

ORIGINAL ARTICLE

Breast conserving surgery in patients with multifocal/multicentric breast cancer

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Summary

Purpose: To retrospectively evaluate the outcome of patients with multifocal (MF) and multicentric (MC) breast cancer treated with conservative surgery.

Methods: We evaluated 59 patients who had undergone breast conserving surgery (BCS) for MF/MC cancer between 1998-2008. We used sentinel lymph node (SLN) biopsy for all 59 patients and we performed axillary lymph node dissection in those with positive SLN. Local control, overall survival (OS), disease-free survival (DFS) and identification of predictive factors for recurrence were evaluated.

Results: Twenty patients with modified radical mastectomy because of persistent positive margins were excluded from the study. Evaluated were 55 patients with MF (93.2%) and 4 (6.8%) with MC disease. Thirty-four patients (57.6%) had 2, 20 patients (33.9%) had 3 and 5 (8.5%) had 4 or more

tumor foci. Median follow up time was 20 months (range 2-97). The projected 5- and 8-year OS were 95% and 89% respectively, and DFS 92.3%. At multivariate analysis, over-expression of human epidermal growth factor receptor 2 (HER-2) was associated with a higher ipsilateral breast cancer recurrence. Menopausal status, MF/MC disease, number of tumor foci (2 vs. ≥ 3), histological grade, extracapsular extension (ECE), lymphovascular invasion (LVI), and hormone receptor status were not associated with ipsilateral breast cancer recurrence.

Conclusion: Our study demonstrates that in selected patients with MF/MC breast cancer, wide conservative surgery is a safe therapy.

Key words: breast cancer, conservative surgery, multicentric, multifocal

Introduction

MF/MC tumors are defined by the presence of simultaneous independent multiple infiltrating and macroscopically measurable tumors in the same breast [1]. Practically, the distinction between multifocality and multicentricity is based on topographic anatomy. Multifocality is defined by the presence of multiple foci in the same quadrant of the same breast; multicentricity involves the occurrence of separate tumors at a distance of at least 5 cm in different quadrants [2].

The presence of multiple foci of cancer within the same breast has traditionally been considered a contraindication for conservative surgery due to the difficulty in obtaining a clear margin and the risk of local recurrence. In fact, many surgeons continue to propose mastectomy for MF/MC because earlier series have demonstrated high rates of local recurrence following BCS [3-8].

More recently two new reports demonstrated that in selected patients with MF/MC breast cancer, wide conservative surgery is not associated with poor local disease control, is oncologically safe and can be considered whenever acceptable cosmetic results can be achieved [9,10].

The aim of this study was to retrospectively evaluate the outcome of patients with MF/MC breast cancer who had undergone conservative surgery with special attention being paid to local control, OS, DFS and to identify predictive factors for recurrence in these patients.

Methods

We retrospectively analysed 556 breast cancer patients with stage 0-IIb (T1-2 N1) treated at the Istanbul University Medical School, Division of the Breast

Clinic between 1998 and 2008. All 556 patients underwent BCS (lumpectomy or quadrantectomy). Of 556 patients, 477 (86%) had unifocal and 79 (14%) MF/MC disease. MC was defined as 2 or more distinct cancers in same quadrant of the breast in the pathologic reports. Multicenter cancer was defined as separate lesions at a distance of at least 5 cm in different quadrants [2]. Patients were staged according the American Joint Committee on Cancer (6th edition). Margin status was classified as clear, close (cancer cells within 1 mm of the specimen edge) or involved. Re-excision or modified radical mastectomy was performed in 27/79 (34%) patients with involved margins. Seven of 27 (26%) patients underwent immediate second re-excision after frozen sections revealed positive margins. Modified radical mastectomy was performed in 20/27 (74%) patients due to persistent positive margins after second re-excision. Twenty patients with primary modified radical mastectomy were excluded from study, leaving MF/MC patients with lumpectomy or quadrantectomy for analysis. SLN biopsy was taken in all 59 patients and axillary lymph node dissection in those with positive SLN was performed.

Estrogen receptor (ER), progesterone receptor (PR) and HER-2 status were investigated by immunohistochemistry. Eighty-one percent of patients had either ER or PR positive tumors; 95.4% of these patients received adjuvant hormonal therapy (tamoxifen or aromatase inhibitors) and 71.2% were administered adjuvant chemotherapy (53/59). External radiation therapy (RT) was delivered to 84.7% of the patients.

Statistical analysis

DFS was defined as the time from first operation to recurrence of breast cancer and OS as the time from first operation of breast cancer to death. Five-year DFS and OS curves were calculated by the Kaplan-Meier method. Prognostic factors such as age, menopausal status, tumor size, hormone receptor status, ECE, LVI, tumor grade, and HER-2 status were evaluated with univariate and multivariate Cox regression analysis. A *p*-value <0.05 was considered statistically significant. All data were analysed using the SPSS, version 16.0 (SPSS Inc, Chicago, IL, USA).

Results

The patient median age was 49 years (range 24-77). Median follow-up time was 20 months (range 2-97). Table 1 shows patient and tumor characteristics. Fifty-five patients (93.2%) had MF and 4 (6.8%) MC

Table 1. Patient and tumor characteristics

Characteristics	Patients, n	%	Univariate analysis <i>p</i> -value	Multivariate analysis <i>p</i> -value
Age, years				
Median (range)	49 (24-77)			
Menopause			0.177	0.869
Premenopausal	37	62.7		
Postmenopausal	22	37.3		
Tumor size			0.918	0.138
Tis	2	3.4		
T1	32	54.2		
T2	25	42.4		
Number of foci			0.704	0.972
Multifocal	55	93.2		
Multicentric	4	6.8		
Number of tumors			0.914	0.598
2	34	57.6		
≥3	25	42.4		
Histological type			0.405	0.594
Invasive ductal	33	55.9		
Invasive lobular	9	15.3		
Mixed	15	25.4		
DCIS	2	3.4		
Other	2	3.4		
Histological grade			0.171	0.221
1-2	21	35.5		
3	25	42.3		
Unknown	13	22.2		
ECE			0.532	0.481
Positive	16	27.2		
Negative	40	67.8		
Unknown	3	5.0		
LVI			0.426	0.468
Positive	34	57.7		
Negative	22	37.3		
Unknown	3	5.0		
Local recurrence			0.001	0.588
Yes	2	3		
No	57	97		
Hormone receptors			0.565	0.364
Negative	8	13.6		
Positive	48	81.3		
Unknown	3	5.1		
CerbB2			0.086	0.027
Negative	47	79.7		
Positive	4	6.8		
Unknown	8	13.5		

DCIS: ductal carcinoma in situ, ECE: extracapsular extension, LVI: lymphovascular invasion

disease. Thirty-four patients (57.6%) had 2, 20 patients (33.9%) had 3 and 5 (8.5%) had 4 or more tumor foci.

Only 2 patients died at the 38th and 47th months. One of them died of multiple lung metastases and the second patient died from unknown reasons. OS was 93.3% (Figure 1). Local recurrence within the breast was detected in only 2 patients at the 47th and 50th

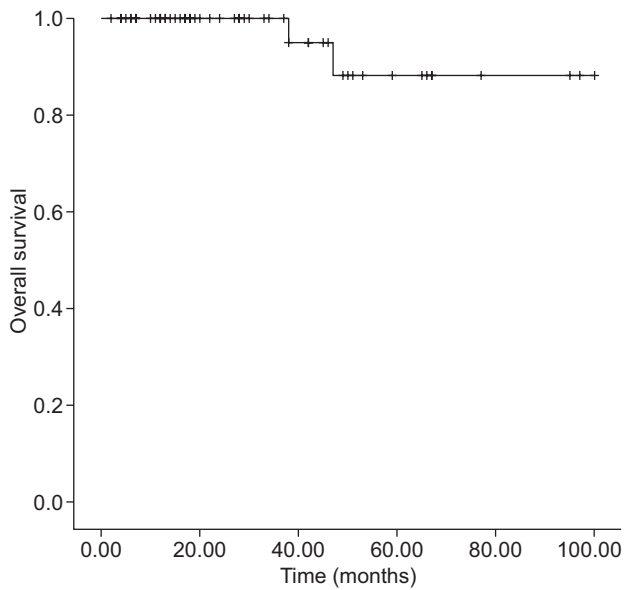


Figure 1. Overall survival for all 59 MF/MC patients.

months who subsequently underwent quadrantectomy. After surgery the patients were subjected to RT and chemotherapy. The 5- and 8-year OS were 95% and 89% respectively, and DFS 92.3% (Figure 2).

At multivariate analysis, overexpression of HER-2 was associated with a high ipsilateral breast cancer recurrence, although this was not associated in univariate analysis. Menopausal status, MF/MC disease, number of tumor foci (2 vs. ≥ 3), histological grade, ECE, LVI, and hormone receptor status were not associated with ipsilateral breast cancer recurrence (Table 1).

Discussion

Kurtz et al. [3] reported that patients with macroscopically multiple invasive breast cancer were at a higher risk of local failure if tumors were clinically or radiological apparent (36% rate of local recurrence). They also compared 61 patients with multiple cancers and 525 patients with unifocal tumor. Their results showed that patients with multifocal cancer had a higher local recurrence rate than patients with a unifocal lesion (25 vs. 11%; $p < 0.005$), but they haven't found any difference in 10-year survival between the 2 groups.

Cho et al. [11] reported that in selected cases with MF/MC the combination of conservative surgery and radiation therapy resulted in acceptable local-regional control, based on their experience with 15 patients affected by multiple ipsilateral invasive breast cancer. Okumura and colleagues [12] compared 34 patients with multiple invasive breast cancer and 594 patients with unifocal disease and did not find any difference in

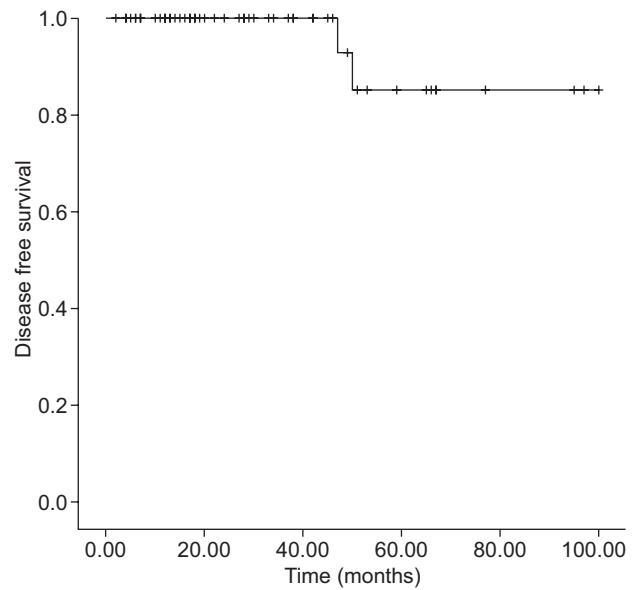


Figure 2. Disease free survival for all 59 MF/MC patients.

terms of local control, DFS or cosmetic result. It is interesting to note that despite the high rate of nodal metastases (55% of the patients), as expected in MF/MC breast cancer [13-15], distant metastases occurred in only 10.7% of the patients. One might speculate that the high rate of endocrine-responsive tumors in this series (87.6%), which is probably related to the high prevalence of invasive lobular carcinomas, might lead to a better outcome following adequate adjuvant treatment at least during the first 5 years. Furthermore, patients with lobular or ductal carcinoma had a similar outcome in terms of local recurrence (4.4 and 6.1%, respectively). This confirms that, despite the common multifocality and bilaterality of invasive lobular carcinoma, its occurrence does not by itself preclude breast conservation, as long as it is adequately excised.

More recently two important studies were published [9,10]. Lim et al. [10] retrospectively compared the local recurrence rate (LRR), DFS and OS of BCS with mastectomy for MF cancer. In addition, the LRR of BCS for MF cancer was compared with unifocal cancer. The 5-year OS was 93.38% for BCS and 94.53% for mastectomy (log rank, $p = 0.208$). The 5-year DFS was 89.08% for BCS and 91.88% for mastectomy (log rank, $p = 0.451$). Local failure occurred in 3 (2.0%) of 147 patient who had undergone BCS, and 3 (0.9%) of 331 patients with mastectomy ($p = 0.378$). Compared with BCS for unifocal cancer patients, the LRR of patients with MF cancer was not statistically different (2.0% for MF, 1.3 for unifocal; $p = 0.445$). The authors concluded that their study demonstrates that BCS for MF cancer is oncologically safe in selected patients. Gentilini et al. [9] also demonstrated that in selected patients with MF/MC

breast cancer, wide conservative surgery is not associated with poor local disease control and can be considered whenever acceptable cosmetic results can be achieved [16-18].

In our study the projected 5- and 8-year OS were 95% and 89% respectively, and DFS 92.3% in MF/MC patients with BCS. Only 2 patients died at the 38th and 47th months. One of them died due to multiple lung metastases and the second patient died of unknown reasons. Local recurrence happened in only 2 patients at the 47th and 50th months.

Gentilini et al. [14] reported that at multivariate analysis, overexpression of HER-2 and lack of both ER and PR were associated with higher rate of ipsilateral breast cancer reappearance. Our retrospective analysis showed that, while overexpression of HER-2 was associated with ipsilateral breast cancer recurrence, menopausal status, MF/MC disease, number of tumor foci (2 vs. ≥ 3), histologic grade, ECE, LVI, and hormone receptor status were not associated with ipsilateral breast cancer recurrence. However, our study cohort was smaller and median follow-up time was shorter than in the Gentilini et al. study.

Few studies about BCS for MF/MC patients reported a high risk of local failure [3,4]. Despite these reports, analysis of two recent retrospective studies [6,7] and our study showed that in selected patients with MF/MC breast cancer, wide conservative surgery is not associated with poor local control and acceptable cosmetic results can be achieved.

References

- Greene FL, Page DL, Fleming ID. Breast. In: American Joint Committee on Cancer Staging Manual (6th Edn). New York, New York: Springer-Verlag, 2002, pp 223-240.
- Lagios MD. Multicentricity of breast carcinoma demonstrated by routine correlated serial subgross and radiographic examination. *Cancer* 1977; 40: 1726-1734.
- Kurtz JM, Jacquemier J, Amatric R et al. Breast conserving therapy for macroscopically multiple cancer. *Ann Surg* 1990; 212: 38-44.
- Wilson LD, Beinfeld M, McKhan CF, Haffty BG. Conservative surgery and radiation in treatment of synchronous ipsilateral breast cancers. *Cancer* 1993; 72: 137-142.
- Morrow M, Strom EA, Bassett LW et al. Standard for the management of ductal carcinoma in situ of the breast (DCIS). *CA Cancer J Clin* 2002; 52: 256-276.
- Nos C, Bourgeois D, Darles C et al. Conservative treatment of multifocal breast cancer: a comparative study. *Bull Cancer* 1999; 86: 84-88.
- Leopold KA, Recht A, Schnitt S 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.
- 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.
- 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.
- Lim W, Park EH, Choi SL et al. Breast conserving surgery for multifocal breast cancer. *Ann Surgery* 2009; 249: 87-90.
- 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.
- 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.
- Andea AA, Wallis T, Newman LA, Bouwman D, Dey J, Visscher D. Pathologic analysis of tumor size and lymph node status in multifocal/multicentric breast carcinoma. *Cancer* 2002; 94: 1383-1390.
- Gentilini O, Trifiro G, Soteldo J et al. Sentinel lymph node biopsy in multicentric breast cancer. The experience of the European Institute of Oncology. *Eur J Surg Oncol* 2006; 32: 507-510.
- Cabioglu N, Hunt KK, Sahin AA et al. Role for intraoperative magrin assessment in patients undergoing breast-conserving surgery. *Ann Surg Oncol* 2007; 14: 1458-1471.
- Smitt MC, Nowels KW, Zdeblick MJ et al. The importance of the lumpectomy surgical margin status in long-term results of breast conservation. *Cancer* 1995; 76: 259-267.
- Renton SC, Gazet JC, Ford HT et al. The importance of the resection margin in conservative surgery for breast cancer. *Eur J Surg Oncol* 1996; 22: 17-22.
- Papa MZ, Zippel D, Koller M et al. Positive margins of breast biopsy: is reexcision always necessary? *J Surg Oncol* 1999; 70: 167-171.