Original Article

Defining the T status in breast cancer: Where do we stand?

Ramamurthy Rajaraman, Subbiah Shanmugam, Anitha Gandhi, Deepa Shunmugam

Department of Surgical Oncology, Centre for Oncology, Government Royapettah Hospital, Chennai, Tamil Nadu, India

ABSTRACT

Background: Tumor size in breast cancer is a key factor for staging, prognosticating, and deciding the choice of treatment. Currently, there are no standard rules for measuring the T status in breast cancer. The purpose of this study was to determine an accurate method to evaluate the T status by various parameters compared with the actual size in fresh specimens. **Materials and Methods:** This prospective study was conducted on 134 breast cancer patients scheduled to undergo a modified radical mastectomy. The paired *t*-test was used for analyses. **Results:** Using a paired *t*-test, the differences in tumor size as measured by physical examination ($P \leq 0.001$) and in the formalin-fixed specimen ($P \leq 0.001$) when compared with the postoperative fresh specimen were highly significant. These differences indicated that the physical examination and formalin-fixed specimen measurements were inaccurate in estimating tumor size. Tumor size, as measured by a mammogram and ultrasonogram when compared with the referenced $P = 0.077$ and 0.149, respectively, showed that the ultrasonogram is the most accurate method of determining tumor size *in vivo*. The mean percentage decrease in size of the formalin-fixed specimen was 7.8, which was significant enough to downstage two patients from T2 to T1 and seven patients from T3 to T2. **Conclusion:** An ultrasonogram is the most accurate way of defining tumor size *in vivo* as measured in postoperative fresh specimens. Tumor shrinkage with formalin fixation may give a false T status.

Key words: Breast cancer, formalin, mammography, physical examination

INTRODUCTION

The accurate determination of tumor size is crucial for staging, prognosticating, and deciding the choice of treatment options for breast cancer.[1] The methods for preoperative tumor measurement include a clinical examination, mammography, and ultrasonogram. The accuracy of these modalities has been studied by numerous authors with varying results.[2-6] The limitations of those studies include small sample size and number of modalities used.[2,3,6] None of the studies compared all three modalities. Presently, there are no standard rules for measuring the T status in breast cancer (personal communication from Dr. M. Gress, RHIT, CTR, AJCC Technical Specialist, dated 8/1/2016).

Address for correspondence: Prof. Ramamurthy Rajaraman, Government Royapettah Hospital, "RAMA SWATHI," 11/25, 7th Main Road, Raja Annamalaipuram, Chennai - 600 028, Tamil Nadu, India. E-mail: rajaanu1@rediffmail.com

Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.183495

Objective

The objectives of this study were as follows:

1. To assess the accuracy of these three modalities in estimating the tumor size in breast cancer patients *in vivo*
2. To determine the fallacy of pathological T size in a formalin-fixed specimen due to its shrinkage.

MATERIALS AND METHODS

This study was conducted in 134 histologically proven breast cancer patients who were to undergo a modified radical mastectomy in the Department of Surgical Oncology, Center for Oncology, Government Royapettah Hospital and Kilpauk

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Cite this article as: Rajaraman R, Shanmugam S, Gandhi A, Shunmugam D. Defining the T status in breast cancer: Where do we stand?. Clin Cancer Investig J 2016;5:305-8.

Medical College, between August 2013 and December 2015. Among these patients, 48 of them received three to four courses of neoadjuvant chemotherapy. Patients with fungating masses and previous lumpectomies were excluded. All of the 134 patients underwent a preoperative assessment of tumor size within 15 days of the definitive surgery. The largest diameter of the tumor was measured by clinical examination, mammogram, and ultrasonogram. This study was approved by the Ethical Committee, Kilpauk Medical College, Chennai. Informed consent was obtained from all patients.

Measurement by a physical examination was done using a vernier caliper. Both a standard craniocaudal view and medial-lateral oblique projections were done using a digital mammography instrument (Allenger's mammography). The single largest diameter in both of the views was recorded. Ultrasonogram was performed by an experienced radiologist on a MyLab Six ultrasound unit using a 7–12 MHz broadband probe.

After the modified radical mastectomy, the breast specimens were immediately examined and cut sagittally into parallel slices of approximately 1 cm in thickness. The largest diameter of the tumor was measured using a vernier caliper. Then, the entire specimen was immersed in 10% of buffered formalin. After 24 h, the measurement was again done using the vernier caliper. In patients without a clinically palpable tumor and no gross tumor in fresh specimen following neoadjuvant chemotherapy, an examination under a microscope was done to evaluate the size of the residual tumor, if any.

To eliminate interobserver variation, the measurements of all 134 patients were recorded by the same surgeon and radiologist.

Statistical analysis

Statistical analysis was done after tabulating the results using IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp). A paired *t*-test was applied by calculating the differences between each pair and testing whether or not the mean difference of each pair was different from zero.

RESULTS

The median patient age was 50 years (range: 24–80 years). The histological type of tumor was infiltrating ductal carcinoma in 130 patients (97.02%) and infiltrating lobular carcinoma in the remaining four patients (2.98%) [Table 1]. Table 2 shows the tumor size calculated by various methods.

Table 3 shows that, in the calculation of the Pearson's correlation coefficient, there is a good linear correlation between these three modalities with the postoperative fresh specimen size. However, mere correlation does not indicate the accuracy of the modality in tumor size measurement for which a paired *t*-test was applied.

Table 4 shows that the *P* values for the comparison of tumor size in the clinical examination with tumor size in the fresh specimen and formalin-fixed specimen size with fresh specimen size are highly significant, suggesting that a clinical examination and formalin-fixed specimen are not accurate in determining tumor size. The size measurement by a mammogram, when compared with a fresh specimen, shows a $P = 0.077$. The ultrasonogram size had good concordance with the fresh specimen size ($P = 0.149$).

Table 5 shows that among the modalities compared, the ultrasonogram value was the closest to the real pathological size (fresh).

Table 1: Patient tumor characteristics

Feature	Value
Age (year)	
Median (range)	50 (24-80)
Histologic subtype (%)	
Infiltrating ductal carcinoma	130 (97.02)
Infiltrating lobular carcinoma	4 (2.98)
Grade, *n* (%)	
1	61 (45.5)
2	51 (38)
3	22 (16.4)
Neoadjuvant chemotherapy, *n* (%)	
Yes	48 (35.8)
No	86 (64.2)

Table 2: Tumor size by various methods

Methods	Total number	Range (mm)	Mean (mm)	SD
Clinical	134	117.04	46.43	21.55
Mammogram	134	84.40	34.72	15.78
Ultrasonogram	134	76.90	32.06	14.75
Fresh specimen	134	76.40	33.33	16.04
Formalin-fixed	134	71.79	30.70	14.41

SD: Standard deviation

Table 3: Pearson's correlation coefficient (*r*) in comparison with fresh specimen

Parameters	*r*	*P*
Clinical examination	0.867	<0.001
Mammogram	0.893	<0.001
Ultrasonogram	0.868	<0.001
Formalin-fixed specimen	0.990	<0.001

Table 4: Paired *t*-test in comparison with fresh specimen

Parameters	SD	*t*	*P**
Clinical examination	11.06	13.71	<0.001
Mammogram	7.24	1.76	0.077
Ultrasonogram	7.78	−1.451	0.149
Formalin-fixed specimen	2.70	−11.252	<0.001

t=Paired *t*-test value: **P*<0.01, highly significant, **P*=0.011-0.05, significant, **P*=0.051-1.00, not significant. SD: Standard deviation

Among the patients who received neoadjuvant chemotherapy, two patients had no measurable tumor by a clinical examination, but a residual lesion was present on a mammogram in one patient and on an ultrasonogram in one patient. In two other patients, who had a clinically palpable lump after chemotherapy, no residual tumor was found both radiologically or postoperatively in either patient.

The mean tumor size in the fresh specimen and after the formalin fixation was 33.33 mm (range: 0–76.4 mm) and 30.7 mm (range: 0–71.79 mm), respectively. The mean difference between these two parameters was 2.62 mm (range: 0.89–14.12 mm). The mean percentage in shrinkage of the specimen after the formalin fixation was 7.8 (range: 2.39–26.82%). Table 6 shows that among the 91 patients who were in the T2 category in the fresh measurement, two patients (2.2%) were downstaged to T1 after the formalin fixation and seven patients (35%) in T3 were downstaged to T2.

DISCUSSION

Tumor size in breast cancer is an important prognostic factor.[1] The accurate assessment of tumor size is crucial, as it influences the choice of primary treatment and helps to decide on adjuvant treatment. The issue of discrepancy in tumor size measurement by various methods has been addressed in numerous studies, and there are currently no definitive guidelines for measuring the true T status of breast cancer.[2,3,6] The present study attempted to estimate the accuracy of physical examination, mammogram, ultrasonogram, and formalin fixation of specimens in estimating the correct T size by comparing them with the size in fresh postoperative specimens.

A good Pearson's correlation does not mean that there is greater agreement between the compared methods because it is dependent on the range of chosen values, a wide range guaranteeing a good coefficient.[5,7] In our study, all the four methods (clinical examination, mammogram, ultrasonogram, and formalin-fixed specimen) showed good correlation based on the Pearson's correlation coefficient; however, they are not accurate methods in determining the correct T status. Kald *et al*. emphasized this in their study.[5]

Table 5: Mean difference in comparison with fresh specimen (mm)

	Mean difference
Clinical examination	13.10
Mammogram	1.12
Ultrasonogram	−0.976
Formalin-fixed specimen	−2.63

Table 6: T size comparison between fresh and formalin-fixed specimen (number of patients)

T stage	Fresh specimen	T stage change	Formalin-fixed specimen
T1*	23	T2 to T1=2	25
T2†	91	T3 to T2=7	96
T3‡	20	-	13
Total	134		134

*T1≤20 mm, †T2>20 mm to ≤50 mm, ‡T3>50 mm

Clinical examination often leads to overestimation of the tumor size.[3,4,6,8] The reason for this overestimation may be due to the fact that measurements by palpation are 2-fold, including the thickness of the skin and surrounding soft tissues, which is not deducted typically.[3] Dixon *et al*. attempted to correct this by subtracting the thickness of the skin, fat, and subcutaneous tissue in the corresponding area in the contralateral breast from the clinical measurement obtained using calipers.[3] This adjusted clinical size in their study never differed by more than a fraction of a centimeter from the actual size.[3] This approach was not validated in further studies. In our study, clinical examinations overestimated tumor size by a mean of 13.10 mm, similar to the studies by Dixon *et al*., Pain *et al*., Choi *et al*., and Verma *et al*.[3,4,6,8]

In our present study, mammograms overestimated tumor size by a mean of 1.12 mm, as shown in studies by Fornage *et al*. and Heusinger *et al*.[2,9] This overestimation may be attributed to the difficulty in mammographic measurements because of poor demarcation of the tumor opacity in dense breasts as mentioned in the study by Fornage *et al*.[2] Ultrasonograms underestimated tumor size by a mean of 0.976 mm in our study in concordance with studies of Kald *et al*., Choi *et al*., and Verma *et al*.[5,6,8] In a recent study by Gruber *et al*., ultrasonograms underestimated the tumor size by a mean of 8 mm.[10] In their study, they state that this underestimation may be due to varying individual interpretations of malignancy criteria, such as the hyperechoic margin of a tumor and dorsal acoustic attenuation, by different sonologists.[10] However, in our study, the measurements were recorded by the same radiologist, eliminating the bias.

By paired *t*-test, the differences in tumor size as measured by a physical examination and in a formalin-fixed specimen when compared with a postoperative fresh specimen value were highly significant ($P \leq 0.001$), indicating that both modalities were not a good method to estimate tumor size. Tumor size as measured by a mammogram and ultrasonogram, when compared with the reference, had a $P = 0.077$ and 0.149, respectively. This showed that ultrasonogram was the most accurate method of determining tumor size.

A recent retrospective study by Jiang *et al*. involving 1296 patients, concluded that preoperative measurements

tend to overestimate the actual tumor size by a mean of 5 mm.[11] Pathological size was measured in the postoperative fresh specimen within 1 h following resection with a standard ruler.[11] This overestimation in tumor size has been attributed to infiltration and/edema around the tumor.[11] In this retrospective study, all patients were not imaged using all of the imaging modalities, and a paired *t*-test was used for presurgical and postsurgical sizes. Ours is a prospective study where all patients were imaged using both a mammogram and ultrasonogram.

Formalin processing has shown to alter tumor dimensions in many solid organ cancers, including the lung, gastrointestinal system, oral cavity, vulva, and breast.[12-16] In their study on the effect of tissue fixation and processing on breast cancer size, Pritt *et al*. and Yeap *et al*. have documented a decrease in the size of the specimen after the formalin fixation.[16,17] In a study by Horn and Naugler, the formalin fixation did not have an effect on tumor size.[18] The difference between the fixed state and unfixed state was 3 mm. Our study found that the postfixation size reduction was significant enough to downstage the tumor stage from T2–T1 in two patients and T3–T2 in seven patients. This finding significantly affects both the adjuvant treatment modality and the analysis of results.

One of the limitations of this study is the small sample size. Another limitation of this study is that magnetic resonance imaging has not been included as an imaging modality because its role in measuring tumor size has not been standardized.

CONCLUSION

Ultrasonogram is the most accurate way of defining the tumor size *in vivo* when compared with a postoperative fresh specimen. The fixation of the specimen in formalin reduces the tumor size, which is significant enough to influence the adjuvant treatment decisions and analysis of results. We recommend that the tumor size in the fresh state, which is the real size, should be considered for pathological staging. Furthermore, larger studies are needed to validate this finding. Once validated, this may bring a paradigm shift in tumor measurement guidelines.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Edge SB. AJCC Cancer Staging Hand Book. 7th ed. Chicago: Springer; 2009.
2. Fornage BD, Toubas O, Morel M. Clinical, mammographic, and sonographic determination of preoperative breast cancer size. Cancer 1987;60:765-71.
3. Dixon JM, Senbanjo RO, Anderson TJ, Forrest AP, Elton RA. Clinical assessment of tumour size in primary breast carcinoma. Clin Oncol 1984;10:117-21.
4. Pain JA, Ebbs SR, Hern RP, Lowe S, Bradbeer JW. Assessment of breast cancer size: A comparison of methods. Eur J Surg Oncol 1992;18:44-8.
5. Kald BA, Boiesen P, Ronnow K, Jonsson PE, Bisgaard T. Preoperative assessment of small tumours in women with breast cancer. Scand J Surg 2005;94:15-20.
6. Verma VP, Kaur N, Agarwal N, Bhargava SK, Singh UR, Saha S, *et al.* Intra-operative measurement of tumour size in breast cancer and its comparison with other methods: A prospective study. Ecancermedicalscience 2008;2:96.
7. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-10.
8. Choi KH, Bae JW, Lee JB, Koo BH. Clinical, mammographic, and ultrasonographic assessment of breast cancer size. J Korean Surg Soc 2000;58:331-6.
9. Heusinger K, Löhberg C, Lux MP, Papadopoulos T, Imhoff K, Schulz-Wendtland R, *et al.* Assessment of breast cancer tumor size depends on method, histopathology and tumor size itself. Breast Cancer Res Treat 2005;94:17-23.
10. Gruber IV, Rueckert M, Kagan KO, Staebler A, Siegmann KC, Hartkopf A, *et al.* Measurement of tumour size with mammography, sonography and magnetic resonance imaging as compared to histological tumour size in primary breast cancer. BMC Cancer 2013;13:328.
11. Jiang YZ, Xia C, Peng WT, Yu KD, Zhuang ZG, Shao ZM. Preoperative measurement of breast cancer overestimates tumor size compared to pathological measurement. PLoS One 2014;9:e86676.
12. Hsu PK, Huang HC, Hsieh CC, Hsu HS, Wu YC, Huang MH, *et al.* Effect of formalin fixation on tumor size determination in stage I non-small cell lung cancer. Ann Thorac Surg 2007;84:1825-9.
13. Gopalswamy N, Shenoy VN, Choudhry U, Markert RJ, Peace N, Bhutani MS, *et al.* Is *in vivo* measurement of size of polyps during colonoscopy accurate? Gastrointest Endosc 1997;46:497-502.
14. Johnson RE, Sigman JD, Funk GF, Robinson RA, Hoffman HT. Quantification of surgical margin shrinkage in the oral cavity. Head Neck 1997;19:281-6.
15. Palaia I, Bellati F, Calcagno M, Musella A, Perniola G, Panici PB. Invasive vulvar carcinoma and the question of the surgical margin. Int J Gynaecol Obstet 2011;114:120-3.
16. Pritt B, Tessitore JJ, Weaver DL, Blaszyk H. The effect of tissue fixation and processing on breast cancer size. Eur J Radiol 2003;48:285-92.
17. Yeap BH, Muniandy S, Lee SK, Sabaratnam S, Singh M. Specimen shrinkage and its influence on margin assessment in breast cancer. Asian J Surg 2007;30:183-7.
18. Horn CL, Naugler C. Breast specimen shrinkage following formalin fixation. Pathol Lab Med Int 2014;6:11-4.