Axillary Surgery in Breast Cancer: an overview

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Abstract

Axillary surgery is an important part of the treatment of breast cancer. It is critical to the staging of disease, prescription of adjuvant therapy and prognosis. Sentinel lymph node biopsy is a safe and accurate minimally invasive method for detecting axillary lymph node involvement. Axillary lymph node dissection can be avoided in many situations without oncologic impairment. The management of the axilla in the presence of isolated tumor cells, micrometastases and even in some cases of macrometastases in sentinel lymph node biopsy is controversial. We discuss the evolution of axillary surgery in breast cancer, the management of the axilla after sentinel lymph node biopsy and the best axillary approach for each patient.

Key words: sentinel lymph node biopsy; breast cancer; axillary surgery; axillary lymph node dissection

Introduction

Breast cancer is one of the most common cancers with greater than 1.300.000 cases and 450.000 death each year worldwide. It is a heterogeneous disease and its treatment has changed substantially throughout the last few decades.

The principle of Halsted’s radical mastectomy that removes not only the breast but also the adjacent musculature and axillary content, was based on the belief that the disease spreads in an orderly fashion from the breast to the regional lymph nodes and then to
distant sites. Thus, aggressive local tumor control might prevent systemic tumor spread and potentially prevent death from breast cancer.

On the other hand, the hypothesis by Fisher et al showed the concept that breast cancer becomes systemic early, although the systemic disease may remain subclinical. So, aggressive local surgery may not affect overall survival. The better understanding of breast cancer biology revealed that aggressive surgical therapy alone is inadequate. Breast-conserving surgery followed by radiotherapy for women with early-stage breast cancer gets equivalent long-term survival as traditional mastectomy.

The axillary node dissection (ALND) has been part of breast cancer surgery since the description of the radical mastectomy and the axillary staging is an important step in the treatment of breast carcinoma. It is known that lymphatic drainage of the breast is 90-95% to the axilla. The significance of internal mammary nodes involvement is unclear and its surgical approach didn’t show survival benefits. Although lymphatic dissemination is the most common dissemination way, not all breast cancer cases will develop axillary lymph node metastases. To predict the axillary status is not easy. Clinically palpable lymph nodes prove to be false positive in 25-30% of patients and about 40% have positive results after ultrasound with or without fine-needle aspiration node negativity. The risk of axillary lymph nodes involvement is proportional to tumor size. Thus, early diagnosis reduces this probability. Studying 24,740 women with invasive breast cancer, Carter et al showed that approximately 80% with tumor size < 1cm, 50% with up to 5 cm and 30% with > 5 cm had negative axilla, a fact suggesting that metastases do not occur exclusively via the axillary lymph nodes, but rather lymph node status serves as an indicator of the tumor’s ability to spread. There is a subset of favorable histological types that show lower risk of axillary metastases, like medullary, mucinous, papillary, tubular and adenoid cystic carcinomas. Mammograms can only identify grossly involved nodes. Because imaging techniques have limited sensitivity, the axilla must be explored surgically.

ALND identifies nodal metastases and maintains regional control, but the contribution of local therapy to breast cancer survival is controversial.
The histological status of the axillary lymph nodes is an important prognostic factor in patients with breast cancer and it remains the most powerful predictor of recurrence and survival. In the 1990s, sentinel lymph node biopsy (SLNB) was introduced in breast cancer as a method by which to identify the first lymph node in the nodal basin that could contain metastases. This technique provides surgeons with information that allows axillary dissection to be avoided if the sentinel node is negative.

Modern screening methods make it possible to diagnose breast cancer at an early stage when the axillary lymph nodes are free of metastases. As a result, routine axillary dissection may constitute excessive treatment, exposing patients to the complications of the procedure, with no benefit. In early breast carcinomas with clinically negative axilla, up to 70 percent of patients don’t show lymph node metastases on the axillary dissection.

The aim of this article is to review the evolution and modifications of breast cancer axillary surgery based on scientific evidence through the last decades, report the management of the axilla after SLNB and discuss the best axillary approach for each patient.

Methods

This literature review was done by data base from LILACS, PubMed, BIREME and a search for articles using Google. The search was carried out during November and December of 2012, using the terms sentinel lymph node biopsy, breast cancer, axillary surgery and axillary lymph node dissection. Articles were selected by their title, year of publication and scientific evidence. Sixty-five articles were preselected by their abstract or full text. Forty-eight articles were used to confection the present study.

Clinically negative axilla

Axillary Lymph Node Dissection versus Sentinel Lymph Node Biopsy

Over the last two decades, there have been significant changes in the surgical management of breast cancer, but the axillary lymph assessment has remained an integral part of breast surgery. ALND was the standard procedure in breast cancer surgery during decades. In 1990, the National Institutes of Health Consensus Conference concluded that the treatment of potentially curable
breast cancer should include levels I and II axillary lymph node dissection. The need for routine ALND was challenged by the introduction of the sentinel lymph node biopsy. In 1994, Giulliano et al published a study about the accuracy and efficiency of SLNB and demonstrated that the status of the SLNB accurately reflected the status of the entire axillary basin draining a primary breast tumor.In 2001, during The Philadelphia Proceedings of the Consensus Conference, the SLNB was considered able to be used in substitution of ALND for breast cancers T1 and T2 with clinically negative axilla. SLND is a less invasive method of checking for nodal involvement.

The most commonly involved axillary lymph nodes are those in level I (i.e., those lymph nodes lateral to the pectorallis minor). They are involved in 91-96% of the patients with any axillary nodal involvement.

Although risks such as lymphedema are present with SLNB surgery, the incidence of arm lymphedema is significantly less than with ALND (7% vs 25%). The false-negative rate of SLNB has been demonstrated to be approximately 9.8% in the literature and the rate of locoregional tumor recurrence in patients with negative sentinel lymph nodes who did not have ALND has ranged from 0.1% to 1.5%.

Smith et al, in a series of 439 patients with negative sentinel lymph node (SLN), found an axillary tumor recurrence of 0.46% after 26 months of follow-up. A meta-analysis of 3,184 patients with a negative sentinel lymph node from 13 studies, with 21 months of follow-up, showed an axillary tumor recurrence of 0.25%.

In the ALMANAC trial, an important multicenter randomized study, the failed sentinel node localization rate was 2%. Comparing SLNB versus ALND, the SLNB group showed less incidence of lymphedema (5% vs 13%; p<0.001), arm sensory deficit (11% vs 31%; p<0.001) and impairment of shoulder function (p=0.004). It was demonstrated less axillary drain usage (p<0.001), mean hospital stay days (p<0.001) and time from surgery to return to normal day-to-day activities (p<0.001) in the SLNB group. The false-negative rate of SLNB was 5.2% for patients with T1 tumors, 7.7% for T2 tumors and 8.8% for multifocal lesions. In the National Surgical Adjuvant Breast and Bowel Project B32 (NSABP B32), the false-negative rate was 10.3% for T1 tumors. In the IGASSU study, the false-negative rate was 13.6% for multicentric or multifocal tumors,
demonstrating that some different clinical settings can influence the accuracy of SLNB \(^{18}\). These studies demonstrated no significant difference in disease-free survival between the groups.

ALND has been associated with significant morbidity compared with SLNB alone. Giuliano et al compared the postoperative complication rate of women undergoing SLNB versus SLNB plus ALND in the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial. They found that women in the ALND group had a significantly greater incidence of postoperative complications than the SLNB group (70% vs 25%). Complications included: infection, seromas, paresthesias, brachial plexus injury and lymphedema \(^{19}\).

The accuracy in identifying the sentinel lymph node was 97% in a multicenter validation study with 443 patients undergoing SLN and ALND \(^{20}\).

As recommended by the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN), SLNB is the standard axillary approach for patients with clinically negative axilla.

Positive sentinel lymph node

In cases of a positive SLN, standard treatment has been a completion ALND as outlined by the consensus statement from ASCO and NCCN \(^{21,22}\). These guidelines stem from a meta-analysis of 69 trials including 8,059 patients who underwent SLNB and subsequent ALND. The results demonstrated that 53% of patients with a positive SLN were found to have disease in non-sentinel lymph nodes \(^{23}\).

The incidence of non-SLN involvement changes considerably with the extent of disease in the SLNs. For patients with SLN involved by macrometastases, the incidence of non-sentinel lymph node involvement is reported to be 40% to 58% \(^{24}\). When the SLN is involved by micrometastatic disease, the incidence of non-sentinel lymph node involvement is 20% and in the case of SLN with isolated tumor cells the incidence decreases to 12% \(^{25,26}\).

Recently, the SLN has been demonstrated to be the only positive lymph node in many cases. Data from high-volume breast cancer centers indicate that the SLN is the only site of nodal metastases in 40-60% of axillary dissections \(^{27}\). In three studies of SLNB and
subsequent ALND, Veronesi et al, Krag et al and Giuliano et al found that SLN was the only metastatic lymph node respectively in 44%, 62% and 67% of the cases. 

Recent data from the ACOSOG Z0011 trial suggest that ALND may be omitted in selected patients. In this trial, 813 patients with clinical T1-T2 node negative tumors who were found to have hematoxylin and eosin-positive SLN were randomized to ALND versus no further axillary surgery. Patients with palpable lymph nodes, T3 tumors, more than 2 positive sentinel nodes and patients undergoing mastectomy, neoadjuvant chemotherapy and partial breast radiation were excluded from the study. Protocol mandated the use of standard whole-breast radiation without an axillary field. At 6,3 years of follow-up, no differences were found between the 2 groups in the rates of axillary recurrence (0,5% vs 0,9%), in-breast recurrence (3,6% vs 1,9%), overall locoregional recurrence (4,1% vs 2,8%), disease-free survival (82,2% vs 83,8%) and overall survival (91,9% vs 92,5%). The majority of women in this trial were older than 50 years (64%), had clinical T1 tumors (68%), had ER-positive tumors (77%), had only 1 positive SLN (60%), received whole-breast radiation (89%) and received systemic therapy (96%). Forty percent of patients had micrometastases or isolated tumor cells in the sentinel nodes. Additional positive axillary node were found in 27,3% of the ALND patients.

The results from ACOSOG Z0011 are potentially practice changing and ALND may be omitted for patients who meet all the criteria used in the trial.

The significance of micrometastases in SLN is studied by many authors. Galimbert et al of the International Breast Cancer Study Group (IBCSG) trial 23-01, in a recent randomized, multicenter, phase III clinical trial that compared axillary dissection versus no axillary dissection for patients with micrometastases in SLNB, enrolled 934 patients and found no difference on 5-year disease-free survival (87,3% vs 88,4%; p=0,48) and overall survival (97,6% vs 98%; p=0,35) between the groups.

In the American College of Surgeons Oncology Group (ACOSOG) Z0010 trial, a prospective observational study of SLNB, occult metastases were found by immunohistochemistry (IHC) in 8,9% of 3,945 patients who were negative by hematoxylin and eosin (HE). The 5-year survival was not different between those patients who were HE negative and IHC negative, and those who were HE
negative and IHC positive (95.8% vs 95.1%; p=0.53). Similar results were demonstrated in the NSABP B32 trial, which found 15.9% of occult metastases by IHC in 3,887 HE negative patients. The results of ACOSOG Z0010 and NSABP B32 trials suggest that SLN micrometastases found only by IHC are clinically insignificant and that IHC staining of SLN is unnecessary. Therefore, routine use of IHC staining of SLN is not recommended. Its use has not been supported by ASCO and the College of American Pathologists and it was abandoned by many institutions after the data from these two studies were reported.

Another large study comparing SLNB alone versus ALND for node positive breast cancer containing 97,314 patients, after a median follow-up of 63 months, concluded that ALND does not appear to improve outcomes for breast cancer patients with microscopic nodal metastases (no difference in axillary recurrence and overall survival between the groups). For patients with macroscopic disease, there was also no significant difference between the groups.

Sentinel lymph node biopsy after neoadjuvant chemotherapy

There is controversy in the use of SLNB after preoperative systemic therapy due to the possibility of nonuniform, selective sterilization of lymph nodes. After neoadjuvant chemotherapy, the standard surgical treatment has been consisted of residual tumor resection and axillary level I and II lymphadenectomy to improve local control. Neoadjuvant chemotherapy downstages 20% to 40% of preoperative documented axillary metastatic lymph nodes, with a complete pathologic response in 32%. In this scenario, a negative SLNB may still be associated with lymph nodes harbor metastatic disease, resulting in reduced accuracy and unacceptably high false negative rates. Studies thus far, however, do not support this theory and overall demonstrated similar accuracy and false negative rates, especially in patients with a clinically negative axilla prior to systemic therapy. The NSABP B27 trial, in which 428 patients had SLNB followed by complete axillary dissection, evaluated SLNB after preoperative chemotherapy. SLNs were successfully identified in 85% and the false negative rate was 11%. A meta-analysis of 21 published studies, which included 1,273 patients who underwent SLNB with subsequent ALND after neoadjuvant chemotherapy, reported a SLN identification rate of 90% and a false negative rate of 12%. The Ganglion Sentinelle et Chemothérapie Neoadjuvant,
a French prospective multicentric study, enrolled 195 patients from 12 institutions and found a detection rate of 90% and a false negative rate of 11.5% \(^{38}\).

These studies confirm the feasibility of SLNB after neoadjuvant chemotherapy in the case of large operable breast cancer. The detection rate, false negative rate and accuracy do not differ from those obtained in the case of early breast cancer without neoadjuvant chemotherapy. Patients who are node negative, based on clinical examination, radiological examination and/or fine needle aspiration, may undergo SLNB after completion of preoperative systemic therapy at the same time as the surgical treatment of their primary breast cancer.

**Clinically positive axilla**

In patients with clinically positive axilla, the standard approach of surgical treatment consists in ALND to improve the disease local control \(^{39}\).

A small retrospective analysis of SLNB after preoperative chemotherapy reported a higher false negative rate (25%) in patients who have cytologically documented axillary lymph node involvement prior to chemotherapy \(^{40}\). However, in the NSABP B27 trial, the false negative rate was not different for clinically node positive patients \(^{36}\). The real role of SLNB in patients with clinically positive axillae undergoing induction chemotherapy is being evaluated by the ACOSOG Z1071 trial. Until the results of this large trial that enrolled patients with stage II and stage III breast cancers and documented axillary lymph node metastases prior to systemic therapy are found it is uncertain whether patients in whom axilla clinical examination is positive prior neoadjuvant chemotherapy are candidates for SLNB.

Data actually documenting the utility of SLNB in patients with inflammatory breast cancer are limited and its use is not supported.

**Predictive Models**

Many factors associated with the likelihood of additional non-SLN metastases have been investigated in an effort to distinguish which patients could avoid extensive axillary surgery. Aspects of primary tumor, such as size, grade, hormone receptor status, Her-2 profile, multifocality, mean proliferative fraction and lymphovascular
invasion have all been studied. SLNs features, such as size of metastases, number of positive SLNs, ratio of positive to resected SLNs and the extracapsular spread have been also examined. Barbosa et al found that the major prognostic factors for non-SLN metastases are the primary tumor size, size of SLN metastases and number of positive SLN. However, none of these characteristics individually can determine a subset of patients for whom ALND is unnecessary.

Some mathematical models have been developed to predict the risk of non-SLN involvement in patients with SLN-positive breast cancer. There are four nomograms: the Memorial Sloan-Kettering Cancer Center (MSKCC), Mayo, Cambridge and Stanford. There are also three scoring systems: Tenon, MD Anderson Cancer Center and Saidi, and two recursive partitioning tools developed by Kohrt et al.

In a study designed to compare some of these methods, Hatschbach et al found an accuracy to predict additional metastases in axillary lymph nodes of 64.6% for MSKCC, 62.7% for Stanford and 46% for Tenon model. Although not flawless, the MSKCC and Stanford nomograms were superior to the clinical judgment to predict presence or absence of axillary non-SLNs disease.

In the future, diagnosis of sentinel node involvement can be made using the One-Step Nucleic Acid Amplification (OSNA). It is an automated assay for the detection of cytokeratin message, CK 19 mRNA, present in approximately 98% of breast cancers. OSNA provides an opportunity to make an intraoperative diagnosis within 30 minutes, avoiding frozen section and allowing a one-stage procedure. Tsujimoto et al, Feldman et al and Tamaki et al found a concordance of OSNA and histopathology of 98%, 96% and 93% respectively. It is likely that in time OSNA will replace histopathological examination of SLN because of its ease, accuracy and potential for enabling almost all patients to have a one-stage operation for early breast cancer.

Conclusions

Sentinel lymph node biopsy is a step forward in the conservative surgery of breast carcinoma. The avoidance of complete axillary dissection has a good impact on arm mobility and lowers the risk of arm edema. When indicated, sentinel lymph node biopsy gives information about axillary staging and spares the patient unnecessary dissection of all the axillary lymph nodes.
We have transitioned from the era of routine axillary lymph node dissection on all breast cancer patients to identifying patients who need ALND based on results from SLNB. Currently, the approach to the axilla has become even more selective.

It is possible that not all minor tumor foci in axillary lymph nodes progress to local recurrences. According to Al-Hajj et al, only a minority of cancer cells potentially give metastases and most isolated tumor cells are not viable and do not have the ability to form new tumors \(^6\). There may be two different breast cancer cell populations, true stem cells that have the capacity to develop metastases and the non stem cells that never grow and are finally destroyed \(^7\).

Evaluation of the SLN has evolved and data from recent trials support abandoning the routine use of IHC to identify occult metastases.

The findings from the ACOSOG Z0011 trial are practice-changing and they evoke the principle demonstrated in NSABP B04: not all axillary disease becomes clinically detectable or relevant with respect to recurrence and survival \(^8\). The recurrence and survival demonstrated in ACOSOG Z0011 are far superior to those in NSABP B04, representing the evolution of breast cancer care received by contemporary women.

Although the findings of ACOSOG Z0011 are impressive, in practice we must remember that the data are applicable to a limited number of cancer patients: those with T1-T2 primary tumors with clinically negative axilla and 1 to 2 positive SLN(s) who underwent breast-conserving surgery and adjuvant whole-breast irradiation.

For patients with known positive lymph node metastases preoperatively, those with palpable adenopathy and those with more than 2 positive SLNs or lymph nodes with extracapsular tumor extension, ALND should be recommended.

Although nodal staging has become less invasive for more women, ALND still plays an important role for regional tumor control and staging for many breast cancer patients.

Surgeons are seeking to find a balance between the needs of the majority to have minimal axillary surgery with minimal postoperative morbidity against the possibility that a minority will suffer relapse, morbidity and possible increased mortality from
undertreatment. A predictive model which accurately estimates the likelihood of additional disease in the axilla might help the surgical approach and individual care, and identify those most likely to benefit from completion ALND. Genetic assays defining prognostic markers and new intraoperative tests detecting accurately SLN involvement will help in early therapeutic decision making in the future.

An alternative to axillary surgery might be axillary radiation therapy. This topic is being evaluated in a prospective randomized study by the European Organisation for Research and Treatment of Cancer (EORTC) called AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery) trial. It is a phase III study comparing ALND with axillary radiation therapy in patients with proven axillary metastases by SLNB. The main objective of the trial is to prove equivalent locoregional tumor control and reduced morbidity for axillary radiation therapy.

As the understanding of breast cancer biology deepens and adjuvant therapies become more effective, more individualized and multidisciplinary treatment is possible. Important questions with regard to management of the axilla in additional subsets of patients may be answered in the future, with the next generation of trials.

References


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