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Breast Cancer

Breast Cancer Multifocality and Multicentricity and Locoregional Recurrence

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Multifocal • Multicentric • Breast cancer • Locoregional • Outcomes

Abstract

Background. The impact of multifocal (MF) or multicentric (MC) breast cancer on locoregional (LR) control rates is unknown.

Methods. MF was defined as two or more separate invasive tumors in the same quadrant of the breast. MC was defined as two or more separate invasive tumors occupying more than one quadrant of the same breast. Patients were categorized by LR treatment: breast conservation therapy (BCT; $n = 256$), mastectomy ($n = 466$), or mastectomy plus postmastectomy radiation therapy (PMRT; $n = 184$). All patients with MC disease had mastectomy (10 patients treated with BCT for MC disease were excluded). The Kaplan-Meier product limit method was used to calculate 5-year LR control rate. Cox proportional hazards models were used to determine independent associations of multifocality or multicentricity with LR control.

Results. A total of 906 patients had either MF disease ($n = 673$) or MC disease ($n = 233$). With median follow-up of 52 months, the 5-year LR control rate was 99% for MF, 96% for MC, and 98% for unifocal tumors ($p = .44$). Subset analysis revealed no difference in LR control regardless of the LR treatment ($p = .67$ for BCT, $p = .37$ for mastectomy, $p = .29$ for mastectomy plus PMRT). There were five in-breast recurrences after BCT in the MF group. MF and MC did not have an independent impact on LR control rate on multivariate analysis.

Conclusion. MF and MC disease are not independent risk factors for LR recurrence. Patients with MF and MC breast cancer had rates of LR control similar to those of their unifocal counterparts. These data suggest that BCT is a safe option for patients with MF tumors and that MF or MC disease alone is not an indication for PMRT. ***The Oncologist*** 2013;18:1167–1173

Implications for Practice: This work reviews the risk of locoregional recurrences in patients with breast cancer treated with different approaches, as currently recommended by standard guidelines. We looked at 2,816 cases with unifocal disease, 673 cases with multifocal (MF) disease, and 233 cases with multicentric (MC) disease. We showed that MF and MC breast cancers are not independently associated with increased locoregional recurrence rates and that breast conservation therapy is a safe option for patients with MF tumors. MF or MC disease alone is not an indication for postmastectomy radiation therapy.

Introduction

Multifocal (MF) and multicentric (MC) breast cancers are relatively common clinical entities, with incidence in the literature ranging from 6% to 60% and large variability because of differences in definitions used, inclusion or exclusion of in situ disease, and method of pathologic sampling [1, 2]. As advances in preoperative imaging continue, the number of MF and MC tumors identified increases [3–5], and better guidelines for their management are needed. In particular, questions still exist regarding the optimal locoregional (LR) therapy for MF and MC breast cancer.

Tumor size has long been recognized as a strong predictor of LR recurrence (LRR) [6–8], and it would seem logical that the presence of more than one synchronous unilateral tumor would also be a risk factor for LRR; however, studies have shown conflicting results. In the absence of compelling evidence to dictate otherwise, the convention according to current TNM staging guidelines has been to stage MF and MC patients according to the diameter of the largest lesions, without taking other foci of disease into consideration [9]. This approach assumes that prognosis is dependent only on the largest lesion and the presence and extent of lymph node involvement. In addition, although the location and distance between tumors often dictates surgical strategies, MF and MC alone are not standard indications for postmastectomy radiation therapy (PMRT).

We have previously shown in the same large, single-institution cohort that, although associated with a number of poor

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prognostic factors (e.g., higher T-stage, increased incidence of nodal involvement, higher grade and more lymphovascular invasion [LVI]), the presence of MF or MC disease alone is not an independent predictor of relapse-free survival (both local and distant combined), breast cancer-specific survival, or overall survival [10]. The purpose of this study is to further analyze the effect of multifocality and multicentricity on the LRR rate with respect to different LR treatment modalities.

Materials and Methods

Patient Selection

Using the Breast Cancer Management System database of the University of Texas MD Anderson Cancer Center (MDACC), we retrospectively identified all patients diagnosed with invasive breast cancer between 1997 and 2010. We excluded patients with metastatic disease at diagnosis and those treated with neoadjuvant chemotherapy, leaving 6,735 patients. We excluded an additional 2,811 patients who did not have MF and MC information, pathological tumor size, or nodal status available. We further excluded 192 patients who did not receive adjuvant radiation therapy after breast conserving surgery because all patients who underwent conservative surgery received radiation therapy. Another 10 patients who were treated with breast conservation therapy (BCT) for MC disease against physician advice were also excluded.

MF was defined as two or more separate invasive tumors in the same quadrant of the breast. MC was defined as two or more separate invasive tumors occupying more than one quadrant of the same breast. If patients had both MF and MC disease, they were classified as MC. Patients who had MF or MC in situ disease only were excluded. Determinations were made by pathology review only; clinical and radiographic data were not considered. All pathology specimens were independently reviewed by dedicated breast pathologists at MDACC at the time of initial treatment. A total of 3,722 patients were included in the analysis. Of these, 2,816 patients (76%) had unifocal (UF) breast cancer, and 906 patients (24%) had MF ($n = 673$) or MC ($n = 233$) breast cancer in their pathology specimens. LRR was defined after BCT as recurrence in either the ipsilateral breast or regional lymph nodes (axillary, infraclavicular, supraclavicular, or internal mammary), and after mastectomy as recurrence in the ipsilateral chest wall or regional lymph nodes (axillary, infraclavicular, supraclavicular, or internal mammary). The institutional review board of the University of Texas MDACC approved the retrospective study.

Statistical Methods

Patients were categorized as having UF, MF, or MC breast cancers. The MF and MC tumors were analyzed as separate entities and as a group (MF/MC). Patient characteristics including age, menopausal status, race, tumor size, nodal status, histology, nuclear grade, presence of LVI, tumor subtype, LR treatment modality, surgical margin status, LRR location, and adjuvant systemic treatment (chemotherapy and hormonal therapy) were tabulated and compared between groups by the chi-square test. Time to LRR was measured from the date of diagnosis to the date of the first documented LRR (regardless of whether it occurred first or after a systemic recurrence); patients not experiencing the event were censored at last follow-up. Five-year LR control rate was calculated using the Kaplan-Meier product limit method; groups were compared with the log-rank statistic. A subgroup analysis was performed by LR therapy (BCT, mastectomy only, and mastectomy followed by PMRT). Cox proportional hazards models were used to determine the association of MF, MC, and the combination of the MF and MC groups with LR control after adjustment for other patient and disease characteristics. A p value $<.05$ was considered statistically significant; all tests were two-sided. Statistical analyses were carried out using SAS 9.1 (SAS Institute, Inc., Cary, NC) and S-Plus 7.0 (Insightful Corp., Seattle, WA).

Results

Patient and Tumor Characteristics

MF or MC disease was seen in 906 patients, or 24% of the total patient population; 673 (18.1%) had MF and 233 (6.3%) had MC tumors (Table 1). As we have reported previously, in comparison with patients with UF disease, patients with MF or MC breast cancer were younger and thus more likely to be premenopausal [10]. They had higher T stages and N stages. Histologically, MF and MC tumors were associated with more grade 3 disease, more LVI, lobular differentiation, and HER2 positivity. In terms of treatment received, these patients were more likely to undergo mastectomy, with or without radiation ($p < .001$). More patients with MF and MC tumors received adjuvant chemotherapy ($p < .001$), but there was no difference in the proportion of patients who received adjuvant hormonal therapy ($p \geq .40$) [10]. In terms of LR therapy, 62.4% of UF tumors were treated with BCT compared with 38% of MF tumors ($p < .001$). In addition, 31.7% of UF tumors were treated with mastectomy alone compared with 48.1% of MF tumors ($p < .001$) and 60.9% of MC tumors ($p < .001$). Only 5.9% of UF tumors were treated with mastectomy and PMRT compared with 13.8% of MF tumors ($p < .001$) and 39.1% of MC tumors ($p < .001$). In the UF group, 87 patients (3.1%) had close (<2 mm) or positive surgical margins (including invasive cancer and ductal carcinoma in situ but not lobular carcinoma in situ) compared with 5.3% in the MF group ($p = .007$), 3.4% in the MC group ($p = .70$), and 4.9% in the MF/MC group ($p = .02$). The low rate of positive margins in the MC group likely represents the fact that all of these patients were treated with mastectomy.

LR Control

The median follow-up among all patients was 52 months (range: 1–162 months). Sixty-four patients (1.7%) had LRR: 49 (1.7%) in the UF group, 9 (1.3%) in the MF group, and 6 (2.6%) in the MC group (Table 2). There was no difference in the 5-year LR control rate among the UF group (98%), the MF group (99%), and the MC group (96%) ($p = .44$) (Fig. 1).

The sites of LRR are detailed in Table 1. There was no difference in terms of recurrence location among the UF, MF, and MC groups ($p \geq .21$). Specifically, there were only 5 (1.95%) in-breast recurrences after BCT in the MF group compared with 18 (1.02%) in the UF group.

To evaluate the independent impact of MF and MC on LRR, a multivariate Cox proportional hazards model was applied. Risk factors that were significant on univariate analysis (age, tumor size, grade, LVI, histologic subtype, adjuvant hormonal therapy) were evaluated (Table 2). The results are shown in

Table 1. Treatment and site of recurrence among all patients

	UF ($n = 2,816$)		MF ($n = 673$)		MF vs. UF	MC ($n = 233$)		MC vs. UF	MF/MC ($n = 906$)		MF/MC vs. UF
Treatment	**No.**	**%**	**No.**	**%**	***p* value**	**No.**	**%**	***p* value**	**No.**	**%**	***p* value**
Locoregional therapy											
Breast conservation therapy	1,757	62.4	256	38.0	<.001	0	0.0		256	28.3	<.001
Mastectomy only	893	31.7	324	48.1	<.001	142	60.9	<.001	466	51.4	<.001
Postmastectomy radiation therapy	166	5.9	93	13.8	<.001	91	39.1	<.001	184	20.3	<.001
Surgical margins											
Negative	2,729	96.9	637	94.7		225	96.6		862	95.1	
Close/positive	87	3.1	36	5.3	.007	8	3.4	.70	44	4.9	.02
Adjuvant chemotherapy											
No	1,494	53.1	298	44.3		78	33.5		376	41.5	
Yes	1,322	46.9	375	55.7	<.001	155	66.5	<.001	530	58.5	<.001
Adjuvant hormonal therapy											
No	697	24.8	177	26.3		59	25.3		236	26.0	
Yes	2,119	75.2	496	73.7	.40	174	74.7	.85	670	74.0	.43
Recurrence location											
Axillary	2	4.1	0	0.0		0	0.0		0	0.0	
Chest wall/skin	10	20.4	0	0.0		1	16.7		1	6.7	
IMC	2	4.1	1	11.1		1	16.7		2	13.3	
Infraclavicular	2	4.1	1	11.1		2	33.3		3	20.0	
Supraclavicular	8	16.3	2	22.2		0	0.0		2	13.3	
Ipsilateral breast	21	42.9	5	55.6		2	33.3		7	46.7	
IMC/supraclavicular	1	2.0	0	0.0		0	0.0		0	0.0	
Infra/supraclavicular	3	6.1	0	0.0	.68	0	0.0	.21	0	0.0	.29

Abbreviations: IMC, internal mammary chain; MC, multicentric; MF, multifocal; UF, unifocal.

Tables 3 and 4. On multivariate analysis, only age ≤50, high tumor grade (grade 3), and the presence of LVI (for MC tumors only) independently increased the risk of LRR. MF tumors (hazard ratio [HR]: 0.73; 95% confidence interval [CI]: 0.32–1.67; $p = .46$), MC tumors (HR: 1.35; 95% CI: 0.55–3.34; $p = .51$), and combined MF/MC tumors (HR: 0.95; 95% CI: 0.49–1.83; $p = .88$) were not independent predictors of LRR.

Subset Analyses

A subset analysis was performed based on the LR treatment modality received. There was no difference in the LR control between the MF/MC and UF groups treated with BCT ($p = .67$), mastectomy alone ($p = .37$), or PMRT ($p = .29$) (Fig. 2A–2C).

Discussion

In this large, single-institution cohort, MF and MC disease were not independent risk factors for LRR. This was true regardless of the LR treatment modality received. Several previous studies had similar findings. In an early study, Fowble et al. reported on 88 patients with stage I–II clinically or radiographically gross MC breast cancer ($n = 57$) or diffuse microcalcifications ($n = 31$), all of whom were treated with modified radical mastectomy and 15 of whom received PMRT. After a median follow-up of 4 years, no difference was seen in the rate of isolated LRR (8% vs. 7%, no *p* value given) [11]. Oh et al. reviewed 97 patients with clinically diagnosed MF/MC breast cancer who were subsequently treated with neoadjuvant anthracycline-based chemotherapy followed by BCT, mastectomy, or mastectomy plus PMRT and found no difference in the 5-year rate of LRR (UF 10% vs. MF/MC 7%, $p = .78$), regardless of the LR treatment modality received [12]. In a population similar to ours, Cabioglu et al. examined 1,322 patients with T1–3 invasive breast cancer who were not treated with neoadjuvant chemotherapy [13]. In their study, 147 (11%) had MF or MC tumors (not distinguished as separate entities), defined as more than one simultaneous macroscopically separated tumor in the same breast on surgical pathology evaluation. Of the MF/MC patients, 30 underwent BCT and 117 underwent mastectomy; 77 received PMRT. With a median follow-up of 55 months, the rate of LRR was not significantly different between those with the MF/MC tumors (5.4%) and the UF tumors (3.7%) ($p = .36$). Huang et al. reviewed 84 patients with stage II–IV (ipsilateral supraclavicular adenopathy) MF and MC breast cancer (defined on pathology as either microscopic MF/MC disease or macroscopic MF/MC disease) who were all treated with neoadjuvant chemotherapy, modified radical mastectomy, and PMRT. No difference was found in the rate of LRR after a median follow-up of 70 months ($p < .05$) [14]. This represents a different (and higher risk) patient population because these patients had residual MF or MC disease after treatment with neoadjuvant chemotherapy; however, the findings were still similar.

In contrast to our findings, Katz et al. reported a study of 149 patients with stage II and IIIa MF/MC breast cancer, all

Table 2. Five-year locoregional control estimates by patient and clinical characteristics among all patients

Characteristic	No. of patients	Locoregional control		
		No. of events	5-yr estimate (95% CI)	*p*
All	3,722	64	0.98 (0.98–0.99)	
Focal group				
Unifocal	2,816	49	0.98 (0.98–0.99)	
MF	673	9	0.99 (0.97–0.99)	
MC	233	6	0.96 (0.92–0.98)	.44
MF/MC				
No	2,816	49	0.98 (0.98–0.99)	
Yes	906	15	0.98 (0.97–0.99)	.71
Age				
≤50	1,247	37	0.97 (0.95–0.98)	
>50	2,475	27	0.99 (0.98–0.99)	<.001
Race				
Nonblack	3,390	58	0.98 (0.98–0.99)	
Black	332	6	0.98 (0.96–0.99)	.57
Tumor size				
T1	2,747	39	0.99 (0.98–0.99)	
T2	840	23	0.97 (0.95–0.98)	
T3	135	2	0.98 (0.9–0.99)	.008
Lymph Nodes				
N0	2,557	38	0.99 (0.98–0.99)	
N1	1,004	24	0.98 (0.96–0.99)	
N2	99	2	0.97 (0.89–0.99)	
N3	61	0	1	.341
Stage group				
T1–2N0	2,519	38	0.98 (0.98–0.99)	
T1–2N1	938	22	0.98 (0.96–0.99)	
T3 or N2–3	265	4	0.98 (0.94–0.99)	.44
Histology				
Ductal	2,850	57	0.98 (0.97–0.99)	
Lobular	354	4	0.99 (0.96–1)	
Other	518	3	0.99 (0.97–1)	.054
Nuclear grade				
1 or 2	2,230	11	1 (0.99–1)	
3	1,480	53	0.96 (0.95–0.97)	<.001
Lymphovascular invasion				
Negative	2,936	42	0.99 (0.98–0.99)	
Positive	786	22	0.97 (0.95–0.98)	.003
Subtype				
Hormone receptor-positive	1,846	19	0.99 (0.98–0.99)	
HER2-positive	448	13	0.97 (0.94–0.98)	
Triple negative	239	13	0.95 (0.9–0.97)	<.001
Locoregional therapy				
Breast conservation therapy	2,013	32	0.98 (0.98–0.99)	
Mastectomy only	1,359	29	0.98 (0.97–0.99)	
Mastectomy plus radiation	350	3	0.99 (0.96–1)	.37
Surgical margins				
Negative	3,591	62	0.98 (0.98–0.99)	
Close/positive	131	2	0.99 (0.9–1)	.76
Adjuvant chemotherapy				
No	1,870	24	0.99 (0.98–0.99)	
Yes	1,852	40	0.98 (0.97–0.99)	.07
Adjuvant hormonal therapy				
No	933	34	0.96 (0.94–0.97)	
Yes	2,789	30	0.99 (0.98–0.99)	<.001

Abbreviations: CI, confidence interval; MC, multicentric; MF, multifocal.

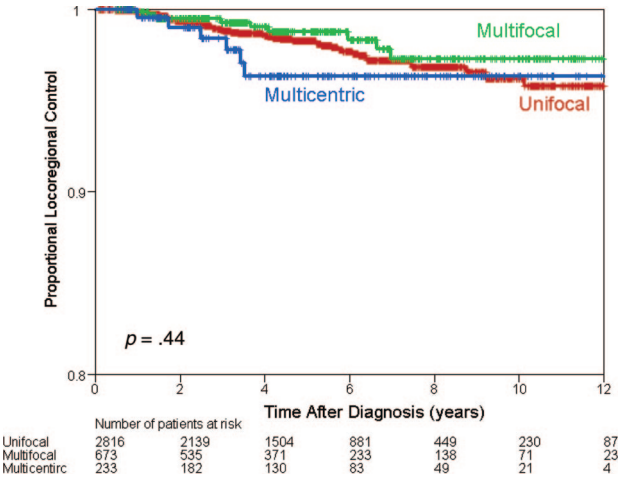

Figure 1. Kaplan-Meier estimates of locoregional control among all patients.

treated with mastectomy (without PMRT) and adjuvant anthracycline-based chemotherapy [15]. Tumors were classified as MF (two or more separate areas of invasive carcinoma within the same quadrant and/or <4 cm apart by mammography or gross pathology evaluation), microscopic MC, and gross MC (two or more areas of invasive disease in more than one quadrant of the breast and separated by ≥4 cm by clinical or pathologic analysis). Of note, patients with more than one microscopic focus of invasive disease in the same breast quadrant were classified as unicentric. When considered as a separate entity, gross MC disease was found to have an increased rate of LRR at 10 years (37% vs. 17%, $p = .01$), a difference that persisted in multivariate analysis ($p = .0001$). This difference in outcomes is likely because of the difference in patient populations (our cohort included patients with stage I breast cancer), and the more stringent definition of MC that was used in the study by Katz et al. Weissenbacher et al. reported on 288 patients with early stage MF and MC breast cancer compared with a matched cohort of patients with UF disease [16]. MF and MC disease was defined clinically and radiographically and thus likely represented a similar population to the gross MC group of Katz et al. After a median follow-up of 70 months, MF and MC patients had an LRR rate of 17.4% compared with 7.3% for UF tumors ($p < .001$). Of note, 43.1% were treated with BCT (compared with 50.3% in the UF group).

In our cohort, 256 patients underwent BCT for MF breast cancer and 1,757 underwent BCT for UF disease. There were 5 (1.95%) in-breast recurrences after BCT in the MF group compared with 18 (1.02%) in the UF group. There was no difference in LRR (including nodal basins) between the MF and UF groups treated with this modality. Several small, early studies showed that patients with MF or MC disease have an increase in LRR following BCT [11, 17–20] (LRR ranged from 23% to 40% at 5-year follow-up in these trials). Based on these trials, mastectomy became the standard of care for women with MF or MC disease. As diagnostic tools advance, MF and MC tumors are more commonly diagnosed, and cancers that previously would have been classified as UF now can be detected as MF or MC. In addition, LR treatment modalities have improved sig-

Table 3. Multivariable Cox proportional hazards models by multifocality, multicentricity, or both on locoregional control

By multifocality	HR	95% CI	p
MF: yes vs. no	0.73	0.32–1.67	.46
Age: >50 vs. ≤50	0.62	0.33–1.17	.14
Tumor size: T2–3 vs. T1	1.11	0.56–2.2	.77
Grade: 3 vs. 1/2	13.56	3.94–46.59	<.0001
LVI: positive vs. negative	1.79	0.91–3.5	.09
Subtype: HER2 positive vs. hormonal receptor positive	0.93	0.4–2.18	.87
Subtype: triple negative vs. hormonal receptor positive	1.23	0.41–3.68	.71
Adjuvant hormonal therapy: yes vs. no	0.82	0.34–1.97	.65
By multicentricity	**HR**	**95% CI**	**p**
MC: yes vs. no	1.35	0.55–3.34	.51
Age: >50 vs. ≤50	0.49	0.25–0.94	.033
Tumor size: T2–3 vs. T1	1.10	0.55–2.16	.79
Grade: 3 vs. 1/2	18.50	4.24–80.73	.0001
LVI: positive vs. negative	2.32	1.18–4.55	.014
Subtype: HER2 positive vs. hormonal receptor positive	0.84	0.35–2	.69
Subtype: triple negative vs. hormonal receptor positive	1.72	0.56–5.32	.34
Adjuvant hormonal therapy: yes vs. no	1.00	0.39–2.53	.99
By both MF and MC	**HR**	**95% CI**	**p**
MF/MC: yes vs. no	0.95	0.49–1.83	.88
Age: >50 vs. ≤50	0.55	0.3–1	.05
Tumor size: T2–3 vs. T1	1.12	0.6–2.1	.72
Grade: 3 vs. 1/2	14.58	4.29–49.54	<.0001
LVI: positive vs. negative	1.80	0.97–3.34	.06
Subtype: HER2 positive vs. hormonal receptor positive	0.81	0.36–1.83	.61
Subtype: triple negative vs. hormonal receptor positive	1.44	0.53–3.94	.48
Adjuvant hormonal therapy: yes vs. no	0.78	0.34–1.78	.55

Abbreviations: CI, confidence interval; HR, hazard ratio; LVI = lymphovascular invasion; MC, multicentric; MF, multifocal.

Table 4. Multivariable Cox proportional hazards model to assess risk of locoregional failure

Variable	Hazard ratio	95% confidence interval	p
Multifocal vs. unifocal	0.75	0.33–1.7	.49
Multicentric vs. unifocal	1.43	0.58–3.51	.44
Age: >50 vs. ≤50	0.55	0.3–1.01	.05
Tumor size: T2–3 vs. T1	1.07	0.57–2.02	.84
Grade: 3 vs. 1/2	14.59	4.29–49.59	<.0001
Lymphovascular invasion: positive vs. negative	1.78	0.95–3.32	.07
Subtype: HER2 positive vs. hormonal receptor positive	0.79	0.35–1.78	.57
Subtype: triple negative vs. hormonal receptor positive	1.46	0.53–4	.46
Adjuvant hormonal therapy: yes vs. no	0.77	0.34–1.77	.54

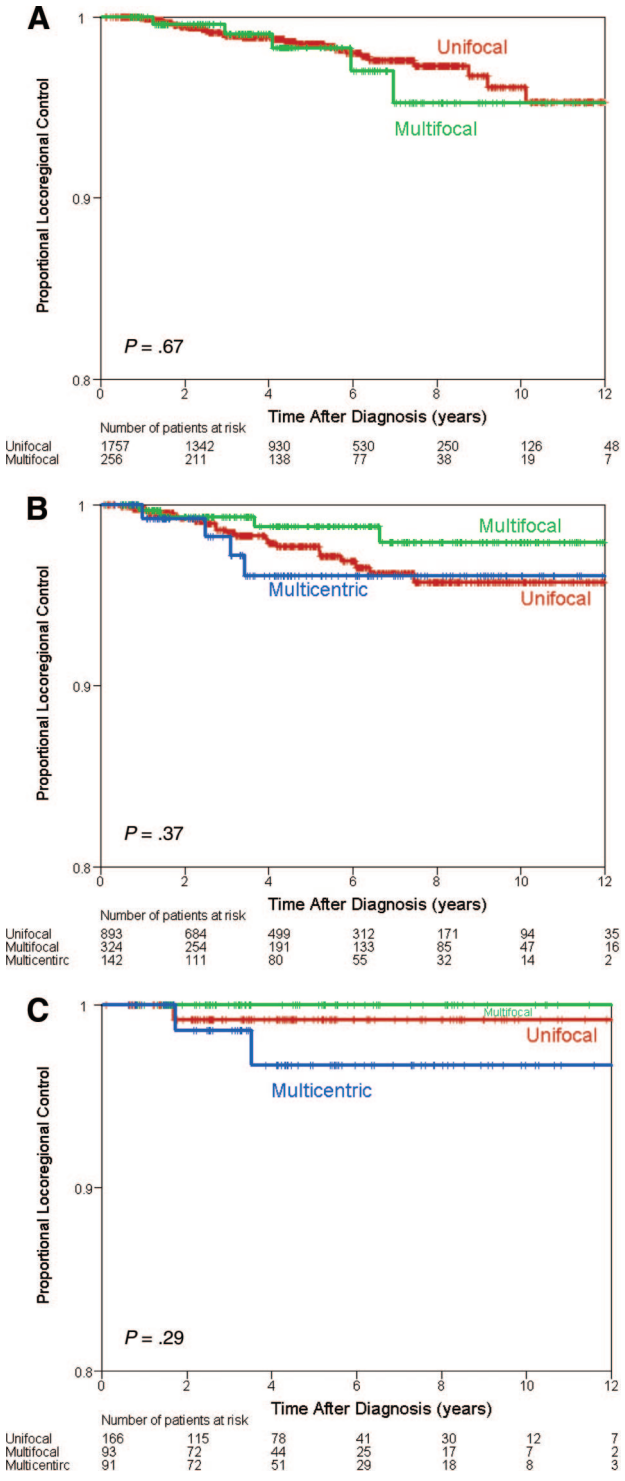

Figure 2. Kaplan-Meier estimates of locoregional control by locoregional treatment modality. **(A)**: Breast conserving surgery followed by adjuvant radiation. **(B)**: Mastectomy alone. **(C)**: Mastectomy plus postmastectomy radiation therapy.

nificantly over the past decade. More recent studies reflect these advances in diagnosis and treatment.

In their series of 97 patients with clinically diagnosed MF/MC breast cancer who were subsequently treated with neoadjuvant chemotherapy, Oh et al. reported no in-breast recurrences for patients treated with BCT for MF disease [12]. Baumann et al. retrospectively reviewed the charts of 22 women with an average follow-up of 3.5 years, with only 1 patient (4.5%) experiencing an in-breast recurrence [21]. Min et al. reviewed 251 stage II/III (node-positive) patients who had LRR after neoadjuvant therapy and BCT. Of these, 74 had clinical MF (cMF) disease at presenta-

tion and 11 had residual MF disease on pathology evaluation (pMF) after primary systemic therapy. The median follow-up was 55 months. There was a trend toward worse 5-year LRR-free survival (unicentric, 91%; cMF, 86%; pMF, 82%; $p = .15$) and ipsilateral breast tumor recurrence-free survival (unicentric, 92%; cMF, 89%; pMF, 82%; $p = .23$) for the patients with clinically and pathologically MF disease, but it was not statistically significant [22].

Debate continues as to whether BCT is an appropriate option for women with MC disease. This question was not addressed in this analysis because it is not currently routine practice at our institution; therefore, numbers were insufficient to make any conclusions.

PMRT has been shown in randomized controlled trials to reduce the rate of LRR and can improve overall survival rates in high-risk patients [23, 24]; however, the presence of MF and/or MC disease has not been identified as a high-risk feature mandating PMRT. In our subgroup analysis, patients with MF and MC disease had similar LRR after mastectomy, regardless of whether or not they received PMRT. Although Katz et al. [15] showed an association between MF/MC disease and LRR in patients treated with mastectomy and adjuvant anthracycline-based chemotherapy, none of these patients received PMRT; therefore, it is unknown if its addition would have significantly negated some of that risk. In addition, in a subset analysis of 23 patients with T1–2 tumors with only one, two, or three involved lymph nodes, they found no independent impact of MC disease on the risk of LRR. Similar to our findings, Oh et al. found in their series of 97 patients with clinical MF/MC disease at the time of diagnosis (who were subsequently treated with neoadjuvant chemotherapy) that there was no difference in the LR control rate between patients treated with mastectomy alone ($n = 44$) and those treated with mastectomy plus PMRT ($n = 33$) (91% vs. 93%, respectively) [12].

This study is limited by its retrospective nature and thus possible treatment biases. In addition, one of the biggest obstacles in interpreting the current literature on MF and MC breast tumors is the lack of a standard definition. These data apply to patients with MF and MC disease diagnosed on initial surgical pathology, and caution should be taken when applying the data to patients with MF or MC disease based on a different definition or after neoadjuvant chemotherapy.

Conclusion

Patients with MF and MC breast cancer had rates of LR control similar to those of their UF counterparts when receiving appropriate local treatment modalities. Our data suggest that BCT is a safe option for patients with MF tumors and that MF or MC disease alone is not an indication for PMRT. Future research should focus on the feasibility and safety of BCT for MC tumors.

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Author Contributions

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Disclosures

Gabriel N. Hortobágyi: Allergan, Genentech, Novartis, AstraZeneca, Sanofi Aventis (C/A); Novartis (RF). The other authors indicated no financial relationships.

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References

1. Yerushalmi R, Kennecke H, Woods R et al. Does multicentric/multifocal breast cancer differ from unifocal breast cancer? An analysis of survival and contralateral breast cancer incidence Breast Cancer Res Treat 2009;117:365–370.

2. Egan RL. Multicentric breast carcinomas: Clinical-radiographic-pathologic whole organ studies and 10-year survival. Cancer 1982;49:1123–1130.

3. Wilkinson LS, Given-Wilson R, Hall T et al. Increasing the diagnosis of multifocal primary breast cancer by the use of bilateral whole-breast ultrasound. Clin Radiol 2005;60:573–578.

4. Sardanelli F, Giuseppetti GM, Panizza P et al. Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in Fatty and dense breasts using the whole-breast pathologic examination as a gold standard. AJR Am J Roentgenol 2004;183:1149–1157.

5. Houssami N, Ciatto S, Macaskill P et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: Systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol 2008;26:3248–3258.

6. Katz A, Strom EA, Buchholz TA et al. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: Implications for postoperative irradiation. J Clin Oncol 2000;18:2817–2827.

7. Fowble B, Gray R, Gilchrist K et al. Identification of a subgroup of patients with breast cancer and histologically positive axillary nodes receiving adjuvant chemotherapy who may benefit from postoperative radiotherapy. J Clin Oncol 1988;6:1107–1117.

8. Recht A, Gray R, Davidson NE et al. Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: Experience of the Eastern Cooperative Oncology Group. J Clin Oncol 1999;17:1689–1700.

9. Edge SB, Byrd DR, Compton CC et al. eds. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2009.

10. Lynch SP, Lei X, Chavez-Macgregor M et al. Multifocality and multicentricity in breast cancer and survival outcomes. Ann Oncol 2012;23:3063–3069.

11. Fowble B, Yeh IT, Schultz DJ et al. The role of mastectomy in patients with stage I-II breast cancer presenting with gross multifocal or multicentric disease or diffuse microcalcifications. Int J Radiat Oncol Biol Phys 1993;27:567–573.

12. Oh JL, Dryden MJ, Woodward WA et al. Locoregional control of clinically diagnosed multifocal or multicentric breast cancer after neoadjuvant chemotherapy and locoregional therapy. J Clin Oncol 2006;24:4971–4975.

13. Cabioglu N, Ozmen V, Kaya H et al. Increased lymph node positivity in multifocal and multicentric breast cancer. J Am Coll Surg 2009;208:67–74.

14. Huang EH, Tucker SL, Strom EA et al. Predictors of locoregional recurrence in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy, mastectomy, and radiotherapy. Int J Radiat Oncol Biol Phys 2005;62:351–357.

15. Katz A, Strom EA, Buchholz TA et al. The influence of pathologic tumor characteristics on locore-

gional recurrence rates following mastectomy. Int J Radiat Oncol Biol Phys 2001;50:735–742.

16. Weissenbacher TM, Zschage M, Janni W et al. Multicentric and multifocal versus unifocal breast cancer: Is the tumor-node-metastasis classification justified? Breast Cancer Res Treat 2010; 122:27–34.

17. Kurtz JM, Jacquemier J, Amalric R et al. Breast-conserving therapy for macroscopically multiple cancers. Ann Surg 1990;212:38–44.

18. Wilson LD, Beinfield M, McKhann CF et al. Conservative surgery and radiation in the treatment of synchronous ipsilateral breast cancers. Cancer 1993;72:137–142.

19. Leopold KA, Recht A, Schnitt SJ et al. Results of conservative surgery and radiation therapy for multiple synchronous cancers of one breast. Int J Radiat Oncol Biol Phys 1989;16:11–16.

20. Hartsell WF, Recine DC, Griem KL et al. Should multicentric disease be an absolute contraindication to the use of breast-conserving therapy? Int J Radiat Oncol Biol Phys 1994;30:49–53.

21. Bauman L, Barth RJ, Rosenkranz KM. Breast conservation in women with multifocal-multicentric breast cancer: Is it feasible? Ann Surg Oncol 2010;17(suppl 3):325–329.

22. Min SY, Lee SJ, Shin KH et al. Locoregional recurrence of breast cancer in patients treated with breast conservation surgery and radiotherapy following neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys 2011;81:e697–e705.

23. Overgaard M, Hansen PS, Overgaard J et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997;337: 949–955.

24. Ragaz J, Jackson SM, Le N et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 1997;337:956–962.