Review Article

Positron emission tomography/computerized tomography in lung cancer

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Abstract: Positron emission tomography (PET) using 2-(18F)-flouro-2-deoxy-D-glucose (FDG) has emerged as a useful tool in the clinical work-up of lung cancer. This review article provides an overview of applications of PET in diagnosis, staging, treatment response evaluation, radiotherapy planning, recurrence assessment and prognostication of lung cancer.

Keywords: Positron emission tomography (PET); lung cancer; solitary pulmonary nodule (SPN); staging; radiotherapy planning; prognosis; therapy response

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Introduction

Lung cancer is the most common form of cancer and despite major advances in prevention and treatment, it is still the leading cause of cancer related death throughout the world (1,2). Non small cell lung cancer (NSCLC) constitutes more than 85% of the cases and small cell lung cancer (SCLC) constitutes the rest (3). Imaging techniques play a crucial role in the diagnosis, staging and follow-up of patients with lung cancer. Although presence of good physical performance, absence of weight loss and female gender predicts better prognosis; the most important prognostic indicator is the stage determined based on tumor, node, metastasis (TNM) classification (4). Besides its prognostic value, staging is of great importance in deciding the treatment plan. Staging in NSCLC is performed according to TNM staging system, which was updated in 2009 by the International Union Against Cancer and American Joint Committee on Cancer with the proposals of International Association for the Study of Lung Cancer (IASLC). Although TNM staging is applied occasionally, a more simplified method is used in the evaluation of SCLC; classifying the disease as limited or extensive (5).

Positron emission tomography/computerized tomography (PET/CT) using 2-(18F)-flouro-2-deoxy-D-glucose (FDG) has emerged as a useful tool in the clinical work-up of lung cancer with its accuracy in diagnosis (6), staging (7), evaluation of response to chemotherapy and/or radiotherapy and differentiation of fibrosis versus viable tumor. FDG PET scan is superior to other noninvasive imaging modalities in detecting mediastinal nodal involvement, thus in N staging of lung cancer (8-11). Moreover distant metastasis to bones, adrenal glands, liver and soft tissues, which are the most common sites of spread in lung cancer, can be evaluated in a single examination with good accuracy (12-16). The prognostic value of FDG PET derived metabolic parameters such as maximum standard uptake value (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been demonstrated in lung cancer in various studies (17-19). An overview of the utility of PET/CT in lung cancer patients is presented below.

PET/CT in solitary pulmonary nodule (SPN) evaluation

A SPN is defined as a single spherical or oval lesion which is less than 3 cm in diameter and completely surrounded by pulmonary parenchyma without accompanying atelectasis or adenopathy. For SPNs greater than 8 mm diameter, evaluation with PET/CT is recommended in patients with low risk (5-20%) and moderate risk (20-80%) of malignancy depending on risk factors and radiological characteristics (6). In addition to that, for patients with high risk of malignancy

the scan may play a role in assessment of disease extent and may change patient management by detecting unsuspected nodal and metastatic disease. An overall sensitivity of 96% (range, 83-100%) and a specificity of 73.5% (range, 50-100%) can be expected for FDG PET/CT in evaluation of pulmonary nodules (20). Although the specificity of FDG PET scan is better than that of CT it is still far from being ideal. For this reason, dual time-point FDG PET/CT by acquisition of delayed imaging has also been proposed in order to improve the diagnostic specificity of SPNs (21). However, the additive value of the technique remains controversial, with the literature demonstrating arguments both in favor of and against its usage. A meta-analysis by Barger *et al*. (22) demonstrated that the sensitivity and specificity of dual time-point FDG PET/CT was 85% and 77% respectively, similar to the values of single time-point FDG PET/CT in terms of sensitivity and specificity.

There are several potential pitfalls in the assessment of SPNs with FDG PET. Inflammatory conditions such as pneumonia, aspergillosis, tuberculosis, active sarcoidosis, Wegener's granulomatosis may demonstrate high metabolic activity due to increased granulocyte and/or macrophage activity (23). False-negative results may occur due to limited spatial resolution of current PET/CT cameras which is around 7-8 mm. Thus, a critical mass of metabolically active malignant cells is required in order to be detected in PET imaging. Therefore lesions <1 cm and tumors demonstrating low metabolic activity (e.g., carcinoid tumors, bronchioloalveolar carcinoma) may contribute to false negativity on PET scan (24,25).

Because of its high negative predictive value (NPV), FDG PET excludes malignancy in the vast majority of SPNs. However, further investigation is warranted where clinical suspicion for infectious or granulomatous condition exists due to relatively low positive predictive value (PPV) of the scan.

PET/CT in staging of NSCLC

Accurate staging has a major role in the management of patients with proven lung cancer. Stage directs the therapy plan by discriminating the candidates for surgical resection and patients with unresectable tumors who will benefit from chemotherapy, radiotherapy, or both.

T stage

The extent of the primary tumor is frequently evaluated with thoracic CT, occasionally supplemented by magnetic resonance imaging (MRI); in situations where superior sulcus extension, thoracic wall invasion or relationship with the heart or large vessels are of significance (26). In this respect, the major contribution of PET/CT is better delineation of tumor from surrounding postobstructive atelectasis, which may be a challenging issue in central tumors (27,28). Moreover, it has been suggested that PET/CT may have an added role in detection of chest wall invasion (29). Determination of the etiology of pleural effusion, whether it is malignant or benign is important in decision of resectability and use of radiotherapy. In this respect, PET/CT may provide beneficial information in evaluating pleural effusions with high NPV, where computed tomography does not provide a reliable discrimination for the etiology of pleural effusion (30), while thoracocentesis and pleural biopsy lack sensitivity (31). Similarly MRI, has failed to discriminate benign from malignant causes of pleural effusions with high accuracy (32). In a study by Erasmus *et al*. (33) pleural effusions of 25 patients with NSCLC were evaluated. Twenty one of 22 (96%) patients with malignant pleural effusion and 2 of 3 patients (67%) with no evidence of malignancy in pleural space were correctly identified by PET/CT. The sensitivity, specificity, PPV, NPV and accuracy of FDG PET for detecting pleural metastases were calculated to be 95%, 67%, 95%, 67%, and 92%, respectively. In another study, FDG PET imaging correctly detected malignant involvement of pleura and malignant pleural effusion in 16 of 18 patients, and excluded malignancy in 16 of 17 patients with biopsy proven NSCLC in whom CT showed pleural effusion and/or pleural thickening or nodular involvement (34). Sensitivity, specificity, and accuracy of PET/CT in detecting malignant pleural effusion and/or involvement were calculated to be 88.8%, 94.1%, and 91.4%, respectively. In this regard, the high NPV of PET in evaluation of pleural involvement may be of great value in reducing repeat thoracentesis or thoracoscopic biopsies in patients with pleural effusion and negative findings on PET.

Locoregional lymph node staging

In lung cancer cases where distant metastasis is not present, regional lymphatic spread determines the therapeutic approach and prognosis of the patient. Patients without malignant nodal involvement in mediastinum are usually treated with surgery, whereas patients with nodal disease are candidates for induction chemotherapy, followed by surgery

and/or radiotherapy (35,36). For this reason, N staging has a great importance in evaluation of lung cancer.

Being easily accessible, relatively inexpensive and non invasive, the most commonly used technique for N staging of patients with lung cancer is CT. Mediastinal and hilar lymph nodes which have a short axis greater than 10 mm are widely classified as enlarged (37). However, regarding only the size of the lymph node provides poor specificity for metastatic involvement, as considerable enlargement occurs in benign conditions such as infectious and inflammatory diseases. Besides, small sized nodes may also contain tumoral deposits (38). In concordance with the general limitations of the size criterion, median sensitivity and specificity of CT in mediastinal staging was shown to be 61% and 79%, respectively which is far from ideal (8). Recently advanced MR pulse sequences such as magnetization transfer imaging, diffusion weighted imaging and dynamic enhanced imaging have been proposed for improved accuracy in mediastinal staging with comparative studies using PET/CT (39,40). However, further investigation is warranted for determining efficacy of MRI in improved mediastinal staging of patients with lung cancer. A critical advantage of PET/CT over CT and MRI is its ability to identify neoplastic mediastinal adenopathy smaller than 1 cm. PET/CT was established to be superior to CT in mediastinal staging as confirmed in different meta-analyses (8-11). In one of the meta-analyses conducted by Gould *et al*., where 39 studies were assessed, authors reported median sensitivity and specificity of CT as 59% and 79%, respectively, whereas 81% and 90%, respectively, for FDG-PET (8). Similarly, a pooled analysis of 3,438 patients from 20 studies revealed that CT had a sensitivity and a specificity of 57% and 82%, respectively. Evaluation of 1,045 patients from the same study, resulted in a sensitivity and a specificity of 84% and 89%, respectively for mediastinal staging with FDG-PET (9). Similar findings were confirmed as well in a prospective trial, where 149 patients results of mediastinal staging with PET/CT was confirmed histopathologically either by mediastinoscopy, thoracotomy or both. This study established an overall sensitivity, specificity, PPV and NPV of 70%, 94%, 64% and 95%, respectively (41). The authors concluded that due to relatively low PPV of PET/CT, invasive mediastinal sampling should be carried out in order to eliminate the risk of denying potentially curative surgical decision. False positivity could be a significant confounding factor especially in areas endemic for granulomatous diseases, thus histopathological confirmation should be performed in case of clinical suspicion (42). In contrast, invasive sampling of mediastinal lymph nodes may be safely omitted relying on the high NPV of PET/CT. False negative findings may be seen in cases of low tumoral burden in metastatic lymph nodes. Some refer to this as 'minimal N2', where a reasonable prognosis after surgical resection is expected. However, in the presence of centrally located tumor or hilar lymphadenopathy, mediastinoscopy should still be carried out since limitations in spatial resolution may result in masking of metabolic activity of nearby lymph nodes with highly active hilar lymph nodes or tumoral lesions.

Extrathoracic staging

Identification of distant metastases in patients with NSCLC has major implications on management and prognosis. Metastatic disease is present in nearly half of the patients at the time of diagnosis. The adrenal glands, bones, liver and brain are the most common sites of metastases. Computed tomography can demonstrate presence of metastatic disease in 11-36% of patients with lung cancer (43). However, the addition of metabolic information by means of FDG PET reveals occult distant metastases up to 29% of patients (44). According to the current guidelines, in patients with lung cancer where abnormal clinical findings exist, evaluation with PET/CT is recommended. Furthermore, PET imaging is also recommended for patients who are candidates for surgery to evaluate for metastases outside the brain (42).

Computed tomography reveals enlarged adrenal glands in nearly 10% of patients with NSCLC. Two thirds of these adrenal lesions are asymptomatic or benign (45). Although low attenuation values (<10 Hounsfield Units) and regular contours on contrast unenhanced CT are interpreted in favor of benignity, this appearance is not distinguishing in many cases (46). PET/CT has high sensitivity (>95%) and specificity (≥80%) in diagnosis of metastatic adrenal disease in NSCLC (47-49). This high accuracy of PET/CT usually eliminates the necessity of invasive sampling of detected adrenal lesions (12). However, partial volume effect must be kept in mind in evaluating small lesions (<1 cm). False positives have also been reported, thus histopathological confirmation is warranted in case a treatment decision is to be made on based an isolated adrenal gland finding. Further evaluation using adrenal washout CT or chemical-shift MRI have also been suggested, with reported sensitivities and specificities of 83-93% and 93-98%, respectively for CT and 97% and 93%, respectively for MRI (50-52). Nevertheless, the data considering accuracy of these techniques are limited and invasive sampling via biopsy or

adrenelectomy may still be needed.

Scintigraphy using Tc99m diphosphonates is considered to be the most practical technique for assessing the entire skeleton for detection of osseous involvement in NSCLC. Bone scan has a good sensitivity (90%), but low specificity (60%) owing to nonselective uptake of radionuclide in any area of increased osteoblastic activity (i.e., degenerative changes, post traumatic abnormalities, inflammatory processes, etc.) (13). Moreover, purely osteolytic lesions and slow growing lesions with insufficient reactive bone formation may not be detectable on bone scan (53). Furthermore, additional studies, such as plain radiographs, CT or MRI are needed occasionally for differential diagnosis of positive findings detected on bone scan. Metastatic evaluation of bones using FDG PET/CT is reported to have a similar sensitivity (≥90%), but better specificity (≥98%) and accuracy (≥96%) compared to bone scan, allowing better differentiation between benign and malignant lesions (12,13,15). Bone scan images the entire skeleton, whereas a standard FDG PET/CT scan is acquired beginning from the head to just below the pelvis, thus, lesions in lower extremities may be missed. Furthermore, studies indicate the presence of false-negative FDG PET findings in breast cancer patients with osteoblastic lesions (54). The reason for this finding is poorly understood, with the literature proposing different mechanisms for low glycolytic activity of blastic lesions. Osteoblastic proliferation results in an increase in bone matrix and a relative decrease in cell density, which in turn may lead to lower FDG uptake (55). Another possible mechanism is effect of various cytokines, such as transforming growth factor-β (TGF-β), which stimulates osteoblasts to form new bone, as well as having an inhibitor effect on tumor growth. This inhibitor affect was postulated to be the cause of low FDG uptake (54). Critical role of other factors, like parathormone related peptide (PTHrP), various interleukins (IL) (i.e., IL 1, IL 6, IL 8, IL 11), tumor necrosis factor-α, insulin like growth factor-1, endothelin 1 have also been proposed for development of bone metastases in various cancers, which may have influence on different levels of FDG uptake (56-58). Furthermore, degree of malignancy may also effect glycolytic activity, as osteoblastic metastases in breast cancer with low FDG uptake showing better outcomes compared to their osteolytic counterparts with high FDG uptake (54). For these reasons, whether FDG PET/CT can replace bone scan for evaluation of bony involvement in NSCLC remains a question, needing further clinical workup.

The assessment of hepatic metastasis in patients with NSCLC is less chalenging, since the liver is less frequently involved as an isolated site of disease. The standard method for detection of liver metastases is ultrasonography or CT. The main advantages of FDG PET are the ability to detect hepatic lesions that were not determined by conventional methods and differentiate lesions that are indeterminate on other imaging modalities. Data from staging studies of NSCLC suggests superiority of PET over CT in evaluating liver lesions (12,14,16). In a study, by Hustinx *et al*., PET scan provided new and more accurate information over conventional methods in 15 of 64 (23.4%) patients with various cancers evaluated for possible liver involvement (59).

High physiological glucose uptake of the gray matter limits the diagnostic power of FDG PET for detection of brain metastases. Furthermore, small size of most brain metastases is a chalenging factor for detection with PET. Thus, sensitivity of the technique remains low (60%) (12). However, accuracy of integrated PET/CT is demonstrated to be close to that of diagnostic CT of the brain, thus obviating the need for a diagnostic CT afterwards (60). In this context, MRI remains the method of choice in evaluation of the brain with high diagnostic power (61). Since detection of brain metastases is critical, routine imaging with brain MR is recommended for patients with advanced stage disease (stages III-IV) and also for patients in whom neurological examination reveals abnormality (42). Moreover, it is postulated that, in the future total body PET/MRI may improve the accuracy of detection of metastases especially in the sites like brain where PET/CT imaging is far from ideal (62).

Besides its added value on metastatic involvement of most expected sites, PET/CT may also unveil metastases that otherwise escape detection (e.g., soft tissue lesions, retroperitoneal lymph nodes, small supraclavicular lymph nodes). New sites of metastases were shown to be detected on PET in 5-29% of patients after conventional imaging (7,12,14,16,63-66). However, the chance of false positivity on PET must be kept mind, and histopathological confirmation should be carried out in otherwise surgical candidates where only a single metastatic lesion is present.

Literature, has shown that use of FDG PET for staging may result in change of the stage in 27-62% of the patients and the scan may alter patient management in 19-52% of patients with NSCLC (7,14,63,64,67-69). In a study, conducted by Hicks *et al*., major impact on the treatment plan based on PET stage was detected in 54 of 153 (35%) patients with newly diagnosed NSCLC (67). Of 54 patients,

therapy design was changed from curative to palliative in 34 and from palliative to curative in 6. In 14 patients, treatment modality was changed without a change in treatment intent.

In summary, use of PET/CT in staging of NSCLC provides valuable information that may have great impact on clinical management decisions.

Radiotherapy planning

Radiotherapy is the choice of treatment with curative intent in early stage (stage I-II) NSCLC patients who are not suitable for surgery (e.g., due to accompanying cardiopulmonary comorbidities, massive functional impairment, or contralateral lymph node involvement). Most of the studies using FDG PET were performed in the preoperative setting for staging purposes. However, the metabolic information given by the scan could be of similar interest in radiotherapy planning process. Accurate identification of locoregional tumor load will not only determine the therapeutic intent (i.e., curative vs. palliative), but also the volume of the tumor targeted with radiotherapy and therefore, the toxicity. Computed tomography is used in order to draw the target volume for irradiation in classical radiotherapy planning process. The main disadvantages of this method are poor delineation of some tumors on CT mainly due to accompanying atelectasis and its limited accuracy in lymphatic involvement. Due to higher accuracy of diagnostic information available, PET/CT based radiotherapy planning approach will result in less chance of geographic miss of tumor and unnecessary irradiation of non-tumoral normal nearby tissues. Furthermore, PET data may lead to significant modification of the treatment strategy and radiotherapy planning in a substantial number of patients with NSCLC (70). Studies on the impact of FDG PET on radiotherapy planning demonstrated alteration of both the tumoral and nodal contours in >50% of patients with probable improved tumoral coverage (27,71). Besides, tumor volumes derived from PET/CT were demonstrated to be mostly smaller than those derived by CT alone, which render radiation dose escalation possible while respecting all relevant normal tissue constraints (71). In one study, where 21 patients with clinical CT stage N2-3 tumors were enrolled, gross tumor volume (GTV) of the nodes decreased from 13.7±3.8 cm^3 on the CT scan to 9.8±4.0 cm^3 on the PET CT scan (P=0.011). With incorporation of FDG PET CT data in the radiotherapy planning process, estimated doses to esophagus and lungs were decreased, thus the delivered dose to the tumor could significantly be escalated with better tumor control probability using PET CT based planning approach in the whole patient population (72). Moreover, interobserver variabilities drawing the tumor volumes were shown to be diminished when FDG PET was used for planning purposes (28). Besides its added clinical value in radiotherapy planning field, in a cost-effectivity analysis evaluating the use of PET/CT in radiotherapy treatment decision making, therapeutic strategy was modified in 40% of the patients with NSCLC which resulted in an overall cost reduction in this group (73).

Therapy response evaluation and monitoring of recurrences

In oncological settings, early assessment of therapeutic response is of great importance which enables alteration of treatment strategy in the case of a nonresponse. Response assessment using conventional imaging mainly depends on volumetric changes in the tumor. However, anatomical appereance does not necessarily correlate with viability of tumoral cells and outcome. From this point of view, mollecular imaging offers the benefit to further characterise the tissues on the basis of their biochemical and biological features. Furthermore, the evaluation of metabolic activity by means of FDG PET provides valuable information earlier in time after therapy compared to conventional structural imaging modalities.

Response evaluation using FDG PET in patients with previous chemoradiotherapy has been extensively evaluated (74-77). Studies comparing PET and CT favor added role of PET as being a better predictor of therapy response (78). When correlated with histopathological analysis of the surgical specimens after completion of chemoradiotherapy, changes in metabolic activity of tumors on FDG PET scan were found to be significantly higher in responders (74). In addition to that, the change in SUVmax after chemotherapy/chemoradiotherapy was shown to have a near linear relationship with percent of nonviable tumor cells in the resected tumors (r^2=–0.75, P<0.001) (75). In concordance with these findings, FDG PET has high accuracy in detection of residual viable tumor, especially for primary lesion (76). Although the literature demonstrates conflicting results for the accuracy of FDG PET in detection of residual metastases in lymph nodes, PET/CT may still be of great importance since the outcomes of the patients with complete metabolic responses were shown to be better than non-responders (76-79). In one study, where 57 patients with stage IIIB or IV disease were evaluated, reduction of

tumoral FDG uptake by more than 20% was demonstrated to be associated with longer time to progression and overall survival in these patients (79). Furthermore, studies also indicate that evaluation with FDG PET, even early in the course of chemo- and/or radiotherapy may provide additional prognostic information considering disease free survival (79,80). In addition to its role in response evaluation of neoadjuvant chemotherapy in NSCLC, FDG PET/CT has shown promise in monitoring response to novel agents like endothelial growth factor receptor (EGFR) inhibitors, mainly erlotinib (81).

High recurrence rates are seen in NSCLC patients, even if they have been treated with curative intent. Even, approximately 20% of stage I NSCLC patients experience recurrence after curative surgery. Therefore, a method of selecting patients with increased risk of recurrence for further adjuvant therapy would be of great use. Thus, imaging plays a central role in lung cancer recurrence detection. However, interpretation of chest radiographs and CT scans can be quiet challenging due to post-treatment anatomical changes such as distortion of bronchi, infiltration of lung parenchyma and fibrosis. In this setting, FDG PET may be used as a powerful adjuct in the follow up of patients after completion of therapy. After radiotherapy, local tumor recurrence usually occurs within 2 years, but may create a diagnostic challange due to accompanying mass-like pattern of radiation induced fibrosis (82). FDG PET may provide great help in distinguishing recurrent tumor from fibrosis, however timing is important ensuring that sufficient time (i.e., at least 3 months post-therapy) has elapsed for examination in order to eliminate the risk of false positivity related to inflammatory changes (83). Because radiation pneumonitis associated persistent uptake of FDG may last up to 15 months post-radiotherapy, sequential imaging with FDG PET, and occasionally other diagnostic and interventional procedures may be needed in order to establish a proper diagnosis (84). Because of high NPV of FDG PET, presence of little or no uptake of FDG requires no further intervention, and follow-up with only CT is often sufficient. The value of FDG PET in 62 patients with suspected recurrence after surgery for NSCLC was evaluated and FDG PET was shown to have a sensitivity, specificity and accuracy of 93%, 89% and 92%, respectively for detection of relapses (85). Furthermore, the FDG uptake of the recurrent tumor was identified to be an independent prognostic factor. Moreover, FDG PET shows promising results even in the detection of recurrences in forms of lung cancer known to be less FDG avid like bronchioloalveolar carcinoma (86). Despite the extensive literature showing excellent results for staging of NSCLC with FDG PET, the latest edition of American College of Chest Physicians (ACCP) evidence-based guidelines did not recommend PET/CT for routine surveliance after curative-intent treatment (87). Another issue is the occurence of distant metastases in the follow-up of patients, which is the main form of NSCLC recurrences. In a study by Kanzaki *et al*. (88), PET/CT showed high diagnostic performance for detection of recurrences in 241 consecutive patients who had undergone potentially curative surgery for NSCLC. The authors proposed that further imaging by means of conventional methods (except brain MRI) can be omitted in cases where FDG PET/CT is negative for recurrences relying on the high NPV for detection of recurrences.

PET/CT in lung cancer prognostication

Lung cancer is a heterogeneous group of disease with wide variety of course and prognosis. Accurate staging plays an important part in guiding the therapy as well as providing prognostic information. Despite being the most accepted prognostic indicator for lung cancer, differences in patient prognoses with the same stage disease cannot be explained by TNM staging system (89,90). In addition, this staging system, which is defined entirely by anatomic features of the tumor and other involved nodes and organs, still needs to be improved (91). Like most of the malignant tumor lines, physiopathology of lung cancer reveals important derangements in carbohydrate metabolism which may in turn support the theory that an *in vivo* indicator of glucose metabolism might have a role in prognostication. Metabolic activity of primary lesion is well known to be associated with indicators of aggressive biologic behavior such as tumor doubling time and degree of differentiation (92). Thus the metabolic information given by FDG PET scan may provide added prognostic information by showing biologic behavior of the tumor. In a study by Sasaki *et al*. which included 162 consecutive patients with stage I-IIIb NSCLC, presence of low tumoral SUV was associated with higher 2 year disease free survival both in the early stage (I-II) and in the late stage (IIIa-IIIb) group (93). In another patient series in which 315 cases were examined, findings were in consistence for stage Ib, II and IIIa disease (17). In a study including 487 patients, Downey *et al*. showed that SUVmax was an independent prognostic determinant apart from the TNM stage but had no contribution to the prognostic value of pathologic staging (94). These findings support that metabolic activity which is an index of tumoral

behavior, may be superior to the anatomical features used for TNM staging in prognostic stratification of patients with lung cancer. In this context, different series pointed out the prognostic value of FDG uptake of the primary tumor, as depicted by SUVmax in NSCLC (17-19,95). In a study, where 155 patients were enrolled patients with greater primary lesion SUV had significantly lower median survival compared to patients with lower values and SUV >10 was found to be a independent prognostic factor for patients with NSCLC (95). Besides, recent evidence also support that other metabolic indices like MTV and tumor lesion glycolysis (TLG), both on the whole body tumor burden and primary tumor level might have even better prognostic implications compared to SUV (96,97).

In addition to its prognostic value in pre-treatment evaluation, in a recent prospective trial, higher post-treatment tumor SUV was found to be associated with worse prognosis in patients with stage III NSCLC (98).

PET/CT in SCLC

SCLC, which accounts for 15-20% of all lung cancer cases is characterised by rapid doubling time and aggressive clinical behaviour with high prevalance of disseminated disease at the time of diagnosis (3). Although TNM staging is applied occasionally, a more simplified dichotomous classification method as limited stage (LS) and extensive stage (ES) is used for characterization of disease stage in SCLC. LS is attributed to the disease if the tumor is confined to one hemithorax with hilar, mediastinal and supraclavicular lymph nodes which can be covered within a tolerable radiation field while the remainder is defined as ES. The standard way of therapy is concurrent chemotherapy-radiotherapy (CTRT) for patients of good performance status with LS disease, and palliative chemotherapy for patients with ES disease. Despite initial chemosensitivity, overall prognosis is poor due to relapses. Given the difference in treatment strategy, accurate staging of the disease has a crucial role. In comparison to NSCLC, the data on the use of FDG PET/CT for SCLC is scarce, with relatively a small number of studies evaluating its role in staging (99-102), radiotherapy planning (99,100), therapy response evaluation (103,104) and prognosis (103-106). In a study performed by Brink *et al*. sensitivity of PET/CT was found to be superior to that of CT in evaluation of extrathoracic lymphatic involvement (100% *vs*. 70%). Although FDG PET was significantly less sensitive than MRI/CT detecting brain metastases, both the sensitivity and specificity of PET was higher in detection of distant metastases (101). In a prospective study, where 29 patients with SCLC were included, PET/CT improved staging compared to standard staging using CT, bone scan and bone marrow biopsy and led to change of stage in 17% (102).

A recent study on the role of FDG PET/CT in the evaluation of therapy response of 29 patients with SCLC demonstrated survival benefit in patients with complete metabolic response as assessed with PET/CT (103). Moreover, change in metabolic volumes after radiotherapy was shown to correlate with survival in patients with LS disease (104). In addition to that, FDG PET/CT may alter extent of radiotherapy field by providing further information both on the borders of the primary tumor and lymphatic involvement. Studies indicate that the incorporation of PET/CT data in initial staging led to changes in radiation fields up to 37% of patients (100). Based on these results, recent studies evaluated the consequences of dose escalation and omission of PET negative elective nodal irradiation in SCLC which showed promising results (107). Furthermore, studies on the role of pretreatment evaluation of metabolic activity for patient outcome have also been conducted (105,106). It was demonstrated that the higher mean values of maximal standardized uptake values (mean SUVmax) of the malignant lesions in pretreatment FDG PET/CT scan were associated with poorer overall and disease free survival both in LS and ES SCLC patients (105). Moreover, whole-body MTV of F18-FDG was shown to be of prognostic value in SCLC and incorporation of metabolic data to TNM staging was proposed for a better prognostic information (106).

Conclusions

PET using FDG has become a commonly used modality in routine clinical workup of lung cancer by being both accurate and noninvasive. Widespread availability of PET/CT scans has revolutionised both the staging and radiotherapy planning process of lung cancer. It provides valuable information by means of response evaluation early after therapy with high accuracy in assessment of recurrences. In addition to that, FDG PET scan provides information about biologic aggressiveness of the tumor and prognosis.

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