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LYMPHATIC MAPPING AND SENTINEL LYMPHADENECTOMY IN BREAST CANCER

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Lymphatic mapping and sentinel lymphadenectomy was utilized to detect axillary lymph node metastases in patients with breast cancer. Aim of the study was to evaluate lymphatic mapping in identification of sentinel axillary lymph node in patients with breast cancer to ensure accurate staging. The study was done on 84 patients with a mean age of 51 years (29-73 years) between July 1995 and October 1999 at departments of Surgery, Mansoura University and johann Wolfgang Goethe Frankfrut University hospitals. It was the M.D Thesis of the first author. After general anesthesia, (2-5 ml) of Isosulfan blue vital dye was injected into the breast mass and at the surrounding axillary side and submitted to both histological examination and immunohistochemical staining using cytokeratin. The sentinel lymph node(s) accurately identified axillary node status in 60 of 68 patients (88.2%). Two of eight sentinel lymph nodes stained positive for metastases by immunohistochemical staining (25%). The total number of patients with axillary metastases (sentinel and non sentinel)was 30 (35.7%). Succesful (SN) identification was done in 27 patients with a false negative rate 6/27 (22.2%). The sentinel / non-sentinel histology in agreement was 88.2%. On conclusion, intra-operative lymphatic mapping and sentinel lymph node biopsy is a highly accurate, minimally invasive, safe and cheap method for staging of patients with breast cancer favoring more conservative treatment.

Key words: Lymphatic mapping; sentinel lymphadenectomy-breast cancer.

Abbreviation:
ALND = Axillary lymph node dissection.
SLND = Sentinel lymph node dissection.
SN = Sentinel node.
FNAC = Fine needle Aspiration cytology.
H&A = Haematoxylin and Eosin.

INTRODUCTION

An accurate knowledge of axillary lymph node involvement is essential when planning treatment of apparently operable breast cancer irrespective of what primary surgical treatment is undertaken and it is the best available guide when attempting to evaluate prognosis. The overall incidence of metastatic disease in the axilla is about 46 percent.(1)

The only way for assessing axillary lymph node status accurately is by total axillary clearance which exposes a large number of node negative women to long term post operative morbidity for no benefit.(2)

Intra-operative mapping and selective sentinel lymphadenectomy was used to identify lymph node metastases in patients with primary cutaneous melanoma with a false negative rate of less than 1% (3)

The same technique was utilized to detect axillary lymph node metastases in patients with breast cancer to identify which and how many lymph nodes should be excised to ensure accurate staging ? and it is a minimally invasive alternative to total axillary lymphadenectomy .

Aim the work:

Was to evaluate lymphatic mapping in identifying the sentinel node (SN), i.e the axillary lymph node most likely to contain breast cancer metastases to achieve staging accuracy.

PATIENTS AND METHODS

Between July 1995 and October 1999, 84 female patients with a mean age of 53 years (29 – 73 years), presented to the breast outpatient clinic in El-Mansoura and Johann wolfgang Goethe Frankfurt University hospitals were studied.

All patients had a potentially curable breast carcinoma including medially located tumors and were planned to undergo ALND as apart of their standard treatment (modified radical mastectomy or a segmental mastectomy with enbloc lymph node dissection)

The clinical diagnosis of breast cancer was confirmed by mammography, breast sonography and biopsy including FNAC, core biopsy, frozen section and excision biopsy. All clinically, poorly localized tumors were pre-operatively marked by a needle under ultrasonographic or mammographic control (Fig. 1). All patients had no clinically suspicious nodal and / or distant metastases. Patients with prior axillary operation (dissection / excision biopsy) and pregnant patients were excluded. Informed consent was obtained from all patients.

Methods:

The technique of lymphatic mapping and sentinel lymphadenectomy for melanoma was modified for patients with breast cancer. After induction of general anaesthesia, Isosulfan blue vital dye (lymphazurin, Hirsch industries, inc., Richmond) (2 – 5ml) was injected with 25- gauge needle (yellow) into the breast mass and the axillary side of the surrounding breast parenchyma of the primary tumor has been excised previously, the dye was injected into the axillary side of the wall of the biopsy cavity through several points along the incision. (Figs 2&3).

A transverse incision was made just below the hair bearing region of the axilla. Blunt dissection was performed to identify a blue stained lymphatic tract which was followed proximally to the tail of the breast to reach the first blue stained lymph node (SN) (Fig.4). The node was carefully excised and submitted as a separate specimen (Fig.5) for histological examination using Haematoxylin and Eosin (H&E) staining.

For patients undergoing segmental mastectomy, ALND was completed (Fig 6) and the primary breast tumor was excised through a separate incision. The mastectomy with enbloc axillary dissection was completed. All lymph nodes in the ALND specimen were processed for histologic examination using (H&E). No internal mammary lymph node dissection was performed.

The time of dye injection and the time of axillary incision were recorded. All axillary specimens were examined by consultant pathologist with a special interest in breast cancer at El-Mansoura and Frankfurt University hospitals.

Sentinel lypmhadenectomy specimens (SLND)

After frozen section, the sentinel node tissue was processed routinely for permanent section each lymph node is blocked individually resulting in two permanent section levels for paraffin block.

A cytokeratine immunohistochemical stain is performed on all sentinel nodes staining negative with (H&E). Cytokeratin staining was done with an anti- body cocktail (MAK- 6, Ciba- corning, Alameda, (CA) to low and intermediate – molecular weight cytokeratin. Approximately 6-8 histologic levels for each SN were examined by immunohistochemical staining.

Sentinel node was considered true positive if it was negative for metastases while all other axillary lymph nodes in completion ALND specimen were also negative, positive for metastases while one or more of other axillary lymph nodes in completion ALND specimen were also positive, or positive for metastases while other axillary lymph nodes completion ALND specimen were negative. False negative if it was negative for metastases while one or more of other axillary lymph nodes in completion ALND specimen positive for metastases.

Sentinel node:

Completion axillary lymphadenectomry specimens (ALND) were dissected fresh by routine surgical pathology techniques for isolation of lymph nodes. Multiple lymph nodes were embedded per block, two or three levels / node were examined with (H&E) staining but not with immunohistochemical staining . Micrometastases were identified as lymph node metastases < 2 mm in greatest dimension.

Statistical analysis:

Data were analyzed by the members of the biostatistical unit at Frankfurt University hospitals. A likelihood ratio chi square test was used to compare the difference between two proportions. The statistical package of SAS procedures, FREQ, was used in the analyses.

RESULTS

There were 33 Primary tumor detection included physical examination in 55 cases (65.5%), mammography in 15 cases (17.8%) and breast ultrasonography in 14 cases (16.7%). Diagnosis was confirmed in all cases by pathological examination.

Surgical procedures for treatment of breast cancer included modified radical mastectomy in 25 cases (29.8%) and segmental mastectomy with ALND in 59 cases (70.2%) .Site of the primary tumor in the breast was variable : in the upper outer quadrant in 36 cases (42.9%), in the upper inner quadrant in 13 cases (15.5 %), in the lower outer quadrant in 9 cases (10.7%), in the lower inner quadrant in 9 cases (10.7%) and central in 17 cases (20.2%). Size of the primary tumor was also variable, 51 cases (60.7%) were T1, 26 cases (31%) were T2, and 7 cases (8.3%) were T3. Histologic examination of the axillary lymph nodes revealed 30 cases (35.7%) with evidence of metastases.

The blue stained sentinel node was identified in 68 of 84 (81%) procedures and its identification failed in 16 cases (19%). Of these 16 cases no metastases in the axillary lymphadenectomy specimen were found in 3 cases (18.75%). Thirteen cases (81.25 %) from those on whom no SN was identified had positive axillary lymphadenectomy specimens (Fig 7).

More than one lymph node was sometimes found of sentinel lymphadenectomy specimen. From a total of 68 cases of successful identification, 92 sentinel lymph node were examined, 52 cases had only one sentinel lymph node per case, 11 cases had 2 sentinel nodes per case, 2 cases had 4 sentinel nodes per case (Fig 8). The mean number was 1.35 node per case. The accuracy of lymphatic mapping was then examined by comparing the histopathology of sentinel node and non-sentinel nodes (ALND) specimens.The sentinel nodes accurately identified axillary nodes status in 60 of 68 cases (88.2 %). In 8 cases, the sentinel node was falsely negative using H&E staining i.e no tumor was identified in the sentinel node. The eight false negative sentinel nodes specimens were retrospectively reexamined and then studied with immunohistochemical technique using anti bodies to cytokeratin for metastatic breast cancer, that is to say that using the immunohistochemical study the conversion rate from sentinel node negative to positive was 25%.

The total number of cases with axillary metastases (sentinel and nonsentinel) was 30 (35.7%) from those successful sentinel node identification negative rate 22.2% (Fig.9). The overall sensitivity of the sentinel node was 91.2% with a specifity of 100%. The overall positive and negative predictive values were 100% and 87% respectively.

To determine whether the uptake of the dye by the lymph nodes containing metastases was random, we analyze 6 cases in which only one to two tumor positive node (s) and at least one sentinel nodes examined in these 6 cases, 6 were sentinel: tumors were found in all of them 100% and in only 1 of 90 (1.1%) non- sentinel nodes ($p < 0.0001$ likelihood ratio chi square analysis) Thus ,it was highly unlikely that the uptake of the dye by an involved nodes was as a result of a chance alone. We compared the sensitivity of lymphatic mapping and sentinel lymphadenectomy with that of random biopsy (blind biopsy) we calculated the probability of detecting nodal metasteses using each of these techniques in 30 clinically negative / histologically positive axillae in which a sentinel node could be identified. The 27 dissections yielded a total of 414 lymph nodes 96 were tumor positive in these axillae, there were 30 sentinel nodes , 19 were tumor positive. Therefore in patients with subclinical axillary metastases the probability of excising a positive node was 36/414 (23.2%) versus 19 / 30 (63.3 %) using lymphatic mapping ($p <0.0001$: likelihood ratio of chi square analysis).

Complications were observed in 5 patients (61%) in the form of blue staining of the wound that disappears completely in a week. Two cases (2.4%) had blue stained urine for 2 days post – operatively.

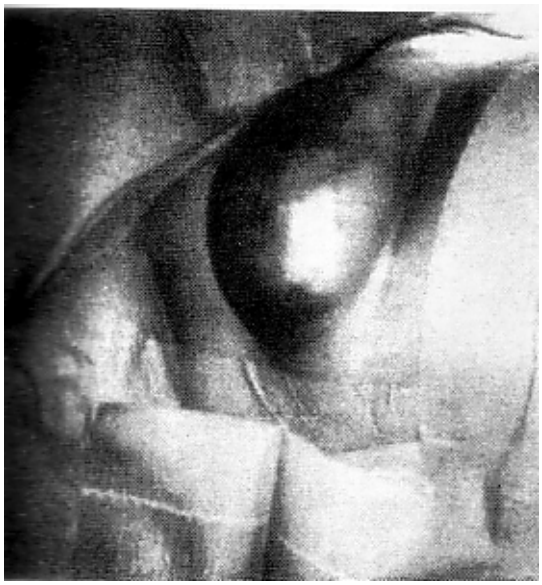


Fig.(1): A clinically poorly localized breast mass preoperatively marked by a needle under ultrasound control

Fig. (2): Isosulfan blue vital dye is injected in the breast tissue.

Fig. (3) : Isosulfan blue vital dye is injected in the axillary side of the wall of the breast biopsy cavity.

Fig. (4) : A blue stained lymphatic tract followed to a blue stained lymph node (SN).

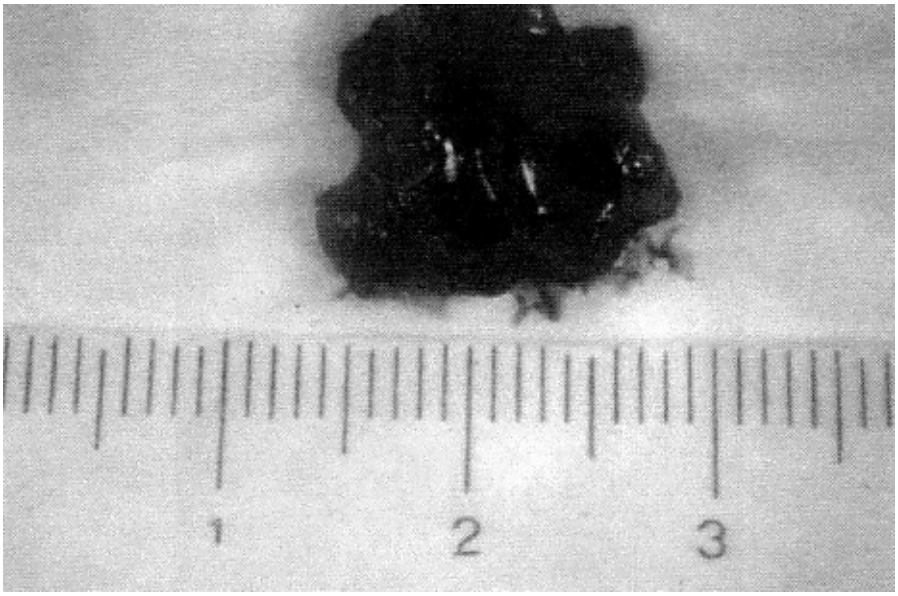


Fig. (5) : The sentinel node as a separate specimen .

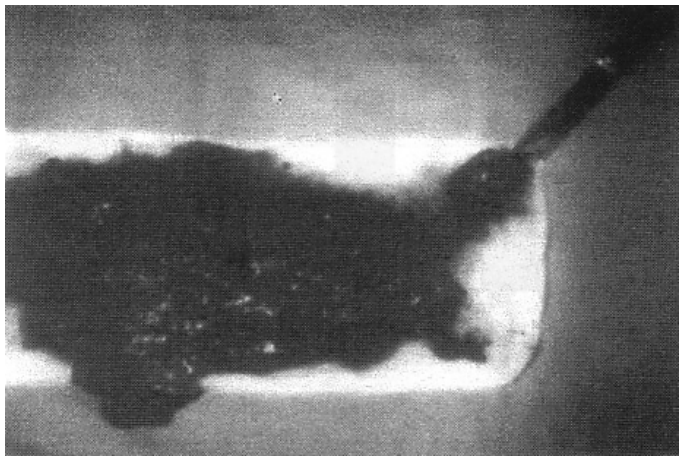


Fig. (6) : A completion ALND specimen .

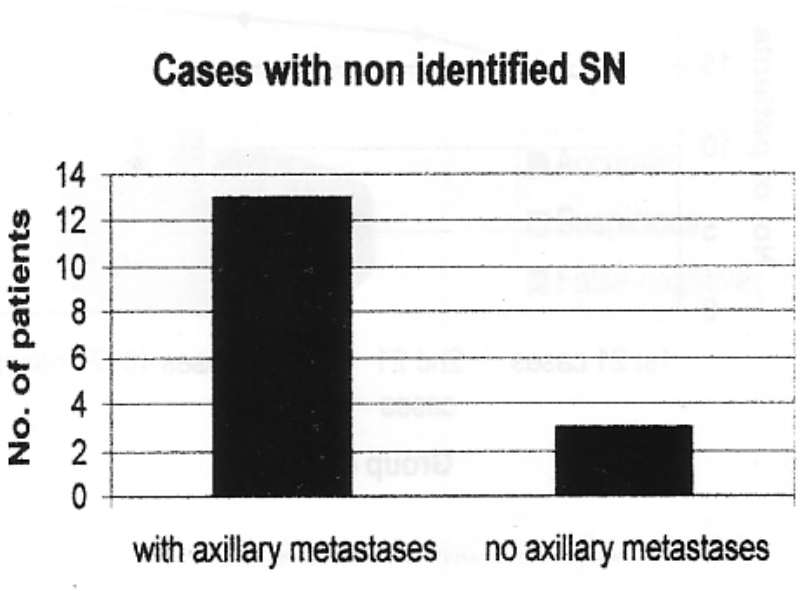
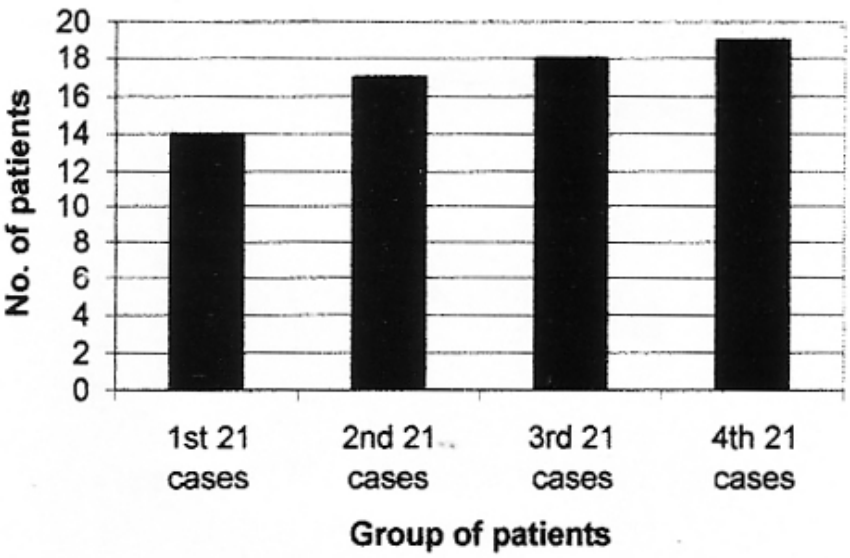


Fig. (7) : Distribution of pationts with non identified SN .



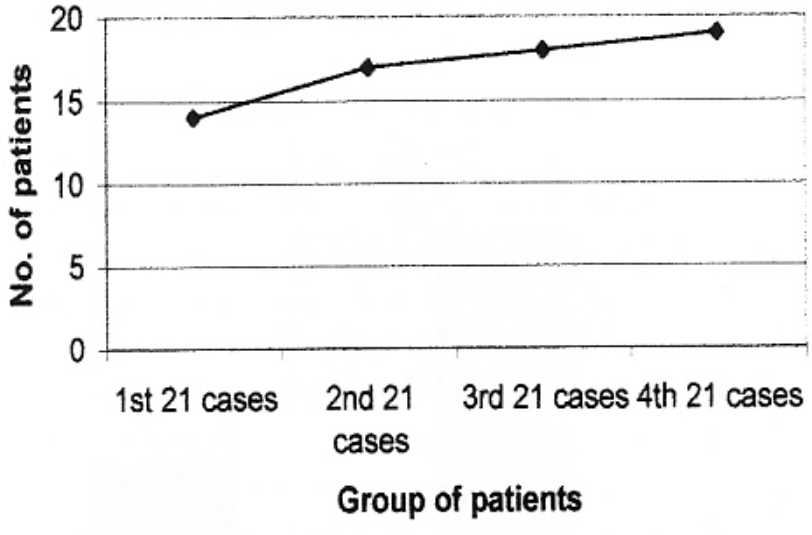


Fig. (8) : The learning curve for SN detection .

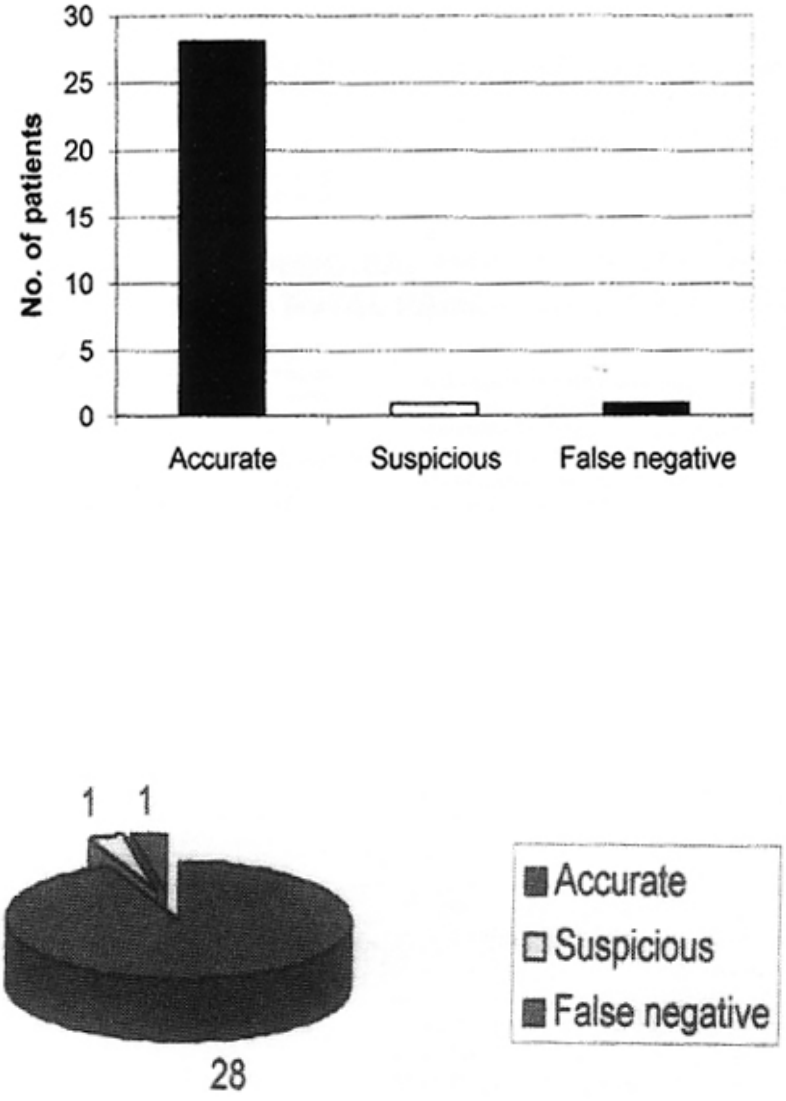


Fig. (9) : Results of SN frozen section histopathological examination.

DISCUSSION

Determination of the status of the axillary lymph nodes is essential for staging of breast cancer for choosing of adjuvant protocols.

Axillary dissection required for accurate staging ranges from total axillary dissection to sampling procedures. Total axillary dissection offers the greatest staging accuracy but has a significant morbidity including post-operative lymphoedema of the involved extremity, neouropathy of the arm, seroma formation, formation of painful neuroma, or

local wound problems. These complications are associated with increased hospitalization, increased overall cost, and considerable discomfort to the patient [4,5]. Axillary sampling is related to the number and location of the excised nodes. Adequate sampling procedure was defined by excision of at least 10 axillary lymph nodes.[6,7].

Complete axillary dissection results in recurrence rate approaching zero at 50 months and provides accurate staging[8]. The accuracy of sampling only can be equivalent to complete dissection if level I and level II axillary dissection is done [9].

Excision of the sentinel lymph nodes has extremely low morbidity, high degree of accuracy, short operation and minimal discomfort to the patient. Blue stained SNs were identified in 68 of the 84 patients (81 %). In 16 patients no SNs were identified. The primary tumor was situated in the medial half of the breast in eleven of these patients. Similar rates of failure were reported [10,11].

In our study the highest number of SLN(s) detected is 4 and this was only in 3 patients. However, some other [12,13] reported the number 8. This could be due to the long period of latency between injection of the dye and identification of the nodes.

In our study, the (SNs) accurately identified axillary node status in (88.2%).The sentinel / non sentinel nodal histology in agreement in our study was 88.2%. However this agreement was 97.9% in other reports[14,15].

Detection of occult metastases in (SN)s may be enhanced by immunohistochemical staining[15], decreasing the actual false negative cases.

On conclusion, intra-operative lymphatic mapping and sentinel node biopsy are highly accurate, minimally invasive, and cheap method for staging of patients with breast cancer favoring more conservative treatment. Frozen section microscopy can save a two – stage procedure for treatment but this may take up an extra operating room time.

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