ROLE OF MYOEPITHELIAL CELLS IN BENIGN AND MALIGNANT SALIVARY GLAND TUMORS

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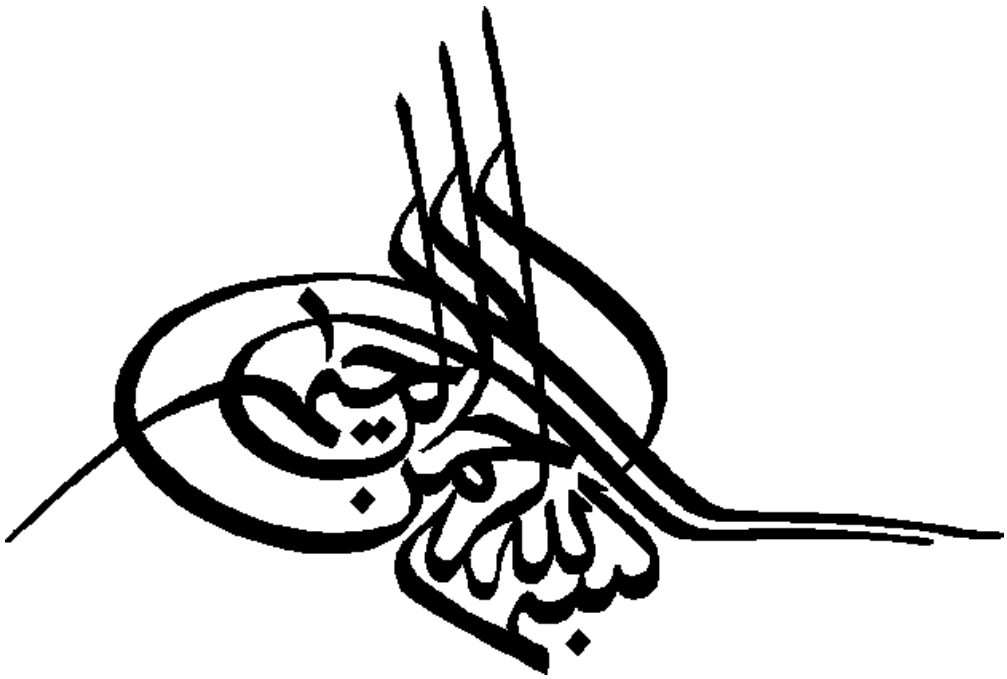
بسم الله الرحمن الرحيم

To My Great Parents

My Beloved Mother & Father In Law

My Sisters & Brothers

My Wonderful Husband, Amr

Who Gave Me All The Possible Time,
Support And Encouragement I Ever Needed

My Beautiful Daughters,

Mariam And Judy

May All Your Dreams Come True

And Your Wishes Be Granted

To All Who Will Read This One Day And
Find It Useful,

Thank You For Your Time And Trust

And God Bless You All

Alaa

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دور الخلايا الطلائية العضلية في أورام الغدد اللعابية الحميدة و الخبيثة

رسالة

مقدمة لكلية طب الأسنان جامعة عين شمس لإستيفاء جزء من متطلبات

درجة الماجستير في أمراض الفم

مقدمة من

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المشرفون

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Introduction

Salivary gland tumors (SGTs) are a morphologically and clinically diverse group of neoplasms which may present significant diagnostic and management challenges. These tumors are rare, with an overall incidence in the western world of approximately 2.5 cases to 3.0 cases per 100,000 per year[(1)].

In the USA, salivary gland cancer (SGC) accounts for 6% of all head and neck cancers and 0.3% of all malignancies[(2a)]. Nearly 80% of these tumors occur in the parotid glands, 15% in the submandibular glands and the remaining 5% in the sublingual and minor salivary glands. Benign neoplasms make up about 80% of parotid tumors, 50% of submandibular tumors and less than 40% of sublingual and minor salivary gland tumors[(3)]. The highest incidence occurs between 30 and 60 years of age[(4)].

The entire glandular structure of the salivary gland exhibits a two-tiered organization comprising luminal (acinar and ductal) and abluminal cells (myoepithelial and basal cells). The secretory acini and intercalated ducts are wrapped by myoepithelial cells (MECs), while the striated ducts and subsequent conducting portion are supported by basal cells. The above cell types form the basis of the extraordinarily diverse array of SGC. The neoplastic process can arise from one type of cell alone or much more commonly both the inner and outer cell types participate in the tumors[(4)].

The classification of salivary gland neoplasms is complex and essentially based on morphology. The classification of these lesions is encompassing nearly forty different entities according to the World Health Organization (WHO) classification. Precise classification and terminology is essential for an accurate diagnosis and for the allocation of neoplasms to prognostic groups[(1)].

Over the years, there has been some progress in clarifying specific causes of SGC. There is compelling evidence implicating exposure to ionizing radiation and the development of SGTs. Long term follow up studies of the survivors of the atomic bomb explosions in Hiroshima and Nagasaki show an increased relative risk of 3.5 for benign and 11 for malignant salivary gland neoplasms. The risk was directly related to the level of exposure to ionizing radiation. There was a high frequency of both mucoepidermoid carcinomas and Warthin tumors in these patients. Therapeutic radiation, particularly of the head and neck region, has been linked with a significantly increased risk of developing SGCs. There appears to be a risk from iodine used in the treatment of thyroid disease as the isotope is also concentrated in the salivary glands[(2a)].

There is evidence that exposure to routine dental radiographs is associated with an increased risk of SGC. Exposure to ultraviolet radiation has also been implicated. There appears to be no excess risk in those exposed to radon or the microwaves of cellular telephones[(2a)].

A number of viruses have been implicated in the pathogenesis of SGTs. There is a strong association between Epstein Barr virus (EBV) and lymphoepithelial carcinomas, but there is no convincing association between human SGTs and other viruses, including polyoma virus and papilloma virus[(2a)].

It has been shown that workers in a variety of industries have an increased incidence of salivary gland carcinomas. These include rubber manufacturing, exposure to metal in the plumbing industry and nickel compounds, woodworking in the automobile industry and employment in hairdressing and beauty shops[(2a)].

No association was found between tobacco use and alcohol consumption and SGCs in a case/control study. However, there is a strong association between

smoking and Warthin tumor[2a].Most patients with benign tumors of the major or minor salivary glands present with a painless swelling. Neurological signs, such as numbness or weakness caused by nerve involvement, typically indicate a malignancy[5].

Histologically, SGTs represent the most heterogeneous group of tumors of any tissue in the body[6]. This complexity has been attributed to the myoepithelial component of these tumors[7]. In view of the difficulty in identifying these MECs by routine hematoxylin and eosin (H&E) staining and even by special techniques, immunohistochemistry has been found to be a useful tool in the distinction of these cells, contributing to an improved differential diagnosis of SGTs[8].

The proper management of SGTs requires an accurate diagnosis by the pathologist, correct interpretation by the surgeon, knowledge of the surgical anatomy of salivary glands with a clear understanding of the factors leading to recurrence and complications[9].

The variable nature of SGTs creates difficulty in determining prognosis. Outcomes for patients with SGTs depend on the site of tumor, histology, extent of disease, completeness of surgery, and/ or adjuvant radiation therapy, though there are many exceptions[10].

Thus, the behavior of this malignancy is quite variable and leads to much uncertainty for the patients afflicted with this disease. Even the most common benign salivary tumor, pleomorphic adenoma (PA), has a propensity for malignant transformation and possible recurrence[11].

List of Abbreviations

5-Aza: Methyltransferase inhibitor 5-aza-2-deoxycytidine

ACC: Adenocystic Carcinoma

AF: Area Fraction

ANOVA: Analysis Of Variance

ATPases: Adenosine Triphosphatases

BAD: Bcl-2-associated death promoter

BAX: Bcl-2-associated X protein

BCC: Basal Cell Carcinoma

Bcl-2: B-cell lymphoma 2

bFGF: Basic Fibroblast Growth Factor

BM: Basement Membrane

BMPs: Bone Morphogenetic Proteins

BRCA1: Breast cancer type 1

Ca^{2+}: Calcium ion

CaP: Calponin

CD10: Cluster of Differentiation 10

CD44: Cluster of Differentiation 44

Cdc25: Cell division cycle 25

Cdc25A: Cell division cycle 25 A

Cdc25B: Cell division cycle 25 B

Cdc25C: Cell division cycle 25 C

CDK1: Cyclin-Dependent Kinase 1

cDNA: Complementary Deoxyribonucleic Acid

CH1K: Checkpoint Kinase

CH-domain: Calponin Homology domain

CK14: Cytokeratin 14

CK5: Cytokeratin 5

CLIK23: Calponin-Like repeats

CpG: Cytosine-phosphate-Guanine

CXCL14: Chemokine (C-X-C motif) Ligand 14

CXPA: Carcinoma ex-Pleomorphic Adenoma

DAB: Diaminobenzidine

DCIS: Ductal Carcinoma In Situ

df: Degrees of freedom

Diff: Difference

DNA: Deoxyribonucleic Acid

DPX: Distyrene, a Plasticizer and Xylene

EBV: Epstein Barr Virus

ECM: Extracellular Matrix

EFP: Estrogen-induced zinc Finger Protein

EGF: Epidermal Growth Factor

EMC: Epithelial Myoepithelial Carcinoma

ERK1/2: Extracellular signal-regulated kinase 1 and 2

F-actin: Filamentous actin

G1: Gap 1 phase of cell cycle

G2: Gap 2 phase of cell cycle

GFAP: Glial Fibrillary Acidic Protein

GISTs: Gastrointestinal Stromal Tumors

H&E: Hematoxylin and Eosin

HEM: Human Epithelial Marker

HGF: Hepatocyte Growth Factor

kDa: Kilodalton

M: Mitosis phase of cell cycle

MAP: Mitogen-Activated Protein

Maspin: Mammary serine protease inhibitor

MECs: Myoepithelial Cells

MgATPases: Magnesium Adenosine Triphosphatases

MMPs: Matrix Metalloproteinases

mRNA: Messenger Ribonucleic Acid

N: Number

P21: Protein 21

P53: Protein 53

P63: Protein 63

PA: Pleomorphic Adenoma

PBS: Phosphate Buffered Saline

PCNA: Proliferating Cell Nuclear Antigen

pH: Power of hydrogen

pI: Isoelectric point

PKC: Protein Kinase C

PLGA: Polymorphous Low-Grade Adenocarcinoma

RNA: Ribonucleic Acid

S: Synthesis phase of cell cycle

SAGE: Serial Analysis of Gene Expression

SCC: Squamous Cell Carcinoma

Ser: Serine

SGC: Salivary Gland Cancer

SGTs: Salivary Gland Tumors

Sig: Significance

SMA: Smooth Muscle Actin

SMCs: Smooth Muscle Cells

SMM-HC: Smooth Muscle Myosin Heavy Chain

SPSS: Statistical Package for Social Science

Std: Standard

TA: Transcriptionally Active

TGF-β: Transforming Growth Factor Beta

Thr: Threonine

TIMP-1: Tissue Inhibitor of Metalloproteinase-1

Tyr: Tyrosine

USA: United States of America

VEGF: Vascular Endothelial Growth Factor

WHO: World Health Organization

ΔN: Dominant negative