Role of integrated F-18 fluoro-deoxy-glucose positron emission tomography and computed tomography in evaluation of lung cancer

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SUMMARY

Lung cancer is one of the leading causes of death in the world. It is generally divided in two groups: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Positron emission tomography (PET)/CT using the glucose analogue labeled with 18-fluor (F-18): fluoro-deoxy-glucose (F-18-FDG), is unique integrated imaging modality that offers simultaneous anatomic and metabolic information valuable in the diagnosis, staging and follow-up of both types of lung cancer and in particular in NSCLC. FDG accumulation in tissue is proportional to the amount of glucose utilization. Increased consumption of glucose is a characteristic of almost all types of lung cancer except in bronchoalveolar carcinoma and well differentiated neuroendocrine tumors. The objective of this brief review is to highlight the clinical role of F-18-FDG PET/CT in detection, staging, re-staging, and assessment of therapy response and follow up in lung cancer. The performance of F-18-FDG PET/CT in specific clinical situations is of special interest: in the differentiation of indeterminate lung lesions, the staging of NSCLC for lymph node and extra thoracic metastases, for therapy planning, the detection of recurrent lung cancer and the use in SCLC. In conclusion, F-18-FDG PET/CT helps in characterization of suspicious lesions, provides more precise staging of NSCLC than other imaging techniques, allows better patients' selection for new modalities of treatment, helps in restaging after induction therapy, allows better delineation for radiotherapy planning and helps in follow up evaluation by differentiating residual or recurrent tumor from post treatment scar.

Key words: *Lung Neoplasms; Diagnostic Imaging; Positron-Emission Tomography and Computed Tomography; Magnetic Resonance Imaging; Fluorodeoxyglucose F18; Carcinoma, Non-Small-Cell Lung; Small Cell Lung Carcinoma*

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Lung cancer is the leading causes of cancer related death in the Western World (1). It is the most frequent malignancy and cause of cancer death in men in Serbia (2). In women lung cancer is third malignancy and second cause of cancer death (2). Non-small cell lung cancer (NSCLC) accounts for 75-80% and small cell lung cancer (SCLC) represents approximately 15-20% of lung cancers overall. Only one-third of patients are amenable to potentially curative treatment at initial presentation. Unfortunately, many patients after treatment develop local recurrence or distant metastases (3). Optimal staging and restaging of lung cancer is important in order to determine the best possible therapeutic option, to clarify operability and to have an idea about the outcome of the patient.

In diagnosis, staging and restaging of lung cancer, chest x ray, multi detector computed tomography (MDCT) and magnetic resonance imaging (MRI) provide structural information (4). Traditionally MDCT has been mainstay on non invasive staging. Although provides excellent anatomical description it has limitations (5).

Over a past decade the diagnostic workup of patients with suspected or proved lung cancer was improved by the introduction of positron emission tomography (PET) with F-18-fluorodeoxyglucose (FDG-PET), and especially by integrated PET/CT examination (6-8). PET is based on the biological activity of malignant cells. Lung cancer cells demonstrate increased cellular uptake of glucose and a higher rate of glycolysis compared to normal cells (9).The radiolabeled glucose analog F-18-FDG undergoes the same cellular uptake as glucose and is phosphorylated by hexokinase, generating F-18-FDG phosphate. The combination of increased uptake of F-18-FDG and a decreased rate of dephosphorylation by glucose phosphatase in malignant cells results in an accumulation of F-18-FDG- phosphate in these cells (10). Exceptions are brochoalveolar carcinoma and well differentiated carcnoid tumors that do not have high glucose activity. They are known to have higher false-negative rate on F-18-FDG PET (11, 12). Different concentration of F-18 from F-18-FDG in cells in the human body can be identified and detected by PET scanner. Therefore F-18-FDG PET is a metabolic imaging based on the function and biochemical characteristics o f the tissue, rather than its anatomy. Integrated PET/CT scanning which is current standard imaging, combines advantages of PET (high sensitivity) with that of CT which is excellent spatial resolution and depiction of anatomical details (13). Recent studies demonstrated that integrated PET/CT imaging outperforms the evaluation of the tumor, nodal stage and distant metastases in patients with lung cancer (14-16). The objective of this brief review is to highlight the clinical role of F-18-FDG PET/CT in lung cancer.

The most important indications of F-18-FDG PET/CT in lung cancer are:

- evaluation of indeterminate solitary pulmonary nodules
- staging of NSCLC according to current TNM classification (17, 18):
  - Tumor staging (T stage)
  - Nodal staging (N stage)
  - Distant metastases staging (M stage)
- restaging and detection of tumor recurrence after treatment
- image guided biopsy
- role in radiotherapy planning

EVALUATION OF INDETERMINATE SOLITARY PULMONARY NODULES

Diagnosis of lung cancer often begins with identification of suspected nodule on chest radiography or CT. Evaluation of potential malignancy in peripheral lung nodules, solitary pulmonary nodules (SPN) is important in definitive confirmation or exclusion of lung cancer. (19). CT is considered as first line and excellent method for detection and localization, but has been shown to have poor specificity in characterization of SPN (20). There are several systemic meta-analysis and publications that report diagnostic performance of FDG PET in the evaluation of indeterminate of SPN (19, 21-23). Reported sensitivity range from 87 to 97% and specificity from 78 to 83% (19, 21-23) .Up to now, this high diagnostic accuracy has not been proven for any other imaging modality including CT and MRI. In patients with increased uptake of FDG in SPN (usually uptake much greater than in blood pool—anything substantially greater than standardized uptake value -SUV of 2.5) it is appropriate to perform invasive procedures, a transthoracic needle biopsy or bronchoscopy to make histopathological diagnosis (19, 24) (Figure 1). If SPN did not show increase uptake of FDG, follow up with CT at 3-6 months for 2 years is usually recommended (19, 24) (Figure 2).

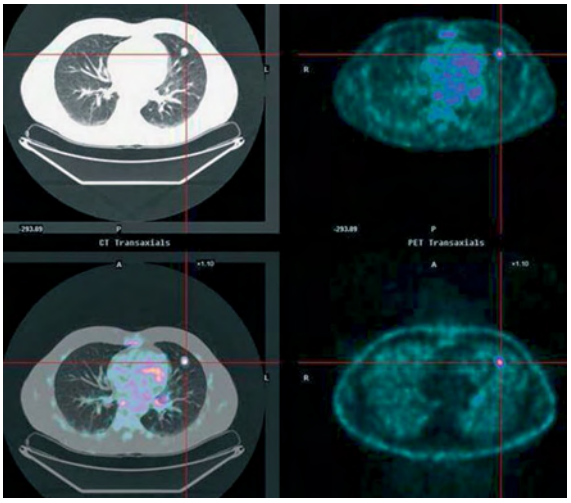


Figure 1. Solitary pulmonary nodule in the left lung with increased uptake of F-18-FDG (SUVmax 6.7)

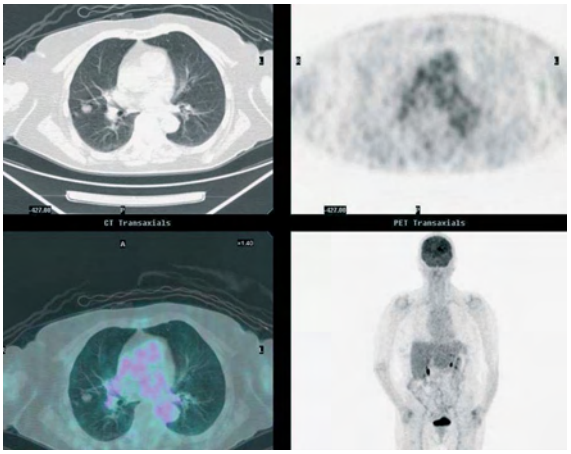


Figure 2. Solitary pulmonary nodule in the right lung without F-18-FDG uptake

Limitation of FDG PET in evaluation of SPN is related to increase uptake of FDG in inflammatory lesions. False negative finding of FDG PET is related to the small size nodule (less than 8 mm) due to limited spatial resolution of current PET scanners (about 7 mm). Well differentiated tumors with very low glucose metabolic activity and faint FDG uptake such as bronchoalveolar carcinoma and carcinoid tumors can cause false negative FDG PET finding (11, 12, 25). Therefore, American College of Chest Physician (ACCP) in evidence based clinical practice guidelines reported recommendation for use FDG PET/CT in evaluation SPN (26):

PET recommended: Probability of cancer low to moderate (5%-60%) and an indeterminate nodule measures at least 8-10 mm.

PET NOT recommended: SPN that has a high probability of malignancy (>60%) or nodule < 8-10 mm.

STAGING OF NSCLC

The primary goal of pre-treatment staging is to determine the extent of disease so that management and prognostication can be done. Staging is based on: tumor size and location (T stage), nodal involvement (N stage) and presence/absence of distant metastases (M stage). The seventh edition of TNM staging for lung tumor has been released in 2009 (17). The major determinant chosen for development of subgroups of T, N and M classification and stage grouping was the overall survival. The most important decision in using this system is to decide if the disease is surgically resectable (17). FDG-PET/CT makes important contributions to lymph node staging and detection of unexpected metastases missed by other staging modalities (6, 14-16).

In T staging FDG-PET does not have added value over MDCT if SUVmax value in tumor tissue is around 2.5. In T staging FDG-PET could be false positive in infectious and inflammatory lesions or false negative in carcinoid, certain adenocarcinomas, uncontrolled diabetes, cavity with necrotic center, lesion < 8 mm (27).

In nodal staging FDGPET and especially integrated PET/CT imaging demonstrate significantly better diagnostic accuarcy in the detection mediastinal lymph node involvement than CT. Reported sensitivity range from 74 -85% and specificity from 85 to 92% for the differentiation of N0/1 verusus N2/3 stage (26, 28-31). Factors that cause reduced sensitivity of FDG PET/CT in evaluation lymph node assessment are: low FDG uptake of primary tumor (SUV value near 2.5), hyperglycemia, lymph node next tu the primary tumor in central tumor localization and too short waiting time for FDG distribution before start acquisition (less than one hour). In patients being treated with curative intent, with positive mediastinal lymph nodes, invasive confirmation should be performed. If the patients had enlarged mediastinal lymph nodes on CT without increased upake of FDG on PET, invasive confirmation may be ommited. Patients should go to invasive staging if reduced sensitivity of FDG-PET is expected (2, 6, 26, 27).

FDG-PET/CT has added diagnostic value over CT and other conventional techniques in detection of unexpected distant metastases missed by other diagnostic modalities (6). Distant metastases in the body apart from primary lung tumor and mediastinal lymph node involvement could be detected in a single investigation, because FDG-PET/CT is whole body examination. Different studies and meta-analysis reported high sensitivity

(93%) and specificity (96%) for detection of distant metastases, with the rate of unexpected metastases from 7.5% to 24% (32, 33) Unexpected metastases are usually in bones and adrenals (34) (Figure 3). However, in a recent prospective randomized study in 189 patients FDG PET/CT was reported to be more accurate in preoperative staging in comparison with conventional staging method, with the reduction of futile thoracotomies, but without effect on patients' survival (35).

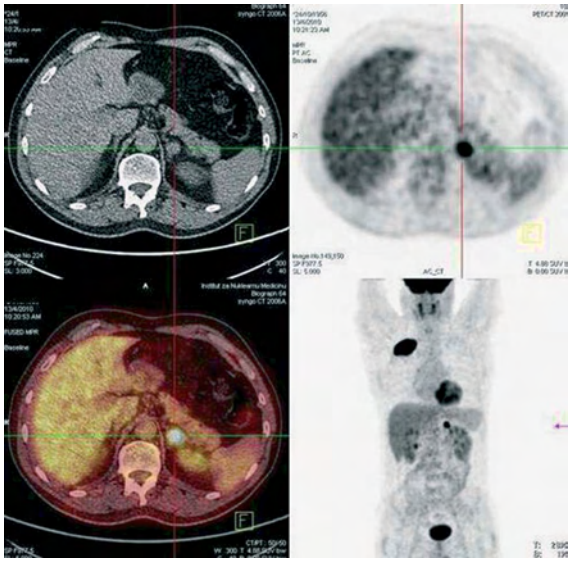


Figure 3. Increased F-18-FDG uptake (SUVmax 12.3) in the left suprarenal gland-unexpected distant metastases of non small cell lung cancer (NSCLC)

Due to above considerations, ACCP in evidence based clinical practice guidelines reported recommendation for use FDG PET/CT in staging of NSCLC (26):

- In patients with clinical IA stage lung cancer being treated with curative intent for mediastinal and extrathoracic staging
- Patients with clinical IA-IIIB lung cancer being treated with curative intent, should undergo PET scanning (where available) for mediastinal and extrathoracic staging
- In patients with and abnormal FDG-PET scan, further evaluation of the mediastinum with sampling of the abnormal lymph node should be performed prior to surgical resection of the primary tumor.
- Routine imaging for extrathoracic metastases (head CT/MRI, PET/CT or bone scanning plus abdominal CT scanning) should be performed in patients with clinical stage IIIA and IIIB disease.

DETECTION OF RECURRENT LUNG CANCER AFTER TREATMENT

Follow up of patients with NSCLC is aimed at early detection of recurrence, second lung tumor or treatment related complications. (36).Unfortunately, tumor recurrence is common following surgical resection for NSCLC. Several studies and meta-analysis reported high accuracy of FDG PET/CT for detection of viable tumor tissue and differential diagnosis with fibrosis and necrosis, i.e. for diagnosis of recurrent NSCLC (Sn 97-100%, Sp 62-100%, Acc 78-98%) (37-39). Therefore, in lung cancer following curative intent therapy, FDG PET/CT should be performed for restaging if recurrence is suspected by CT and re-treatment is planned (6).

IMAGE GUIDED BIOPSY

There are reports of FDG PET/CT being used for guiding percutaneous biopsy procedures because of the dual information about morphology and metabolic tumor activity.

FDG PET/CT has been reported to be of use in fine-needle aspiration cytology of lung masses (40, 41). However, more studies are necessary for practical recommendation of use this technique in clinical practice in patients with lung cancer.

ROLE IN RADIOTHERAPY PLANNING

The introduction of functional data into the radiotherapy treatment planning process is currently the focus of significant scientific, clinical and technical development.

The integrated PET/CT systems form an inherently fused anatomical and functional dataset, provided an imaging modality which could be used as the prime tool in the delineation of tumor volumes and the preparation of patient treatment plans, especially when integrated with virtual simulation. F-18-FDG PET imaging provides data on metabolically active tumor volumes. These functional data have the potential to modify treatment volumes and to guide treatment delivery to cells with particular metabolic characteristics (Figure 4). In that way FDG-PET/CT helps in directing the radiation towards the metabolic active tumor and lymph nodes and in sparing the non-tumor collapsed lung tissue (42-44). Protocols for the implementation of FDG-PET/CT remain to be defined.

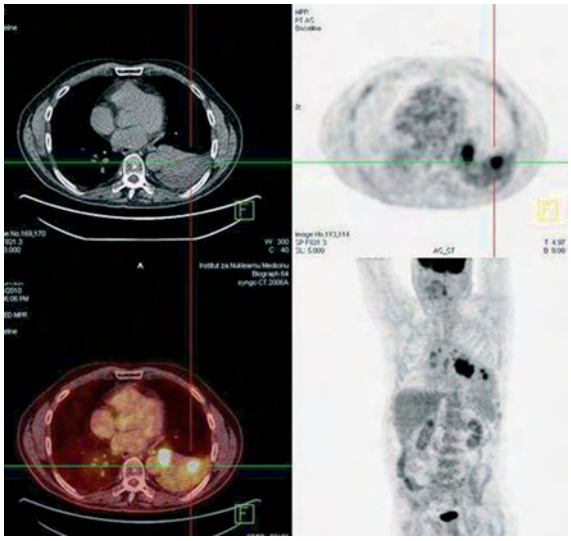


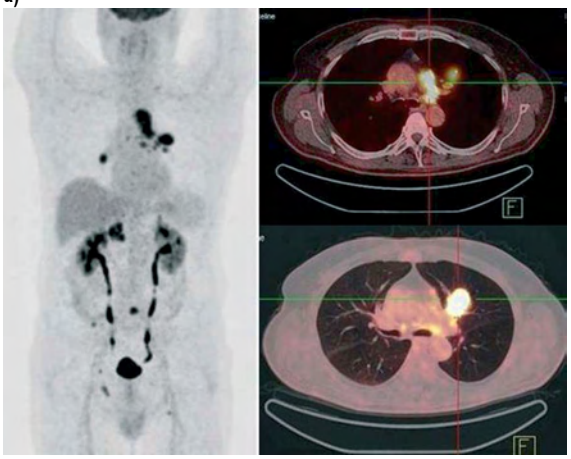
Figure 4. Increased focal uptakes of F-18-FDG in the left lung indicate NSCLC viable tumor tissue. FDG-PET/CT helps in directing the radiation towards the metabolic active tumor and in sparing the non-tumor collapsed lung tissue

STAGING OF SMALL CELL LUNG CANCER (SCLC)

SCLC is aggressive disease, often disseminated at the time of diagnosis (45). In clinical practice simple staging in two patients' subgroups has been used: Limited disease (LD) (disease confined in one hemithorax), and extensive disease (ED - outside one hemithorax) (Figure 5a and 5b). Standard treatment in patients with LD is chemotherapy combined with radiotherapy, while in patients with ED, chemotherapy alone is therapy of choice (46).Therefore, accurate staging is important in order to select combined

modality treatment to those patients who might benefit from it. Hellwing and coworkers (6) reported the additional use of FDG PET/CT in patients with SCLC, and recommended its use if an extensive disease stage is not already known. In systemic meta-analysis of Ung and coworkers sensitivity of FDG PET in staging SCLC range between 89-100%, and specificity from 78 to 95% (34). Recent study reported that both clinical and pathological TNM staging are important in the evaluation and reporting of SCLC based on 7th TNM staging system, similar to NSCLC. The International Association for the Study of Lung Cancer (IASLC) proposes that TNM staging become the standard for all cases of SCLC (47).

a)



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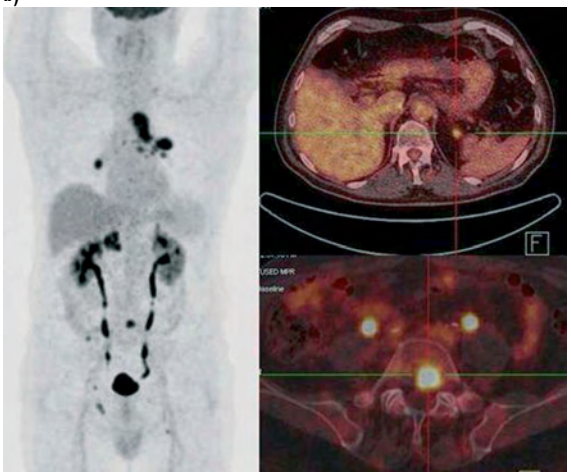

Figure 5a and 5b. IncreasedF-18-FDG uptake (SUVmax 18.5) in the primary small cell lung cancer in the left lung (SCLC), with increased accumulation of F-18-FDG in mediastinal lymph nodes, contralateral hilar lymph node, left suprarenal gland and bones- extensive disease, Stage 4.

In conclusion, F-18-FDG PET/CT helps in characterization of suspicious lesions, provides more precise staging of NSCLC than other imaging techniques, allows better patients' selection for new modalities of treatment, helps in restaging after induction therapy, allows better delineation for radiotherapy planning and helps in follow up evaluation by differentiating residual or recurrent tumor from post treatment scar.

In patients with SCLC F-18-FDG PET/CT becomes important in the relevant clinical staging limited disease versus extensive disease, or in TNM staging with impact on therapeutic management of these patients.

Conflict of interest

We declare no conflicts of interest.

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