ANATOMICAL ASPECTS OF SENTINEL NODE BIOPSY IN BREAST CANCER

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ABSTRACT

Emergence of lymphatic mapping sentinel lyrnph node biopsy in early stage breast cancer patients has ensured a proper patient selection for elective axillary dissection. This protects histopathologically node negative patients from over treatment and unnecessary complications of axillary dissection. In increasing number of breast management protocols, it has become a standard procedure for detection of occult metastases in clinically node negative patients. Sentinel node biopsy concept has evoked a necessity to understand anatomical principles of lymphatic system as well as lyrnphatic drainage of breast. Although various aspects of lymphatic drainage and their impact on contrast and dye drainage to lymph nodes are still not well defined, this article has reviewed current literature regarding anatomy of breast as well as its clinical application in sentinel lymph node biopsy in breast cancer.

Keywords

Lymphatic Drainage, Sentinel Lymph node Biopsy, Breast cancer

1. INTRODUCTION

Breast cancer is the most common cancer in women world wide with more than one million new cases being detected annually [1]. Axillary lymph node involvement is the main prognostic factor in early breast cancer and histopathological examination of nodes is still the most accurate method to assess for metastases [2].

Till the introduction of sentinel node concept elective axillary node dissection was a necessary routine in breast cancer management protocols [3]. With introduction and application of this concept in breast cancer treatment, a minimally invasive procedure became available for clinically occult lymph node metastases. This procedure brought a significant reduction in the number of comprehensive axillary dissections thereby resulting in reduced post operative morbidity and better quality of life for large numbers of early stage breast cancer patient [4].

The present study has the objective to review the anatomical knowledge of lymphatic drainage of the breast and its clinical application in sentinel node biopsy for breast cancer management. At the same time it also aims to evaluate anatomical factors which may affect lymphatic drainage and its implications on radiotracer or contrast uptake during this procedure.

2. History

Lymphatic route of cancer spread and its implications for treatment and survival has been studied for centuries. Bertholin was the first to notice the existence of a lymphatic in 1653. In l9th cenfury Virchow observed that lymph nodes filter particulate matter from lymph. Several investigators introduced inanimate particles or tumour cells in afferent lymphatics of animal models to complement the Virchow's Hypothesis [5], [6]. In l908 Lord Moynihan stated "The surgery of malignant diseases is not the surgery of the organ; it is anatomy of the lymphatic system" [7].

Next logical step in evolution of breast cancer treatment was the introduction of Radical Mastectomy by William Halsted towards the end of l9th century based on principle of 'step by step' anatomical progression of breast cancer along lymphatic channels to axillary lymph nodes and only then haematogenous spread to distant organs. Later on Patey & Dyson (1948) and Ackerman (1952) ratified Halstedian model of en-block resection to more conservative approach of Modified Radical Mastectomy with equally good results [8], [9], [10].

In 1960s spectrum and systemic hypothesis of breast cancer was reintroduced which along with advancement in Radiotherapy and Systemic therapy brought significant changes in guiding principles of breast surgery. This was followed by introduction of Breast Conservation Surgery and later on Sentinel Node Biopsy concept [11-17].

3 General Anatomy and physiology of Lymphatic System

Lymphatic capillaries consist of single layer of endothelial cells with discontinuous basement membrane and are 10-50pm in diameter. Collagen filarnents anchored to the surrounding connective tissue prevent collapse of these capillaries18. Filling of lymphatic capillaries depend on the osmotic pressure gradient and fluctuation in intraluminal pressure created by contractions associated with forward flow of lymph [19]. Peristalsis in lymph vessels is regulated by filling pressure, humoral mediators (Serotonin, prostaglandins) and neural mechanisms [20]. Lymph flow is unidirectional and controlled by valves. Sustained external pressure reduces the flow speed while intermittent external pressure enhances it. Lymphatic capillaries drain into larger afferent collecting vessels which finally drain into marginal and medullary sinuses of a lymph node. The efferent lymphatics from lymph nodes join to form larger lymphatic trunks which finally drain into venous system.

According to Ludwig, although most of the lymph passes through sinuses of a lymph node but certain afferent lymphatics run through the lymph node or over its surface without discharging its contents into that node. This has clinical significance, as it implies that tumour cells may bypass the first draining lymph node and it may explain the finding of false negative sentinel node [21].

4. Lymphatic Drainage of the Breast

Anatomy of lymphatic system of the breast has been studied for many centuries. Its detailed history and description was presented by Haagensen [22], Cruikshank and Mascagni in l8th century described two main lymphatic drainage routes in the

breast as external system and internal system [23], [24]. Sappey in 1830 used mercury injection into lymphatic of the breast and concluded that most of the lymph from breast tissue drain centripetally into the subareolar plexus and then into the axillary lymph nodes [25]. This was supported by studies of Rouviere, Grant and Borgestein [26- 28]. Although Sappy and Rouviere emphasized on the importance of the subareolar plexus in lymphatic drainage of resting breast, it was disputed by Turner-Warwick, who suggested that breast lymphatic run in parenchyma and drain directly to axilla [29]. This view was supported by later studies of mastectomy specimens and lymphoscintigraphy [21], [30]. Lymphatic drainage to internal mammary lymph nodes was first identified by Camper in 1770. This was confirmed by studies using vital dyes and it was found that deep lymphatic pierce through pectoral and the intercostal muscles to directly drain into internal mammary lymph nodes [22], [29].

Macea and Fregnani (2006) [31] described four intercommunicating lymphatic channels in the breast: two superficial and two deep ones. Superficial plexi are located in the dermis and superficial subcutaneous planes. One of the deep plexi is located in Pectoralis major muscle fascia (Fascial Plexus) and other in the parenchyma of breast including lobes and ducts (Glandular Plexus). Glandular plexus drain through lymphatics along lactiferous ducts into subcutaneous plexus beneath areola (Sappey's Plexus) and then into axillary lymph nodes. Fascial Plexus communicates with subcutaneous plexus by lymphatics running along fibrous fasciculi of stroma. The deep fascial plexus may also directly drain to internal mammary interpectoral lymph nodes, lymphatic plexus of liver and diaphragm. Some lymphatics from superficial plexus may drain into posterior intercostal nodes and directly to supraclavicular lymph nodes [29], [32].

In 1950s Turner Warwick concluded, that while more than 75o% of lymph from breast drains into ipsilateral axillary lymph nodes, the internal mammary chain also receives significant drainage from both lateral and medial halves of the breast [29]. Other uncommon routes of drainage have also been described like Interpectoral (Rotter's Nodes) and Intra-mammerian nodes present in the route from breast to axi11a [33- 35]. In rare instances, lymphatic obstruction by tumour or ablation by irradiation and surgery may lead to subcutaneous drainage to contralateral axilla or retrograde flow to liver from internal mammary chain [36].

5. Evolution of Sentinel Node Concept

Jamison & Dobson in 1907 described the significance of neoplastic cells spreading initially to lymph nodes37. Gould et al in 1960, reported the 'Sentinel Node, which is the first node encountered by lymphatic vessels draining a parotid gland cancer. During parotidectomies, intraoperative assessment of this lymph node present in its typical anatomical location, guided decision for radical neck dissection [38]. Later on Cabanas in his studies on penile cancer observed the existence of sentinel node in the lymphatic drainage of penis and emphasized on the value of lymphatic mapping. He reported 5 year survival of 90% in node negative patients which fell down to 70% when sentinel node was metastatic. He concluded that if sentinel node is not involved on histopathological examination, further lymph node dissection is immediately not needed. This concept of sentinel node was further supported by lymphoscintigraphy studies of testicular cancers by Chiappa et al [40], Weissbach & Boedefeld [41], of melanoma by Morten et al [42] and other investigators working on other cancers [13], [28], [43].

Kett et al [44] using a blue dye in study of breast lymphatics reported ‘Sorgius node’ while Christensen et al [45] used breast scintigraphy and observed ‘Primary draining lymph node’. Haagensen [22] in a study of routes of breast cancer metastases reported that nodes of central group are most often and most exclusively involved. Apptication of this technique of using Blue dye in study of sentinel nodes for breast cancer was initially introduced by Giuliano et al [13].

The concept of sentinel node is based on principles of existence of an orderly and predictable pattern of lymphatic spread of solid cancers to regional lymph node basins and functioning of first lymph node, as an effective barrier for cancer cells [30], [46]. Histopathological evaluation of sentinel lymph node will accurately predict the status of metastases in regional nodes, as metastatic involvement of secondary nodes is rare with early breast cancer. Turner et al [47] reported that if the sentinel node is not involved by tumour cell, probability of involvement of non sentinel node is <0.1%.

Clinical application of this concept in breast cancer involves, use of Vital Dyes like patent blue or iso-sulphan blue and direct visualization at surgery or Radiopharmaceutical for scintigraphic mapping to guide, intraoperative localization of sentinel node. This has been validated by numerous studies [13], [48]. Recently mammography screening protocols, have resulted in detection of early stage as well as non palpable tumors which have low probability (20-30%) of axillary metastases. Combined with clinically negative axilla, these tumors present a legitimate concern regarding histopathological status of axillary nodes. This issue is further compounded by low negative predictive value of various non invasive tests like MRI, ɣ-scintigraphy and PET. In such clinical conditions sentinel node biopsy, which avoids complications of routine axillary dissection offers a new acknowledged standard of care for patients with early breast cancer. More over focusing on sentinel lymph node for extensive histopathological evaluation increases the accuracy of staging of axilla [49].

According to NCCN guidelines 2007, in women with breast cancer and clinically undetectable axillary lymph nodes, it is crucial to find sentinel lymph node in order to define whether there is a need for lymphadenectomy, while CCN guidelines 2012 recommend sentinel lymph node biopsy as preferred method of axillary lymph node staging [50],[51]. When axillary lymph nodes are involved, other lymph nodes are involved in 50% of patients, thus involvement of sentinel node is an indication for lymphadenectomy. It has been reported, that sentinel node biopsy method has 96% accuracy, false negative rate of < 5-l0% and negative predictive value of> 95% [52], [53].

6. Clinical Implications of Anatomy of Lymphatics

Structure of lymphatic vessels, their drainage pattern and factors affecting lymph flow have significant implications, on technique as well on interpretation of results of sentinel node biopsy procedure in breast.

7. Radio-tracer and Dye uptake

Radiotracer uptake is attached to particles of organic and inorganic nature. The size of particle is an important determinant for migration along lymphatics and its concentration in the lymph node. Smaller particles (3-12nm) like antimony trisulfide rapidly enter the lymphatics through opening in inter-endothelial junction (10-25nm) and are quickly transported to sentinel node. But disadvantage with these particles is that they pass rapidly through sinuses without being phagocytozed and tracer moves to next lymph node, which is not a sentinel node. At the same time, concentration in sentinel-node is poor. Large particles (50-l000nm) enter the lymphatics slowly by pinocytosis and move slowly but achieve higher concentration in sentinel node without passing to a secondary node [21], [32]. Optimum particle diameter suggested for sentinel node biopsy is between l0-100 mm [13], [21], [54].

(i) Amount of dye and radiotracer injected

There is no consensus on amount of tracer or dye injected. The volume of radiotracer used is as low as 2ml to as high as l6ml, while the range reported for blue-dye is 5.0-7.5ml. As we know that lymph now is dependent on delicate balance between pressure inside and outside the lymphatic vessels, reports favoring low volume tracer are based on non interference with lymph flow physiology. This avoids risk of visualization of non-sentinel secondary node and 88-99% visualization rates for sentinel node [21], [28], [55- 57]. Contrary to these reports favoring large volume of tracer, intend to increase the chances of visualization of lymph node but have disadvantage of interference with sentinel node visualization, due to increased diffusion zone of tracer at injection site [15], [48], [58].

It is now recommended that a radiotracer injection between 4-8 ml should be used for preoperative lymphoscintigraphy, with small additional volume of dye injection immediately prior to surgery [21].

(ii) Site of injection

Breast and overlying skin share the same lymphatic drainage, as both are embryologically derived from ectoderm. Combined with the anatomical fact that density of lymphatics is greater in the skin in comparison to parenchyma, intra-dermal injection has higher visualization rates for lymphatics with better ability to distinguish sentinel node from secondary nodes32. It has an added advantage, that it can be injected anywhere over breast with minimum interference by scattered radiation. Injection of contrast at other sites like sub dermal,

subareolar peri-tumoral and intra-tumoral locations have also provided good results. In general, epithelial cancers have dysplastic lymphatics so intra-tumoral injection of radiotracer or dye appears less logical. Moreover intra-tumoral or peri-tumoral injection, may lead to passage of contrast to nodes outside axilla e.g. internal mammary lymph node in up to35% of cases, which may be due to contrast entering into deep plexus. Dissection of these lymph nodes is not recommended as determination of their histopathological status does not give any additional benefit to survival.

(iii) Timing of Radiotracer and Dye Injection

For performing sentinel lymph node biopsy the radiotracer is injected up to 24 hours before operation so that it gets concentrated in sentinel node. The method is more accurate if additional dye is injected 5-10 minutes before the procedure and breast is gently massaged to facilitate lymph flow. Dye helps in coloring of lymphatics and its temporary accumulation helps in identification of sentinel node. Other factors, which can influence the pattern and speed of flow of lymph drainage thereby affecting radiotracer and dye flow and accumulation, are age, hydration, humoral mediators and neural mechanisms [21],[59] .Anesthetic drug Halothane has been reported to decrease lymph flow rates by 25 - 5 9% [18].

8. Summary and Conclusions

Identification of sentinel lymph node has become a standard practice in management of early stage breast cancer patients with achieved success rates>95%. Anatomical and clinical investigations have strongly validated the concept as well as results achieved by this technique. This technique has benefited early stage breast cancer patients by avoiding unnecessary axillary dissection and associated complications. Insight into anatomy of lymphatic drainage of breast is essential for accurate and safe practice of this technique as well as to achieve best possible results. Intra-dermal injection of radiotracer and dye seem to be reasonably adequate and accurate for this procedure. Combined use of Radiotracer and dye is the preferred method; still blue dye alone can give satisfactory results if radio-nuclear facilities are not available. Further studies, are required for refinement of this technique, to make it universally applicable as well as to study impact of identification of non-axillary sentinel lymph nodes for management of breast cancer.

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