Surgical attitudes for axillary dissection in breast cancer

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Abstract

Axillary dissection is of great importance in breast surgery. Since the Halsted or Fisher era, the concepts have significantly changed. In the 1990-ies, the concepts evolved considerably. Nowadays, the contemporary sentinel lymph node serves as a modern treatment approach, considering it as an indicator or predictor in the prognosis of breast cancer. This technique can predict the patient's prognosis and of course the radicalism of surgery treatment. It has been recently reported the outcome of this technique in the international literature, but in Albania several issues should be considered in this regard. Nevertheless, the contemporary sentinel lymph node is a worldwide accepted approach, and this review tends to be focused on it, in order to revitalize our surgery treatment.

Keywords: breast surgery, complete axillary lymph node dissection, contemporary sentinel lymph node.

Introduction

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 of "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 the surgical technique. In the "Fisher era", the primary objective of ALND was prognostication to guide systemic therapy and local control. Nowadays, we know that both the Halsted and Fisher hypotheses were right. 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 by Krag et al. (3) and Giuliano et al. (4). The SLN is the first axillary lymph node draining the tumor site and it could predict the status of axillary nodes. The SLN hypothesis found that a negative SLN is highly predictive of a negative axilla (5) and the node most likely to be positive if metastasis occurs (6). Sentinel lymph node dissection (SLND) has therefore become a routine technique for staging breast cancer with an axillary involvement.

Axillary lymph node dissection

Primary axillary lymph node dissection

The main goals of axillary surgery are: local control, survival, and staging. Axillary recurrence after primary ALND is very low (<2%) (7-9). The prognostic 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 (11). 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). 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, did 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). 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 extracapsular invasion of the nodes still influence the adjuvant therapy and radiotherapy.

Indications for primary ALND include clinically positive axilla, axillary node metastasis on fine needle aspiration (FNA) or core biopsy (CB), failed SLND, positive SLN on intraoperative examination, and axillary local recurrence.

Sentinel lymph node

The sentinel lymph node/s is/are the first lymph node/s that drains 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.

Mapping

There are two validated techniques for SLN identification: blue dye (Patent blue dye, PBD) and/or a radioisotope (technetium, Tc99m). 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). 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. The dye is injected in the subdermal plane, directly above the tumor, by the surgeon in the operating room, some time before the surgery. All lymph nodes that show blue coloration are dissected. 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 (21). The cost of this technique is inferior to that using radionuclide and just a bit more expensive than using blue dye alone.

Site of injection

The tracer (PBD, Tc99m or ICG) injection site can influence the SLN identification rate. Intra-tumoral 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).

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).

Sentinel lymph node dissection

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 is described SLND must be performed. The SLND contraindications are inflammatory carcinoma (T4) and a C5 diagnosis on any axillary lymph node's FNA, node diameter >3 cm, multicentrical lesions, prior surgery and male breast carcinoma, whereas neoadjuvant therapy, pregnancy, "in situ" lesions and prophylactic mastectomy, are debatable. 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

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). 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).

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:

- 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.
- Micrometastasis (greater than 0.2 mm and/or more than 200 cells, but no greater than 2.0 mm).
- 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. 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: i) micrometastasis and ITC were associated in the absolute reduction in the 5-year rate of DFS of nearly 10%; ii) patients who received systemic adjuvant therapy (systemic chemotherapy and hormonal therapy), the 5-year rate of DFS was significantly improved (36); iii) 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); iv) 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). Hence, 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 (n=446) compared to no further axillary treatment (n=445). The patients all had cT1-2 N0 tumors, breast conserving surgery, whole breast RT, no axillary RT,

and no more than two SLN-positives; 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, nevertheless 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 the early breast cancer patients' management.

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