VALUE OF NODAL DRAINAGE PATTERNS AND TUMOR LOCATION FROM LYMPHOSCINTIGRAPHIC MAPPING IN DETECTING AXILLARY SENTINEL LYMPH NODE STATUS IN BREAST CANCER: EXPERIENCE AT KAOSHIUNG MEDICAL UNIVERSITY HOSPITAL

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Sentinel lymph node (SLN) biopsy is an alternative to axillary node dissection for staging breast cancer treatment. In this article, we investigated nodal drainage patterns and tumor location using lymphoscintigraphy to predict the axillary sentinel lymph node status. We enrolled 88 patients with clinically suspicious or biopsy-proven breast cancer from March 2001 to October 2002. The average age of subjects was 48 ± 4 years and the clinical stage was T1-2N0Mx. Tc-99m sulfur colloid was used in a hybrid combination of subdermal and perilesional injections around the selected corners of the tumor or biopsy site. Sentinel lymphoscintigraphy was performed 16–20 hours before surgery. Sentinel nodes were marked on the skin. An intraoperative gamma probe was used to confirm the sentinel lymph node location before biopsy. Most primary tumors were in the outer upper quadrant (52.3%), followed by the inner upper quadrant (17.0%), outer inferior quadrant (12.5%), central areolar area (11.4%), and inner inferior quadrant (6.8%). The nodal drainage patterns on 2-hour lymphoscintigraphy were as follows: axillary alone (76.1%), internal mammary nodes alone (1.1%), both axillary and internal mammary nodes (11.4%), and no drainage (11.4%). Internal mammary lymphatic drainage is related to tumor location in the inner quadrants of the breast. About 11.4% of all patients had poorly identified SLNs on lymphoscintigraphy within a 2-hour period, but there was improvement in the overall detection rate up to 95% by intraoperative gamma probe the next day. Preoperative lymphoscintigraphic mapping has value in providing individual lymphatic drainage patterns and tumor location that are important in the interpretation of the results of SLN biopsy during surgery.

Key Words: sentinel lymph node, lymphoscintigraphy, breast cancer

a tailored incision plan before intraoperative detection with the gamma probe.

Taiwan has experienced rapid growth in the incidence of breast cancer: fivefold over the last two decades with a concomitant threefold increase in mortality. The diagnosis of early breast cancer had risen from 40% in 1980 to 60% in the late 1990s. The age at breast cancer diagnosis in Taiwan is lower than in Western populations [5].

In this study, we focused on Taiwanese patients with breast cancer to assess the value of axillary sentinel node prediction using lymphoscintigraphy.

**Patients and Methods**

**Patient selection**

During a 21-month period, from March 2001 to October 2002, 87 females and one male, aged 31 to 76 years (mean, 48 years), scheduled to undergo curative surgery in our hospital were enrolled in the study. The clinical stage of patients was T1–2N0Mx. The average primary tumor size, measured by ultrasonography, was 2.7 ± 1.2 cm (range, 1.5–5.0 cm). The tumor was located in one of five sections of the breast (four quadrants and the areola). An areolar location refers to the areola and its border. Twenty-three cases, 26.1% of enrolled patients, had undergone excision biopsy 1–2 weeks previously in other hospitals and were diagnosed with malignant tumors. The remaining patients were diagnosed as having malignant tumors from cytology or a strong clinical suspicion.

**Lymphoscintigraphy**

All patients underwent preoperative sentinel lymphoscintigraphy 16 or 20 hours before surgery. A standard dose of 0.4–0.6 mCi 99mTc-labeled sulfur colloid without filtration (Syncor, Taiwan) in 1.0–2.0 mL of saline was injected in two to four selected corners of the tumor or in the area adjacent to the biopsy site in a hybrid combination of subdermal and perilesional injections. The corners were selected from palpation and previous ultrasonography. Immediate dynamic images (E.CAM, LEHR collimator, Siemens, IL, USA) were acquired using established techniques of grade shield enhancement and simultaneous vertical angle dual-head images. Dual-head images were obtained 30 minutes to 1 hour later for image protocol. A 2-hour delayed image was needed in some cases, where nodal uptake was poorly identified. Certain imaging process techniques, such as summation of dynamic images, were helpful in identifying tiny and hypofunctional sentinel nodes. Finally, we marked the location of sentinel nodes on the skin of the breast using a point source matched technique and provided the surgeon with a map of the lymphatic drainage basin for intraoperative gamma probe guidance the next day.

**Intraoperative gamma probe detection**

Surgeons detected the sentinel nodes based on the previous skin marker indication using a sterile-packed gamma probe (neo2000™, Neoprobe Corp, Dublin, OH, USA). Radioactive or hot nodes were removed first in patients who had already undergone tumor biopsy. In patients with a cytologic diagnosis or clinical suspicion of malignancy, both primary tumor excision and sentinel node biopsy were performed at the same time. A count below 10% of the most radioactive lymph nodes was regarded as background radiation. Routine ALND including levels I–II was performed to avoid missing “skip” metastases after definite results of intraoperative frozen section histopathology in all patients.

Biopsy specimens from sentinel and axillary lymph nodes, half sectioned and stained with hematoxylin and eosin, were assessed by pathologists.

**Results**

**Tumor location**

The most common tumor location was the outer upper quadrant (OUQ; Figure 1), as in previous studies. The least common location was the inner inferior quadrant (IIQ; 6.8%). Breast malignancies occurred about twice as often in the right breast as in the left in this study.

**Lymphoscintigraphy**

After the subdermal injection of the tracer at selected corners of the tumor, the pattern of lymphatic drainage and sentinel node uptake depends on tumor location. Most sentinel nodes drained into the axillary basin alone (76.1%), while only one drained into the internal mammary basin alone (Figure 2). The most common sentinel node distribution was in the low axilla of the axillary lymphatic basin, especially in patients with OUQ tumors. Of all tumors, 87.5% had SLNs in the axilla. Both axillary and internal mammary node activity was seen in 11.4% of tumors. However, sentinel node activity was poorly identified on 2-hour lymphoscintigraphy in 11.4% of patients, probably because of the short imaging time.

Figure 3 summarizes the relationship between tumor location and the direction of lymphatic drainage on lymphoscintigraphy. Tumors in the outer parts of the breast...
mainly had axillary sentinel node distribution (82.4% in the OUQ and 87.5% in the outer inferior quadrant [OIQ] in the right breast; 66.9% in the OUQ and 100% in the OIQ in the left breast). There was also a high percentage of axillary sentinel node distribution in areolar tumors. Tumors in the inner part of the breast were more likely to have both axillary and internal mammary drainage. Figure 4 shows an example of axillary and internal mammary lymphatic drainage. Axillary SLN detection improved up to 95.5% using the intraoperative gamma probe 16–18 hours after 2-hour lymphoscintigraphy.

Pathology

From histology, the most common breast tumors in our patients were infiltrating ductal carcinomas, accounting for about 65% in the final diagnosis; intraductal carcinoma and medullar carcinoma were also found. The negative predictive rate of SLN biopsy in our cases was about 10%.
DISCUSSION

Cabanas first described the value of SLNs in his studies of patients with penile cancer in 1977 [6]. SLNs are considered the first afferent nodes for lymphatic drainage from the tumor site to the adjacent lymphatic basin. Accurate location and biopsy of sentinel nodes will predict regional nodal status. Krag et al originally reported location of the sentinel node in 82% of 22 patients, with 100% accuracy in predicting axillary node status using intraoperative gamma probe detection of previously injected $^{99m}$Tc sulfur colloid in breast cancer [7]. In this study, we used radiotracer tagging sulfur colloid to identify the sentinel nodes and determine the relationship between tumor location and regional sentinel node drainage by lymphoscintigraphy. After accurate location and biopsy of sentinel nodes, regional axillary node status can be predicted and compared with the result of traditional ALND.

Many factors, including technical issues of lymphoscintigraphic mapping and probe detection, will result in variations in the accuracy of SLN detection. Alazraki et al concluded that the major technical variables are the radiopharmaceutical used, the injection site, volume, activity, and the use of the imaging result [4,8]. From our experience, we agree that small-particle radiopharmaceuticals, such as phytate, allows easy detection of SLNs in breast cancer [9]. We had a similar result using phytate and sulfur colloid for sentinel node detection in the same patient (Figure 4). Smaller particles facilitate rapid transfer into the lymphatic system, yet are only retained in SLNs for several hours. Larger colloid particles show a much slower rate of clearance from the interstitial space and are likely to show a slower accumulation in SLNs [2,4,8]. Sufficiently large particles do not seem to leak from SLNs. Therefore, we used variable-sized unfiltered large sulfur colloid particles with similar representation of tumor spread within the local lymphatic drainage around the breast tumor, especially in our 2-day protocol. With unfiltered sulfur colloid, adequate radiotracer volume and activity are necessary to reveal the true distribution of regional lymphatic drainage and enhance detection of SLNs on lymphoscintigraphy [4]. Although the intraoperative gamma probe has high sensitivity in detecting SLNs, preoperative lymphoscintigraphy still has a role to play in identifying regionally functional lymphatic anatomy in breast cancer. It not only provides the planning map for the surgeon, but also serves as an imaging record. In this study, we used a grade-shield and simultaneous vertical angle imaging technique to enhance sentinel node detection [10]. Using unfiltered sulfur colloid and established imaging techniques, SLN detection reached 87% on lymphoscintigraphy within a 2-hour period and improved up to 95% with intraoperative gamma probe after a 16- to 18-hour period.

The status of lymph vessels around the breast lump and individual variations are also major factors resulting in variable regional lymphodynamic patterns and the final detection of SLNs on lymphoscintigraphy. The rates of lymph flow within lymphatic collecting vessels vary in different cutaneous parts of the body, the most rapid flow occurring in the leg and foot (10.2 cm/min) and slower flow in the head and neck (1.5 cm/min) [11]. The lymphatic flow rate in the cutaneous part of the anterior trunk is about 2.8 cm/min. The lymphatic vessels have an intrinsic pump mechanism maintaining steady lymph flow [12], but this mechanism responds to an increase in hydrostatic pressure by significantly increasing lymph flow. Local heat, inflammation, and external massage will increase lymph flow [13]. Because of its embryologic origin in the ectoderm, the mammary gland is, in a sense, an organ of the skin [2,14]. Therefore, lymphatic drainage in the breast closely parallels lymph flow in the overlying skin [2,14]. After subdermal injection at the corners of the lump, sentinel nodes could not be identified in 11.4% of our cases on 2-hour lymphoscintigraphy. Of patients with poorly identified sentinel nodes, two had undergone recent biopsy, the average tumor size was 2 cm, and the ratio of inner to outer tumor location was 4:5. Only two patients were older than 65 years and the other patients were younger than the overall average (48
years). This suggests that tumor location in the inner part of the breast is a factor causing delayed lymphatic drainage into axillary SLNs. Age and tumor size were not significantly related to poor identification of sentinel nodes in this study. However, we believe that lymphatic flow is relatively delayed in older patients and probably in those with larger tumors. Borgstein et al reported significant correlation between mapping success and invasive tumor size of less than 5 cm [1]. However, other investigators found no correlation [15,16]. Prior breast surgery with scar formation may alter the original lymph drainage and lead to detection failure or even false-negative sentinel nodes [14]. We agree that scarring will disturb the lymphatic drainage, but this does not include recent biopsy.

In this study, the most common location of breast tumors was the OUQ (52.3%); tumors around the areola constituted about 11% of cases, while those in the IIQ constituted only 6.8%. This was very similar to previously reported distributions: 52% in the OUQ, 14% in the inner upper quadrant, 6% in the IIQ, 16% in the OIQ, and 12% in the central areola area [14]. The distribution of lymphatic drainage from the breast was approximately proportional to the three routes of blood supply: most of the lymph drains to the axillary lymph nodes, about 3% drains to the parasternal internal mammary chain nodes while, under normal circumstances, the posterior intercostal lymph nodes receive small proportions of lymph flow from the breast [2]. Overall, 87.5% of patients in this study had axillary lymphatic drainage, but internal lymphatic drainage alone was rare (Figure 2). Tumors in the outer quadrant of the breast, including those in the areolar area, always drained into the axillary lymphatic system, while those in the inner quadrant had a higher ratio of internal mammary drainage (Figure 3). Dupont et al found 2.4% of cases with internal mammary nodes using the gamma probe, and 73% of these were associated with inner quadrant lesions [16].

Some authors suggest that subareolar injection is an extremely accurate and cost-effective method of sentinel node identification in breast cancer [17]. We prefer a hybrid combination of subdermal and peritumoral injections around the corners of the tumor, especially in the inner part of the breast, because the chance of internal mammary node visualization is increased when the primary tumor is located medially [18].

Generally speaking, there is a concordant result of pathology between SLNs and axillary lymph nodes. However, the approximately 10% false negative rate with sentinel nodes in this study was similar to those from previous reports [19–21]. The fact that one-third of patients with positive SLN metastasis had a negative result on traditional axillary node biopsy demonstrates the great value of sentinel nodal biopsy for nodal staging of tumors.

In conclusion, SLNs in the low axilla are identified in most breast cancer patients in Taiwan. Several factors, such as age, scarring and tumor status, will interfere with the dynamic pattern of local lymphatic flow in the breast. Lymphoscintigraphic mapping provides individual lymphatic drainage patterns in addition to tumor location, which is important in the interpretation of the results of SLN biopsy.

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REFERENCES


乳癌淋巴顯譜定位造影中淋巴引流與腫瘤分佈
對腋下前哨淋巴狀態之偵測價值 — 高醫經驗

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對乳癌病患的診斷分級與治療而言，前哨淋巴切片是傳統腋下淋巴隨機取樣清除術的替代性方法，本研究中，我們以臺灣癌病患為根據，討論在淋巴顯譜造影中，腫瘤分佈與淋巴引流型態，對腋下前哨結狀態之預測。從 2001 三月至 2002 十月期間，我們收集 88 名臨床懷疑或切片診斷乳癌病患，其平均年齡為 48 ± 4 歲，乳癌臨床分級為 T1-N0-M0。病患接受 0.4 to 0.6 毫居里鉬 99m 標誌硫化錠體，腫瘤周邊混合式皮下注射後，前哨淋巴造影 (西門子 E.CAM) 根據本院已建立步驟，於手術十六至十八小時前進行。根據造影結果，定位於病患皮膚上，並於隔日術中以伽瑪碼諜測筆諜測切片取樣，並送病理診斷。腫瘤分佈如下：外上象限 (52.3%)，外下象限 (12.5%)，內上象限 (17.0%)，內下象限 (6.8%) 及乳暈周圍 (11.4%)。在 2 小時內前哨淋巴造影中，淋巴引流方向為：單獨腋下方向 (76.1%)，單獨內乳方向 (11.4%)，同時腋下及內乳方向 (11.4%) 及不引流 (11.4%)。內乳淋巴引流出現與腫瘤位於乳房內側有一定之相關性。其中 11.4% 病患在 2 小時內前哨淋巴造影無法諜測者，於隔日術中藉伽瑪碼諜測筆諜測，可提升至 95% 前哨淋巴諜測率。術前前哨淋巴定位造影，如同地圖般，在不同腫瘤分佈方位下，提供淋巴引流方向，協助術中前哨淋巴切片取樣有其價值。

關鍵詞：前哨淋巴結，淋巴顯譜造影，乳癌
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