Role of FDG-PET CT in differentiating adenocarcinomas from squamous cell carcinomas of the lung

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Presented by

Amr Muhammad Abdo Salem

M.B.B.CH. – Ain Shams University

Supervised by

Prof. Dr. Laila Hosny Hussein

Professor of Radiodiagnosis

Faculty of Medicine

Ain Shams University

Asst. prof. Ahmed Mohamed Osman

Assistant professor of Radiology

Faculty of Medicine

Ain Shams University

Faculty of Medicine

Ain Shams University

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Abbreviation	Stands for
AC	Adenocarcinoma
AIS	Adenocarcinoma in situ
ALK	Anaplastic lymphoma kinase
ATS	American Thoracic Society
BAC	Bronchioloalveolar carcinoma
CT	Computed tomography
EBUS	Endobronchial ultrasound
EGFR	Epidermal growth factor
ERS	European Respiratory Society
FDG	Fluoro-deoxyglucose
IASLC	International Association for the Study of Lung Cancer
LR+	Positive likelihood ratio
LR-	Negative likelihood ratio
MIA	Minimally invasive adenocarcinoma
NPV	Negative predictive value
NSCLC	Non-small cell lung cancer

Cont. List of abbreviations

Abbreviation	Stands for
PET-CT	Positron emission tomography-computed tomography
PPV	Positive predictive value
ROC curve	Receiver operating characteristic curve
SCC	Squamous cell carcinoma
$SUV_{average}$	Average standardized uptake value
SUV_{max}	Maximum standardized uptake value
TLR	Tumor-to-liver ratio
TNM	Tumor node metastases
WHO	World health organization

Introduction

Lung cancer is considered to be the leading cause of malignancy related deaths worldwide ***(Volpi et al., 2018; Siegel et al.,2014)***. Histologically, it is divided into two major types; non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC contributes to 86% of lung cancers. NSCLC is further subdivided into three main subtypes adenocarcinoma (AC), squamous-cell carcinoma (SCC), and large-cell carcinoma which constitute 60%, 20% ,and 3% of lung cancers, respectively ***(Barta et al., 2019).***

The combination of fluorine-18 fluoro-deoxyglucose positron emission tomography (FDG-PET) and computed tomography (CT) has a great impact on the diagnosis, staging, and hence on the treatment plan and follow up of lung cancer patients. It helps in non-invasive mediastinal staging and decrease the number of unnecessary thoracotomies and mediastinoscopies ***(Volpi et al., 2018).***

PET-CT is more accurate than conventional CT at diagnosing the presence of metastases. It has been reported that up to 10% of patients are found to have metastases on PET-CT that were not detected on prior CT, and therefore offers an important additional benefit to patient staging ***(Volpi et al., 2018).*** It is used also in planning of radiation treatment and in the follow

up of patients to detect recurrence of the disease and to assess the early response to chemotherapy ***(Messerli et al., 2019)***.

Maximum standardized uptake value (SUV_{max}) is a semi-quantitative index which is easily performed and the most widely used quantitative parameter for the analysis of 18F-FDG PET images and for the estimation of metabolic activity. It is used to differentiate benign lesions from malignant lesions ***(Wang et al., 2014).*** Zhu et al., concluded that tumors with high SUV_{max} have higher malignant or metastatic potential ***(Zhu et al., 2013)***. Sim et al., have found that increasing SUV_{max} is associated with increasing the possibility of malignancy ***(Sim et al., 2013)***.

Lin et al., indicated that increasing SUV_{max} is linked to increased tumor, node, and metastasis (TNM) stage ***(Lin et al., 2014)***. Özgül et al, demonstrated that SUV_{max} was significantly associated with tumor size ***(Özgül et al., 2013)***.

Prior studies have found a link between FDG uptake and the degree of differentiation of lung cancer ***(Zhu et al., 2013; Sim et al., 2013;Karam et al., 2018)***. Karam et al., have found that poorly differentiated NSCLC showed more uptake than well differentiated ones ***(Karam et al., 2018)***.

Differentiating AC from SCC of the lung has a great impact on the chemotherapy treatment choice. For example Pemetrexed

is more effective in patients with advanced lung AC rather than SCC. Also, Bevacizumab is contraindicated in patients with SCC ***(Travis et al., 2011)***.

The gold standard way of differentiating between different histopathological sub-types is the tissue biopsy. Peripheral tumors are more accessible to CT-guided biopsy and this carries the risk of pneumothorax ***(Lang et al., 2018).*** Central tumors are more accessible to transbrocnhial biopsy and this carries the risk of hemorrhage ***(Hetzel et al., 2019)***

Studies have shown that different pathological types of NSCLC produce different SUV_{max} values on PET-CT ***(Karam et al., 2018; Kim et al., 2015; Wang et al., 2015).*** SCC exhibited higher SUV_{max} than AC ***(Messerli et al., 2019)***.This may explain the poorer prognosis noted of lung cancer with SCC histological subtype than AC histological subtype ***(Ito et al., 2014).***

Aim of work

To evaluate the role of FDG-PET CT in differentiating AC from SCC of the lung by comparing their FDG uptake measured as SUV_{max}.

Pathology of squamous cell carcinoma and adenocarcinoma of the lung

The concept of the personalized medicine is considered one of the great advances in lung cancer in the past decade. It entails taking therapeutic decisions based on the specific histologic and genetic characteristics of the patient's tumor. This raised the importance of classification of NSCLC into specific pathologic subtypes e.g., AC versus SCC, because this determines the eligibility of the patient for specific molecular testing and therapeutic strategies ***(Travis et al., 2015)***.

Therapeutic strategies and pathology clinical practice have been revolutionized by the discovery of epidermal growth factor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements as effective targets for EGFR tyrosine kinase inhibitors or ALK inhibitors in patients with advanced lung AC ***(Travis et al., 2011).***

The need for differentiating AC from SCC is summarized as: 1) EGFR mutations and rearrangements of ALK and c-ros oncogene 1 (ROS1) are found primarily in AC.

2) Pemetrexed is more effective in patients with advanced lung AC rather than SCC.

3) Bevacizumab is contraindicated in patients with SCC.

4) Nivolumab (a programmed death-ligand [PDL] antibody) was recently approved by the U.S. Food and Drug Agency for the treatment of advanced lung SCC.

(Travis et al., 2011)