

Predictors of Completion Axillary Lymph Node Dissection in Patients With Immunohistochemical Metastases to the Sentinel Lymph Node in Breast Cancer

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ABSTRACT

Background. Axillary lymph node dissection (ALND) in patients with immunohistochemistry (IHC)-determined metastases to the sentinel lymph node (SLN) is controversial. The goal of this study was to examine factors associated with ALND in IHC-only patients.

Methods. Retrospective review of an institutional SLN database from July 1997 to July 2003 was performed. We compared sociodemographic, pathologic, and therapeutic variables between IHC-only patients who had SLN biopsy alone and those that had ALND.

Results. Our study group consisted of 171 patients with IHC-only metastases to the SLN. Young age, estrogen receptor negative status, high Memorial Sloan-Kettering Cancer Center nomogram score, and chemotherapy were associated with ALND. Among patients who had ALND ($n = 95$), 18% had a positive non-SLN. Rates of systemic therapy were similar between those with and without positive non-SLNs at ALND. No axillary recurrences were observed in this series with a median follow-up of 6.4 years. The percentage of patients who were recurrence-free after 5 years was 97% (95% confidence interval, 92.1–98.6).

Conclusions. On the basis of our findings and the lack of prospective randomized data, the practice of selectively limiting ALND to IHC-only patients thought to be at high

risk and to patients for whom the identification of additional positive nodes may change systemic therapy recommendations seems to be a safe and reasonable approach.

The status of the regional lymph nodes is the most important prognostic factor for patients with invasive breast cancer.¹ Historically, routine axillary lymph node dissection (ALND) was a standard component of the surgical management of breast cancer.² ALND has been demonstrated to be both prognostic and therapeutic. It provides local control to the axilla in addition to guiding a variety of multidisciplinary care decisions.

During the 1990s, a major advance was made through the work of Giuliano et al. and Krag et al. These researchers, using Cabanas's concept of a "sentinel node" in penile cancer, demonstrated that lymphatic mapping and sentinel lymph node (SLN) biopsy in breast cancer can accurately stage the axilla.^{3–5} SLN biopsy minimizes patient morbidity with a lower incidence of complications than ALND.^{6,7} Largely for these reasons, SLN biopsy has been adopted at most centers as a standard part of the evaluation of early-stage breast cancer patients.⁸

SLN biopsy provides pathologists with a smaller amount of tissue than ALND, allowing for enhanced pathologic evaluation with serial sectioning and immunohistochemistry (IHC) stains. With this technique, pathologists can detect very small amounts of disease in the axilla. Initial reports regarding the prognostic significance of small amounts of axillary disease were difficult to interpret as a result of varying pathologic techniques and terminology.⁹

However, it is clear that small-volume metastases to the axilla can be reliably identified with rigorous pathologic techniques, and there is increasing evidence that they may be of prognostic importance.^{9–11}

Without prospective randomized evidence for or against ALND in patients with IHC-only metastases, different treatment approaches have been debated. We report here a large single-institution series of patients with IHC-only metastases to the SLNs in whom ALND was selectively performed. The purpose of this study was to determine factors associated with ALND in IHC-only patients.

METHODS

After approval from our institutional review board, retrospective review of the Breast Service's prospectively maintained SLN database was performed. Consecutive patients with invasive cancers who underwent SLN biopsy between July 1997 and July 2003 were included. The protocol for lymphatic mapping, lymphoscintigraphy, and pathologic analysis of the SLNs in this database has been previously described.¹² Patients were excluded for synchronous bilateral disease, neoadjuvant therapy, and/or stage IV presentation. With the exception of nonmelanoma skin cancer, patients were excluded if they had any non-breast malignancy diagnosis within the 5 years before the diagnosis of the index breast cancer. Of 4446 eligible patients in the SLN database, 1470 patients (33.1%) with positive SLNs met the inclusion criteria. Our study group consisted of 171 (11.6%) of 1470 patients with IHC-only metastases. By definition, the SLN metastases in this cohort were identified with IHC stains (AE1:AE3) and could not be seen on serial sections with hematoxylin and eosin (H&E) evaluation, including deeper cuts.

Comorbid medical conditions were classified according to Adult Comorbidity 27 score and divided into groups of none/mild and moderate/severe for the purpose of this study.¹³ Memorial Sloan-Kettering Cancer Center (MSK) nomogram scores for prediction of non-SLN metastases were determined by a widely available Web-based calculator (<http://www.nomograms.org>).¹⁴ The χ^2 , Fisher's exact, and Wilcoxon rank sum tests were used for statistical analysis. Time to recurrence from date of SLN biopsy until date of recurrence or last follow-up was estimated by methods of Kaplan-Meier. SAS version 9.1 software (SAS Institute, Cary, NC) was used for all statistical analyses.

RESULTS

There were 171 patients with positive SLNs detectable only by IHC. Table 1 shows the cohort characteristics and their association with ALND. Patients having ALND were

significantly younger than those who did not (median age 53 vs. 59 years, $P = .002$). Patients treated with mastectomy tended to have ALND at higher rates than patients treated with breast conservation (66% vs. 50%, $P = .055$). No association was noted between comorbidity score and ALND. The only pathologic feature significantly associated with ALND was estrogen receptor-negative status ($P = .026$). Tumor size, tumor type, histologic grade, nuclear grade, progesterone receptor status, HER2/neu status, lymphovascular invasion, and multifocality were not associated with ALND. High MSK nomogram scores were associated with ALND (median predicted positive non-SLN rate 8.1% vs. 4.2%, $P = .001$). Patients undergoing ALND were more likely to receive chemotherapy, but no relationship between ALND and the use of endocrine therapy or axillary irradiation was observed. However, only a small number of patients in this study (3.2%) received radiotherapy to an axillary field.

Among patients treated with ALND, 17 (18%) of 95 patients had additional positive non-SLNs identified on routine H&E. The median number of positive non-SLNs identified was 1 (range, 1–12). Receipt of adjuvant therapy did not differ between ALND patients with and without positive non-SLNs (Table 2).

No axillary recurrences were observed in this series with a median follow-up of 6.4 years (range, 0–10 years), and the percentage of patients who were recurrence-free after 5 years was 97% (95% confidence interval, 92.1–98.6). Kaplan-Meier curves for recurrence-free survival for all patients and for patients based on axillary treatment group are shown in Figs. 1 and 2. Of nine total recurrences, six were distant and three were local. Eight of the nine patients with recurrences were in patients treated with ALND (Table 3).

DISCUSSION

IHC stains are known to identify malignant-appearing cells in 10% to 30% of SLN biopsy samples.^{9,15–17} A previous study that used our institution's SLN protocol by Tan et al. found that 98% of the 50 IHC-only patients had malignant cells, or clusters of cells, no greater than .2 mm in size.¹¹ These patients would be considered to have N0(i+) disease by the American Joint Committee on Cancer's (AJCC's) 6th edition staging criteria. Because method of detection was a primary descriptor for small-volume metastases over the time course of this study (1997–2003) and data on lymph node metastasis size were not routinely provided before the enactment of AJCC's 6th edition, we used the method of detection as a surrogate for lymph node metastasis size for the purposes of this study. We acknowledge that IHC-only metastases have good but not perfect correlation to the AJCC's current N0(i+) category.

TABLE 1 Variables associated with ALND in patients with immunohistochemistry-only SLNs

Variable	SLN biopsy alone (<i>N</i> = 76)		ALND (<i>N</i> = 95)		<i>P</i>
	<i>N</i> (%)	<i>N</i> , median (range)	<i>N</i> (%)	<i>N</i> , median (range)	
Sociodemographic characteristics					
Age (y)		76, 59 (38–87)		95, 53 (29–87)	.002
Comorbidities					
None/mild	62 (81.6)		83 (87.4)		.392
Moderate/severe	14 (18.4)		12 (12.6)		
Conservation operation	55 (72.4)		55 (57.9)		.055
Pathologic characteristics					
Tumor size (cm)		76, 1.3 (0.1–4.5)		92, 1.5 (0.2–6.2)	.171
Tumor type					
Ductal	60 (79)		76 (80)		.999
Lobular	16 (21.1)		19 (20)		
Histologic grade					
I	4 (6.6)		4 (5.3)		.430
II	12 (19.7)		22 (29.3)		
III	45 (73.8)		49 (65.3)		
Estrogen-receptor negative	6 (9.4)		19 (24.4)		.026
Progesterone-receptor negative	21 (32.8)		31 (39.7)		.484
Presence of lymphovascular invasion	16 (21.1)		20 (21.1)		.999
HER2/neu positive	10 (18.9)		11 (17.2)		.814
Multifocal disease	19 (25)		31 (32.6)		.313
Nomogram score (% predicted)		61, 4.2 (0–25)		72, 8.1 (0.3–46)	.001
Treatment characteristics					
Chemotherapy	42 (62.7)		77 (87.5)		<.001
Hormone therapy	60 (89.6)		73 (83)		.353
Axillary irradiation	3 (4.6)		2 (2.2)		.650

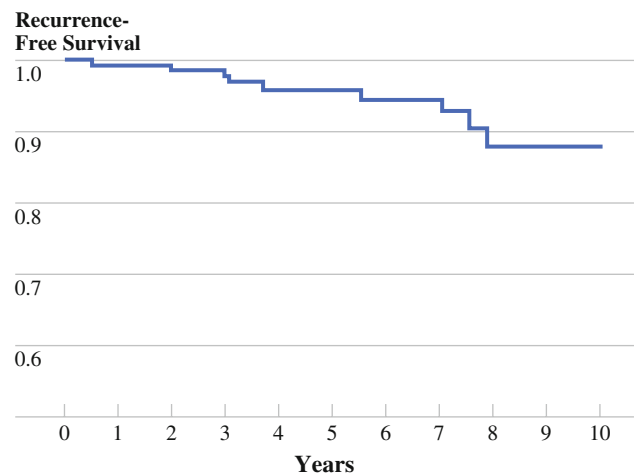
ALND axillary lymph node dissection, SLN sentinel lymph node

TABLE 2 Treatment decisions in patients treated with ALND

Treatment	Negative ALND, <i>n</i> (%) (<i>N</i> = 78)	Positive ALND, <i>n</i> (%) (<i>N</i> = 17)	<i>P</i>
Chemotherapy	64 (87.7)	13 (86.7)	.999
Antiestrogen treatment	60 (83.3)	13 (81.3)	.999
Axillary radiation	1 (1.35)	1 (6.3)	.326

ALND axillary lymph node dissection

Controversy exists regarding the prognostic and therapeutic significance of this staging category, and it is currently unknown whether IHC-only or N0(i+) disease alone should be an indication for ALND.^{18–20} The American Society of Clinical Oncology practice guidelines recommend ALND to patients with positive SLNs. They specifically include micrometastatic disease (N1mi) in this recommendation and state that the significance of isolated malignant cells (N0(i+)) is unknown. The National Cancer

**FIG. 1** Recurrence-free survival for all immunohistochemistry-only patients

Center Network practice guidelines state that ALND should be recommended to patients with SLN disease seen on H&E sections. These recommendations demonstrate the

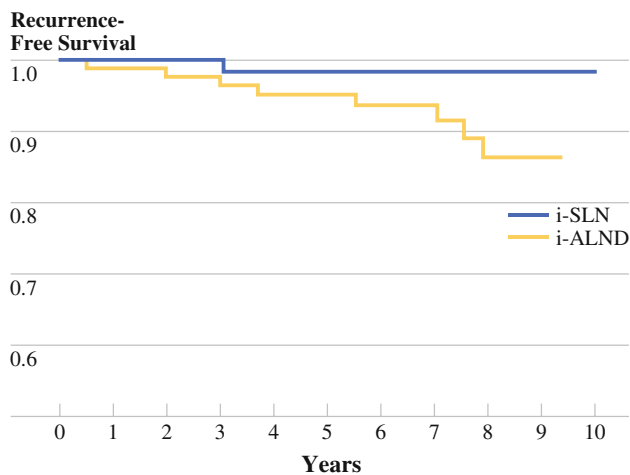


FIG. 2 Recurrence-free survival based on axillary therapy

relative lack of consensus regarding the use of ALND in patients with small-volume metastases.

Our center has used a selective approach to ALND in IHC-only patients, and this study demonstrates that young age and estrogen receptor–negative status were associated with ALND. It is known that young age at diagnosis and estrogen receptor–negative tumors are poor prognostic factors that are associated with higher recurrence rates and greater benefit from chemotherapy.²¹ In this subset of patients with IHC-only disease, ALND may offer additional local control and staging benefits.

The MSK nomogram for risk of additional nodal metastasis uses pathologic data to estimate the likelihood of a non-SLN metastasis in patients with positive SLN biopsy results.¹⁴ This tool was retrospectively created using characteristics from 702 SLN positive patients (63 with IHC-only disease) and prospectively validated on a population of 373 SLN-positive patients (18 with IHC-only disease). The nomogram has been further validated in independent and varied populations by at least 20 other institutions. To be included in the nomogram study, patients had to have primary invasive breast cancer, a clinically negative axilla, no prior systemic treatment, a

successful SLN biopsy in which metastatic disease was identified, and a completion ALND. Although ALND was considered standard of care for all patients with positive SLN biopsy findings over the time period of the nomogram study (1996–2002), it was not mandatory, and 140 patients were excluded from the nomogram study because they did not receive ALND.¹⁴ Therefore, inclusion in the nomogram study does not confound this data set, and given that most of the patients in this study were treated before the publication of the nomogram, the association of high MSK nomogram score and ALND likely reflects the fact that clinicians were considering the nomogram and/or variables used by the nomogram when selecting IHC-only patients for avoidance of ALND.

In our patients selected for ALND, the risk of macrometastases to the non-SLNs was substantial (18%). This relatively high rate of positive non-SLNs likely reflects selection bias in the ALND group. Other studies have used more routine ALND in their IHC-only patients. Chu et al. and Freneau et al. both report a very low rate of non-SLN positivity (0% and 3%, respectively).^{22,23} They suggest that ALND can be omitted for some IHC-only patients. Other studies by Marin et al., Abdessalam et al., Bergkvist et al., and Mignotte et al. document higher rates of non-SLN positivity in IHC-only patients (22%, 20%, 17%, and 16%, respectively), supporting the potential benefits of ALND for IHC-only patients.^{24–27} Cserni et al. pooled the published data, containing 347 IHC-only patients treated with completion ALND, and found an 11% rate of non-SLN metastasis.²⁸ A similar analysis by van Deurzen et al. found 12.9% of N0(i+) patients treated by ALND had non-SLN metastases.²⁹ This study recommended that patients with N0(i+) SLN metastases without indications for adjuvant systemic therapy might be considered candidates for ALND.

When comparing patients with and without positive non-SLNs in our study's patients treated with ALND, the rates of chemotherapy administered did not differ. However, chemotherapy was associated with ALND. This suggests that the decision to give chemotherapy was

TABLE 3 Description of recurrences

Patient	Site of recurrence	Group	Final N stage	Years to recurrence	Status
1	Local	ALND	N1a	3.0	DOD
2	Local	ALND	N0 (i+)	7.9	NED
3	Local	ALND	N0 (i+)	0.5	NED
4	Distant	ALND	N1a	3.7	AWD
5	Distant	ALND	N1a	5.6	AWD
6	Distant	ALND	N1mi	7.1	AWD
7	Distant	ALND	N1mi	7.6	AWD
8	Distant	ALND	N3a	2.0	AWD
9	Distant	SLN biopsy alone	N0 (i+)	3.1	AWD

ALND axillary lymph node dissection, DOD dead of disease, NED no evidence of disease, AWD alive with disease, SLN sentinel lymph node

strongly related to patient and primary tumor characteristics. However, the retrospective nature of this study makes it difficult to determine whether ALND was performed to help make decisions regarding adjuvant therapy or if ALND was performed for additional local control in high-risk patients already selected for systemic therapy.

To optimize length of follow-up, we only included patients with SLN biopsies performed during the first half of our SLN experience (July 1997–July 2003). With a median follow-up of 6.4 years (range, 0–10 years), only nine instances of recurrence occurred, none of which were axillary recurrences. The fact that eight of nine recurrences occurred in patients treated with ALND reflects the selection of high-risk patients for this procedure. However, there continues to be a low rate of recurrences documented in IHC-only patients.^{30,31} Therefore, it will likely require a large, prospective study to answer questions regarding the prognostic and therapeutic implications of IHC-only SLN metastases. With thousands of randomized patients and blinded enhanced pathology, the NSABP B-32 and ACoSOG Z0010 trials have the potential to answer these questions. Pending results from these and other such trials, the prognostic and therapeutic significance of IHC-only patients will likely continue to be a matter of debate.

This study is unique because it focuses on a large cohort of IHC-only patients and considers the factors associated with a controversial component of their surgical decision making. The calculation of MSK nomogram scores and Adult Comorbidity 27 scores attempt to best quantitate estimations of risk used when making these clinical decisions; however, it is impossible to remove the limitations inherent to retrospective database review. These limitations make it difficult to answer specific questions regarding the primary reasons for ALND in this patient population. Therefore, we are uncertain how much individual concerns such as prognosis and local control played into decision making.

In summary, without the benefit of prospective, randomized data for or against ALND in patients with IHC-only metastases, we think that the practice of limiting ALND to IHC-only patients thought to be at high risk for recurrence, and to patients in whom the identification of additional positive nodes would change systemic therapy recommendations, seems to be a safe and reasonable approach.

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