Local Control of Breast Conservation Therapy versus Mastectomy in Multifocal or Multicentric Breast Cancer: A Systematic Review and Meta-Analysis

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Keywords

Breast cancer · Breast conservation therapy · Multifocal/multicentric breast cancer · Prognosis · Local relapse

Abstract

Objective: Breast conservation therapy (BCT) for female patients with multifocal or multicentric (MF/MC) breast cancer remains controversial. The purpose of the present meta-analysis was to explore whether BCT was feasible for female patients with MF/MC breast cancer and to compare the results of treatment with those of female patients with unifocal breast cancer who underwent BCT and female patients with MF/MC breast cancer who underwent mastectomy. **Methods:** Online databases, including PubMed and Embase, were independently searched from inception to January 2018 and reviewed by two authors. The present meta-analysis compared local relapse (LR) of BCT versus mastectomy for patients with MF/MC breast cancer and LR of patients with unifocal breast cancer versus patients with MF/MC breast cancer who underwent BCT. Ten studies comprising 19,272 patients were included. **Results:** The cumulative incidence of LR was 5.6% (65/1,163) for MF/MC disease treated with BCT, 4.2% (750/17,656) for unifocal disease treated with BCT, and 2.0% (9/453) for MF/MC disease treated with mastectomy. Thus, the cumulative incidence of LR for MF/MC patients treated with BCT was significantly higher than for mastectomy ($p < 0.001$). However, the forest plot analysis showed no significant differences in LR between BCT and mastectomy procedures (OR = 1.22, 95% CI = 0.49–3.00, $p = 0.67$, $I^2 =$

0%). Compared with the unifocal group treated with BCT, BCT for MF/MC breast cancer showed a significant difference in LR (OR = 2.25, 95% CI = 1.48–3.42, $p = 0.0001$, $I^2 = 0\%$). **Conclusion:** The LR of BCT for patients with MF/MC breast cancer was higher than that of BCT for patients with unifocal breast cancer. However, no significant difference was found in the incidence of LR between the BCT group and the mastectomy group in patients with MF/MC breast cancer.

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Introduction

The incidence of multifocal or multicentric (MF/MC) breast cancer ranged from 4 to 50% [1, 2]. According to the American Joint Committee on Cancer staging guidelines, the greatest dimension of the largest tumour focus of patients with MF/MC breast cancer is used to stage the disease, and adding an “m” to the T stage records multiple tumours with no impact on the overall staging category. In other words, specific guidelines were not well established for MF/MC breast cancer. Nevertheless, breast conservation therapy (BCT) for selected patients with early-stage breast cancer has been demonstrated to have equivalent outcomes compared to mastectomy in long-term survival [3–5]. MF/MC breast cancer is still considered contraindicated for BCT because of an elevated risk of local recurrence, which may eventually result in an increased rate of distant metastasis and a decrease in overall survival [6–8]. Few individual studies have reported outcomes of BCT for

women with MF/MC breast cancer. These results varied from no effect to a 10-fold increase in the risk of local recurrence [9, 10]. However, the number of patients enrolled in most previous studies was small, and the baseline characteristics of patients were variable. Thus, the actual impact of BCT in MF/MC breast cancer remains controversial. For breast cancer patients, successful BCT requires not only a good prognosis, but also a good breast appearance after surgery. Meanwhile, with the increase in and progress of adjuvant therapy before and after the operation, incremental data showed that the choice of surgical strategy does not affect the prognosis of MF/MC breast cancer patients [10, 11]. In many studies, the size, number and distribution of tumours were important factors affecting surgical decision-making and appearance after BCT. Here, we report a meta-analysis aimed at estimating the feasibility of BCT for the treatment of patients with MF/MC breast cancer by comparing the LR (local relapse) in patients with unifocal breast cancer who underwent BCT and patients with MF/MC breast cancer who underwent mastectomy.

Materials and Methods

Data Sources and Searches

All studies were searched based on PubMed and Embase, both from their inception to January 2018. The search strategy included “breast neoplasm” or “breast cancer” or “breast tumor” and “breast-conserving surgery” or “breast conservation surgery” and “multifocal” or “multifocality” or “multicentric” or “multicentricity.” The retrieved articles were reviewed manually to ensure the sensitivity of the search strategy.

Study Selection

The inclusion criteria were as follows: (1) patients were pathologically diagnosed with breast cancer; (2) studies documented the LR and 95% confidence interval (CI) or a p value; (3) studies compared the outcome of BCT for MF/MC breast cancer versus BCT for unifocal breast cancer or the outcome of BCT for MF/MC breast cancer versus mastectomy for MF/MC breast cancer. Case reports, case series, conference reports, reviews without primary data and studies published in languages other than English were excluded. All the titles and abstracts of the study identified by the search strategy were evaluated, and the full text of all potentially relevant publications was retrieved by one reviewer. The eligible papers were then evaluated individually by two independent reviewers.

Data Extraction and Statistical Analysis

All data were extracted by two independent reviewers, and disagreements were resolved by consensus. The following details were extracted from each eligible study: name of the publication, year of publication, median follow-up, age, oestrogen receptor, HER-2/neu status and study end points of LR. Odds of LR were extracted from tables or text of the article or estimated from Kaplan-Meier survival curves here applicable. Statistical analysis was performed by using the Cochrane Review Manager Software 5.2. Statistical heterogeneity was assessed using Cochran's Q and I^2 statistics. An analysis with $I^2 > 50\%$ was performed with a random effects model and otherwise with a fixed effects model. All statistical tests were two-sided, and statistical significance was defined as $p < 0.05$.

Results

Characteristics of Eligible Studies

Of the 468 studies identified initially, 41 full-text articles were retrieved based on the dedicated evaluation. Finally, 10 studies with 19,272 patients were enrolled, of whom 1,616 were diagnosed with MF/MC breast cancer and 17,656 were diagnosed with unifocal breast cancer. The year of publication ranged from 1989 to 2015. The sample size of the included studies ranged from 55 to 11,983 patients. The characteristics of the 10 eligible studies are summarized in Table 1. The PRISMA statements of search results are presented in Figure 1.

The cumulative LR was 5.6% (65/1,163) for MF/MC disease treated with BCT, 4.2% (750/17,656) for unifocal disease treated with BCT, and 2.0% (9/453) for MF/MC disease treated with mastectomy.

Meta-Analysis Results

Eight studies compared the LR between the MF/MC breast cancer group and the unifocal breast cancer group in patients who underwent BCT [6, 9–15]. The total patient population for the 8 studies was 1,008 in the MF/MC breast cancer group and 17,656 in the unifocal group. There was, however, considerable heterogeneity observed across the studies ($OR = 2.41$, 95% $CI = 1.39–4.19$, $p = 0.002$, $I^2 = 60\%$) (Fig. 2). The LR of BCT for women with MF/MC breast cancer was significantly worse than for women with unifocal breast cancer. Considering the heterogeneity, we conducted a sensitivity analysis by removing some studies and recalculating the combined estimate on remaining studies. There was no significant heterogeneity among the 6 studies, and the LR was statistically significant ($OR = 2.25$, 95% $CI = 1.48–3.42$, $p = 0.0001$, $I^2 = 0\%$) (Fig. 3) [9, 10]. The analysis confirmed the stability of our results.

Three studies compared the LR between the BCT group and the mastectomy group in patients with MF/MC breast cancer [11, 16, 17]. No significant differences were observed in LR between the two groups based on the random effects model ($OR = 1.22$, 95% $CI = 0.49–3.00$, $p = 0.67$, $I^2 = 0\%$) (Fig. 4), and there was no evidence of significant heterogeneity between individual trials.

Discussion

In this study, we found that the LR of BCT for women with MF/MC breast cancer was higher than that for women with unifocal breast cancer ($p = 0.002$). However, when comparing the LR between the BCT group and the mastectomy group in patients with MF/MC breast cancer, no significant differences were found ($p = 0.67$).

Fig. 1. Flow diagram of search strategy and included studies.

Table 1. Characteristics of included studies

First author, year	Patients (MF/MC/UF)	Median/mean age (range)	Type of study	Median FU, months	ER+	HER-2+	End point(s) reported	Type of breast cancer in comparison population	NOS score
Lynch [12], 2013	673/2,816	NR	retrospective	52 (1–162)	NR	NR	LR	UF	7
Kurtz [6], 1990	61/525	MF/MC: 50 UF: 52	retrospective	71	MF/MC: 64% UF: 59%	NR	LR 10-year survival	UF	6
Okumura [13], 2004	34/564	MF/MC: 48 UF: 50	retrospective	98	MF/MC: 65% UF: 52%	NR	LR 5-year local control 5-year DFS	UF	6
Leopold [14], 1989	10/707	NR	retrospective	MF/MC: 64 UF: 75	NR	NR	LR	UF	6
Neri [15], 2015	36/491	63 (25–94)	retrospective	88	NR	NR	LR regional recurrence distant recurrence	UF	6
Chung [9], 2012	164/999	MF: 57.7 UF: 57.7	retrospective	112	MF: 89.7% UF: 86.8%	NR	LR 10-year DFS 10-year OS	UF	6
Yerushalmi [10], 2012	300/11,683	BCT: 57 (48–67)	retrospective	94.8	73.4%	NR	LR	UF	6
Lim [11], 2009	478/930	MF: 44.78 UF: NR	retrospective	59.33	MF: 105/147 UF: NR	NR	LR	UF/MF	6
Kaplan [16], 2003	55/–	56 (37–80)	prospective	45	85.5	NR	LR distant 5-year DFS	MF/MC	7
Kadioglu [17], 2014	222/–	BCT: 46 mastectomy: 49	retrospective	55 (10–102)	BCT: 74.8 mastectomy: 73.8	BCT: 10.9 mastectomy: 24.3	LR OS	MF/MC	7

FU, follow-up; ER, oestrogen receptor; NOS, not otherwise specified; OS, overall survival; DFS, disease-free survival; LR, local relapse; MF, multifocal; MC, multicentric; UF, unifocal; NR, not reported.

Fig. 2. LR of BCT for MF/MC versus unifocal breast cancer.

Fig. 3. Sensitivity analysis of LR comparing MF/MC and unifocal breast cancer.

Fig. 4. LR of BCT versus mastectomy for MF/MC breast cancer.

LR for MF/MC Breast Cancer

MF/MC breast cancer has been considered a risk factor for prognosis. Previous studies have shown that MF/MC breast cancer is associated with a higher incidence of lymph node metastasis compared with unifocal tumours in the same T stage and may consequently result in dele-

rious clinical outcomes [18–20]. In addition, risk factors, including age, tumour grade, hormone receptor status and HER-2 status, have been considered to be correlated with MF/MC breast cancer [21]. Current studies have affirmed the role of BCT for unifocal breast cancer, which is considered to be the treatment of choice for women

with stage I-II breast cancer [3, 4]. Moreover, with the development of systemic therapy, the absolute risk of a recurrence is likely to be lower than before. This meta-analysis illustrated that BCT for MF/MC breast cancer failed to be as effective, with regard to LR, as BCT for unifocal breast cancer (OR = 2.41, 95% CI = 1.34–4.19, $p = 0.002$). However, it is still not determined whether this result is due to MF/MC breast cancer itself having a high local recurrence feature, rather than a different surgical method.

Few previous publications have compared BCT with mastectomy in patients with MF/MC breast cancer. In a study by Lim et al. [11], with a mean follow-up period of 59.33 months, local failure occurred in 3 (2.0%) of 147 patients who underwent BCT and in 3 (0.9%) of 331 patients who underwent mastectomy ($p = 0.378$). Studies from Kaplan et al. [16] and Kadioğlu et al. [17] both reported that there were no significant differences in the local control rate between the group of patients treated with BCT and the group of patients treated with mastectomy. The combined result of the studies from the three individuals also showed no significant LR benefits from mastectomy compared with BCT (OR = 1.22, 95% CI = 0.49–3.00, $p = 0.67$).

Long-Term Survival for MF/MC Breast Cancer

Overall survival (OS) and disease-free survival (DFS) are considered to be the most important outcome indicators in evaluating the benefits of treatment strategies. Unfortunately, only a few studies have reported related data. For patients who underwent BCT, no significant differences in the 5-year DFS (93 vs. 90%, $p = 0.63$) were found between the MF/MC breast cancer patients and the single-lesion breast cancer patients after a median follow-up of 98 months, as reported by Okumura et al. [13]. In a study by Chung et al. [9], the MF breast cancer group had a lower 10-year DFS (97.7 vs. 89.3%, $p < 0.001$) and OS (98.4 vs. 85.8%, $p < 0.001$) than the unifocal breast cancer group.

Aesthetic Considerations

As for breast cancer patients, postoperative breast appearance is as important as prognosis. However, there are few reports about the appearance effects of breast-conserving surgery in MF/MC breast cancer patients. Tan et al. [22] followed up 34 MF/MC breast cancer patients with BCT for 3 years. Among them, 20 patients self-evaluated the appearance after BCT. These patients all thought that the cosmetic effect was satisfactory or relatively satisfactory. However, when clinicians evaluated the appearance effect, 90% of patients were satisfied [22]. In the Chinese population, the breast volume is generally small; therefore, it is difficult to maintain a good appearance after surgery, and the willingness of patients to undergo

breast-conserving treatment is not strong; thus, the breast-conserving rate of MF/MC breast cancer patients is relatively low [23].

Tumour Distribution and Clinical Strategies

MF/MC breast cancer is divided into MF breast cancer and MC breast cancer according to the location of tumours. However, there are no data to confirm whether there are differences in biological behaviours and prognoses between MF and MC breast cancers. Rosenzanz [24] noted that MC breast cancer may be associated with a low OS, while MF breast cancer does not affect the OS. Lynch et al. [25] found that both MF breast cancer and MC breast cancer were associated with earlier onset age, higher tumour stage and higher lymph node stage. Therefore, more follow-up data are needed to clarify whether there are differences in the choice of surgical methods for MF breast cancer and MC breast cancer and whether BCT will have different effects on the prognosis of these patients. Currently, most studies believe that BCT is suitable for patients with limited distribution of early- and middle-stage MF/MC breast cancer. BCT is not recommended for patients with diffuse ductal carcinoma in situ because it is difficult to obtain a negative margin.

Whether BCT for MF/MC breast cancer patients requires more adjuvant treatment after surgery is not currently conclusive. In most studies, the principle of treatment for MF/MC breast cancer is the same as that of unifocal breast cancer. For radiotherapy, whether patients with unifocal breast cancer need radiotherapy after surgery depends on the surgical approach and axillary lymph node metastasis. For MF/MC breast cancer patients undergoing BCT, as there may be a high risk of LR, whether it is necessary to expand the radiation range or increase the radiation dose of radiotherapy requires further research.

Limitations

There are some limitations to this study. As the number of articles was small, the source of heterogeneity was difficult to determine. Most of the included publications were single-centre retrospective studies with inherent limitations, including selection bias and data analysis bias. In addition, several studies only addressed a small number of patients, and the follow-up of some studies was relatively short. Another inevitable limitation was that the patients included in the meta-analysis were treated from 1989 to 2015, which may lead to methodology flaws due to dramatic changes in chemotherapy, radiotherapy, endocrine therapy and targeted therapy for breast cancer.

Conclusion

In MF/MC breast cancer patients, LR may be higher in patients undergoing BCT compared to patients undergoing mastectomy. However, BCT can be performed in selected patients, as no difference within the forest plot analysis was seen. Further prospective studies should be investigated to refine the prognosis and to optimize the treatment in patients with MF/MC breast cancer.

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