Retrospective Study on Discordance Between ER, PR, HER2 Receptors Before and After Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer

Thesis

Submitted for Fulfillment of Masters Degree in Clinical Oncology and Nuclear Medicine

Presented By

Ahmed Nader El Guindy

Resident of Clinical Oncology, Faculty of Medicine, Ain Shams University

Under Supervision of

Professor Doctor Manal Moawad

Professor and Head of Department of Clinical Oncology Department-Faculty of Medicine, Ain Shams Unversity

Professor Doctor Khaled El Husseiny Nasr

Professor of Clinical Oncology, Faculty of Medicine, Ain Shams University

Doctor Doaa Atef Mohammed

Lecturer of Clinical Oncology, Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2018

سورة البقرة الآية: ٣٢

Acknowledgement

First and foremost I feel indebted for ***Allah,*** *the most kind and most merciful.*

I would like to express my respectful thanks and profound gratitude to ***Prof. Dr. Manal Moawad,*** *professor & Head of Clinical Oncology & Nuclear Medicine – Faculty of Medicine – Ain Shams University for her keen guidance, kind supervision, valuable advice and continuous encouragement, which made possibility of completion of this work.*

I am also delighted to express my deepest gratitude and thanks to ***Prof. Dr. Khaled El Husseiny,*** *Professor of Clinical Oncology and Nuclear Medicine – Faculty of Medicine – Ain Shams University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful for ***Dr. Doaa Atef,*** *Lecturer of Clinical Oncology and Nuclear Medicine – Faculty of Medicine – Ain Shams University, for her great help, active participation and guidance.*

I would like to express my hearty thanks to all ***my family*** *for their support till this work was completed.*

Last but not least, I would like to thank all patients participated in this study.

Ahmed Nader

List of Contents

List of Abbreviations

Abb.	Full term
5-FU	*5-Fluorouracil*
AC	*Adriamycin , Cyclophosphamide*
ADH	*Atypical Ductal Hyperplasia*
AGO	*German Gynecological Oncology Group*
AJCC	*American Joint Committee on Cancer*
ALH	*Atypical Lobular Hyperplasia*
ALND	*Axillary Lymph Node Dissection*
AR	*Androgen Receptor*
ASCO	*American Society of Clinical Oncology*
BC	*Breast Cancer*
BCNF	*Breast Carcinoma with Neuroendocrine Features*
BCS	*Breast Conserving Surgery*
BCT	*Breast-Conserving Therapy*
BI-RADS	*Breast Imaging Reporting and Data System*
BMI	*Body Mass Index*
CA15-3	*Cancer Antigen 15–3*
CAP	*College of American Pathologists*
carb	*Carboplatin*
cDNA	*Complementary DNA*
CEA	*Carcinoembryonic Antigen*
CEF , FEC	*Cyclophosphamide, Epirubicin, and 5-fluorouracil*
CI	*Confidence Interval*
CIS	*Cisplatin*
CNB	*Core Needle Biopsy*
cT	*Clinical Tumor Size*
D.M	*Diabetes Mellitus*
DCIS	*Ductal Carcinoma in Situ*

List of Abbreviations (Cont...)

Abb.	Full term
DES	*Diethylstilbestrol*
DFS	*Disease-Free Survival*
DNA	*Deoxyribonucleic Acid*
EBCTCG	*Early Breast Cancer Trialists' Collaborative Group*
ER	*Estrogen Receptor*
etc.	*Et cetera*
FAC	*5-Fluorouracil, Adriamycin , and Cyclophosphamide*
FdUMP	*5-Fluorodeoxyuridine Monophosphate*
FISH	*Florescence in Situ Hybridization*
FNA	*Fine Needle Aspirate*
FNAC	*Fine Needle Aspiration Cytology*
GEP	*Gene Expression Profile*
HCV	*Hepatitis C Virus*
HER 2	*Human Epidermal Growth Factor Receptor 2*
HR	*Hormonal Receptor*
HRT	*Hormonal Replacement Treatment*
HTN	*Hypertension*
IDC	*Invasive Ductal Carcinoma*
IHC	*Immunohistochemistry*
IHD	*Ischemic Heart Disease*
ILC	*Invasive Lobular Carcinoma*
IMPC	*Invasive Micropapillarycarcinoma*
Ki67-LI	*Ki67-Labeling Index*
LABC	*Locally Advanced Breast Cancer*
LBC-A	*Luminal A*
LBC-B	*Luminal B*
LN	*Lobular Neoplasia*

List of Abbreviations (Cont...)

Abb.	Full term
LRC	*Lipid-Rich Carcinoma*
LVI	*Lympho Vascular Invasion*
MA	*Molecular Apocrine*
MBC	*Metaplastic Breast Carcinoma*
MC	*Mucinous Breast Carcinoma*
MRI	*Magnetic Resonance Imaging*
NCT	*Neoadjuvant Chemotherapy*
NE	*Neuroendocrine*
NEG	*Negative*
NSABP	*National Surgical Adjuvant Breast and Bowel Project*
NST	*No Specific Type*
OC	*Oral Contraceptive*
OS	*Overall Survival*
PALB2	*Partner and Localizer of BRCA2*
pCR	*Pathological Complete Response*
PET/CT	*Positron Emission Tomography/Computed Tomography*
PLC	*Pleomorphic Lobular Carcinoma*
PLCIS	*Pleomorphic Lobular Carcinoma in Situ*
POS	*Positive*
PR	*Progesterone Receptor*
pT	*Pathological Tumor Size*
PTEN	*Phosphatase and Tensin Homolog*
RNA	*Ribonucleic Acid*
RS	*Recurrence Score Assay*
STK11	*Serine/Threonine Kinase 11*
TDLU	*Terminal Duct Lobular Unit*
Tis	*Tumor in situ*

List of Abbreviations (Cont...)

Abb.	Full term
TKI	*Tyrosine Kinase Inhibitor*
TMA	*Tissue Microarray*
TN	*Triple Negative*
TNM	*Tumor Node Metastatsis*
TP 53	*Tumor Protein 53*
TXT	*Taxotere*
U.S	*United States*
UICC	*Unio Internationalis Contra Cancrum*
US	*Ultrasonography*
VEGF	*Vascular Endothelial Growth Factor*
wb-MRI	*Whole-Body Magnetic Resonance Imaging*
wPTX	*Weekly Paclitaxel*

List of Figures

List of Figures (Cont...)

List of Tables

List of Tables (Cont...)

Abstract

A review of the literature revealed 32 relevant studies that investigated the concordance of the hormone receptors (ER and/or PR) and HER2 after NAC with or without trastuzumab. Discordance of the hormone receptor status was reported in four out of eight studies in 8-33% of the patients. About half of the studies that tested the ER and PR receptor status separately reported discordances of 2.5-17% and 5.9-51.7% respectively. Studies that concluded that ER and/or PR receptor remained stable after NAC were performed with evidently lower number of patients compared to studies that reported a change. Good concordance of the HER2 amplification tested with FISH was reported, although the HER2 expression measured with immunohistochemistry was more discordant. A switch to a negative HER2 receptor in up to 43% of the patients was reported when NAC was combined with trastuzumab.

The timing of the surgical resection of a breast cancer relative to the chemotherapy regimen needed to minimize metastatic recurrence depends upon the disease presentation and input from the patient. A reasonable, clear indication for neoadjuvant chemotherapy is the need to reduce tumor size in an effort to provide breast conservation as an option. A typical patient for this would be a woman with small to medium breast size with a relatively large cancer who would prefer breast conservation as an option. This down staging of tumor size to avoid a mastectomy has been well documented with long-term loco-regional recurrence and survival rates being similar to traditional adjuvant chemotherapy treatment.

Keywords: Vascular Endothelial Growth Factor - Unio Internationalis Contra Cancrum - Tumor Node Metastatsis

INTRODUCTION

In 2015, an estimated 231, 840 new cases of invasive breast cancer would be diagnosed among women, as well as an estimated 60, 290 additional cases of in situ breast cancer. In 2015, approximately 40, 290 women were expected to die from breast cancer. Only lung cancer accounts for more cancer deaths in women. In 2015, about 2.350 men were diagnosed with breast cancer and 440 men would die from the disease ***(Area, 2015).***

In Egypt, the estimated incidence rates of breast cancer among females in Lower, Middle, Upper Egypt are 33.8 %, 26.8 %, 38.7 % respectively ***(Amal et al., 2014).***

Various risk factors, for example, increasing age, early menarche, late menopause, nulliparity or first child birth after the age of 30 years, lack of breastfeeding, sedentary lifestyle, etc., have been proposed ***(Aich et al. 2016).***

Hereditary Breast cancer, which is usually caused by a mutation in BRCA1 and BRCA2 genes, is responsible for 5% To 10% of all these cancer cases as well as 10% To 15% of ovarian cancer cases. This Type of breast cancer follows autosomal dominant pattern inheritance and tends to occur as an early onset, high intensity, and bilateral form of the disease ***(Mehrguo and Akouchekian, 2016).***

Most of the breast malignancies are adenocarcinomas, which constitute more than 95% of breast cancers. Invasive ductal carcinoma (IDC) is the most common form of invasive breast cancer. It accounts for 55% of breast cancer incidence upon diagnosis. Breast carcinomas arise from the same segment of the terminal duct lobular unit (TDLU). The typing of invasive breast carcinoma and its histological variants is well established. In general, breast carcinoma is divided into ductal carcinoma in situ (DCIS) and IDC. DCIS is a noninvasive potentially malignant intraductal proliferation of epithelial cells that is confined to the ducts and lobules. Invasive or infiltrative carcinoma refers to malignant abnormal proliferation of neoplastic cells in the breast tissue, which has penetrated through the duct wall into stroma. Invasive carcinoma and carcinoma in situ were classified as ductal and lobular based on the site from which the tumor originated. Cancers originating from the ducts are known as ductal carcinomas, while those originating from the lobules are known as lobular carcinomas. However, it is now found that this sort of tumor growth variation is not related to the site or the cell of origin, but there could be differences in tumor cell biology: whether the tumor cells express E-cadherin or not ***(Makki, 2015).***

Classical immunohistochemistry (IHC) markers such as ER, PR and HER2, together with traditional clinicopathological variables including, e.g., tumor size, tumor grade and nodal involvement, are conventionally used for patient prognosis and management ***(Dai et al., 2015).***