



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكرو فيلم

بسم الله الرحمن الرحيم



HANAA ALY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



HANAA ALY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



HANAA ALY

**Estimation of Progression Free Survival (PFS)
in patients with hormone positive metastatic
breast cancer in cohort of Egyptian patients
(Retrospective Cohort Study)**

A Thesis

Submitted for Partial Fulfillment of Master Degree In
Clinical Oncology & Nuclear Medicine

By

Ahmed Mohammed El-Saeed Abd El-Fattah

M.B, B.Ch,

Under Supervision of

Prof. Ali Mohammed Azmy

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

Prof. Mohammed Sabry EL-Qady

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

Assist. Prof. Amr Shafik

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

**Faculty of Medicine
Ain Shams University
2021**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢



Acknowledgments

First of all, thanks to **Allah**, Most Merciful and compassionate. Without the help of **Allah**, nothing could be done.

I would like to express my sincere gratitude and deep appreciation to **Prof. Ali Mohammed Azmy**, Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine Ain Shams University, for his continuous scientific guidance. Words cannot adequately express my great thanks and gratitude to him. I really have the honor to complete this work under his supervision.

I would like to express my sincere gratitude to **Dr. Mohammed Sabry El-Qady**, Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine Ain Shams, for his valuable help, cooperation, and encouragement without which this work wouldn't be completed.

I would like to express my great thanks to **Assist. Prof. Dr. Amr Shafik**, Assistant Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine Ain Shams, for his valuable help, cooperation, and encouragement without which this work wouldn't be completed.

I can't forget to thank with all appreciation all members of my **Family**, specially my dear **Mother** and commemorating the death of my **dear Father**, who his memory will be with me always, I will be grateful for their support and their great role in my life and numerous sacrifices for me and for my sisters; may Allah bless his soul.

Last but not least, many thanks for my Sisters and my Wife for their support.

 **Ahmed Mohamed El-Saeed**

List of Contents

| <i>Subject</i> | <i>Page No.</i> |
|----------------------------------------------|------------------------|
| List of Abbreviations..... | i |
| List of Tables..... | iii |
| List of Figures | iv |
| Introduction | 1 |
| Aim of the Work..... | 2 |
| Review of Literature | |
| Epidemiology and Risk Factors | 3 |
| Breast cancer Biomarkers | 12 |
| Management of Metastatic Breast Cancer | 38 |
| Patients and Methods..... | 57 |
| Results..... | 62 |
| Discussion | 87 |
| Summary and conclusion | 94 |
| References | 97 |
| Arabic Summary | — |

List of Abbreviations

| <i>Abbr.</i> | <i>Full-term</i> |
|--------------|----------------------------------------------|
| AI | : Aromatase inhibitor |
| AR | : Androgen receptor |
| ASCO | : American Society of Clinical Oncology |
| BCI | : Breast cancer index |
| BL1 | : Basal-like 1 |
| BL2 | : Basal-like 2 |
| BLIA | : Basal like immune activated |
| BLIS | : Basal-like immunosuppressed |
| CDC | : Centers for Disease Control and Prevention |
| DCIS | : Ductal carcinoma in situ |
| DFS | : Disease-free survival |
| dMFS | : Distant metastasis-free survival |
| ER | : Estrogen Receptor |
| GEP | : Gene expression profiling |
| GGI | : Genomic Grade Index |
| GR | : Glucocorticoid receptor |
| HER2 | : Human epidermal growth factor receptor 2 |
| HR | : Hormone receptor |
| IBC | : Invasive breast cancer |
| IM | : Immunomodulatory |
| LAR | : Luminal androgen receptor |
| LCIS | : Lobular carcinoma in situ |
| MAPK | : Mitogen activated protein kinase |

| | |
|--------------|-----------------------------------------------|
| MBC | : Metastatic breast cancer |
| MC | : Molecular classification |
| MES | : Mesenchymal |
| MSL | : Mesenchymal stem-like |
| OS | : Overall survival |
| PAM50 | : Prediction Analysis of Microarrays 50 |
| pCR | : Pathological complete response |
| PFS | : Progression free survival |
| PgR | : Progesterone receptor |
| QNBC | : Quadruple negative breast cancer |
| ROR | : Risk-of-recurrence |
| RS | : Recurrence score |
| RTK | : Receptor tyrosine kinase |
| SPSS | : Statistical Package for Social Science |
| SEER | : Surveillance, Epidemiology, and End Results |
| SREs | : Skeletal-related events |
| TNBC | : Triple negative breast cancer |
| TNF | : Tumor necrotic factor |

List of Tables

| Table No. | Title | Page No. |
|--------------------|----------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Table (1): | Estimated New Female Breast Cancer Cases and Deaths by Age..... | 4 |
| Table (2): | Age-specific Probability of Developing Invasive Breast Cancer for US Women..... | 5 |
| Table (3): | Commercially available prognostic multi-gene signatures for breast cancer patients | 35 |
| Table (4): | CDK4/6 inhibitors phase 3 trials according to endocrine sensitivity/resistance patients representation and outcome results | 43 |
| Table (5): | Distribution of the studied patients according to patient criteria..... | 62 |
| Table (6): | Distribution of the studied patients according to disease criteria | 63 |
| Table (7): | Distribution of the studied patients according to adjuvant treatment criteria | 64 |
| Table (8): | Distribution of the studied patients according to metastasis and its management | 65 |
| Table (9): | Progression free survival among the studied patients..... | 66 |
| Table (10): | Relation between menopausal status and progression free survival among the studied patients | 67 |

| | |
|----------------------------------------------------------------------------------------------------------------------------------|----|
| Table (11): Relation between family history of MBC and progression free survival among the studied patients..... | 68 |
| Table (12): Relation between Pathological types and progression free survival among the studied patients | 69 |
| Table (13): Relation between PR nuclear stain and progression free survival among the studied patients | 70 |
| Table (14): Relation between HER2 overexpression and progression free survival among the studied patients | 71 |
| Table (15): Relation between proliferative index Ki67 and progression free survival among the studied patients..... | 72 |
| Table (16): Relation between surgical management and progression free survival among the studied patients..... | 73 |
| Table (17): Relation between adjuvant chemotherapy and progression free survival among the studied patients | 74 |
| Table (18): Relation between breast irradiation and progression free survival among the studied patients..... | 75 |
| Table (19): Relation between adjuvant hormonal treatment and progression free survival among the studied patients..... | 76 |
| Table (20): Relation between onset of metastatic evolution and progression free survival among the studied patients | 77 |

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Table (21): Relation between site of metastasis and progression free survival among the studied patients | 79 |
| Table (22): Relation between first line therapy of metastasis management and progression free survival among the studied patients..... | 81 |
| Table (23): Relation between type of hormonal therapy for metastasis management and progression free survival among the studied patients..... | 83 |
| Table (24): Relation between ovarian ablation in premenopausal patients and progression free survival among the studied patients | 85 |

List of Figures

| <i>Figure No.</i> | <i>Title</i> | <i>Page No.</i> |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Figure (1): | Proportions of familial risk of breast cancer explained by hereditary variants | 11 |
| Figure (2): | Genes evaluated by multigene assays to calculate a recurrence risk score | 34 |
| Figure (3): | Kaplan Meier plot showing progression free survival among the studied patients | 66 |
| Figure (4): | Kaplan-Meier plot showing relation between progression free survival and menstrual history | 67 |
| Figure (5): | Kaplan-Meier plot showing relation between progression free survival and family history | 68 |
| Figure (6): | Kaplan-Meier plot showing relation between progression free survival and pathological type | 69 |
| Figure (7): | Kaplan-Meier plot showing relation between progression free survival and presence of progesterone receptor nuclear stain | 70 |
| Figure (8): | Kaplan-Meier plot showing relation between progression free survival and HER2 overexpression | 71 |
| Figure (9): | Kaplan-Meier plot showing relation between progression free survival and proliferative index (Ki67) | 72 |

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Figure (10): Kaplan-Meier plot showing relation between progression free survival and type of surgical management..... | 73 |
| Figure (11): Kaplan-Meier plot showing relation between progression free survival and type of adjuvant chemotherapy..... | 74 |
| Figure (12): Kaplan-Meier plot showing relation between progression free survival and breast irradiation..... | 75 |
| Figure (13): Kaplan-Meier plot showing relation between progression free survival and type of adjuvant hormonal therapy..... | 76 |
| Figure (14): Kaplan-Meier plot showing relation between progression free survival and onset of metastatic evolution | 78 |
| Figure (15): Kaplan-Meier plot showing relation between progression free survival and site of metastasis | 80 |
| Figure (16): Kaplan-Meier plot showing relation between progression free survival and first line of treatment of metastatic disease..... | 82 |
| Figure (17): Kaplan-Meier plot showing relation between progression free survival and type of hormonal therapy..... | 84 |
| Figure (18): Kaplan-Meier plot showing relation between progression free survival and ovarian ablation | 86 |

Introduction

Breast cancer is the most common type of cancer diagnosed in women, comprising 30% of all women's cancer diagnoses in the United States. The American Cancer Society estimated that 252, 710 new cases of breast cancer were diagnosed in women in 2017 (along with about 2470 cases in men). Breast cancer is the second leading cause of cancer-related death in women after lung cancer, accounting for 12% of cancer-related deaths (**Siegel et al., 2017**).

The use of systemic therapies such as hormonal therapy, chemotherapy or new biological treatment is to reduce tumour masses, improve survival and preserve quality of life. Whatever the initial efficacy of the treatment undertaken in metastatic setting, almost every patient will relapse. The main goal is to improve progression free survival (PFS) (**Dickson et al., 2005**).

Michiels et al. (2016) assessed to what extent PFS may be used as a surrogate for OS in randomized trials of anti-HER2 agents in HER2+ MBC. PFS moderately correlates with OS at the individual level and treatment effects on PFS correlate moderately with those on overall mortality, providing only modest support for considering PFS as a surrogate. PFS does not completely substitute for OS in this setting.