Definition of Risk Groups in Oral Cavity Squamous Cell Carcinoma Patients and Prediction of Their Outcomes by Using ^{18}F-FDG PET/CT

Thesis

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بسم الله الرحمن الرحيم

اِقْرَأْ باسم ربِّكَ الّذي خَلَق * خَلَقَ الإِنْسَانَ مِنْ عَلَق * اِقْرَأْ

وربُّكَ الأَكْرَم * الّذي عَلَّمَ بالقَلَمِ * عَلَّمَ الإِنْسَانَ مَا لَم يَعْلَم *

صدق الله العظيم

سورة العلق، الآيات 1-5

Abstract

Post-operative radiotherapy (RT) or chemoradiation (CRT) is indicated in the presence of adverse features *“extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, selected pT2N0-N1 disease, nodal disease in levels IV or V, perineural invasion, vascular embolism”* The prognostic factors that may modify the outcome have been described as patient-related *(gender, age, smoking, drinking, chewing betel quid)*, tumor-related *(site, stage, thickness, extracapsular spread, differentiation, perineural invasion, angiogenesis, human papilloma virus infection)*, and treatment-related factors *(resection margin, adjuvant post-operative therapy, and cervical lymph node dissection)*.

Key word

- OSCC- Tumor-Related - Treatment-Related- Patient-Related SCC- VS

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List of Abbreviations

AJCC	American Joint Committee on Cancer
AUC	Area Under Curve
CCRT	Concomitant ChemoRadioTherapy
CGMH	Chang Gung Memorial Hospital
CI	Confidence Interval
COX	Cycolooxygenase
CRT	ChemoRadioTherapy
CT	Computed Tomography
CWU	Conventional Work-Up
DFS	Disease Free Survival
DICOM	Digital Imaging and Communications in Medicine
DMFS	Distant Metastases Free Survival
DOD	Died Of Disease "cancer death"
DSS	Disease Specific Survival
ECS	Extra-capsular Spread
EORTC	European Organisation for Research and Treatment of Cancer
FDG	Fluodeoxyglucose
FLT	Fluoromisonidazole
FMISO	Fluoromisonidazole
FWHM	Full Width at Half Maximum
HIF	Hypoxia Inducible Factor
HNC	Head and Neck Cancer
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papilloma Virus
HR	Hazards Ratio
JD	Jugulodigastric
JD	Jugulo-Digastric
JO	Jugulo-omohyoid
LC	Local Control
LGI	Larson Ginsberg Index
LN	Lymph Node
LND	Lymph Node Dissection
MD	Moderately-Differentiated
MIC	Molecular Imaging Center
MRI	Magnetic Resonance Imaging
MS	Masticator Space
MTV	Metabolic Tumor Volume
MVA	Multivariate Analyses
NC	Neck Control

NCCN	National Comprehensive Cancer Network
NER	No Evidence of Recurrence
ns	Not significant
$_N$SUV	Standardized Uptake Value of the Lymph Nodes
$_N$TLG	Total Lesion Glycolysis of Lymph Nodes
OL	Oral Leukoplakia
OS	Overall Survival
OSCC	Oral Squamous Cell Carcinoma
PD	Poorly-Differentiated
PET/CT	Positron Emission Tomography/Computed Tomography
PVE	Partial Volume Effect
RMT	Retromolar Trigone
ROC	Receiver Operating Characteristics
ROI	Region Of Interest
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
S/B Ratio	Signal to Background Ratio
SCC	Squamous Cell Carcinoma
SCM	Sternocleidomastoid
SD	Standard Deviation
SIL	Squamous Intraepithelial Lesion
SOHND	Supra-Omohyoid Neck Dissection
SUV	Standardized Uptake Value
SUVavg	Average Standardized Uptake Value
SUVlean	Standardized Uptake Value normalized to Lean Body Mass
SUVmax	Maximum Standardized Uptake Value
SUVpeak	Peak Standardized Uptake Value
TLG	Total Lesion Glycolysis
TNM	Tumor, Node and Metastasis
$_T$SUV	Standardized Uptake Value of the Primary Tumor
$_T$TLG	Total Lesion Glycolysis of the Primary Tumor
UADT	Upper Aerodigestive Tract
US	Ultrasound
UVA	Univariate Analyses
VC	Verrucous Carcinoma
VEGF	Vascular Endothelial Growth Factor
VEGF	Vascular Endothelial Growth Factor
VOI	Volume Of Interest
WD	Well-Differentiated
WHO	World Health Organization

Introduction

Oral cancer is the eighth most common cancer worldwide, with epidemiologic variations between different geographic regions (1). The World Health Organization (WHO) expects a worldwide rising incidence in the next decades (2).

Surgery is the main stay for resectable oral squamous cell carcinoma (OSCC). Post-operative radiotherapy (RT) or chemoradiotherapy (CRT) is indicated in the presence of specific adverse features (3).

Numerous prognostic factors have been identified including clinical, anatomical and pathological risk factors; however, and in spite of the ready accessibility of the oral cavity to direct examination, these malignancies still often not detected until a late stage, and the survival rate for oral cancer has remained essentially unchanged over the past three decades (4).

The possibility of identifying novel prognostic factors in oral cancer may help in stratifying different risk groups and personalizing the cancer management process.

Recently, standardized uptake value (SUV), a simplified index of glucose uptake of the tumor measured from ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), has been strongly introduced as a possible prognostic factor in many cancers, including head and neck cancer (5-10). However, some drawbacks are inherent to the use of SUV, one of these drawbacks is being a single pixel value not reflecting the real tumor heterogeneity (11).

The concept of total lesion glycolysis (TLG) has been introduced by *Larson et al.* to study the change of glucose metabolism pre- and post-therapy (12). It was calculated as the product of tumor volume from PET/CT and the average SUV within this volume.

Their results set the stage for other groups at Memorial Sloan-Kettering Cancer Center to study TLG among other parameters in evaluation of lung cancer after radiation treatment (13) and to predict long-term outcomes in patients with rectal cancer (14). They found good correlation between TLG with treatment response and outcomes. TLG also was investigated in patients with esophageal cancer (15, 16), soft tissue sarcoma (17), osteosarcoma (18) and melanoma (19), with encouraging results.

The potential prognostic role of baseline SUV and TLG measured at the primary tumor and neck lymph nodes has not been studied in patients with OSCC.

Aim of the Work

To evaluate the potential prognostic role of presurgical standardized uptake value (SUV) and total lesion glycolysis (TLG), measured from FDG PET/CT at the primary tumor and neck lymph nodes, in identifying different risk groups of oral cavity squamous cell carcinoma (OSCC) and predicting their outcomes.

Anatomy of the Oral Cavity

Oral cancer can be divided into two main categories: one arising in the oropharynx and one arising in the oral cavity. The latter, *which is the focus of this review*, is subdivided into oral cavity proper and lip vermilion ***(Figure 1)*** (4).

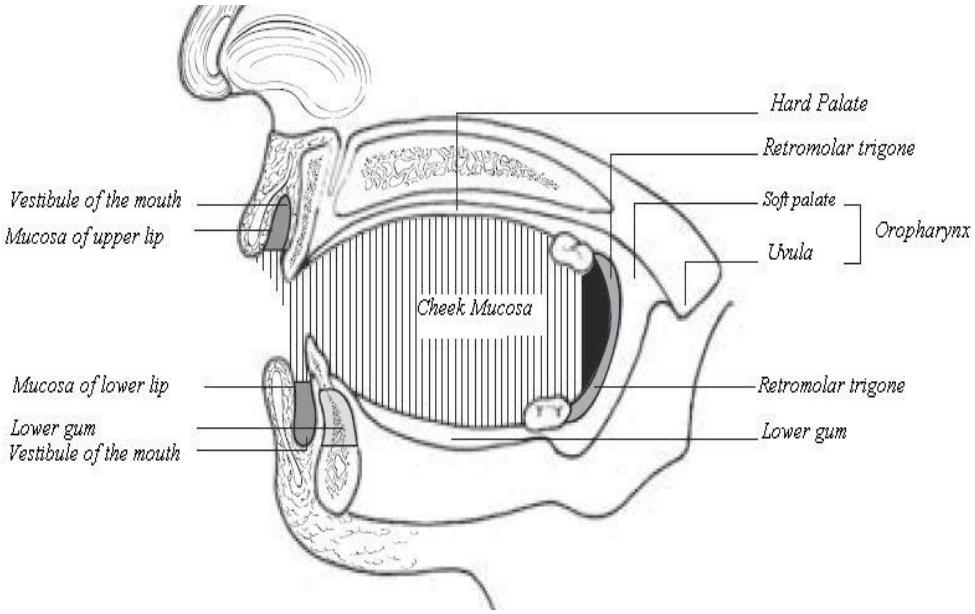

Figure 1: *Anatomical sites and sub-sites of the oral cavity (20)*

I. Lips

The lip begins at the junction of the vermillion border, which marks the beginning of the red transitional zone between the skin and the mucous membrane of the lip, and includes only the vermillion surface *(that portion of the lip that comes into contact with the opposing lip).* It is well defined into an upper and lower lip joined at the commissures of the mouth (20).

Beneath the lip skin is a layer of subcutaneous tissue with many muscles, nerves, and vessels. This subcutaneous tissue lies just superficial to the orbicularis oris muscle, which forms the main bulk of the lips. Deep to that muscle are numerous labial salivary glands, each with a small duct penetrating the mucosal membrane. The