



Prognostic Impact of Chemotherapy-Induced Amenorrhea in Premenopausal Patients with Breast Cancer Following Adjuvant Chemotherapy

Thesis

Submitted For Partial Fulfillment of Master Degree
in Clinical Oncology and Nuclear Medicine

By

Huda Mohammed Saad Mohran
M.B.B.Ch.

Under supervision of

Dr. Khaled Abdel Karim Mohammed

Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University

Dr. Dalia AbdelGhany AbdelAI

Assistant Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University

Dr. Christine Reda Wahba

Lecturer of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University

**Department of Clinical Oncology and
Nuclear Medicine Ain Shams University
2019**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢



First and foremost, I feel always indebted to **ALLAH**, the Most Kind and Most Merciful.

*I'd like to express my respectful thanks and profound gratitude to **Prof. Dr. Khaled Mohammed Abd El Karim**, Professor of Clinical Oncology and Nuclear Medicine - Faculty of Medicine- Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made the completion of this work possible.*

*I am also delighted to express my deepest gratitude and thanks to **Dr. Dalia Abdelghani Abdel-Al**, Assistant Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, for her kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

*I am deeply thankful to **Dr. Christine Reda Wahba**, 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 my sincere thanks and appreciation to all patients participated in this study.

Huda Mohammed Saad Mohran

Contents

<i>Subjects</i>	<i>Page</i>
List of abbreviations	II
List of figures	IV
List of tables	V
• Introduction	1
• Aim of the Work	4
• Review of Literature	
♦ Chapter (1): Epidemiology, Etiology & Management Principles of Early Invasive Breast Cancer	5
♦ Chapter (2): Impact of Chemotherapy on the Ovarian Cycle.....	25
♦ Chapter (3): Incidence of Chemotherapy-Induced Amenorrhea & Factors Affecting It.....	36
♦ Chapter (4): Relation between Chemotherapy- Induced Amenorrhea, Disease-Free Survival & Overall Survival.....	47
• Patients and Methods	52
• Results	55
• Discussion	69
• Summary	82
• Conclusion	85
• Recommendations	86
• References	87
• Arabic Summary	

List of Abbreviations

Abb.	Full term
AI s	Aromatase inhibitors
AJCC	American Joint Committee on Cancer
ALND	Axillary lymph node dissection
APBI	Accelerated partial breast irradiation
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
Bcl-2	B-cell lymphoma 2
BCS	Breast conservative surgery
BI-RADS	Breast Imaging Reporting and Data System
CIA	Chemotherapy-induced amenorrhea
CNB	Core needle biopsy
CT	Computed tomography
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
EBCTCG	The Early Breast Cancer Trialists' Collaborative Group
EGFR	Epidermal growth factor receptor
EORTC	The European Organization for Research and Treatment of Cancer
ER	Estrogen receptor
FNAB	Fine Needle Aspiration Biopsy
HER2	Human epidermal receptor
HR	Hormone receptor

List of Abbreviations

IDC		Invasive ductal carcinoma
ILC		Invasive lobular carcinoma
LCIS		Lobular carcinoma in situ
LVI		Lymphovascular invasion
MRM		Modified radical mastectomy
NCCN		National Comprehensive Cancer Network
NSABP		National Surgical Adjuvant Breast and Bowel Project
OC		Oral contraceptives
OS		Overall survival
PET		Positron emission tomography
PR		Progesterone receptors
SEER		Surveillance, Epidemiology, and End-Results
SERMs		Selective estrogen receptor modulators
TNM		Tumor, node, metastasis classification
TTC		Time to chemotherapy
WHO		World health organization

List of Figures

<u>No.</u>	<u>Figure</u>	<u>Page</u>
<u>1</u>	Estimated breast cancer mortality and incidence rates across various geographic regions.	6
<u>2</u>	Staging of breast cancer according to AJCC 7th edition.	13
<u>3</u>	Staging of breast cancer according to AJCC 7th edition.	13
<u>4</u>	Histologic classification of Breast cancer subtypes.	15
<u>5</u>	Heterogeneity in breast cancer and different treatment strategies.	16
<u>6</u>	Stages of human follicle development& the effect of chemotherapeutic agents.	29
<u>7</u>	TAp63 signaling pathway.	30
<u>8</u>	Diagram explaining the PI3K pathway.	32
<u>9</u>	Mechanism of action of cyclophosphamide & anthracyclins causing cell death.	34
<u>10</u>	Mechanism of action of taxanes.	35
<u>11</u>	Risk for chemotherapy-induced amenorrhea based on age and type of chemotherapy.	44
<u>12</u>	Chemotherapy induced amenorrhea.	58
<u>13</u>	Age distribution according to CIA rate.	59
<u>14</u>	Kaplan-Meier survival curve of 4 years disease-free survival according to CIA.	67
<u>15</u>	Kaplan-Meier survival curve of 4 years overall survival.	68

List of Tables

<u>No.</u>	<u>Table</u>	<u>Page</u>
<u>1</u>	Different definitions of chemotherapy-induced amenorrhea present in literature.	37
<u>2</u>	Incidence of amenorrhea with different chemotherapy regimens.	40
<u>3</u>	Initial Patient Characteristics.	55
<u>4</u>	Chemotherapy induced amenorrhea.	58
<u>5</u>	Relation between age at diagnosis and CIA.	59
<u>6a</u>	Comparison between CIA and non-CIA group regarding patient characteristics.	60
<u>6b</u>	Comparison between CIA and non-CIA group regarding patient characteristics.	61
<u>7</u>	Retrospective Analysis for predictors of CIA	62
<u>8a</u>	Factors affecting disease-free survival.	63
<u>8b</u>	Factors affecting disease-free survival.	64
<u>9a</u>	Factors affecting overall survival rate.	65
<u>9b</u>	Factors affecting overall survival rate.	66

Introduction

Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers). It is the most common cancer in women both in more and less developed regions with slightly more cases in less developed (883,000 cases) than in more developed (794,000) regions. Incidence rates vary nearly four-fold across the world regions, with rates ranging from 27 per 100,000 in Middle Africa and Eastern Asia to 92 in Northern America and ranks second as a cause of cancer death in women .¹

Breast cancer is ranked as the most prevalent cancer among women in the MENA region.¹

In Egypt, breast cancer is the most common type of cancer in females, that constitutes for 38.8% of all cancers in females.²

Progression free survival (PFS) and overall survival (OS) have been improved by different adjuvant treatment modalities in breast cancer patients.³

Adjuvant treatments for breast cancer can include chemotherapy, hormonal therapy, human epidermal growth factor receptor (HER2) directed therapies, and radiation.⁴

Chemotherapy in premenopausal patients may cause ovarian suppression together with estrogen deficiency side effects. Early menopause causes vasomotor effects in the form of hot flashes, psychological effects of depression , increased risk of cardiovascular diseases , skeletal effects of osteoporosis, and genitourinary atrophy, Prolonged ovarian failure with amenorrhea causes infertility.⁵

Breast cancer survivors suffer these same long-term side effects. It has been stated that premenopausal women who were diagnosed with breast cancer are at high risk of menopause and infertility.⁶

Published data show an improvement in relapse-free and overall survival in women younger than 50 who underwent any mode of ovarian ablation.⁷

Women who developed amenorrhea, even temporarily after cyclophosphamide–methotrexate–fluorouracil (CMF) chemotherapy when compared with those who continued to menstruate ,were found to have a better prognosis.⁸

The chief factors of chemotherapy induced amenorrhea are patient's age, intensity of chemotherapy. Older women (>40 years) are more likely to have amenorrhea after adjuvant chemotherapy.⁹

Most anthracycline-based regimens produce a lower incidence of amenorrhea, probably due to the lower cumulative cyclophosphamide dosages when compared with the classic CMF regimen.¹⁰

Chemotherapy induced amenorrhea has a prognostic value, where many studies correlated the incidence of chemotherapy-induced amenorrhea with improvement in disease-free survival and overall survival in comparison to patients who didn't experience amenorrhea due to chemotherapy.³

More than half (52.2 to 77.7%) the number of premenopausal women who received either neoadjuvant or adjuvant chemotherapy are subjected to chemotherapy-induced amenorrhea, which leads to infertility, psychological distress, and prolonged exposure to risks of menopause.¹¹



Aim of the Work

The aim of this study is to analyze through the recorded data of files the prognostic effect of chemotherapy-induced amenorrhea in premenopausal patients with breast cancer following adjuvant chemotherapy.

1^{ry} objective: 4 years disease -free survival (DFS) & its correlation to amenorrhea: defined as the time from the date of diagnosis to the date before local, regional, or distant recurrent breast cancer; occurrence of contralateral breast cancer; occurrence of a second primary cancer; or death from any cause.

2^{ry} objective: 4 years Overall-survival & its correlation to amenorrhea: defined as the time from the date of diagnosis to the date of death from any cause or date of data analysis.

Chapter (1)

Epidemiology, Etiology & Management Principles of Early Invasive Breast Cancer

Breast cancer is the second most common cancer in the world. It is considered the most frequent cancer among women with an estimated 1.7 million new cancer cases diagnosed in 2012. It represents 25% of all new cancer cases among women. Breast cancer occurs in more and less developed regions, with more cases in less developed (883,000 cases) than more developed ones (794,000). ¹

It is considered the fifth cause of cancer related death (522,000 deaths) overall. It is the most common cause of cancer related death in women in less developed regions (324,000 deaths, 14.3% of total) and the second cause of cancer related death in more developed regions (198,000 deaths, 15.4%) after lung cancer. ¹

According to American Cancer Society, one in every eight women in the United States will develop breast cancer in her life. ¹²

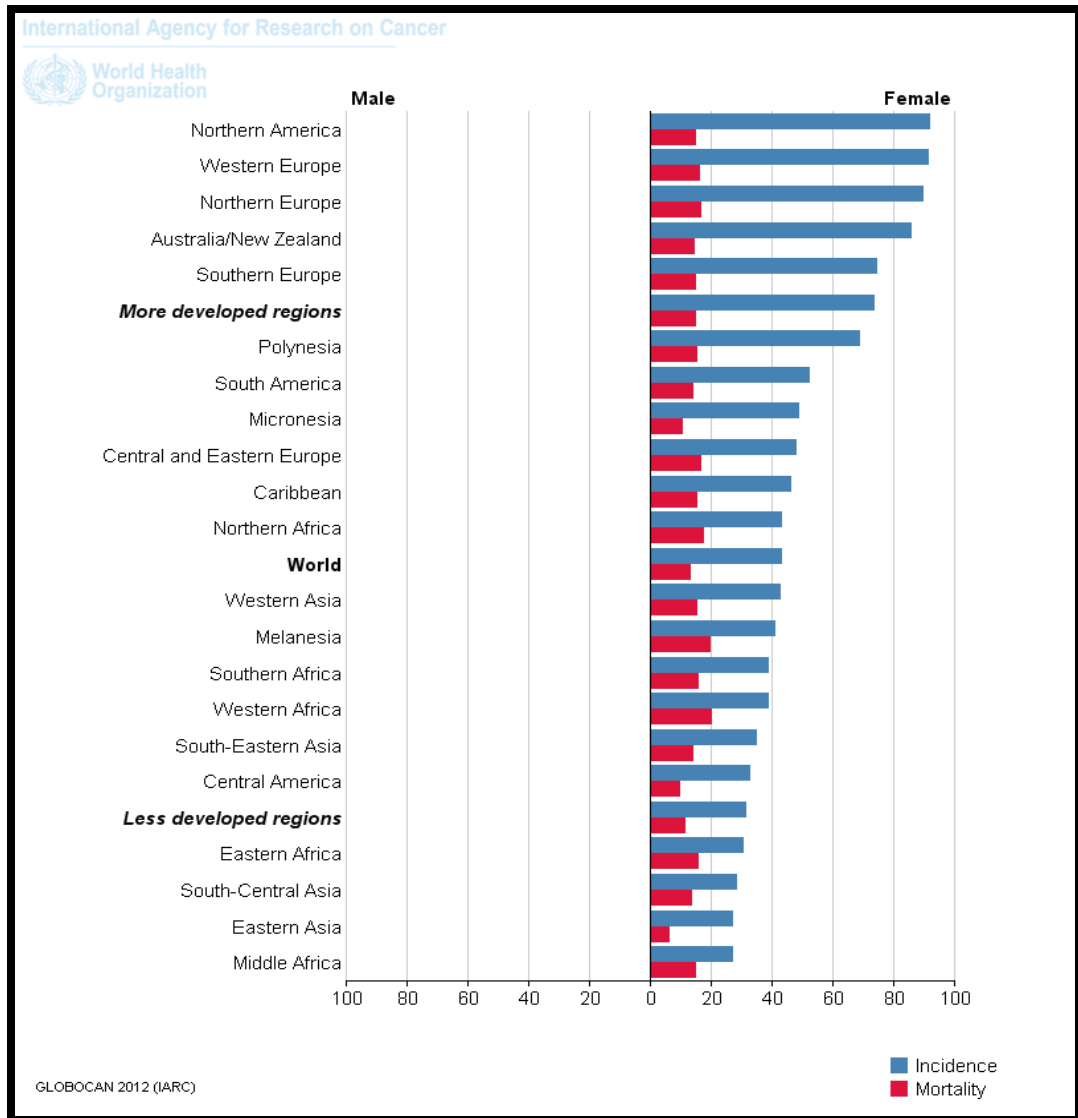


Figure (1): Estimated breast cancer mortality and incidence rates across various geographic regions.¹

In Egypt, breast cancer is the most frequent cancer among females. It accounts for 38.8 % of all cancers in women. The age specific incidence rates show a progressive increase after the age of 30 years with special geographic distribution along different regions as lower, middle, and upper Egypt, breast cancer incidences represented 33.8%, 26.8% and 38.7% respectively.²

A Five Years Retrospective Clinico-epidemiological Study of Breast Cancer Patients at the Clinical Oncology Department of Ain Shams university from 2010 to 2014 showed that the age at diagnosis ranged from 20 years to 93 years with the majority of patients (69.6%) in the age group from 40 to 65 years, whereas (14.2%) were younger than 40 and (9.4%) were older than 65.¹³

Etiology & Risk Factors

According to multiple intensive studies conducted over the past decades, various risk factors were identified to be associated with 20-30% of newly diagnosed breast cancer cases as they may be incorporated into the process of neoplastic transformation of breast cells. These risk factors can be divided into two categories; one includes inherent factors that are independent parameters such as age, sex, race and genetic mutations while the second category constitutes extrinsic factors conditioned by lifestyle as diet or long term medical intervention.¹⁴
