

Original Research Article

A predictive factor for axillary lymph node metastasis in invasive ductal breast cancer: the value of tumor and breast volume ratio

Mehmet Kubat^{1*}, Soykan Dinç²

¹Department of General Surgery, Alanya Education and Research Hospital, Antalya, Turkey

²Department of General Surgery, Bozok University Faculty of Medicine, Yozgat, Turkey

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*Correspondence:

Dr. Mehmet Kubat,

E-mail: dr.m.kubat@gmail.com

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ABSTRACT

Background: The objective of this study was to witness the effect of tumor volume/breast volume ratio on the presence of axillary lymph node metastasis and to examine the strategy in surgical treatment approach for patients.

Methods: This study was carried out prospectively by examining the patients undergoing modified radical mastectomy surgery due to breast cancer (n=99). Breast volumes were measured through liquid overflow method in graduated bowl tumor volume was measured according to ellipsoid volume formula with diameters determined by pathological specimen, ultrasonography or MRI.

Results: Axillary lymph node metastasis (ALNM) was positive in 64.6% of them (n=64). Average breast volume was found to be 693.89cm³ in the measurement of mastectomy materials. Average tumor volume was found to be 9.58cm³. In line with these results, average tumor volume/breast volume (vTm/vMm) ratio was: 0.0176. Author found axillary lymph node metastasis possibility significantly higher in patients with vTm/vMm ratio>0.016 (Odds ratio 9.437, p-value 0.007).

Conclusions: The presence of ALNM is the most important factor in indicating the prognosis of patients with invasive breast cancer and planning the treatment. Thus, knowing whether there exists an ALNM or not during preoperative period draws the attention of both the doctors performing treatment and patients. In this study efficiencies of largest tumor diameter, tumor volume and tumor volume (vTm)/Breast volume (vMm) ratio in indicating ALNM presence in cases with T2 invasive ductal breast cancer were evaluated. It was found that vTm/vMm ratio was a recent and effective prognostic criterion in determining ALNM.

Keywords: Axilla, Breast cancer, Lymphatic metastasis, Organ volume, Tumor volume

INTRODUCTION

Breast cancer was the most frequently occurring cancer type among women in the world and an estimated 1.38million new cases of cancer were diagnosed in 2008.¹ According to a study conducted by International Agency for Research on Cancer (IARC) affiliated with World Health Organization (WHO), the risk of developing lifelong breast cancer for a woman living to the age of 80 was 12.8% and there was a risk of developing breast cancer in one of every eight women.¹ Surgery was the

initial and most effective treatment in breast cancer. When the history of breast cancer surgery examined, it is observed that surgical procedures result in less morbidity and more patient comfort.²

TNM (Tumor-Node-Metastasis) staging system of American Joint Committee on Cancer (AJCC) was widely used in breast cancer staging. The presence and number of metastatic lymph nodes in axilla are the most important prognostic indicators in breast cancer. The state of axilla was directive in terms of staging and planning

adjuvant therapy.³ 5year survival was stated as 94.4% for patients without axillary lymph node metastasis (ALNM) and it was noted as 58% for patients with more lymph node metastasis.⁴

Tumor was another variable, which means the largest diameter (dTm) of it determines the stage in breast cancer. Particularly for patients with negative lymph node involvement, the diameter of primary tumor (dTm) becomes a very important prognostic indicator in survival.

While ALNM positivity risk was 8% in T1a tumors, it increases to 12% in T1b tumors.^{5,6} The objective of this study was to witness the effect of tumor volume (vTm)/breast volume (vMm) ratio on the presence of ALNM in cases with T2 invasive ductal breast cancer and to examine the strategy in surgical treatment approach for patients.

METHODS

This study was carried out prospectively by examining the patients undergoing modified radical mastectomy (MRM) surgery due to breast cancer between January 2010 and June 2013. In order to have a homogenous study, only invasive ductal carcinomas within T2 stage according to TNM staging of AJCC were included.

The multicentric-multifocal cases, male patients, preoperative or postoperative distant metastatic cases, other pathological subtypes and patients who had mixed types, underwent breast conserving surgery, received preoperative radiotherapy, chemotherapy and/or hormone therapy and patients whose lymph node could not be dissected in axillary dissection and tumor diameter/size could not be determined due to excisional biopsy were excluded from the study.

The study was carried out with remaining 99 patients. Modified radical mastectomy was performed on all the patients. While level 1 and level 2 axillary dissection was carried out in patients, level 3 dissection was also performed where necessary. All the mastectomy and axillary dissection materials removed after surgery were sent for histopathological evaluation.

Breast volumes were measured through liquid overflow method in graduated bowl before fixing postoperative pathological specimen. 0.9% NaCl solution was used in this measurement in order to prevent damage to pathological specimen and axillary dissection material was excluded from the measurement.⁷ Three diameters of the tumor were determined by pathological specimen, ultrasonography or MRI. Measurements were verified with histological preparations. Tumor volume was measured according to ellipsoid volume formula ($V=\pi/6*(a*b*c)$) ($\pi=3.14$) by using the three diameters of the tumor (a,b,c) ($a\geq b\geq c$).⁸ Grouping was carried out according to tumor classification of WHO after

evaluating with haematoxylin-eosin stain of primary tumor. Estrogen and progesterone receptor levels were evaluated with immunohistochemical hybridization and C-erb 2 level was evaluated with either immunohistochemical or in-situ hybridization. Tumor and breast volume ratio were calculated. The data was analyzed through SPSS for Windows 11.5 package software.

RESULTS

Around 99 female patients undergoing MRM surgery due to T2 stage ductal invasive breast cancer between January 2013 and June 2015 in general surgery clinic of XXX were included in this study. The youngest among the patients included in the study was 26years old while, the oldest was 77, the average age was 50.88 ± 11.87 . 48.5% of the patients were 50years old and over (n = 48).

Tumor indicated 57.6% right (n=57), 42.4% left (n=42) breast, 56.6% upper outer quadrant (n=56) and 43.4% other quadrants (n=43) in the patients. While axillary lymph node was negative in 35.4% of the patients (n=35) it was positive in 64.6% of them (n=64). When axillary dissection materials were examined, it was identified that average 18.8 lymph nodes were dissected (SD:6.989, min=7, max=35) and average 3.38 of these dissected lymph nodes were metastatic (median:1, SD:5.120, min=0, max=27).

Table 1: Demographic and clinical characteristics of patients diagnosed with T2 ductal invasive breast cancer.

Variant	Classification	% (n=)
Age	≤49	51.5 (51)
	≥50	48.5 (48)
Laterality	Right	57.6 (57)
	Left	42.4 (42)
Tm location	Upper outer quadrant	56.6 (56)
	Other quadrants	43.4 (43)
ALN metastasis	Negative	35.4 (35)
	Positive	64.6 (64)
pN	0	35.4 (35)
	1	32.3 (32)
	2	22.2 (22)
	3	10.1 (10)
Tm nuclear grade	1	8.1 (8)
	2	68.7 (68)
	3	23.2 (23)
Estrogen receptor	Positive	67.7 (67)
	Negative	32.3 (32)
Progesteron receptor	Positive	45.5 (45)
	Negative	54.5 (54)
C-erb B2	Positive	25.3 (25)
	Negative	74.7 (74)

ALN=Axillary lymph node, pN=Axillary lymph node stage, Tm=Tumor.

As a result of histopathological evaluations, tumor nuclear grade was found as grade 1 in 8.1% of the patients (n=8) and grade 2 in 68.7% of the patients (n=68), grade 3 in 23.2% of the patients (n=23). Estrogen receptor status was evaluated as positive in 67.7% of the patients (n=67) and negative in 32.3% of them (n=32), progesterone receptor status was evaluated as positive in 45.5% of the patients (n=45.5) and negative in 54.5% of them (n=54).

Again, in the same evaluations while c-Erb B2 receptor of the patients was evaluated as positive in 25.3% of the patients (n=25) it was observed as negative in 74.7% of the patients (n=74) (Table 1).

Average breast volume was found to be 693.89cm³ (median: 655cm³, min=180cm³, max=1800 cm³) in the measurement of mastectomy materials.

Average of the largest tumor diameter (dTm) was observed as 3.15cm (median: 3cm, min=2cm, max=5cm). The following values were found in tumor volumes obtained through " $V=\pi/6*(a*b*c)$ " formula of tumor diameters, average value 9.58cm³, median: 6.28cm³, minimum and maximum values: 0.63 and 45.01cm³. In line with these results, average tumor volume (vTm)/breast volume (vMm) was 0.0176 (median: 0.0109, min=0.0011, max=0.1329) (Table 2). The difference of median values between positive lymph node metastasis (LN MET (+)) and negative lymph node metastasis (LN MET (-)) groups was evaluated with Mann Whitney U test.

It was observed that dTm, vTm, vTm/vMm values were all significantly different (for dTm: p-value 0.022, for vTm: p-value <0.001 and for vTm/vMm: p-value <0.001) (Table 3).

Table 2: Characteristics of patients diagnosed with T2 ductal invasive breast cancer.

Measurements	Average	Median	Min	Max
vMm (cm ³)	693.8	655	180	1800
dTm (cm)	3.15	3	2	5
vTm (cm ³)	9.58	6.28	0.63	45.01
vTm/vMm	0.0176	0.0109	0.0011	0.1329

vMm= Breast volume, dTm =Largest tumor diameter, vTm = Tumor volume

Table 3: Clinical measurements of cases according to lymph node metastasis (-) and lymph node metastasis (+).

Measurements	LN MET (-) (n:35)	LN MET (+) (n:64)	p-value
dTm (cm)	2.5 (2-5)	3.2 (2-5)	0.022
vTm (cm ³)	4.6 (1.0-36.6)	8.0 (0.6-45.0)	<0.001
(vTm)/(vMm)	0.009 (0.001-0.023)	0.015 (0.002-0.133)	<0.001

vMm= Breast volume; dTm =Largest tumor diameter; vTm = Tumor volume; LN MET= Lymph node metastasis.

Table 4: ROC analysis results and diagnostic performance levels of clinical measurements in separating LN MET (+) and LN MET (-) groups.

Indicators	Definitions	dTm	VTm	vTm /vMm
AUC		0.639	0.710	0.709
%95 confidence interval		0.527-0.752	0.606-0.814	0.608-0.810
p-value		0.022	<0.001	<0.001
Best cut-off point		>2.6	>5.98	>0.016
Number of cases	N	99	99	99
Sensitivity	TP/(TP+FN)	48/64 (%75.0)	42/64 (%65.6)	31/64 (%48.4)
Selectivity	TN/(TN+FP)	19/35 (%54.3)	26/35 (%74.3)	33/35 (%93.9)
PPV	TP/(TP+FP)	48/64 (%75.0)	42/51 (%82.4)	31/33 (%93.9)
NPV	TN/(FN+TN)	19/35 (%54.3)	26/48 (%54.2)	33/66 (%50.0)
Accuracy	(TP+TN)/(N)	67/99 (%67.7)	68/99 (%68.7)	64/99 (%64.6)
p-value		0.004	<0.001	<0.001

vMm= Breast volume; dTm =Largest tumor diameter; vTm = Tumor volume; AUC= Area under the curve (roc curve); TP= True Positive; FN= False Negative; TN= True Negative; FP= False Positive; PPV= Positive Predictive Value; NPV= Negative Predictive Value.

Clinical measurements in separating LN MET (+) and LN MET (-) groups are analyzed with ROC curve test (Figure 1) (Table 4). As a result of examining combined effects of clinical measurements in separating LN MET

(+) and LN MET (-) groups through multivariate logistic regression analysis p-value (0.007) of vTm/vMm ratio was found significant. Estimated relative risk (odds ratio) was found as 9.437 (95% and confidence level: 1.866-

47.479) (Table 5). Combined effects of clinical measurements in separating LN MET (+) group and stage I, stage II and stage III respectively were examined through multivariate logistic regression analysis.

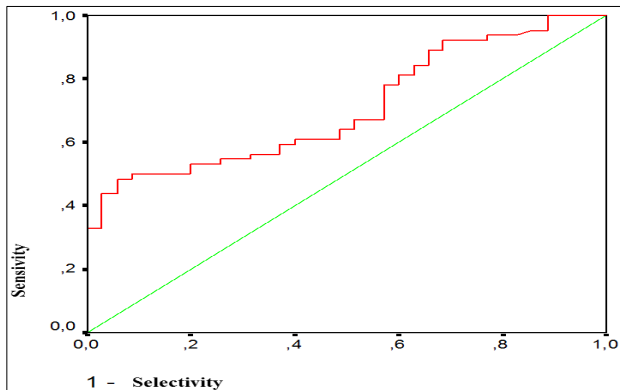


Figure 1: ROC curve on tumor volume/breast volume measurements in separating LN met (+) and LN met (-) groups.

Cases with the values of largest tm diameter >2.6cm, vTm>5.98cm³ and vTm/vMm >0.016 for pN1 weren't found significant. It was found significant for pN2 as vTm/vMm ratio >0.016 p-value <0.001 (odds ratio: 26.439, %95 confidence interval: 3.776-185.723).

Table 5: Examining the combined effects of clinical measurements in separating LN MET (+) and LN MET (-) groups through multivariate logistic regression analysis.

Variables	Odds ratio	%95 confidence interval		p-value
		Lower limit	Upper limit	
dTm >2.6	0.982	0.302	3.190	0.976
vTm >5.98	2.474	0.710	8.620	0.155
vTm/vMm >0.016	9.437	1.866	47.729	0.007

LN MET=Lymph node metastasis, vMm=Breast volume, dTm=Largest tumor diameter, vTm = Tumor volume.

Table 6: Examining the combined effects of clinical measurements in separating LN MET (+) group and LN MET stage I, stage II and stage III respectively through multivariate logistic regression analysis.

Variables	Odds ratio	%95 confidence interval		P value
		Lower limit	Upper limit	
Stage I				
dTm>2.6	0.994	0.262	3.771	0.993
vTm>5.98	2.975	0.746	11.868	0.123
vTm/vMm >0.016	3.483	0.603	20.127	0.163
Stage II				
dTm >2.6	1.060	0.188	5.986	0.948
vTm >5.98	1.099	0.178	6.787	0.919
vTm / vMm >0.016	26.439	3.776	185.123	<0.001
Stage III				
dTm >2.6	0.442	0.013	15.469	0.652
vTm >5.98	9.283	0.317	271.547	0.196
vTm / vMm >0.016	30.802	2.690	352.722	0.006

LN MET=Lymph node metastasis, vMm=Breast volume, dTm=Largest tumor diameter, vTm=Tumor volume

It was found significant for pN3 as vTm/vMm ratio >0.016 p-value 0.006 (odds ratio: 30.802, %95 confidence interval: 2.690-352.722) (Table 6).

DISCUSSION

Today, incidence of cancer has been increasing. Efforts are exerted to develop more advanced imaging methods to diagnose the disease and it has been tried to obtain modalities with less morbidity and better survival results for treatment of the disease. Various prognostic factors have been indicated to extend disease-free survival and to organize treatment planning. For this purpose, the search for new prognostic factors was still ongoing. The presence of Axillary Lymph Node Metastasis (ALNM)

was the most important factor in indicating the prognosis of patients with invasive breast cancer and planning the treatment.

Thus, knowing whether there exists an ALNM or not during preoperative period draws the attention of both the doctors applying the treatment and patients. Correlations of various clinical, pathological and molecular characteristics with ALNM possibility was shown in the studies conducted.⁹⁻¹¹ Various nomograms involving factors such as age of patient, size and placement of tumor, lymphovascular invasion status, type and grade of tumor, estrogen and progesterone receptor levels, being multi-centric or multifocal were developed to evaluate ALNM possibility.¹²

Axillary Lymph Node Dissection (ALND) was a surgical method with complications. Search for other methods were conducted in order to have an idea about axilla before performing axillary dissection due to the requirement of having knowledge about axillary lymph nodes. Sentinel lymph node examination was proposed due to this necessity. However, 5611 female patients with invasive breast cancer evaluated in the study conducted by Krag DN et al, and 9.8% false-negative rate was found for SLNB.¹³ This also shows that SLNB couldn't be enough being widely used. In this study, author found correlation between tumor volume/breast volume ratio and ALNM and thus, it was observed that patients with higher vTm/vMv ratio would need higher rates of ALND. In other words, more secure SLNB technique could be used in patients with lower vTm/vMm ratio. Various scoring methods were described for patient selection in SLNB.^{14,15} In this study it was observed that tumor size used in this scoring appeared to be weaker than tumor volume or tumor volume/breast volume ratio in indicating ALNM. Similar results were also found in various studies in literature.¹⁶

Breast cancers are three dimensional solid masses. Few of them are true spherical. Wapnir IL et al, evaluated 165 invasive breast cancer in a study and stated that tumor volume was more effective than largest tumor diameter in staging cases with smaller invasive breast cancer.⁸ In this study we found that tumor volume was more effective in indicating ALNM ($p < 0.001$) and also vTm/vMm ratio was under approximate value with ALNM demonstration activity (ROC: Tm volume AUC: 0.710, Tm volume/breast volume AUC: 0.709).

Fein DA et al, evaluated 1598 cases with stage I and stage II breast cancer in a study founded ALNM positivity incidence as 0% in non-palpable tumors with the size of ≤ 5 mm and as 20% in palpable tumors with same sizes.¹⁷ Considering palpable breast was directly related to breast volume having a palpable tumor will be easier as vTm/vMv ratio increases in masses with same sizes. The results of previous study adjust to this study results. In this study, author found ALNM (+) possibility significantly higher in patients with vTm/vMv ratio > 0.016 (Odds ratio 9.437, p -value 0.007). In other words, ALNM possibility significantly decreases as the breast volume increases in cases with same tumor size.

In a study performed by Chao C et al, 3192 patients with breast cancer and lymphatic drainage and SLNB characteristics of cases with palpable breast cancer were evaluated. It was presented that cases with palpable breast cancer were at a younger age were ALNM positive in a higher ratio and had higher SLNB diagnostic value. It was demonstrated the fact that tumor was palpable constituted an independent risk factor for ALNM regardless of tumor size.¹⁸ The fact that palpable tumor regardless of tumor size influences ALNM has indicated that metastasis was related to breast size. In this study, author evaluated breast size in volume as one of the

factors. However, author did not exclude tumor volume by evaluating tumor volume/breast volume ratio. Author found this study compatible because tumor volume/breast volume ratio had an influence on palpable tumor.

Cunningham JE et al, found that relation of ALNM with breast cancer distance to the skin was examined in 209 cases with T1 and T2 breast cancer, it was found that distance of tumor to the skin was more than 14mm in all 26 ALNM positive cases. Distance averages of ALNM positive and ALNM negative cases to the skin were found to be similar. Distance of palpable tumors to the skin was found significantly closer. It was stated that ALNM positive cases tended to be more palpable. However, breast volumes weren't measured and it was stated that tumor size could change the distance to skin by means of breast size.¹⁹ Author found that tumor size/breast size ratio was significant in evaluating ALNM without evaluating the distance of tumor tissue to the skin.

As stated by Cunningham JE et al, distance averages of tumor tissue to the skin were found to be similar in node positive and node negative groups. In this study author used both variable together with tumor volume/breast volume ratio and found it significant in terms of ALNM positivity. 233 cases with T1 and T2 breast cancer were evaluated in a retrospective way by Ansari B et al, and in this study it was found that the distance of tumor tissue in ALNM positive patients to the skin was significantly.²⁰ It was found that increasing tumor volume/breast volume ratio was related to ALNM (for ALNM (-) vTm/vMm med: 0.009, for ALNM (+) vTm/vMm med: 0.015, p -value < 0.001). Considering the study of Ansari B et al, it was considered that increasing tumor volume/breast volume ratio decreased ALNM ratio by raising the distance of tumor tissue to the skin and papilla. Parameter of breast size or volume which they shared as a missing point of the study was investigated in this study.

In a study performed by Martić K et al, predictive value of tumor volume/breast volume ratios of 136 patients with T1c invasive ductal breast cancer on ALNM was evaluated. In this study it was found that median value of tumor volume/breast volume ratio was higher in ALNM positive group than the negative group. When analyzed by ROC curve AUC estimated for tumor volume/breast volume was found higher than the AUC estimated for tumor volume and the difference was significant. Predictive value of tumor volume/breast volume ratio for ALNM was found higher.¹⁶ In this study, author found that tumor volume/breast volume ratio was significant as an independent predictive value in indicating ALNM. Author found the specificity for Tm volume/breast volume ratio > 0.016 as 94.3 % and PTD 93.9%. Torstenson T et al, examined 401 cancer cases in which 79 of these cases (19.7%) were evaluated as ALNM positive. They found the distance of tumor tissue in ALNM positive group to skin and papilla significantly higher than ALNM negative group (p value 0.0007).

They observed that ALNM predictability increased when papilla and skin distance values were placed in nomograms of Memorial Sloan-Kettering Cancer Center and MD Anderson Cancer Center.²¹ This, gives the idea that nomograms used in order to determine ALNM could be utilized for increasing the predictability as was the study of Torstenson T et al. We believe that this relation could be demonstrated through the studies to be conducted on this subject. There are various factors that limit this study despite all these findings. This study was limited to the cases with T2 stage invasive ductal breast cancer for group homogeneity. Factors such as histopathological grade of tumor and lymphovascular invasion presence having independent effects on ALNM were ignored.

In this study effect of vTm/vMm ration on ALNM was found significant and it was considered that this ratio was correlated to increasing ALNM when tumor was palpable in various studies of literature. However, it was obvious that tumors in same volume with closer placement to breast skin would be easily palpable in the tumor with same size although the increase in breast size and volume decreases palpability of tumor.

Therefore, it was not expected that the effect of vTm/vMm ratio on ALNM that was subjected to this study would exactly match. As a result of this study, we don't put forth the replacement of vTm/vMv ratio to currently used SLNB technique however it should be considered that lymph node positivity rate of patients was higher, and it was useful to be watchful against a possible negative result particularly while performing SLNB in cases with lower breast volume and higher tumor volume.

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