دور العلاج الكيمائي المسبق (neoadjuvant) في علاج سرطان الثدي مرحلة ١، ٢أ للإناث بحجم ثدي أ،ب،ج

رسـالة

وتوطئة للحصول على درجة الماجستير فى الجراحة العامة

مقدمة من

الطبيب/ كيرلس بهجت عدلى

بكالوريوس الطب والجراحة

كلية الطب - جامعة عين شمس

تحت إشراف

أ.د. / وليد عاطف عليان

أستاذ الجراحة العامة

كلية الطب – جامعة عين شمس

أ.د / أحمد جمال الدين عثمان

أستاذ مساعد جراحة عامة

كلية الطب – جامعة عين شمس

د. / مصطفي عمر عبد العزيز

مدرس الجراحة العامة

كلية الطب – جامعة عين شمس

كلية طب

جامعة عين شمس

٢٠١٨

Role of neoadjuvant chemotherapy in stage 1, 2a breast cancer in female patients breast cup (A-C)

Thesis

Submitted for partial fulfillment of master degree in general surgery

Presented By

Kerolos Bahgat Adly

M.B.B.CH

Faculty of Medicine, Ain Shams University

Supervisors

Prof. Dr. Walid Atef Elilan

Professor of General Surgery

Faculty of Medicine, Ain Shams University

Prof. Dr. Ahmed Gamaleldin Osman

Assistant Professor of General surgery

Faculty of Medicine, Ain Shams University

Dr. Mostafa Omar AbdelAziz

Lecturer of General Surgery

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

2018

First and forever, thanks to God Almighty for giving me the strength and faith to complete my thesis and for everything else.

I would like to express my sincere gratitude to **Prof. Dr. Walid Atef Elilan**, Professor of General Surgery, Faculty of Medicine-Ain Shams University, under his supervision, I had the honor to complete this work, I am deeply grateful to him for his professional advice, guidance and support.

My deep gratitude goes to **Prof. Dr. Ahmed Gamaleldin Osman**, Assisstant Professor of General Surgery, Faculty of Medicine-Ain Shams University, for his patience, guidance and valuable comments on this thesis.

My sincere thanks also goes to **Dr. Mostafa Omar AbdelAziz**, Lecturer of General Surgery, Faculty of Medicine-Ain Shams University, for his efforts, knowledge and meticulous supervision throughout this work and Dr. Amira Maher for her support and encouragement

Last but not least, I like to thank all my Family, especially my beloved mother, father and brothers for their kind care, help and encouragement. I would like to thank my patients, who were the corner stone of this study.

Kerolos Bahgat Adly

Abstract

Background: breast cancer is considered the most common cancer diagnosed in women worldwide with an incidence of 1.7 million new cancer cases in 2012. It is the fifth most common cause for cancer related mortality worldwide with a trend for increased mortality rates despite recent advances in breast cancer management. Currently, breast cancer is the most common cancer and one of the major health burdens for both developing and developed countries.

Purpose: to evaluate the impact of neoadjuvant chemotherapy in female patients stage 1, 2a breast cancer with breast cup (A-C)

Patients and Methods: we collected data from the records of female patients with breast cancer of stage 1,2a who had undergone documented preoperative biopsy and underwent chemotherapy neoadjuvant therapy at Ain Shams University Hospitals from September 2017 to June 2018. An informed consent was taken from all the patients sharing in the study.

Results: this study favors the idea of Neoadjuvant chemotherapy usage prior to any surgical intervention in early stage breast cancer. However, there were other studies that questions its role and demand a reconsideration about the oncological and clinical outcome which require further investigation.

Conclusion: it is clinically important to evaluate the value of the neoadjuvant chemotherapy in early stage breast cancer as it directs the future therapy. Although there is no obvious opinion with or against the neoadjuvant chemotherapy but through our studies the result support its significant role in downsizing and downgrading the tumor.

Keywords: Neoadjuvant Chemotherapy - Breast Cancer - Adenoid Cystic Carcinoma

List of Contents

List of Abbreviations

AC	Anthracyclins/ Cyclophosphamides
ACC	Adenoid cystic carcinoma
ACR	American college of radiologists
ADH	Atypical ductal hyperplasia
AI	Aromatase inhibitors
ASR	Age standardized rate
BCS	Breast conservation surgery
BI-RADS	Breast Imaging and Reporting Data System
BMI	Body mass index
BSE	Breast self examination
CBCS	Carolina breast cancer study
CBE	Clinical breast examination
CMF	Cyclophosphamide/ Methotrexate/ Fluorouracil
CT	Chemo-therapy
DCIS	Ductal carcinoma in situ
DEXA	Dual energy X-ray absorption
DFS	Disease free survival
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
ET	Endocrine therapy
FISH	Fluorescence in situ hybridization
FNA	Fine-needle aspiration

LIST OF ABBREVIATIONS *(CONT...)*

G-CSF	**Granulocyte colony-stimulating factor**
GEP	Gene expression profiling
GnRH	Gonadotrophin releasing hormones
HER2	Human Epidermal growth factor Receptor type 2
IDC NOS	Invasive ductal carcinoma not otherwise specified
IHC	Immuno-histochemistry
ILC	Invasive lobular carcinoma
IR	Incidence rate
LCIS	Lobular carcinoma in situ
MR	Mortality rate
MRI	Magnetic resonance imaging
NCI	National cancer institute
NPI	Nottingham prognostic index
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PBM	Prophylactic bilateral mastectomy
PBSO	Prophylactic bilateral salpingo-oophorectomy
PCM	Prophylactic contralateral mastectomy
pCR	Pathological complete response
PET	Positron emission tomography
PFS	Progression free survival
PMRT	Post-mastectomy radiotherapy

LIST OF ABBREVIATIONS *(CONT...)*

PR	**Progesterone receptor**
RT	Radiation therapy
SERM	Selective Estrogen Receptor Modulator
SLNB	Sentinal lymph node biopsy
TC	Taxanes/ Cyclophosphamide
TNBC	Triple negative breast cancer
TNM	Tumor – Node – Metastasis
US	Ultra-sonography
USG	Ultrasound guided
VABB	Vacuum-assisted breast biopsy
WBRT	Whole breast radiation therapy
WHO	World Health Organization

List of Tables

List of Figures

INTRODUCTION

Breast cancer is considered the most common cancer diagnosed in women worldwide with an incidence of 1.7 million new cancer cases in 2012. It is the fifth most common cause for cancer related mortality worldwide with a trend for increased mortality rates despite recent advances in breast cancer management. Currently, breast cancer is the most common cancer and one of the major health burdens for both developing and developed countries ***(Ferlay et al., 2012).***

In countries where screening programs for breast cancer are implemented, an abnormal mammography is usually the cause of presentation. However, almost 15% of patients are diagnosed with breast cancer in the absence of a breast mass that is detectable on mammogram and these are categorized as mammographically occult disease. Also 30% of patients develop a breast mass in the interval between mammograms and are referred to as interval cancers ***(Esserman et al., 2011).***

Incidence rate

The global burden of breast cancer in women, measured by incidence or mortality, is substantial and rising. Breast cancer is the most commonly diagnosed invasive cancer worldwide for females of all racial and

ethnic groups. Breast cancer accounts for more cancer deaths among women than any site other than lung cancer. Breast cancer also occurs in men, but the disease is rare among men and there is a pronounced female-to-male disparity in breast cancer incidence ***(Coughlin and Ekwueme, 2008).***

Breast cancer is the most common cancer seen in women, constituting 22% of all cases worldwide. In 2000, the estimated number of new cases of breast cancer was 579, 000 in developed countries and 471, 000 in less developed countries. Many differences with respect to age, stages at presentation, and biological characteristic exist between various countries. In the United States, approximately 50% of all women with newly diagnosed breast cancer are older than 63 years while in many so-called developing countries almost half of women with newly diagnosed breast cancer are younger than 50 years of age. In-situ disease has become more common in the developed world yet locally advanced and metastatic disease at presentation remains very common in the developing countries ***(Urban and Rietjens, 2013).***

In Egypt; National Cancer Institute in Cairo registry reported breast cancer to represent 35.1% of female cancers. An age-standardized incidence rates (ASRs) of 49.6 in the region of Gharbiah, Egypt in 2002 was reported.

Extensive disease at presentation was reported. A recent article about breast cancer in Cairo indicates a higher than expected detection rate of 8 per 1000 breast cancer cases upon first screening a target group of 4116 invited women aged 35-64 living in a geographically defined area in Cairo, which suggests that many women in the community with early but palpable breast cancer fail to seek medical attention until their cancer is advanced. National Cancer Institute of Cairo data showed breast cancer stages III and IV to be around 80-90% while it becomes 60% during this study. This study showed benefit from clinical breast examination and reduction of the incidence of locally advanced disease, and improvement of breast-conserving surgery rates ***(Khaled et al., 2014).***

The recommended workup of localized invasive breast cancer includes history and physical examination, bilateral sonomammography, determination of tumor hormonal receptor status, determination of HER2 receptor status and pathologic review. Chest and abdomen +/- pelvic diagnostic computed tomography as well as bone scan are recommended for stage III tumors or in the presence of symptoms or elevated alkaline phosphatase ***(NCCN Guidelines Version, 2016).***

Breast cancer is staged using the American Joint Committee on Cancer and the International Union for

Cancer Control (AJCC-UICC) classification system for tumor, nodes, and metastases (TNM). In the TNM system, patients are assigned a clinical stage (cTNM) preoperatively. Following surgery, the pathologic stage (pTNM) is then determined. For patients who undergo neoadjuvant (preoperative) treatment, the final pathologic stage is designated by the letter y (ypTNM) ***(Edge et al., 2010).***

Neoadjuvant (preoperative) treatment of early breast cancer has many advantages both for patients and for the 'rich'track of clinical, translational and scientific research that can be carried out. Published evidence confirms a reduction in mastectomy rates with increasing use of neoadjuvant therapy. The relationship between pathological response and longer-term outcome in women with early breast cancer receiving neoadjuvant systemic therapy is highly complex and its' dependencies are multifactorial. Neoadjuvant (preoperative) treatments and trials should therefore retain their place at the forefront of research and treatment for high risk early breast cancer ***(Earl et al., 2015).***

Neoadjuvant chemotherapy (NAC) also has the advantage of allowing for the acceleration drug development given the shorter time required to obtain response phenotypes (weeks to months) in comparison with

survival phenotypes as in the adjuvant setting (5–10 years). Accordingly, the US Food and Drug Administration (FDA) has published a "guidance to industry" on the use of pCR (pathological complete response) as an endpoint to support accelerated approval of investigational drugs ***(FDA. Guidance for Industry Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer).***