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Multifocal breast cancer and survival: Each focus does matter particularly for larger tumours

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ABSTRACT

Purpose: The objective of this study is to determine whether the aggregate tumour size of every focus in multifocal breast cancer more accurately predicts 10-year survival than current staging systems which use the largest or dominant tumour size.

Patients and methods: This study examined the original histological reports of 848 consecutive patients with invasive breast cancer treated in New South Wales (NSW), Australia between 1 April 1995 and 30 September 1995. Multifocal tumours were assessed using two estimates of pathologic tumour size: largest tumour focus diameter and the aggregate diameter of every tumour focus. The 10-year survival of patients with multifocal tumours measured in both ways was compared to that with unifocal tumours.

Results: At a median follow-up of 10.4 years, 27 of 94 patients (28.7%) with multifocal breast cancer have died of breast cancer compared to 141 of 754 (18.7%) with unifocal breast cancer ($P = .022$). Ten-year survival was not affected by size for tumours measuring 20 mm or less, whether or not dominant tumour size (87.9%) or aggregate tumour size (87.0%) was used for multifocal tumours, compared to unifocal tumours (88.1%). For tumours larger than 20 mm, 10-year survival was 72.1% for unifocal tumours compared to 54.7% ($P = .008$) for multifocal tumours using dominant tumour size, but this was 69.5% and not significant when multifocal tumours were classified using aggregate tumour size ($P = .49$). Multivariate analysis also confirmed the above-mentioned results after adjustment for important prognostic factors.

Conclusion: Aggregate size of every focus should be considered along with other prognostic factors for metastasis when treatment is planned. The current convention of using the largest (dominant) lesion as a measure of stage and associated breast cancer survival needs further validation.

1. Introduction

Numerous studies have shown that the tumour size is an independent prognostic factor for survival.[1–4] For unifocal disease, tumour staging is dependent on the maximum dimension of the tumour and is used as an approximation of tumour volume.

Multicentricity (separate tumours within the same quadrant) is understood to imply more than one site of origin, whereas multifocality (separate tumours in different quadrants) indicates multiple foci of the same tumour.[5–8] Detailed serial-section examination of the total mastectomy specimen identifies additional separate tumour deposits in approximately 30% of women with breast cancer[7,9] and this is

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associated with adverse patient outcome and a possible increased risk of local recurrence following breast-conserving surgery.[10]

Currently, the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer recommendations are used to stage multifocal tumours using the diameter of the largest tumour focus and lymph node status. This assumes that the prognosis is dependent solely on the largest (and presumed more aggressive) focus and extent of axillary lymph node involvement. The question of whether multifocality confers any additional overall survival disadvantage, when controlling for known prognostic factors, remains controversial.[11–13]

The probability of survival decreases with tumours of more advanced stage when classified by the AJCC criteria.[14,15] Some authors have demonstrated that aggregate tumour size[16] or estimates of tumour volume[17] may be a more accurate predictor of tumour behaviour when there is more than one focus of cancer present. In a previous study we found that nodal status was more likely to be related to aggregate tumour size for patients with multifocal breast cancer.[18]

The aim of this study is to assess the 10-year actuarial breast cancer-specific survival ('10-year survival') of patients diagnosed with unifocal disease and compare this to patients with multifocal disease, where the tumour size was classified using either

(1) the dimension of the largest focus as used in the current AJCC or tumour, node, metastasis (TNM) staging system, (dominant tumour size) or
(2) the aggregate tumour size of every tumour focus (aggregate tumour size).

Multifocality was defined as the presence of two or more foci of invasive breast cancers, separated by either normal breast tissue or *in situ* disease identified either within one quadrant or within multiple quadrants of the breast.

The study investigated whether aggregate tumour size in multifocal breast cancer more accurately predicts 10-year survival than current staging systems where only the size of the largest or dominant tumour is used to determine "T-stage".

2. Patients and methods

2.1. Patient selection

The population studied included 848 consecutive patients with invasive breast cancer who had the original histological reports and were treated in New South Wales (NSW), Australia between 1 April 1995 and 30 September 1995. This was a population study collecting data from multiple treatment centres via a notification process involving a central cancer registry.

All patients who had surgery in their breast and axillary clearance surgery were included.[18] Sentinel node biopsy techniques was used at that time.

2.2. Data collection

Multifocal tumours were assessed using two estimates of pathologic tumour size: largest tumour focus diameter ('dominant tumour size') and the aggregate diameter of every tumour focus. For unifocal tumours, the dominant tumour size was defined as the largest microscopic diameter of the invasive component. If microscopic size was not available, the macroscopic tumour size measured by the pathologist was used. Multifocality, for the purpose of this study, included all patients who had more than one pathologic *invasive* tumour described, irrespective of its location in the breast. This included patients with multicentric tumours in different quadrants of the breast. Patients with surrounding DCIS (extensive or otherwise) or lymphatic invasion were included in the study when two or more discrete areas of invasion were separately described and measured. In all cases, only the invasive areas were measured and the distance between two invasive carcinomas was not included in the aggregate tumour size. Details on the data collection have been reported in a previous paper.[18]

2.3. Data analysis

The outcome factor was 10-year survival, and the study factors were age at diagnosis (<50 years and $\geqslant$50 years), the dominant or aggregate tumour size (1–10 mm, 11–20 mm, 21–30 mm, 31–40 mm, 41–50 mm and >50 mm), histologic grade (1, 2 or 3), pathologic nodal status (node-negative or node-positive) and multifocality (no or yes). The frequency of key characteristics, such as age at diagnosis, histologic tumour grade and type and hormone receptor status, was not significantly different for unifocal or multifocal tumours as defined by dominant tumour size.[18] The only difference was nodal positivity, which was significantly higher for multifocal tumours (37.5% versus 52.1%, $P = .006$). Unpaired *t*-test indicated that the mean age of patients with multifocal tumours was slightly lower than that of women with unifocal tumours (unifocal disease 58.1 years versus multifocal disease 54.8 years, $P = .02$).

Survival analysis was conducted using Kaplan–Meier methods and differences were compared using the log-rank test for statistical significance. Women were censored from the calculation of overall survival at the time of loss to follow-up (if not known to be dead), death from intercurrent illness, or death from breast cancer after 10 years ($n = 2$). Univariate analysis and multivariate analysis to determine independent predictors of survival were undertaken using a Cox proportional hazards regression. Univariate and multivariate analyses were carried out separately for small tumours ($\leqslant$20 mm) and large tumours (>20 mm). All breast cancer deaths were included in the Cox proportional hazards regression. Two-sided *P* values of less than .05 were considered statistically significant. All statistical analyses were performed using the SPSS® statistics program (version 15.0; SPSS, North Sydney). Survival plots were generated using SAS statistical software (version 9; SAS Institute, Cary, NC).

3. Results

Histologic analysis of 848 women with invasive breast cancer treated with primary surgery and axillary dissection showed 94 women (11.1%) with multifocal breast tumours. Sixty-eight of these 94 women (72.3%) had two tumour foci, 20 (21.3%) had three foci and six (6.4%) had four or more foci.

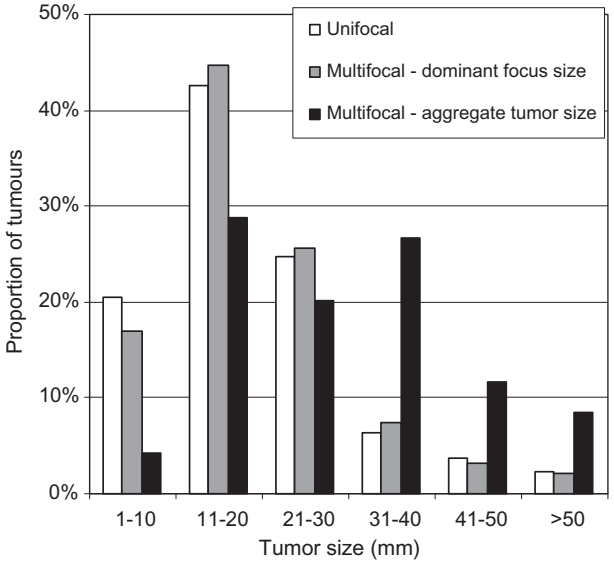

Fig. 1 – Distribution of unifocal and multifocal breast cancers by tumour size.

The use of aggregate tumour size increased the tumour size and reclassified significant numbers of patients with multifocal tumours to a higher T-stage, and increased the mean tumour size from 20.3 mm (unifocal tumours) or 21.1 mm (multifocal and dominant tumour size) to 31.3 mm (multifocal and aggregate tumour size).

Of 58 patients with multifocal tumours classified as pT1 (⩽20 mm diameter) using the dominant tumour size, 27 (46.6%) would be reclassified as pT2 (21–50 mm diameter) when the aggregate foci dimension was used and none to >50 mm or pT3. The 10-year survival of these 27 tumours was 88.9% which was not significantly different from that of the dominant pT1 group (87.9%). When dominant tumour size was used, 58 of 94 patients with multifocal disease (62%) were classified as having a pT1 tumour compared with 31 of 94 patients (33%) when aggregate tumour size was used ($P < .001$) versus 63% for unifocal pT1 tumours. There was no significant difference in the distribution of T-stage between unifocal tumours and multifocal tumours classified by dominant tumour size, but when aggregate tumour size was used to stage multifocal disease there was a significant difference of all tumour size groups except in the 21–30 mm group (Fig. 1).

At a median follow-up of 10.4 years, 27 of 94 patients (28.7%) with multifocal breast cancer have died of breast cancer compared to 141 of 754 (18.7%) with unifocal breast cancer (χ^2 (1) = 5.29, $P = .022$). Ten-year survival was not affected by size for tumours measuring 20 mm or less, whether or not dominant tumour size (87.9%, RR = 0.92, $P = .837$) or aggregate tumour size (87.0%, RR = 0.99, $P = .979$) was used for multifocal tumours, compared to unifocal tumours (88.1%).

For tumours larger than 20 mm, 10-year survival was 72.1% for unifocal tumours compared to 54.7% (RR = 2.21, $P = .002$) for multifocal tumours using dominant tumour size, but this was 69.5% (RR = 1.30, $P = .275$) and not significant when multifocal tumours were classified using aggregate tumour size (Table 1, Figs. 2a and 2b). Table 1 also shows that the relative risk (RR) of dying calculated by univariate analysis was significantly higher with increasing, histologic grade and nodal status for both small and large tumours. A separate

Table 1 – Univariate analysis of impact of multifocality using dominant tumour size on 10-year breast cancer survival for small and large tumours.

Variable	Univariate analysis							
	Tumour size ⩽ 20 mm				Tumour size > 20 mm			
	Survival% (*n*) (95% CI)	*P*	Relative risk (95% CI)	*P*	Survival% (*n*) (95% CI)	*P*	Relative risk (95% CI)	*P*
Age								
(Referent) <50	85.4 (158) (79.9–90.9)		1		66.8 (106) (57.8–75.8)		1	
⩾50	87.1 (375) (83.6–90.6)	.590	0.87 (0.53–1.44)	.591	68.6 (209) (62.1–75.1)	.717	0.675 (0.61–1.38)	.675
Tumour grade								
(Referent) 1	96.2 (141) (92.9–99.5)		1		89.1 (32) (77.5–100.0)		1	
2	86.7 (218) (82.2–91.2)	.003	3.80 (1.47–9.85)	.006	67.5 (102) (58.1–76.9)	.025	2.64 (0.93–7.48)	.067
3	76.4 (125) (69.0–83.8)	<.001	7.41 (2.87–19.14)	<.001	61.2 (144) (53.2–69.2)	.003	3.78 (1.37–10.42)	.010
Unknown	84.9 (49) (74.7–95.1)	.006	4.32 (1.37–13.62)	.012	78.2 (37) (64.9–91.5)	.176	2.03 (0.63–6.59)	.239
Nodal status								
(Referent) Node-negative	91.0 (372) (88.1–93.9)		1		81.2 (144) (74.7–87.7)		1	
Node-positive	76.5 (161) (69.8–83.2)	<.001	2.94 (1.83–4.72)	<.001	57.0 (171) (49.4–64.6)	<.001	2.75 (1.75–4.30)	<.001
Multifocality								
(Referent) Unifocal	88.1 (475) (85.0–91.2)		1		72.1 (279) (66.6–77.6)		1	
Multifocal	87.9 (58) (79.5–96.3)	.837	0.92[a] (0.42–2.01)	.837[a]	54.7 (36) (46.3–63.1)	.008	2.21[b] (1.35–3.61)	.002[b]

Abbreviations: RR: Relative risk of dying; 95% CI: 95% confidence interval of survival or relative risk. *P* value is for comparison of each category with the reference category.

[a] RR = 0.99 and $P = 0.979$ when aggregate tumour size was used.

[b] RR = 1.30 and $P = 0.275$ when aggregate tumour size was used.

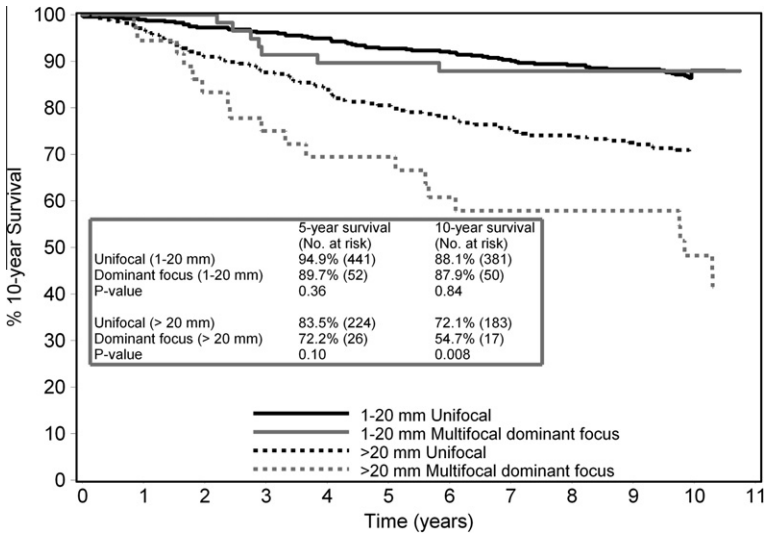

Fig. 2a – Ten-year survival for comparison of unifocal and multifocal breast tumours; dominant tumour size for varying tumour dimensions.

multivariate analysis for small tumours (⩽20 mm) and large tumours (>20 mm) confirmed that for small tumours multifocality was not significant for both dominant and aggregate tumour size (Table 2). For large tumours multifocality was significant for dominant tumour size ($P = .012$) but not for aggregate tumour size ($P = .267$) after adjustment for other important prognostic factors (Table 2).

4. Discussion

In this population-based study of breast cancer in the highest population state of the 8 states and territories of Australia, New South Wales, approximately 10% of the women had multifocal tumours, which is consistent with many other published findings.[19–21] In a previous study of this cohort we found that multifocal tumours had a higher incidence of positive axillary lymph nodes if dominant tumour size was used, as recommended in the AJCC criteria.[18]

Previous studies have also shown a higher incidence of axillary nodal involvement with multifocal tumours, assessed using only the dominant focus size, than with unifocal tumours. When aggregate tumour size was used, the frequency of lymph node positivity was not significantly different from that of unifocal tumours.[16] However, none of the above studies examined the relationship between the long-term survival and multifocal aggregate tumour size. Further, multifocal tumours are known to have a higher incidence of sentinel node positivity both in the axilla and the internal mammary chain and hence may not be biologically equivalent to unifocal tumours.[22]

Recent development in diagnostic imaging technology, including the use of digital mammography in screening pro-

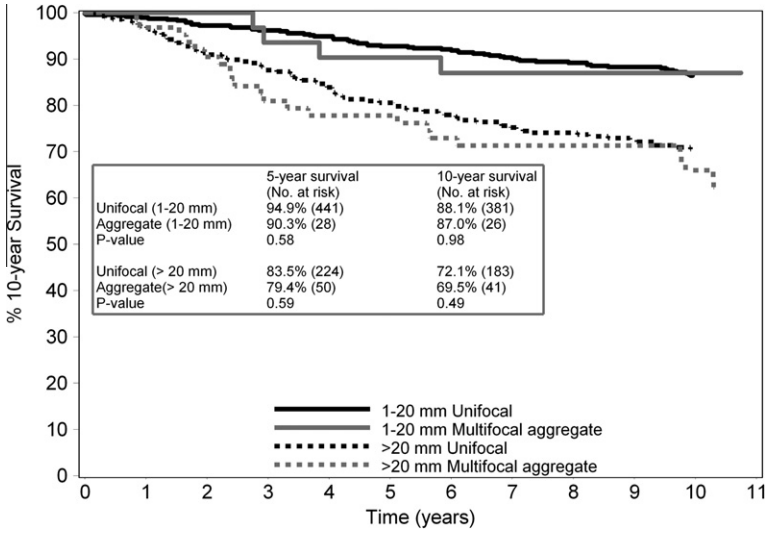

Fig. 2b – Ten-year survival for comparison of unifocal and multifocal breast tumours; aggregate tumour size for varying tumour dimensions.

Table 2 – Multivariate analysis of impact of multifocality using dominant or aggregate tumour size on 10-year breast cancer survival of smaller and larger tumours.

Variable	Multivariate analysis							
	Tumour size ⩽ 20 mm				Tumour size > 20 mm			
	Dominant		Aggregate		Dominant		Aggregate	
	n (*P*)	RR (95% CI)	*n* (*P*)	RR (95% CI)	*n* (*P*)	RR (95% CI)	*n* (*P*)	RR (95% CI)
Age								
(Referent) <50	158	1	146	1	106	1	118	1
⩾50	375 (.953)	1.02 (0.61–1.69)	360 (.860)	1.05 (0.62–1.77)	209 (.957)	0.99 (0.65–1.50)	224 (.961)	1.01 (0.67–1.51)
Tumour grade								
(Referent) 1	141	1	136	1	32	1	37	1
2	218 (.014)	3.30 (1.27–8.58)	207 (.021)	3.10 (1.19–8.10)	102 (.008)	2.48 (0.87–7.02)	113 (.046)	2.88 (1.02–8.15)
3	125 (<.001)	6.26 (2.41–16.30)	118 (<.001)	6.30 (2.41–16.44)	144 (.016)	3.47 (1.26–9.59)	151 (.009)	3.89 (1.41–10.77)
Unknown	49 (.016)	4.11 (1.30–12.96)	45 (.013)	4.29 (1.36–13.53)	37 (.290)	1.89 (0.58–6.16)	41 (.205)	2.14 (0.66–0.6.96)
Nodal status								
(Referent) Node-negative	372	1	356	1	144	1	160	1
Node-positive	161 (<.001)	2.57 (1.60–4.14)	150 (<.001)	2.40 (1.48–3.91)	171 (<.001)	2.39 (1.52–3.78)	182 (<.001)	2.78 (1.77–4.36)
Multifocality								
(Referent) Unifocal	475	1	475	1	279	1	279	1
Multifocal	58 (.695)	0.86 (0.39–1.87)	31 (1.00)	1.00 (0.36–2.76)	36 (.012)	1.91 (1.15–3.16)	63 (.267)	1.31 (0.82–2.09)

Abbreviations: RR: Relative risk of dying; 95% CI: 95% confidence interval of survival or relative risk. *P* value is for comparison of each category with the reference category.

grammes has resulted in improvements in the rates of detection of small tumour foci. This is likely to improve further with the use of pre-operative magnetic resonance imaging.[23,24] Many clinicians account for multifocality when making decisions regarding breast conservation. If the disease is in more than one quadrant and is clearly multicentric, a mastectomy and radiotherapy are generally indicated. However, our study looked at only histology-based multifocal cancer in 1995 irrespective of how the patient was treated.

Fowble et al. found that patients with multifocal breast cancer treated with mastectomy and radiotherapy had rates of locoregional recurrence comparable to those of patients with unifocal disease. Despite a significantly higher incidence of four or more positive nodes, patients with multicentric disease had an overall survival comparable to the group of patients with unifocal disease treated with conservative surgery and radiation. However, the median follow-up of this study was only four years.[25]

In a study from the MD Anderson Hospital, patients with clinical multifocal or multicentric breast cancer treated with neoadjuvant chemotherapy, followed by locoregional therapy, had similar 5-year rates of locoregional control, disease-free survival and overall survival as those with unicentric disease. Clinically detected multifocal breast cancer did not predict for inferior outcome. The mean follow-up of this study was five and a half years.[26]

We approached the question of prognosis for patients with multifocal breast cancer by examining whether the use of dominant tumour size or aggregate tumour size for multifocal tumours influences 10-year survival. One of the strengths of our study is that it involved every patient treated in NSW over a 6 month period. Pathology reporting was standardized in NSW with increasing use of check-list type formatted reports. Reports were obtained from the NSW Central Cancer Registry as part of a mandatory reporting system, and survival was calculated by linking the database with the centralised NSW Registry of Births, Deaths and Marriages at a median duration of follow-up of this study of 10.4 years.

This study pre-dates the advent of sentinel node biopsy, and every patient underwent a full axillary clearance. There is therefore no selection bias. More recent publications have examined nodal status following a sentinel node biopsy for patients with multifocal breast cancer.[27] In this selected group, patients with palpable axillary disease have already been excluded. Studies that assert that nodal positivity or survival is dependent on only the largest tumour focus must assume that the remaining foci do not contribute to the tumour burden nor have metastatic potential.[27] For this hypothesis to be valid either the smaller foci cease to function as invasive tumours or these foci no longer release tumour cells into the lymphatic system. This statement appears at odds with reason and common sense.

Taking into account the distribution of the tumour stage, subtype and grade, tumour size was found to be identical between the tumour groups.[18] The reduced 10-year survival in this study for tumours larger than 20 mm (72.1% for unifocal tumours and 54.7% for multifocal tumours (Fig. 2a); and relative risk of death in multivariate analysis (RR = 1.91; $P = 0.012$) is likely to be explained by the additional tumour foci in the multifocal group (Table 2).

The extent of lympho-vascular invasion (LVI) was not systematically reported for this dataset and therefore could not be included in the analysis. O'Daly et al.[27] reported that the incidence of multifocality was not related to the presence of LVI. Fifteen percent of all patients with LVI and 16.9% of patients without LVI had multifocal tumours ($P = .76$). Previous studies have also reported that a multifocal tumour based on dominant tumour size is a significant predictive factor of axillary lymph-node metastases even after adjustment for LVI.[22,28]

The foci other than the largest tumour focus would not be accounted for in conventional staging although most oncologists use this factor for making decisions particularly on choices of whether or not breast conservation is possible. Including the dimensions of every tumour focus in the estimate of aggregate tumour size gives a more accurate estimate of tumour load and in this population based study, a case can be made for adding the tumour foci together to estimate prognosis particulary when that tumour size is over 20 mm. This aggregate dimension takes account of all measured foci and when used predicted 10-year survival to be identical with a size-matched group of unifocal tumours (Figs. 2a and 2b).

This report defines that, at least for tumours >20 mm, tumour volume as estimated by an aggregate of tumour size not only impacts on nodal status but also ultimately on outcome. Aggregate size of every focus should be considered along with other prognostic factors for metastasis when treatment is planned. However, further validation studies are advised with larger number of multifocal tumours before the current staging system is changed, particularly as the classification already allows for, at least, the notation of multifocality.

Conflict of interest statement

None declared.

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