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Does Conservative Surgery for Breast Carcinoma Still Require Axillary Lymph Node Evaluation? A Retrospective Analysis of 1156 Consecutive Women With Early Breast Cancer

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Abstract

We performed a retrospective analysis of 1156 patients affected by early breast cancer in order to estimate the real incidence of patients with T1 tumors presenting > 2 metastatic lymph nodes. The advantage of axillary surgery seems to be limited only to a specific subgroup of T1 patients who are undergoing conservative surgery plus radiotherapy.

Background: The role of axillary surgery for early breast carcinoma treated with conservative surgery and radiotherapy is currently the subject of considerable investigation. Recent studies have supported the noninferiority of avoiding axillary surgery in terms of overall survival when sentinel lymph node biopsy (SLNB) presents ≤ 2 positive lymph nodes, thus sparing the patients from complications. There are some ongoing studies investigating the possibility of omitting SLNB. Axillary study seems to be sufficiently replaced by SLNB for staging the disease. Axillary surgery maintains a therapeutic role in the presence of > 2 metastatic lymph nodes at SLNB. **Patients and Methods:** We performed a retrospective analysis of 1156 patients with early breast cancer to estimate the real incidence of patients with T1 tumors presenting > 2 metastatic lymph nodes. **Results:** Of the 1156 cases, only 106 (9.2%) had > 2 axillary metastatic lymph nodes. More specifically, 38 (4.3%) of 884 T1 cases, and 6 (2.3%) of 257 of T1b cases had > 2 metastatic lymph nodes. **Conclusion:** The advantage of axillary surgery seems to be limited only to a specific subgroup of T1 patients who are undergoing conservative surgery plus radiotherapy. The ongoing studies on avoiding SLNB will likely prove the noninferiority of omitting biopsy because these studies are conducted in the whole population of early breast cancers. It is necessary to identify more accurately the subpopulation of patients who may benefit from axillary surgery.

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Introduction

The purpose of surgery for breast tumors is to improve overall survival as well as to achieve local control of the disease and maintain an acceptable quality of life. The current treatment of early

breast carcinoma is based on conservative surgery tailored to the volume of disease in association with whole-breast radiotherapy and specific medical therapy. Sentinel lymph node biopsy (SLNB) provides information regarding the lymph node spreading of the tumor: if positive nodes are detected, the surgery is completed by axillary lymph node dissection (ALND).

Axillary surgery for breast cancer is currently considered a staging procedure that does not seem to influence breast cancer mortality, although SLNB alone provides sufficient information in the therapeutic setting. Moreover, ALND is burdened by complications that negatively affect quality of life.

Several studies have suggested that ALND could be an over-treatment, even in the case of positive sentinel lymph node (SLN). The American College of Surgeons Oncology Group (ACOSOG)

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Conservative Surgery for Breast Carcinoma

Z0011 trial found that for clinically negative lymph node tumors (T1/T2 N0 M0) with SLN metastases in ≤ 2 nodes, ALND can be safely avoided, and surgeons are still provided with adequate information to permit surgical staging and comparable locoregional control and survival.¹

Another trial (International Breast Cancer Study Group [IBCSG] 23-01)² conducted on patients with micrometastatic SLN positivity and tumor < 5 cm in size demonstrated the noninferiority of avoiding ALND, thus sparing the patient from the complications of axillary surgery. A randomized clinical trial by Agresti et al³ performed on T1N0 breast cancers supported the noninferiority, in selected groups of low-risk patients and in terms of overall survival, of breast-conservation surgery without ALND compared to breast conservation plus ALND. The 2014 American Society of Clinical Oncology and 2015 St Gallen 2015 guidelines now suggest that ALND may be omitted in selected patients with 1 to 2 positive SLNs who are undergoing conservative surgery and radiotherapy without affecting survival or risk of local recurrence.^{4,5} The SOUND (Sentinel node vs. Observation after axillary Ultra-SouND) trial is currently ongoing to evaluate SLNB with or without ALND versus no axillary surgical staging.⁶ Also ongoing is the Intergroup-Sentinel-Mamma (INSEMA) trial, which is testing the noninferiority of no axillary surgery compared to SLNB.⁷

Because avoiding ALND is to be considered safe when SLNB presents ≤ 2 positive lymph nodes, the obvious question that arises is, how many patients who undergo conservative surgery have > 2 metastatic axillary lymph nodes? This group of patients could possibly benefit from ALND given the absence of benefits when metastatic axillary lymph nodes are ≤ 2 .

The aim of this study was to retrospectively evaluate a population of patients with early breast cancer treated with a conservative approach to obtain cases of > 2 metastatic axillary lymph nodes after ALND.

Patients and Methods

We retrospectively evaluated a cohort of 1156 consecutive women with early breast cancer (2 patients had bilateral carcinoma) between January 2001 and December 2013. All patients underwent breast-conserving surgery and SLNB; when the SLNB results were positive, axillary dissection was performed. After surgery, all patients were treated by external-beam radiotherapy on the whole breast through 2 tangential fields (50 plus 10 Gy as a boost to the tumor bed) with a linear accelerator. We evaluated the number and percentage of patients with positive SLN, patients with positive SLN treated with ALND, patients with negative axillary lymph nodes after ALND, and, globally, the percentage of patients with > 2 metastatic axillary lymph nodes. According to the tumor, node, metastasis classification system, SLNs with micrometastasis were considered positive and SLNs with isolated tumor cells negative.

Results

The median age of patients was 57.2 years (range, 29-86 years). The average tumor diameter was 16 mm, with a median of 15 mm. Patient characteristics are summarized in Table 1. A total of 648 patients had SLN localization by radiocolloid, 248 by blue dye, and 262 by combined techniques, as previously reported.^{8,9} Of 1156

Table 1 Patient Characteristics

Characteristic	Value
Total No. of Cases	1156
T1	884
T2	257
Median age (years)	57.2 (29-85)
Mean Tumor Diameter	16 mm
G1	344 (29.8%)
G2	538 (46.5%)
G3	274 (23.7%)
ER ⁺	984 (85.1%)
ER ⁻	146 (12.6%)
ER ND	26 (2.3%)
PR ⁺	828 (71.6%)
PR ⁻	302 (26.1%)
PR ND	26 (2.3%)
HER-2 0	212 (18.2%)
HER-2 1 ⁺	553 (47.9%)
HER-2 2 ⁺	226 (19.6%)
HER-2/HER-2 3 ⁺	121 (10.5%)
HER-2 ND	44 (3.8%)

Abbreviations: ER = estrogen receptor; G = grade; HER-2 = human epidermal growth factor receptor 2; ND = not determined; PR = progesterone receptor.

cases, 884 were of T1 disease and 272 T2 disease. SLNB results were negative in 770 cases (66.6% of cases) and metastatic in 386 (33.4%). Of the latter, in 283 cases (24.5%) there was a macrometastasis and in 103 cases (8.9%) a micrometastasis. A total of 380 of 386 patients with metastatic SLN underwent ALND; in 234 patients (61.6%), the axilla results were negative. Overall, 274 patients had ≤ 2 metastatic lymph nodes and 106 (9.2%) had > 2 metastatic lymph nodes (Table 2). Considering only the 884 T1 tumors (Table 2), SLNB results were negative in 650 cases (73.5%) and metastatic in 234 (26.5%); of these, 166 (18.8%) were macrometastasis and 68 (7.7%) micrometastasis. ALND was performed in 233 of 234 cases of positive SLNB; histology was negative for 166 cases (71.3%). Therefore, only 38 (4.3%) of 884 T1 patients had > 2 axillary metastatic lymph nodes. Instead, SLNB results were negative in 199 (77.4%) of 257 T1b patients, and metastatic disease occurred in 35 patients (13.6%).

In 35 patients who underwent ALND, results were negative in 24 patients (68.6%). In only 6 (2.3%) of 257 T1b patients did the axilla contain > 2 metastatic lymph nodes.

Discussion

If we accept the premise that axillary surgery offers a real advantage to patients who undergo conservative surgery and radiotherapy and who present with > 2 metastatic axillary lymph nodes, then according to the data obtained from this unselected population, it emerges that the majority of T1 patients with positive SLNB results were overtreated by axillary surgery. Only 4.3% of T1 patients had > 2 metastatic lymph nodes and thus obtained benefit from extending surgery to the axilla; this percentage decreased to 2.3% for T1b patients. The limitation is that these results come

Table 2 Characteristics of Axillary Lymph Nodes

Disease	SLN ⁻	SLN ⁺ Macrometastasis	SLN ⁺ Micrometastasis	ALND ⁻	LN ⁺ ≤2 at ALND	LN ⁺ >2 at ALND
Total (n = 1156)	770 (66.6%)	283 (24.48%)	103 (8.84%)	234/380 (61.6%)	270 (23.3%)	106 (9.2%)
T1 (n = 884)	650 (73.5%)	166 (18.8%)	68 (7.7%)	166/233 (71.5%)	194 (22.2%)	38 (4.3%)
T1b (n = 257)	199 (74.4%)	25 (9.7%)	10 (3.9%)	24/35 (68.6%)	29 (11.3%)	6 (2.3%)

Abbreviations: ALND = axillary lymph node dissection; LN = lymph node; SLN = sentinel lymph node.

from an observational study based on historical data and not from a randomized population. Our results come from a single-center, single-surgical-team experience. The patients were not selected; some were symptomatic at the time of discovery of the disease, and some came to us as a result of cancer screening campaigns. This population therefore reflects the real incidence of disease in the general population. SLN evaluation still marks a watershed in the management of early breast carcinoma.

SLNB has resulted in an improvement in the quality of life of patients who undergo breast surgery by reducing the complications that may arise from nonselective axillary surgery.¹⁰ Initial contraindications, such as multifocal and multicentric tumor or previous excisional biopsy, have been eliminated.^{11,12} Furthermore, there is improved understanding regarding the lymphatic drainage of the breast into the axillary lymph nodes. The progression and metastatic spreading of tumor is now known to occur in a stepwise, continuous fashion from the periphery of the axilla in 97.4% of patients, and only in 2.6% of cases does it involve axillary level II, skipping axillary level I.¹³

The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial¹⁴ found that women who underwent SLNB alone experienced less lymphedema and sensory deficit than did women who underwent ALND. In addition, the women were also able to resume their normal daily activities more quickly than women who underwent ALND.^{15,16}

Some criticisms had been leveled at the ACOSOG Z0011 trial resulting from the “favorable” nature of the disease in the enrolled randomized patients, where only 27% of the patients had additional metastatic nodes after ALND, compared to a higher percentage in other studies. Moreover, the younger population and those with estrogen receptor–negative tumors were insufficient in number to consider avoidance of ALND a safe prospect for this group. These criticisms, however, do not detract from the value of this landmark trial.

Dengel et al,¹⁷ in a prospective study designed to determine how often ALND can be avoided in patients meeting ACOSOG Z0011 eligibility criteria, reported that 84% of patients, not selected on the basis of age, tumor characteristics, axillary imaging, or nomogram predictions, were found to have metastases in ≤ 2 axillary nodes, thus suggesting that these patients had a low axillary tumor burden.

The role of SLNB is currently under investigation, given the reduced information coming from the axillary status and as a result of the emerging role of tumor biology in the choice of tailored therapy. A randomized multicenter trial is underway in patients with a negative preoperative axillary assessment, tumor ≤ 2 cm, and patients eligible for conservative surgery to evaluate SLNB with or without axillary dissection versus observation (no axillary surgical

staging).⁶ The primary end point of the trial is disease-free survival. The results obtained from the preliminary analysis regarding the impact of different types of surgery on postoperative physical function and symptoms of the ipsilateral upper limb are that SLNB significantly worsens early postoperative physical function and symptoms of ipsilateral upper limb compared to no surgery of the axilla. This finding is limited to the first week after the operation and is no longer present at 6 and 12 months.¹⁸

The routine assessment of the axilla by means of ultrasound, combined with fine-needle biopsy, has reduced the rate of positive SLNBs^{19,20} and has enabled the identification of patients with axillary metastases who require ALND. A retrospective study of 1140 patients (T1/T2) at the Mayo Clinic in Rochester, Minnesota (all of whom were negative for axillary ultrasound and fine-needle aspiration), reported 13% of patients to be SLNB positive. Only 3% of patients had ≥ 3 positive SLNs.²¹ The reported SLN positivity rate of < 20% in patients with early breast cancer in the era of mammograms raises questions about that same role for SLNB, and consequently the need for performing ALND when the SLNB is positive and the patient is receiving adjuvant treatment (radiotherapy or medical therapy).

Radiotherapy actively contributes to the success of the conservative approach. The AMAROS (Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer) trial found that ALND and axillary radiotherapy after a positive SLNB finding provided excellent and comparable axillary control for patients with T1-2 primary breast cancer and no palpable lymphadenopathy, but that radiotherapy provided significantly less morbidity.²² It is recognized that whole-breast radiotherapy decreases the regional recurrence rate of tumors, most likely caused by accidental irradiation of part of the axilla. In fact, the lower part of the axilla is currently irradiated and receives a nearly therapeutic dose, depending on the upper limit of the tangential fields to the breast or chest wall.²³ A meta-analysis by van Wely et al²⁴ showed that external-beam radiotherapy to the breast was associated with a lower axillary recurrence rate compared to that in patients who did not receive it as part of initial therapy. Although it may not be considered therapeutic,²⁵ the dose delivered to the region in which the SLNs are normally found could well influence the natural evolution of residual tumor cells.

The presence of lymph node metastases does not necessarily imply a further clinically evident development of the disease. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial demonstrated that less than half of the patients with occult nodal metastases developed clinically detectable lymph nodes. None of the patients received adjuvant systemic therapy.²⁶ Systemic therapy plays a key role in achieving low regional recurrence rates.

Conservative Surgery for Breast Carcinoma

Adjuvant systemic therapy significantly reduces locoregional recurrence,²⁷⁻²⁹ and neoadjuvant medical therapy can eradicate axillary lymph node metastases.³⁰

The subtypes may be predictive of locoregional recurrence and survival even after postmastectomy radiotherapy and neoadjuvant chemotherapy.³¹⁻³³ In a meta-analysis conducted by Lowery et al,³⁴ locoregional recurrence rates varied between different subtypes. In particular, luminal tumors exhibited the lowest rates of local recurrence. Patients with triple-negative and HER-2/neu—overexpressing breast tumors were at increased risk of developing local recurrence after conservative surgery or mastectomy. Furthermore, several studies have suggested that the triple-negative tumor subtype may predict a lower risk of nodal involvement.³⁵⁻³⁹ Because biology and systemic therapy influence the natural evolution of disease, the indications for axillary surgery should take these factors into consideration.

Single-center studies do not demonstrate any benefits in performing axillary surgery, but meta-analyses lead to a different conclusion. A recent meta-analysis shows an advantage of axillary surgery both for overall survival and recurrence-free survival.⁴⁰ It was conducted on patients with operable primary breast cancer to determine the clinical impact of ALND in the treatment of invasive breast cancer. ALND seems to positively affect overall and recurrence-free survival from breast cancer.

Another meta-analysis concluded that for patients with micrometastasis at SLN, SLNB alone is noninferior to completion ALND. For patients with macrometastases to the axilla, omitting ALND may also be considered a feasible option, provided that the patients receive appropriate systemic chemotherapy and hormone therapy. However, this should be considered with caution because this meta-analysis had a smaller number of patients with a macrometastatic sentinel node.⁴¹

A large review conducted on patients with 1 to 2 metastatic lymph nodes who underwent SLNB or ALND showed an increase of breast cancer—specific survival limited to patients younger than 50 years old with hormone receptor—negative tumors who underwent ALND.⁴² It seems that only some subgroups of patients draw benefit from ALND, not the entire population.

Conclusion

The real advantage of axillary surgery in patients who are undergoing conservative surgery with whole-breast radiotherapy appears limited to those with > 2 metastatic lymph nodes (ie, only 4.3% of T1 tumor cases, according to our data).

Currently ongoing trials such as SOUND and INSEMA,^{6,7} because they are conducted on the entire population of early breast cancers, may lack a sufficient number of events and consequently will demonstrate the noninferiority in avoiding ALND. By considering the other emerging factors^{42,43} that influence survival after ALND in breast carcinoma, such studies should investigate specific subgroups, not the entire population of patients.

Clinical Practice Points

- This study retrospectively investigated the real incidence of early breast cancers (treated with conservative surgery plus radiotherapy) presenting > 2 metastatic lymph nodes after axillary surgery.

- The role of axillary lymph node surgery is under investigation because SLNB is sufficient to stage the disease.
- Axillary surgery is burdened with complications that affect quality of life.
- Recent studies have demonstrated that ALND might be safely avoided if SLNB presents ≤ 2 positive lymph nodes.
- The real advantage of axillary surgery seems to be limited only to a specific subgroup of T1 patients who are undergoing conservative surgery plus radiotherapy.
- The role of SLNB is under investigation; ongoing trials have demonstrated the noninferiority of omitting this procedure. However, these trials are directed to the entire population and thus will likely confirm this hypothesis.
- We think that these studies should be conducted for specific subgroups of patients (according to the biology of the tumor and other emerging factors that affect tumor behavior) to determine who will receive benefit from axillary dissection.

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