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Tumor size and survival in multicentric and multifocal breast cancer

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ABSTRACT

Purpose: Current AJCC/UICC staging of early breast cancer defines tumor stage using the largest focus, adding the suffix "(m)" to indicate multiplicity. This method may underestimate the total tumor burden in multifocal and multicentric breast cancer (MMBC). This study examines other measures of tumor size in MMBC to determine which provides the best fit in a multivariate model for survival outcomes.
Patients and methods: This prospective cohort study used data from the Australian Capital Territory and New South Wales Breast Cancer Treatment Group database to identify 812 women with ipsilateral invasive breast cancer; 141 of these women had MMBC. The pathology slides of all women with MMBC were reviewed and all foci of invasive breast cancer were re-measured. The measures of interest were the diameter of the largest deposit, the aggregate diameter and the aggregate volume. These measures of tumor size were included with other clinicopathological features of MMBC in a multivariate analysis to assess their relationship with progression-free survival (PFS) and overall survival (OS).
Results: Tumor size was associated with PFS and OS in MMBC using any of the three measures; however, the diameter of the largest deposit provided the best fit in the multivariate model for OS.
Conclusion: Tumor size is an important prognostic factor for MMBC, and the diameter of the largest deposit provides a better fit in a multivariate model for OS than aggregate diameter and aggregate volume. Therefore, tumor size in MMBC should continue to be measured using the diameter of the largest deposit.

Introduction

Multifocal and multicentric breast cancer (MMBC) is common, with a reported incidence of 9–75%.[1] Incidence varies according to the extent of breast tissue sampling, but this wide range of reported incidence also reflects the lack of a standard definition of MMBC. Definitions of multifocality and multicentricity vary, and some definitions of MMBC encompass intraductal cancer, lobular neoplasia and invasive carcinoma.[2] The distinction between multifocal and multicentric breast cancer is made topographically with the assumption that multifocal breast cancer arises within the same duct collecting system (tumors are in the same quadrant or less than 5 cm apart), whereas multicentric breast cancer arise in different duct collecting systems (tumors are in different quadrants or more than 5 cm apart). The underlying assumption in these definitions is that multifocal breast cancers are monoclonal and multicentric breast cancers are not. It has been shown that most synchronous ipsilateral multiple breast cancers are monoclonal and therefore in this paper the two entities are classified together.[3–7] The current American Joint Committee on Cancer (AJCC) and International Union for Cancer Control (UICC) staging system classifies multiple simultaneous primary tumors in one breast by recording the T-stage of the largest tumor and indicating multiplicity using the suffix (m). Tumor size is a well-recognized prognostic factor in breast cancer, but multiplicity is not included as a prognostic factor in the AJCC/UICC system.[8] By not including all foci of MMBC, estimates of the risk of recurrence and death may be understated, which could affect recommendations for adjuvant treatment.

The current staging system implies that each tumor deposit arises independently and therefore the patient's prognosis is estimated based on the size of the largest deposit. This assumption may

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be incorrect, because MMBC is associated with a higher risk of pathological axillary nodal involvement[9–13] and may be associated with a higher risk of local relapse[14–16] and a poorer prognosis.[11,17–19] The increased risk of nodal involvement may be due simply to the current staging system under-estimating the number of tumor clonogens, or it may be that MMBC is a biologically more aggressive type of cancer. In either case, accurate estimations of prognosis are important for clinical decision making, such as the decision whether to use more aggressive adjuvant therapies.

A number of studies have evaluated different measures of tumor size in MMBC, including whether these methods help to predict nodal involvement.[11–13] A consistent finding of these studies is that women with MMBC have a higher risk of nodal involvement than women with unifocal cancer when the current method of staging is used, and this higher risk of nodal involvement is also found when tumor size is measured using aggregate volume or aggregate surface area.[20] When aggregate diameter is used, however, no significant difference is found in risk of nodal involvement for women with MMBC compared to women with unifocal cancer.[12,13,20] These studies used nodal status as a surrogate measure for survival outcomes, but it is not known whether this is a valid assumption.

This study evaluates measures of tumor size to determine which correlates best with progression-free survival (PFS) and overall survival (OS) in a multivariate model.

Patients and methods

Patient selection

This prospective cohort study used data from the Australian Capital Territory and South East New South Wales Breast Cancer Treatment Group (ACT & SE NSW BCTG) database to identify women with ipsilateral invasive breast cancer from July 1997 to June 2004. Patients in this study gave informed consent for details of their demographic indicators, disease pathology and treatment to be recorded in a database and for their disease status to be followed up annually. Patients were included in the study if the pathology was reported at ACT Pathology, the largest provider of breast pathology services in the region. Patients were excluded if they had neo-adjuvant treatment, or were known to have had a previous breast cancer or bilateral cancer. Pathology reports were reviewed to obtain tumor size in the unifocal group, and nodal status and other pathological parameters in all women.

In this study, MMBC was defined as cancer with multiple invasive foci (of any size) separated by at least 4 mm of normal breast tissue. This definition was based on the thickness of standard dissection blocks. If the foci were closer than 4 mm, or if there were two abutting tumors of different histological sub-types, the tumor was classified as a unifocal cancer. Multifocal and multicentric breast cancers are grouped together in this study under the acronym “MMBC”. All women with multifocal cancer were included in the survival analyses; however, if a woman had more than 10 foci or if the size of the foci could not be re-measured, she was not included in analysis of aggregate tumor size measurements.

Tumor size measurements

The specimens of all women on this study were handled according to a standard protocol. Lumpectomy specimens were cut in 4 mm slices, as were the areas of macroscopic tumor on mastectomy specimens. In mastectomy specimens, 3–4 representative sections were examined from the index tumor. Following current recommended practices, the remaining breast was then examined macroscopically for tumor deposits, suspicious areas were sectioned and then random quadrant biopsy was conducted.[1] Blocks were also obtained from around the lumpectomy cavity if a completion mastectomy was performed.

The original slides for all MMBC cases were obtained and diameters of all the foci were re-measured and recorded. If the diameter of the tumor was greater than 20 mm, the macroscopic maximal dimension was estimated using the slice dimensions described in the pathology report. Tumors with a diameter of 20 mm or smaller were measured using a Vernier scale.

The MMBC tumor foci were recorded using three measures:

(1) The diameter of the largest deposit (LD)
(2) The aggregate diameter of all deposits (AD) — the sum of all the largest diameters of the individual foci
(3) The aggregate volume (AV) — the sum of the volumes of individual foci, calculated using the largest dimension of each focus and assuming that all the foci were spherical (that is, the volume for each focus is $4/3\pi r^3$ where r is the radius of the foci. An equivalent diameter was calculated for each AV measurement using $d = 2r$).

The three measurements of tumor size were entered into a multivariate model to assess which method best correlated with survival endpoints.

For the unifocal cancers, the measure of size was the reported macroscopic measurement for tumors with a diameter greater than 20 mm, and the reported microscopic measurement for tumors with a diameter of less than or equal to 20 mm.

Data collection

All pathology reports were reviewed to obtain nodal status, tumor histological type and grade, hormone receptor status, and whether there was associated lymphovascular space invasion and/or pre-invasive disease. The presence of Her-2/neu over-expression on immunohistochemistry was routinely recorded for all tumors after January 2003. For multifocal tumors in which the foci differed in histological or immunohistochemical features, the following rules were adopted: if there were differences in histological subtype, the type of the index tumor was used, except if the index tumor was a low risk sub-type in which case the higher risk subtype was recorded; if there were differences in the grade of the foci, the highest grade was recorded; if there were differences in the receptor status between foci, the tumor was recorded as being receptor-positive; if the Her-2/neu status differed in immunohistochemical score, the higher score was used.

Survival and relapse data were obtained from the ACT & SE NSW BCTG database on 23 March 2009.

Statistical analysis

Statistical analyses were conducted using SPSS statistical software (Version 18.00). Univariate analysis was conducted to assess differences in patient, tumor and treatment factors between women with unifocal and multifocal disease. Univariate and multivariate Cox regression analyses for PFS and OS outcomes were conducted for all women. The three measures of tumor size were compared in the multivariate models using the Wald test to determine which measure best correlated PFS and OS. A forward likelihood method was used to enter variables into the model. The variables entered were age, nodal status, grade, histology, the presence of lymphovascular space invasion, the presence of pre-invasive disease, estrogen and progesterone status, focality, and whether adjuvant treatments were given (chemotherapy, post-mastectomy radiotherapy and/or endocrine

therapy). A further subgroup analysis of the MMBC group alone was conducted using the same statistical methods.

Results

An initial review of the database found 861 women who fulfilled the inclusion criteria; however, on review of the pathology reports, 11 women were found to have pre-invasive disease only, one woman had had pre-operative chemotherapy and 37 women had prior breast cancer. When these women were excluded, the study included 812 women, 141 women with MMBC and 671 with unifocal breast cancer.

These figures include 18 women who were classified as having MMBC on the database but who were re-classified as having unifocal disease for this study: 13 women had foci less than 4 mm apart and 5 women had collision tumors (tumors of different histological sub-type abutting one another). A further 31 women were classified as having unifocal disease on the database but were found to have MMBC on the pathology report, which was subsequently confirmed on histological review. Nodal status was unknown in 55 women (including 7 women with MMBC). Of the women with MMBC, 6 women had more than 10 foci or the size of the foci could not be re-measured due to insufficient pathological material; aggregate tumor sizes could not be measured for these women.

Following pathological review of the MMBC cases, there were 29 cases in which the number of foci changed or the size of the tumors recorded varied by greater than 4 mm when compared to the pathology report. In 14 cases, the reviewing pathologist found that the foci were larger by more than 4 mm and in 8 cases the tumors were smaller by more than 4 mm. These changes resulted in three breast cancers being down-staged and three being up-staged across the T1 to T2 categories, and two breast cancers being down-staged from T3 to T2. In summary, eight women with MMBC had a change in AJCC/UICC T-category as a result of the pathology review.

The patient demographics and tumor characteristics are shown in Table 1. Univariate analysis found that compared to women with unifocal breast cancer, women with multifocal breast cancer were more likely to be less than 50 years of age, have nodal involvement, and to have associated lymphovascular space invasion (LVSI) and pre-invasive disease. There was no association between MMBC and histological sub-type, grade, or receptor status.

Table 1
Patient demographics and tumor characteristics.

Characteristic	MMBC tumors *N* (%)	Unifocal tumors *N* (%)	*P* value
All women	141(17.4)	671 (82.6)	
Age in years			
<50	51 (36.2)	162 (24.1)	0.003
Mean	55.2	57.6	
Nodal status			0.001
Positive	70 (49.6)	226 (33.7)	
Unknown	7 (5.0)	48 (7.2)	
Mean no. positive[a]	2.2	1.5	
Mean no. removed	14.6	12.0	
Tumor grade			0.061
Grade 1	35 (24.8)	217 (32.3)	
Grade 2	71 (50.4)	266 (39.6)	
Grade 3	35 (24.8)	184 (27.4)	
Unknown	0	4 (0.6)	
Histology			0.220
Ductal (677)	114 (80.9)	563 (83.9)	
Lobular (62)	17 (12.1)	45 (6.7)	
Mixed ductal(15)	3 (2.1)	12 (1.8)	
Low risk (51)	6 (4.3)	45 (6.7)	
Other (7)	1 (0.7)	6 (0.1)	
Hormone receptor status			0.258
ER[b] positive	121 (85.8)	541 (80.6)	
Unknown ER	1 (0.7)	15 (2.2)	
PR[c] positive	103 (73.0)	415 (61.8)	
Unknown PR	2 (1.4)	32 (4.8)	
LVSI[d]			0.005
Present	49 (34.8)	157 (23.4)	
Absent	86 (61.0)	485 (72.3)	
Equivocal	1 (0.7)	19 (2.8)	
No comment	5 (3.5)	10 (1.5)	
Associated pre-malignant disease			<0.001
Absent	9 (6.4)	165 (24.6)	
DCIS[e]	103 (73.0)	443 (66.0)	
LCIS[f]	16 (11.3)	48 (7.2)	
No comment	13 (9.2)	15 (2.2)	
Adjuvant therapy			
Chemotherapy	94 (66.7)	287 (42.8)	<0.001
Hormonal therapy	113 (74.5)	113 (80.1)	0.158
PMRT[g]	57 (49.1)	99 (35.7)	0.013
Tumor size	23.5 mm	20.5 mm	0.006
(Mean)	(21.1–22.5)	(19.4–21.6)	
(Range)	(3–120 mm)	(0.3–140 mm)	

[a] Mean number of positive nodes removed from women who had nodal surgery ($n = 757$).
[b] ER: Estrogen receptor positivity of those with known status ($n = 796$).
[c] PR: Progesterone receptor positivity of those with known status ($n = 778$).
[d] LVSI: Lymphovascular invasion.
[e] DCIS: Ductal carcinoma in situ.
[f] LCIS: Lobular carcinoma in situ.
[g] PMRT :Post-mastectomy radiotherapy given to 393 women who had a mastectomy.

Tumor size and progression-free survival

At the end of the study period, 672 women were alive and free from disease, with a median follow-up of 60 months. Nodal involvement, increasing tumor size, high tumor grade, negative estrogen receptor status and lack of adjuvant chemotherapy were all associated with reduced disease-free survival (see Table 2). When tumor size was assessed as a continuous variable, increasing size was associated with disease progression and death for all measures of tumor size. AV was the measure that best fit the multivariate model for all the patients on the study, although this was only marginally better than using LD. The Wald tests in the multivariate model when comparing the three measures were: AV = 17.56, LD = 17.58 and AD = 16.41. Multifocality was not found to be associated with reduced PFS.

Tumor size and overall survival

At the end of the study period, 750 women were alive, with a median follow-up of 60 months. Nodal involvement, estrogen receptor negativity, increasing tumor size and lack of adjuvant chemotherapy were all associated with a reduced likelihood of survival (see Table 3). Increasing tumor size was associated with a reduced likelihood of survival for all measures of tumor size; however, LD was the measure that provided the best fit in the multivariate model for OS in the entire cohort. The Wald test scores in the multivariate model when comparing the three measures were: LD = 29.22, AV = 28.06, and AD = 23.58. MMBC was also not found to be associated with a reduced likelihood of survival.

Tumor size in the MMBC patients

When the unifocal cases are excluded from the model, only estrogen receptor negativity and increasing tumor size were associated with reduced PFS and these two factors and lack of adjuvant chemotherapy were associated with poorer OS (see Tables 4 and 5).

Table 2
Multivariate analysis of disease progression for all patients using AV measurement for tumor size.

Prognostic factor $N = 812$	Hazard ratio	95% confidence interval	P value
Nodal status			<0.001
Negative	1		
Positive	3.11	1.85–5.24	<0.001
Unknown	0.73	0.17–3.09	0.67
Grade			0.02
Grade 1	Referent		
Grade 2	2.68	1.23–5.85	0.01
Grade 3	3.29	1.42–7.64	0.06
Estrogen receptor			0.04
Negative	1		
Positive	0.41	0.25–0.70	0.01
Unknown	0.44	0.10–1.87	0.25
Adjuvant chemotherapy			0.013
Yes	Referent		
No	1.96	1.17–3.29	0.01
Offered, not received	0.447	0.06–3.25	0.43
Tumor size (Aggregate volume)	1.38	1.19–1.61	<0.001

Variables that did not enter into model ($p > 0.05$): Histological sub-type, pre-invasive disease, age, lymphovascular space invasion, progesterone receptor status, focality, adjuvant endocrine therapy, post-mastectomy radiotherapy.

Measurement of the largest tumor diameter provided the best correlation with PFS and OS. The Wald test scores in the multivariate model when comparing the three measures were: LD = 8.73, AV = 8.71 and AD = 4.41 for progression and LD = 19.57, AV = 14.02 and AD = 15.74 for OS.

Discussion

This study confirms that tumor size is an important prognostic factor in early breast cancer. It also demonstrates that for MMBC the diameter of the largest deposit provides the least variance in predicting survival compared to aggregate measures of tumor size. Although aggregate volume appeared to relate marginally better to PFS than the diameter of the largest deposit, the difference was minimal. Given the additional work required to obtain this measurement, it is unlikely to be practical or warranted in routine clinical practice. Therefore, tumor size should continue to be measured using the current AJCC/UICC method for MMBC.

Table 3
Multivariate analysis of overall survival for all patients using LD measurement for tumor size.

Prognostic factor $N = 812$	Hazard ratio	95% confidence interval	P value
Nodal status			<0.001
Negative	1		
Positive	4.26	2.56–7.07	<0.001
Unknown	2.18	0.99–4.79	0.052
Estrogen receptor			<0.001
Negative	1		
Positive	0.36	0.23–0.57	<0.001
Unknown	0.16	0.02–1.22	0.08
Adjuvant chemotherapy			<0.001
Yes	1		
No	3.40	2.14–5.39	<0.001
Offered but not received	–	–	0.97
Tumor size (largest diameter)	1.47	1.28–1.69	<0.001

Variables that did not enter into model ($p > 0.05$): Histological sub-type, pre-invasive disease, age, grade, lymphovascular space invasion, progesterone receptor status, focality, adjuvant endocrine therapy, post-mastectomy radiotherapy.

Table 4
Disease progression multivariate analysis for MMBC group only using LD measurement for tumor size.

Prognostic factor $N = 141$	Hazard ratio	95% confidence interval	P value
Estrogen receptor			0.01
Negative	1		
Positive	0.16	0.05–0.55	0.003
Unknown	–	–	0.99
Tumor size (LD)	1.74	1.20–2.51	0.003

Variables that did not enter into model ($p > 0.05$): Nodal status, histological sub-type, pre-invasive disease, age, grade, lymphovascular space invasion, progesterone receptor status, focality, adjuvant endocrine therapy, adjuvant chemotherapy, post-mastectomy radiotherapy.

Multifocality was not shown to be an independent prognostic factor for PFS or OS in this study. Patients with MMBC were more likely to be younger, have nodal involvement, a larger tumor size and have lymphovascular space invasion — all of which are well-recognized independent prognostic factors.[21] In this study, women with MMBC were also more likely to have received adjuvant chemotherapy and adjuvant post-mastectomy radiotherapy, which may have confounded these results.

A number of studies have consistently shown that multifocality is associated with a higher risk of nodal involvement than unifocal disease.[9–13,22] This increased risk may be partly explained by the fact the non-dominant foci are not included in the estimate of tumor size and hence tumor burden is underestimated. There have been a number of attempts to account for these additional foci by measuring an aggregate size of the tumors. Andea et al. found an increased risk of nodal involvement in MMBC compared to unifocal disease when the diameter of the largest deposit was used to record tumor size. However, when an aggregate diameter was used, unifocal breast cancer and MMBC showed a similar frequency of nodal involvement.[12] In a later study, Andea et al. assessed aggregated volumes and surface areas and found that there was a higher frequency of nodal involvement for MMBC tumors than for unifocal tumors of similar surface area or volume. They concluded that MMBC had a greater propensity to dissemination than unifocal cancers, even when the entire tumor size is accounted for,[20] suggesting that MMBC is more biologically aggressive than unifocal disease.

Coombs et al. also found that using an aggregate diameter when measuring MMBC, rather than the size of the largest diameter, removed the excess node positivity of MMBC when compared to unifocal cancers.[13] Our group has also previously compared the measurement of aggregate diameter with the diameter of the largest deposit in MMBC and found the aggregate measurement more closely approximated the relationship to nodal status seen in

Table 5
Overall survival multivariate analysis for MMBC patients only using LD for measurement of tumor size.

Prognostic factor $N = 141$	Hazard ratio	95% Confidence interval	P value
Estrogen receptor			0.002
Negative	1		
Positive	0.17	0.06–0.52	0.02
Unknown	–	–	0.99
Adjuvant chemotherapy			0.01
Yes	1		
No	4.81	1.69–13.75	0.003
Offered but not received	–	–	0.99
Tumor size (LD)	1.96	1.46–2.64	<0.001

Variables that did not enter into model ($p > 0.05$): Nodal status, histological sub-type, pre-invasive disease, age, grade, lymphovascular space invasion, progesterone receptor status, focality, adjuvant endocrine therapy, and post-mastectomy radiotherapy.

unifocal cancers.[23] Two smaller studies, however, did not confirm these findings.[24,25]

In the Andea and Coombs studies, nodal involvement is used as a surrogate for survival.[12,13,20] Multivariate analysis conducted in this study found that although women with MMBC were more likely to have nodal involvement, this did not translate into a reduced likelihood of survival. Whether MMBC is an adverse prognostic factor in breast cancer remains controversial. In our study, MMBC was associated with a number of known adverse prognostic factors and so it was not surprising that MMBC was not a factor in the multivariate model.

The largest study to assess multifocality as a prognostic factor was reported by Joergensen et al.[22] using data from the Danish Co-operative Breast Cancer Group. Multifocality was defined as more than one focus of invasive carcinoma separated by benign tissue. Tumor size in multifocal cancer, for the purpose of determining the treatment protocol, was defined in a standard way, so it is assumed that women with multifocal cancers on protocol were treated no differently after surgery than those with unifocal breast cancers. There were 7024 women included in the study including 945 with multifocal breast cancer. In the multivariate Cox analysis, multifocality was a significant prognostic factor for PFS (HR: 1.16, CI: 1.03–1.31) but not for OS (HR: 1.05, CI: 0.93–1.20). There was a strong correlation between multifocality and nodal involvement.

Fish et al.[11] assessed survival endpoints, examining three alternate measures of tumor size in multifocal breast cancer: summing the largest diameters of each of the foci, calculating an aggregate surface area measurement, and calculating an aggregate volume using ellipsoid and sphere formulas. Tumor size was included in a Cox regression using each of the four measures, together with other prognostic factors to investigate the effects on time to death from breast cancer. Tumor size was associated with breast cancer survival when all patients (unifocal and multifocal cancers) were considered, however, size was only associated with breast cancer survival in the multifocal group, when tumor volume or surface area measurements were included in the model. These findings are in contrast to those found in the current study. Tumor size when measured taking the diameter of the largest focus or an aggregate diameter of the foci, was not included in the final step-wise model for breast cancer survival.

There are some limitations to this study and practical issues that warrant discussion. Only the histopathology of MMBC cases was directly reviewed by a pathologist to measure the tumor size —the unifocal tumor sizes were based on the pathology report. The histological review of the MMBC cases meant that tumors were re-classified as unifocal or multifocal in 49 cases, and in 29 cases of multifocal disease there was a change in the number of foci recorded or there was more than a 4 mm size discrepancy in at least one of the foci. In part, the reason for the discrepancy was due to the definition of MMBC used in this study requiring that the foci are at least 4 mm from each other ($n = 7$) and in many cases, the tumor size was imprecisely recorded by the original pathologist ($n = 17$). The other discrepancies were due to differences judging tumor orientation in re-excision specimens or transcription errors. In all cases in which a difference of 4 mm in size or number of foci was observed, the values measured by our reviewing pathologist (KR) were used. As there is currently no standard definition of what constitutes “separate foci” we chose to specify a 4 mm separation as this constitutes the thickness of a standard dissection block. It is unlikely that this had any meaningful impact on the results. While the use of whole mount studies would have enabled better delineation of separate tumor foci histologically it is currently not available in our region and is not the current recommended practice for assessment of breast cancer.[1]

In summary, our results did not show multifocality or multicentricity to be independent prognostic factors for OS in early breast cancer. Tumor size correlated with survival in MMBC irrespective of the measure of tumor size; however, when measuring tumor size using the largest diameter in MMBC, there is less variance. Therefore, the results of this study support the current AJCC/UICC staging method for MMBC.

Conflict of interest statement

There are no conflicts of interest.

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