LB, Offersen BV, Danù H, et al: DBCG-IMN: A population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. J Clin Oncol 34:314-320, 2016
22. Mamounas EP, Tang G, Fisher B, et al: Association between the 21-gene recurrence score assay and risk of locogreional recurrence in node-negative, estrogen receptor-positive breast cancer: Results from NSABP B-14 and NSABP B-20. J Clin Oncol 28:1677-1683, 2010
23. Woodward WA, Barlow WE, Jagsi R, et al: The 21-gene recurrence score and locoregional recurrence rates in patients with node-positive breast cancer treated on SWOG S8814. Int J Radiat Oncol Biol Phys 96:S146, 2016
24. Donker M, van Tienhoven G, Straver ME, et al: Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): A randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 15:1303-1310, 2014
25. Savolt A, Peley G, Polgar C. Eight-year follow result of the OTOASOR trial: the optimal treatment of the axilla- surgery or radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III non-inferiority trial. EJSO 43:672-679, 2017
26. Louis-Sylvestre C, Clough K, Asselain B, et al: Axillary treatment in conservative management of operable breast cancer: dissection or radiotherapy? Results of a randomized study with 15 years of follow-up. J Clin Oncol 22:97-101, 2004
27. Classe JM, Bordes V, Campion L, et al: Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: results of Ganglion Sentinelle et Chimiotherapie Neoadjuvante, a French prospective multicentric study. J Clin Oncol 27:726-732, 2009
28. Hunt KK, Yi M, Mittendorf EA, et al: Sentinel lymph node surgery after neoadjuvant chemotherapy is accurate and reduces the need for axillary dissection in breast cancer patients. Ann Surg 250:558-566, 2009
29. Kuehn T, Bauerfeind I, Fehm T, et al: Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): A prospective, multicentre cohort study. Lancet Oncol 14:609-618, 2013
30. Boughey JC, Suman VJ, Mittendorf EA, et al: Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: The ACOSOG Z1071 (Alliance) clinical trial. JAMA 310:1455-1461, 2013
31. Mamounas EP, Anderson SJ, Dignam JJ, et al: Predictors of locoregional recurrence after neoadjuvant chemotherapy: Results from combined analysis of national surgical adjuvant breast and bowel project B-18 and B-27. J Clin Oncol 30:3960-3966, 2012