Assessment of Sentinel Lymph Nodes in Early Breast Carcinoma

Thesis

Submitted for Partial Fulfillment of Master Degree in General Surgery

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Abstract

Background and Aims: Sentinel lymph node biopsy is the widely acceptable method for the examination of the breast cancer in the patients. This biopsy is considered as the best method for identifying the axillary involvement. Various dyes are used in this biopsy to find the sentinel lymph node. However, methylene blue dye (MBD) is considered to have a low risk of anaphylaxis, be cost effective and widely available. The results of previous studies made SLNB the standard of care for axillary staging in patients with early breast cancer and clinically negative ALNs. The most important function of axillary staging is to anatomically group patients to determine the treatment algorithm and prognosis. Accurate axillary staging carries a substantial importance in comparing the treatment results among the studies. **Aim of the Work:** We assessed the role of sentinel lymph node detection in early breast carcinoma management, assessed methylene blue dye in sentinel lymph node biopsy and its complications and detected axillary level of SLN. **Methods:** This was a prospective study, included 50 female Egyptian patients with early breast carcinoma (T1, T2) stage and clinically negative axilla by palpation (N0) or high grade ductal carcinoma in situ. **Results:** The rate of SLN detection was 84%, sensitivity of methylene blue dye was 93.31%, and specificity was 93.1%. Complications of methyline blue dye were observed in 10 patients (20%). More than one lymph node was sometimes found in SLNB specimen. Level of axillary LN (where SLN was detected in 42 cases) was 33 cases at level I, 8 cases at level II and one case had SLN at level III and also another SLN at level II**.** Surgical procedures for axilla were 22 cases underwent ALND and 28 cases underwent only SLNB with P- value = 0.00001. Complications of the surgery were observed in 15 patients (30%). **Conclusion:** Axillary dissection can be spared in SLNB in about half of cases of early breast cancer. Sentinel lymph node biopsy (SLNB) is a minimally invasive procedure to stage the axilla in patients with breast cancer, SLNB results in a significant reduction of postoperative morbidity and improved quality of life. A learning curve was clearly observed; the rate of SLN detection increased with experience.

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List of Abbreviations

99Tc Technetium-99
ACOSOG …… American College of Surgeons Oncology Group
AJCC ..... American Joint Committee on Cancer
ALH .....atypical lobular hyperplasia
ALND .....axillary lymph node dissection
ALN .....axillary lymph node
ASCO..... American Society of Clinical Oncology
CBE ..... Clinical breast examination
CBS..... conservative breast surgery
CC.....craniocaudal
CDH1..... cadherin
CNB .....Core needle biopsy
CT .....Computed tomography
DCis .....ductal carcinoma in situ
DFS.....disease free survival
DIEP ..... deep inferior epigastric perforating
ECG ..... electrocardiogram
FN .....false negative
FNAC..... Fine-needle aspiration cytology
H&E.....hematoxylin and eosin
HR .....hormone receptor
IBCSG ..... International Breast Cancer Study Group
IDC ..... invasive duct carcinoma
IHC ..... immunohistochemistry
ILC.....invasive lobular carcinoma
IM ..... internal mammary
LABC..... Locally advanced breast cancer
LCis ..... Lobular carcinoma in situ
LIQ ..... lower inner quadrant
LN.....lymph node
LOQ .....lower outer quadrant
Lt .....left
MBD .....methylene blue dye
ML ..... mediolateral

MLO ..... mediolateral oblique
MRI..... Magnetic resonance imaging
NCCN .....National Comprehensive Cancer Network
NOS ..... not otherwise specified
NNT .....number needed to treat
OS ..... overall survival
PBD ..... Patent Blue Dye
QOL .....quality of life
Rt ..... right
RT-PCR ..... reverse transcriptase polymerase chain reaction
SEER ..... Surveillance Epidemiology and End Results
SLN..... sentinel lymph node
SLNB .....sentinel lymph node biopsy
UIQ ..... upper inner quadrant
UOQ..... upper outer quadrant
US ..... ultrasound

Introduction

The first lymph node to receive lymphatic drainage from the site of a primary tumor is called Sentinel Lymph Node (SLN), a concept established since 1977 by Cabanas, who introduced the sentinel lymph node biopsy (SLNB) in penile carcinoma ***(Si-Qi Qiua et al., 2018)***.

In 1993, used the Technetium-99 (99Tc) in SLNB for melanoma. In 1994, Giuliano, using the patent blue dye in breast tumor, validated the concept of sentinel lymph node (SLN) in breast carcinoma ***(Paulo et al., 2015)***.

In 2013, Veronesi established that SLNB was a safe and accurate method of screening axillary nodes for metastasis in women with small breast tumors ***(Veronesi et al., 2013)***.

Recently, SLNB has replaced axillary dissection in early-stage breast carcinoma in clinically tumor-free patients ***(Lyman et al., 2014)***.

Axillary staging is important in patients with breast cancer. This was initially performed as axillary lymph node dissection (ALND).This procedure has changed since randomized trials showed that sentinel lymph node biopsy (SLNB) reflects the overall axillary lymph node (ALN) status. There is no difference in regional control, disease free survival (DFS) and overall survival (OS) between SLNB and ALND in patients with clinically negative nodes ***(Veronesi et al., 2006; Krag et al., 2010)***. The SLNB experience an improved quality of life (QoL) and upper extremity function ***(Mansel et al., 2006; Ashikaga et al., 2010)***.

The results of previous studies made SLNB the standard of care for axillary staging in patients with early breast cancer and clinically negative ALNs ***(Lyman et al., 2005)***. Now, there is increasing interest in properly selecting patients with a low probability of ALN metastasis and therefore might not even require a SLNB ***(Gentilini and Veronesi, 2012)***.

In several developing countries, including China and Egypt, only blue dye is available for SLNB ***(Li et al., 2015)***. Blue dye carries a risk of allergic reactions in around 1% of the patients ***(Cady, 2002)*** for the whole spectrum and 0.2% ***(Krag et al., 2007)*** for severe reactions. The SLNB using a blue dye is highly dependent on a surgeons' experience and the guidance of devices such as a gamma probe used in radioisotope guided SLNB, and obviously relies on visual detection of the SLN ***(Ang et al., 2014)***.

The most important function of axillary staging is to anatomically group patients to determine the treatment algorithm and prognosis. Accurate axillary staging carries a substantial importance in comparing the treatment results among the studies ***(Edge et al., 2009)***. In 1960, TNM staging system for breast cancer published by UICC. Revisions to the staging system were updated in 1962 and the 8th edition was published in 2018 ***(Haffty et al., 2018)***.

Early stage breast cancer is a disease confined to the breast with or without axillary lymph node involvement, and the absence of distant metastases. The early stage breast cancer is potentially curable, and patients with distant metastatic disease are not. In developed countries, there is long-term survival rate after surgery in more than 80% of patients with early stage breast cancer, and in some cases systemic therapy such as chemotherapy, hormone therapy, targeted therapy and local radiation. By contrast, breast cancer patients with distant metastatic disease have rare long-term survival rate ***(Coleman et al., 2008)***.

Treatment of early stage breast carcinoma always includes surgical removal of the breast tumor and removal of some axillary lymph nodes. Surgery alone results in long-term survival for some patients. Systemic therapy and local radiation have significant improvement of the chances of long-term survival depending on the stage of disease and biologic subtype of breast carcinoma. Therefore, the systemic therapy found having more benefits than surgery alone. Systemic therapies include hormone therapy (tamoxifen and aromatase inhibitors), chemotherapy, and targeted therapy such as trastuzumab ***(Burstein et al., 2014)***.

For many patients, surgical removal of the primary breast tumor and axillary node biopsy is the first procedure, followed by systemic therapy and radiation if indicated. In these circumstances, patients can be treated either with modified radical mastectomy, conservative breast surgery or mammoplasty. In patients who undergo CBS, it is critical for the malignant tumor to be completely removed with negative margins on pathologic assessment, and these patients should always receive whole breast radiation. Patients who undergo mastectomy will benefit from post-mastectomy radiation if they have extensive breast tumors or involved axillary lymph nodes ***(Early Breast Cancer Trialists' Collaborative Group, The Lancet, 2011)***.

Breast cancer is no longer known as a single disease, but it's a series of diseases defined by biologic characteristics based on hormone receptor status

and HER2 status. Tumors positivity for either Estrogen or Progesterone receptor can be considered hormone receptor (HR) positive. Hormone therapy has benefits only for patients with HR positive tumors, and trastuzumab and similar HER2 targeted therapies are only helpful in women with HER2 positive cancers. For many patients, surgical removal of the primary breast tumor and axillary node biopsy is the first procedure, followed by systemic therapy and radiation if indicated ***(Giordano et al., 2014; Davies et al., 2013)***.

Aim of the work

We are going to assess the role of sentinel lymph node detection in early breast carcinoma management. To assess methylene blue dye in sentinel lymph node biopsy and its complications. To detect axillary level of SLN.

Review of literature

Chapter 1: Embryology of breast.

The skin consists of two main layers, the dermis and epidermis. The epidermis is derived from ectoderm and consists of epidermal cells, melanocytes, Merkel cells derived from neuroendocrine cells and Langerhans cells from the bone marrow. Melanocytes produce melanin to protect the skin from sun damage. The Merkel cell is a nerve ending for pressure-sensitive end organs and Langerhans cells are responsible for antigen presentation. The dermis is derived from mesoderm that contains supporting structures like blood vessels, nerve endings, and a collagen layer. The single layer of ectoderm with its underlying mesoderm proliferates to form multilayer and specialized epidermal structures like hair and hair follicles, nails, and teeth and gives rise to sebaceous, eccrine, apocrine, and mammary glands during the fourth week of intrauterine life ***(Adone et al., 2012)***.

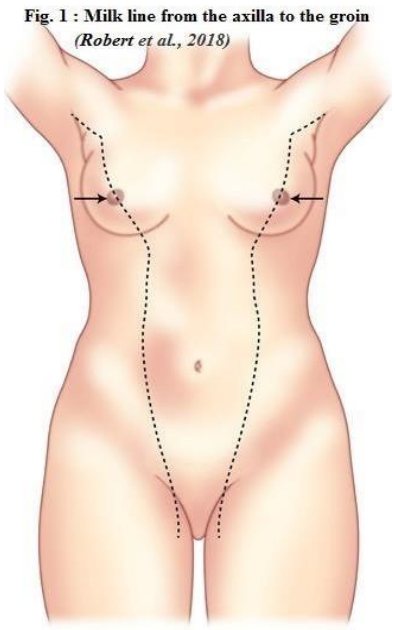

Fig. 1 : Milk line from the axilla to the groin *(Robert et al., 2018)*

The sebaceous, eccrine, and mammary glands are epidermal glands that develop as downgrowths or diverticula of the epidermis to the dermis. The mammary gland is a modified apocrine gland. During the 4th week of gestation, a paired epidermal thickening develops mammary ridges that are a part of the milk duct line that extends from the axilla to the medial thigh (Fig. 1). This mammary ridge or milk line becomes curvilinear due to the differential epidermal growth around the umbilical cord and lateral folding during development. In humans, the mammary ridges disappear, except at the 4th intercostal space on the mid-axillary thorax. There are 2 pairs of mammary glands that develop in human beings. These numbers and locations vary between different species corresponding to the number of offspring ***(Robert et al., 2018)***.

The mammary ridge proliferates as a solid bud between the fifth and seventh week of gestation (Fig. 2). The mammary bud grows downward into

the dermis and starts branching to the secondary bud around the twelfth week. This downward growth and branching is due to inductive influence of the extracellular matrix of the primary mesoderm on the mammary bud. This epithelial and mesenchymal signaling is through paracrine and juxtacrine mechanisms. The mesoderm and underlying adipose tissue produce growth factors and hormones, around the bud, which interact with receptors on the mammary bud ectodermal cells to proliferate and grow downward. These hormones and growth factors derive from lipids from adipose tissue. These buds elongate to form lactiferous ducts at about the twentieth week ***(Kalimuthu et al., 2015)***.

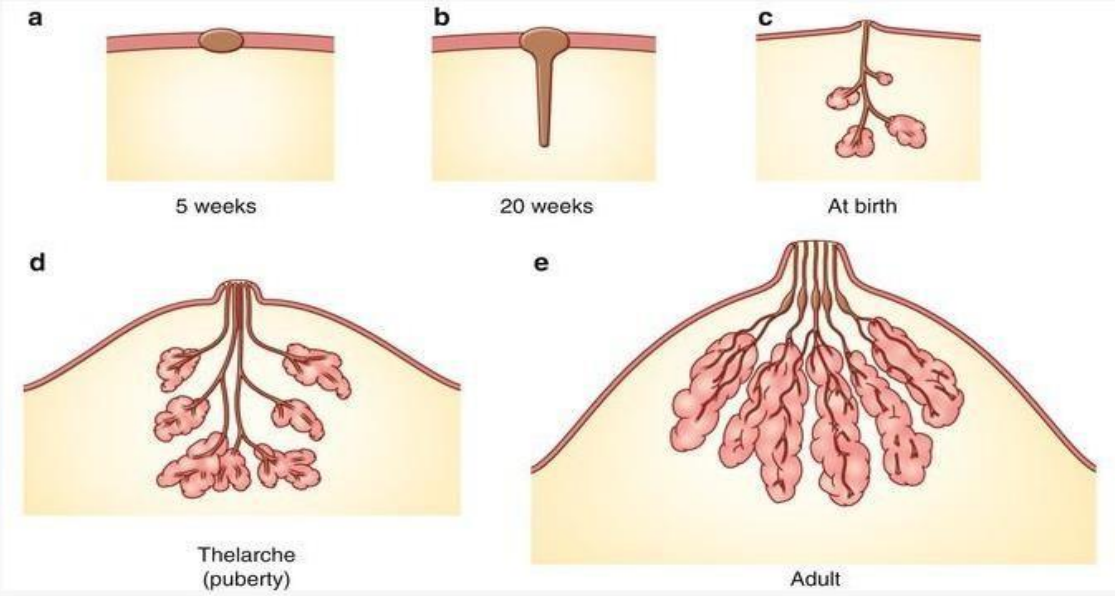

Fig. 2
Development of breast. (**a**) Mammary ridge. (**b**) Elongation of the mammary bud and canalization of the lactiferous duct in 20 weeks. (**c**) Rudimentary mammary glands. (**d**) Further development to form the adult ductal system in the mammary gland during puberty. Connective tissue and deposition of fat. (**e**) Functional gland with secretary alveoli ***(Robert et al., 2018)***

The canalization of the mammary bud which is transformed into lactiferous ducts is influenced by placental hormones circulating through the fetal circulation. The placental hormones consist of progesterone, growth hormone, insulin-like growth hormone, estrogen, prolactin, adrenoglucocorticoid, and triiodothyronine. There are about 15 to 20 lobes of glandular tissue formed with lactiferous ducts. The mammary gland is surrounded by mesenchyme that forms connective tissue, fat, and vasculature and intersects mammary nerves.