Prospective Non Interventional Study Evaluating Prognostic and Predictive Value of PDL-1 Expression and Associated T-cell Infiltration in Primary Laryngeal Squamous Cell Carcinoma

Thesis

Submitted for Partial Fulfillment of M.D. In Clinical Oncology and Nuclear Medicine

By

Maha Maher Tawfik

M.B.B.Ch., MSc

Faculty of Medicine - Ain Sham University

Under Supervision of

Prof. Dr. Hesham Mahmoud Hassan El Wakiel

Professor of Clinical Oncology and Nuclear Medicine

Faculty of Medicine - Ain Sham University

Dr. Amr Lotfy Farag

Assistant Professor of Clinical Oncology and Nuclear Medicine

Faculty of Medicine - Ain Sham University

Dr. Dalia Abd El Ghany Abd El Aal El Khodry

Assistant Professor of Clinical Oncology and Nuclear Medicine

Faculty of Medicine - Ain Sham University

Dr. Marwa Mosaad Shakweer

Assistant professor of Pathology

Faculty of Medicine - Ain Sham University

Faculty of Medicine

Ain Sham 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. Hesham Mahmoud Hassan El Wakiel,** *Professor of Clinical Oncology and Nuclear Medicine Faculty of Medicine - Ain Sham 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 **Dr. Amr Lotfy Farag,** *Assistant Professor of Clinical Oncology and Nuclear Medicine Faculty of Medicine - Ain Sham University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful to **Dr. Dalia Abd El Ghany Abd El Aal El Khodry,** *Assistant Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, for her great help, active participation and guidance.*

I wish to introduce my deep respect and thanks to **Dr. Marwa Mosaad Shakweer,** *Assistant professor of Pathology, Faculty of Medicine, Ain Shams University, for her kindness, supervision and cooperation in this work.*

Maha Maher Tawfik

List of Contents

List of Tables

List of Tables Cont...

List of Tables Cont...

List of Tables Cont...

List of Figures

List of Figures Cont...

List of Figures Cont...

List of Abbreviations

Abb.	Full term
A/E	Adverse events
ADH	Alcohol dehydrogenase
ALDH	Aldehyde dehydrogenase
APC	Antigen presenting cells
CAFs	Carcinoma-associated fibroblasts
CCRT	Concurrent chemoradiotherapy
Chth	Chemotherapy
CPS	Combined positive score
CRT	Chemoradiation
CT	Computed Tomography
CTLA-4	Cytotoxic T lymphocytes associated protein-4
CTLs	Cytotoxic T lymphocytes
DNA	Deoxyribonucleic acid
EBV	Epistein bar virus
ECOG	Eastern Cooperative Oncology Group
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ENE	Extra nodal extension
EORTC	European Organization for Research and Treatment of Cancer
FDG PET/CT	^{18}F fluorodeoxyglucose positron emission tomography/computed tomography
FISH	Fluorescence in situ hybridization
FNA	Fine needle aspiration
GETTEC	Groupe d'Etude des Tumours Tete et Cou
GORTEC	Groupe d'Oncologie Radiotherapie Tete et Cou
GRB	Guanine Nucleotide Releasing Proteins
Gy	Grey
HDAC	Histone Deacetylase

List of Abbreviations Cont...

Abb.	Full term
HIF-1	Hypoxia inducible factor 1
HIV	Human immunodeficiency virus
HNC	Head and Neck Cancer
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
HR	Hazard ratio
HSV	Herpes simplex virus
IC	Immune cells
IL	Interleukin
IMRT	Intensity-modulated Radiotherapy
LFS	Laryngectomy free survival
M	Metastasis
MACHNC	Meta-Analysis of Chemotherapy on Head and Neck Cancer
miRNAs	MicroRNAs
MRI	Magnetic Resonance Imaging
MTV	Metabolic tumor volume
N	Node
NICD	NOTCH intracellular domain
NKs	Natural killer cells
NO	Nitric oxide
NSCLC	Non-small-cell lung cancer
OR	Odds ratio
OS	Overall survival
OSCC	Oral squamous cell carcinoma
pAKT	Phosphorylated AKT
PD-1	Programmed death-1
PDL-1	Programmed death ligand-1
PET	Positron emission tomography

List of Abbreviations Cont...

Abb.	Full term
PFS	Progression free survival
QOL	Quality of life
Rb	Retinoblastoma gene
RFS	Relapse-free survival
RR	Relative risk
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
SBRT	Stereotactic body radiation therapy
SCC	Squamous cell carcinoma
SOS	Son of Sevenless
STAT3	Signal transducer and activator of transcription 3
SUV_{max}	Standardized uptake value
T	Tumor
TC	Tumor cells
TCR	T cell receptor
TF	Transcription factors
Th	T helper
TILs	Tumor infiltrating lymphocytes
TLG	Total lesion glycolysis
TLM	Transoral laser microsurgery
TLS	Transoral laser surgery
TME	Tumor micro environment
TOLM	Transoral laser microsurgery
TPF	Taxotere /platinum/fluorouracil
Tregs	T regulatory cells
UADT	Upper aerodigestive tract
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization

INTRODUCTION

The immune system can have an important role in eliminating tumor cells, although the immune microenvironment may enable malignant cells to become more aggressive and escaping immunological surveillance ***(Lee et al., 2011)***.

As the tumors cause immunosuppression, the human immune reactivity against solid tumors becomes ineffective. Current cancer immunotherapies focus on overcoming this inhibition, either by activation of the immune system in general or by local manipulation of immunoregulatory molecules in the tumor microenvironment, including what is called immune checkpoints ***(Hodi et al., 2010).***

Recently, evaluation of PDL-1 status in tumor specimens could guide in selection of patients for treatment with PD1 checkpoint inhibitors. But accurate measurement of PDL-1 protein levels in tumor samples is limited by the absence of reliable antibodies and uncertain positive cutoff value ***(Maria et al., 2016).***

The immune suppressive molecule programmed death-1 (PD-1) is upregulated in activated T lymphocytes and inhibits T-cell function by binding to its ligands. PD-1/PDL-1 interactions are a major mechanism of immune suppression within the tumor microenvironment. Antibodies directed against PD-1 and B7-H1