Clinical Assessment of Lung Cancer Using ¹⁸F-FDG PET-CT

Seyyed Hossein Hassanpour¹* and Seyyedeh Zeinab Karami²

¹Young Researchers and Elite Club, Yasooj Branch, Islamic Azad University, Iran

²Department of Biology, Faculty of Basic Sciences, Yasouj University, Iran

*Corresponding author: Seyyed Hossein Hassanpour, Young Researchers and Elite Club, Yasooj Branch, Islamic Azad University, Yasooj, Iran, Tel: +98 9171452844; Email: Dr.hossein1366@yahoo.com

Abstract

Cancer is a main threaten human health and lung cancer is responsible death individual worldwide. Early detection of cancers can diminish problem resulted from them and ¹⁸F-FDG PET-CT can be helpful to solve this problems. ⁸F-FDG PET-CT depicts metabolic and anatomical information about tumor. It facilitates treatment planning and enhances overall survival in patients with lung cancer. ¹⁸F-FDG-PET-CT has potential ability to detect early metabolic response to chemotherapy. ¹⁸F-FDG, PET/CT is a prominent and key tool for assessment and staging lung cancer and today it widely serve for demonstration of lung cancer. In addition, it has pivotal role in personalized patient management. Here, we reviewed important of ¹⁸F-FDG PET-CT in detection of lung cancer. This study was designed as chronological order based on studies conducted by 2014 to 2017. The papers were searched from valid databases such as Wiley; Scopus; Science Direct; Springer and PubMed.

Keywords: Lung cancer; ¹⁸F-FDG PET-CT; Early detection; Treatment planning; Overall survival

Abbreviations: NSCLC: Non–small cell lung cancer; SUV: Standardized uptake values; ADC: Apparent diffusion coefficient; OS: Overall survival; MTV: metabolic tumor volume; TLG: total lesion glycolysis; RECIST: Response evaluation criteria in solid tumors; ITV: Internal target volume; SBRT: stereotactic body radiation therapy; TF: tumor textural feature; DSC: Dice similarity coefficient; HD: Hausdorff distance; PSF: point spread function; EANM: European Association for Nuclear Medicine.

Introduction

Cancer burdens enormous problem to health society so that is main responsible human death worldwide. Therefore, today effort for accurate diagnosis, staging and restaging in order to control and management of cancer is essential gold in health field [1]. Lung cancer is considered as one of the main reason human health particularly in women [2]. Based on statistical findings, lung cancer is second reason mortality worldwide [3]. If patients suffered from lung cancer undergo surgery, the survival reduced in them furthermore accurate diagnosis can help them to increase survival [2]. The non–small cell lung cancer (NSCLC) is considered as common type of lung cancer and given that only half of patients with NSCLC are potential to treat as surgical resection and radiotherapy, thus early diagnosis in order to manage treatment-related complications is very essential in these patients [4]. Meanwhile, manifestation of disease is late in patient with NSCLC and disease presents in stage III or stage IV that are inoperable so that reduce their treatment efficacy [5]. Patients with stage III or stage IV NSCLC suffer from chemotherapy, or a combination of chemotherapy and radiation but early detection of disease leads to surgical resection of tumor with high

efficacy [6]. In addition, all patients not respond to chemotherapy, on the other hand chemotherapy leads to obvious side effect thus they have dire need to reliable early diagnosis for increase of survival value [7]. Early and reliable diagnosis of tumor has pivotal role in treatment planning and ultimately survival of patients [8]. Based on data obtained from National Health Service of United Kingdom during 60 years ago, it have been observed obvious development in early and reliable diagnosis of many cancer that led to increase of survival rates for many cancer such as breast, colon, rectal, and cervical cancers. Unfortunately survival rate of stomach, pancreas, and lung cancers is now low [8,9]. Use of PET and PET/CT were one of the strategies to solve this problem by tracing high level of metabolism and glycolysis in cancer cells [9,10]. Given that tumor requires to high level of glucose for proliferation and malignancy thus it can be helpful marker to trace malignancy through 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG), an analogue of glucose by positron emission tomography (PET) [1,11]. This method offer important information about tumor status based on amount of glucose uptake and glycolysis of cancer cells that demonstrated metabolic abnormalities before morphological alterations [1]. Today, it has been confirmed efficacy of ^{18}F-FDG PET in diagnosis of many cancers and even tracing of treatment [12-17]. In addition, it has been reported that ^{18}F-FDG PET has high sensitive, specific and accurate in diagnosis of lung cancer ^{18}. PET has pivotal role to determine staging of lung cancer because metabolic differences between benign and malignant tumors is simply traceable through PET with ^{18}F-FDG as glucose analog [13,19,20]. Meanwhile, detection of anatomic information and determination of location and extent of malignancies can obtain through CT as a tomographic imaging technique by an x-ray beam [11]. Thus, combination of PET and CT prepare useful information about metabolic and anatomic properties of tumors [11]. Today, it have been reported that PET-CT provide information about tumor location, shifting status from benign to malignancy by measurement of parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) in tumors [12,21-23]. This study, we reviewed role of ^{18}F-FDG PET-CT in diagnosis of lung cancer based on chronological order from 2014 to 2017.

Review Method

The aim of this review study was to explain conducted papers on role of ^{18}F-FDG PET-CT in assessment of lung cancer from 2014 to 2017. To achieve this goal, we searched keywords such as ^{18}F-FDG PET-CT imaging, lung cancer, and non-small cell lung cancer, clinical assessment of lung cancer and so on in valid databases such as Wiley; Scopus; Science Direct; Springer and PubMed. After collecting of articles, we fully read and summarized them. Here, the findings of articles were showed based on publication year. Indeed; our goal was to review articles based on chronological order.

Role of ^{18}F-FDG PET-CT in Assessment of Lung Cancer

Table 1 depicts articles related to 2014 in conjunction with important of ^{18}F-FDG PET-CT imaging in diagnosis of lung cancer that were summarized in following sentences. In a study, in order to evaluation of role of ^{18}F-FDG PET/CT imaging, biopsy obtained from patients who suffered from lung cancer was investigated. The results of this study showed that ^{18}F-FDG PET/CT imaging is a prominent tool to prognosis overall survival particularly in younger patients (less than 70 years old). In addition, it can be a good tool to trace primary treatment [24]. Study on patients suffered from stage III non-small-cell lung cancer was revealed that metabolic tumor volume and total lesion glycolysis as ^{18}F-FDG PET/CT parameters related to volume-based have efficacy more than maximum standardized uptake value to prognosis survival independent of tumor stage [25]. Comparison of ^{18}F-FDG PET/MR imaging and ^{18}F-FDG PET/CT in order to evaluate diagnosis potential in subjects with non-small cell lung cancer approved by histopathological parameters were showed that ^{18}F-FDG PET/MR imaging compared with ^{18}F-FDG PET/CT cannot benefit in order to trace non-small cell lung cancer during thoracic staging [26]. Study on comparison between visual assessments of intratumor ^{18}F-FDG PET uptake distribution with a textural-features automated quantification on patients with non–small cell lung cancer was revealed that there is a significant correlation between visual assessment and quantification assessment of ^{18}F-FDG uptake heterogeneity in non–small cell lung cancer. In addition, quantification assessment using textural feature reduced interobserver variability and can be consider as a good prognostic tool in these patients [27]. A research group was traced radical chemoradiation therapy in patients with non-small cell lung cancer (stage I–III) by serial PET/CT with ^{18}F-FDG and 3′-deoxy-3′-^{18}F-fluorothymidine. The results were revealed that PET/CT using ^{18}F-FDG and 3′-deoxy-3′-^{18}F-fluorothymidine can be a good strategy to trace therapy in non-small cell lung cancer. In addition, ^{18}F-FLT PET/CT has more sensitive to early treatment response than ^{18}F-FDG PET/CT [28]. Evaluation of standardized uptake values and metabolic tumor volume in ^{18}F-FDG PET/CT in order to predict survival of patients with locally advanced non–small cell

lung cancer after early stage of concurrent cisplatin-based chemotherapy regimen was demonstrated that reduction of metabolic tumor volume during ^{18}F-FDG uptake through primary tumor indicates higher long-term overall survival. Meanwhile, this study was confirmed that repeated ^{18}F-FDG PET/CT can be helpful to assess survival during chemoradio therapy [29]. Use of ^{18}F-FDG PET/CT for detection of lung adenocarcinoma through measurement of parameters such as standardized uptake value, metabolic tumor volume and total lesion glycolysis can reveal prominent information in association with lung adenocarcinoma [30]. Although tumor molecular profile is a good predictor for activity of epidermal growth factor receptor inhibitors in non-small-cell lung cancer but

tumor heterogeneity and tissue availability diminish its role predicting. In order to solving of this problem, a research group were investigated role of ^{18}F-FDG PET/CT in order to detect *KRAS* and *EFGR* mutation status in non-small-cell lung cancer. The results were showed that in non-small-cell lung cancer patients with tumors harboring of *KRAS* mutations, ^{18}F-FDG PET/CT uptake was dramatically higher than patients with wild-type gene. In addition, evaluation of ^{18}F-FDG PET/CT uptake in association with parameters such as age, gender, AJCC stage and minimum standardized uptake value was demonstrated that ^{18}F-FDG PET/CT can offer important information about *KRAS* mutation status in patients with stage III or IV non-small-cell lung cancer [31] (table 1).

Subjects	Performed procedures	Finding(s)	References
261 biopsy-proven lung cancer patients	Evaluation of OS using Kaplan–Meier plots by a Mantel–Cox log-rank test	To be as an important criteria to prognosis overall survival spatially in younger patients (≤70 year-old)	24
194 consecutive patients with stage IIIA NSCLC treated with surgical resection and 115 patients treated with nonsurgical therapy	Evaluation of MTV, TLG, SUVmax	MTV and TLG are good tool more than SUVmax in order to prognosis survival independent of tumor stage	25
22 patients with NSCLC	Comparison of ^{18}F-FDG PET/MR and by measurement of SUV mean, SUVmax and maximum diameter of the primary tumor	^{18}F-FDG PET/MR imaging compared with ^{18}F-FDG PET/CT has not validity to diagnosis NSCLC under thoracic staging	26
102 patients with NSCLC	Detecting of intratumor heterogeneity, tumor volumes, visual interobserver agreement and correlations with quantitative assessment by κ test and Spearman rank (ρ) coefficient	To have a correlation between visual assessment and quantification assessment. Reduction of interobserver variability by quantification assessment with textural feature	27
20 patients with stage I–III NSCLC	Evaluation of tumor response to serial PET/CT with ^{18}F-FDG and 3′-deoxy-3′-^{18}F-fluorothymidine as semi-quantitative through visual response criteria	Both can be benefit biomarkers to trace chemoradiation therapy in patients with NSCLC but 3′-deoxy-3′-^{18}F-fluorothymidine is more sensitive to early treatment response	28
53 patients with locally advanced NSCLC	Measurement of SUV_{mean}, SUV_{max} and MTV	Repeated ^{18}F-FDG PET/CT can predict survival during chemoradiotherapy. Reduction of MTV during ^{18}F-FDG uptake reveals higher long-term OS.	29
106 patients with lung adenocarcinoma	Measurement of SUV, MTV and TLG in conjunction with EGFR gene mutation status	Can be helpful in prognosis of lung adenocarcinoma	30
340 patients with NSCLC	Measurement of SUV (peak, max, mean) and assessment of its relation with *KRAS* and *EGFR* mutation status	^{18}F-FDG PET/CT can reveal prominent data about *KRAS* mutation status in patients with NSCLC	31

Table 1: Findings of papers published by 2014 in association with role of 18F-FDG PET-CT in assessment of lung cancer

In a study potency of 18F-FDG imaging in order to predict response or survival in patients treated with erlotinib was examined. The results were showed that response to erlotinib is correlated with reduced heterogeneity in 18F-FDG PET imaging. Meanwhile, changes in first-order entropy are independently related to treatment response and overall survival [32]. Study on role of 18F-FDG PET/CT in determination of local relapse after chemoradiotherapy in patients with inoperable stage II or III non-small cell lung cancer were confirmed that High 18F-FDG uptake can indicate that occur local relapse after chemoradiotherapy so that should be increase radiotherapy dose escalation [33]. Investigation on role of various metabolic parameters measured by 18F-FDG PET/CT as prognosis values for detection of stage IA non–small cell lung cancer after complete surgical resection were confirmed that total lesion glycolysis is a pivotal prognostic factor for overall survival in these patients [34]. In association with efficacy of apparent diffusion coefficient (ADC) and standardized uptake values (SUV) in detection of lymph node metastases of non-small cell lung cancer, a research group was used hybrid 18F-FDG PET/MRI. Their findings were demonstrated that prognostic value (ADC, SUV) measured by 18F-FDG PET/MRI can complete necessary information for treatment response [35]. According to findings of a retrospective single-center study in association with role of 18F-FDG PET/CT to predict local control and survival in patients who suffered from non–small cell lung cancer during concomitant radiochemotherapy were revealed that early assessment of total lesion glycolysis response through 18F-FDG PET/CT imaging within concomitant radiochemotherapy of non–small cell lung cancer might be related with survival [36]. In order to efficacy of 4D-18FDG-PET/CT in target delineation of stereotactic body radiation therapy (SBRT) in patients with central versus peripheral lung tumors, a study on patients with lung tumor were designed. The results of this study were showed that 4D-18FDG-PET/CT offers helpful information about target delineation of SBRT so that can avoid geographic misses [37] (table 2).

Subjects	Performed procedures	Finding(s)
47 NSCLC patients treated with erlotinib	Evaluation of MTV, TLG, SUVmax, measurement of response to erlotinib by RECIST	To correlate between response to erlotinib and reduced heterogeneity in 18F-FDG PET imaging, to relate changes in first-order entropy with treatment response and overall survival as independent
39 patients with inoperable stage II or III NSCLC	Determination of SUV_{max} threshold	High 18F-FDG uptake is related to local relapse after chemoradiotherapy
248 patients with stage IA NSCLC	Detection of SUV_{max} and TLG	To confirm significant role of TLG as a prognostic factor in these patients
38 patients with NSCLC	Assessment of ADC and SUV	To complete require data for detection of lymph node metastases of NSCLC by 18F-FDG PET/MRI
31 patients with unresectable or locally NSCLC	Assessment of SUVmax, variation of hypermetabolic tumor volume and the variation of TLG	TLG may be associated with survival in these patients.
21 patient with lung tumor (11 cases with peripheral lesions and 10 cases with central lesions)	Analysis of ITV delineation of central and peripheral lung lesions	4D-18FDG-PET/CT can be helpful in target delineation of SBRT in patients with lung tumor

Table 2: Findings of papers published by 2015 in association with role of 18F-FDG PET-CT in assessment of lung cancer

Study about repeatability features of [18F] FDG-PET/CT in patients with non-small-cell lung cancer were revealed that due to more sensitive of these features than simple standardized uptake value they can offer reliable results in these patients [38]. In addition, [18F] FDG-PET/CT is a good predictor of metastasis in patients suffered from

early-stage non-small-cell lung cancer and can be helpful in administration of appropriate remedy in these patients in order to reduce effects of metastasis. Because, evaluation of quantitative parameters analyzed by [^{18}F] FDG-PET/CT can facilitate predicting of metastasis [39]. Use of ^{18}F-FDG PET/CT as an interpretational system to predict therapy response and survival in patients with lung cancer proved by biopsy were determined that ^{18}F-FDG PET/CT regardless histology of tumor and treatment strategy is a reliable tool with high accuracy in order to therapy response interpretation [40]. Given that accurate determination of tumor heterogeneity is pivotal in order to precise characterization of tumor lesions, a research group were examined efficacy of respiratory motion and levels of varying noise on quantification of textural parameters measured by ^{18}F-FDG PET in patients suffered from lung cancer. The results of this study were confirmed that when there are respiratory motion artifacts and varying levels of image noise, textural parameters tested by ^{18}F-FDG PET are robust [41].

Change in ^{18}F-FDG uptake can be one of the way predictions of response to anticancer treatment. To achieve this goal, a study was conducted in association with evaluation of repeatability of quantitative ^{18}F-FDG PET/CT uptake measures in patients with lung cancer. The findings were showed that changing in SUV_{mean}/SUV_{peak} (15% during 60 min after injection) can be helpful in assessment response in patients with advanced non-small cell lung cancer for up to 5 PERCIST (response criteria in solid tumors) target lesions. In addition, lower thresholds is usable for averaged PERCIST (response criteria in solid tumors) target lesions [42]. Furthermore, evaluation of ^{18}-FDG-PET/CT by PERCIST (response criteria in solid tumors) was revealed that although there are different in parameters affecting ^{18}-FDG-PET/CT uptake, but use of ^{18}-FDG-PET/CT with PERCIST within treatment can be useful to diagnose non-responders from responders because their overall survival and point spread function were statistically difference [43] (table 3).

Subjects	Performed procedures	Finding(s)	References
11 patients with NSCLC	Receiving two baseline whole-body PET/CT scans and their reconstruction through PSF and EANM	[^{18}F] FDG-PET/CT can offer valid results in these patients	38
101 patients with early-stage NSCLC	Analyzing of quantitative measurements such as statistical, histogram-related, morphologic, and texture features	Quantitative parameters analyzed by [^{18}F] FDG-PET/CT help to predicting of metastasis	39
201 patients with biopsy-proven lung cancer	Use of qualitative 5-point scale for assessment of primary tumor, mediastinum, distant metastatic site	^{18}F-FDG PET/CT has high accuracy for therapy response interpretation regardless histology of tumor and treatment modality	40
60 patients with lung cancer	Evaluation of optimal-respiratory-gating algorithm and reconstruction of non-gated images of varying statistical quality for investigation of image noise effects	Textural parameters tested by ^{18}F-FDG PET are robust within presence of respiratory motion artifacts and varying levels of image noise	41
11 NSCLC patients	Determination of SUV_{max}, SUV_{mean}, SUV_{peak}, TLG, metabolically active tumor volume, and tumor-to-blood and -liver ratios	To predict target lesions through changing in ^{18}F-FDG uptake	42
21 patients with locally advanced NSCLC	Analyzing of PERCIST, determination of OS and PFS	Evaluation of ^{18}-FDG-PET/CT by PERCIST during treatment separate non-responders from responders	43

Table 3: Findings of papers published by 2016 in association with role of ^{18}F-FDG PET-CT in assessment of lung cancer.

Table 4 is related to results performed in 2017 that following sentences were explained. Comparison of variation in thoracic tumor staging between ^{18}F-FDG PET/CT and PET/MR in patients with non-small cell lung cancer was demonstrated that although there is thoracic different between ^{18}F-FDG PET/CT and PET/MR in TNM-

staging, but both them results in equal therapeutic decisions in patients with non-small cell lung cancer. Meanwhile, it can be suggest that ^{18}F-FDG PET/MR replace ^{18}F-FDG PET/CT for clinical NSCLC staging [44]. A research group were designed a study in order to development of a framework for segmentation and labeling of homogeneous versus heterogeneous in lung tumor so that areas with high-uptake simply delineate. Their findings were showed that ^{18}F-FDG-PET can offer a suitable automatic framework for segmentation and labeling of homogeneous versus heterogeneous in lung tumor [45].

Subjects	Performed procedures	Finding(s)	References
77 NSCLC patients	Evaluation of thoracic tumor staging between ^{18}F-FDG PET/CT and PET/MR	Both lead to similar therapeutic decisions despite of differences in thoracic tumor staging	44
70 patients with lung cancer	Analyzing of TF, segmentation accuracy, evaluation of volumetric by DSC and HD	^{18}F-FDG-PET can exhibits an automatic framework for segmentation and labeling of homogeneous *versus* heterogeneous in lung tumor	45

Table 4: Findings of papers published by 2017 in association with role of ^{18}F-FDG PET-CT in assessment of lung cancer.

Conclusions

In this study, we reviewed important of ^{18}F-FDG-PET-CT in diagnosis of lung cancer. Given that early and reliable detection of cancer leads to suitable treatment strategy to control disease and reduction of mortality thus presence of efficient tools is require to solve this problem. Based on studies, ^{18}F-FDG PET-CT can be helpful to diagnose tumor when it is curable because ^{18}F-FDG PET-CT offer metabolic and anatomic information about tumor It is a valid criteria to prognosis overall survival by evaluation metabolic tumor volume and total lesion glycolysis. Use of ^{18}F-FDG PET/CT is very helpful in order to predict survival within chemoradio therapy. In addition, changing in ^{18}F-FDG PET/CT predict target lesions in patients with lung cancer. Furthermore, it facilitates treatment decision for patients. Finally, we offer that ^{18}F-FDG PET/CT is a suitable tool to control and manage lung cancer and it can reduce mortality rate in patients suffered from lung cancer.

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