Comparison of Outcomes of Breast Conserving Therapy in Multifocal and Unifocal Invasive Breast Cancer

Alice P Chung, MD, FACS, Kelly Huynh, MD, Travis Kidner, MD, Parisa Mirzadehgan, MPH, Myung-Shin Sim, PhD, Armando E Giuliano, MD, FACS

BACKGROUND: There is controversy about whether breast conserving therapy (BCT) should be contraindicated in multifocal (MF) breast cancer. Few studies have reported on the oncologic safety of BCT in MF breast cancer.

STUDY DESIGN: We reviewed a prospective database of 1,169 women with invasive breast cancer who were treated with segmentectomy and whole breast irradiation from 1991 through 2009 and followed at our institution. Multifocal breast cancer was defined as 2 or more distinct tumors excised with a single incision or segmentectomy. We compared 2 groups, MF and unifocal breast cancer patients, with respect to demographics, tumor characteristics, adjuvant systemic therapy, local recurrence (LR), disease-free survival (DFS), and overall survival (OS).

RESULTS: One hundred sixty-four patients with MF and 999 with unifocal invasive breast cancer were treated with BCT. Median follow-up was 112 months. Compared with the unifocal group, patients in the MF group had higher 10-year LR (0.6% vs 6.1%, $p < 0.001$) and lower 10-year DFS (97.7% vs 89.3%, $p < 0.001$) and OS (98.4% vs 85.8%, $p < 0.001$). On multivariable analysis, multifocality was independently significantly associated with local recurrence-free survival (LRFS), DFS, and OS.

CONCLUSIONS: Our data suggest that BCT in MF breast cancer is oncologically safe but may result in a slightly inferior outcome compared with BCT in unifocal breast cancer. (J Am Coll Surg 2012;215: 137–147. © 2012 by the American College of Surgeons)

Breast conserving surgery (BCS) was introduced in the early 1980s as an alternative, less invasive surgical approach for the treatment of breast cancer. Long-term follow-up of patients from several large, randomized controlled trials has demonstrated equivalent overall survival in patients undergoing mastectomy compared with BCS.[1-4] Because these trials included only women with unifocal breast cancer, multifocal (MF) and multicentric (MC) breast cancer were considered relative contraindications to breast conserving therapy (BCT). As a result, mastectomy has been the standard surgical treatment of MF and MC breast cancer.

Disclosure Information: Nothing to disclose.

Presented at the Western Surgical Association 119th Scientific Session, Tucson, AZ, November 2011.

Received January 6, 2012; Revised April 30, 2012; Accepted May 2, 2012.

From the Department of Surgery, Division of Surgical Oncology, Cedars-Sinai Medical Center, Los Angeles, CA (Chung, Mirzadehgan, Giuliano) and the Departments of Molecular Oncology (Huynh), Surgical Oncology (Kidner), and Biostatistics (Sim), John Wayne Cancer Institute, Santa Monica, CA.

Correspondence address: Alice P Chung, MD, FACS, Cedars-Sinai Medical Center, Department of Surgery, 310 N San Vicente Blvd, Suite 316, Los Angeles, CA 90048. email: alice.chung@cshs.org

The increased use of breast MRI in women with newly diagnosed breast cancer has identified additional ipsilateral foci of cancer in 6% to 38% of cases.[5-21] This has resulted in increased preoperative detection of MF and MC disease and has been shown to lead to more mastectomies when compared with patients who have not had preoperative MRI.[22-25] However, many of these patients may desire breast conservation. There is controversy about whether BCS should be contraindicated in MF or MC breast cancer. Due to the ambiguity in defining MF and MC breast cancer among previous studies, it is difficult to draw definitive conclusions from data reported. The objective of our study was to compare the outcomes of BCT in patients with MF breast cancer with those of patients with unifocal breast cancer.

METHODS

Female patients older than age 18, diagnosed with unilateral stage I to III breast cancer and treated with BCS at the John Wayne Cancer Institute between January 1991 and December 2009 were identified from a prospectively maintained database. All patients were treated by surgical staff of

ISSN 1072-7515/12/$36.00
http://dx.doi.org/10.1016/j.jamcollsurg.2012.05.006

Abbreviations and Acronyms

BCS = breast conserving surgery
BCT = breast conserving therapy
DFS = disease-free survival
LR = local recurrence
LRFS = local recurrence-free survival
MC = multicentric
MF = multifocal
OS = overall survival
Uni = unifocal

the John Wayne Cancer Institute and had adjuvant whole breast irradiation. Patients were excluded if they were male, had previous ipsilateral breast cancer, had segmentectomy with partial breast irradiation, or had segmentectomy without subsequent radiation.

We identified 1,246 patients who had BCT for treatment of invasive breast cancer. Within this group, we then identified patients who had MF invasive breast cancer, comprising the MF group. MF breast cancer was defined as 2 or more distinct invasive tumors excised with a single incision or segmentectomy; those with a distinct separate focus of in situ disease were not included in this study. MC breast cancer was defined as 2 or more distinct invasive tumors that would require more than 1 incision or segmentectomy. Those who had a single focus of invasive cancer excised with a segmentectomy comprised the unifocal (Uni) group. The database was reviewed with documentation of clinicopathologic data. Patient characteristics included age at diagnosis, presentation, breast imaging findings, tumor size, number of invasive cancer foci, grade, estrogen-receptor status, nodal status, tumor stage, surgical treatment, adjuvant systemic treatment, and date and status of last follow-up.

Chi-square analysis was used to compare the MF with the Uni group with respect to categorical variables such as tumor features, patient characteristics, and treatment options. Continuous variables were analyzed using the Student's *t*-test and Wilcoxon rank sum test. The variables associated with survival in the univariable Cox proportional hazard regression model were selected using the criteria of $p < 0.1$ for inclusion in the multivariable Cox regression model. A p value of 0.1 was selected in order to account for variables that were not significant in the univariable analysis due to interactions that could become significant in the multivariable analysis. The final model was obtained by stepwise selection (combination of forward and backward) method and the factors that were significantly associated with survival, including local recurrence-free survival (LRFS), disease-free survival (DFS), and overall survival (OS), were identified. Survival curves for each group were generated using Kaplan-Meier methods. A patient was censored for OS if she was alive at the time of last follow-up; a patient was censored for DFS if she did not have any recurrence at the time of last follow-up; and a patient was censored for LRFS if she did not have a local or regional recurrence at the time of last follow-up. This study was approved by the John Wayne Cancer Institute IRB.

RESULTS

We identified 197 patients with MF or MC breast cancer and 1,049 with Uni breast cancer. Within the MF group, 6 (3.0%) had MC disease, 8 (4.1%) did not receive adjuvant radiation therapy, 1 (0.5%) was treated with accelerated partial breast radiation, and in 18 (9.1%), it was unknown whether the patient received adjuvant radiation therapy. Within the Uni group, 5 (0.05%) did not receive adjuvant radiation therapy, 31 (3.0 %) received accelerated partial breast irradiation, and in 14 (1.3%), it was unknown whether the patient received adjuvant radiation therapy. After excluding these cases from the dataset, 164 cases of MF breast cancer treated with adjuvant whole breast irradiation remained in the MF group and 999 patients comprised the Uni group. The mean age at diagnosis of all 1,163 patients was 57.7 years (range 26 to 87 years). Overall, there were 644 of 1,163 (55.4%) patients with stage I breast cancer, 398 of 1,163 (34.2%) patients with stage II, and 47 of 1,163 (4.0%) who presented with stage III disease. In 75 of 1,163 (6.4%), there was inadequate information in the database to provide final pathologic stage. Median follow-up was 112 months (range 1 to 230 months).

Table 1 compares the 2 groups of patients with respect to tumor characteristics. The Uni group had a higher proportion of patients with stage I tumors compared with the MF group (61% vs 48%, $p < 0.0001$). There was a difference between the 2 groups with respect to T status ($p = 0.001$). The MF group had more T2 and T3 tumors compared with the Uni group. With regard to histology, there was a difference between the 2 groups ($p < 0.001$); the Uni group contained more patients with invasive ductal carcinoma and the MF group had more tumors with lobular histology. There was no significant difference between the 2 groups with respect to mean age at diagnosis, tumor grade, nodal status, estrogen receptor status, and use of adjuvant systemic therapy.

In our analysis of LRFS, we identified age, T stage, use of hormonal therapy, and presence of multifocal disease (MF) to be significantly associated with LRFS on log-rank univariable analysis (Table 2). We included age, T stage, estrogen receptor status, use of hormonal therapy, and presence

Table 1. Patient Characteristics in Multifocal and Unifocal Groups

Characteristic	Multifocal (n = 164)	Unifocal (n = 999)	p Value
Age, mean ± SD, y	57.7 ± 12.0	57.7 ± 11.8	1.00*
Pathologic stage (missing, 75), n (%)			<0.0001†
I	77/160 (48.1)	567/928 (61.1)	
II	67/160 (41.9)	331/928 (35.7)	
III	16/160 (10.0)	30/928 (3.2)	
Tumor size (missing, 68), n (%)			0.001†
T1	104/160 (65.0)	709/935 (75.7)	
T2	48/160 (30.0)	210/935 (22.5)	
T3	8/160 (5.0)	16/935 (1.7)	
Node status (missing, 43), n (%)			0.06
N0	110/161 (68.3)	723/959 (75.6)	
N+	51/161 (31.7)	236/959 (24.7)	
Histology, n (%)			<0.0001
Carcinoma NOS	1/164 (0.6)	8/999 (0.8)	
Ductal	96/164 (58.5)	816/999 (81.7)	
Ductal + lobular	27/164 (16.5)	100/999 (10)	
Lobular	40/164 (24.4)	75/999 (7.5)	
Grade (missing, 82), n (%)			0.73
Low	45/148 (30.4)	292/933 (31.3)	
Intermediate	67/148 (45.3)	392/933 (42.0)	
High	36/148 (24.3)	249/933 (26.7)	
ER status (missing, 162), n (%)			0.33
Positive	131/146 (89.7)	742/855 (86.8)	
Negative	15/146 (10.3)	113/855 (13.2)	
Chemotherapy (missing, 239), n (%)			0.80
Yes	83/162 (51.2)	382/763 (50.1)	
No	79/162 (48.8)	380/763 (49.9)	
Hormone (missing, 132), n (%)			0.23
Yes	128/159 (80.5)	664/872 (76.2)	
No	31/159 (19.5)	208/872 (23.8)	

*Student's *t*-Test (otherwise, analysis by chi-square analysis).
†Analysis by Cochran Armitage Test.
ER, estrogen receptor; NOS, not otherwise specified.

of multifocality in the multivariable analysis and found that T stage, estrogen receptor status, and MF continued to have a significant association with LRFS at 10 years. Of the local recurrences, there were only 2 nodal failures, both in the Uni group: 1 that presented alone and was categorized as a locoregional recurrence and 1 that presented with distant metastases and was therefore categorized as a distant failure. Univariable analysis identified age, T stage, MF, and administration of hormonal therapy to be strongly associated with DFS at 10 years (Table 3). These variables, along with use of adjuvant chemotherapy, were included in the multivariable analysis, and MF, use of hormonal therapy, and T stage remained significant factors associated with DFS. In the univariable analysis of 10-year OS, age, T stage, MF, use of hormonal therapy, and histology were significantly associated with OS (Table 4). These factors were included in the multivariable analysis, and age, T stage, hormonal therapy, and MF were significantly associated with OS.

Within the MF group, 35 of 164 (21.3%) patients presented with multiple ipsilateral lesions on preoperative mammogram or ultrasound. In 5 of 164 cases (3.0%), preoperative imaging reports were unavailable. In the remaining 124 of 164 (75.6%) MF cases, MF disease was detected by pathologic analysis of the lumpectomy specimen. We compared the group of MF patients who had lesions detected preoperatively with those whose MF was detected only by pathology with respect to LRFS and DFS, and we found no significant difference between the 2 groups, as demonstrated in Tables 2 to 4.

Figure 1 shows the Kaplan-Meier curves of the MF and Uni groups. The Uni group had a significant improvement

Table 2. Univariable and Multivariable Analysis over a 10-Year Follow-Up Interval Using Cox Proportional Hazard Models for Local Recurrence-Free Survival

		Univariable - log rank test	Univariable - Cox proportional hazard model		Multivariable - Cox proportional hazard model	
Variable	Events/total, n	p Value	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Group*						
Uni	6/999		Reference		Reference	
MF	10/164	<0.0001	14.4 (5.15, 40.32)	<0.0001	23.87 (5.81, 98.11)	<0.0001
T stage*						
T1	9/813		Reference		Reference	
T2	3/258	0.0017	1.09 (0.3, 4.03)	0.89	0.62 (0.13, 3)	0.55
T3	2/24		9.61 (2.6, 44.88)	0.004	6.88 (1.36, 34.79)	0.02
Lymph node status						
N0	11/833	0.67	Reference			
N+	3/287		0.76 (0.21, 2.72)	0.67		
Histology						
Carcinoma NOS	0/9		NA	0.99		
Ductal	10/912	0.38	0.4 (0.11, 1.46)	0.17		
Ductal + lobular	3/127		0.87 (0.18, 4.33)	0.87		
Lobular	3/115		Reference			
Grade						
Moderately diff	7/459	0.12	5.04 (0.62, 40.95)	0.13		
Poorly diff	6/285		7.08 (0.85, 58.81)	0.07		
Well diff	1/337		Reference			
ER status*						
Negative	4/128	0.06	Reference			
Positive	9/873		0.34 (0.1, 1.1)	0.07	0.15 (0.04, 0.55)	0.004
Chemotherapy						
No	6/459	0.43	Reference			
Yes	9/465		1.52 (0.54, 4.27)	0.43		
Hormonal therapy*						
No	7/239	0.04	Reference			
Yes	8/792		0.36 (0.13, 0.99)	0.05		
Radiology						
MF-no radiology	8/124	0.45	Reference	0.46		
MF-radiology	1/35		0.46 (0.06–3.68)			
Age*	16/1,163		0.94 (0.9, 0.98)	0.01		

*Variables used in multivariable analysis.
Diff, differentiated; ER, estrogen receptor; MF, multifocal disease present; MF-no radiology, multifocal disease not detected by preoperative imaging; MF-radiology, multifocal disease detected by preoperative imaging; NOS, not otherwise specified; Uni, unifocal.

in 10-year LRFS, DFS, and OS compared with the MF group, with the greatest difference seen in OS (99.1 % vs 92.2%; 97.7% vs 89.3%; and 98.4% vs 85.8%, respectively, $p < 0.0001$ for all 3 outcomes measures). On review of causes of mortality, only 30% of deaths in the MF group were known to be due to breast cancer; in the remaining 70% of patients, cause of death was either unknown or was due to causes other than breast cancer. Because the MF group and Uni group differed with respect to T stage and lymph node status, we conducted a stratified analysis by pathologic stage in an attempt to account for this variable as a confounder. The MF group continued to have worse outcomes than the Uni group for all 3 outcomes measures over 10 years ($p < 0.001$).

DISCUSSION

Our data show that MF invasive breast cancer is associated with inferior LRFS, DFS, and OS when compared with Uni invasive breast cancer in patients treated with BCT. Early reports of BCT in patients with MF breast cancer, defined as multiple ipsilateral breast lesions, identified high

Table 3. Univariable and Multivariable Analysis over a 10-Year Follow-Up Interval Using Cox Proportional Hazard Models for Disease-Free Survival

		Univariable - log rank test	Univariable - Cox proportional hazard model		Multivariable - Cox proportional hazard model	
Variable	Events/total, n	p Value	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Group*						
Uni	17/999		Reference		Reference	
MF	14/164	<0.0001	7.27 (3.55, 14.88)	<0.0001	5.86 (2.57, 13.33)	<0.0001
T stage*						
T1	16/813		Reference		Reference	
T2	9/258	<0.0001	1.85 (0.82, 4.19)	0.14	2.16 (0.88, 5.27)	0.0919
T3	4/24		11.41 (3.8, 34.31)	<0.0001	17.03 (5.06, 57.28)	<0.0001
Lymph node status						
N0	17/833	0.53	Reference			
N+	8/287		1.31 (0.56, 3.03)	0.53		
Histology						
Carcinoma NOS	0/9		NA	0.99		
Ductal	22/912	0.54	0.52 (0.2, 1.38)	0.19		
Ductal + lobular	4/127		0.69 (0.18, 2.56)	0.57		
Lobular	5/115		Reference			
Grade						
Moderately diff	11/459		1.33 (0.49, 3.59)	0.58		
Poorly diff	11/285	0.26	2.17 (0.8, 5.86)	0.13		
Well diff	6/337		Reference			
Estrogen receptor status						
Negative	5/128	0.31	Reference			
Positive	20/873		0.6 (0.23, 1.6)	0.31		
Chemotherapy						
No	10/459	0.07	Reference			
Yes	20/465		2.01 (0.94, 4.29)	0.072		
Hormonal therapy*						
No	12/239	0.01	Reference		Reference	
Yes	14/792		0.37 (0.17, 0.79)	0.01	0.21 (0.09, 0.48)	<0.01
Radiology						
MF-no radiology	9/124	0.75	Reference			
MF-radiology	3/35		1.24 (0.34, 4.59)	0.75		
Age*	31/1,163		0.97 (0.94, 1)	0.03		

*Variables used in multivariable analysis.
Diff, differentiated; ER, estrogen receptor; MF, multifocal disease present; MF-no radiology, multifocal disease not detected by preoperative imaging; MF-radiology, multifocal disease detected by preoperative imaging; NA, not available; NOS, not otherwise specified; Uni, unifocal.

local recurrence rates ranging from 25% to 40%.[26-28] In these early studies, microscopic margin status was not a consideration and re-excisions were not routinely performed. Since then a number of retrospective series evaluating resection margins for microscopic disease have accumulated, reporting lower rates of LR in selected patients with MF or MC breast cancer than reported in the earlier studies. Cho and colleagues[29] reported no LR in 15 patients with MF breast cancer, detected by either physical examination, imaging, or gross pathologic examination, treated with BCT and followed for a median of 76 months. Margins of resection in this study were microscopically clear and all patients received adjuvant radiation and systemic therapy. Kaplan and associates[30] compared 36 patients with MF breast cancer, detected by either physical examination or preoperative imaging and treated with BCT, with 19 patients with MF breast cancer treated with mastectomy. They found no LR in the mastectomy group and only 1 LR in the BCT group, with mean follow-up of 45 months. Margins were considered clear when greater than 1 mm in the BCT group. At our institution we require resection margins to be free of microscopic disease, and our LR rates were low in both cohorts, although the LR rate in the

Table 4. Univariable and Multivariable Analysis over a 10-Year Follow-Up Interval Using Cox Proportional Hazard Models for Overall Survival

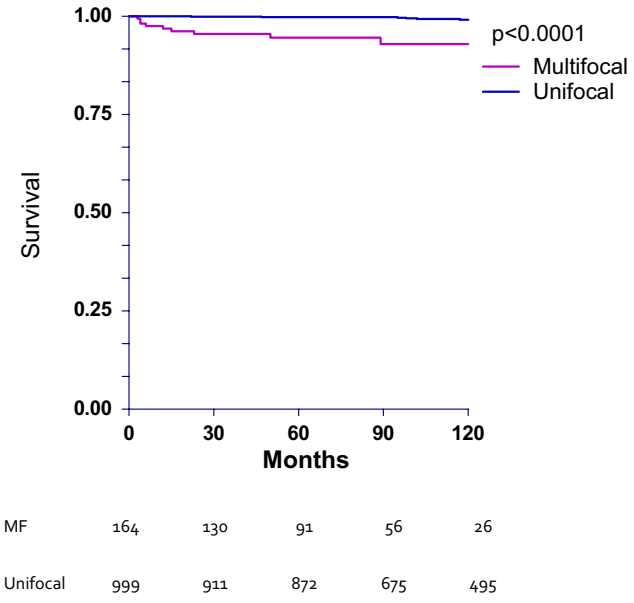
		Univariable - log rank test	Univariable - Cox proportional hazard model		Multivariable - Cox proportional hazard model	
Overall survival	Events/total, n	p Value	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Group*						
Uni	11/999	<0.0001	Reference		Reference	
MF	12/164		11.3 (4.95, 25.92)	<0.0001	10.57 (4.2, 26.59)	<0.0001
T stage*						
T1	9/813		Reference		Reference	
T2	9/258	<0.0001	3.36 (1.33, 8.47)	0.01	4.95 (1.79, 13.69)	0.002
T3	3/24		16.12 (4.35, 59.81)	<.0001	36.77 (8.66, 156.18)	<.0001
Lymph node status						
N0	11/833	0.7	Reference			
N+	5/287		1.23 (0.43, 3.54)	0.7		
Histology*						
Carcinoma NOS	0/9	0.0003	NA	0.99		
Ductal	12/912		0.18 (0.07, 0.43)	0.0001		
Ductal + lobular	3/127		0.32 (0.09, 1.21)	0.09		
Lobular	8/115		Reference			
Grade						
Moderately diff	7/459		1.22 (0.36, 4.12)	0.75		
Poorly diff	9/285	0.15	2.63 (0.81, 8.55)	0.11		
Well diff	4/337		Reference			
Estrogen receptor						
Negative	4/128	0.44	Reference			
Positive	17/873		0.66 (0.22, 1.95)	0.45		
Chemotherapy						
No	12/459	0.7	Reference			
Yes	10/465		0.85 (0.37, 1.97)	0.7		
Hormonal therapy*						
No	10/239	0.02	Reference			
Yes	12/792		0.39 (0.17, 0.91)	0.03	0.21 (0.08, 0.55)	0.002
Radiology						
MF-no radiology	10/124	0.4	Reference	0.42		
MF-radiology	1/35		0.43 (0.05, 3.33)			
Age*	16/1,163		1.07 (1.04, 1.11)	0.0001	1.1 (1.06, 1.15)	<.0001

*Variables used in multivariable analysis.
Diff, differentiated; ER, estrogen receptor; MF, multifocal disease present; MF-no radiology, multifocal disease not detected by preoperative imaging; MF-radiology, multifocal disease detected by preoperative imaging; NA, not available; NOS, not otherwise specified; Uni, unifocal.

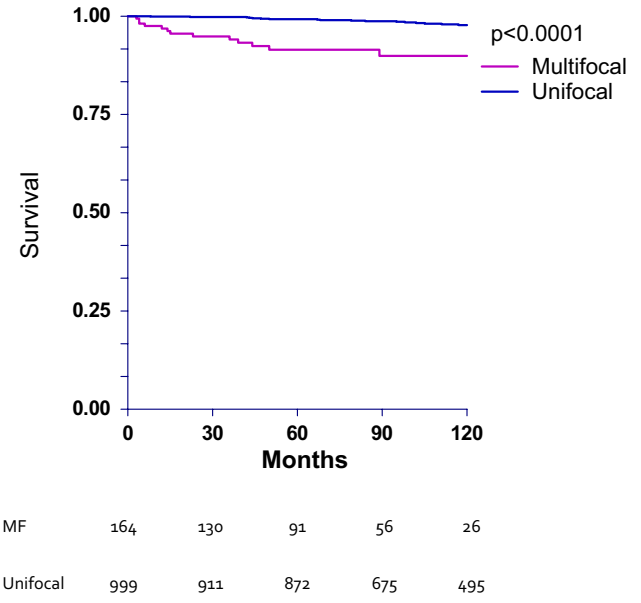
Uni group was lower than in the MF group. Our study includes a larger sample size and longer follow-up than many of these reports.

Only 21% of patients in the MF group in this study had MF detected by preoperative imaging. This study population consists largely of tumors that were found to be MF only by pathologic review of the lumpectomy specimen. There was no difference in local recurrence or survival between those patients whose MF was detected by preoperative imaging and those whose MF disease was detected by pathology. This suggests that altering the surgical approach in the event that MF disease is incidentally identified in the lumpectomy specimen would not make a difference in outcomes. A large majority of these patients were treated before the era of preoperative breast MRI. If preoperative MRI had been used in all patients, perhaps some of the additional MF tumors that were detected only by pathology would have been detected by MRI. Nevertheless, detection by preoperative imaging was not found to be associated with outcomes.

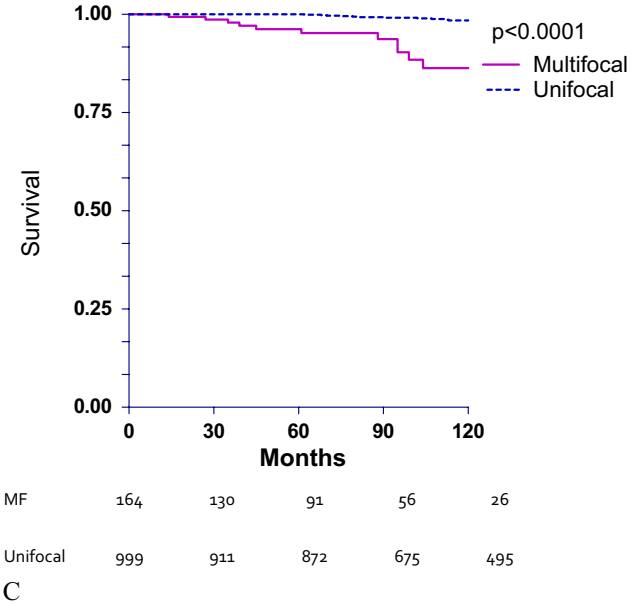
This study did not evaluate patients with MF breast cancer who were treated by mastectomy, introducing a potential selection bias as to which patients are offered



A



B



C

Figure 1. Kaplan-Meier curves for survival in the multifocal (MF) group and the unifocal group: (A) 10-year local recurrence-free survival, 99.1% vs 92.2%, respectively, $p < 0.0001$; (B) 10-year disease-free survival, 97.7% vs 89.3%, respectively, $p < 0.0001$, and (C) 10-year overall survival, 98.4% vs 85.8%, respectively, $p < 0.0001$.

or receive BCT. There have been several studies in the literature that included mastectomy in their comparisons of surgical treatment for MF or MC disease. Nos and colleagues[31] followed patients with MF breast cancer (defined as tumors separated by less than 5 cm) and MC (defined as tumors separated by 5 cm or more) disease for 5 years; 56 had BCT and 132 had mastectomy. The LR was 11% in both groups and OS was 94% in the BCT group compared with 90% in the mastectomy group. Kaplan and coworkers[30] conducted a similar comparison and did not find a difference between the BCT and mastectomy groups with respect to LR or DFS.

There are few studies in the literature with sample size or length of follow-up that are comparable to our study. Gentilini and colleagues[32] published one of the largest retrospective series of BCT in MF (defined as tumors within the same quadrant) or MC (defined as tumors in different quadrants) breast cancer, including 421 patients with MF and 55 patients with MC breast cancer. With a median follow-up of 73 months, 24 (5%) developed an ipsilateral breast recurrence. The reported LR rate of 5% is very low in

Table 5. Studies on Local Recurrence Rate in Breast Conserving Therapy for Multifocal or Multicentric Disease

Study, y	MF or MC*	Patients, n	Local recurrence, %	Median follow-up, mo
Leopold, 1989[28]	MFMC	10	40	64
Kurtz, 1990[26]	MFMC	61	25	71
Wilson, 1993[27]	MF	13	25	72
Hartsell, 1994[42]	MC	27	3.7	53
Nos, 1999[31]	MF	56	11	60
Cho, 2002[29]	MFMC	15	0	76
Kaplan, 2003[30]	MFMC	36	3	45
Okumura, 2004[43]	MFMC	34	0	58
Oh, 2006[35]	MFMC	97	6	66
Gentilini, 2008[32]	MFMC	476	5	73
Lim, 2009[44]	MF	147	2	59
This study	MF	164	6.1	112

*MFMC denotes that the population included those with MF and MC breast cancer.
MC, multicentric; MF, multifocal.

their large population of MF and MC breast cancer patients with long follow-up; however, there was no control group for comparison of outcomes. The LR rate in our MF group was only 6.1%, but the Uni group in our study had an LR rate of only 0.6%, suggesting a significant difference in local control. Table 5 summarizes LR rates, determined by the Kaplan-Meier method, reported in the major studies comparing outcomes of BCT in MF or MC and unifocal breast cancer.

In addition to LR, we found MF disease to be associated with lower DFS and OS. The deaths in the MF group may have been from causes other than breast cancer, suggesting a possible selection bias where patients with higher morbidity were selected for BCS over mastectomy in this group of patients. There have been a number of studies evaluating the prognostic significance of multifocality. Several investigators who compared outcomes between patients with unifocal disease and MF disease have reported a strong correlation between MF and nodal involvement,[33,34] but this did not translate into a significant difference in DFS or OS. Oh and colleagues[35] investigated whether presence of MF disease was associated with an inferior outcome in 706 patients treated with neoadjuvant therapy. They found no difference in 5-year DFS and OS between patients with unicentric and MF breast cancer among patients treated with BCT. These studies had relatively short follow-up.

This study is one of few in the literature to report MF disease to be one of the strongest predictors of survival among patients with BCT. Weissenbacher and associates[36] identified 288 patients with MF breast cancer and, in a matched-pair analysis with a mean follow-up of 7 years, found that those with MF disease had an inferior breast cancer-specific survival, relapse-free survival, and distant metastasis-free survival. Ustaalioglu and colleagues[37] recently published their findings on 697 patients with invasive breast cancer, 107 of whom had MF disease; they reported a significantly lower DFS in patients with MF breast cancer compared with those with unifocal cancer. Yerushalmi and coauthors[38] reported the largest series of patients with MF breast cancer. Among 1,554 patients with MF disease and 23,766 patients with unifocal disease, this large population-based study found MF breast cancer to be a significant predictor of breast cancer-specific survival, but not OS.

These findings, along with our results, raise the question of whether the current TNM staging classification underestimates the true risk of MF breast cancer. As we know, the present TNM staging system does not account for multifocality. Because T status is based only on the largest tumor focus and disregards the smaller tumor foci, it is not a true reflection of the volume of tumor in the breast. Several authors have suggested that combining sizes of the various tumor foci to determine T status may more accurately reflect prognosis in multifocal disease. Andea and colleagues[39] analyzed 101 specimens containing multiple breast tumors and compared nodal status between those whose T status was the tumor size of the largest tumor focus and those whose T stage was the aggregate tumor size calculated by adding the diameters of each tumor focus. They did not find a difference between the 2 groups with respect to nodal involvement. When O'Daly and colleagues[40] combined the sizes of multiple tumor foci in patients with MF disease, they upstaged the pathologic T status of 34% of the patients. They similarly did not find a difference in nodal positivity among those who were upstaged. Conversely, Coombs and Boyages[41] conducted a similar comparison in 94 patients with multifocality and found that use of aggregate dimensions reclassified a significant number of multifocal tumors at more advanced stage. These authors concluded from their findings that tendency of breast cancer to metastasize is a reflection on the total tumor load rather than the diameter of the largest tumor focus. The factor of tumor volume may explain our findings of decreased OS.

CONCLUSIONS

In conclusion, our data suggest that MF invasive breast cancer is associated with inferior survival vs survival in patients with unifocal breast cancer, stage for stage. Inferior OS in the MF group was possibly due to a high rate of death from causes other than breast cancer, although the

cause of death in many cases was unknown. There was a slight difference in DFS and LRFS between the MF group and the Uni group, but the rates in both groups were acceptable. The rate of LR in both groups was low (6.1% in MF vs 0.6% in Uni), suggesting that BCS is an acceptable approach to the treatment of multifocal breast cancer.

Author Contributions

Study conception and design: Chung, Giuliano
Acquisition of data: Chung, Huynh, Kidner, Mirzadeghan
Analysis and interpretation of data: Chung, Sim
Drafting of manuscript: Chung, Sim
Critical revision: Chung, Giuliano

REFERENCES

1. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–1241.
2. Jacobson JA, Danforth DN, Cowan KH, et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. N Engl J Med 1995;332: 907–911.
3. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227–1232.
4. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. J Natl Cancer Inst 2000;92: 1143–1150.
5. Harms SE, Flamig DP. MR imaging of the breast. J Magn Reson Imaging 1993;3:277–283.
6. Harms SE, Flamig DP. MR imaging of the breast: technical approach and clinical experience. Radiographics 1993;13:905–912.
7. Harms SE, Flamig DP, Hesley KL, et al. MR imaging of the breast with rotating delivery of excitation off resonance: clinical experience with pathologic correlation. Radiology 1993;187: 493–501.
8. Orel SG, Schnall MD, Powell CM, et al. Staging of suspected breast cancer: effect of MR imaging and MR-guided biopsy. Radiology 1995;196:115–122.
9. Boetes C, Mus RD, Holland R, et al. Breast tumors: comparative accuracy of MR imaging relative to mammography and US for demonstrating extent. Radiology 1995;197:743–747.
10. Mumtaz H, Hall-Craggs MA, Davidson T, et al. Staging of symptomatic primary breast cancer with MR imaging. AJR Am J Roentgenol 1997;169:417–424.
11. Liberman L, Morris EA, Dershaw DD, et al. MR imaging of the ipsilateral breast in women with percutaneously proven breast cancer. AJR Am J Roentgenol 2003;180:901–910.
12. Bedrosian I, Schlencker J, Spitz FR, et al. Magnetic resonance imaging-guided biopsy of mammographically and clinically occult breast lesions. Ann Surg Oncol 2002;9:457–461.
13. Esserman L, Hylton N, Yassa L, et al. Utility of magnetic resonance imaging in the management of breast cancer: evidence for improved preoperative staging. J Clin Oncol 1999;17:110–119.
14. Drew PJ, Chatterjee S, Turnbull LW, et al. Dynamic contrast enhanced magnetic resonance imaging of the breast is superior to triple assessment for the pre-operative detection of multifocal breast cancer. Ann Surg Oncol 1999;6:599–603.
15. Pediconi F, Miglio E, Telesca M, et al. Effect of preoperative breast magnetic resonance imaging on surgical decision making and cancer recurrence rates. Invest Radiol 2012;47:128–135.
16. Ha GW, Yi MS, Lee BK, et al. Clinical outcome of magnetic resonance imaging-detected additional lesions in breast cancer patients. J Breast Cancer 2011;14:213–218.
17. 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.
18. Girardi V, Carbognin G, Camera L, et al. Multifocal, multicentric and contralateral breast cancers: breast MR imaging in the preoperative evaluation of patients with newly diagnosed breast cancer. Radiol Med 2011;116:1226–1238.
19. Tendulkar RD, Chellman-Jeffers M, Rybicki LA, et al. Preoperative breast magnetic resonance imaging in early breast cancer: implications for partial breast irradiation. Cancer 2009;115: 1621–1630.
20. Godinez J, Gombos EC, Chikarmane SA, et al. Breast MRI in the evaluation of eligibility for accelerated partial breast irradiation. AJR Am J Roentgenol 2008;191:272–277.
21. Al-Hallaq HA, Mell LK, Bradley JA, et al. Magnetic resonance imaging identifies multifocal and multicentric disease in breast cancer patients who are eligible for partial breast irradiation. Cancer 2008;113:2408–2414.
22. Adkisson CD, Bagaria SP, Parker AS, et al. Which eligible breast conservation patients choose mastectomy in the setting of newly diagnosed breast cancer? Ann Surg Oncol 2012;19:1129–1136.
23. Turnbull L, Brown S, Harvey I, et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. Lancet 2010;375:563–571.
24. Houssami N, Hayes DF. Review of preoperative magnetic resonance imaging (MRI) in breast cancer: should MRI be performed on all women with newly diagnosed, early stage breast cancer? CA Cancer J Clin 2009;59:290–302.
25. Bleicher RJ, Ciocca RM, Egleston BL, et al. Association of routine pretreatment magnetic resonance imaging with time to surgery, mastectomy rate, and margin status. J Am Coll Surg 2009; 209:180–187; quiz 294–185.
26. Kurtz JM, Jacquemier J, Amalric R, et al. Breast-conserving therapy for macroscopically multiple cancers. Ann Surg 1990;212:38–44.
27. Wilson LD, Beinfield M, McKhann CF, Haffty BG. Conservative surgery and radiation in the treatment of synchronous ipsilateral breast cancers. Cancer 1993;72:137–142.
28. 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.
29. Cho LC, Senzer N, Peters GN. Conservative surgery and radiation therapy for macroscopically multiple ipsilateral invasive breast cancers. Am J Surg 2002;183:650–654.
30. Kaplan J, Giron G, Tartter PI, et al. Breast conservation in patients with multiple ipsilateral synchronous cancers. J Am Coll Surg 2003;197:726–729.
31. Nos C, Bourgeois D, Darles C, et al. [Conservative treatment of multifocal breast cancer: a comparative study]. Bull Cancer 1999;86:184–188.

32. Gentilini O, Botteri E, Rotmensz N, et al. Conservative surgery in patients with multifocal/multicentric breast cancer. Breast Cancer Res Treat 2009;113:577–583.
33. 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.
34. Pedersen L, Gunnarsdottir KA, Rasmussen BB, et al. The prognostic influence of multifocality in breast cancer patients. Breast 2004;13:188–193.
35. 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.
36. 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.
37. Ustaalioglu BO, Bilici A, Kefeli U, et al. The importance of multifocal/multicentric tumor on the disease-free survival of breast cancer patients: single center experience. Am J Clin Oncol 2011 [ePub ahead of print].
38. 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.
39. Andea AA, Wallis T, Newman LA, et al. Pathologic analysis of tumor size and lymph node status in multifocal/multicentric breast carcinoma. Cancer 2002;94:1383 –1390.
40. O'Daly BJ, Sweeney KJ, Ridgway PF, et al. The accuracy of combined versus largest diameter in staging multifocal breast cancer. J Am Coll Surg 2007;204:282–285.
41. Coombs NJ, Boyages J. Multifocal and multicentric breast cancer: does each focus matter? J Clin Oncol 2005;23:7497–7502.
42. 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.
43. Okumura S, Mitsumori M, Yamauchi C, et al. Feasibility of breast-conserving therapy for macroscopically multiple ipsilateral breast cancer. Int J Radiat Oncol Biol Phys 2004;59:146–151.
44. Lim W, Park EH, Choi SL, et al. Breast conserving surgery for multifocal breast cancer. Ann Surg 2009;249:87–90.

Discussion

INVITED DISCUSSANT: DR NORA HANSEN (Chicago, IL): Traditionally, the surgical option for a patient with multicentric (MC) cancer is mastectomy, and many surgeons would advocate a mastectomy for multifocal (MF) cancer. This group looked at disease-free survival (DFS) and overall survival (OS) outcomes for patients with MC and MF cancer and compared them with patients with unicentric breast cancer. They demonstrated both a decrease in DFS and OS in patients undergoing breast conservation (BC) for MC or MF cancer compared with unicentric cancer. In the article, they conclude that BC is an acceptable approach in these MC/MF cancers but they do have higher local recurrence rates and lower survival rates compared with those patients undergoing BC for unifocal cancer. These results, although provocative, lead me to ask several questions: Did you look at the presence of ductal carcinoma in situ (DCIS) in your cohort of patients and did the presence of associated DCIS have an impact on outcomes such as local recurrence in your cohort of patients? You looked at prognostic factors such as estrogen receptor and did not demonstrate a significant impact between your groups, but I did not see data on human epidermal growth factor receptor 2 (HER2) status. Did you collect data on HER2/neu status and, if so, did this have any impact on your results? Because all of these patients underwent BC with postoperative radiation therapy (RT), did all of your patients receive a boost dose of RT and, if not, were there any differences in the boost dose between the 2 groups? For example, did your patients with MC cancer receive boosts to both sites and did the use of a boost impact local recurrence rates and ultimately OS? The fact that you noted a decrease in OS in the group with MC/MF cancer is an interesting one. Have you looked at your patients with MF/MC who underwent mastectomy and compared them with those patients with MF/MC undergoing BC to see if there was a difference in OS? I would imagine the decrease in OS is due more to biologic factors than surgical choice. Were there other factors that impacted OS not related to breast cancer, such as the older patient with MF or MC cancer who chose conservation because of medical reasons? In your article, you suggest that the TNM staging system might be inaccurate because it does not evaluate tumor burden in terms of volume; rather, it only accounts for the size of the largest tumor deposit. In this study, were you able to quantify the tumor burden in those patients with MF or MC cancer and to truly evaluate if it is the tumor volume that impacts DFS and OS? Finally, if a patient presents to you tomorrow with MC or MF cancer, how do you counsel them as to the type of surgical options they have, and do you recommend BC to them?

DR ARMANDO GIULIANO (Los Angeles, CA): We did not look at DCIS. Perhaps we should because I think an extensive burden of DCIS would have affected the local recurrence rate. And we did not look at HER2/neu status. Many of these patients, if not most, were in the pre-HER2 testing era.

It is our routine practice to boost the site of invasive cancers. We would boost both sites for MC cancers. There were very few MCs. And we would boost a large site for the MF.

All patients had a lumpectomy. We did not compare those patients with those who had mastectomy. I think much of the difference in OS is selection bias. If you have a patient with a lot of morbidity and 2 primary breast cancers, you would be more likely to do a big lumpectomy than a mastectomy. So I think the survival is not due to the breast cancer but due to the selection of the patients.

I am very interested in the concept of tumor burden because the T system is based on the largest of the 2 tumors. It seems to me that there should be some summation of the 2 to determine the size. I am not surprised that this is not done though. It would be complicated. Dr Chung is now trying to estimate the size of the 2 tumors and whether the actual tumor burden affected survival and outcomes.

We have always counseled patients with MC cancer that a lumpectomy for BC is appropriate, but I have always said to them that I think local recurrence is higher. And we set out to do this study to see just how much higher it is. I was surprised by the fact that it was only 5% or 6%.