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Late Axillary Recurrence After Negative Sentinel Lymph Node Biopsy Is Uncommon

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Abstract

Background—To determine incidence of late axillary recurrence (AR) in patients with negative sentinel lymph node biopsy (SLNB) and provide a comparison with SLNB-positive patients who underwent axillary lymph node dissection (ALND).

Methods—Retrospective analysis of prospectively collected data on all breast cancer patients with negative SLNB from 1/1997–12/2000 was performed on a large institutional database. Primary outcome was cumulative incidence of AR as a first event with/without concurrent local recurrence. SLNB-positive patients who went on to ALND during the same timeframe were comparatively analyzed.

Results—1529 eligible patients were identified (median age 58 yrs, median tumor size 1.0 cm). 1297 (85%) underwent lumpectomy; 1099 (75%) received adjuvant radiation. 874 (80%) were estrogen receptor-positive. At 10.8 yrs (0–16) median follow-up, overall incidence of AR as a first event was low (n=13). Cumulative incidence was 0.6% (95% confidence interval [CI] 0.2–0.9) 5 years after SLNB, and 0.9% (95% CI 0.4–1.4, 95% CI 0.5–1.6) at 10 and 15 years. Late AR (>5 years after surgery) occurred in 5 patients. Median overall survival after AR was 4.6 yrs; median distant disease-free survival after axillary recurrence was 3.8 yrs. Late AR was also low in a contemporaneous group of SLNB-positive patients undergoing ALND. In this group, cumulative incidence of AR was 0.7% (95% CI 0.1–1.3) 5 years after surgery, and 0.8% (95% CI 0.2–1.5) at 10 and 15 years.

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Discussion—Late axillary recurrence after negative SLNB is rare, with the majority of axillary recurrences occurring in the first 5 years after surgery. Prognosis after these events is poor. SLNB remains a safe and effective procedure for axillary evaluation in breast cancer.

Keywords

sentinel lymph node biopsy; axillary recurrence; breast cancer

INTRODUCTION

Sentinel lymph node biopsy (SLNB) has proven to be an accurate and safe method to identify axillary metastases in clinically node-negative breast cancer patients. Large randomized trials comparing node-negative patients who underwent SLNB alone to SLNB followed by axillary lymph node dissection (ALND) show false-negative rates less than 10% and axillary recurrence rates less than 2% in each group.^{1–4} These studies were concluded in the early to mid-2000s, and while the rates of axillary recurrence in the first 5 years after surgery were low, little is known about the incidence of late axillary events, particularly in the era of modern multimodality therapy. To address this, we evaluated the incidence of late axillary recurrence events using a large prospective database of patients who underwent SLNB with follow-up of at least 10 years.

METHODS

With institutional review board approval, we retrospectively analyzed our prospectively collected institutional database of patients who underwent SLNB between January 1997 and December 2000. Patient characteristics collected included age of patient, type of breast surgery, pathologic tumor size, number of nodes removed, nuclear grade, estrogen receptor (ER), progesterone receptor (PR), HER2 receptor (HER2), and receipt of radiation, chemotherapy, and hormone therapy. SLNB negative patients who had no further axillary surgery comprised our patient population. For comparison, we also collected data on SLNB positive patients who underwent subsequent ALND during the same time period. Patient characteristics were summarized using frequency and percent for categorical covariates, and median and range for continuous covariates.

The primary outcome was the incidence of axillary recurrence (AR) as a first event, with or without concurrent local recurrence (ipsilateral breast or chest wall). Cumulative incidence of AR was estimated using competing risks methodology with non-axillary local regional recurrence (LRR) defined as metastases to supraclavicular or internal mammary chain lymph nodes and distant metastasis (DM)/death as competing events. Time to event was defined as time from SLNB to the first event, whether AR, non-axillary LRR, DM, or death, and was censored at the time of last follow-up. Associations between covariates and AR were assessed using Fine and Gray regression. All statistical analysis was done in SAS 9.3 (SAS Institute, Cary, NC) and R 3.0.1 (R Foundation, Vienna, Austria) with the survival and cmprsk packages. P-values less than 0.05 were considered significant.

Secondary outcomes were overall survival and recurrence-free survival for the entire population, overall survival after AR, and distant disease-free survival after AR. Overall

survival, recurrence-free survival and distant-disease-free survival were estimated using Kaplan-Meier methods and compared using the log rank test. Overall survival was defined as the time from SLNB to death, and recurrence-free survival was defined as the time from SLNB to the recurrence or death. Distant disease-free-survival after AR was defined as the time from AR to DM or death. Overall, recurrence-free and distant-disease-free survival were censored at the time of last follow-up.

RESULTS

We identified 1529 SLNB-negative patients with no further axillary surgery during the study period. Median follow-up was 10.8 (0–16) years, and a median of 3 (1–25) sentinel nodes were removed. The median patient age was 58 years, and the majority of patients underwent breast-conserving surgery (85%) for small, ER/PR positive, low-to-intermediate-grade tumors (Table 1). During the time of this study, only a small number of tumors were evaluated for HER2 status. The median number of lymph nodes removed was 3, but there was a wide range (1–25). This is because the database used was designed to capture variables on the technical aspects of sentinel lymph node biopsy at a time when the technique was new. The operating surgeon designated all the nodes as sentinel or non-sentinel nodes and they were entered and analyzed as such. We only included patients in our study with no positive nodes (sentinel or non-sentinel). Only 3% of patients had more than 10 lymph nodes removed, and this would not impact outcomes in the SLNB-only group. The number of patients with 5 or more lymph nodes removed was much larger, with 449 patients in this group, but when comparing those patients with more than 5 lymph nodes removed to those with fewer than 5 removed, there was no significant difference in axillary recurrence ($p=0.28$). The majority of patients received radiation therapy, 75% overall (85% in the breast conservation group and 15% in the mastectomy group), 37% received chemotherapy, and 62% received hormone therapy (Table 1).

The incidence of AR as a first event was very low with only 13 total events, including 3 patients with concurrent local recurrence. Cumulative incidence was 0.6% (95% confidence interval [CI] 0.2–0.9) at 5 years after SLNB, 0.9% (95% CI 0.4–1.4) at 10 years, and 1.0% (95% CI 0.5–1.6) at 15 years (Fig. 1). Univariate analysis of factors associated with AR showed high nuclear grade to be the only factor significantly associated with the event (Table 2). There was no association with the type of treatment received for the primary tumor. Late AR (defined as more than 5 years after negative SLNB) occurred in 5 patients ranging from 5.6 to 12.5 years post-surgery. Three of these patients had ER positive and HER2 negative primary tumors, one primary tumor was triple negative, and one primary tumor was HER2 positive.

10-year overall survival for the entire population was 84% (95% CI 82–86%) (Fig. 2a). Outcomes after AR were poor, with a median time of 3.8 years (95% CI 0.42–not reached [NR]) from AR to distant metastases or death. Median overall survival after AR was 4.6 years (95% CI 0.8–NR) (Fig. 2c, 2d). There were 102 non-axillary local recurrence events and 286 patients with distant metastases or death for an overall 10-year recurrence-free survival of 78% (95% CI 76–81%) (Fig. 2b).

Rates of AR in a contemporaneous group of SLNB positive patients who had ALND

SLNB has a known false-negative rate of 5–10% meaning there are some patients who have cancer in their lymph nodes that is not recognized.^{5–9} We compared the outcome of the SLNB negative patients who had no further axillary surgery group to a contemporaneous group of SLNB positive patients undergoing ALND. There were 902 patients in this group, and 7 had ARs as a first event, with 6 occurring in the first 5 years after surgery. In this group, the cumulative incidence of AR was 0.7% (95% CI 0.1–1.3) at 5 years after surgery, 0.8% (95% CI 0.2–1.5) at 10 years, and 0.8% (95% CI 0.2–1.5) at 15 years. As expected, the cancer characteristics in this population were consistent with their higher disease stage and thus, these patients had more mastectomies, and received chemotherapy and hormone therapy at a higher rate, than the SLNB negative patients (Table 4).

Overall survival after AR was similar between the 2 groups, with median overall survival of 4.9 years (95% CI 0.9–NR) in the ALND (SLNB positive) group of 7 patients and 4.6 years (95% CI 0.8–NR) in the SLNB negative group of 13 patients ($p=0.83$). Distant-disease-free survival *after* AR was not statistically different with median distant disease-free survival of 1.7 years in the ALND (SLNB positive) group and 3.8 years in the SLNB negative group ($p=0.85$), again with very small numbers of patients in either group.

Treatment after AR in the SLNB negative population was patient dependent. The majority of patients (12 of 13, 92%) underwent ALND. Only one patient received axillary radiation therapy after surgery. Nine patients received chemotherapy and 6 patients received hormone therapy for their recurrence. All 3 HER2 positive patients who had their AR in the trastuzumab era received this therapy.

DISCUSSION

SLNB for axillary staging has been shown in numerous large studies to be accurate and safe, and is now the standard of care.^{1–5,7,9–11} Very low rates of AR after negative SLNB, ranging from 0.4% to 0.9%, have been reported, but the follow-up times have not extended beyond 8 years, leaving lingering questions about the incidence of late AR. With the increasing use of systemic therapies and their impact on locoregional recurrence^{1–4,12–15}, there has been concern that axillary events may present in a delayed fashion. This may be particularly relevant for patients with ER positive breast cancer in whom late systemic recurrences are more of a concern.^{16,17} This study provides evidence that this concern is unfounded. The majority of ARs, either isolated or in association with local recurrence, occurred within the first 5 years after initial negative SLNB, with rare events in years 5–10 and even fewer between years 10–15. At a median follow-up of nearly 11 years, the cumulative rate of AR was 1% in this study of 1529 patients.

The comparison of the rates of AR in the group of patients with negative sentinel nodes undergoing SLNB alone with the group having ALND after a positive sentinel node helps to put the AR rate in perspective. Given that the false-negative rate for SLNB can be as high as 10%^{5,9}, a number of the patients in the SLNB alone group likely harbored some disease in the remaining nodes, but the AR rates were similar to those seen in node-positive patients undergoing ALND. In the ACOSOG Z0011 trial where patients with 1–2 involved sentinel

nodes were treated with SLNB alone, the AR rate at 5 years was 0.9%, very similar to what was observed in our study at 5 years. Our study also shows that the time course of recurrence is similar among patients undergoing SLNB alone, where recurrence represents the growth of subclinical disease left behind at surgery, and those undergoing ALND who are rendered surgically disease free, with the majority of recurrences seen in the first 5 years post-surgery. This finding is consistent with that of other studies.^{18,19}

The patients in this study are from an era prior to HER2 targeted therapies, and the most current chemotherapy and endocrine therapy regimens. With the changes in systemic therapies over the last decade, the rates of axillary recurrence for patients treated in the last 10 years are likely even lower than those found in this study. Acknowledgement of the low rates of late axillary recurrence, even in patients treated prior to the current therapeutic era, provides historical reinforcement for the current practice of omitting extensive axillary treatment in select patients as in the ACOSOG Z0011 trial.

Our study confirms earlier data that suggest that most residual disease in the axilla does not become clinically evident as AR. The NSABP B-04 trial was the first to suggest that this might be the case.²⁰ Even in the absence of systemic therapy or radiation, AR was observed in only 18.6% of clinically node-negative patients treated with total mastectomy, although 40% of patients undergoing radical mastectomy had axillary metastases.^{20,21} A meta-analysis of several randomized trials of ALND versus no surgery in the axilla in clinically node-negative patients showed an acceptable rate of AR, between 1.8% and 3% in the no-ALND arms when pathologic nodal disease was found in 21–28% of patients in the dissection arms.²² Finally, the ACOSOG Z0011 trial, in which 27% of patients randomized to ALND had residual nodal disease, reported an AR rate of less than 1% at a median follow-up of 6.3 years.²³

Our data indicate that AR, regardless of when it occurs, is associated with a poor outcome. This was true for the population of patients with negative sentinel nodes as well as those with positive sentinel nodes. In the event of an AR, treatment should be individualized.

Locoregional recurrence is an independent, poor prognostic factor even after a long event-free interval²⁴, and many patients will develop distant disease within a short time. Local control can be achieved with surgery or radiation therapy or both, but systemic treatment is a key component of the treatment.²⁵

In summary, we observed that the population of patients who underwent SLNB alone with negative results had a very low rate of local recurrence, even over 10 years after the initial procedure. This reinforces the concept that leaving behind small amounts of disease in the axilla does not compromise oncologic outcomes. In this large, typical breast cancer patient population, the majority of ARs occurred in the first 5 years, and prognosis after these events was poor. SLNB remains a safe and effective procedure for axillary evaluation.

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Synopsis

SLNB is standard for axillary staging in breast cancer. Axillary recurrence is rare in the first 5 years, but little is known about late events. We found the incidence of late events to be low with >10 years follow-up.

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Fig. 1.
Cumulative incidence of axillary recurrence after negative sentinel lymph node biopsy.
Abbreviations: SLNB, sentinel lymph node biopsy

Fig. 2.

Outcomes after negative sentinel lymph node biopsy: a) overall survival; b) overall recurrence-free survival; c) overall survival after axillary recurrence; d) distant-disease-free survival after axillary recurrence.

Abbreviations: SLNB, sentinel lymph node biopsy; AR, axillary recurrence

Table 1

Study population characteristics

Characteristic n=1529	n (range or %)
Median age	58 (12–88)
Surgery	
Breast conservation	1297 (85)
Mastectomy	232 (15)
Median total # nodes removed	3 (1–25)
Median tumor size n=1489	1.0 cm (0.1–5.0)
Nuclear grade n=1189	
Low	147 (12)
Intermediate	711 (60)
High	331 (28)
ER positive n=1090	874 (80)
PR positive n=1082	671 (62)
HER2 status n=771	
Positive	110 (14)
Negative	571 (74)
Equivocal	90 (12)
Adjuvant therapy	
Radiation n=1456	1099 (75)
Mastectomy n=227	5 (2)
Breast conservation n=1229	1094 (89)
Chemotherapy n=1453	536 (37)
Endocrine therapy n=1401	865 (62)
T stage n=1491	
T1a	290 (19)
T1b	467 (31)
T1c	603 (40)
T2	131 (9)
T3	0 (0)

Abbreviations: ER, estrogen receptor; PR, progesterone receptor

Table 2

Univariate analysis of factors associated with axillary recurrence after negative sentinel lymph node biopsy

	Hazard ratio (95% confidence interval)	p-value
Age *	0.99 (0.95–1.03)	0.54
Nuclear grade (high vs low and intermediate)	5.12 (1.52–17.26)	<0.01
ER positive	1.00 (0.21–4.74)	1
PR positive	0.61 (0.18–2.09)	0.43
HER2 status (equivocal excluded)	1.31 (0.15–11.76)	0.81
Mastectomy (vs breast conservation)	0.45 (0.06–3.48)	0.45
RT for primary	1.07 (0.29–3.89)	0.92
Chemo for primary	1.03 (0.34–3.15)	0.95
Endocrine therapy for primary	0.95 (0.31–2.91)	0.93
Tumor size ^	1.15 (0.68–1.95)	0.6
Total # nodes removed	0.93 (0.76–1.14)	0.48
Lymphovascular invasion	1.90 (0.52–6.87)	0.33

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; RT, radiotherapy

* HR change per one year increase in age.

^ HR change per one cm increase in size.

Table 3

Comparison of treatment characteristics in the SLNB negative group to the contemporaneous group of SLNB positive converted to ALND

	SLNB only (SLNB negative)	ALND (SLNB positive)	p-value
Mastectomy	232 (15%)	356 (39%)	<0.01
Chemotherapy	536 (37%)	714 (83%)	<0.01
Endocrine therapy	865 (62%)	629 (75%)	<0.01
High nuclear grade	331 (28%)	333 (44%)	<0.01

Abbreviations: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection