ASSESSMENT OF CLINICAL SIGNIFICANCE OF MULTIFOCAL BREAST CANCER AS REGARDS SURVIVAL RATES, OUTCOME AND CHOICE OF SURGICAL TREATMENT

تقييم الاهمية الاكلينيية لسرطان الثدى متعدد البؤر من حيث معدلات النجاه،المصير واختيار العلاج الجراحي

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لشروط الحصول على درجة
دكتورالفلسفة في الطب فى الجراحة

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INTRODUCTION

Multifocal (MF) and multicentric (MC) breast cancers are relatively common clinical entities, with incidence in the literature ranging from 6% to 60%.This large variability is due to differences in definitions used, inclusion or exclusion of in situ disease, and methods of pathologic sampling.[1,2] Most commonly, MF breast cancer typically refers to two or more synchronous areas of disease confined within the same quadrant versus MC disease, which refers to two synchronous areas of disease within different quadrants. Regardless of the definition, the tumor with the greatest diameter is typically used for staging purposes.[3]

As advances in preoperative imaging continue, the number of MF and MC tumors identified increases,[4–6] and better guidelines for their management are needed. In particular, questions still exist regarding the optimal loco-regional (LR) therapy for MF and MC breast cancer. Multifocality and multicentricity are regularly considered as a relative contraindication for breast-conservation therapy.[7,8] The reasoning for this traditional paradigm is based on two assumptions. **Firstly**, the perceived higher risk for in-breast recurrence since it is assumed that in MF/MC cancer the risk of more invasive foci in the breast is greater, and therefore radiotherapy possibly less effective. **Secondly**, the expected less good cosmetic outcome due to wide excisions and larger boost volumes with more fibrosis. Consequently, the vast majority of patients with MF/MC, either clinically detected or visible on standard imaging (mammography, ultrasound) is advised to be treated with a mastectomy However, such a tendency towards a more extensive surgery is debated. The COMICE trial did not show any reduction of local recurrence or any improvement of long-term survival in patients undergoing preoperative MRI.[9]

Three more recent developments may change this traditional paradigm.

First, the introduction of MRI has led to the identification of more small cancer foci besides the index cancer.

Secondly, more effective neo-adjuvant chemotherapy result in more complete or near complete remissions or substantial reductions in the extent of cancers. **Thirdly**, improved surgery by better localization techniques and oncoplastic procedures allow for more precise and complete breast conserving resections.

Furthermore, Multifocal/MC disease has also been implicated as a prognostic factor. Studies have demonstrated that MF/MC cancers may have an increased susceptibility to axillary lymph node (LN) involvement.[10] It is unclear whether this is due to inaccurate staging by using the largest tumor dimension or if these malignancies have an inherent biologic capacity to spread.

In addition, MF/MC disease has been found to correlate with known risk factors suggesting an aggressive biology such as young age, higher grade, negative hormone receptor status, negative HER-2 status, and lymphovascular invasion.[11]Yet the impact on outcomes is unclear with studies demonstrating mixed results.[12,13]

Unfortunately, due to the relatively heterogeneous cohort of patients with MF/MC breast cancer, standardized guidelines are not well established.

Therefore, it remains unclear whether MF/MC breast cancers should be considered a separate category with a potentially unfavourable impact on prognosis and whether these lesions require specific treatment with more extensive surgery or committed adjuvant therapies.

The present study is directed to analyze, in a large retrospective series of breast cancer patients treated at a single institution, the impact of (MF) breast cancers on the long-term survival in relation to other known pathological and clinical factors and to the type of treatment received. Furthermore, the prospective limb of this study is directed to evaluate the outcomes of oncoplastic techniques as a surgical management for multifocal breast cancer.

AIM OF THE WORK

This work aims to:

Primary objective:

Evaluating the application of oncoplastic surgical techniques in the surgical treatment of multifocal breast cancer as regards; successful resection of tumor burden, disease control (recurrence) and cosmetic results.

Secondary objectives:

1. Determine the burden of multifocal breast cancer among Egyptian population.
2. Determine to what extent the presence of (MF) is associated with the use of mastectomy.
3. Determine the factors that are associated with the use of BCT in the presence of (MF) disease.
4. Determine whether the presence of (MF) increased the rate of local relapse in patients treated with BCT.
5. Exploring the association between multifocality and overall survival and loco-regional relapse.
6. Stating a reliable recommendations for management of multifocal breast cancer.

PATIENTS

This study includes two groups of patients:

Group (A): All patients with operable breast cancer , admitted and managed at the Surgical Oncology unit, Alexandria Faculty of Medicine, between Jan.2010 to Dec.2015, their data are retrospectively reviewed and analyzed.

Group (B): All patients with operable multifocal breast cancer excluding those indicated for neoadjuvant therapy and those diagnosed as inflammatory breast cancer admitted between May.2017 to May.2018 will be offered oncoplastic breast conserving surgery and prospectively evaluated for 24 months as regards the outcomes of using different oncoplastic techniques to extend the clinical utility of BCT as a surgical management for multifocal breast cancer.

METHODS

For group (A) patients The following data of will be included and recorded:

- Age at diagnosis: young patients are defined as younger than 35 years.
- Surgery performed:

  a-Breast conservation: involves lumpectomy with oncologically appropriate safety margins with either sentinel lymph node detection or axillary lymph node dissection according to the triple assessment of the patients. The introduction of different oncoplastic procedures in breast cancer surgery allows more breast conservation.

  b-Mastectomy: modified radical mastectomy.
- Tumor characteristics: size, nodal status, presence of lympho-vascular invasion, amount of intraductal component, tumor grade, margin status, hormone receptor, and Her2 neu status(if available).
- Pathological determination of multifocal and unifocal tumors.
- The follow-up period of the patients was registered.
- The occurrence of loco-regional recurrence or distant metastases during the follow-up period was recorded and considered as an end point for follow-up.

  Local recurrence is defined as recurrence in the original tumor bed (for BCS) or field of mastectomy.

Regional recurrence refers to metastatic disease in the ipsilateral axilla or supraclavicular lymph nodes or ipsilateral involvement of internal mammary nodes.

Loco-regional recurrence-free survival of patients who are pathologically multi-focal and uni-focal will be estimated using the Kaplan-Meier method and compared among different categories using log-rank tests (univariable analysis

of risk factors for loco-regional recurrence among multi-focal and uni-focal breast cancer patients).

Distal recurrence-free survival for both groups will be analyzed using the same test (univariable analysis of risk factors for distal recurrence).

Associations with local recurrence in uni-focal and multi-focal breast cancer patients are further evaluated using multivariable Cox proportional hazards regression model and summarized with hazard ratios 95 % confidence intervals (CIs).

Associations with distal recurrence uni-focal and multi-focal breast cancer patients will be further evaluated using multivariable Cox regression model.

For group (B) patients the following data will be retrieved:

- Age at diagnosis: young patients are defined as younger than 35 years.
- Surgical techniques: Preoperatively all patients will undergo physical examination of both breasts and axillae as well as bilateral mammograms and ultrasonography of both breasts. Histopathological diagnosis of cancer will be made prior to surgery. The planned procedure will be discussed. Different oncoplastic techniques will be utilized to achieve oncologically appropriate margins with either sentinel lymph node detection or axillary lymph node dissection according to the triple assessment of the patients . Surgical margins were determined by macroscopic and histologic examination of frozen sections of the breast specimens in the operating room. An adequate safety margin of 1cm was always insured. Breast remodeling will be done according to breast size, degree of ptosis and size of defect.

- Tumor characteristics: size, nodal status, presence of lympho-vascular invasion, amount of intraductal component, tumor grade, margin status, hormone receptor, and Her2 neu status.
- Margins will be regarded as negative when permanent histological examination found no ink on the tumor.
- Postoperative surgical complications will be documented if happened; seroma formation, hematoma and or wound dehiscence.
- Cosmetic outcome: The postoperative esthetic result will be evaluated asking the patients to rate the postoperative cosmetic result and their degree of satisfaction compared to the preoperative breast using a five-point scale (excellent, 5; good, 4; fair, 3; poor, 2;bad, 1). Objective assessment of the cosmetic result was done by two surgeons, rated on a visual analog scale from 1 (unacceptable result) to 10 (excellent result). Evaluation is based on 5 criteria, namely: breast symmetry, glandular tissue defects, nipple and areola reconstruction, scar quality and/or retraction, and the resultant breast shape. [14]
- The occurrence of loco-regional recurrence or distant metastases during the follow-up period was recorded and considered as an end point for follow-up.

ETHICS OF RESEARCH

Research on human or human products:

- [v] Prospective study: Informed consent will be taken from patients. In case of incompetent patients the informed consent will be taken from the guardians.
- [v] Retrospective study: Confidentiality of records will be considered
- [ ] DNA / genomic material: Informed consent for DNA / genomic test and for research will be taken from patients. No further tests will be carried out except with further approval of committee and patients. If the samples will travel outside Egypt the researcher will be responsible for transportation and security approval.
- [ ] All drugs used in the research are approved by the Egyptian Ministry of Health

Research on animal:

- [ ] The animal species are appropriate for the test.
- [ ] After test, if the animal will suffer, it will be euthanized and properly disposed.
- [ ] After operation, it will have a proper postoperative care.

RESULTS

The results of this study will be assessed, tabulated and statistically analyzed in appropriate figures and tables.

DISCUSSION

The results will be discussed in view of achievement of the aim, their significance and their comparison with previous related researches.

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