# *Factors Contributing to Local Recurrence after Conservative Breast Surgery for Early Breast Cancer*

Thesis

Submitted for partial fulfillment of the MD degree in General Surgery

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بسم الله الرحمن الرحيم
قَالُوا سُبْحَانَكَ
لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا
إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ
صدق الله العظيم
سورة البقرة
الآية (٣٢)

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**Mohamed Gamal**

# Dedication

*To my parents who devoted their life for us and always push me forward.*

*To my kids Yaseen and Sondos who provide me with the power and motivation in my life.*

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# List of Abbreviations

| | |
|---|---|
| ALND | Axillary lymph node biopsy |
| BCS | Breast conserving surgery |
| BCT | Breast conserving therapy |
| BIRADS | Breast Reporting and Data System |
| CC | Craniocaudal |
| CNB | Core needle biopsy |
| DCIS | Ductal carcinoma in situ |
| DFS | Disuse free survival |
| DNA | Deoxy Necleic acid |
| EBCTCG | Early Breast Cancer Trialists' Collaborative Group |
| ECD | Extracellular domain |
| EORTC | European Organization for Research and Treatment of Cancer |
| ER | Estrogen receptor |
| FDA | Food and drug administration |
| FDG | Flurodeoxy glucose |
| FNA | Fine needle aspiration |
| GEP | Gene expression profiling |
| HER-2 | Human epidermal growth factor receptor-2 |
| IBTR | Unilateral breast tumor recurrence |
| IDC | Invasive ductal carcinoma |
| IHC | Immunohistochemistry |
| ILC | Invasive lobular carcinoma |

| | |
|---|---|
| IORI ..... | Intra operative radio therapy |
| LCIS..... | Lobular carcinoma in situ |
| LR ..... | Local recurrence |
| LRR ..... | Local recurrence rater |
| MDT ..... | Multidisciplinary team |
| MLO ..... | Mediolateral oblique |
| MRI..... | Magnetic resonance imaging |
| MRM ..... | Modified radical mastectomy |
| NST..... | No special type |
| PBI ..... | Partial breast irradiation |
| PET ..... | Positron emission tomography |
| PR ..... | Progesterone receptor |
| RT ..... | Radiotherapy |
| VAB..... | Vacuum assisted biopsy |

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# Introduction

Breast conservative surgery has been a recognized method of treatment of early breast cancer. This method includes quadrantectomy or wide local excision combined with ipsilateral axillary nodal dissection followed by radiotherapy. Modified radical mastectomy continues to be appropriate for some patients, but breast conservation therapy is now regarded as the optimal treatment for most of the patients ***(Luini et al., 2009).***

Several randomized trials with very long follow-ups have established that breast-conserving therapy and mastectomy share equivalent outcomes in terms of overall survivals. Breast-conserving surgery followed by a course of postoperative radiotherapy is considered to be the current standard of care for patient with early operable breast cancer ***(Alain et al., 2007).***

The technique of breast conservative surgery has gained enormous popularity over the last two decades. The aim of such treatment is to eradicate the breast cancer while preserving the maximum amount of the breast tissue without increasing risk of local recurrence ***(Fisher et al., 2005).***

Contraindications to breast conservative surgery includes two or more primary tumors located in different quadrants of the breast associated diffuse micro calcifications which appear malignant, or a woman with previous breast irradiation. Breast irradiation cannot be given during pregnancy, but it may be possible to perform breast conserving surgery in the third trimester and irradiation can be administered after delivery ***(Silverstein et al., 2006).***

The greatest concern in breast-conserving surgery remains the local recurrence, which can provoke serious anxiety to the patient ***(E. Botteri et al., 2010).***

The risk factors for local recurrence of breast cancer which have been reported include large tumor size, multifocality, axillary lymph node involvement, young age, high nuclear grade, extent of the intraductal component and positive surgical margin status. Among these, the most important factor involved in local recurrence is positive surgical margin status ***(Luini et al., 2009).***

An important treatment related risk factor for local recurrence is the adequacy of surgical excision. This is demonstrated by the fact that most recurrence after breast conservative surgery occurs at the same side of and are clonally related to their primary lesions ***(Bijker et al., 2006).***

Clinical history, physical examination and breast imaging are the most effective means of follow up. Physical examination should be performed every three to six months for the first three years following surgery, and every six months in the years four and five. After five years, annual physical examination provides adequate follow up. Patients at exceptionally high risk of recurrence or development of a second primary tumor should be watched more closely. Magnetic Resonance (MR) mammography is important for the early recognition of recurrence and should then be done at least annually ***(Veronesi et al., 2006).***

In our study, we will report our experience with 137 patients with early breast cancer who are candidates for conservative breast surgery to detect factors contributing to local recurrence.

# Aim of the Study

Our study aims to highlight factors that may contribute to local recurrence after conservative breast surgery for early breast cancer.

# Cytogenetics and Pathology of Breast Cancer

## *Carcinogenesis of breast carcinoma:-*

Carcinogenesis is a multistep process characterized by genetic alternations that influence key cellular pathways involved in growth and development **(Cynthia et al., 2004).**

As regards breast cancer, malignancy results from step wise genetic alternations of normal host cells , and , possibly from other non genetic (or epigenetic) changes in the behavior of not only malignant cells but also host cells that interact with the tumor , such as immune , vascular, and stromal cell **(Balmain et al. ,2003).**

## *(A) Oncogenes :-*

Oncogenes refer to genes whose activation can contribute to the development of cancer. Activation can occur through gene amplification such that more of protein encoded by the gene is present; hence, its function is enhanced. An example of such a mode of oncogene activation is that of HER-2 (Human Epidermal Growth Factor Receptor-2), which is seen in about 20% of primary breast cancer cases (**Downward, 2003).**

Amplification and overexpression of these oncogenes and oncogene products are the major mechanisms though which these genes participate in carcinogenesis. Amplification may involve short chromosomal regions to chromosomal arms, involving hundreds of genes, to entire chromosomes. The following are descriptions of those oncogenes and proto-oncogenes (pre-activation) as well as their role in breast cancer carcinogenesis **(Cynthia et al., 2004).**

## *(1) The HER-2 oncogenes:*

The HER-2 (also known as The HER-2/neu or c-erbB-2) gene is located on chromosome 17q and encodes a 185-KDa transmembrane tyrosine kinase growth factor receptor **(Yarden and Sliwkowski, 2001).**

Numerous studies have strongly suggested its association with higher recurrence risk in early stage breast cancer and, to a lesser extend increased resistance to hormonal therapy **(Ross et al., 2003).**

## *(2) Myc oncogene:*

C-myc oncogene has been localized to chromosome 8q24 and encodes a nuclear phosphoprotein that acts as a transcriptional regulator involved in cellular proliferation, differentiation and apoptosis It is amplified and overexpressed in 15%-20% of breast cancer, and in some series, has been associated with worse prognosis or more aggressive clinical features **(Nass and Dickson, 1997) .**

While many agree that overexpression of this gene is clearly associated with breast cancer, still a controversy about whether or not aberrant Myc expression alone is sufficient for breast carcinogenesis. On the other hand, Myc plays a role in hormone responsiveness and chemotherapy resistance to the breast tumors **(Carroll et al., 2002).**

## *(B) tumor suppressor genes:*

Tumor suppressor genes are usually negative regulators of growth or other functions that may affect invasive and metastatic potential, such as cell adhesion and regulation of protease activity. Although inherited abnormalities account for a minority of breast cancer cases, germline mutations occur in tumor suppressor genes.

These some genes can harbor sporadic acquired somatic mutations. In both cases, the tumor typically contains a mutation in one allele and a deletion of the remaining allele in keeping with the long standing "two-hit" hypothesis formulated by Alfred Knudson in reference to retinoblastoma, which states that both gene alleles must be lost to unmask the malignant phenotype **(Knudson, 2000).**

## (1) The retinoblastoma (pRb) gene:

It was the first tumor suppressor gene to be discovered**.** In breast cancer, mutation or loss of pRb gene is present in up to 30% of cases of breast cancer **(Andersen et al., 1992).**

## (2) p16 gene:

One of the most commonly inactivated tumor suppressor genes in human cancer is p16 gene. P16 gene is a cyclin-dependant kinase inhibitor that regulates progression through G1 phase of the cell cycle by binding and inhibiting cyclin-dependent kinases 4 and 6, P16 alleles can be inactivated during neoplastic progression by multiple mechanisms, including deletion and mutation **(Deshmane and Fentiman, 2002).**

## (3) p53 gene:-

Mutation of P53 is estimated to occur in up to half of all human cancers and in approximately 20%-30% of breast cancers **(Hollstein et al., 1991).**

Li-Fraumeni syndrome, a rare autosomal dominant familial predisposition to a Variety of malignancies including breast cancer, sarcomas, leukemia, and brain tumours as early as the second and third decades of life, has been shown to result from germline alternations of p53, and multiple mutation sites have been reported. The risk of cancer of these patients has been