Evaluation of the impact of breast-conserving surgery on cancer outcomes of multiple (multifocal or multicentric) ipsilateral breast cancer

Mohamed F. Abdelfattah[a], Yasmine H. Elzohery[b]

[a]Department of Surgical Oncology Faculty of Medicine, Al Azhar University, [b]Department of General Surgery, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Correspondence to Yasmine H. Elzohery, MD, General Surgery, Faculty of Medicine, Ain Shams University, Cairo 11595, Egypt. Tel: +0106 554 8383; e-mail: yasminehany@med.asu.edu.eg.com

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Background
Breast conservative therapy (BCT) includes conservative breast surgery (CBS) with adjuvant radiotherapy and is now considered a standard treatment for early-stage breast cancer to achieve survival with acceptable aesthetic outcomes.
Management of multiple ipsilateral breast cancer (MIBC) is a challenge, since the choice of optimal surgical procedures is controversial. Recently, many breast surgeons have advocated CBS is technically feasible to safely excise MIBC in selected cases.

Aim
This study aimed to evaluate the outcome of MIBC patients who received CBS with special attention on local control and recurrence.

Patient and method
This retrospective study was carried out on 90 patients at Al Azhar University Hospital and Ain Shams University Hospitals between January 2021 and January 2023.

Results
The majority of patients 85 (94.4%) had two foci of disease while five (5.5%) patients had three foci. The distance between the lesions ranges between 0.5 and 6.5 cm. The most common type of CBS was wide local excision en bloc resection of all lesions with normal tissue in between was done in 85 (94.4%) patients and five (5.5%) patients had two separate incisions leaving normal tissue in between. Clear margins were reported in 79 (87.7%) patients. 15 (5.5%) patients had different pathological lesion types (heterogeneous). One patient had a recurrence and another had distant metastases.

Conclusion
With good patient selection, there is no difference between CBS and mastectomy in the management of MIBC. CBS is oncological safe provided that an adequate excision with clear margins followed by whole-breast radiation therapy and adjuvant systemic therapy.

Keywords:
conservative breast surgery, multicentric, multifocal, multiple ipsilateral breast cancer

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List of abbreviations: CBS, conservative breast surgery; MC, multicentric; MF, multifocal; MIBC, multiple ipsilateral breast cancer; RT, radiotherapy; UF, unifocal.

Introduction

Breast conservative therapy (BCT) includes conservative breast surgery (CBS)with adjuvant radiation therapy (RT) is now considered a standard treatment for early-stage breast cancer [1].

Multifocal (MF) traditionally has been considered a relative contraindication for CBS and an absolute contraindication for multicentric breast cancer, many earlier studies have recorded high recurrence rates and worse cosmetic results [2].

Recently this traditional treatment has been changed due to improved surgical techniques by better localization and oncoplastic techniques that allow en bloc resection of all lesions without affecting the aesthetic outcome. This is facilitated also by the increased use of neoadjuvant treatments to downsize the tumor. This has resulted in a shift away from mastectomy to CBS [3].

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Management of multiple ipsilateral breast cancer (MIBC) is a challenge since the choice of optimal surgical procedures is controversial. Recently, many breast surgeons are advocating CBS is technically feasible to safely excise multifocal multicentric breast cancer in selected cases [4].

Historically, there are many anatomical definitions of multicentricity and multifocality in the literature. Most commonly, MF tumors are located in the same quadrant while MC tumors are located in different quadrants, the use of breast quadrants to classify and define cancers is now considered inappropriate. Another commonly used definition based on the distance between the lesions, MF tumors located within 2–5 cm and when tumors lie beyond these distances the disease is MC [5].

Such differences in definitions might be due to different tumor growth morphogenesis. MF disease is the result of a single tumor cell clone spreading within an intraductal system of one quadrant, however, in MC disease several focuses of tumor growth, appear in the intraductal system of different quadrants and require an independent transformation of two separate cell groups [6].

The recent pathological definition of MIBC is the presence of multiple simultaneous primary lesions (of any size) separated by normal breast parenchyma without malignant tissue between them whether in the same or a different quadrant and regardless of the distance between the foci [7].

The widespread use of mammographic screening and increased use and accuracy of diagnostic imaging such as MRI has led to an increase in the incidence of identified additional foci of cancer that would have remained undetected by conventional imaging. This leads to increase the incidence of MIBC [8].

Evaluation of biomarker is important. MIBC usually have a single phenotype. Heterogeneity in histopathology and in biomarker are considered a bad prognostic index [9].

Aim

This study aimed to evaluate the outcome of patients with MIBC including MF and MC cancers who received CBS with special attention on local control and recurrence.

Patient and method

This retrospective study was carried out after ethical committee approval. Between January 2021 and January 2023, 90 patients were enrolled in this study. This research was done at the surgery department at Al Azhar University Hospital and Ain Shams University Hospitals.

Patient selection

Inclusion criteria

All age groups were considered in this study, with a minimum age of 18 years. Patients with unilateral invasive breast cancer and/or ductal carcinoma *in situ* (DCIS) diagnosed as MIBC before or after surgery (histological diagnosis) at the final pathological report were eligible for enrollment.

Exclusion criteria

(1) Patients with distant metastases and locally advanced disease.
(2) Patient has contraindication to radiation.
(3) Patients had unifocal lesion.

All patients provided signed written informed consent after being informed about the study characteristics and the data confidentiality.

Data collection included patient age, clinical finding, laterality, radiology finding, biopsy diagnosis, surgical excision technique, clinicopathological characteristics, tumor size, number of pathologic lymph nodes, other treatment modalities (chemotherapy, radiotherapy, and hormonal therapy), postoperative complications and follow-up details as regard local-regional recurrence or distant metastasis.

Clinical management

Diagnosis of multiple invasive breast cancer was performed clinically by examination, followed by radiologically and pathological assessment.

Surgical technique

The surgery begins by marking the incision which is designed according to the size, site of the lesions, ptosis, the distribution of lesions, and the need for axillary intervention.

The surgical approaches include wide local excisions, volume displacement and oncoplastic techniques.

Patients with large breast are good candidates for volume displacement techniques as breast reduction techniques that allow the excision of tumor in any quadrant using many therapeutic mammaplasty techniques and various pedicles.

The tumor was excised and further imaging of the specimen and frozen section was performed to ensure that the tumor was excised.

Marking of the surgical specimens should be accurate as re-excision of positive margins is challenging in the context of multiple foci and an aesthetically restored breast.

Histopathological examination

Evaluation of tumor histology (ductal/lobular/*in situ*), number of positive LN, surgical margin (negative/positive), grade of the tumor, estrogen receptor, lymph vascular invasion (LVI), size and site of the different foci and their relation to each other and the distance between the foci (inter-lesional distance) were recorded.

The T stage is determined in the pathological tumor, node, metastasis (TNM) (pTNM) classification based on the diameter of the largest lesion.

Multidisciplinary meeting was done pre and postoperative to discuss every case.

The clinical and radiological follow-up evaluation was done every 6 months.

Postoperative complications were recorded as infection, seroma, hematoma, and flap necrosis.

Cosmetic outcomes were reported using a questionnaire where patient satisfaction was assessed on a scale ranging from 1 (very bad) to 5 (excellent). These assessments were done postoperative and every 6 months.

Evaluation of outcomes

Loco-regional recurrence or distant metastases during the follow-up period.

Statistical analysis

Data were collected and analyzed using an IBM-compatible personal computer with Statistical Package for the Social Sciences (SPSS) version 25. Qualitative data will be expressed as Number (N) and percentage (%), while quantitative data were expressed as mean, standard deviation (SD) and range (minimum-maximum).

Results

Between January 2021 and January 2023, 90 patients were included in this study. The mean age is 48 years old (range of 30–71 years). 76 (84%) patients had multifocal breast cancer and 14 (15.6%) had multicentric breast cancer.

A total of 86 (95.6%) females clinically presented with mass, nonpalpable lesions detected during screening were present in 2 (2.2%) females and nipple discharge was present in 2 (2.2%) females.

A total of 78 (86.6%) females presented with mass, 8 (8.8%) presented with microcalcifications and 4 (4.4%) presented with architectural distortion.

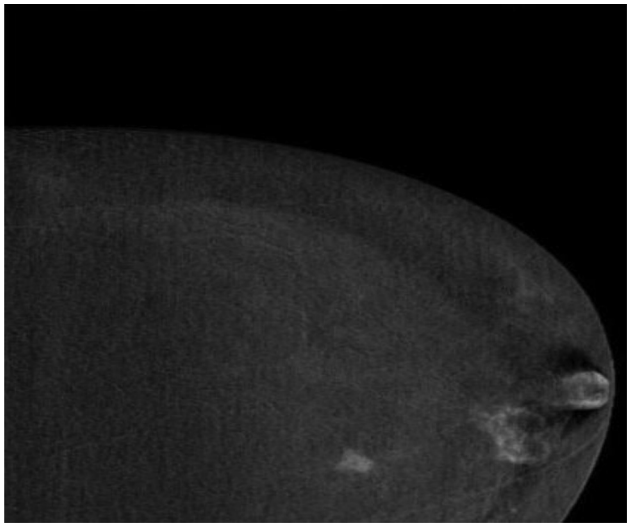
Further imaging modalities were used to detect multicentricity by Contrast Enhanced Spectral Mammography (CESM) which was done in 70 (77.8%) patients, MRI (Magnetic Resonance Imaging) was done in eight (8.8%) patients, PEM (positron Emission Mammography) was done in eight (8.8%) and four (4.4%) patients did not need contrast study for diagnosis as mammography was fatty breast American college of radiology (ACR) A (Figs 1 and 2).

The reported tumor size was the largest tumor focus. The median size of the largest lesions on preoperative imaging was 1.7 cm (range 0.8–5.0 cm). The majority of patients 85 (94.4%) had two foci of disease while five (5.5%) patients had three foci (Table 1).

Table 1 Clinical and radiological findings

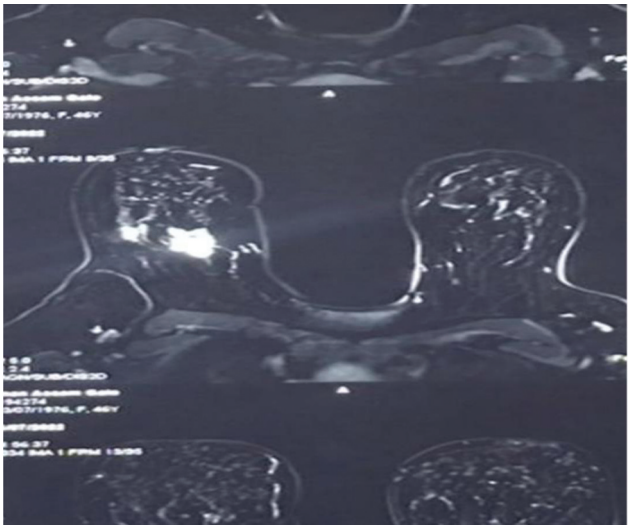
	Cases (*n*=90)
Age (y)	
Range	30–71
Mean±SD	48.12±8.95
Density	
ARC a	7 (7.8)
ARC b	51 (56.7)
ARC c	30 (33.3)
ARC d	2 (2.2)
Side	
Left	42 (46.7)
Right	48 (53.3)
Site	
UOQ	49 (54.4)
LIQ	4 (4.4)
LOQ	6 (6.7)
Retro-areolar	13 (14.4)
UIQ	20 (22.2)
Size of lesions(cm)	
Range	0.8–5
Mean±SD	2.37±0.9
Distance from the nipple	
Retro-areola	21 (23.3)
Away	69 (76.7)

Figure 1



40 year-old female had a left breast architectural distortion in screening mammogram. Contrast Enhanced Spectral Mammography showed multifocal disease with a marked degree of enhancement. Conservative breast surgery revealed multifocal IDC G3.

Figure 2



46-year-old woman with multifocal disease. MRI images confirm multiple lesions that could not be retrospectively recognized in the mammogram. Conservative breast surgery revealed multifocal G2 IDC.

The most common type of CBS was wide local excision (WLE) en bloc resection of all lesions with normal tissue in between was done in 85 (94.4%) patients and five (5.5%) patients only had two separate incisions leaving normal tissue in between.

Quadrantectomy was done by long radial incision for 33 (36.6%) patients, other oncoplastic techniques were performed depending on the size and the location of the tumors as 10 (11.1%) patients underwent inferior pedicle reduction mammoplasty, 11 (12.2%) patients underwent superior pedicle reduction mammoplasty, eight (8.8%) patients underwent batwing mastopexy, seven (7.7%) patients underwent round block technique (donut technique), 10 (11.1%) patients underwent lazy S or true S technique, six (6.6%) patients underwent central quadrantectomy (Table 2).

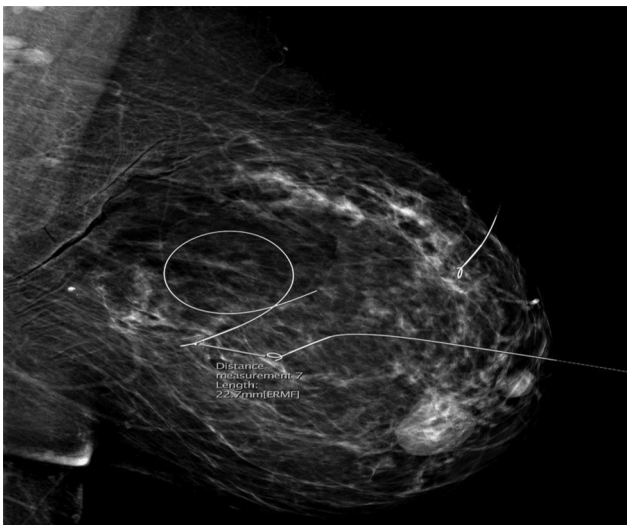
For nonpalpable lesions, localization was performed preoperatively by ultrasound or stereotactic guide-wire placement in 62 patients (Fig. 3).

The diagnosis of the excised specimens was in (Table 3), median pathologic size of the largest focus of the tumor was 1.5 cm (range 0.5–4 cm).

Table 2 Types of surgical techniques

	No. (%)
Quadrantectomy	33 (36.6)
Inferior pedicle reduction mammoplasty	10 (11.1)
Superior pedicle reduction mammoplasty	11 (12.2)
Batwing mastopexy	8 (8.8)
Round block	7 (7.7)
Lazy S or true S	10 (11.1)
Central quadrantectomy	6 (6.6)
Axillary surgery	
AC	32 (35.6)
SLN	56 (72.2)
SLN then AC	2 (2.2)
Localization by wire	
No	28 (31.1)
Yes	62 (68.9)

Figure 3



Mammogram showing multiple lesions wire localization for a 52-year-old female with a preoperative core biopsy diagnosis of IDC with multicentric disease.

Table 3 The pathology of the specimen

	No. (%)
IDC	55 (61.1)
ILC	7 (7.7)
Invasive mixed ductal-lobular	8 (8.8)
Invasive tubular/cribriform	2 (2.2)
Micropapillary	1 (1.1)
DCIS	2 (2.2)
Heterogenous	15 (5.5)
Lymph vascular invasion	32 (35.6)
Size of resected tissue (cm)	
Range	3–17
Mean±SD	9.71±3.49
Size of mass(cm)	
Range	0.5–4
Mean±SD	1.92±0.82
Distance between lesion (cm)	
Range	0.5–6.5
Mean±SD	2.55±1.729

15 (5.5) patients had different pathological lesion types (heterogenous), nine (10%) patients with one site of DCIS and others site of invasive duct carcinoma (IDC), four (4.4%) patients had one site of IDC site and others of ILC, two (2.2%) patients had one site of DCIS site and others ILC.

The majority of patients (82 patients) had estrogen receptor (ER) positive (91.1%) and 80 (88%) patients had progesterone receptor (PR) positive tumors, 11 (12.2%) patients had HER2+ disease.

13 (14.4%) patients' marker was done for each focus, we found six (6.6%) patients had a mismatch in estrogen receptor, three (3.3%) patients had ER negative in the main lesions, while ER was positive in the other smaller lesion. Two (2.2%) patients had ER positive in the main lesions, while ER negative was found in the other smaller lesion.

Only one patient had a difference in HER-2 status, where the index lesion was HER-2 positive and the others were HER-2 negative.

By following the current TNM staging system, 54 (60%) patients were found in T1 stage, 34 (37.7%) in T2 stage, and two (2.2%) in the T3 stage. No CBS was done for T4. The staging method was done by using the largest dimension of the lesions.

The distance between the lesions ranges between 0.5 and 6.5 cm.

13 (14.4%) patients was grade 1, 65 (72%) patients were grade 2 and 12 (13.3%) patients were grade 3.

Table 4 Distribution of the studied cases as regards outcome

	Cases (*n*=90)
Cosmetic outcome	
Excellent	68 (75.6)
Good	17 (18.8)
Bad	5 (5.6)
Re-surgery	11 (12.2)
Recurrences	1 (1.1)
Distant metastases	1 (1.1)
Complications	
Seroma	12 (13.3)
Hematoma	15 (16.7)
Infection	3 (3.3)
Flap necrosis	3 (3.3)

79 of the patients successfully completed breast conservation in a single operation. Clear margins were reported in 79 (87.7%) patients. All patients with positive margins underwent re-surgery as a second operation to achieve negative margins.

Re-operation (mastectomy or re-lumpectomy) was done on 11 (12.2%) patients. Two patients underwent mastectomy and nine of the patients with involved margins underwent wider local excision.

20 patients had postneoadjuvant therapy status for IDC.

35 (38.8%) patients received adjuvant chemotherapy, all ER-positive patients received hormonal therapy.

All patients received adjuvant post-CBS radiotherapy except one patient who had multiple co-morbidity, old age and T1mN0.

At follow-up range from 6 to 24 months, we reported one patient had recurrence with a median time to relapse of 14 months postoperative and one patient had distant metastases 17 months postoperative.

As regard cosmetic outcomes there were 68 (75.6%) excellent outcome, 17 (18.8%) good and 5 (5.6%) bad (Table 4).

Discussion

Earlier series often cited MF/MC as an aggressive disease in comparison to unifocal disease and considered an indication for mastectomy [10,11].

More recently, many international studies and St. Gallen International Consensus Guidelines recommendations have found that MF/MC disease is not an absolute contraindication for CBS [12].

Successful clearance in combination with adjuvant RT and systemic therapy has been associated with comparable rates of recurrence to mastectomy [8].

MRI is still considered one of the most appropriate techniques in the detection of disease extension and multiple lesions. However, limited availability, suboptimal specificity and higher cost led to the development of CESM [13].

In our study, we used CESM in most of the 70 (77.8%) patients and MRI (Magnetic Resonance Imaging) was done in 8 (8.8%) patients.

The study done by Girometti R, *et al.* concluded that CESM improved the additional lesions detection compared with DM (Digital mammography)+DBT (Digital breast tomosynthesis) [14].

Covington, *et al.* concluded that CEM was easier to access, cheaper and interpret than MRI and quicker to perform and patients who underwent both techniques preferred CEM [15].

A recent meta-analysis conducted by Haussami and colleagues on 19 studies (n=2610) reported that MRI detected an additional 16% cancer foci in clinical unifocal breast cancer [16].

The standard procedure in our study was WLE en bloc resection of all lesions which was done in 85 (94.4%) patients and 5 (5.5%) patients two incisions were done.

A recent ACOSOG Z11102 (Alliance) trial recommended resection through single or multiple incisions prospectively evaluated the safety and feasibility of CBS in MF and MC disease [17].

Also, the ACOSOG Z11102 (Alliance) trials concluded that CBS then postoperative RT to the whole breast with a boost dose to each tumor bed was feasible in most MF and MC cases [17].

In our study, oncoplastic techniques were performed depending on the size and the location of the tumors as 10 (11.1%) patients underwent inferior pedicle reduction mammoplasty, 11 (12.2%) patients underwent superior pedicle reduction mammoplasty, eight (8.8%) patients underwent batwing mastopexy, seven (7.7%) patients underwent round block technique (donut technique), 10 (11.1%) patients underwent lazy S or true S technique, six (6.6%) patients underwent central quadrantectomy.

De Lorenzi F, *et al.* provided that their study was the most available evidence suggesting that the oncoplastic techniques were safe and effective procedures in the treatment of MIBC [18].

Savioli F, *et al.* suggested that Extreme Oncoplastic Breast Conservation Surgery must be offered to cases who would usually be exclusively offered mastectomy [19].

Silverstein *et al.*, found that the extreme oncoplastic procedure had successful outcomes and improved the quality of life in MIBC cases. On examination of 66 patients, clear margins were achieved in 83%. Re-surgery was performed in six (9.1%) patients and mastectomy was done in four (6.1%) patients. In other study negative margins were found in 87 (78.3%) patients, while 42 (37.8%) and 15 (13.5%) needed re-surgery respectively [20].

In our study, 79 of the patients completed breast conservation successfully in a single operation. Clear margins were reported in 79 (87.7%) patients.

Re-operation (mastectomy or re-lumpectomy) were performed on 11 (12.2%) patients. Two patients underwent mastectomy and nine of the patients with involved margins underwent wider excision.

Rosenkranz and colleagues concluded that in the case of MIBC, CBS is possible, with 67.6% negative margins. However, conversion to mastectomy was 7.1% [21].

Kaplan *et al.* [22] also conducted in study of 55 cases had MIBC, in which CBS was done to 36 patients and 19 underwent mastectomy. In that study, 56% of patients underwent re-surgery to obtain negative margins with a recurrence rate of 3%.

Andea and colleagues [23] concluded an increased rate of LN positivity in MIBC in comparison with the unifocal tumor when the dimensions of the largest tumor were done. While, when an aggregate dimension was done, unifocal disease and MIBC had the same rate of LN involvement. Also, Andea *et al.* analyzed 101 patients who had MIBC and compared LN involvement between those whose T stage was the size of the largest focus and those whose T status was the aggregate size. No difference between the two groups was found about LN status.

Coombs and Boyages [24] concluded in a comparative study of 94 cases that the use of aggregate diameter

reclassified a significant number of MF tumors at a more advanced stage. The total tumor load reflect the tendency of breast cancer to metastasize rather than the diameter of the largest tumor focus. Also, concluded increased LN involvement in MIBC versus UF disease. 49 (52.1%) cases had node positive versus 283 of 754 (37.5%) cases in the UF disease.

Lynch *et al.* [25] found that MF in comparison with unifocal disease was accompanied by higher clinical stage ($P<0.001$), lymph vascular invasion ($P<0.001$) and higher LN involvement rate.

Similar to previous studies, we conducted a significant relation between MIBC and an increase in the rate of LN involvement, 32 (35.6%) patients had LN involvement and 32 patients had lymph vascular invasion.

In MIBC, less than 4% of patients may experience heterogeneity requiring change in the therapeutic decision. However, heterogeneity did not have a significant effect on survival and recurrence [26].

Heterogeneity of ER, progesterone receptor, human epidermal growth factor (HER2), or Ki67 was found in 24% of cases with MIBC. Biomarker heterogeneity affects the adjuvant hormonal therapy and had a bad disease outcomes [27].

There is controversy between old and recent series as regard local recurrence (LR) after conservative surgery for MIBC.

Earlier series reported higher risks of local recurrence. One of the first studies in this realm by Kurtz *et al.* [10] found a higher rate of LR in 25% of MIBC patients, compared with 11% for those with UF disease in the study of 61 patients as adjuvant therapy did not follow a fixed protocol.

However, Wolters *et al.* found that management MIBC according to German guidelines by CBS, 683 of 1398 (48·9%) versus mastectomy 329 of 1398 (23·5%) showed no significant differences in 5-year recurrence-free survival [28].

In our study, one patient had disease recurrences with a median time to relapse of 14 months postoperative and one patient had distant metastases 17 months postoperative.

In many published systematic reviews and meta-analysis comparing the outcome between MIBC and UF disease, the result was not conclusive and most of the studies were not randomized based on patient preference of CBS [29].

The Z11102 clinical trial concluded that CBS with adjuvant RT that included WLE site boosts yields an acceptably low 5-year LR rate for MIBC. This evidence supports CBS as a reasonable surgical option for patients with two to three ipsilateral foci, with disease evaluated with preoperative breast MRI [30].

Conclusion

With good patient selection, the majority of the recent studies found no difference between CBS and mastectomy as regards LR and disease-free survival in the management of MIBC.

The present study showed that conservative surgery is oncological safe as an alternative surgical option in MIBC provided that an adequate excision with clear margins followed by whole-breast RT and adjuvant systemic therapy, acceptable cosmetic results can be achieved.

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Conflicts of interest

Declarations: the authors declare that they have no conflict of interest.

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