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Pathologic Evaluation and Prognostic Implications of Nodal Micrometastases in Breast Cancer

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Using modern sentinel lymph node techniques, occult nodal metastases including micrometastases or isolated tumor cells are being increasingly discovered in up to 10% of early-stage breast cancers. Furthermore, the rate of nonsentinel lymph node involvement is approximately 10%. However, the impact of these findings on disease-free survival is low, particularly with regards to axillary recurrences. Current evidence suggests small-volume lymph node involvement in breast cancer patients is only one of several factors that should guide adjuvant therapy options. In otherwise favorable patients, adjuvant radiation and systemic therapy can help mitigate the risk of recurrence when omitting axillary lymph node dissection.

Introduction

Surgical treatment of breast cancer involves both primary tumor surgical excision and axillary staging. While axillary lymph node dissection (ALND) has been replaced by sentinel lymph node (SLN) biopsy in clinically node negative (cN0) patients, the most appropriate treatment for clinically node positive patients was historically thought to be ALND, providing clearance of disease in the axilla as well as important prognostic information. Indeed, axillary node metastasis has historically been defined as the most significant prognostic factor in the management of early-stage breast cancer.[1]

Analysis of the National Surgical Adjuvant Breast and Bowel Project data, stratified based on the number of positive nodes, has classically been used for clinical trial enrollment.[1] However, recently published 10-year results from the American College of Surgeons Oncology Group Z0011 trial found that, in cN0, SLN positive patients receiving adjuvant therapy including whole breast radiation, SLN alone had equivalent survival compared to completion ALND.[2] With fewer nodes to assess, adoption of techniques with increasing sensitivity has led to increased detection of what has been defined as isolated tumor cells or micrometastasis.[3,4] The American Joint Committee on Cancer Cancer Staging Manual defines isolated tumor cells (ITCs, staged as pN0[i+]) as deposits ≤0.2 mm and micrometastases (staged as pN1mi) as deposits >0.2 to ≤2.0 mm.[5] The purpose of this review is to highlight current pathologic techniques in the evaluation of SLNs and review the literature regarding prognosis and treatment implications for patients with pN0[i+] or pN1mi disease.

References Search

We performed a PubMed (National Center for Biotechnology Information, US National Library of Medicine) search during development of this review by using the following search equation: ("micrometastasis" OR "isolated tumor cells") AND ("breast cancer") AND ("lymph node" OR "lymph nodes"). The final search was performed on March 20, 2018 by 2 authors (S.W.D, J.T.M) and produced 603 references. While not a formal systematic review, 118 abstracts reporting on either clinical results or pathologic techniques were reviewed. Relevant studies and important references found within were included in this review.

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Pathologic Evaluation

The pathologist has a significant role in guiding treatment and management of patients with breast cancer by providing the initial diagnosis, tumor grading, and final staging of tumors. This is done through careful gross and histologic examination, which consists of detailing the overall macroscopic tissue appearance, sampling sections of the tumor, and analyzing the curated tissue sections under the microscope to determine tumor type, grade, and pathologic stage.

A key part to the staging of breast cancers is the pathologic evaluation of SLNs. As gatekeepers to the axillary lymphatic system, SLNs are believed to be first involved by potential metastatic spread of disease, and their status of metastatic involvement is an important determinant of stage and need for further surgical dissection and/or nodal irradiation. In cases of early-stage and clinically node-negative breast cancer, SLNs can demonstrate a range of involvement by metastatic spread from macrometastases (>2 mm), micrometastases (>0.2 to ≤2.0 mm), and isolated tumor cells or ITCs (≤0.2 mm or 200 cells).[5] The metastatic size categories are defined by the threshold limits for a 1000-fold difference in spherical volume of tumor cell deposits.[6] The lower limit of 2 mm for macrometastatic disease is the mathematical set-point for which a single hematoxylin and eosin (H&E) level, from a lymph node sliced at 2 mm intervals, can demonstrate a 2 mm tumor deposit; this was originally defined by a 1970 landmark study.[6-8]

The negative prognostic value of macrometastases in SLN is well-known, meaning a SLN with a macrometastatic deposit is associated with worse disease-free survival.[1] However, it is less clear whether the presence of micrometastases or ITCs produces the same prognostic impact, as discussed in the later sections. Recent studies have demonstrated minimal differences in prognosis and attribute other factors such as primary tumor size and genetic profile to having greater prognostic significance in this setting.[6] Thus, clinical utility of micrometastatic burden in low-stage breast cancers is undetermined. Therefore, it has generally been agreed in the pathology community that SLN evaluation should focus on the detection of macrometastatic deposits.[7,9,10] SLN evaluation should conform to the consensus standard as defined by the College of American Pathologists and American Joint Committee on Cancer for the detection of macrometastatic deposits. SLNs are sectioned along the long axis in 2 mm intervals and submitted entirely for histologic analysis. One level for H&E staining is cut from each submitted tissue block, and immunohistochemical stains, such as keratin, are not ordered in the upfront histologic analysis. Previous studies have demonstrated that, while "enhanced pathology" techniques reveal more occult metastatic disease, these methods do not necessarily translate into a clinical benefit and are not cost-effective.[7,11]

While the majority of SLNs are histologically analyzed from the H&E slides alone, occasionally immunohistochemical stains are needed. This is especially true for cases of low-grade lobular carcinoma where single tumor cell infiltration can be difficult to ascertain from H&E.[7] However, routine upfront keratin IHC is not recommended for the initial evaluation of SLNs in the detection of minimal metastatic disease, for the same reasons stated above.[7,12] A SLN is considered involved by metastatic disease if there is clear infiltration of tumor cells with morphologic features consistent with the patient's primary breast cancer, as demonstrated in Figures 1 and 2.

Additional Non-SLN Involvement in Cases of pN0[i+] or pN1mi Disease

In order to frame the discussion to current treatment dilemmas regarding the management of micrometastatic disease, it is important to recognize the rate of non-SLN disease. Table 1 lists relevant studies, mostly retrospective, which evaluated patients who underwent completion ALND in the setting of pN0[i+] or pN1mi disease. For pN0[i+] disease, the rate of non-SLN involvement ranges from 4.9% to 16%. For pN1mi disease, the rate is slightly higher across studies, ranging from 0% to 27%.

Two prospective randomized trials, including American College of Surgeons Oncology Group Z0011 and International Breast Cancer Study Group (IBCSG) 23-01, were performed, which randomized patients with positive SLN biopsies to either SLN-biopsy alone or completion ALND.[12,13] Among those with pN1mi on SLN biopsy and

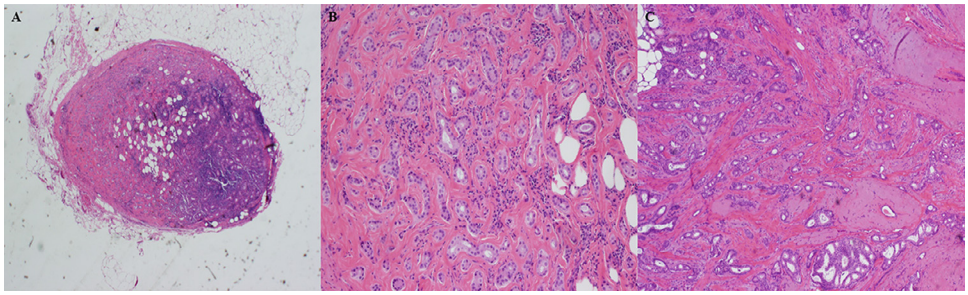

Figure 1 Macrometastatic ductal carcinoma (3 mm) of sentinel lymph node. Full cross-section of the sentinel lymph node demonstrates macrometastatic involvement, measuring 3 mm in greatest dimension, by ductal carcinoma (A, 4x). The metastatic deposit demonstrates ductal carcinoma (B, 10x) with similar morphologic features to the patient's primary tumor, invasive ductal carcinoma grade 1 (C, 4x). This patient did not receive a complete axillary dissection, due to patient's age and preference as well as comorbidities.

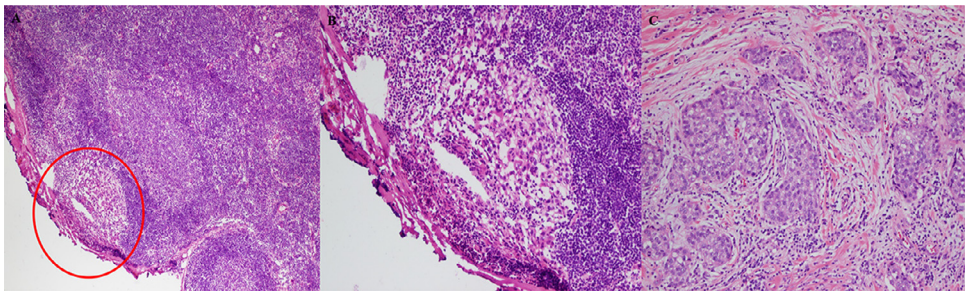

Figure 2 Micrometastatic ductal carcinoma (1 mm) involving sentinel lymph node. A single micrometastatic deposit (circled in red), measuring 1 mm in greatest dimension, was identified in the sentinel lymph node on intraoperative frozen section analysis (A, 4x; B, 10x). The morphologic features of the metastatic deposit are similar to the patient's primary tumor, invasive ductal carcinoma grade 3 (C, 10x). The patient received a complete axillary dissection, which demonstrated no evidence of additional metastatic disease. (Color version of figure is available online.)

randomized to completion ALND, 10% and 13% were found to have additional non-SLN involvement in the Z0011 and IBCSG 23-01 trial, respectively. While the rate of non-SLN involvement in an undissected axilla can be alarming to clinicians and patients, mature results from Z0011 show that completion ALND is unnecessary in occult nodal disease, particularly when appropriate adjuvant therapy (radiotherapy, chemotherapy, hormonal therapy, or a combination thereof) is delivered. Therefore, current 2018 National Comprehensive Cancer Network guidelines recommend no further axillary surgery in the case of only micrometastases seen on SLN biopsy.[14]

Prognosis for pN0[i+] or pN1mi Disease

Most clinical outcome data on micrometastases and ITCs has occurred within the past decade, as a result of the SLN procedure having replaced the more morbid ALND procedure for appropriately selected early stage patients.[15,16] Therefore, long-term outcome data with greater than 5-year follow-up are limited. Table 2 highlights important landmark studies evaluating the prognosis of occult nodal disease.

Boer et al, as part of the MIRROR study (Micrometastases and ITC: Relevant and Robust or Rubbish?), identified 856 patients who were pN0 and had not received systemic adjuvant therapy, 856 patients who were pN0[i+] or pN1mi who had not received systemic adjuvant therapy, and 995 patients who were pN0[i+] or pN1mi who had received systemic adjuvant therapy. In their report, an approximately 10% decrease in 5-year disease-free survival was found in patients with pN0[i+] or pN1mi disease compared to pN0 disease (85.7% vs 76.5%). However, those with pN0[i+] or pN1mi disease experienced an approximately 10% 5-year disease-free survival benefit with the addition of systemic adjuvant therapy. The study included patients managed with more conservative use of older first or secondary generation chemotherapy regimens. Therefore, patients currently being treated with modern chemotherapy regimens may experience further improved outcomes.

Weaver et al reported outcomes after performing additional pathologic examination using thinner sectioning on 3884 patients with originally pathologically negative SLN

Table 1 Rate of Additional Lymph Node Involvement for Patients With Isolated Tumor Cells or Micrometastasis on Sentinel Lymph Node Biopsy, Who Then Underwent Completion Axillary Dissection

Study	% With Isolated Tumor Cells and Additional Non-SLN Involvement	% With Micrometastasis and Additional Non-SLN Involvement	Notes
Ganaraj 2003[28]		2/24 (8.3%)	0/17 (0%) IDC 2/7 (29%) ILC
Fournier 2004[29]		1/16 (6.3%)	
Calhoun 2005[30]	3/61 (4.9%)		
Fan 2005[31]		3/18 (16.7%)	
Rutledge 2005[32]		1/29 (3%)	
Houvenaeghel 2006[33]	30/187 (16%)	43/301 (14.3%)	
Van Deurzen 2007[34]	3/23 (13%)	20/101 (19.8%)	
Cserni 2008[35]	7/82 (8.5%)	79/435 (18.2%)	Classified according to the EWGBSP study rules
Cox 2008[36]	10/107 (9.3%)	15/97 (15.5%)	
Reed 2009[37]		11/41 (27%)	
Giuliano 2011[12]		14/137 (10%)	ACOSOG Z0011 trial
Galimberti 2013[13]		59/447 (13%)	IBCSG 23-01 trial
Zanghi 2015[38]		0/10 (0%)	

Abbreviations: ACOSOG, American College of Surgeons Oncology Group; EWGBSP, European Working Group for Breast Screening Pathology; IBCSG, International Breast Cancer Study Group; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; SLN, sentinel lymph node.

Table 2 Clinical Outcomes for Breast Cancer Patients With Micrometastasis or Isolated Tumor Cells

Study, Year Published	5-Year DFS	5-Year OS	Notes
Boer 2009[39]	pN0 without adjuvant systemic therapy = 85.7% pN0[i+] or pN1mi without adjuvant systemic therapy (n = 856) = 76.5% pN0[i+] or pN1mi with adjuvant systemic therapy (n = 995) = 86.2% ($P < 0.001$)		Retrospective. Median F/U 5 years. 84.6% of patients with systemic therapy also received ALND ± axillary irradiation compared to 61.1% of no systemic therapy group
Weaver 2011[11]	pN0 = 89.2% pN0[i+], pN1mi, or pN1 = 86.4% ($P = 0.02$)	pN0 = 95.8% pN0[i+], pN1mi, or pN1 = 94.6% ($P = 0.03$)	MIRROR study. Survival given as Kaplan-Meier estimates
Galimberti 2013[13]	87.8% without ALND 84.4% with ALND (log-rank $P = 0.16$) <1% nodal recurrence in the no ALND arm		IBCSG 23-01 trial. Randomized to ± ALND for micrometastatic disease. Median F/U 5 years. Most patients treated with BCS (91%) and most (95%-97%) received RT or systemic treatment (or both)
Van der Heisen 2013[40]	90.0% pN0 89.7% pN0[i+] 89.2% pN1mi		Netherlands cancer registry (n = 18,370). After controlling for tumor and treatment, pN1mi DFS HR = 1.38 compared to pN0 ($P = 0.002$)

Abbreviations: ALND, axillary lymph node dissection; DFS, disease free survival; HR, hazard ratio; IBCSG, International Breast Cancer Study Group; MIRROR, micrometastases and isolated tumor cells: relevant and robust or rubbish?; OS, overall survival; SLN, sentinel lymph node.

biopsy who were a part of the National Surgical Adjuvant Breast and Bowel Project B-32 trial, which randomized one arm to completion ALND.[11] Occult metastases were observed in 616/3268 patients (15.9%), which included 430 (11.1%) with ITC clusters, 172 (4.4%) with micrometastases, and 14 (0.4%) with macrometastases. Five-year Kaplan-Meier estimates for disease-free survival and overall survival for occult metastases was 86.4% and 94.6%, respectively, which was significantly less compared to patients without occult metastases (disease-free survival = 89.2%; overall survival = 95.8%; $P < 0.05$ for each). However, the absolute difference between those with or without occult metastases was small (1%-3% for disease-free survival and overall survival). On subgroup analyses, the authors were able to show there was a smaller detriment on overall survival with ITCs compared to micro- or macrometastases, justifying their separate classification. The prevalence of occult metastases was significantly associated with an age less than 50 years, a clinical tumor size greater than 2.0 cm, and planned mastectomy, consistent with other studies.[17] Interestingly, the presence of occult metastases was not a predictor for cancer recurrence in these patients. Also, the presence of occult metastases was not known by the treating physicians, so, while occult metastases patients were more likely to receive adjuvant therapy, these treatment selections were likely associated with the other poor prognostic tumor factors previously mentioned. Lastly, while the authors noted that the minimal differences do not justify changes in clinical management, their multivariable hazard ratio analysis identified adjuvant endocrine therapy and radiation as improving overall survival in these patients.

Galimberti et al reported outcome results from the IBCSG 23−01trial,[13] which randomized patients with primary tumors less than 5 cm and one or more micrometastatic lymph nodes on SLNB to observation vs ALND. In their study, 5-year disease-free survival for patients with micrometastatic disease was 84.4% and 87.8% with ALND and observation, respectively (log rank $P = 0.16$). Most patients were treated with breast conserving surgery (91%) and most (95%-97%) received adjuvant radiotherapy and/or systemic treatment. In this trial's setting, the rate of recurrence in the regional nodes was very low (<1%) in the group assigned to SLN only, without completion ALND being performed.

In summary, disease-free survival appears to be only slightly reduced for cases of micrometastasis or ITCs; however, patient specific adjuvant therapy (radiotherapy, hormone therapy, and/or chemotherapy) may offset this detriment. Long-term outcome and overall survival data with 10 or more years of follow-up are limited.

Adjuvant Radiotherapy in pN0[i+] or pN1mi Disease

To contribute to the clinical question regarding the role of radiation in high-risk early-stage breast cancer patients, there are 2 recent randomized trials that identified a high-risk population that may benefit from comprehensive nodal radiation using both the traditional tangential fields as well as another radiation field to cover the supraclavicular and high axillary nodal volume. One of these studies, the National Cancer Institute of Canada Clinical Trials Group MA.20 trial, randomized 1832 women with early-stage breast cancer receiving breast conserving surgery who were either node-negative with high-risk features or node positive to whole breast

irradiation ± regional nodal irradiation.[18] The node-positive patients were required to have a level I or II axillary dissection, and all patients were required to receive adjuvant systemic therapy with either chemotherapy, endocrine therapy, or both. At 10 years, disease-free survival was 82% in the nodal irradiation group and 77% in the whole breast irradiation only group ($P = 0.01$), with the primary difference in recurrence being in the axillary nodes. No survival benefit was observed at 10-year follow-up ($P = 0.38$) with nodal irradiation, and more adverse events including acute pneumonitis (1.2% vs 0.2%) and lymphedema (8.4% vs 4.5%) were observed in the nodal irradiation group. This study required central review of each institution's radiation plans, making it robust in assessment of the radiation fields.

Similarly, the European Organization for Research and Treatment of Cancer (EORTC) 22,922/10,925 phase 3 trial randomized high-risk, early-stage breast cancer patients to whole breast or chest wall radiation ± regional nodal irradiation. Patients with centrally or medially located primary tumors irrespective of axillary involvement or a laterally located tumor with axillary involvement were included in this study. Of note, 44% of the high-risk patients were node negative. The majority of patients (76.1%) underwent breast conserving surgery followed by whole breast radiation, and 73.4% of the mastectomy patients underwent chest wall irradiation. Ninety-nine percent of node-positive disease patients and 66.3% of node-negative disease patients also received systemic treatment. They reported a small but significant benefit in disease-free survival, distant disease-free survival, and breast cancer mortality at 10-year follow-up, but overall survival did not quite meet significance.[19] Interestingly, adjuvant treatment with both chemotherapy and hormone therapy was associated with improved survival.

A drawback to both of these studies for our assessment is that all patients with a positive SLN underwent complete ALND, limiting the applicability to patients with disease seen only on SLN, without completion ALND. In addition, the applicability of both of these studies to low-volume nodal disease is unclear as neither study provided information on pN1mi or pN0[+] disease, though low-volume nodal disease patients would likely be considered high risk as the study also included high-risk N0 patients. It remains unclear whether further stratification of the patients and longer follow-up will identify the higher risk patients who would receive a survival advantage from comprehensive nodal radiation.

To contribute to the clinical question regarding SLN management in the absence of an ALND, the Z0011 trial randomized early breast cancer patients receiving breast conserving surgery identified as clinically N0 on exam but found to have a positive SLN at surgery to ALND vs observation. The number of patients with pN1mi ranged from 37% to 44% in the treatment arms. All patients received whole breast radiation therapy. However, the varying radiotherapy field design in patients treated on the Z0011 trial has led to controversy regarding the optimal radiation technique in patients with positive SLNs.[2,20] In this study, detailed radiotherapy records were available for only a minority of patients, but the completed radiation detail case forms from the available patients revealed a good deal of variability in the treatment fields. For example, while nodal-directed radiotherapy with a third radiation treatment field to cover the high axillary and supraclavicular nodes was against protocol, it was given to 15% of patients, most commonly to those patients with greater nodal involvement ($P < 0.001$), although its use was similar between treatment arms. Furthermore, while 81% of patients received tangent only radiation, high tangents, which can cover the low level 1 and 2 axillary lymph nodes, were used in 50% of patients.[21] Therefore, with complete records for all patients being unavailable, it is reasonable to consider that radiation oncologists, who were not blinded to patients' treatment arm or to axillary nodal involvement status, may have contributed to the very low axillary recurrence rates with coverage of the axillary nodal basins.

Similarly, the IBCSG 23-1 trial, which randomized pN1mi patients on SLN-biopsy to ± completion ALND also showed a very low rate of axillary recurrences in the SLN-alone arm despite the 13% rate of additional nodal involvement seen in the ALND arm. Most patients were treated with breast conserving surgery (91%) and most (95%-97%) received adjuvant radiotherapy or systemic treatment (or both). However, 19% of the patients receiving radiation in both groups received intraoperative radiotherapy alone, which would not have targeted the low-lymph node basins. Interestingly, they reported 6 total regional recurrences in the axilla alone (1 in the ALND arm and 5 in the SLN arm), with 4 out of 6 of these patients having received either no radiation (2) or intraoperative radiation alone (2). Receipt of radiation and endocrine therapy were associated with a survival advantage in this trial. While whole breast irradiation field design details are not known in this trial, their data suggest that adjuvant systemic therapy and whole breast irradiation could eliminate low-volume axillary metastases.

The EORTC After mapping of the axilla: radiotherapy or surgery? (AMAROS) study does provide some insight into the management of SLN positive patients with either surgery or radiation.[22] This study was a noninferiority trial that randomized clinically N0 patients found to be node positive on SLN to either ALND or axillary radiotherapy, with inclusion of all 3 axillary levels and a supraclavicular field. Of note, over 80% of patients in each arm underwent breast conserving surgery with whole breast radiation. Approximately 40% of the patients had either pN0[i+] or pN1mi disease; interestingly, the eligibility criteria was modified after 2008 to no longer include isolated tumor cells as SLN positive. The 5-year disease-free survival and overall survival were not different in the 2 groups. Axillary recurrence rates were 0.43% vs 1.19% in the ALND vs nodal radiation groups, respectively, and the planned noninferiority test was underpowered based on the low number of events. There was also less lymphedema at 5 years in those with axillary radiation vs ALND (11% vs 23%, $P < 0.001$). This study provides data to support the concept that irradiation to an undissected axilla provides adequate local control for early stage, clinically N0 breast cancer patients when directly compared to ALND.[22]

Table 3 Trials Evaluating Adjuvant Radiotherapy in Early Stage Breast Cancer

Trial (Year Published, Follow-Up, N)	Surgery, Eligibility, Randomization	Radiation Fields	Outcome	Notes
ASOSOG Z0011 (2017, 10 years, n = 891)[2]	BCS + SLN biopsy T1-T2, cN0/pN1(SN) +/− ALND	All: WBI alone	OS, DFS similar	50% received high tangent fields, and 15% received level III and supraclavicular nodal RT (against protocol)
NCIC MA.20 (2015, 10 years, n = 1832)[18]	BCS + ALND; N+ or T3 or T2 with high risk features (G3, ER-, LVI) +/− nodal RT	Control: WBI alone Exp: WBI + Axilla, IMN, and SCV nodes	OS similar DFS 77.0% (control) vs 82.0 (exp) (P = 0.01)	Boost permitted. All patients received adjuvant systemic therapy with chemotherapy, endocrine therapy, or both
EORTC 22922/10925 (2015, 10 years, n = 4004)[19]	BCS or mastectomy + ALND T1-T3, N any medial T1-T3, pN+	Control: WBI or CW only Exp: WBI or CW + IMN and SCV nodes	OS 80.7% (control) vs 82.3 (exp) (P = 0.06) DFS 69.1% (control) vs 72.1% (exp) (P = 0.04)	Nearly all patients with node-positive disease (99.0%) and 66.3% of patients with node-negative disease received systemic treatment
EORTC AMAROS (2014, 5 years, n = 4823)[22,41]	BCS or mastectomy + SLN biopsy T1-T2, cN0/pN1(SN) ALND vs nodal RT	ALND: WBI or CW (if indicated) Axillary radiation: WBI or CW (if indicated) + Axilla levels I-III and SCV	OS, DFS similar Axillary recurrence: 0.43% (ALND) vs 1.19% (axillary RT)	Of the positive SLN, 29% were micrometastasis and 10% were ITCs in the axillary RT group

Abbreviations: ACOSOG, American College of Surgeons Oncology Group; ALND, axillary lymph node dissection; AMAROS, After mapping of the axilla: radiotherapy or surgery?; BCS, breast conserving surgery; DFS, disease free survival; EORTC, European Organisation for Research and Treatment of Cancer; Exp, experimental arm; HR, hazard ratio; ITC, isolated tumor cells; NCIC, National Cancer Institute of Canada; OS, overall survival; RT, radiation therapy; SCV, supraclavicular; SLN, sentinel lymph node; WBI, whole breast irradiation.

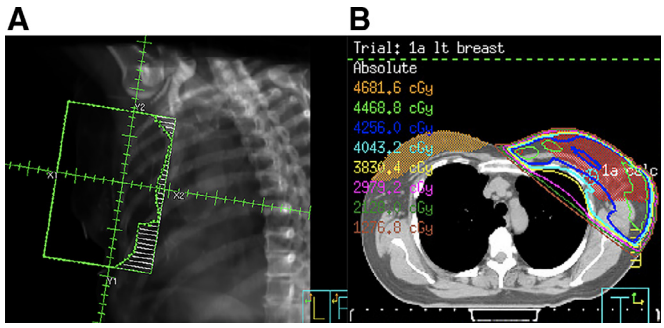

Figure 3 Representative patient (pathologic stage IA, pT1c, pN0[sn, i+]) with left-sided breast cancer who had a central/medial tumor and isolated tumor cells on sentinel lymph node biopsy. She was treated to 42.56 Gy in 16 fractions with deep inspiratory breast hold utilized to minimize heart dose targeting level I-II axilla and the left IMN chain with high tangential beams. She was recommended adjuvant hormonal therapy by medical oncology, starting after radiation therapy. (A) Left lateral tangential field with raised cranial border to cover the at-risk axillary nodes. (B) Isodose lines showing coverage of the whole breast, internal mammary nodes, and at-risk axillary nodes.

The majority of the studies discussed above focus on the potential role of radiation therapy for SLN positive patients receiving breast conserving surgery. These patients will receive at least whole breast radiation with consideration of comprehensive nodal coverage as per either Z0011 or AMAROS trials. The AMAROS study also included approximately 17%-18% of patients receiving mastectomies. From this limited information, it appears that SLN positive patients can be treated with chest wall and comprehensive nodal radiation instead of an ALND. While multiple randomized trials and a meta-analysis have revealed a survival advantage for postmastectomy radiation for pN1 disease patients, these historical studies typically involved macroscopic nodal disease in patients receiving surgical axillary clearance with an ALND.[23-25]

It is less clear, what is the most appropriate treatment for patients found to have low-volume SLN disease after mastectomy. The EORTC trial included 24% of patients who underwent mastectomy, with inclusion criteria of high-risk node-negative or node-positive patients being randomized to chest wall irradiation at the institution's discretion ± comprehensive nodal irradiation. Seventy-three percent of patients in both groups did ultimately receive chest wall radiation therapy. While 44% of patients were N0, all N+ patients did receive an ALND. As previously summarized, the patients receiving comprehensive nodal radiation had improved disease-free survival, distant disease-free survival, and breast cancer mortality. While N0, high-risk patients having multiple risk factors including lymphovascular invasion, grade 3 disease, T2+, close surgical margins, and age less than 50 may also be considered for postmastectomy radiation based on retrospective analyses, the overall benefit for postmastectomy radiation in these lower risk populations is thought to be more limited in the age of modern systemic therapy. Indeed, while the EORTC study did include a large number of lower risk patients, including N0 disease, the specific outcomes of the mastectomy patients with low-volume lymph node disease receiving ALND are not completely characterized.

Table 3 provides a summary of these important randomized trials. To put the outcomes of these trials in the context of current treatment trends, a National Cancer Database study from the years 2013 to 2014 found that 57% of patients with micrometastases underwent SLN-biopsy alone, vs 23% of those with macrometastases.[26] This implies increased surgeon comfort with omitting ALND, with the idea that adequate radiation fields and systemic therapy will control micrometastatic disease. Until further prospective trials are performed with rigorous radiotherapy quality assurance, it is reasonable for radiation oncologists to treat patients with pN0[i+] or pN1mi disease who would have been eligible for Z0011 or AMAROS (T1-T2, cN0/pN1[*sn*]) with either high tangents covering the level I-II nodes or comprehensive nodes, including level III and the supraclavicular region. In addition, extrapolation of Z0011 and AMAROS radiation field designs in postmastectomy patients would also be reasonable. Multiple tumor factors should be considered in adjuvant treatment recommendations, including but not limited to tumor size, age, grade, and hormone receptor status, and this information may also help guide radiation treatment recommendations and radiation field design. When weighing this multitude of information in calculating the patients' risk, it is reasonable to adjust radiation treatment fields to match that risk. Inclusion of levels I-II can be performed with minor adjustments to standard tangential fields.[21,27] Schlembach et al reports that the SLN region and axillary levels I-II are often covered by extending the cranial border to 2 cm below the humoral head and 2 cm deep to the chest wall-lung interface.[27] Figure 3 is a clinical example.

Conclusions

Pathologic evaluation of SLNs is focused almost exclusively on the detection of clinically-significant macrometastatic disease. To advance the field of micrometastatic pathologic interrogation, we must first be able to prove the prognostic significance of micrometastatic disease in SLNs. As the data thus far have not proven this definitively, it may be more reasonable to set out to prove predictive significance, meaning that the presence of

micrometastatic deposits alters clinical treatment.[6] In the modern era of treatment, this low-volume nodal disease may play a larger role in adjuvant treatment recommendations, including both systemic and radiation therapy. As the oncologic field progresses with the push to accomplish more with less tissue, it is important that pathologic evaluation keep prognostic and predictive significance to the applied methods at the forefront, or else the time and cost of the evaluation may not be justified.

Long-term follow-up data will help clarify the prognosis and optimal management of patients with micrometastases or ITCs. Based on the available data, current guidelines support omitting ALND in cases of small-volume nodal metastasis. Patient preference, tumor risk factors, adjuvant therapy selection, and radiation field design all should be accounted for during the decision-making process in the postoperative management of occult nodal metastases.

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