
Significance of Sentinel Lymph Node Micrometastases in Human Breast Cancer

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- BACKGROUND:** The significance of micrometastatic disease in the sentinel lymph nodes (SLN) of patients with invasive breast cancer has been questioned. The objective of our study was to review the impact of micrometastatic carcinoma detected by SLN biopsy.
- STUDY DESIGN:** Between January 1997 and May 2004, 2,408 patients with invasive breast cancer and an SLN with micrometastatic (N0[i+], N1mi) or no metastatic (N0[i-]) disease were identified through our breast database. Slide review was performed and reclassified by the 6th edition of the *American Joint Committee on Cancer Staging Manual*. Of these, 27 were excluded from analysis because of evidence of macrometastatic disease on slide review or enrollment in the American College of Surgeons Oncology Group Z10 study.
- RESULTS:** Of 2,381 patients, 2,108 were N0(i-), 151 were N0(i+), and 122 were N1mi. Overall and disease-free survivals of patients with an N1mi SLN were substantially worse than those in patients with an N0(i-) SLN ($p < 0.001$ and $p = 0.006$, respectively). Additional positive non-SLNs were identified in 15.5% (15 of 97) of N1mi patients and 9.3% (10 of 107) of N0(i+) patients undergoing completion axillary lymph node dissection. Overall survival of the N0(i+) SLN patients not undergoing axillary dissection was substantially less than those undergoing axillary dissection ($p = 0.02$).
- CONCLUSIONS:** Detection of micrometastatic carcinoma (N1mi) in the SLNs of invasive breast cancer patients is a major indicator of poorer survival compared with N0(i-) patients. Although survival of patients with an N0(i+) SLN does not statistically differ from that of N0(i-) patients, 9.3% of these patients had additional axillary nodal disease on axillary dissection, and N0(i+) patients had a decreased survival when axillary dissection was omitted. (*J Am Coll Surg* 2008;206:261-268. © 2008 by the American College of Surgeons)
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Sentinel lymph node (SLN) mapping for breast cancer has become the primary way to accurately assess nodal metastasis. The sensitivity of this technique is greatly enhanced with the use of cytokeratin immunohistochemical staining (CK-IHC). A histologically negative SLN evaluated with CK-IHC stains predicts a negligible risk of finding a positive non-SLN (false negative assessment), as validated by Turner and colleagues.¹ Our initial experience of 120 patients undergoing SLN biopsy with hematoxylin and eosin

(H&E) and cytokeratin staining, followed by mandatory completion axillary dissection, had one false negative case.² Early studies with short-term (2 to 3 years) followup reported a 0% to 0.25% incidence of axillary recurrences in patients with CK-IHC-negative pathologic findings of the SLN.³⁻⁵ These findings clearly support the notion that a CK-IHC-negative SLN accurately reflects the negative status of the remaining nodal basin.

Prospective trials are currently underway to define the clinical significance of micrometastatic disease within SLNs. The American College of Surgeons Oncology Group Z0010 trial and the National Surgical Adjuvant Breast and Bowel Project B32 trial have recently completed accrual. These studies were designed to settle the debate about the utility of CK-IHC staining. Previous trials have demonstrated an improved overall sensitivity in identifying an SLN with very small amounts of disease.^{1,6,7} So, identification of submicroscopic amounts of disease within the

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Abbreviations and Acronyms

CK-IHC	=	cytokeratin immunohistochemical staining
H&E	=	hematoxylin and eosin
SLN	=	sentinel lymph node

SLN has become a diagnostic dilemma in terms of how to manage such patients, both surgically and medically.

The American Joint Committee on Cancer (AJCC) staging system has been modified to accommodate the fact that most breast surgeons throughout the US requested that CK-IHC staining be performed on their patients to find such isolated tumor cells, defined as single cells or small groups of cells with a maximal diameter of 0.2 mm. The modified classification now reflects this nodal status as N0(i+), meaning the node is considered negative by standard H&E examination, but positive by CK-IHC staining. Because this classification was added years after the beginning of the SLN mapping era, previous pathology reports did not differentiate between N0 and N0(i+) nodal disease. Additionally, micrometastatic disease within an SLN was also redefined as firmly identified on H&E staining, measuring between 0.2 and 2 mm in diameter. Such nodes are designated as pN1mi to distinguish them from more traditional, H&E-positive macrometastases, or N1 disease.

There are two major issues surrounding the significance of CK-IHC-positive SLNs. The first is whether the surgeon should perform a completion axillary lymph node dissection in the face of CK-IHC disease. It has been noted that the presence of CK-IHC stained cells, whether indicating N0(i+) or N1mi disease within the SLN, is associated with a 4% to 20% chance of additional H&E-positive non-SLNs within the remaining axillary basin.^{6,8-15} So, if a complete axillary lymph node dissection is not performed, there remains a 4% to 20% chance of understaging the patient because of non-SLN disease being present within the remaining nodal basin.

The second issue, whether micrometastatic disease within the SLN is clinically significant to the patient's disease-free or overall survival, is still controversial. This particular issue has been addressed by several investigators.¹⁶⁻²⁰ Previous studies have retrospectively analyzed patients found to be pathologically node negative, examining the paraffin-embedded blocks with CK-IHC and finding no difference in survival in patients with evidence of CK-IHC disease only.¹⁷⁻¹⁹ But because these patients had already undergone a complete axillary lymph node dissection, patients with N1 disease were excluded from the analysis. So it is still controversial as to whether such information can be used by the clinician to inform treatment decisions and additional surgical intervention. The chance of finding addi-

tional disease within non-SLNs on completion axillary lymph node dissection is as high as 20%, subsequently resulting in the upstaging of such patients to N1 disease.

This study represents one of the largest to date in terms of total number of SLNs examined in a prospective fashion, focusing on the detailed microscopic analysis of SLNs from patients with breast cancer. All derived SLNs underwent a prospective, standardized pathologic evaluation with both routine H&E and CK-IHC analysis. The overall objective of this study was to analyze the clinical significance of CK-IHC disease within the SLNs of breast cancer patients through the prospective use of CK-IHC staining. Second, was to define the role of complete axillary dissection in the patients with CK-IHC (+) disease only (N0[i+] and N1mi) nodal disease.

METHODS

An Institutional Review Board-approved Health Insurance Portability and Accountability Act (HIPAA)-compliant breast cancer database and electronic health record (IRB# 102554) prospectively accrued 3,874 patients undergoing 4,137 SLN biopsies for invasive breast cancers between January 1997 and May 2004. Under separate IRB approval (IRB# 100461), this database was queried for invasive breast cancer patients with pathology reports showing either micrometastatic (N0[i+] or N1mi) or no metastatic disease N0(i-) on SLN biopsy, all of which had undergone CK-IHC evaluation. There were 2,408 patients identified who fulfilled this requirement. Routine pathologic evaluation included intraoperative imprint cytology of nodes; then nodes were sectioned into 2-mm sections, placed sequentially in cassettes, embedded in paraffin, faced, cut, and stained with H&E. Cuts were made at 50 μ m and 100 μ m, stained for CK-IHC (CAM 5.2, Becton Dickinson), and, as a control for the IHC stains, counterstained with hematoxylin.

All patients with an initial diagnosis of micrometastatic carcinoma had their original H&E and CK-IHC (cytokeratin) slides reanalyzed by two surgical pathologists (VV and ND). The final staging classification was reclassified according to the sixth edition of the *AJCC Cancer Staging Manual*. Six patients were removed from the study because they had occult macrometastases on SLN biopsy. Twenty-one patients were excluded because they were previously included in the American College of Surgeons Oncology Group Z-10 trial, in which the CK-IHC analysis was blinded. Tumor deposits > 0.2 mm but \leq 2 mm were classified as N1mi. Patients with SLNs having isolated tumor cells \leq 0.2 mm were classified as N0(i+). SLNs with no epithelial cells on either H&E or immunostaining were classified as N0(i-). Patients who had followup axillary dissections for N0(i+) or N1mi disease had all slides from

Table 1. Patient Group Comparison (n = 2,381)

Patients	n	Median age (range), y	Median tumor size (range), cm	Histologic type, %	Grade, %	Lympho vascular invasion present, %	Treated with chemotherapy, %	Treated with hormones, %	Median followup (range), y
N1mi	122	56 (26–90)	1.5 (0.2, 5.3)	Ductal, 76 Lobular, 11 Mixed, 11 Other, 2	1, 22 2, 46 3, 25 Unknown, 7	58	48	35	1.5 (0–7)
N0(i+)	151	57 (33–86)	1.5 (0.2–6.5)	Ductal, 76 Lobular, 17 Mixed, 3 Other, 4	1, 26 2, 40 3, 22 Unknown, 12	51	42	45	2.0 (0–9)
N0(i–)	2,108	60 (20–94)	1.3 (0.01–8.5)	Ductal, 79 Lobular, 9 Mixed, 7 Other, 5	1, 26 2, 40 3, 28 Unknown, 6	4	22	39	2.1 (0–9)
N0(i–) versus N0(i+) p value		0.10	<0.001	0.004	0.05	<0.001	<0.001	0.17	
N0(i–) versus N1Mi p value		0.07	<0.001	0.23	0.48	<0.001	<0.001	0.36	
Test		Van der Waerden	Van der Waerden	Chi-square	Chi-square	Chi-square	Chi-square	Chi-square	

the completion axillary node dissection reviewed by a single surgical pathologist (VV) to ensure accurate measurement of subsequent metastases. Additional non-SLNs were evaluated by bivalving the lymph node and staining with H&E. Followup data were obtained from our IRB-approved (IRB #102554) breast cancer database. To improve the accuracy of survival data for all patients, our database was checked by the Social Security Death Index on-line database (<http://ssdi.rootsweb.com>).

Kaplan-Meier survival curves for disease-free and overall survival were generated for various groups of patients. The log-rank test was used to compare survival of groups based on final SLN staging. For comparing clinical and demographic features of the patients within each group, the chi-square test and Fisher's exact test were used. The Van der Waerden two-sample test was used for continuous features. Statistical significance was set at the 0.05 level for all tests, and SAS software was used to perform all analyses.

RESULTS

Patient comparison

A total of 2,381 patients underwent SLN biopsy, forming the basis of the study; 2,108 (88.5%) were N0(i–), 122 (5%) were N1mi, and 151 (6%) were N0(i+). Table 1 outlines the characteristics of each of these groups. Comparing the N1mi group with the N0(i–) group, statistically significant differences were seen in the larger tumor size group ($p < 0.001$), and with the presence of lymphovascular invasion ($p < 0.001$). More patients were also found to have received previous chemotherapy ($p < 0.001$) within the N1mi group. A comparison of the N0(i+) and N0(i–) groups found a statistically significant difference based on tumor size ($p < 0.001$), lymphovascular invasion ($p < 0.001$), and the percentage treated with chemotherapy ($p < 0.001$). In addition, statistically significant dif-

ferences were noted in the histology ($p = 0.004$) and grade ($p = 0.05$) of the tumors between the N0(i+) and N0(i–) groups. Totals of 79.5% (97 of 122) of N1mi patients and 70.9% (107 of 151) of N0i+ patients went on to receive a completion axillary lymph node dissection. Reasons for not undergoing axillary dissection were not always evident in the clinical notes, but the only statistically significant differences in comparing those who did and did not receive axillary dissection included tumor histology in the N1mi patients and followup times in the N0(i+) patients (Tables 2, 3).

Survival in patients with micrometastatic disease on sentinel lymph node biopsy

Overall and disease-free survivals for patients with N1mi (+) SLNs differed substantially from patients with N0(i–) SLNs ($p = 0.0007$ and $p = 0.006$, respectively; Figs. 1, 2). Overall and disease-free survivals of patients with N0(i+) SLNs were not notably different from those of patients with N0(i–) SLNs ($p = 0.99$ and $p = 0.48$, respectively; Figs. 1, 2).

Prediction of additional axillary disease in patients with micrometastatic disease within the sentinel lymph nodes

Additional positive non-SLNs were subsequently identified in 15.5% (15 of 97) of N1mi patients and 9.3% (10 of 107) of N0(i+) patients undergoing axillary dissection. The additional nodes were macrometastatic (N1) in 93% (14 of 15) of N1mi patients and 90% (9 of 10) of N0i+ patients. Two patients had N1mi non-SLNs detected by H&E after undergoing axillary dissection. In this series, the proportion of patients with additional positive non-SLNs on completion axillary dissection generally increased with tumor size (Figs. 3, 4).

Table 2. Comparison of N0(i+) Sentinel Lymph Node Patients by Completion Axillary Nodal Dissection (n = 151)

n	Median age (range), y	Median tumor size (range), cm	Histologic type, %	Grade, %	Lympho vascular invasion present, %	Treated with chemotherapy, %	Treated with hormones, %	Median followup (range), y
107	57 (33–86)	1.5 (0.3–6.5)	Ductal, 76 Lobular, 18 Mixed, 3 Other, 4	1, 29 2, 40 3, 20 Unknown, 11	52	42	49	2.1 (0–9)
44	57 (38–86)	1.5 (0.2–6.0)	Ductal, 75 Lobular, 16 Mixed, 4.5 Other, 4.5	1, 20 2, 39 3, 27 Unknown, 14	48	41	36	1.6 (0–8)
P value	0.35	0.69	0.94	0.60	0.61	0.90	0.17	0.04
Test	Van der Waerden	Van der Waerden	Chi-square	Chi-square	Chi-square	Chi-square	Chi-square	Van der Waerden

Survival with and without completion nodal dissection for patients with micrometastatic disease on sentinel lymph node biopsy

Overall survival of the N0(i+) SLN patients who did not receive a complete axillary lymph node dissection was substantially worse than that of those undergoing axillary dissection ($p = 0.02$; Fig. 5). Overall survival of the N1mi SLN patients did not differ substantially between those who did and did not receive an axillary dissection ($p = 0.47$; Fig. 6).

Local axillary recurrence rates without complete axillary nodal dissection

There was 1 local axillary recurrence in the 44 N0(i+) patients (2.27%) who did not receive an axillary dissection. This compares with 6 local axillary recurrences in 2,109 N0(i-) patients (0.28%). This difference was not statistically significant ($p = 0.13$ using Fisher's exact test). To date, there have been no axillary recurrences in the 25 patients with N1mi disease who did not receive a complete axillary dissection.

DISCUSSION

The clinical significance of micrometastatic disease found on SLN biopsy in patients with breast cancer remains controversial. Gershenwald and colleagues²¹ demonstrated that 10 of 243 patients with melanoma (4.1%) went on to

experience a locoregional or distant metastatic recurrence within 18 months when found to be histologically negative by H&E alone. Using the application of IHC analysis of SLNs with specific antibodies such as S-100, HMB-45, and MELAN-A, 8 of 10 patients (80%) were found to have micrometastatic disease on a more detailed analysis of the SLNs. With this knowledge in melanoma patients, the utility of CK-IHC has been applied to patients with breast cancer through the thorough analysis of SLNs with CK-IHC. Indeed, it became necessary to avoid false negative assessment of the nodal basin for which, unlike in melanoma, completion axillary node dissection in breast cancer management was the standard of care.

Examining SLNs with CK-IHC stains results in accurate prediction of the status of the remaining nodal basin, with a consistent false negative rate of 2%.^{1,2} Although SLN technology is a highly marked predictor of the remaining axillary basin when the SLN is CK-IHC negative, a CK-IHC (+) SLN predicts the potential for major remaining nodal disease. In this study, we found additional H&E (+) disease within non-SLNs in 15.5% of patients with N1mi SLN disease and 9.3% of N0(i+) SLN patients. For these patients, the chance of finding additional positive nodes generally increased with tumor size. Although this was a retrospective study, and reasons for performing an axillary dissection were not always available, our results for finding additional axillary disease are similar to previous published data.^{6,8-15}

Table 3. Comparison of N1mi Sentinel Lymph Node Patients by Completion Axillary Nodal Dissection (n = 122)

Patients	n	Median age (range), y	Median tumor size (range), cm	Histologic type, %	Grade, %	Lympho vascular invasion present, %	Treated with chemotherapy, %	Treated with hormones, %	Median followup (range), y
CAND	197	56 (26–84)	1.5 (0.2–5.3)	Ductal, 76 Lobular, 9 Mixed, 13 Other, 1	1, 23 2, 46 3, 26 Unknown, 5	55	52	64	1.5 (0–7)
No CAND	25	59 (34–90)	1.5 (0.8–3.5)	Ductal, 76 Lobular, 16 Mixed, 0 Other, 8	1, 20 2, 48 3, 28 Unknown, 4	68	36	32	1.7 (0–7)
CAND vs no CAND p value		0.08	0.51	0.03	1.0	0.25	0.16	0.70	0.24
Test		Van der Waerden	Van der Waerden	Fisher's exact	Fisher's exact	Chi-square	Chi-square	Chi-square	Van der Waerden

CAND, completion axillary nodal dissection.

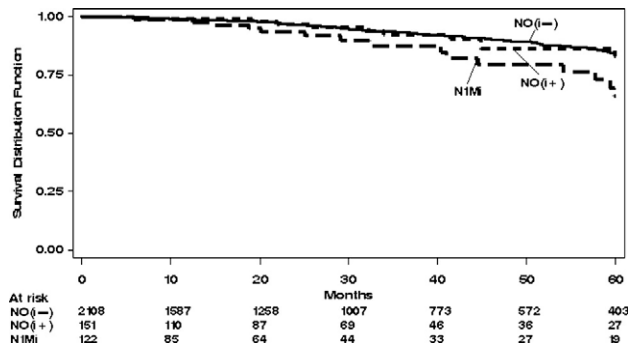


Figure 1. Overall survival comparisons between invasive breast cancer patients with N1mi sentinel lymph nodes (SLN), NO(i+) SLN, and NO(i-) SLN.

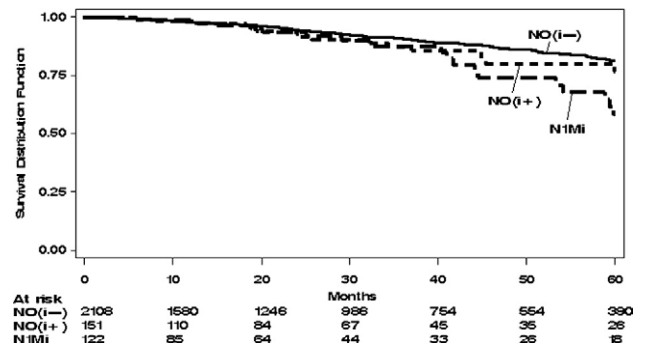
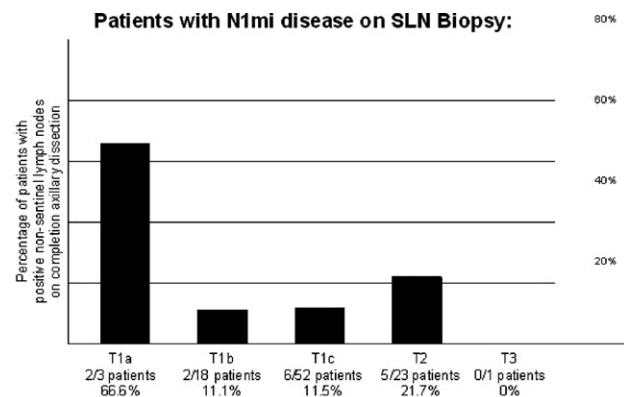


Figure 2. Disease-free survival comparisons between invasive breast cancer patients with N1mi sentinel lymph nodes (SLN), NO(i+) SLN, and NO(i-) SLN.

The detection of micrometastatic carcinoma (N1mi) in the SLNs of patients with invasive breast cancer is a major predictor of overall survival. Not surprisingly, these patients were treated more aggressively compared with patients with NO(i+) disease, with the former receiving recommendations for completion lymph node dissection and adjuvant chemotherapy. Although nodal tumor clusters of < 0.2 mm may not in themselves be major detriments to patient survival, it is clear that when such disease is found

within the SLN, it is predictive of the possible existence of additionally positive nodal disease within the remaining nodal basin, as identified by H&E in 9.3% of patients. At first glance, it appears counterintuitive to see a survival difference because of axillary dissection noted in the NO(i+) group and not in the N1mi group because it seems that patients with less disease within the nodes responded better with more aggressive surgical treatment. The survival difference may be an issue of the overall small numbers of patients analyzed and would need to be confirmed in larger, prospective studies.

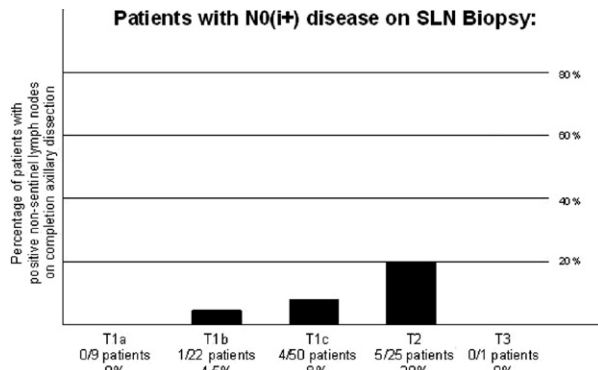


T Size	# patients with N1mi disease on SLN biopsy	# patients who underwent follow-up CAND	# patients with positive non-SLN on CAND	% patients with positive non-SLN on CAND
T1a	3	3	2	66.6%
T1b	22	18	2	11.1%
T1c	66	52	6	11.5%
T2	30	23	5	21.7%
T3	1	1	0	0%
All	122	97	15	15.5%

Figure 3. Breakdown of patients with N1mi disease on sentinel lymph node (SLN) biopsy.

It is possible that patients with NO(i+) disease are being understaged and possibly undertreated as a result. A survival difference was not noticed in the N1mi group, possibly because these patients are treated more aggressively, as witnessed by the fact that only 25 of 122 patients did not receive axillary dissections and more patients with N1mi SLN received chemotherapy (48% to 42%, $p = 0.27$). In addition, the NO(i+) subset had greater overall statistical power because 44 patients did not receive an axillary dissection. Interestingly, there was 1 local axillary recurrence in the 44 NO(i+) patients who did not receive an axillary dissection. This approximates a 10-fold increase in local recurrence when compared with NO(i-) patients (2.27% versus 0.28%), but it is not statistically significant ($p = 0.13$). Although the numbers of patients in the NO(i+) group were quite small, the question remains as to the adequacy of locoregional control by avoiding a completion axillary node dissection in this at-risk group of patients.

In reviewing our data, the only subset of patients that could possibly safely avoid axillary dissection after a finding of micrometastatic disease on SLN biopsy would be patients with T1a and T1b tumors and NO(i+) disease. This group of patients had only 1 incident of additional positive non-SLN in 31 axillary dissections. But the finding of improved survival of NO(i+) patients undergoing axillary dissection demonstrated by our data would suggest caution if axillary dissection was omitted in this subset.



T Size	# patients with N0(i+) disease on SLN biopsy	# patients who underwent follow-up CAND	# patients with positive non-SLN on CAND	% patients with positive non-SLN on CAND
T1a	14	9	0	0%
T1b	28	22	1	4.5%
T1c	71	50	4	8%
T2	36	25	5	20%
T3	2	1	0	0%
All	151	107	10	9.3%

Figure 4. Breakdown of patients with N0(i+) disease on sentinel lymph node (SLN) biopsy.

Advocates opposed to performing a completion lymph node dissection in the face of N0(i+) disease point out the additional morbidity involved with this procedure. Other modalities, such as adjuvant radiation and chemotherapy, are often discussed. Such alternatives not only fail to provide similar local control of disease, but are not without their own associated adverse side effects and risks. The morbidity of a complete axillary lymph node dissection is well established, with the known complication of chronic lymphedema ranging from 10% to 37%.²²⁻²⁶ The use of axillary radiation as single treatment modality has a re-

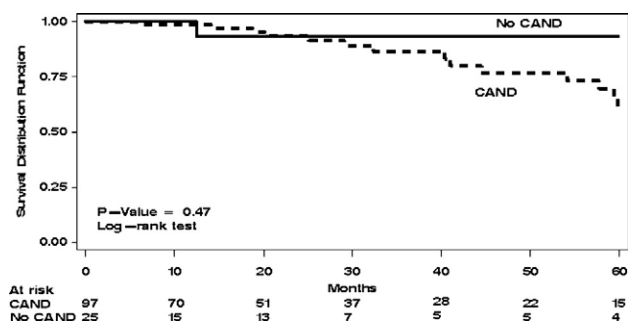


Figure 6. Overall survival of the N1mi sentinel lymph node (SLN) patients with and without completion axillary nodal dissection (CAND).

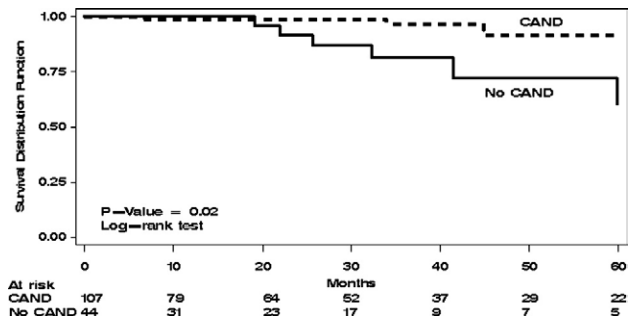


Figure 5. Overall survival of N0(i+) sentinel lymph node (SLN) patients with and without completion axillary nodal dissection (CAND).

ported lymphedema rate of approximately 10%.^{27,28} In terms of local control, Louis-Sylvestre and associates²⁸ compared adjuvant axillary radiation to clinically node negative patients to axillary dissection in more than 600 patients with a mean followup of 15 years. When radiation was given in absence of an axillary dissection, they found a statistically significant increase in local recurrences ($p = 0.04$). With regard to chemotherapy, complete pathologic response has been noted in the axilla in 23% to 27% of patients undergoing neoadjuvant chemotherapy, incompletely eliminating disease from the axilla in the majority of patients.^{29,30} Last, the use of axillary radiation and systemic adjuvant chemotherapy fails to offer any staging information, as opposed to that obtained from a complete axillary lymph node dissection, which, in most instances, provides the most detailed information regarding the accurate staging of breast cancer patients. Such staging information is critical in discussing adjuvant therapy decisions for patients, affecting and changing the management decisions in up to 12% of patients who undergo completion axillary lymph node dissection.²⁰

In conclusion, thorough and detailed evaluation of the SLN with H&E and CK-IHC staining allows the surgeon to accurately stage the nodal basin, identifying patients requiring a completion axillary lymph node dissection. Final staging for patients with an N0(i-) SLN can be definitive based on SLN biopsy alone. But final staging of breast cancer cannot reliably be determined after the finding of micrometastatic disease in a SLN. Final staging for patients with N0(i+) or N1mi disease on SLN biopsy should be based on the findings from a complete axillary nodal dissection instead. Corollary to this fact is that retrospective cooperative group trials that base staging on axillary dissection specimens demonstrating N1mi or N0(i+) disease cannot be extrapolated to N1mi and N0(i+) disease seen on SLN biopsy. It is important to realize that the natural history and clinical course of breast cancer is variable, often remaining indolent for many years, only to recur years later

after the initial diagnosis. We must always be critical of new technologic advancements, erring on the side of the patient with regard to applying such technologies to clinical decision making. A noncompromising position for performing a completion axillary lymph node dissection assures the safety of the patient by surgically achieving maximal local control. It will also greatly reduce the longterm morbidity for those who would eventually suffer recurrence in the axillary basin, providing the benefits of accurate staging and a subsequent decision concerning adjuvant chemotherapy. The results of this study may certainly herald the final clinical outcomes of the American College of Surgeons Oncology Group Z-10 trial. In the meantime, we recommend that patients with breast cancer, who are found to have N0(i+) and N1mi disease within the SLN, should subsequently be offered a complete axillary lymph node dissection.

Author Contributions

Study conception and design: C Cox, Kiluk, J Cox
Acquisition of data: Kiluk, J Cox, Allred, Ramos, Vrcel, Diaz
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Critical revision: C Cox, Kiluk, Riker, J Cox, Dupont

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