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Research Article

Clinico - pathological profile of axillary lymph node status in early breast carcinoma - a tertiary care centre experience

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ABSTRACT

Background: Surgical dissection is the accepted mode of staging the axilla in breast cancer. However, the associated morbidity has led researchers to look at less invasive options like sentinel lymph node biopsy. Proper prediction of axillary node positivity can help towards stratifying patients for dissection or sentinel biopsy. The primary objective of the study was to assess the factors influencing pathological axillary lymph node positivity in early carcinoma breast. Secondary objective was to assess the reliability of clinical evaluation of axillary lymph nodes in these patients.
Methods: This was an Observation study, conducted from January 2012 to December 2014, at Government Medical College Hospital, Trivandrum, Kerala, India. 100 Consecutive cases of early carcinoma breast admitted in the general surgery wards during this period were included in this study.
Results: Axillary lymph node positivity was found to be more in younger age group, pre-menopausal patients, lobular pathology, and HER 2 neu positive patients. Premenopausal women and outer quadrants tumours have more axillary lymph node positivity. Clinical palpation for axillary lymph nodes was found to have a sensitivity of 58.18%, specificity of 62.22%, and positive predictive value of 65.31% and negative predictive value of 54.9%.
Conclusions: Younger age, HER 2 neu positivity and higher histological grade are associated with more risk of axillary disease. Also, the clinical examination of axillary lymph nodes is associated with significant false negative and false positive rates in early breast carcinoma. Axillary involvement and thus the need for loco-regional treatment can be predicted from the patients' clinico-pathological characteristics.

Keywords: Axilla, Breast cancer, Lymph nodes, Palpation, TNM staging

INTRODUCTION

Breast cancer remains the most common cancer among women across the world. It attains significance in being a major determinant of both morbidity and mortality in the affected female population. Breast cancer management requires a comprehensive assessment of multiple aspects in addition to the simple extirpation of the primary tumour, including sophisticated imaging, advanced pathology, nuclear medicine and a variety of adjuvant therapies, both local and systemic. Axillary lymph node involvement is shown to be the single most important prognostic factor for survival in breast cancer patients, and consequently information about it provides both staging information and guidance regarding treatment. Though triple assessment is the standard for evaluating carcinoma breast, clinical assessment of axilla is not infallible and pathological examination is the only way to confirm disease in nodes, especially micro-metastases. Hence axillary lymph node dissection (ALND) has been a standard part of breast cancer treatment, for accurate pathologic staging of axilla.

The axilla is a pyramid shaped space located at the lateral border of the human breast. It primarily contains the axillary lymph nodes, axillary sheath, axillary vessels as

well as the brachial plexus. The apex of the axilla is at the junction of clavicle, upper border of scapula and first rib. The base comprises the axillary fascia. The anterior wall is composed of pectoralis major, pectoralis minor and subclavius muscles together with the fascia that envelope these muscles. The posterior wall is composed of scapula and three related muscles - subscapularis, teres major and latissimus dorsi. The lateral wall is formed by bicipital groove of humerus bone. The medial wall is formed by the chest wall which includes the second to sixth ribs and the serratus anterior muscle. From the surgeons' point of view, the axillary lymph nodes are stratified into three levels according to the relationship to the pectoralis minor : Level I Nodes : lymph nodes located lateral to the muscle, Level II Nodes: lymph nodes located deep to the muscle, Level III Nodes: lymph nodes located medial to the muscle.

Axillary lymph node status is accepted as one of the most powerful prognostic factors in breast cancer and ALND the standard approach for local staging in lymph node positive patients. There has been evidence for an inverse correlation between a low number of removed axillary lymph nodes and overall survival. Therefore prevalent guidelines recommend the removal of at least 10 lymph nodes, based on a mathematical model which determined the cut off at 10 to allow a 90% certainty of a true negative axillary status.

The international breast cancer study group (IBCSG) studied LRR (Loco-Regional Recurrence) among 5352 breast cancer patients treated with mastectomy without PMRT (Post Mastectomy Radiation Therapy) and followed for a median of 14.5 years. The number of positive axillary nodes and tumour grade were significant risk factors for LRR. In addition, peri-tumoural vessel invasions (PVI) for premenopausal patients and tumour size for postmenopausal patients were also significant prognostic factors. Several other groups have found younger age to be associated with a significantly higher predicted risk of LRR.[1-5]

Currently, axillary surgery for breast cancer is considered as staging procedure that does not seem to influence the breast cancer mortality, since the risk of developing metastasis depends mainly on the biological behavior of the primary (seed-and-soil model). Due to the increasing awareness about carcinoma breast, routine use of mammography and early detection of cases, less cases are node positive at detection.

Hence these patients may undergo unnecessary axillary nodal dissection and have to suffer the associated morbidity. In many centers, axillary dissection has been replaced by the less invasive sentinel node biopsy in women with a clinically negative axilla. Axillary surgery seems even less important in elderly women because of the high mortality from competing events and the ability of hormone therapy to achieve long-term disease control. Another problem is the clinical fallibility of the TNM classification of the breast. The classical N stage detected by bed-side palpation is highly unreliable, with false positive and false negative rates of around 30%.[6-10]

With this background, this study was undertaken to find the clinico-pathological profile of axillary lymph node status in early breast cancer. Primary objective of the study was to assess the factors associated the occurrence of axillary lymph node metastases in early carcinoma breast. Secondary objective was to find out the reliability of clinical evaluation of axillary lymph nodes in early carcinoma breast by comparing with pathological status.

METHODS

This Observation study was conducted between January 2012 to December 2014 at the Government Medical College Hospital, Thiruvananthapuram, Kerala, India. The protocol was approved by the Institutional Review Board. 100 Consecutive cases of carcinoma breast admitted in the General Surgery wards during this period were included.

Inclusion criteria

Cytologically proven cases of carcinoma breast with tumour size up to 5 cm without signs of skin fixity, chest wall fixity, no clinically enlarged axillary lymph node or only mobile axillary nodes, female sex.

Exclusion criteria

Pregnancy or lactation; prior surgery or radiation to the affected breast or axilla; any form of neo-adjuvant chemotherapy.

After informed consent, all cases were subjected to investigations to confirm the diagnosis and to rule out metastases. Thus patients with clinical stages T1N0, T0N1, T1N1, T2N0, and T2N1 were included in the study. The patient's clinical characteristics were recorded in the performa. These underwent either Modified Radical Mastectomy or Wide local excision with Axillary lymph node dissection, depending on the patients' wishes as well as tumour characteristics.

Histopathological reports of these selected patients were reviewed from the department of pathology. From these data, the clinical and pathological characteristics of the primary were analyzed to find out their relation with axillary lymph nodal metastasis. Relative risk was calculated from these variables. To evaluate the efficacy of clinical tool, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. All relevant data is presented as mean ± standard deviation. A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

Table 1: Analysis of factors influencing pathological axillary node positivity.

Variable	Sub -group	Total number (n)	Lymph node + (P+)	Lymph node - (P-)	Relative risk	p value
Age group	20-30	4	4	0	1.88	<0.001
	31-40	7	4	3	1.68	0.0012
	41-50	31	18	13	1.08	0.6742
	51-60	30	13	17	0.72	0.1579
	61-70	14	6	8	0.75	0.3773
	71-80	4	0	4	0.18	0.1945
Menopausal	Pre	48	32	16	1.5	0.0275
	Post	52	23	29	0.66	0.0275
BMI	< 20	2	1	1	0.91	0.9038
	21 - 25	30	11	19	0.58	0.0359
	26 - 30	58	36	22	1.37	0.1109
	> 30	10	7	3	1.31	0.2357
Site of tumour	C	10	2	8	0.34	0.0908
	LI	14	4	10	0.48	0.0909
	LO	10	7	3	1.31	0.2357
	UI	30	13	17	0.72	0.1579
	UO	36	23	23	1.28	0.1661
Size of tumour	T1	12	10	2	1.63	0.0032
	T2	88	45	43	0.61	0.0032
Pathology	Lobular	2	2	0	1.85	<0.001
	Ductal	98	53	45	0.54	<0.001
Grade	1	51	22	29	0.64	0.0185
	2	42	29	13	1.57	0.0127
	3	7	4	3	1.04	0.9038
ER		90	44	36	1	0
PR			41	27	1.38	0.1509
HER 2 neu			9	1	1.76	0.0001

BMI: Body Mass Index; C: central. LI: lower inner; LO: lower outer; UI: upper inner; UO: upper outer; T1:<2 cm. T2: 2-5 cm; ER: estrogen receptor; PR: progesterone receptor

In this study, patients belonging to 41-50 year age group were found to constitute the maximum. The youngest patient was 23 years, while the oldest was 78. 48 patients were premenopausal.

The majority patients: 61: had lesion in the right breast. 36 patients had primary lesion in the upper outer quadrant, which was followed closely by the upper inner quadrant in 30 patients. Only 14 patients had lesion in the lower inner quadrant, while 10 patients each had lesion in the lower outer and central areas. The highest BMI was 33.28 while the lowest was 19.05, while the mean BMI was found to be 26.15+/-2.87. Among the total 100 patients, 88 had lesions more than 2 cm clinically: T2. The remaining 12 patients had lesions less than 2 cm: T1. 49 patients were clinically axillary lymph node positive: N1, while 51 had no palpable axillary nodes: N0. Pathologically, 98 were invasive ductal cancers while 2 were lobular. Pathological grade 3 was found in 7 patients, grade 2 in 42 patients and grade 1 in 51 patients. ER was positive in 80 patients, while PR was found to be positive in 68 patients. HER 2 neu was positive in 10 patients only.

Out of the 12 patients with clinical T1, 8 had pathologically T1 itself, while 4 had pathological T2. Of the 88 patients who had T2 tumours clinically, 80 patients remained pT2 itself, while 2 had T3 status pathologically. The remaining 6 had T1 tumours pathologically.

Out of the 51 patients with clinically absent nodes, 28 had no pathological nodes, while 18 had pN1 and 5 had pN2 nodes. Of the 49 patients with palpable nodes, 17 had no pathological nodes, 23 had pN1 and 9 had pN2 nodes pathologically. On further analysis, axillary lymph node positivity was found to be associated with younger age group, pre-menopausal status, lobular pathology and her 2 neu positivity, grade 2 histology and tumour size less than 2 cm (Table 1). Clinical palpation for axillary lymph node positivity was found to have a sensitivity of 58.18%, specificity of 62.22%, PPV of 65.31% and NPV of 54.9% (Table 2).

Table 2: Diagnostic test evaluation of clinical examination of axilla.

	Value	95% Confidence interval
Sensitivity	58.18%	44.11% to 71.35%
Specificity	62.22%	46.54% to 76.23%
Positive predictive value	65.31%	50.36% to 78.33%
Negative predictive value	54.90%	40.34% to 68.87%
Positive likelihood ratio	1.54	1.00 to 2.38
Negative likelihood ratio	0.67	0.46 to 0.99

DISCUSSION

In this study the most frequent involvement of lymph nodes is seen in tumours occupying the upper outer and lower outer quadrants. The maximum number of patients had histological grade 2 tumours and these patients had maximum lymph node positivity. The factors associated with axillary lymph node positivity were found to be younger age group, pre-menopausal status, and lobular pathology and HER 2 neu positivity. Unexpected association of axillary lymph nodes was found with smaller tumours (rather than bigger tumours) and grade 2 pathological status (rather than grade 3). This finding might be because of the very less number of patients with T1 tumour size and grade 3 pathologies. The clinical palpation for axillary lymph nodes was found to have moderate sensitivity and specificity only.

The results of this study agree with most of the existing literature on this area. Pathologic examination of the axillary lymph node provides objective and reliable node metastasis information. Barth et al. found that lymph vascular invasion (LVI), tumour size, and histological grade can be used to estimate the risk of ALNM. HER2 positivity is associated with higher aggressiveness in invasive breast cancer, and is accepted as an important prognostic factor in breast cancer patients. Also, patients with larger tumour size have increased risk of ALNM. Chu and Coll, in a cohort of women with a mean age of 52 years, after evaluating numerous possible predictive factors, found that only the size of primary tumour and of SN metastases were significant and hence they proposed not to perform AND in small primary (T1a, T1b) and SNB showing only micro metastases.[11-14]

Non-invasive techniques that are considered to exclude axillary metastases include axillary physical examination (PE), axillary ultrasound (AUS) and positron emission tomography-computed tomography (PET/CT). In AUS, a longitudinal-transverse axis ratio (LT ratio) <2, eccentric cortical thickening, and/or an absent fatty hilum as well as higher peripheral vascularity are reported as the most reliable criteria to predict lymph node metastases. The combination of AUS and FNA (Fine Needle Aspiration) has led to a specificity improvement to nearly 100%, but the sensitivity may not be substantially increased (between 30.6 and 62.9%). However, most of these methods lack sensitivity and NPV. Sensitivity is 25-35.5 % for PE, 43.5-72.3 % for AUS and 56-62.7 % for PET/CT. The NPV is 81.7 % for PE, 81.6-83.3 % for AUS and 79.1 % for PET/CT. MRI seems to be the most promising non-invasive nodal staging technique with a highest median sensitivity of 84.7 % and NPV of 95.0 %. Also, exclusion of nodal metastatic infiltration is impossible with any imaging technique in about 25% of nodal metastases due to a size of ≤ 5 mm, which is below the cut-off for detection.[15-19]

Of late, local treatment of the axilla in clinically node-negative, early-stage breast cancer patients is hotly debated after the release of the American college of surgeons oncology group (ACOSOG) Z0011 and European organization for research and treatment of cancer (EORTC) AMAROS trial data. The ACOSOG Z11 trial randomized clinically node-negative women with cancers less than 5 cm in size treated with lumpectomy and RT to completion axillary dissection versus no further surgery after a positive SN. There was extremely low rate of LRR in both groups. Another recently published randomized trial on women 60 years of age with breast cancer and a clinically node-negative axilla compared surgery with axillary dissection and surgery without axillary dissection followed by tamoxifen for 5 years. This study found that presence of axillary lymph node involvement did not affect disease-free or overall survival.[20,23]

CONCLUSION

In conclusion, axillary lymph node positivity is associated with younger age group, pre-menopausal status, lobular pathology and her 2 neu positivity. The possibility of having axillary involvement and thus the need for adjuvant therapy may be predicted from the characters of the primary tumour. However, clinical assessment of axilla and tumour size is associated with significant false negative and false positive rates in early breast carcinoma and hence cannot replace imaging modalities. The modern approach in breast cancer care should include more detailed screening diagnostics, pathological evaluation, improved planning of surgical and radiation therapy, and more effective systemic treatment.

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