Sentinel Node Biopsy and Axillary Dissection

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6.1 Historical Background

The extent of axillary dissection has changed over time according to the evolution in understanding breast cancer characteristics. The first complete axillary lymph node dissection (ALND) was described in 1894 by Halsted in his reports on the technique for "radical mastectomy"; in the "Halsted hypothesis", in which breast cancer was considered a local disease, ALND was intended to be curative [1].

In the 1970s, Fisher [2] proposed that breast cancer was a systemic disease from the outset and that survival was largely a function of tumor biology, not surgical technique.

In the "Fisher era", the primary objective of ALND was prognostication to guide systemic therapy, a secondary objective was local control; the survival benefit was unproved.

Nowadays we know that both the Halsted and Fisher hypothesis were right: breast cancer is a family of diseases with a wide spectrum of behavior, ranging from predominantly local (Halsted) to predominantly systemic (Fisher) phenotypes.

The contemporary sentinel lymph node (SLN) concepts (first lymph node draining the tumor, reliably mapped, and if negative, an indicator to avoiding ALND) were first reported for breast cancer by Krag et al. [3] (using isotope mapping) and Giuliano et al. [4] (using blue dye), respectively in 1993 and 1994.

The SLN is the first, or first few, axillary lymph node draining the tumor site and it could predict the status of axillary nodes. The SLN hypothesis has

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been validated by randomized studies where routine ALND has been compared with that performed only in the case of metastatic SLN, showing that a negative SLN is highly predictive of a negative axilla [5] and that the SLN is the node likeliest to be positive if metastatization occurs [6].

Sentinel lymph node dissection (SLND) has therefore become a routine technique for staging breast cancer with an axillary involvement.

6.2 Axillary Lymph Node Dissection

6.2.1 Technique

The axillary contents are arbitrarily divided into three "levels": level I lies lateral to, level II lies posterior to, and level III lies medial to the pectoralis minor muscle.

The question of what constitutes an adequate ALND in breast cancer has not been answered yet.

It has been long accepted that ALND should proceed from level I to III step by step, and that at least ten lymph nodes should be obtained from the axillary space.

Nowadays many authors recommend a level I to II ALND as the standard operation (the "skip metastases" hypothesis proved to be simply a level II or III SLN, receiving drainage directly from the breast) and a level III further dissection only in the case of palpably suspicious nodes in levels II to III or other high-risk features such as T3 or T4 cancers.

The possible incisions for ALND are either separate from or contiguous with the incision used for the breast surgery. Separate axillary and breast incisions are almost always cosmetically superior to contiguous ones.

A separate incision is best done transversely, extending from the lateral border of the pectoralis major muscle up to the anterior border of the latissimus dorsi.

After skin incision, the lateral axillary margin, up to the anterior border of the latissimus dorsi, is dissected. The tendinous portion of this muscle crosses the axillary vein in the superolateral operative field.

Then clavipectoral fascia (extending from the coracobrachialis to the pectoralis minor muscle, encompassing it) is then incised superiorly along the axillary vein; the axillary contents are mobilized inferiorly, and the axillary vein is exposed in full view. To incise the clavipectoral fascia as far as possible, the retractor should be placed deep to the pectoral minus. With this manoeuvre, level II of the axilla is also exposed.

When the axillary vein crosses the minor and major pectoralis, the medial pectoral nerve can be found; it lies lateral to the lateral border of the two pectoral muscles and innervates the lower third of the pectoralis major. It should be preserved whenever possible, because if it is injured it causes muscle atrophy, which is visible after mastectomy, especially with implant breast reconstruction. The entire accompanying medial pectoral vessel is ligated and divided.

Fig. 6.1 Intercostobrachial nerve (preservation is not mandatory)

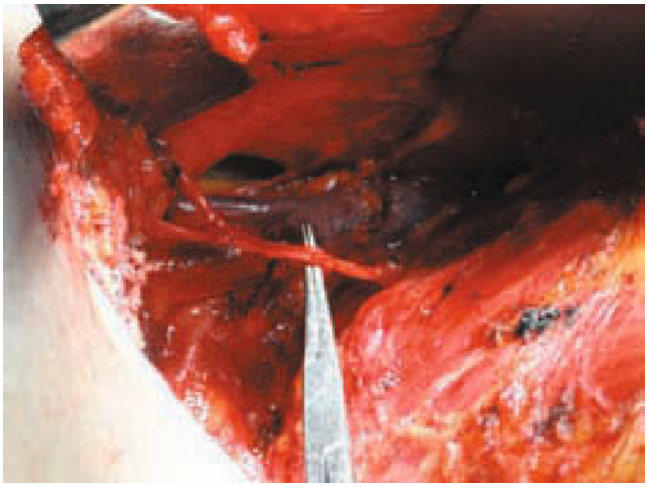

Fig. 6.2 Long thoracic nerve and thoracodorsal neurovascular bundle (their preservation is mandatory)

The intercostobrachial nerve can be sacrificed (Fig. 6.1), but the long thoracic nerve (which runs on the lateral chest wall, near the axilla floor, beneath the thin fascia of the serratus anterior muscle) and the thoracodorsal nerve (which runs medial to the thoracodorsal artery and vein) must be preserved (Fig. 6.2). The thoracodorsal neurovascular bundle lies posteriorly, on the axillary floor, and is better identified after the ligation and dissection of the thoracoepigastric vein (the largest side branch of the axillary vein) and by retracting the axillary contents inferiorly. The entire axillary contents are then removed.

A drain (21 gauge or 10 mm Jackson-Pratt) is put in place, the incision is closed with a multi-layer suture and a compressive dressing is applied (Fig. 6.3).

Fig. 6.3 Surgery field after ALND

6.2.2 Primary Axillary Lymph Node Dissection

The main goals of axillary surgery are:
1. Local control
2. Survival
3. Staging.

6.2.2.1 Local Control

Axillary recurrence after primary ALND is very low (< 2%) [7–9]. The prognostical meaning of axillary recurrence is different if it is combined with distant metastasis (about 50% of the patients) [10].

If recurrent axillary node metastasis show up after primary ALND and it is the only recurrent site, prognosis is similar to that of a new diagnosed cancer with positive lymph node and salvage redo ALND (technically more difficult because of the scar tissue from the previous surgery) is usually curative [11].

6.2.2.2 Survival

In the past, most studies showed that patients who underwent ALND at the time of lymph node metastasis diagnosis had a lower overall survival (OS). This might had been because primary ALND was not performed at the time of breast cancer diagnosis and, most likely, because of the disease understaging, which involved avoiding adjuvant therapy.

On the other hand, recent studies show that ALND does not confer a survival benefit in the setting of early-stage clinically lymph node-negative breast cancer. In a 2009 meta-analysis, even though the axillary local recurrence rate is higher in patients that do not undergo ALND, the OS is not statistically different [12].

A 2011 meta-analysis, enrolling 8560 patients in eight randomized clinical trials, does not show statistically significant differences in disease free survival (DFS), OS and axillary recurrence for patients treated with ALND or (only) SLND, with axillary lymph node-positive or negative. Also SLND, compared to ALND, shows less postoperative complication and a better quality of life in the long term [13].

The neo and/or adjuvant therapy, hormone therapy and radiotherapy play a major role nowadays in the OS after axillary recurrence [14].

The primary ALND can improve DFS and OS in cN0 patients with lymph node metastasis that still have not a systemic hematic diffusion of the disease.

6.2.2.3 Staging

Some years ago a positive axillary lymph node result was considered the main risk factor for distant metastasis. The more lymph nodes that were involved, the higher was the risk. Systemic adjuvant therapy was strongly influenced by the number of axillary lymph nodes involved.

At the 2011 St. Gallen consensus conference, it was stated that the biological characteristics of the tumor play a major role in determining whether systemic therapies have to be used and that ALND is not needed anymore for staging [15].

Even though ALND has lost its former main staging role, the number of lymph nodes involved and the evidence of extra-capsular invasion of the nodes still influence the adjuvant therapy and radiotherapy.

Indications for primary ALND are:

- Clinically positive axilla
- Axillary node metastasis on fine needle aspiration (FNA) or core biopsy (CB)
- Failed SLND
- Positive SLN on intraoperative examination
- Axillary local recurrence (ipsilateral or contralateral).

6.3 Sentinel Lymph Node

The sentinel lymph node/s is/are the first lymph node/s that drain the primary tumor. Anatomical studies showed that the lymphatic drainage of the breast starts from the deep part of the mammary gland (above the muscular fascia), moves to the cutaneous lymphatic system of the skin, especially around the nipple areola complex, and ends in the SLN.

6.3.1 Mapping

There are two validated techniques for SLN identification: blue dye (Patent blue dye, PBD) and/or a radioisotope (technetium, Tc99m). The latter is bound

Fig. 6.4 Patent blue dye tracer allows lymphatic vessel identification

to a carrier, most commonly sulfur colloid in United States and colloidal albumin in Europe.

The identification success rate with blue dye alone varies from 65% to 90%, depending on the surgeon's experience, and reaches 97% in combination with the radioisotope [16–18]. Using the radioisotope is definitely more demanding, both from the spending and organization point of view.

The cost of technetium is very high (with an exponential increasing trend); a nuclear medicine service and a nuclear doctor are required; surgery must follow radioisotope infiltration between 1 and 36 hours and a sensitive hand-held gamma probe must be available in the operating room [19].

On the other hand, the blue dye technique is cheaper (Fig. 6.4). The dye is injected in the subdermal plane, directly above the tumor, by the surgeon in the operating room, some time before the surgery. The volume of dye injected varies from 0.2 to 0.4 mL. All lymph nodes that show blue coloration are dissected (Fig. 6.5).

Patients who undergo this technique show a transient bluish color of the skin and urine. A faint blue stain may persist at the breast injection site for as long as 1 year postoperatively. About 0.5% of patients have an anaphylactic reaction to the blue dye [20].

Fluorescent SLN mapping using green indocyanine (ICG) is currently being tested. When the vital fluorescent dye is injected around the areola, subcutaneous lymphatic channels draining from the breast to the axilla are visible by fluorescence; by tracking the fluorescence, it is possible to choose a better location for skin incision and find the SLN, which is the first lymph node that gets fluorescent (Fig. 6.6) [21].

The cost of this technique is inferior to that using radionuclide and just a bit more expensive than using blue dye alone. A infrared probe is needed to visualize the fluorescence on the surgery site.

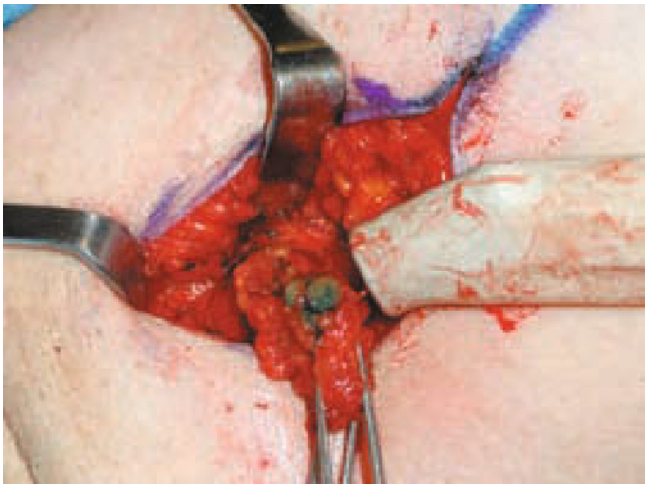

Fig. 6.5 The SLN is blue colored and hypercaptating (note handheld probe on the right)

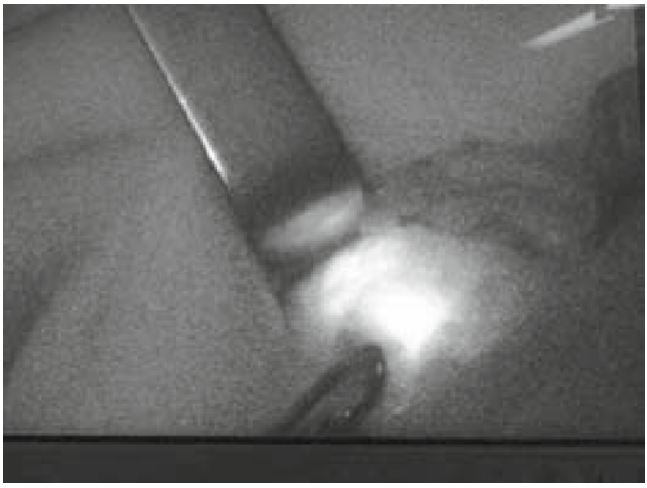

Fig. 6.6 Green indocyanine allows SLN identification by fluorescence (infrared probe visualization)

6.3.2 Site of Injection

The tracer (PBD, Tc99m or ICG) injection site can influence the SLN identification rate. Intratumoral injection has been abandoned because of the low identification rate related to the paucity of lymphatic vessels around the tumor, which causes a slow and sporadic migration to the SLN.

Many studies showed that independently from the subdermal site of injection, in the quadrant of the tumor or in the retroareolar area, or the peritumoral one the SLN identified by the tracer turned out to be the same [22–24].

6.3.3 False Negative Scenario

The effect of the SLND false negative rate on the prognosis is unknown. An overview of 69 papers showed a 7% false negative rate for SLND followed by ALND [17]. However the axillary recurrence rate after negative SLND is less than 1% [25, 26], because other factors influence axillary recurrence (adjuvant therapy/radiotherapy of the axilla in the breast conserving technique, tumor biology and rapidly growing distant metastasis).

6.4 Sentinel Lymph Node Dissection

6.4.1 Technique

SLND can be performed under general anesthesia and under local anesthetic with intravenous sedation. Before starting surgery, blue dye is injected subdermally at a single site over the tumor. Using a hand-held gamma probe, the isotope injection site in the breast (radioisotope injected beforehand) is identified. The axilla is usually explored for SLN through a separate transverse skin line incision prior to the planned mastectomy or breast conservation procedure. As dissection is deepened through the axillary fascia, any blue lymphatics are left intact and traced proximally into the axilla, blue nodes are identified, and the gamma probe is used to identify any hypercaptating nodes. SLN are usually found low in level I, but in about 25% of cases they are found at other locations (along the latissimus dorsi muscle, near the axillary vein, beneath the pectoralis minor in levels II to III, as interpectoral or intramammary SLN).

The gamma probe is very useful throughout this dissection and is indispensable in patients with a very large or fatty axilla, when blue lymphatics or nodes are not found.

All blue SLN and hypercaptating SLN are removed; a median of 2–3 SLN per patient is submitted; when multiple hypercaptating SLN (or a diffusely hypercaptating axilla) are found, every effort must be made to remove the SLN with the highest count. All nodes with a count ≥ 10% of the highest count are submitted together with the SLN. The axillary incision after SLN biopsy is closed without drainage.

The morbidity from SLN biopsy is less than that of ALND but is not zero; patients may experience pain, seroma, hematoma, or infection.

6.4.2 When to Perform Sentinel Lymph Node Dissection

SLND must be performed in patients with diagnosis of invasive breast cancer obtained through: core biopsy (B5b), fine needle aspiration (C5), radiological finding (U5, R5) and definitive anatomopathological finding on the surgical specimen.

SLND can be avoided and ALND can be performed directly in U5 radiological patients with suspected metastasis [27]. If no metastasis are described SLND must be performed.

The SLND contraindications that still hold true are inflammatory carcinoma (T4) and a C5 diagnosis on any axillary lymph node's FNA, the others (node diameter > 3 cm, multicentrical lesions, prior surgery and male breast carcinoma) have been removed.

Some contraindications, neoadjuvant therapy, pregnancy, "in situ" lesions and prophylactic mastectomy, are still under discussion.

In patients who undergo neoadjuvant therapy, the SLN identification rate is comparable to that of other patients, with a false negative value of 8% [28]; nevertheless the false negative value goes up to 25% if the SLND is performed in patients with proved metastasis at the diagnosis [29].

The biological meaning of a possible understaging related to a SLN negativization after neoadjuvant therapy is currently under discussion. The present indication is performing SLND before starting neoadjuvant therapy. However, SLND after neoadjuvant therapy is reasonable in cN0 patients.

The SLN identification rate during pregnancy and breast-feeding is just slightly inferior to the standard and the technique does not cause teratogenic effects. The onset of lactation must be pharmacologically blocked.

In the "in situ" carcinomas SLND must be performed only when the risk of a diagnosis of invasive carcinoma at the definitive pathology test is high (patients with a mass on clinical examination, G3 high-grade disease, distinctive radiological pattern and node diameter > 2.5 cm) and SLND should be performed in patients undergoing mastectomy (because mastectomy precludes it), in case invasive disease is subsequently discovered [30].

Performing SLND in patients undergoing prophylactic mastectomy is still controversial. The incidence of occult disease is low but patients with locally advanced or inflammatory primary breast cancer are at high risk for contralateral disease. This selected group of patients may benefit from SLND at the time of surgery but further studies are needed to prove it [31, 32].

6.5 Axillary Lymph Node Dissection after Positive Sentinel Lymph Node Dissection

When the SLN is negative, SLND alone with no further ALND is an appropriate, safe, and effective therapy in cN0 patients with breast cancer because OS, DFS and local control are statistically equivalent [33].

Although ALND is indicated when there is clinical evidence of disease in the axilla, it is still under discussion whether ALND should be performed in clinically silent or SLND diagnosed metastatic lymph nodes, and if this could positively influence the OS.

The classification of metastatic lymph node is based upon metastasis dimension:

1. Isolated tumor cell clusters (ITC, small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histological cross-section. ITC may be detected by routine histology or by immunohistochemical methods
2. Micrometastasis (greater than 0.2 mm and/or more than 200 cells, but not greater than 2.0 mm)
3. Macrometastasis (greater than 2.0 mm)

In the current TNM classification, ITC are defined as pN0(i+), they are not considered metastasis and therefore they should not be treated with ALND [34–36].

The clinical meaning of micrometastasis, classified as pN1mi, is currently unknown. Micrometastases are thought to have a smaller influence on OS and DFS among patients with early breast cancer.

In some studies, no statistically significant differences were observed in OS and DFS between patients diagnosed pN0 and pN1mi with SLND only [37–39], or between pN1mi treated with SLND only or with SLND plus ALND [40, 41].

On the other hand, the MIRROR study, a retrospective analysis recruiting 2707 patients with early breast cancer, found that: 1) micrometastasis and ITC were associated in the absolute reduction in the 5-year rate of DFS of nearly 10 percentage points; 2) patients who received systemic adjuvant therapy (systemic chemotherapy and hormonal therapy), the 5-year rate of DFS was significantly improved [36]; 3) not performing axillary treatment in a patient with SLN micrometastasis is associated with an increased 5-year regional recurrence rate (2.3% in pT0 and 5.6% in pT1mi); 4) tumor size, grade 3 and negative hormone receptor status are significantly associated with recurrence and ALND is recommended in patients with SLN micrometastasis and unfavorable tumor characteristics [38, 42].

So ALND is not always necessary in patients pN1mi, nevertheless it seems important to be able to reliably identify the patient at high risk of axillary recurrence. When the SLN is macrometastatic ALND should be routinely performed.

However, data from the American College of Surgeons Oncology Group (ACOSOG) ZOO11 trial suggest that ALND may be omitted in select patients with one or two macrometastatic positive SLN/s. In this trial, 891 patients with HE positive SLN were randomized to ALND (446) compared to no further axillary treatment (445). The patients all had cT1-2 N0 tumors, breast conserving surgery, whole-breast RT, no axillary RT, and no more than two SLN-positive; there were no differences between groups in the exposure to adjuvant chemo or hormonal therapy and follow-up was 6.3 years. Additional positive axillary nodes were found in 27% of ALND patients but there was no difference in the rates of axillary recurrence (0.5% in ALND group and 0.9% in SLN-only group). OS and DFS did not show a statistically significant difference between the two groups [43, 44].

Considering the evidences from the Z0011 study ALND could be omitted in selected patients with macrometastasis detected in one or two SLN/s, nev-

ertheless a cautious attitude should prevail since the study is characterized by some methodological and statistical imprecision.

Furthermore, omitting ALND in pN1 patients should be proposed only in clinical trials with backup adjuvant therapy. The importance of ALND for the local control of locally advanced diseases is not under discussion. ALND is also indicated for axillary local recurrence after negative SLND and for those patients who relapse in the controlateral axilla and do not have other distant sites of metastasis.

Further questions are whether ALND (with positive SLN) for detecting the number of positive lymph nodes involved is still necessary to recommend adjuvant therapy and for the planning of the right therapeutic strategy.

A recent study showed that axillary staging does little in addressing adjuvant therapy [45]. Furthermore the gene expression profiling seems to have a more accurate capacity to predict the response to therapy when compared to conventional histopathology alone. In the future, the concept of surgical nodal status staging as a prognostic factor should be replaced by an integrative biological approach, in early breast cancer patients' management.

6.6 Morbidity and Complications

A systemic review of studies concerning the morbidity of patients who had undergone axillary surgery (SLND or SLND followed by ALND) reports great variation in the prevalence of pain (7.5–36%), impairment of range of motion (0–31%), edema (0–14%), decreased strength (11–19%) and sensory disorders (1–66%) [46].

Most of the studies show that women who underwent SLND alone have a better quality of life (physical, emotional and social well-being, together with cognitive function) compared to women who underwent complete ALND [47–49].

Likewise, patients who undergo SLND are significantly less likely to suffer postoperative complications typical of ALND [49–51], such as lymphedema (7 to 82% incidence rate, directly correlated with patient age, body mass index and infection or injury) [52], paresthesia (22.6%, caused by the inadvertent division of the intercostobrachial nerve) [49], restricted arm motion (6.6% after 3 months, with a resolution rate over one year time of 85%) [49] and infection/seroma (21%/16% incidence rate respectively, with a 42% lower risk for wound infection with SLND alone compared to ALND) [50, 53].

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