

THE RELIABILITY OF AXILLARY NODE SAMPLING TO EVALUATE THE AXILLA IN THE MANAGEMENT OF INVASIVE BREAST CANCER

By

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Background: Arm morbidity such as arm edema, pain, numbness, weakness and impaired shoulder mobility are negative side effects of axillary clearance. Less invasive ways to establish the axillary nodal status are therefore of interest.

Patients and methods: One hundred and eighty eight patients with breast cancer (clinical stage T0-3, N0-1, M0) were operated upon by either modified radical mastectomy or breast conserving surgery, in whom the axilla was subjected to five-node biopsy followed in the same session by full axillary dissection in order to evaluate the accuracy of the five-node biopsy compared with full axillary dissection.

Results: The sensitivity of the five-node biopsy was 96.2% with a negative predictive value of 97.3% and negative likelihood ratio of 0.04.

Conclusion: Five-node biopsy of the axilla has good accuracy for staging the axilla. It could be considered as an alternative to sentinel node biopsy in centers not having the facilities for this procedure.

Keywords: Breast cancer, axillary dissection, axillary lymph nodes.

INTRODUCTION

The best management of the axilla in patients with invasive breast cancer remains uncertain, but staging of the disease is important for the prognostic value, as well as to plan adjuvant treatment.⁽¹⁾ The three most important factors used to determine treatment are lymph node status, tumor grade and to a lesser extent tumor size.⁽²⁾

However, axillary surgery to determine the lymph node status is associated with side effects which include nerve damage, sensory loss, lymphedema and decreased shoulder mobility. There has therefore been a move to reduce the extent of axillary surgery since a proportion of women do not have spread to the axilla and therefore do not benefit from the procedure.⁽³⁾ For this reason, sentinel lymph node biopsy and axillary node sampling, which are limited surgical procedures have gained a wide spread acceptance as an option for axillary management in invasive breast cancer.⁽³⁾

A Danish study suggests that clearance of less than 10 lymph nodes may have a negative prognostic implication in terms of survival.⁽⁴⁾ On the other hand, two Scottish

trials suggest that less extensive axillary procedures may provide adequate axillary staging, regional control and survival.^(5,6)

With early detection, the proportion of patients with involved nodes has decreased.⁽⁷⁾ The aim of the present study was to test whether a biopsy of five lymph nodes is informative about histopathological lymph node status of the axilla in operable breast cancer. In a prospective trial women with clinical stage T0-3, N0-1, M0 were subjected to a five- node biopsy followed in the same operation by full axillary dissection.

PATIENTS AND METHODS

One hundred and eighty eight patients with operable breast cancer having clinical stage T0-3, N0-1, M0 were included in this prospective study between July 2000 and May 2004. The study was conducted at the Departments of Surgery and Pathology; Minoufia and Ain Shams Universities. All patients were subjected to full diagnostic and metastatic work-up in the form of mammography, abdominal ultrasound, chest radiograph and laboratory

investigations. All patients were operated upon using the same standardized technique.

The decision to perform modified radical mastectomy (MRM) or breast conserving surgery (BCS) was taken according to the data indicated in the literature. In general; patients with unifocal tumor ≤ 4 cm underwent BCS, while those with multifocal tumors or tumors larger than 4 cm had MRM. Patients who had pre-operative chemotherapy or radiation were excluded from the study.

After breast surgery was completed either mastectomy or lumpectomy, the axillary dissection started with a five node biopsy in the axilla beginning the dissection at the axillary tail of the breast until five lymph nodes had been removed. Each lymph node was submitted to the pathologist in separate boxes and labeled 1-5. After excision of those lymph nodes, the dissection of the axilla was continued until level III lymph nodes had been excised. The rest of the axilla was also submitted to the pathologist as separate specimen. So that every patient became her own control.

All the removed tissue was fixed in formaldehyde and stained with Van Geison or haematoxylin-eosin. Sections of all nodes were examined with routine pathology. Immunohistochemical staining was not used in the examination of the nodes. The breast tumors were also stained with Van Geison or haematoxylin-eosin and examined with routine pathology. A small piece of the tumor was sent for estrogen and progesterone receptors (ER & PR) analysis in most cases.

Statistics:

Data were collected, tabulated and analyzed by using Epi info (2000) statistical package. Data were expressed as number and percentage, and analyzed by calculation of

Odd's ratio (OR), 95% confidence interval test for proportion, sensitivity, specificity, positive and negative predictive values and likelihood ratios. Level of significance was set as P value < 0.05 .

RESULTS

The characteristics of studied patients were given in Table 1. Seventy four percent of patients were postmenopausal (n=139). Clinically, axillary lymph nodes were detected in 74% of patients. Tumor size was more than 3 cm in 60% of patients.

The percentages of lymph node positivity in relation to clinical and pathological characteristics are given in Table 2. Out of the whole population of patients (n=188), pathological examination of the five node biopsy (FNB) revealed node negative in 112 (59.6%). One hundred and nine patients proved to be node negative after full axillary dissection (57.9%) denoting that 3 patients (1.6%) had false negative FNB.

Sensitivity, negative predictive value and negative likelihood ratio of FNB:

The sensitivity of FNB in all patients (n=188) was 96.2% (95% CI 89.3-99.2), and the negative predictive value was 97.3% (95% CI 92.3-99.4). The negative likelihood ratio of the FNB was 0.04 as regards the whole group of patients Table 3.

Since every patient was actually his own control, the specificity and positive predictive values were irrelevant, both reaching high values of 100%. While the positive predictive value could not be calculated statistically as there was no false positive rates.

Table 1. Characteristics of studied patients.

Character	Number n=188	Percentage %
Menopausal status		
Premenopausal	49	26.0
Postmenopausal	139	74.0
Clinical lymph nodes		
+ve	139	74.0
-ve	49	26.0
Tumor size (mm)		
≤ 10	6	3.0
11-20	17	9.0
21- 30	52	28.0
> 30	113	60.0
Tumor type		
Ductal	162	86.0
Lobular	21	11.0
Other	5	3.0
ER status		
+ve	88	47.0
-ve	32	17.0
Unknown	68	36.0
PR status		
+ve	83	44.0
-ve	37	20.0
Unknown	68	36.0

ER: estrogen receptors, PR: progesterone receptors.

Table 2. Relationship between patient's characteristics and lymph node positivity and number of cases with false negative five node biopsy

Item	Axillary LN				Total		OR	95%CI	+ve cases missed in FNB
	+ve n=79 n	%	-ve n=109 n	%	n	%			
Menopause									
Postmenopausal	66	83.5	73	66.9	139	74.0	2.5	1.2-5.5	2
Premenopausal	13	16.5	36	33.1	49	26.0			1
Clinical LN status									
+ve	74	93.7	65	59.6	139	74.0	10	3.5-30.7	1
-ve	5	6.3	44	40.4	49	26.0			2
Tumor size									
≤10 mm	1	1.3	5	4.6	6	3.2	1		0
11-20	3	3.8	14	12.8	17	9.0	1.1	0.1-33.7	1
21-30	9	11.4	43	39.4	52	27.7	1.1	0.1-26.6	0
>30	66	83.5	47	43.1	113	60.1	7.6	0.7-164	2
Tumor type									
Ductal	76	96.2	86	78.9	162	86.2	6.8	1.8-29.6	2
Lobular&Others	3	3.8	23	21.1	26	13.8			1
ER status									
+ve	45	56.9	43	39.4	88	46.8	2.1	1.1-3.8	2
-ve & unknown	34	43.1	66	60.6	100	53.2			1
PR status									
+ve	49	48.1	34	31.2	83	44.1	3.6	1.9-6.9	2
-ve	30	51.9	75	68.8	105	55.9			1

OR: Odd's Ratio, CI: Confidence Interval, FNB: five-node biopsy, ER: estrogen receptors, PR: progesterone receptors.

Table 3: Sensitivity, negative predictive value and negative likelihood ratio of FNB.

Number	All cases n=188
Number of +ve nodes in FNB (%)	76 (40.4)
Number of +ve nodes in level III	79 (42)
NPV of FNB (95% CI)	97.3% (92.3-99.4)
Sensitivity of FNB (95% CI)	96.2% (89.3-99.2)
Negative likelihood ratio	0.04

FNB: five-node biopsy, NPV: negative predictive value, CI: confidence interval.

DISCUSSION

It is generally agreed that axillary node status in potentially curable breast cancer is the best predictor of outcome and the main determinant of benefit from adjuvant therapy.⁽⁸⁾ At the present time, there is no non-invasive technique which can accurately stage the axilla since those techniques have not proved successful. Surgical removal of the axillary lymph nodes for histological examination still remains the corner-stone for such an evaluation. Unfortunately, the extent of axillary surgery is proportional to the severity of postoperative morbidity, and although much of the morbidity is short term, some patients have debilitating impairment of shoulder mobility, lymphedema or, rarely, a

brachial plexus injury. Such complications have a significant physical, as well as psychological impact on an already anxious patient.⁽⁹⁾

Two Danish randomized studies have shown an improved survival after radiotherapy to the axilla in node positive disease,^(10,11) but the addition of this treatment does cause an increase in morbidity. This morbidity is clearly radiation dose dependant,⁽¹²⁾

Three levels to the dissection of the axilla are described, and although there is no uniform agreement as to the appropriate extent of dissection, if the objective of the procedure is to treat the axilla adequately, a level III

clearance is most likely to achieve this, taking into consideration its high incidence of morbidity.⁽⁸⁾ In view of the data supporting the value of axillary sentinel lymph node biopsy (SNB) for staging, it is important to note that the nodes draining the tumor usually enlarge as a consequence of reactive hyperplasia caused by preoperative diagnostic interventions (aspiration or biopsies), and this makes them easier to palpate during sampling. This may cause an overlap with sentinel lymphadenectomy in cases without properly performed lymphatic mapping.⁽¹³⁾

The results of Cserni 1999 on 40 consecutive breast cancer patients undergoing sentinel lymphadenectomy before completing dissection suggest that the sentinel lymph node identified by patent blue mapping is in most cases (95%) included among the five largest/firmer nodes.⁽¹⁴⁾

Similar results were achieved by Macmillan et al (1998) using gamma probe guidance for identifying the sentinel lymph nodes in which >80% overlap was found between the sentinel lymph nodes and four node sample performed before using the gamma probe.⁽¹⁵⁾

The present study differs from previously published similar studies in that the nodes are harvested at the same setting starting by the 5 node biopsy followed by axillary clearance. Our results concluded that FNB of the axilla has a high sensitivity of 96.2% (95% CI 89.3-99.4) with an associated low negative likelihood ratio (0.04), to establish correctly histopathological lymph nodes status in operable breast cancer.

The proportion of women with a false negative test was only 1.6% and the risk of withholding adjuvant treatment from undetected node-positive patients would thus be low. Applying the estimates of reduction of mortality seen in overviews of clinical trials of adjuvant systemic treatment the potential under treatment of the few false-negative cases in this series would at most have a marginal effect on survival.⁽¹⁶⁾

The surgical technique in this trial is different from that of trials reporting inferior survival after sampling of only a few nodes in the axilla.^(4,17) In those trials no attempt was made at time of surgery to identify or confirm the number of lymph nodes in the fatty tissue excised from the axilla, nor was the dissection in the axilla done in an orderly fashion, beginning at the axillary tail of the breast, as in this trial.

The surgical technique used in this study is identical to those of four-node sampling in the Scottish trials comparing four-node sampling with full axillary clearance.^(5,6)

It was also similar to that used in the sentinel node dissection apart from the use of dye or gamma probe for lymph node dissection.

Recently the "sentinel node" procedure has been extensively reported to be a new minimal invasive procedure in axillary surgery in operable breast cancer.⁽¹⁸⁾ This procedure requires lymphoscintigraphy of the axilla and most authors also recommend the combination of lymphoscintigraphy with the injection of vital blue dye. This technique is more laborious than a four or five-node biopsy and cannot be performed in centers that do not have this facility. Even in centers that use the sentinel node technique, a proportion of patients (10%) will show neither a "hot spot" in the axilla nor a blue stained node at the axillary biopsy. In such a situation these patients are likely to be subjected to axillary clearance. This study indicates that the accuracy of FNB followed by routine pathology may be equal to the accuracy reported from the sentinel node procedure.^(18,19)

In a recent study including 200 patients, a four-node biopsy was compared with a sentinel node procedure in the same patient.⁽²⁰⁾ Ten out of 60 node positive patients were not detected by the sentinel node procedure. The corresponding figure for four-node sampling was 1/60.

The aim of FNB and the sentinel node procedure is to reduce arm morbidity without compromising the accuracy of the staging procedure. One of the factors that has been shown to have a negative impact on arm morbidity is the extent of axillary dissection.^(6,21,22) It has been shown that the relative hazard of arm morbidity 1-3 years postoperatively increased by 7% with each lymph node excised from the axilla.⁽²³⁾ It can be justified to use the technique of FNB in patients where the sentinel node procedure is not applicable or its facilities are not available.

It could be concluded that after a FNB the risk of a false-negative outcome is low and that the results of this study compare favorably with the so far published results from the sentinel node procedure, the accuracy is equally high. This will allow patients with negative FNB to be spared from unnecessary treatment of the axilla -almost 60% of patients- while at the same time allowing positive cases to be treated according to the accepted protocols in each center, either by radiation or completion to full axillary dissection. The FNB could therefore be an alternative to axillary clearance and the sentinel node procedure in centers not having the resources to perform lymphoscintigraphy or when the surgeon fails to identify the sentinel node during such a procedure.

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