Curr Surg Rep (2015) 3:19
DOI 10.1007/s40137-015-0095-0

The Role of Axillary Node Dissection in the Post Z0011 Era

Andrea V. Barrio[1] · **Monica Morrow**[1,2]

Published online: 21 May 2015

Abstract Axillary lymph node dissection (ALND), once considered standard of care for all patients with invasive breast cancer, is now obsolete in patients with histologically negative sentinel lymph nodes (SLNs). Alternatives to ALND in patients with histologically positive SLNs are available after the ACOSOG Z0011 and AMAROS trials demonstrated no difference in locoregional recurrence, disease-free survival, or overall survival between SLN biopsy alone (ACOSOG Z0011) or with axillary radiotherapy (AMAROS) and ALND in women with clinical T1-2 invasive breast cancer and 1–2 positive SLNs treated with multimodality therapy, offering the opportunity to reduce the morbidity of treatment. In contrast, the MA.20 and EORTC 22922-10925 studies suggest that similar patient populations benefit from ALND and comprehensive nodal irradiation. Here, we will discuss the contemporary surgical management of clinically node-negative breast cancer patients with metastases in the SLNs.

Keywords Sentinel lymph node metastasis · Axillary lymph node dissection · Regional nodal irradiation

Introduction

In breast cancer patients with pathologically negative axillary lymph nodes, sentinel lymph node (SLN) biopsy has been shown to be equivalent to axillary lymph node dissection (ALND) in terms of overall survival (OS), disease-free survival (DFS), and regional lymph node recurrence [1], but decreases the morbidity of surgery. Several factors have stimulated interest in decreasing the use of ALND in patients with axillary node metastases. These include the observation that non-sentinel node metastases are present in only 48 % [95 % confidence interval (CI) 35–62 %] of SLN-positive patients who undergo ALND [2], and the recognition that effective adjuvant therapy, in addition to reducing distant recurrence, is an important contributor to local control [3]. Additionally, decisions regarding systemic therapy are increasingly based upon biologic characteristics of the primary tumor rather than the number of axillary nodes with metastases [4]. As a result, the role of axillary surgery in pathologically node-positive patients has increasingly been questioned, and randomized trials have offered alternatives to ALND for SLN node-positive patients who will be treated with multimodality therapy [5••, 6•, 7••]. At the same time, other studies have suggested a benefit for axillary dissection and comprehensive node field irradiation [8••, 9••] in similar patients, resulting in considerable confusion regarding the optimal approach to the sentinel node-positive patient in 2015. Here, we will review the contemporary surgical management of breast cancer patients with micrometastases and macrometastases in the axillary nodes.

This article is part of the Topical Collection on *Breast Cancer Surgery*.

✉ Andrea V. Barrio
barrioa@mskcc.org

Monica Morrow
morrowm@mskcc.org

[1] Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 300 E. 66th St., New York, NY 10065, USA

[2] Weill Medical College of Cornell University, New York, NY 10065, USA

Micrometastatic Disease

Enhanced pathologic evaluation of the SLN with serial sectioning and immunohistochemistry (IHC) results in increased detection of micrometastases as compared to ALND, with Giuliano et al. reporting a five-fold difference in detection [10]. In a population-based Danish study of 24,051 patients comparing the detection of micrometastases in the pre- and post-SLN biopsy era, the detection of micrometastases increased from 5.1 % of cases to 9.0 % [odds ratio (OR) 1.85], although the detection rate for macrometastases did not change [11]. Completion ALND in patients with l SLN micrometastasis results in detection of non-sentinel node metastasis in up to 20 % of patients [12, 13], providing the rationale for the procedure.

However, a review of the National Cancer Database indicated that many surgeons were not performing ALND for micrometastatic disease in the SLNs. Of 2203 patients with micrometastatic disease treated between 1998 and 2000, 530 (24 %) had SLN biopsy alone. At a median follow-up of 63 months, there were no differences in axillary recurrence rates (0.6 vs 0.2 %, $p = 0.06$) or relative survival (98.5 vs 98.2 %, $p = 0.72$) for patients having SLN biopsy alone versus completion ALND [14]. Although this study was limited by its retrospective, non-randomized design, it offered evidence that omission of ALND in patients with micrometastatic disease did not result in worse outcomes.

International Breast Cancer Study Group (IBCSG) 23-01 was a multicenter, randomized, non-inferiority trial comparing axillary dissection ($n = 464$) with no axillary dissection ($n = 467$) in early-stage breast cancer patients with SLN micrometastases. Although most patients were treated with breast-conserving surgery, 9 % of patients in each group underwent mastectomy. Nearly all patients received systemic therapy (95 % ALND vs 97 % no ALND), with the majority receiving hormonal therapy alone. Non-sentinel node metastases were present in 13 % of ALND patients, but at a median follow-up of 5 years, regional recurrences were seen in only 1 % of patients treated with SLN biopsy alone compared to <1 % in the ALND group. No differences in DFS or OS were observed, and ALND was not a predictor of DFS on multivariable analysis ($p = 0.13$) [6•].

The effect of micrometastatic disease on breast cancer prognosis has also been studied in two large prospective trials. The American College of Surgeons Oncology Group (ACOSOG) Z0010 study was a prospective multicenter trial initiated in 1999 to evaluate the effect of occult disease in SLNs and bone marrow in women with T1-2 breast cancer with a clinically negative axilla and SLNs which were histologically negative by hematoxylin and eosin (H&E) staining. Occult metastases were identified with IHC in 349 (10.5 %) of 3326 specimens evaluated. Five-year rates of OS did not differ significantly between patients with IHC positive and IHC negative SLNs (95.1 vs 95.7 %, respectively; $p = 0.64$), and IHC-positive SLNs were not associated with a worse survival on multivariable analysis [adjusted hazard ratio (HR) 0.88; $p = 0.70$) [15]. The National Surgical Adjuvant Bowel and Breast Project (NSABP) protocol B-32 trial similarly evaluated the significance of SLN occult metastases on prognosis in 3887 node-negative breast cancer patients participating in a study randomizing patients with negative SLNs to ALND or no further surgery. Occult metastases were detected in 15.9 % of patients; at 5 years, an absolute difference in survival of 1.2 % was present, favoring those without metastases ($p = 0.03$) [16]. However, after 10 years of follow-up, the difference in survival was no longer statistically significant ($p = 0.06$). More importantly, in patients *with* occult metastasis, there was no difference in OS or DFS between the SLN biopsy-only group and the ALND group, suggesting that tumor biology, not extent of local surgery, has the largest impact on prognosis [17]. In aggregate, these studies indicate that ALND is not necessary for patients with SLN micrometastases treated with breast-conserving therapy. This finding, coupled with the observation that the presence of SLN micrometastases does not significantly alter DFS or OS and thus is not an indication for systemic therapy in the absence of other indications, calls into question the routine practice of serial sectioning and IHC of sentinel nodes to facilitate detection of small tumor deposits.

Macrometastatic Disease

Patients with a clinically negative axilla and macrometastatic disease in the SLN are a group of patients for whom ALND has long been considered the standard of care. The landmark NSABP B04 trial addressed the question of whether the removal of the axillary lymph nodes in clinically node-negative patients contributed to survival. Clinically node-negative women were randomized to radical mastectomy versus total mastectomy and nodal radiotherapy (RT) versus total mastectomy alone. At 25 years of follow-up, there were no survival differences among groups. Although 40 % of patients randomized to radical mastectomy had axillary nodal metastases, only 18 % of patients treated with total mastectomy alone required ALND, making the important point that even in patients receiving no RT and no systemic therapy, the majority of nodal metastases do not become evident as axillary first failures [18]. Although NSABP B04 did not result in the demise of ALND due to the prognostic sig-

nificance of nodal status and its use in the 1980s to determine the need for chemotherapy, it supported the conduct of newer trials re-examining the need for ALND in patients treated in the modern era of systemic therapy.

Alternatives to ALND: SLN Biopsy Alone

ACOSOG Z0011

ACOSOG Z0011 was a prospective, randomized, non-inferiority trial comparing ALND to no ALND in women with clinical T1-2 invasive breast cancer and 1–2 positive SLNs. Accrual began in 1999, and the study closed in 2004 before reaching the targeted enrollment of 1900 patients due to slow accrual and a lower-than-anticipated event rate. Patients were eligible if they had a tumor $\leq$5 cm, a clinically negative axilla as determined by physical examination, and <3 SLNs with metastatic breast cancer identified by H&E staining. All patients had breast-conserving surgery with whole-breast RT. Patients were ineligible if they had matted nodes or gross extranodal extension, or if they received neoadjuvant systemic therapy. No criteria regarding microscopic extranodal extension were specified for the study. Overall, 891 patients were enrolled; following exclusions, 420 patients were randomized to ALND and 436 to SLN only [7••].

Patient characteristics are summarized in Table 1 [5••, 7••, 8••, 9••]. Approximately 37 % of ALND patients and 45 % of SLN-only patients had micrometastatic disease only in the sentinel node [19]. The majority of women (89 %) received whole-breast RT, and systemic therapy was delivered to 96 % of ALND patients and 97 % of SLN-only patients. In the ALND group, 27.3 % of patients had additional positive non-sentinel nodes removed by ALND, suggesting that a similar burden of disease was present in the SLN-only group. At a median follow-up of 6.3 years, regional recurrence was seen in 0.5 % of ALND patients compared to 0.9 % of SLN-only patients ($p = 0.45$), and no differences in DFS or OS were observed between groups, with excellent 5-year OS rates of 91.8 % in the ALND group versus 92.5 % in the SLN-only group ($p = 0.25$) [7••]. As anticipated, surgical morbidity was significantly decreased in the SLN-only group, with fewer wound infections ($p = 0.016$), paresthesias ($p < 0.001$), and subjective lymphedema ($p < 0.001$) reported [20].

The results of ACOSOG Z0011 were practice changing, as the study emphasized that effective systemic therapy and RT coupled with less-extensive surgery provided equivalent local control and survival to aggressive axillary surgery in clinically node-negative patients with metastases in 1 or 2 SLNs. Despite compelling results, omission of ALND in patients meeting ACOSOG Z0011 criteria has not been uniform. Critics of the trial stated the women treated on study were a highly select group of postmenopausal women with small, estrogen receptor (ER) positive tumors, and that the results were not applicable to a heterogeneous breast cancer population. Beginning in 2010, the ACOSOG Z0011 eligibility criteria were applied to an unselected, consecutive cohort of breast cancer patients with histologically positive SLNs at Memorial Sloan

Table 1 Comparison of patient characteristics across randomized trials of macrometastatic axillary disease management

	ACOSOG Z0011 [7••]	AMAROS [5••]	MA.20 [8••]	EORTC [9••]
No. of patients	856	1425	1832	3877
Age, median (years)	55	55.5	53	54
T1–T2 (%)	99	99.6	99	96
ER positive (%)	83	Not stated	75	78
Nodal metastasis (%)				
None	4	0	10	44
1–3	79	99	85	43
Breast surgery	BCS	BCS + M	BCS	BCS + M
Randomization	SLN vs ALND	SLN + Axillary RT vs ALND	WBI vs WBI + RNI	WBI vs WBI + RNI
Systemic therapy (%)	97	90	100	84
RT				
Breast tangents	Yes	Yes	Yes	Yes
Axilla	No	Yes	Apex	No
Other node fields	No	SC	SC, IM	SC, IM

BCS breast-conserving surgery, *M* mastectomy, *SLN* sentinel lymph node, *RT* radiotherapy, *ALND* axillary lymph node dissection, *ER* estrogen receptor, *SC* supraclavicular, *IM* internal mammary, *RNI* regional nodal irradiation

Kettering Cancer Center (MSKCC). Of 2157 invasive breast cancer patients undergoing breast-conserving surgery, 380 (18 %) had a positive SLN; 93 were excluded due to non H&E metastasis, neoadjuvant therapy, and conversion to mastectomy, resulting in 287 eligible patients. ALND was performed for metastases in 3 ≥ SLNs or gross extracapsular extension (ECE). Using these criteria, only 45 patients (16 %) required ALND. The MSKCC-unselected patient population was remarkably similar to the Z0011 study cohort [21•], indicating that the Z0011 population is representative of most patients undergoing breast-conserving surgery for T1-2 breast cancer. Of note, more patients in the MSKCC cohort had SLN macrometastasis (73 %) compared to the Z0011 cohort (55 %). Patient age, and ER, progesterone receptor (PR), and HER2 status were not predictive of the need for axillary dissection. At publication, with a median follow-up of 13 months, no axillary recurrences were noted in the SLN-only group [21•]. Median follow-up is now 33 months, and no isolated regional recurrences have been observed (Morrow M, unpublished data).

Chung et al. applied the ACOSOG Z0011 criteria to high-risk, node-positive breast cancer patients undergoing breast conservation [22•] to determine how many were potentially suitable for elimination of ALND by retrospectively identifying women diagnosed between 2000 and 2011 with HER2/neu-positive disease, triple-negative breast cancer, or age <50 years. These groups were selected because they are considered by some to be ineligible for management using ACOSOG Z0011 criteria due to poor prognosis. Overall, 186 high-risk breast cancer patients with at least 1 positive node were identified: 57 (31 %) were HER2 positive, 55 (30 %) were triple negative, and 74 (40 %) were <50 years of age. Of these186 patients, 125 (67 %) would have been eligible for the ACOSOG Z0011 trial. The predominant reason for ineligibility was a clinically positive axilla, which accounted for 57 % of the ineligible patients. After excluding patients with clinically positive nodes, 84 % of the cohort would have been considered eligible to omit ALND, similar to the percentage of eligible patients in the unselected prospective MSKCC cohort [21•]. Of the eligible patients who had an ALND ($n = 105$), 38 % had involvement of non-sentinel nodes, and the median number of positive non-sentinel nodes was only 1 (range 1–3) [22•]. These findings demonstrate that patients with "high-risk" tumor features are not more likely to have a higher burden of residual axillary nodal disease compared to "low-risk" patients, confirming that ACOSOG Z0011 criteria can be applied to a heterogeneous breast cancer population with similar results.

As noted previously, of 605 ACOSOG Z0011 patients with case report forms regarding radiation administration, 89 % received whole-breast irradiation. Although the protocol specified that standard tangential fields should be used and that regional nodal irradiation was not allowed, details regarding radiation field design were not specified or captured, causing many to speculate that the excellent local control rates in the SLN-only arm were the result of treatment with high tangents to axillary levels I and II. Jagsi et al. reviewed the RT treatment records of 228 patients (29 % of enrolled patients); 104 in the ALND arm and 124 in the SLN-only arm. Of these patients, 185 (81 %) received tangent-only treatment. There was no difference in the use of high tangents between the ALND group (50 %) and SLN-only group (52.6 %), and treatment arm was not associated with use of high tangents on univariable or multivariable analysis. Three-field nodal irradiation was delivered to 43 (18.9 %) patients; 22 in the ALND group and 21 in the SLN-only group [23•]. While this study emphasizes the need to standardize RT field design in local therapy studies, the lack of a significant difference in treatment regimens between study arms indicates that the favorable outcome after SLN biopsy alone was not due to the selective use of more extensive RT.

Alternatives to ALND: SLN Biopsy and Regional Nodal Irradiation

AMAROS

After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) was a randomized prospective study designed to evaluate whether axillary RT provided similar axillary local control to ALND with less morbidity in patients with a positive SLN [5••]. From 2001 to 2010, 4806 eligible patients with T1-2 breast cancer and a clinically negative axilla were enrolled in this multicenter, non-inferiority study. 1425 patients had SLN metastases; 744 were randomized to the ALND arm, and 681 were randomized to the axillary RT arm. Axillary RT was delivered to all three levels of the axilla and the medial part of the supraclavicular fossa at a prescribed dose of 50 Gy delivered in 25 fractions. The 5-year rate of axillary recurrence in the ALND group was 0.43 % compared to 1.2 % in the axillary RT group. As the event rate was low, the study was underpowered to test non-inferiority; nevertheless, no significant difference in treatment arms was observed. Lymphedema rates, as measured by circumferential arm measurements, were significantly lower in the axillary RT group (6 %) compared to the ALND groups (13 %) at 5 years ($p = 0.0009$) [5••]. These findings would suggest that axillary RT is an appropriate alternative to ALND in patients with a positive SLN; however, the clinical

Table 2 Outcomes across randomized trials of macrometastatic axillary disease management

Trial	Nodal recurrence		*p* value	OS		*p* value
	ALND (%)	Experimental group (%)		ALND (%)	Experimental group (%)	
ACOSOG Z0011 (5 years) [7••]	0.5	0.9	0.45	91.8	92.5	0.25
AMAROS (5 years) [5••]	0.43	1.2	NA*	93.3	92.5	0.34
MA.20 (10 years) [8••]	2.6	0.7	0.009[x]	81.8	82.8	0.38
EORTC 22922 (10 years) [9••]	4.2	2.7	Not stated	80.7	82.3	0.06

ALND axillary lymph node dissection, *OS* overall survival

* Underpowered to test non-inferiority due to low event rate

[x] *p* value for all locoregional recurrences, not just regional

characteristics of the AMAROS cohort are remarkably similar to the ACOSOG Z0011 cohort [7••], with 80 % of AMAROS patients having a tumor <2 cm, 90 % patients receiving any systemic therapy, and 95 % of patients having only 1–2 positive sentinel nodes (Table 1). Patients in ACOSOG Z0011 treated with SLN biopsy-only demonstrated similar rates of axillary local control [7••] as the AMAROS patients receiving axillary RT (Table 2) [5••, 7••, 8••, 9••]. Thus, while AMAROS indicates that SLN biopsy and nodal RT is an alternative to ALND, it does not demonstrate that RT is necessary in all patients. Mastectomy was performed in 18 % of AMAROS patients [5••]; in this subset of patients with a positive SLN in whom ALND would be recommended, axillary RT may be an acceptable treatment option if the finding of a positive SLN is sufficient indication for postmastectomy RT. However, given the ongoing controversy over the use of postmastectomy RT in patients with T1 and T2 tumors and involvement of 1–3 axillary nodes, knowledge of the extent of lymph node involvement remains important for many physicians.

Axillary Dissection and Regional Nodal Irradiation

MA.20 and EORTC 22922/10925

In contrast to the ACOSOG Z0011 and the AMAROS trials, which suggest that the use of systemic therapy and RT allows a reduction in the extent of axillary surgery, the MA.20 and the European Organisation for Research and Treatment of Cancer (EORTC) 22922/10925 studies suggest that similar patient populations benefit from ALND and comprehensive nodal RT [8••, 9••]. The MA.20 trial randomized patients with positive axillary nodes, detected by ALND or SLN biopsy, or node-negative patients considered to be high risk based on tumor size ≥5 cm, or ≥2 cm with <10 nodes removed and grade 3 histology, or lymphovascular invasion, or ER negativity to whole-breast RT versus whole-breast RT plus RT to the supraclavicular, axillary, and internal mammary nodes in the upper 3 interspaces to a dose of 50 Gy in 25 fractions. All patients received adjuvant systemic therapy. Of the 1832 enrolled patients, 10 % were node negative. Other patient characteristics are summarized in Table 1. After a median follow-up of 9.5 years, 10-year DFS in the nodal RT group was 82 versus 77 % in the breast RT-only group (HR 0.76; 95 % CI 0.61–0.94; $p = 0.01$). The rates of isolated local DFS were 95.2 % with nodal RT versus 92.2 % without (HR 0.59; 95 % CI 0.39–0.88; $p = 0.009$). Although distant DFS was also improved in the nodal RT group, no significant improvement in OS was noted, with a 1 % absolute improvement in the nodal RT group (HR 0.91; 95 % CI 0.72–1.13; $p = 0.38$) (Table 2) [8••]. The EORTC trial evaluated the role of medial supraclavicular and internal mammary node irradiation in 3877 patients undergoing mastectomy or breast-conserving surgery who had node-positive breast cancer or medially located node-negative tumors. Patient age and tumor characteristics were similar to those of patients involved in ACOSOG Z0011, AMAROS, and MA.20 (Table 1), but 44 % of enrolled patients were node negative. Of the remainder, 43 % had 1–3 nodes containing metastases. As in MA.20, 10-year DFS favored the nodal RT group (72.1 vs 69.1 %, $p = 0.04$), but the absolute difference in OS at 10 years was 1.6 % and did not reach statistical significance ($p = 0.06$), even in this large study (Table 2). While severe radiation toxicities were uncommon, the use of nodal RT resulted in significant increases in both acute and long-term sequelae of RT [9••]. In MA.20, the incidence of lymphedema was increased from 4.5 to 8.4 % ($p = 0.001$), and the incidence of pneumonitis, radiation dermatitis, and late changes to the skin and subcutaneous tissues (telangectasia, atrophy) were also significantly increased [8••]. The EORTC trial found a significant increase in pulmonary fibrosis with nodal RT (4.4 vs 1.7 %, $p < 0.001$). With 10 years of follow-up in patients with median ages of 53.5 and 54 years, no increases in cardiac toxicities were observed [9••]. The results of these studies have been interpreted by some to mean that all patients with axillary nodal

metastases, regardless of tumor size or extent of nodal involvement, should receive comprehensive nodal RT. A major conundrum in current practice is resolving the apparently contradictory findings of ACOSOG Z0011 and AMAROS with those of MA.20 and EORTC 22922/10925 (Table 2). Interestingly, although MA.20 and EORTC 22922/10925 included both node-positive and node-negative patients, the 10-year rates of nodal recurrence in the ALND arms of these studies, 1.6 and 1.8 % [8••, 9••], were approximately four times higher than those seen at 5 years in the ALND arms of ACOSOG Z0011 and AMAROS (0.5 and 0.4 %, respectively) [5••, 7••]. This may reflect differences in patient populations since patients with clinically positive nodes were excluded from ACOSOG Z0011 and AMAROS, or may reflect a benefit for nodal RT in the face of limited and non-sentinel node-directed axillary surgery. Fewer than 10 nodes were removed in one-third of patients in the MA.20 study, and the median node count was 12 [8••]. In the EORTC trial, the median number of nodes removed in a complete ALND was 15, and 13 in a partial dissection [9••]. In comparison, in the ALND arms of ACOSOG Z0011 and AMAROS, a median of 17 nodes were removed [5••, 7••]. Given the modest improvement in DFS and the lack of an OS benefit for nodal RT in the setting of limited surgery, the magnitude of benefit with more extensive surgery is of concern. Additionally, lymphedema may be a more significant problem after more extensive ALND and nodal RT than was observed in MA.20 or the EORTC study.

Personalized Axillary Management

Efforts to personalize axillary management have primarily centered upon identification of patients with a heavy tumor burden who are likely to benefit from ALND or RT, and include the use of preoperative imaging to select axillary treatment as well as the identification of histologic features associated with a heavier nodal tumor burden.

Abnormal Preoperative Imaging

Prior to the adoption of ACOSOG Z0011 into clinical practice, axillary ultrasound with biopsy of suspicious nodes was used by many to allocate women with a clinically negative axilla to ALND without the need for SLN biopsy. In order to be clinically useful, axillary imaging and biopsy need to reliably distinguish between patients with metastases in 1 or 2 nodes who are still candidates for SLNB if they otherwise meet ACOSOG Z0011 eligibility criteria, and those with metastases in ≥3 nodes who could proceed directly to ALND. Pilewskie et al. evaluated whether abnormal axillary imaging predicted the need for ALND in a prospective cohort of 425 women with T1-2, clinically node-negative invasive breast cancer undergoing breast conservation with <3 positive sentinel nodes managed according to Z0011 criteria. All patients had a preoperative mammogram, 242 (57 %) had an axillary ultrasound, and 172 (40 %) had a breast MRI. Abnormal nodes were seen on 7, 25, and 30 % of mammograms, ultrasounds, and MRIs, respectively. Overall, 71 patients (17 %) underwent completion ALND, while 354 (83 %) had 1–2 positive SLNs and had SLN biopsy alone. Women with abnormal lymph nodes seen on preoperative imaging were more likely to undergo ALND compared to women with no abnormal nodes identified (27–32 vs 12–15 %, respectively). Notably, almost 70 % of women with abnormal preoperative axillary imaging were able to be managed with SLN biopsy alone (1–2 positive SLNs) and were spared the morbidity of ALND [24]. Pilewskie et al. also examined whether a positive needle biopsy in women with clinical T1-2 cancers and no palpable axillary nodes identified a patient population requiring ALND. In this study of 152 patients, 49 % of those with a positive needle biopsy had metastases in only 1 or 2 axillary (as opposed to sentinel) nodes, indicating that proceeding directly to ALND on the basis of a positive needle biopsy will lead to overtreatment in a minimum of 50 % of patients [25].

Extracapsular Extension

Patients with gross ECE were excluded from ACOSOG Z0011, and gross ECE is generally considered an indication for nodal RT; however, the presence of microscopic ECE was not evaluated in the study. Gooch et al. identified 1109 patients meeting ACOSOG Z0011 eligibility criteria (T1-2, clinically node-negative invasive breast cancer, and 1–2 positive SLNs by H&E staining) treated between 2006 and 2013 [26]. ECE was identified in 331 patients; 180 (54 %) had ≤2 mm ECE, and 151 (46) had >2 mm ECE. Patients with ECE had larger tumors ($p < 0.0001$), were more likely to be hormone-receptor positive ($p = 0.0164$), and had a higher incidence of multifocality ($p = 0.0062$) and lymphovascular invasion ($p < 0.0001$) compared to patients without ECE. In patients in whom completion ALND was performed, additional positive nodes were seen in 54 % of patients with ECE compared to 22 % of patients without ECE ($p < 0.0001$). When patients were stratified by extent of ECE, patients with >2 mm of ECE were more likely to have additional positive non-sentinel nodes (66.1 %) compared to patients with ≤2 mm ECE (42.9 %) ($p < 0.0001$), and 33 % of patients with >2 mm ECE had ≥4 additional positive nodes compared to 8.6 % of those with <2 mm ECE ($p < 0.0001$). On multivariate analysis, the strongest predictor of having ≥4 positive nodes at completion ALND was ECE >2 mm (OR 14.2; 95 % CI 7.1–28.4; $p < 0.0001$) [26]. These findings suggest that

patients with >2 mm of ECE may benefit from additional axillary treatment with either ALND or axillary RT.

Future Directions

Selection of patients for ALND or nodal RT solely on the basis of tumor burden ignores both differences in rates of locoregional recurrence among breast cancer subtypes and does not consider the variable effects of systemic therapy among subtypes. Two different approaches are being studied, which hold promise for individualization of therapy in the future. The first is the use of genomic signatures to identify patients at different risks of locoregional recurrence who would benefit from more or less therapy. Mamounas et al. examined the incidence of locoregional recurrence postmastectomy in 1065 node-positive patients enrolled in NSABP B28 who were treated with chemotherapy, but not RT, in relation to the 21-gene recurrence score [Oncotype Dx (Genomic Health, Redwood City, CA)], and found rates of locoregional recurrence ranging from 3.3 to 12.3 % [27]. In the subset with involvement of ≥4 nodes, a group traditionally considered to require ALND and nodal RT, locoregional recurrence occurred in 5.5 % of those with a low 21-gene recurrence score compared to 23.6 % of those with a high score ($p = 0.006$). Tramm et al. [28] created a genomic signature which is both prognostic for locoregional recurrence and predictive of the benefit of RT using patients treated in the Danish Breast Cancer Group 82b and 82c trials. Low-risk signatures were observed in patients with metastases in ≥4 nodes, and high-risk signatures in those with lower tumor burdens, and were independent of ER, PR, and HER2 status. These signatures require validation in independent datasets, but are a promising approach to further individualizing treatment selection. Alternatively, since the use of less local therapy is predicated upon the effectiveness of systemic therapy, another approach is to use neoadjuvant chemotherapy to identify triple-negative and HER2 positive patients who do not have a complete pathologic response to treatment and thus are at highest risk for locoregional recurrence [29] and would benefit from maximal surgery and RT. This concept is currently being tested in the NRG 9353 and Alliance A11202 trials.

Conclusion

ALND should no longer be considered standard management for all women with nodal metastases. SLN biopsy alone, or in combination with RT for higher-risk subgroups, has been shown to be a safe alternative with lower morbidity in randomized trials. While some patients derive benefit from ALND and nodal RT based on the findings of MA.20 and EORTC 22922-10925, the modest DFS benefit and lack of OS benefit in these studies do not justify treating all node-positive patients with this more morbid approach. Defining the patient subsets best treated with each of these approaches is a critical challenge for the future.

Compliance with Ethics Guidelines

Conflict of Interest Andrea V. Barrio and Monica Morrow declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Wang Z, Wu LC, Chen JQ. Sentinel lymph node biopsy compared with axillary lymph node dissection in early breast cancer: a meta-analysis. Breast Cancer Res Treat. 2011;129(3):675–89.
2. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. Cancer. 2006;106(1):4–16.
3. Mannino M, Yarnold JR. Local relapse rates are falling after breast conserving surgery and systemic therapy for early breast cancer: can radiotherapy ever be safely withheld? Radiother Oncol. 2009;90(1):14–22.
4. Morrow M, Harris JR, Schnitt SJ. Surgical margins in lumpectomy for breast cancer—bigger is not better. N Engl J Med. 2012;367(1):79–82.
5. •• Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, 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. 2014;15(12):1303–10. *Non-inferiority trial demonstrating no difference in axillary recurrence or overall survival in women with positive sentinel nodes treated with axillary radiation versus axillary dissection.*
6. • Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, 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 2013;14(4):297–305. *Randomized prospective trial demonstrating no benefit to axillary dissection in patients with micrometastases in the sentinel node.*
7. •• Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA. 2011;305(6):569–75. *Randomized prospective trial demonstrating no benefit to axillary dissection in women undergoing lumpectomy with T1-2 tumors and sentinel node metastasis.*
8. •• Whelan TJ, Olivotto I, Parulekar W, Ackerman I, Chua B, Nabid A, et al. Regional nodal irradiation in early stage breast cancer. N Engl J Med. 2015 (in press). *Randomized prospective*

trial demonstrating modest benefit in disease-free survival with the addition of regional nodal irradiation to axillary dissection in node-positive breast cancer patients, with associated increased morbidity.

9. •• Poortmans PSH, Collette S, Kirkove C, Van Limbergen E, Struikmas H, Maingon P, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med. 2015 (in press). *Randomized prospective trial demonstrating modest benefit in disease-free survival with the addition of regional nodal irradiation to axillary dissection in node-positive and high-risk node-negative patients, with associated increased morbidity.*
10. Giuliano AE, Dale PS, Turner RR, Morton DL, Evans SW, Krasne DL. Improved axillary staging of breast cancer with sentinel lymphadenectomy. Ann Surg. 1995;222(3):394–9; **discussion 9–401**.
11. Tvedskov TF, Jensen MB, Balslev E, Ejlertsen B, Kroman N. Stage migration after introduction of sentinel lymph node dissection in breast cancer treatment in Denmark: a nationwide study. Eur J Cancer. 2011;47(6):872–8.
12. Cserni G, Gregori D, Merletti F, Sapino A, Mano MP, Ponti A, et al. Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer. Br J Surg. 2004;91(10):1245–52.
13. Kumar S, Bramlage M, Jacks LM, Goldberg JI, Patil SM, Giri DD, et al. Minimal disease in the sentinel lymph node: how to best measure sentinel node micrometastases to predict risk of additional non-sentinel lymph node disease. Ann Surg Oncol. 2010;17(11):2909–19.
14. Bilimoria KY, Bentrem DJ, Hansen NM, Bethke KP, Rademaker AW, Ko CY, et al. Comparison of sentinel lymph node biopsy alone and completion axillary lymph node dissection for node-positive breast cancer. J Clin Oncol. 2009;27(18):2946–53.
15. Giuliano AE, Hawes D, Ballman KV, Whitworth PW, Blumencranz PW, Reintgen DS, et al. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. JAMA. 2011;306(4):385–93.
16. Weaver DL, Ashikaga T, Krag DN, Skelly JM, Anderson SJ, Harlow SP, et al. Effect of occult metastases on survival in node-negative breast cancer. N Engl J Med. 2011;364(5):412–21.
17. Julian TB, Anderson SJ, Weaver D, Krag DN, Harlow SP, Ashikaga T, et al. 10 year follow-up results of occult detected sentinel node disease: NSABP B-32 A randomized phase iii clinical trial to compare sentinel node resection (SNR) to conventional axillary dissection (AD) in clinically node-negative breast cancer patients. Cancer Res. 2013;73:24; **suppl, abstract No. S2-05**.
18. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med. 2002;347(8):567–75.
19. Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg. 2010;252(3):426–32; **discussion 32–3**.
20. Lucci A, McCall LM, Beitsch PD, Whitworth PW, Reintgen DS, Blumencranz PW, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. J Clin Oncol. 2007;25(24):3657–63.
21. • Dengel LT, Van Zee KJ, King TA, Stempel M, Cody HS, El-Tamer M, et al. Axillary dissection can be avoided in the majority of clinically node-negative patients undergoing breast-conserving therapy. Ann Surg Oncol. 2014;21(1):22–7. *This study applied ACOSOG Z0011 criteria to an unselected, consecutive cohort of breast cancer patients and demonstrated that the ACOSOG Z0011 cohort is representative of most patients undergoing breast-conserving surgery for T1-2 breast cancer.*
22. • Chung A, Gangi A, Mirocha J, Giuliano A. Applicability of the ACOSOG Z0011 criteria in women with high-risk node-positive breast cancer undergoing breast conserving surgery. Ann Surg Oncol. 2015;22(4):1128–32. *Retrospective study demonstrating that ACOSOG Z0011 criteria can be applied to women with node-positive breast cancer and high-risk features (ER negative, HER2/neu positive, age < 50 years) with similar results.*
23. • Jagsi R, Chadha M, Moni J, Ballman K, Laurie F, Buchholz TA, et al. Radiation field design in the ACOSOG Z0011 (Alliance) trial. J Clin Oncol. 2014;32(32):3600–06. *Retrospective review of radiation field design in the ACOSOG Z0011 trial, demonstrating no difference in method of radiation delivery between the axillary dissection and no-axillary dissection arm.*
24. Pilewskie M, Jochelson M, Gooch JC, Patil S, Stempel M, Morrow M. Is preoperative axillary imaging beneficial in identifying clinically node-negative patients requiring axillary lymph node dissection? Ann Surg Oncol. 2015 (in press).
25. Pilewskie M, Mautner SK, Stempel M, Eaton A, Morrow M. Does a positive axillary lymph node needle biopsy predict the need for an axillary lymph node dissection in clinically node-negative breast cancer patients in the ACOSOG Z0011 era? Ann Surg Oncol. 2015 (in press).
26. Gooch J, King TA, Eaton A, Dengel L, Stempel M, Corben AD, et al. The extent of extracapsular extension may influence the need for axillary lymph node dissection in patients with T1–T2 breast cancer. Ann Surg Oncol. 2014;21(9):2897–903.
27. Mamounas EP, Tang G, Paik S, Baehner FL, Liu Q, Jeong J, et al. The 21-gene recurrence score (RS) predicts risk of loco-regional recurrence (LRR) in node (+), ER (+) breast cancer (BC) after adjuvant chemotherapy and tamoxifen: results from NSABP B-28. Ann Surg Oncol. 2013;20(Supplement):S6–164.
28. Tramm T, Mohammed H, Myhre S, Kyndi M, Alsner J, Borresen-Dale AL, et al. Development and validation of a gene profile predicting benefit of postmastectomy radiotherapy in patients with high-risk breast cancer: a study of gene expression in the DBCG82bc cohort. Clin Cancer Res. 2014;20(20):5272–80.
29. Mamounas EP, Anderson SJ, Dignam JJ, Bear HD, Julian TB, Geyer CE Jr, 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. 2012;30(32):3960–6.