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Original Article

Which is the best method to measure the size in multiple breast carcinoma in correlation with impact on prognosis? A retrospective study of 418 cases

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Abstract: Background: Breast tumor size influences patient management and prognosis. In unifocal lesions tumor staging depends on the largest diameter of the tumor, whereas in multiple lesions there is no international standard. The aim of this paper is to study the best method of assessing tumor size in multiple invasive carcinomas, correlated with lymph node metastases. Methods: Two measurement methods (largest focus diameter, LD, and aggregate diameter of all foci, AD) were used in 418 primary invasive breast lesions (91 multiple, 327 unifocal) and compared against the nodal status. Multiple breast carcinomas were defined as at least 2 clinically, radiological and histologically confirmed invasive tumor foci separated by uninvolved breast tissue, regardless of the distance between foci or quadrant location. Results: The use of aggregate diameter upstaged 23 patients (25.27%) with multiple tumors (16 from pT1 to pT2 and 7 from pT2 to pT3). No difference in nodal positivity based on pT status appeared between LD and AD. Conclusions: Aggregate diameter is not correlated with an increase in axillary lymph node metastases and should not be used for staging. This supports the current recommendations according to which tumor size should be based on the diameter of the largest lesion in patients with multiple breast cancer.

Keywords: Measurement, multiple breast carcinomas, lymph node metastases, prognosis

Introduction

Tumor size is one of the most important prognostic factors in breast carcinoma, and a determining factor in patient therapeutic management [1-3]. Tumor size assessment in breast carcinomas is problematic, since they have an irregular, stellate shape or they present spicules, with only one third of the tumors being spherical [2]. Therefore, the largest diameter, as assessed by the pathologist, only rarely expresses their real size. In unifocal breast carcinomas, the largest diameter of the tumor is reported for TNM staging, but in multiple (multifocal/multicentric) tumors reporting is not internationally standardized and the possibility of erroneously assessing tumor size is even higher. In these cases, AJCC 2010/TNM 2012 recommend using the largest diameter of the largest tumor focus, and reporting only the presence of multiple foci, between parentheses, although multiple macroscopic tumor foci are often evident [1, 4]. The diameter of additional foci is not reported, either as separate values or under the form of a sum, according to AJCC 2010/TNM 2012 staging systems. In these cases, tumor diameter and volume may be under evaluated and, consequently, the risk of local recurrence and of survival decrease is higher. Several studies revealed a worse prognosis [5-8] and a higher ratio of axillary lymph node involvement in multiple carcinomas [9-13]. Other studies found higher mortality rates and lower 10-year survival rates in multiple carcinomas compared to unifocal carcinomas, especially in tumors over 2 cm in diameter [5].

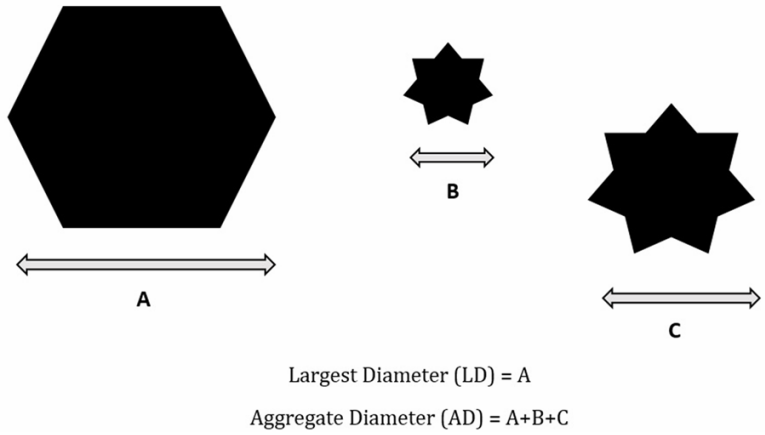

Figure 1. The size in multiple carcinoma foci was assessed using two methods: LD and AD.

Table 1. Clinical and pathologic characteristics of patients with unifocal and multiple breast carcinomas (Tîrgu Mureş, 2007-2009)

Characteristics	M		UF		P
	n	%	n	%	
Patients	91	21.77	327	78.23	
Age, years					
<50	24	26.37	52	15.9	
≥50	67	73.62	275	84.09	0.03
Mean	58.03		60.69		0.05
Histological type					
NST	63	69.23	229	70.03	0.897
Lobular	12	13.18	26	7.95	0.147
Others	16	17.58	72	22.01	0.387
Histological grade					
I	3	3.29	27	8.25	0.165
II	46	50.54	192	58.71	0.188
III	42	46.15	108	33.02	0.025
LN positivity	67	73.62	192	58.71	0.01

Abbreviations: M, multiple carcinoma; UF, unifocal carcinoma; LN, lymph node.

The aim of this study was to determine the optimal method for tumor size assessment in multiple breast carcinomas, in correlation with the development of axillary lymph node metastases.

Material and methods

Patient selection

We have carried out a retrospective study comprising 498 consecutive cases diagnosed with breast carcinoma by a multidisciplinary team between 2007 and 2009 in Targu Mures, Romania. These cases originated in a population that had not been previously screened for breast carcinoma because a national screening program concerning this disease is not available in Romania. Multiple invasive breast carcinoma was defined as at least 2 radiological and macroscopically well demarcated and histologically confirmed invasive tumor foci separated from each other by "uninvolved" breast tissue, containing normal tissue, benign lesions and/or in situ carcinoma, regardless of the distance between the foci and topographic localization (same quadrant/different quadrants) [7].

Only the patients who underwent mastectomy and full axillary lymph node dissection were included. No cases with lumpectomy have been accepted in this study and in none of the cases was sentinel lymph node biopsy performed. Cases that benefitted from neo-adjuvant therapy, those that displayed only in situ multiple carcinomas or cases with recurrent breast cancers who were diagnosed initially before the study period were excluded from the study. In each case the diameter of each tumor focus, the type and grade of the tumor foci, the presence or absence of metastases in axillary lymph nodes were reassesses by two pathologists (SS, MB) on 4 μ thick microscopic sections stained with hematoxylin-eosin, and the mismatches were consensually recorded. The histological type of the tumor foci was assessed according to WHO 2012 classification [1], and tumor grade was established using the Elston-Ellis grading system [14].

Tumor size assessment

Each surgically obtained breast tissue specimen was processed according to a standard protocol that is used in the Pathology Department since 2007 (MD Anderson protocol [15]. The multiple foci were previously identified either by imaging and/or by gross examination in total mastectomy and axillary lymph node

Table 2. Mean diameter and tumor distribution classification according to the two methods of assessing tumor size

	M (n=91)		UF (n=327)	P
Size and classification	LD	AD		
Estimated mean diameter (mm)	38.48	45.51	31.47	0.0026
T1 (1-20 mm) (%)	23.07	5.49	33.02	0.09
T2 (21-50 mm) (%)	54.94	47.25	54.43	
T3 (>50 mm) (%)	21.97	47.25	12.53	

Abbreviations: M, multiple carcinoma; UF, unifocal carcinoma; LD, largest diameter method; AD, aggregated diameter method.

dissection specimens. We correlated the diameters of the lesions that were identified preoperatively by radiologic examination with the diameters of the lesions that were identified during sampling and/or microscopic examination (obtained from pathology reports and by re-assessing the diameters). In foci over 20 mm in diameter, the macroscopically assessed diameter was taken into account, in correlation with the diameter observed on imaging examination and noted in the pathology report; in foci under 20 mm in diameter, focus size was reassessed on the microscopy slides.

In this study the size of tumor foci in multiple breast carcinomas was assessed using two methods:

(1) Largest diameter of the largest tumor focus (LD).

(2) Aggregated diameter of all tumor foci appearing in one specimen (AD) = the sum of the maximum diameters of all individual tumor foci (**Figure 1**).

For statistical purposes, in unifocal carcinomas we used the largest diameter assessed macroscopically in tumors larger than 20 mm and the microscopically measured diameter in tumors smaller than 20 mm.

Data collection and analysis

Each clinical, radiological file and pathology report was analyzed and clinical data regarding age, histological type, grade of the tumors and lymph node status were included in spreadsheets. Statistical analysis was carried out using the GraphPad InStat software (GraphPad Software, Inc., San Diego CA, USA). We used Student's t-test to compare mean ages and mean dimensions of tumor foci between multiple and unifocal carcinomas; Fisher's exact test was used in order to compare the presence of lymph node metastases between the unifocal and the multiple carcinomas, and the chi-squared test was used in order to determine the association between the histological type and grade of the tumors and the proportion of involved axillary lymph nodes, according to T status. A p-value of <0.05 was considered statistically significant. The Ethical Committee of the University of Medicine and Pharmacy of Targu Mures approved this study, and all the procedures were performed in compliance with institutional guidelines and the relevant law.

Results

418 cases remained in the study after applying the selection criteria, out of which 91 (21.77%) displayed multiple invasive tumor foci: 54 (59.34%) cases displayed only 2 tumor foci, and 37 (40.64%) had ≥3 invasive tumor foci. We did not find a statistically significant difference between the mean age of the patients with unifocal carcinomas and that of the patients with multiple carcinomas (60.69 years vs. 58.03 years, P=0.052), but we discovered an increased incidence of multiple carcinomas in younger patients (26.37% of the multiple carcinomas and 15.9% of the unifocal carcinomas were diagnosed in patients under 50 years of age) (P=0.03). The most frequent histological type was the same both in multiple and in unifocal carcinomas: infiltrative breast carcinoma NST (no special type) (69.23% of the multiple carcinomas and 70.03% of the unifocal carcinomas, P=0.897). The ratio of lobular carcinoma was higher in the multiple carcinoma group (13.18% lobular carcinoma in multiple carcinomas vs. 7.95% lobular carcinomas in unifocal carcinomas), but the difference was not statistically significant (P=0.147). Multifocality was associated with a higher histological grade, as 42 (46.15%) of the 91 multiple carcinomas displayed a histological malignancy grade of III (score 8-9), compared to 108 of the 327 unifocal carcinomas (33.02%) (P=0.025).

Multiple carcinomas determined axillary lymph node metastases in 73.62% of the cases,

Table 3. The number and ratio of carcinomas with positive lymph nodes according to estimated size in multiple carcinomas versus unifocal carcinomas

	UF				M (LD)			M (AD)			
Size	N	n	%	P	N	n	%	N	n	%	P
pT1 (1-20 mm)	108	44	40.74	0.094	21	13	61.9	5	2	40%	1
pT2 (21-50 mm)	178	130	73.03	0.859	50	36	72%	43	29	67.4%	0.455
pT3 (>50 mm)	41	37	90.24	1	20	18	90%	43	36	83.72%	0.521

Abbreviations: M, multiple carcinoma; UF, unifocal carcinoma; LD, largest diameter method; AD, aggregated diameter method.

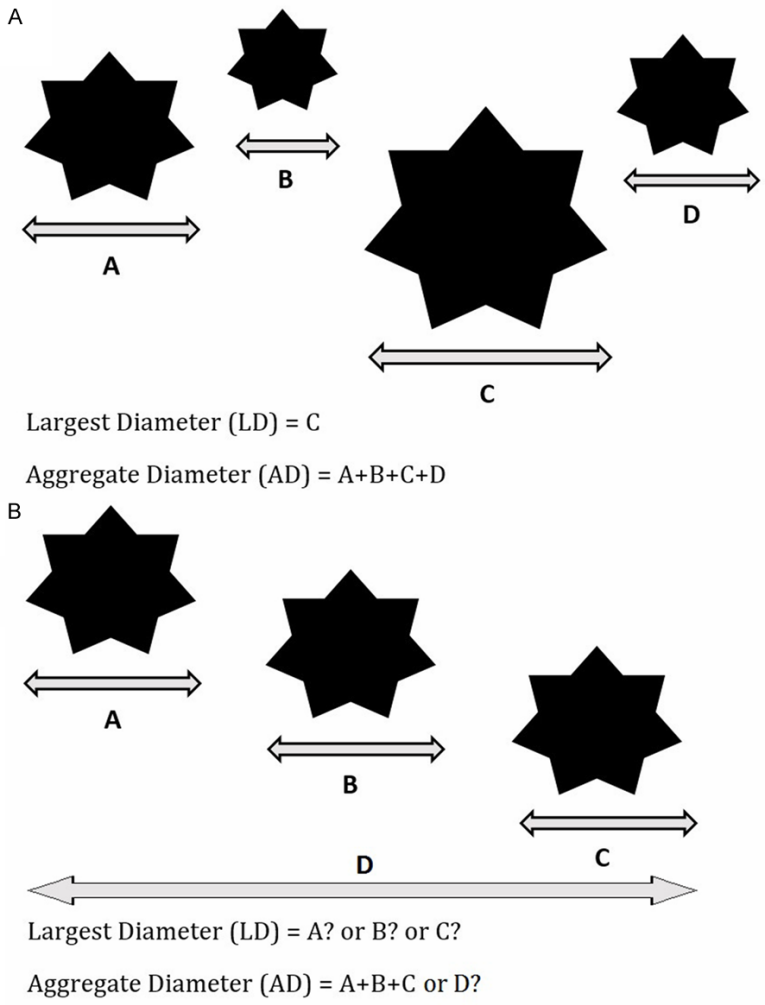

Figure 2. In cases of multiple tumor foci with different size (A) the largest diameter of the largest tumor focus is taken into account, but in cases with multiple foci of equal dimensions (B) this criterion is not applicable.

whereas unifocal carcinomas only in 58.71% of the cases (P=0.01), with the odds ratio OR=1.963 at a confidence interval 95% CI=1.172-3.288 (**Table 1**).

The two methods of assessing tumor size in multiple carcinomas (largest diameter and aggregated diameter) revealed statistically significant differences between the mean values obtained, compared to unifocal carcinomas. These data are summed up in **Table 2**. The mean size of multiple carcinomas was 38.48 mm when using the LD method and 45.51 mm when calculating according to the AD method. Percentage distribution of tumor classification differs according to which one of the two methods was used (**Table 2**). When the recommended approach in assessing multiple tumor size (largest diameter of the largest focus) was used in order to establish tumor staging, 23.07% of the multiple carcinomas were staged as pT1, 54.94% as pT2 and 21.97% as pT3, compared to unifocal carcinomas, in which 33.02% were staged as pT1, 54.43% as pT2 and 12.53% as pT3. When using the aggregated diameter method, only 5.49% of the multiple carcinomas remained categorized as pT1, 47.25% became pT2 and 47.25% became pT3.

23 cases were upstaged when using the aggregated diameter method (16 pT1 cases became pT2 and 7 pT2 cases became pT3).

The frequency of axillary lymph node metastases stratified according to the T staging category in multiple carcinomas (evaluated by using the two size assessment methods) versus uni-

Table 4. Studies analyzing alternative methods of measuring tumor size in multiple breast carcinomas (MBC)

Authors	Findings/Conclusions
Fish et al. [27]	MBC: ↑ risk of ALNM Aggregate area/volume: predictive factors for survival
Andea et al. [9]	LD: ↑ incidence of ALNM AD: MBC and UBC equivalent in terms of ALNM
Andea et al. [26]	Aggregate area/volume of MBC: ↑ proportion of ALNM compared to UBC having the same area/volume
Coombs et al. [11]	LD in MBC: some patients: under staged MF: ↑ tumor volume: significant independent predictive factors for ALNM
Rezo et al. [22]	AD: correlated with ↑ ALNM not correlated with survival
Tressera et al. [18]	LD correlated with ALNM AD: overestimation of tumor size
O'Daly et al. [13]	AD versus LD: no increase of positivity of ALNM
Cabioglu et al. [10]	LD: ↑ proportion of MBC determine ALNM AD: the percentages became similar (compared to UBC) Overall-survival and disease-free survival: similar
Boyages et al. [5]	LD: SS differences in 10-year survival (compared to UBC) AD: no SS differences
Tiong et al. [28]	MBC: ↑ rate of ALNM No SS differences in mortality and relapse rates
Moutaffof et al. [12]	MBC: ↑ rate of ALNM LD: the best method to assess tumor size
Rezo et al. [17]	LD: the best method to assess tumor size
Hilton et al. [29]	Presence of MF/MC and other tumor size measurement (summation/area/volume)- not associated with BCFI (breast-cancer-free-interval)

Abbreviations: MBC, multiple breast carcinoma; UBC, unifocal breast carcinoma; LD, largest diameter; AD, aggregate diameter; ALNM, axillary lymph node metastasis; SS, statistically significant; BCFI, breast-cancer-free interval.

focal carcinomas is shown in **Table 3**. There was no statistically significant difference between axillary lymph node metastasis ratios when using one method versus the other (**Table 3**).

Discussion

One of the most important prognostic factors in breast carcinoma is the axillary lymph node status, i.e. the presence or absence of axillary metastases [1, 2]. Disease-free survival and overall survival decrease proportionally with the increase of the number of positive axillary lymph nodes [1]. Most studies reveal an increased rate of metastases in multiple carcinomas when compared to unifocal carcinomas [8-12, 16-19].

A higher rate of axillary lymph node metastases was noted in multiple carcinomas, compared to unifocal carcinomas in this study (73.62% vs. 58.71%) (P=0.01), these values being similar to those published in other studies [9-11, 13, 18, 20]. Theoretically, this difference may be determined either by the larger tumor "volume" in multiple carcinomas, or by the intrinsic, more aggressive biological features of these tumors.

Regarding the intrinsic parameters evaluated in this study, we did not find statistically significant differences between the histological types of the tumors, as the most frequent type was NST (69.23% of the multiple carcinomas and 70.03% of the unifocal carcinomas), with a higher, but not statistically significant proportion of the lobular carcinomas in the multiple carcinoma group (13.18% of the multiple carcinomas vs. 7.95% of the unifocal carcinomas). After analyzing the histological grade, a higher proportion of the multifocal carcinomas (46.15%) were graded as G3 compared to unifocal carcinomas (33.02%). This difference was statistically significant (P=0.025), suggesting that G3 multiple carcinomas may have a higher aggressiveness. These results were similar to

those reported by other studies that reveal a higher proportion of high grade multiple carcinomas compared to unifocal carcinomas, which may be indicative of more aggressive biological features pertaining to multiple tumors [17, 21].

The risk of lymph node involvement and metastatic dissemination increases in parallel with the increase in tumor size [2-4]. The TNM 2012, AJCC 2010 and ESMO 2013 classification and staging systems recommend using the largest diameter of the largest tumor focus when staging multiple carcinomas (**Figure 2A**) [1, 4, 23]. This recommendation applies only to tumors that contain multiple, separated macroscopically visible foci, but not to cases in which a macroscopic focus is associated with multiple, separated microscopic foci [4]. Several recent guidelines for reporting breast carcinomas recommend that in multiple carcinomas satellite nodules should not be taken into account when establishing the size of the tumor (without defining the aforementioned nodules) but, in cases with multiple dispersed tumor foci of relatively equal dimensions (without specifying these dimensions or a cut-off value), the T staging category should be assessed as an "estimated" diameter and the whole "area" of tumor involved breast tissue should be reported, including normal tissue found between foci (**Figure 2B**) [24, 25]. These recommendations reveal, on one hand, a total lack of standardization concerning measuring methods and, on the other, a confusion regarding the definition and staging of multiple carcinomas.

Previous studies have attempted to assess whether there is a connection between the sum of the diameters of multiple carcinomas (aggregated diameter of multiple tumor foci) and the largest diameter of the largest tumor focus, in correlation with the presence of metastases in the axillary lymph nodes, compared to unifocal carcinomas [5, 9, 10, 12, 13, 17, 18, 22, 26-28]. Some of these studies (but not all of them) have shown that the aggregated diameter is a better predictor of axillary metastases than the largest diameter, and have questioned the accuracy of the available guidelines for staging multiple carcinomas [11, 16, 26] (**Table 4**).

Studies stating that axillary lymph node positivity and survival in multiple carcinomas is strictly dependent on the largest tumor focus should assume that additional tumor foci do not contribute to tumor "volume" and also do not have metastatic potential. In order for this hypothesis to be valid, either smaller tumor foci do not behave as invasive tumors, or they do not "release" tumor cells into the lymphatic system [5]. Conversely, some authors showed in their studies that, sometimes, multiple breast tumors have equal sizes, without having an "index" tumor (the largest diameter focus). In these cases, it is difficult to establish which of the tumor foci should be used for staging [30]. Several studies have pointed out that multiple tumor foci can be heterogeneous, as they could be morphologically different [6, 9, 12, 31-33], and smaller additional tumor focicould sometimes display a higher morphological aggressiveness (a more aggressive histological type or a higher histological grade) than the index tumor. All these elements need to be however carefully considered when assessing the best method to evaluate the dimensions of a multiple breast carcinoma.

In our study, patients with multiple carcinoma had a higher number of axillary lymph node metastases compared to patients with similarly sized unifocal carcinoma (61.9% of the pT1 multiple carcinomas determined axillary metastases vs. 40.74% of the pT1 unifocal carcinomas) (P=0.09); this increased metastatic potential needs to be known and correlated with the fact that multiple carcinomas have a different biology (intrinsic aggressiveness), taking also into account the fact that they were more likely to display a G3 histological grade than unifocal carcinomas.

When analyzing the frequency of axillary lymph node involvement in multiple carcinomas compared to unifocal carcinomas, stratified according to the T category, no statistically significant difference was noted between the rate of axillary metastases that resulted after using the largest diameter method and the one resulted after using the aggregate tumor diameter.

Conclusion

Multiple breast carcinomas could display a different biology, with a higher potential of determining axillary lymph node metastases. By using the aggregate diameter method, some of the patients enrolled in this study were

upstaged to a higher T stage, but this method of assessing tumor diameter does not correlate with a higher rate of axillary metastases and should not therefore be used in the TNM staging of multiple breast carcinomas. Nevertheless, the identification of a morphological and biological heterogeneity of multiple tumor foci in recent studies shows the necessity of carrying out more studies of the type we attempted in order to assess the optimal method of tumor diameter reporting in large patient series and over long periods of time.

Disclosure of conflict of interest

None.

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