Correlation between HIF-1α and BCL2 Expression and Tumor Behavior in Locally Advanced Head and Neck Squamous Cell Carcinoma

Thesis

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Lamiaa Moustafa Abdel Megied

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List of Abbreviations

Abb.	Full term
17-AAG	*17-N-Allylamino-17-demethoxy geldanamycin*
17-DMAG	*17-dimethylaminoethylamino-17 demethoxygeldanamycin*
2ME2	*2-Methoxyestradiol*
ADH	*Alcohol Dehydrogenase*
Akt	*Serine/Threonine-Specific Protein Kinase*
ALDH	*Aldehyde Dehydrogenase*
ARF	*Alternative Reading Frame*
ATP	*Adenosine Triphosphate*
BCL2	*B-cell Lymphoma 2*
BH3	*Bcl-2 Homology 3*
CAIX	*Carbonic Anhydrase 9*
CT	*Computed Tomography*
CTGF	*Connective Tissue Growth Factor*
DAHANCA	*Danish Head and Neck Cancer Group*
DHFR	*Dihydrofolate Reductase*
DNA	*Deoxyribonucleic Acid*
DOI	*Depth of Invasion*
E6-AP	*E6-Associated Protein*
EF5	*([2-(2-nitro-1H-imidazol-yl)-N-(2, 2, 3, 3, 3-pentaflouropropyl) acetamine]*
EGFR	*Epidermal Growth Factor Receptor*
ErbB	*Erythroblastic Leukemia Viral Oncogene Homolog 2*
EORTC	*European Organisation for Research and Treatment of Cancer*
FAZA	*Fluoroazomycinarabinofuranoside*
FDG	*Fluoro-deoxyglucose*
FISMO	*Fluorine 18-Fluoromisonidazole*
GLUTs	*Glucose Transporters*

List of Abbreviations (Cont...)

Abb.	Full term
Grb2	*Growth Factor Receptor-Bound Protein 2*
GTP	*Guanine Triphosphate*
Gy	*Gray*
HBO	*Hyperbaric Oxygen*
HDAC	*Histone Deacetylase*
HER	*Human Epidermal Growth Factor Receptor*
HIF1α	*Hypoxia-Inducible Factor 1 Alpha*
HIG-2	*Hypoxia-Inducible Gene-2*
HNC	*Head and Neck Cancer*
HNSCC	*Head and Neck Squamous Cell Carcinoma*
HPV	*Human Papilloma Virus*
HREs	*Hypoxia Response Elements*
Hsp90	*Heat Shock Protein 90*
IGF-1R	*Insulin-Like Growth Factor-1 Receptor*
IHC	*Immunohistochemistry*
IKK-b	*IkappaB Kinase Beta*
IL	*Interleukin*
INF	*Interferon*
IQR	*Interquartile ratio*
JAK	*Janus Kinase*
LOX	*Lysyl Oxidase*
MAPK	*Mitogen-Activated Protein Kinases*
MDM2	*Mouse Double Minute 2 Homolog*
mm Hg	*Millimeter Mercury*
MOM	*Mitochondrial Outer Membrane*
MRI	*Magnetic Resonance Imaging*
mTOR	*Mammalian Target of Rapamycin*
NRP-1	*Neuropilins*
NRP-2	*Neuropilins*

List of Abbreviations (Cont...)

Abb.	Full term

OPN ..... *Osteopontin*
OPSCC..... *Oropharyngeal Squamous Cell Carcinoma*
OS ..... *Overall Survival*
p53 ..... *Protein p53*
p63 ..... *Protein p63*
p73 ..... *Protein p73*
PDGFR ..... *Platelet-Derived Growth Factor Receptor*
PDK1..... *Pyruvate Dehydrogenase Kinase*
PEITC..... *2-Phenethyl Isothiocynate*
PET-CT..... *Positron emission tomography -Computed Tomography*
PFS ..... *Progression Free Survival*
PHD ..... *Prolyl Hydroxylase Domain*
PI3K..... *Phosphatidylinositol 3-Kinase*
PIP2 ..... *Phosphorylation of Phosphatidylinositol 4, 5-Diphosphate*
PIP3 ..... *Phosphorylation of Phosphatidylinositol 3, 4, 5-triphosphate*
PlGF..... *Placental Growth Factor*
PO2 ..... *Oxygen Pressure*
pRb..... *Retinoblastoma Protein*
R..... *Correlation Coefficient*
Raf ..... *Rapidly Accelerated Fibrosarcoma*
RAS..... *Human Homologs of Murine Sarcoma Virus Oncogenes*
RNA ..... *Ribonucleic Acid*
ROS..... *Reactive Oxygen Species*
RQ..... *Relative Quantitation of gene expression in relation to housekeeper gene.*

List of Abbreviations (Cont...)

Abb.	Full term
RR	*Relative Risk*
RT	*Radiotherapy*
RTKs	*Receptor Tyrosine Kinases*
RTOG	*Radiation Therapy Oncology Group*
SCC	*Squamous Cell Carcinoma*
SD	*Stable Disease*
STAT	*Signal Transducer and Activator of Transcription*
STIR	*Short Tau Inversion-Recovery*
TGF-α	*Transforming Growth Factor-Alpha*
TP53	*Tumor Protein p53*
TPF	*Docetaxel, Cisplatin and 5 Flourouracil*
TPZ	*Tirapazamine*
TSA	*Trichostatin A*
VEGF	*Vascular Endothelial Growth Factor*
VGFR	*Vascular Endothelial Growth Factor Receptor*
VHL	*Von Hippel–Lindau*

ABSTRACT

Background: Head and neck cancer represents more than 550,000 cases annually. It accounts for 380,000 deaths every year. Despite aggressive treatment, only 35% to 55% of patients who present with locally advanced HNC cancer remain alive and free of disease 3 years after standard curative treatment. Thirty percent to 40% of patients develop locoregional recurrences, and distant metastases occur in 20% to 30%. Most recurrences appear quickly within 2 years of initial treatment and an additional 10% of patients will have evidence of distant metastases at the time of first presentation.

Purpose: To retrospectively determine the prognostic effect of T stage in locally advanced head and neck cancer.

Methods: This study retrospectively analyzed 40 patients diagnosed with locally advanced head and neck cancer. Patients were diagnosed by a tissue biopsy and they were staged by endoscope and CT neck or MRI neck with contrast. They received their treatment and were followed up every 3 months by CTs.

Results: We found a statistically significant correlation between T stage and both PFS and OS (95%, CI 1.00 – 3.10, p=0.04 and 95% CI 1.01 – 2.65, p=0.05 respectively).

Conclusion: This study confirmed that the T stage of the tumor is an important prognostic factor in locally advanced head and neck cancer.

Keywords: Locally advanced head and neck cancer. T stage. Prognosis.

INTRODUCTION

Across the world, head and neck cancer (HNC) represents more than 550,000 cases and 380,000 deaths every year. Males are affected more than females with a ratio ranging from 2:1 to 4:1 ***(Fitzmaurice et al., 2017).***

Previous hospital-based studies from Egypt showed that HNC constitutes about 17-20% of all malignancies. A study describing the epidemiology of HNC in Egypt using data from the only population-based cancer registry, a higher incidence of HNC among males than females and higher incidence in urban than rural populations were documented. Overall, the incidence of HNC was highest in the 70+ age group in both males and females ***(Attar, 2010).***

Squamous cell carcinomas represent nearly 90% of all head and neck cancers, arising mainly in the oral cavity but also occurring in the nasal cavity, pharynx and larynx ***(Mehanna et al., 2010).***

The patterns of local invasion and distant spread of head and neck squamous cell carcinoma (HNSCC) differ depending on the intrinsic properties of individual tumors themselves but these events are also strongly influenced by properties of the local tumor microenvironment. For example, the presence of stromal cells, such as cancer associated fibroblasts and of recruited inflammatory cells, markedly influences tumor behavior ***(Wheeler et al., 2014).***

Hypoxia is also considered a major microenvironmental influence and HNSCC, like many solid tumors, develops areas of hypoxia when the blood supply becomes limited due to tumor growth, vascular disturbances or metabolic changes ***(Overgaard, 2011).***

Efficacy of radiation treatment relies on DNA damage, either via direct damage of DNA by ionizing radiation or by free radicals that are generated and subsequently react with DNA, causing damage. Oxygen free radicals are highly reactive and are the primary source of radiation-induced DNA damage, and oxygen is, therefore, a potent radiosensitizer. Hypoxic HNSCC, measured by pretreatment tumor PO2, have been shown to be significantly more likely to persist or recur locoregionally ***(Nordsmark and Overgaard, 2000).***

Hypoxia-inducible factor 1α (HIF1-α) is an intracellular transcription factor that undergoes degradation under well-oxygenated conditions but is stabilized under hypoxic conditions. When HIF1-α is stabilized, it regulates the expression of proangiogenic genes, such as vascular endothelial growth factor (VEGF) ***(Koukourakis et al., 2002).***

In a study of 75 HNSCC specimens, overexpression of HIF1-α, assessed by immunohistochemistry (IHC) was associated with locally aggressive behavior ***(Nordsmark et al., 2007).***