^{18}F-Fluoro-2-Deoxy-D-Glucose PET/Computed Tomography Evaluation of Lung Cancer in Populations with High Prevalence of Tuberculosis and Other Granulomatous Disease

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KEYWORDS

- ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) • PET • Pulmonary tuberculosis • Lung cancer
- Standardized uptake value (SUV)

KEY POINTS

- ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET/computed tomography (CT) is widely used in the diagnosis of lung cancer and other malignancies. Increased ^{18}F-FDG activity on PET/CT imaging, as an indicator of tissue glycolytic activity, serves as a nonspecific tumor marker.
- Accumulation of activated macrophages and lymphocytes in active pulmonary tuberculosis also leads to increased uptake of ^{18}F-FDG in tuberculomas, which cannot be reliably differentiated from malignancy.
- The diagnosis of lung cancer using ^{18}F-FDG PET is compromised in tuberculosis endemic regions, because active tuberculosis granulomas cause significant false positive findings.
- Similar to tuberculosis, many other infections/inflammatory lesions, such as fungal infection, sarcoidosis, inflammatory pseudotumor, and so forth, may cause similar diagnostic dilemmas on ^{18}F-FDG PET imaging.
- In areas with a high incidence of tuberculosis, extra attention should be made to differentiate lung cancer from active pulmonary tuberculosis, so that unnecessary radical procedures can be avoided.

INTRODUCTION

Lung cancer is a leading cause of death by malignancy because of its high morbidity and mortality.[1] Non–small cell lung cancer (NSCLC) accounts for more than 85% of all lung cancer cases.[2] ^{18}F-Fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET/computed

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tomography (CT) has been well established as a crucial tool for detecting, identifying, and staging NSCLC, with obvious superiority compared with traditional anatomy imaging modalities.[2] A standardized uptake value (SUV) greater than 2.5 is often used as a cutoff value for differentiating lung malignancies from benign cases with ^{18}F-FDG PET/CT.[3,4] However, the specificity of ^{18}F-FDG PET/CT has been vigorously challenged. In clinical practice, it is not rare for benign lesions having an SUV higher than 2.5 and resulting in false positive diagnoses.[5]

Pulmonary tuberculosis (TB), caused by a Mycobacterium, is a common worldwide infection, especially in developing countries. It infects one-third of the world's population. Radiologically, it behaves like lung cancer[5–7] with variable manifestations. Such epidemic and radiographic features make pulmonary TB the leading cause of false positive PET/CT finding in lung cancer diagnoses in high prevalence areas, resulted in 57.1% to 92% of false positive diagnoses of primary lung cancer.[8–11] Because of activated immune cells, a TB site also presents an elevated level of glucose consumption,[12] difficult to differentiate from malignancies. Although efforts have been made, such as using delayed image acquisition,[9,13] this inherent shortcoming of ^{18}F-FDG has not been effectively solved.[10]

EPIDEMIOLOGY AND RISK FACTORS OF LUNG CANCER

Lung cancer is the leading cause of cancer deaths in both men and women in the United States. The incidence of lung cancer is higher in men than in women, but at present, the incidence is also increasing in women.[14]

Cigarette smoking is the primary risk factor for lung cancer.[15–17] Heavy smoking is associated with a 20- to 30-fold increase in lung cancer risk compared with nonsmokers. In general, 30% of lung cancers are squamous cell carcinoma, which is strongly associated with smoking. Squamous cell carcinomas, small cell lung carcinoma, large cell carcinoma, and to a lesser extent adenocarcinoma have an increased incidence with increased number of cigarettes smoked per day. Radon, a radioactive gas, is the second cause of lung cancer in the general population[18] and is the main cause of lung cancer in nonsmokers. Secondary smoking is the third leading cause of lung cancer.[19,20]

EPIDEMIOLOGY AND RISK FACTORS OF TUBERCULOSIS

TB is an airborne infectious disease caused by *Mycobacterium tuberculosis* (MTB) and is a major cause of morbidity and mortality, particularly in developing countries.[21–23] The global burden of TB is growing as reflected by increases in new cases and per capita incidence rates of 1.8% and 0.4% per year, respectively, between 1997 and 2000.[22] Worldwide there were 8.6 million new cases of active TB and 1.3 million deaths in 2012.[24] Most cases occur in Southeast Asia and Africa. The prevalence of TB in China accounts for 250,000 patients' annual deaths, the second highest worldwide.[25]

The risk for developing active TB is governed by exogenous and endogenous factors. Exogenous factors accentuate the progression from exposure to infection. Bacillary load in the sputum of the infected person, duration, and proximity to an infectious TB case are key factors. Endogenous factors, on the other hand, lead to the progression from infection to active TB disease.[26] Malnutrition, tobacco smoking, and indoor air pollution from solid fuel have been documented as the most important risk factors for TB worldwide, followed by HIV infection, diabetes, and excessive alcohol consumption.[27]

Extrapulmonary TB occurs in 10% to 42% of patients. The occurrence of the extrapulmonary disease depends on the age, presence or absence of underlying disease, ethnic background, immune status of the individual, and the strain or lineage of MTB.[26] The disease may occur in any part of the body and can mimic many clinical diseases, which potentially delays the diagnosis. HIV coinfection with TB presents major challenges to the diagnosis and treatment of TB.

PATHOPHYSIOLOGY OF TUBERCULOSIS IN RELATION TO ^{18}F-FLUORO-2-DEOXY-D-GLUCOSE UPTAKE

MTB is an aerobic, nonmotile, non-spore-forming rod that is highly resistant to drying, acid, and alcohol. It is transmitted from person to person via droplet nuclei containing the organism and is spread mainly by coughing. Invasion of the pulmonary alveoli with mycobacteria signals the start of TB infection, which later on invades and replicates within the alveolar macrophages.

Inhaled *mycobacteria* are phagocytized by alveolar macrophages, which interact with T lymphocytes, resulting in differentiation of macrophages into epithelioid histiocytes.[28] Epithelioid histiocytes and lymphocytes aggregate into small clusters, resulting in granulomas. In the granuloma, CD4 T lymphocytes (effector T cell) secrete cytokines, such as interferon-γ, which activate macrophages to destroy the bacteria with which they are infected. CD8 T lymphocytes (cytotoxic