Management of the Axilla in Breast Cancer - Routine Practice, Controversies and Outlook

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Abstract
Axillary involvement is the first step before systemic spreading in breast cancer. The management of the axilla is in constant evolution with better comprehension of the pathogenesis of axillary node involvement. The level of achievement of positive nodes is still not correlated with prognosis according to recent trials. We analyzed clinical, diagnostic, and prognostic aspects of the management of the axilla to summarize routine practice, actual controversies and possible outlooks.

Keywords: Breast Cancer; Axillary Dissection; Lymph Node; Biopsy

Introduction
Surgery is the cornerstone of breast cancer treatment. History of breast cancer is correlated with the history of its surgical management. Surgical practices have evolved from the William Stewart Halsted time [1,2]. Initially, loco regional treatments were very mutilating. They have been refined since the systematization of sentinel node biopsy in N0 cancers. More publications on new approaches related to sentinel lymph node biopsy gave us the opportunity to reflect on management of axilla [3,4]. The objective of the present review is to describe the routine management of the axilla, to discuss the main controversies, and to identify new procedures.

Routine Treatment of the Axilla in Breast Cancers
Axillary dissection is the most comprehensive and the oldest treatment of lymph node involvement in breast cancer. Nodes status is the most important prognosis factor. Dissection of the internal mammary chain remains correlated with poor prognosis and increasing morbidity [5]. Axillary lymph node dissection was introduced in late 19th century by Halsted. It consisted of axillary dissection carrying three Berg node’s levels [1,6]. This technique was particularly morbid because it requires the removal of the pectoralis minor and often provided a very disabling lymphedema. Axillary dissection in present days is removing the first and second Berg levels between latissimus dorsi muscle, sub scapular muscle, axillary vein and the Charles Bell nerve.

Sentinel Lymph Node Biopsy (SLNB) has become a standard technique in N0 breast cancer. It removes the first nodes of breast drainage [7–9]. Morbidity, especially lymphedema and neurologic and trophic disorders of the shoulder belt have remarkably decreased [10].

Two main techniques are used to localize sentinel nodes. One draws on technetium sulfur colloid or technetium-labeled albumin and isosulfan blue dye or patent blue dye according to American and European practices [11]. The use of surgical devices for axillary dissection does not seem to modify local and systemic outcome [12].

The development of histological and molecular analysis of the node using immunofluorescence and PCR has allowed the classification of lymph node involvement according to the presence of isolated cells, micro metastasis and macro metastasis [13]. The first step was to delay examination of SLN and used routine hematoxinlin and eosin staining with one section. It was lacking lots of information. Thus it was necessary to redefine new clusters like isolated tumor-cell clusters (ITCs) less than 0.2 mm in size, micrometastasis when the size is between 0.2 and 2 mm and macrometastasis when the tumor clusters are larger than 2 mm [14].

At the second step, numerous teams without a real standardization of routine SLNB decreased the number of second surgery by more than 50%. There were controversies on the cutoff of sections size and on the use of frozen and immunohistochemistry.

The third step was the rise of new molecular tools using PCR and OSNA based on amplification of cytokeratin, RNA and other [15].

Radiotherapy is a powerful tool to sterilize the axilla after node involvement. Despite its efficacy, it is shown to be a great risk factor in the occurrence of lymphedema. It is used in all stages of axillary, supraclavicular, and internal lymph node involvement. Routinely SLNB is followed by ALND despite the inclination to de-escalate. Radiotherapy causes less lymphoedema than dissection for positive nodes. Women who have one or more positive sentinel nodes and plan to have mastectomy with no radiation should be offered axillary lymph node dissection [16].

Controversy in Axillary Management
The ACOSOG Z0011 trial marked a turning point in the management of the axilla. It has randomized over 800 patients in two arms. All patients had positive sentinel node in Hematoxylin and Eosin coloring. One arm had also received axillary dissection. There was no significant difference in survival and local recurrence after six years of follow-up [17]. These results are the same for metastatic lymph node micro achievement evaluated in immunohistochemistry and the presence of isolated tumor cells [11]. The controversy lies in choosing or not choosing axillary dissection after lymph node involvement in one of these three levels.

Neoadjuvant chemotherapy’s role is to reduce lesion size for a conservative surgery, to tackle the micro metastatic disease for locally advanced tumor, to study the clinical and histological response induced by the first regimen. It is evaluated in the node by the therapeutic effect. This is a histological condition and is correlated with the effect on the breast tumor [18]. Sentinel node biopsy after neoadjuvant chemotherapy does not provide information on histological initial damage. It is recommended in
selected patients with favorable prognostic factors [19,20]. It is indeed controversial. N_0 status is a clinical status. The loco regional breast cancer extension is assessed by cytology or microbiopsy in the event of positive axillary node imaging [21].

Depending on the histological type, controversies do exist. Patients with DCIS are not supposed to have lymph node metastasis. Because of the risk of unknown associated invasive carcinoma it is recommended to complete a SLNB. This is a routine choice. Some series trend to prove the opposite. In the era of down staging, it seems that no completion of SLND is needed [22].

The choice of axillary radiation therapy in case of positive node for N_0 patients is a source of controversy. At the time of Z11, because of the great morbidity of axillary dissection, radiation therapy seems to be a alternative therapy to surgery. According to some authors the comparison between external radiotherapy and axillary dissection after positive sentinel node biopsy, showed equivalence of both in terms of local recurrence and superiority of radiotherapy in preventing lymphedema [23]. Depending on the age of the patients, the choice of radiotherapy can be different. Older patients are more likely to be observed in early stages [24].

**Diagnostic and Therapeutic Perspectives in the Management of Axilla**

Conventional imaging of the axilla is based on mammography, ultrasound and MRI. The N_0 status is conventionally assessed using mammography and ultrasound. MRI can refine nodal exploration and optimize ultrasound and cytology at the neo adjuvant setting [25]. Sentinel node biopsy by isotopic method gave an idea in term of axillary node involvement. Mammoscintigraphy and positron emission mammography (PEM) uses Te-MIBI and offers the prospect of functional imaging to highlight involved small nodes. The results obtained in the same direction by PET/CT and PET/ MRI is promising [26].

The availability of radioactive technetium, and the cumbersome circuit for the patient between nuclear medicine, radiology and operating rooms is difficult which made the use of alternative techniques. Many teams are developing new products radioactive colloids, metal magnetic particles such as iron and immunofluorescence such as indocyanine green in combination with infrared camera [27–29]. The fluorescence of the cancer cell proteins is a booming field. The use of integrins alpha v beta 3, transmembranar proteins, which play a great role in angiogenesis mechanisms, are being explored as targets in functional imaging [30].

Genetic and molecular analysis of tumors determined different families of breast cancer beyond their histological differences. These analysis contribute significantly to the prognostic level. For N_0 breast cancer patients, genetic tests such as Oncotype DX and MammoPrint based on the principle of prognostic gene panels expression allow to refine the spectrum of potentially metastatic patients and to change the management of the patient [31,32].

**Conclusion**

Sentinel lymph node biopsy using blue dye and technecium and axillary dissection are the routine techniques in lymph node breast cancer surgery. Many innovations are underway to optimize the management of the axilla, thus decreasing dependence in radioactive technetium without increasing oncological risks. Their contribution is challenged by several studies encouraged by the ACOSOG Z0011 trial. The future of the axillary management in breast cancer remains unclear.

**References**


