Prognostic Impact of KI67 in Localized Prostate Cancer

Thesis

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

By

Asmaa Gamal Mohamed El Sayed
M.B.B.C.H.

Under Supervision of

Prof. Dr. Sherif Ahmed Abd El Wahab
Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University

Prof. Dr. Ramy Refaat Yousef Ghali
Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University

Dr. Mohamed Mohamed Alhefny
Lecturer of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
2019

سورة البقرة الآية: ٣٢

Acknowledgment

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. Sherif Ahmed Abd El Wahab,*** *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 possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to ***Prof. Dr. Ramy Refaat Yousef Ghali,*** *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 to ***Dr. Mohamed Mohamed Alhefny,*** *Lecturer of Clinical Oncology and Nuclear Medicine, Faculty of Medicine – Ain Shams University, for her great help, active participation and guidance.*

Also my deeply thanks to ***Dr. Fatma S Hafez,*** *Lecturer of Pathology, 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.

Asmaa Gamal

List of Contents

List of Tables

List of Figures

List of Figures (Cont...)

List of Abbreviations

Abb.	Full term
ADT	*Androgen Deprivation Therapy*
AJCC	*American Joint Committee on Cancer*
BCR	*Biochemical Recurrence*
C-choline PET/CT	*C-choline Positron-Emission Tomography/Computed Tomography*
DHT	*Dihydrotetosterone*
DRE	*Digital Rectal Examination*
EBRT	*External Beam Radiotherapy*
EPE	*Extra Prostatic Extension*
ERSPC	*European Randomized Study of Screening for Prostate Cancer*
FDA	*Food and Drug Administration*
FISH	*Fluorescence in Situ Hybridization*
GWAS	*Genome Wide Association Studies*
hk2	*human kallikrein 2*
IHC	*Immunohistochemistry*
IMRT	*Intensity Modulated Radiotherapy*
ISUP	*International Society of Urological Pathology*
LH	*Luteinizing Hormone*
LHRH	*Luteinizing Hormone Releasing Hormone*
mpMRI	*Multiparametric MRI*
PCA3	*Prostate Cancer Antigen 3*
PET	*Positron Emission Tomography*
PHI	*Prostatic Health Index*
PI-RADS	*Prostate Imaging Reporting and Data System*
PLCO	*Prostate, Lung, Colorectal, and Ovarian*
PSA	*Prostatic Specific Antigen*
PSMA	*Prostatic Specific Membrane Antigen*

List of Abbreviations (Cont...)

Abb.	Full term
SBRT	*Stereotactic Body Radiotherapy*
SD	*Standard Deviation*
TRUS	*Trans-Rectal Ultrasonography*
USPSTF	*US Preventive Service Task Force*

ABSTRACT

Background: disease heterogeneity is reflected by the diverse clinical courses of indolent, aggressive and lethal prostate cancers. Prostate cancer is the second most commonly diagnosed cancer and the second leading cause of cancer death in males, after lung cancer. Prostate cancer heterogenic presentation is reflected by the diverse clinical courses of indolent, aggressive and lethal disease, so searching for markers that work as a prognostic marker is mandatory to help in the decision of choosing the treatment modality. KI67 is a well-known tissue biomarker that has a prognostic impact in localized prostate cancer.

Aim of the work: The aim of the study is to correlate the percentage of expression of Ki67 with the biochemical failure, disease free survival, Gleason score and PSA level for localized prostate cancer patients.

Results: Our retrospective study included 29 male patients diagnosed with localized prostate cancer with available tissue paraffin blocks. Patients were presented to Clinical oncology department at Ain Shams University hospitals. Patients' records in the period from January 2015 to December 2017 were reviewed with follow up of biochemical failure and progression free survival. Data collected included patients' characteristics, pathological profile, PSA level and Gleason score.

In our study the results show that no statistically significant association between higher Ki 67 and higher PSA levels (P value=0.52)

Results show that higher Gleason Scores are correlated with high Ki67 group (P value=0.03) that shows statistically significant relationship between Ki67 and Gleason Score.

Regarding lymph node status and seminal vesicle invasion there is no correlation with Ki67 in our study population (P value 0.52 and 0.6 respectively).

High Ki67 group shows increase in number of progressive events (68.4%) and median progression rate 0.15 with IQR 0.25 but P value is 0.32 that means numerically patients with higher KI67 had higher progression rates but statistically insignificant. This may be due to small population size and short follow up duration.

Conclusion: KI67 is correlated with Gleason score and there is no correlation between high KI67 and initial PSA level, lymph node status, seminal vesicle invasion and progression free survival.

Keyword: *KI67, localized prostate cancer, Gleason score and prognosis.*

INTRODUCTION

Prostate cancer is the second most commonly diagnosed cancer and the second leading cause of cancer death in males, after lung cancer ***(Siegel et al., 2017).***

Worldwide the number of new cases diagnosed with prostate cancer is 1,276,106 (7.1%) and the number of cancer deaths is 358,989 (3.8%) ***(Bray et al., 2018).***

According to the National Population-Based Registry program of Egypt 2008-2011; incidence of prostate cancer in Egypt is about 4.27% ***(Ibrahim et al., 2014).***

Screening for prostate cancer guidelines have changed massively over the past years. At mid-1990s, it was highly recommend to measure blood PSA levels to screen for prostate cancer. But, recent guidelines are against use of PSA for prostate cancer screening ***(Siegel et al., 2018).***

The main aim for prostate cancer screening is to discover localized prostate cancer earlier and to detect high risk patients aiming for successful treatment and decreasing burden of morbidity and mortality that is associated with metastatic and advanced cases of prostate cancer ***(Sanghera et al., 2018; Alpert et al., 2018).***

The key element of prostatic cancer patients' management is prognostic assessment. This assessment helps

deciding the way of treatment and follow up and predicting the outcome. International society of urological pathology (ISUP) has defined the pathological prognostic parameters as the following; Gleason grade, tumor extent as extra prostatic extension and seminal vesicle invasion, lymph node status, tumor volume, lymphovascular and perineural invasion ***(Gevad et al., 2018).***

Genomic studies help refine prostate cancer screening strategies through identification of different biologically significant biomarkers. This for sure will help for more refining of diagnosis, risk evaluation and management algorithms ***(Isaacs and Xu, 2018; Merriel et al., 2018).***

KI67 is well recognized and used to measure the tumor proliferation rate. It is considered a regulating protein of the cell cycle that is expressed only in the active phases of the cell cycle and immeasurable at resting cells. It can be analyzed by immunohistochemistry ***(Berlin et al., 2017).***

KI67 index may be increased in patients with poor prognosis as it has higher levels in carcinoma than benign hyperplasia, also in metastatic patients than non-metastatic ***(Verma et al., 2015).***

KI67 is considered an independent prognostic biomarker in association with clinical and biochemical recurrence. It is widely used all over the world because of its convenience and

easy interpretation. It has been used for different neuroendocrine, endocrine tumors, brain tumors, breast cancer, prostate cancer and lymphomas. It is used for prognostic impacts, grading, differential diagnosis and response of treatment ***(Tretiakova et al., 2017).***

The Ki-67 protein is well known and widely used to assess the tumor proliferation rate. It is one of the several cell-cycle regulating proteins, which can be demonstrated by immunohistochemistry ***(Richardsen et al., 2017).***

More recently it was found that each 1% increase in Ki-67 expression was associated with a 12% increased risk of prostate cancer-specific death ***(Tollefson et al., 2014).***

The comparison between Gleason's grade and Ki-67 labeling index clearly states that, there exists a linear relationship between Gleason's grading system and Ki-67 labeling index, as they both show an increasing trend in carcinomas ***(Rajeswari et al., 2016).***

Aim of the Work

The aim of the study is to correlate the percentage of expression of Ki67 with the biochemical failure, disease free survival, Gleason score and PSA level for localized prostate cancer patients in Department of clinical oncology and Nuclear Medicine, Ain Shams University hospitals, Cairo, Egypt from January 2015 to December 2017.

Chapter 1
EPIDEMIOLOGY AND RISK FACTORS

Cancer is not one disease, but a heterogeneous cluster of malignancies. Even within one cancer type substantial variations exist, and prostate cancer is no special case to that biological observation. Undoubtedly, disease heterogeneity is reflected by the diverse clinical courses of indolent, aggressive and lethal prostate cancers. Prostate cancer is the second most commonly diagnosed cancer and the second leading cause of cancer death in males, after lung cancer ***(Siegel et al., 2017).***

Incidence of prostate cancer varies greatly worldwide. There are many reasons as the incompletely known risk factors are affected by ethnicity, environment and geography, in addition to lack of proper documentation and registry in some developing countries ***(Duggan et al., 2016).***

Worldwide the number of new cases diagnosed with prostate cancer is 1,276,106 (7.1%) and the number of cancer deaths is 358,989 (3.8%) ***(Bray et al., 2018).***