Original Article

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Effect of Lump Size and Nodal Status on Prognosis in Invasive Breast Cancer: Experience from Rural India

Surgery Section

MONIQUE GARG[1], NITIN NAGPAL[2], DARSHAN SINGH SIDHU[3], AMANDEEP SINGH[4]

ABSTRACT

Introduction: Breast cancer is now the leading cause of cancer among Indian women. Usually large tumour size and axillary lymph node involvement are linked with adverse outcome and this notion forms the basis of screening programs i.e. early detection.

Aim: The present study was carried out to analyse relationship between tumour size, lymph node status and there relation with outcome after treatment.

Materials and Methods: Fifty patients with cytology-proven invasive breast tumours were evaluated for size, clinical and pathologic characteristics of tumour, axillary lymph node status and outcome data recorded on sequential follow-up.

Results: Mean age of all participated patients was 52.24±10 years. Most common tumour location was in the upper outer quadrant with mean size of primary tumour being 3.31±1.80cm. On pathology number of lymph nodes examined ranged from 10 to 24 and 72% of patients recorded presence of disease in axilla. Significant positive correlation ($p<0.013$; $r^2=0.026$) between tumour size and axillary lymph node involvement on linear regression. Also an indicative correlation between size and grade of tumour and axillary lymph node status was found with survival from the disease.

Conclusion: The present study highlights that the size of the primary tumour and the number of positive lymph nodes have an inverse linear relationship with prognosis. Despite advances in diagnostic modalities, evolution of newer markers and genetic typing both size of tumour as T and axillary lymphadenopathy as N form an integral part of TNM staging and are of paramount importance for their role in treatment decisions and illustrate prognosis in patients with invasive breast cancer.

Keywords: Carcinoma breast, Tumour size, Axillary lymph node involvement

INTRODUCTION

The International Agency for Research on Cancer (IARC) in World Cancer Report have predicted that cancer rates will upswing by 50% to 15 million new cases per year by 2020 [1]. The burden of breast cancer is increasing in both developed and developing countries. Around 100,000 new cases occur in India every year [2]. Latest report on national cancer registry website in India suggest breast cancer to be leading cancer in females in a population based survey, surpassing cervical cancer, at both urban and rural locations across India [3]. Goal of treatment of any disease is to achieve cure, but when it comes to cancer quest for cure, largely eludes us. The success of treatment largely depends on the extent of disease at presentation. Hence, identification of prognostic factors and factors predicting response to specific treatment protocols, epitomize an important area in research. Screening in breast cancer helps to detect disease at an early stage, when chances to achieve cure are high. Small tumours confined to the breast, without micro-metastasis have high chances of cure whereas big tumours which spread to axillary lymph nodes are consistently associated with subclinical systemic spread and strongly predict advanced disease [4]. Thus tumour size has significant prognostic implications. Also, presence or absence of palpable axillary lymph nodes is a vital prognostic indicator especially in patients with early breast cancer [2,5]. Increasing number of involved axillary lymph nodes is associated with an increased probability of recurrence and mortality [6]. Various other prognostic factors of value in breast cancer are age, vascular invasion, hormonal receptors status, menopausal status, histological grade, nuclear grade, lympho-vascular invasion, DNA ploidy and various tumour markers [7]. But authors across globe have stressed upon axillary lymph node status being the single most important prognostic indicator in breast cancer inspite of development of new tumour markers [7]. In our setup (a tertiary hospital catering rural population from near indo-pak border) patients mostly belong to low socioeconomic status. This has lead to late presentation of cases, often as large lumps with secondary changes and frequent axillary nodal metastasis. Also, due to paucity of funds, use of tumour markers is not a routine in this part of the country. The seventh edition, as previous editions, of TNM staging in breast cancer by AJCC [8] includes the size of the tumour and the nodal status as the most important prognostic factors. Tumour size, lymph node status along with grade of tumour form basis of another popular prognostic system, the Nottingham prognostic index [9]. Since clinical decision making, establishment of management protocols and prediction of outcome heavily relies on the prognostic indicators.

AIM

The present study was aimed to establish the relationship between these two prognostic factors, tumour size and axillary lymph nodes and their effect on prognosis in the patients of carcinoma breast attending the Department of Surgery, Guru Gobind Singh Medical College and Hospital, Faridkot, India.

MATERIALS AND METHODS

After getting approval from institutional ethical and research committee this prospective study was conducted in Department of Surgery. Fifty patients with cytology-proven invasive breast tumours were identified, between March 2013 to October 2014. All these patients were treated with modified radical mastectomy as first treatment and the pathologic lymph node status was available in all cases.

Inclusion criteria for the present study were the following:

1. Cytology proven invasive breast cancer;
2. Known histological nodal status;
3. No distant metastasis at the time of registration;
4. No previous treatment for breast cancer;
5. No previous or concomitant malignancy;

Patient who had no remnant of primary tumour (post neo adjuvant chemotherapy) or had metastasis from other organs to the breast at the time of registration, unknown pathological nodal status (Nx), immeasurable primary tumour (Tx), ductal or lobular carcinoma in situ and Paget's disease of the nipple with no tumour were excluded.

Data was collected to record details of demographic profile, clinical characteristics of tumour (side and location of tumour) and histological data of tumour (histological types, tumour size, histological grade, skin, nipple and areola invasion). The size of tumour was defined as the largest diameter of tumour reported on pathological examination following surgery. The number of nodes pathologically evaluated, on the likelihood of finding at least one lymph node positive for disease, was counted in each specimen.

Clinical and histological variables were analysed and association between tumour size and its invasiveness (such as axillary lymph node status, skin, areola, and nipple invasion) was noted. The histological type was assessed and grading was done Scarff–Bloom–Richardson (SBR) system. Follow up data was recorded to note details of history, examination, and laboratory and radiology data to study the outcome in terms of local recurrence, distant metastasis and mortality for the duration of study.

STATISTICAL ANALYSIS

Using IBM SPSS 20.0 software descriptive statistics were reported as frequencies and percentage, or as mean and standard deviation. Pearson correlation and linear regression model was used to examine the relation between tumour size and axillary lymph node.

RESULTS

Women in range from 51-60years had highest incidence of breast cancer 44% (22 patients). The Body Mass Index (BMI) was in the range of 22 and 28, mean BMI being 25.20±1.74. All the patients were parous. The tumour location was found more commonly in the upper outer quadrant (UOQ) (52% of cases), followed by central tumours (20%) and is illustrated in [Table/Fig-1]. Skin and nipple areola involvement in patient were 42% and 40% respectively.

The mean size of primary tumour was 3.3140 ±1.808 cm (ranging from 1.0-9.5cm). Based on tumour size patients were classified into 9 groups (I-IX) and their distribution is represented in [Table/Fig-2]. Only 38% patients had presented with a tumour size less than 2cm which highlights the fact that there was a tendency of late presentation in the present subset of patients.

Position of Lump	Patients (%)
UOQ (Upper outer quadrant)	26 (52)
UIQ (Upper inner quadrant)	5 (10)
LOQ (Lower outer quadrant)	4 (8)
LIQ (Lower inner quadrant)	3 (6)
CQ (Center quadrant)	10 (20)
MCT (Multifocal tumour)	2 (4)

[Table/Fig-1]: Distribution of breast lump based on location within breast.

Group	Tumour Size (in millimeters)	Patients (%)
I	10-15	9 (18)
II	16-20	10 (20)
III	21-25	4 (8)
IV	26-30	3 (6)
V	31-35	6 (12)
VI	36-40	4 (8)
VII	41-45	3 (6)
VIII	46-50	5 (10)
IX	>50	6 (12)

[Table/Fig-2]: Distribution of patients based on tumour size.

On histological examination, invasive ductal carcinoma was the most common type (88%), followed by invasive lobular carcinoma (10%) and 2% included other types. On the basis of the Scarff–Bloom–Richardson (SBR) system of histopathologic grading, majority of patients had grade I disease (20 patients) followed by grade II(16 patients) and grade III(14 patients).

On pathological evaluation, mean number of the examined Lymph Nodes (LN) in each specimen was 14.34± 3.42, with minimum examined being 10 and maximum examined being 24. On further evaluation it was observed that, 36 (72.0%) patients showed pathologic involvement of lymph nodes and 14 patients were free from axillary lymph node involvement. This again points to a late presentation in our subset of patients. Distribution of patients based on involvement of number lymph nodes represented in [Table/Fig-3].

It was also observed that, as the tumour size increases more lymph nodes were involved suggesting a significant positive correlation between size of primary tumour and axillary lymph node metastasis and is illustrated in [Table/Fig-4]. On statistical analysis by Linear Regression demonstrated a significant positive correlation ($p<0.013$; $r^2=0.026$) between tumour size and axillary lymph node involvement.

Lymph Node Status	Patients (%)
Negative Node	14 (28)
1 -3 positive node	4 (8)
4 positive node	32 (64)

[Table/Fig-3]: Distribution of patients based on lymph node involvement.

		No. of Patients with positive and negative lymph node		Total	p-value
		N	P		
Tumour size in milimeters (group)	10-15(I)	6	3	9	0.013
		66.7%	33.3%	100.0%	
	16-20(II)	5	5	10	
		50.0%	50.0%	100.0%	
	21-25(III)	2	2	4	
		50.0%	50.0%	100.0%	
	26-30(IV)	1	2	3	
		33.3%	66.7%	100.0%	
	31-35(V)	0	6	6	
		.0%	100.0%	100.0%	
	36-40(VI)	0	4	4	
		.0%	100.0%	100.0%	
	41-45(VII)	0	3	3	
		.0%	100.0%	100.0%	
	46-50(VIII)	0	5	5	
		.0%	100.0%	100.0%	
	> 50(IX)	0	6	6	
		.0%	100.0%	100.0%	
Total		14	36	50	
		28.0%	72.0%	100.0%	

[Table/Fig-4]: Correlation between tumour size and lymph node involvement.

It was observed that as the grade of the tumour increases, percentage of the patients with positive lymph node increases and is represented in [Table/Fig-5]. All patients with grade III had positive nodes in the axilla and it was statistically significant ($p<.006$).

The present study revealed that as the tumour size increases, prognosis of the patient become poorer, is illustrated in [Table/

		No of positive and negative lymph nodes		Total	p-value
		N	P		
Grade	I	10	10	20	0.006
		50.0%	50.0%	100.0%	
	II	4	12	16	
		25.0%	75.0%	100.0%	
	III	0	14	14	
		0%	100.0%	100.0%	
Total		14	36	50	
		28.0%	72.0%	100.0%	

[Table/Fig-5]: Correlation between tumour grade and lymph node involvement.

		Prognosis of the patients		Total	p-value
		Dead	Survival		
Tumour size in milimeters (group)	10-15(I)	1	8	9	0.042
		11.1%	88.9%	100.0%	
	16-20(II)	0	10	10	
		0%	100.0%	100.0%	
	21-25(III)	0	4	4	
		0%	100.0%	100.0%	
	26-30(IV)	0	3	3	
		0%	100.0%	100.0%	
	31-35(V)	0	6	6	
		0%	100.0%	100.0%	
	36-40(VI)	0	4	4	
		0%	100.0%	100.0%	
	41-45(VII)	0	3	3	
		0%	100.0%	100.0%	
	46-50(VIII)	2	3	5	
		40.0%	60.0%	100.0%	
	> 50(IX)	3	3	6	
		50.0%	50.0%	100.0%	
Total		6	44	50	
		12.0%	88.0%	100.0%	

[Table/Fig-6]: Effect of tumour size on survival.

Fig-6]. But one patient having tumour size of 1.5 cm died, suggesting role of other factors in the prognosis of breast cancer. Of the 6 patients who died 5 patients had grade III disease, thus recognised that high grade disease was associated with poor prognosis.

It was observed that all patients who had 4 or more positive lymph node had worst prognosis and is represented in [Table/Fig-7].

Thus, the present study revealed a significant correlation between size and grade of tumour and axillary lymph node status and outcome of the disease. Also, observation that most patients presented with size more than 2cm (62%) and 72% had axillary lymph node involvement reflects on the advanced nature of disease at the time of presentation in our subset of patients.

		Prognosis of the patients		Total	p-Value
		DEAD	SURVIVED		
Axillary Lymph Node Status	NEG	0	14	14	0.173
		0%	100.0%	100.0%	
	1-3 POSTIVE	0	3	3	
		0%	100.0%	100.0%	
	4 POSTIVE	6	27	33	
		18.2%	81.8%	100.0%	
Total		6	44	50	

[Table/Fig-7]: Effect of lymph node involvement on survival.

DISCUSSION

In late 1800s, Sir William Halsted popularized the radical mastectomy on the basis that breast cancer spreads in an organized fashion, initially via the skin and regional lymphatics and then, at a later stage, hematogenously to other organs [7]. But in the present day scenario concepts of management have evolved as for surgery has changed to more conservative than that of radical mastectomy and also use of systemic chemotherapy before locoregional control. Breast cancer survival and prognosis has improved considerably in the last few decades [9,10]. These advances have been possible due to impact of screening programs and improved treatment regimens like use of systemic chemotherapy in a Neo adjuvant manner, targeted therapies for hormone receptor and HER2 neu receptor. Thus, it is very important to recognise and define factors at the time of diagnosis which will help us in predicting clinical outcome with administration of treatment. With respect to breast cancer various prognostic criteria have been defined. In the available literature various factors like younger age, higher histological grade, larger size, high rate of p53 mutations, and Ki-67 staining are usually associated with poor prognosis [11]. Some of these factors require study of gene expression profiles and advanced genomic techniques, but these techniques are at an experimental stage and not widely available [5]. So, even in present day scenario factors like tumour size and nodal status play an important role in appropriate treatment decisions and assessment of prognosis.

Breast carcinomas are associated with a varied range of clinical and pathologic profile, ultimately influencing the clinical outcome. The present study was done to evaluate clinical outcomes and relationships between tumour size, lymph node status, and prognosis in breast cancer. It is well known that in breast cancer, the size of the primary tumour and the number of positive lymph nodes is associated with poor prognosis and survival [12]. The OS (Overall Survival) rate and RFS (Relapse Free Survival) decreased as the size of tumour and number of positive lymph nodes increased [11]. The present study points the strong relationship between primary tumour size and axillary lymph node involvement, as the tumour size increased, the frequency of positive axillary nodes also increased. PP Rosen et al., did a 20 year follow-up for prognosis in T2 lesions and observed that tumours from 2.1 to 3.0 cm (33% chance of recurrence at 20 years) and from 3.1 to 5 cm (44% chance of recurrence at 20 years) thus strongly relating the prognosis to primary tumour size (p=.06) [13]. Also, Christine L Carter et al., studied the relation of tumour size, lymph node status, and survival in 24,740 breast cancer cases, found out that as tumour size increased, survival decreased regardless of lymph node status; and as lymph node involvement increased, survival status also decreased regardless of tumour size [12]. So tumour size plays an important role in both making treatment decisions and predicting outcome. On this basis Port ER et al., suggested that on the basis association between tumour size and survival, the principal goal of screening and early detection should be to identify cancers when they are small and node-negative [14].

Even though there is availability of new tumour markers, axillary lymph node metastasis is albeit remains ultimate prognostic indicator for patients of carcinoma breast [10,15]. Manual clinical examination of the axilla has poor sensitivity and specificity [13,16]. Thus axillary nodal dissection is deemed mandatory to figure the axillary nodal status, which makes level I-II axillary dissection definitive part of surgical treatment of breast cancer. Surgical removal remains the best and most accurate way to assess nodal status [17]. Even though there is no therapeutic implication of axillary lymph node dissection, it is accepted and performed world over for its role in planning treatment of patients with invasive breast cancer [16]. In the present study, we have found that chances of axillary node involvement increased with increasing size of tumour and was consistent with available literature. [4,6,10] Also,

it was found that a positive axillary lymph node status significantly correlates with decreased survival and the finding were consistent with the available literature [4,17]. Pathy NB et al., suggested that ability of the tumour to metastasize evolves as it grows, and that nodal status simply reflects the ability of the tumour to spread, it is this relation between tumour size, nodal status, and survival that forms the basis of TNM staging system [19].

Wo JY et al., studied effect of very small tumour size on cancer-specific mortality in node-positive breast cancer observed that in cases small tumours size associated with extensive lymph node involvement suggest them to be of more aggressive subtype than larger tumours with the same degree of lymph node involvement and thus be representative for biologically aggressive disease in such patients [20]. In our study, there were 5 patients with tumour size less than 2 cm but still they had higher involvement of axillary lymph node. But all of these patients were of SBR grade III and with involvement of skin, nipple and areola, thus depicting the aggressive behaviour of the carcinoma. This suggests that axillary lymph node involvement can be seen even in cases of small size tumour mass and if present is associated with relatively poor prognosis.

Axillary dissection is associated with complications like pain, lymphoedema and shoulder stiffness [21]. Use of sentinel lymph node biopsy reduces the incidence of these complications, but it is a very resource intensive requiring team multiple specialists from different departments (nuclear medicine specialist, radiologist, pathologist and surgeon) at the time of procedure and is expensive which limits its widespread use [4,22].

CONCLUSION

As per observations of this study we conclude that both tumour size and lymph node status are independent prognostic indicators. A short follow-up period and low sample size was limitation of the present study. There was linear relationship between increasing tumour size and mortality. But even small tumour can also have axillary lymph node involvement and distant metastasis. This highlights that both nodal status and survival are reflections of the same biological process, i.e., the ability of the tumour to spread either locally or to distant sites. Nonetheless relevance of lump size in prognosis again highlights the importance of catching the disease early, thus stressing upon the need of betterment of existing screening programs and education of public regarding breast self examination which can prove to be a cost effective screening tool in a country like ours. Tumour size and nodal status form the basis for the TNM system, and remain as crux parameters for making management decisions and estimating prognosis of the patients with invasive breast cancer in developing countries.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Surgery, Maharishi Markendeshwar Medical College, Kumarhatti, Solan, Himachal Pradesh, India.
2. Associate Professor, Department of Surgery, GGS Medical College, Faridkot, Punjab, India.
3. Professor and Head, Department of Surgery, GGS Medical College, Faridkot, Punjab, India.
4. Assistant Professor, Department of Surgery, GGS Medical College, Faridkot, Punjab, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Nitin Nagpal,
79, Medical Campus, Sadiq Road, Faridkot, Punjab, India.
E-mail: drnitinnagpal@gmail.com

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