Editorial, PET/CT.

Impact of FDG PET/CT in Non-small Lung Cancer.

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ABSTRACT:

Non-small cell lung cancer (NSCLC) is the most common of lung cancers. The incidence of lung cancer over 45 years of age increases dramatically. The overall 5-year survival rate for lung cancer around 15.6%. A major shift in the approach to NSCLC treatment occurred when it was recognized that tumor epidermal growth factor receptor (EGFR) mutation status determines the effectiveness of treatments, thus, higher levels of intra tumor heterogeneity were revealed to be closely related to treatment resistance, invasiveness, disease progression, relapse and metastatic spread.

The emergence of PET/CT imaging has significantly helped the investigation of lung cancer by allowing better delineation of areas with increased tracer uptake, it also improves the detection of metastatic disease, guiding therapy and predicting clinical outcomes. PET/CT has become the standard imaging modality for lung nodule characterization, as well as for lung cancer initial staging, treatment planning, treatment response assessment, restaging at recurrence, and surveillance. The wide clinical adoption of FDG-PET/CT in patients with lung cancer has improved staging and restaging accuracy, allowing better treatment planning and better evaluation of response to treatment. Though most studies have reported a reasonably high negative predictive value (NPV) of FDG PET for mediastinal staging. The superiority of PET over bone scansis primarily because of its ability to detect both osteolytic and sclerotic metastases unlike bone scan which has a good sensitivity for detecting sclerotic lesions.

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Lung cancer is the most common malignant tumor and ranked first in morbidity and mortality [1]. Non-small cell lung cancer (NSCLC) is the most common, accounting for ~85% of lung cancers [2-4]. The incidence of lung cancer over 45 years of age increases dramatically [5].

The overall 5-year survival rate for lung cancer in the United States remains at a dismal 15.6%. The situation globally is even worse, with 5-year survival in Europe, China, and developing countries estimated at only 8.9% [6].

Tumor types and degree of pathological differentiations, cellular proliferation and tumor necrosis was reported as prognostic factors in NSCLC patients[7-8]. Thus, higher levels of intra tumor heterogeneity were revealed to be closely related to treatment resistance, invasiveness, disease progression, relapse and metastatic spread[9].

Among NSCLC, EGFR mutations are present almost exclusively in lung adenocarcinomas, often showing terminal respiratory unit-type histology with lepidic, acinar, or papillary patterns[10]. A squamous cell carcinoma harboring EGFR mutation most likely represents an adeno-squamous carcinoma with an un-sampled adenocarcinoma component [11].

A pathological, tumor budding has been attracting increased attention as a factor that reflects the malignant invasion and poor prognosis of digestive tract tumor's [12]. However, only a few studies haveexplored its significance in lung cancer [13], tumor necrosis (TN) has been shown to be related to a poor prognosis in a variety of tumor types. Consequently, TN has been included in pathological classifications and prognostic parameters for several solid organ cancers[14]. However, understanding of TN in NSCLC is poor and TN is not used widely in the clinical context of NSCLC[15]. Koh et al found that TN was associated with various prognostics.

Also, the morphological assessment of tumor-infiltrating lymphocytes (TILs), describing type, density, and location within tumor tissue has been described as a prognostic factor in several tumor types including NSCLC[16].

Hao et al,. Demonstrated that activated cancer stroma characterized as high desmoplasia has prognostic significance in NSCLC patients. Also, demonstrated that functional heterogeneity of desmoplastic Carcinoma-associated fibroblasts (CAF) is a determinant factor of NSCLC aggressiveness[17].

The clinical utility of using a nuclear grading system (e.g. mitotic count and nuclear atypia) has already been established in other major cancers such as breast carcinoma[18]. For lung adenocarcinoma, data are emerging for architectural and

nuclear grading approaches that hopefully will lead to a uniform grading system in the near future[19].

A) Overall Impact of FDG PET/CT on Lung Cancer Staging:

The emergence of PET/CT imaging has significantly helped the investigation of lung cancer by allowing better delineation of areas with increased tracer uptake, it also improves the detection of metastatic disease, guiding therapy, and predicting clinical outcomes [20-21].

The integrated imaging study has a similar accuracy as CT scan[22]. However, sometimes it is difficult to determine the exact tumor location and extent on CT scan due to surrounding atelectasis. In such situations, FDG PET/CT can accurately delineate the viable tumor from surrounding atelectasis and collapse/consolidation [22].

This information can not only demarcate the size and extent of the tumor for accurate T staging [23] but also provide guidance for biopsies if histological confirmation is required or prior biopsy attempts have led to inconclusive pathological results [24].

PET/CT has become the standard imaging modality for lung nodule characterization, as well as for lung cancer initial staging, treatment planning, treatment response assessment, restaging at recurrence, and surveillance. The wide clinical adoption of FDG-PET/CT in patients with lung cancer has improved staging and restaging accuracy, allowing better treatment planning and better evaluation of response to treatment[25-28].

FDG PET/CT is now accepted as the standard procedure in theinitial staging and diagnostic work-up of lung cancer patients [22].There is robust evidence in literature in the form of randomized controlled trials which state that addition of FDG PET to the diagnostic work-up reduces the frequency of futile thoracotomies by 20% [29].

Addition of intravenous (IV) contrast to integrated PET/CT protocols provides comprehensive staging information for the primary site (T stage), nodes (N stage), and distant disease (M stage) [22]. However, FDG PET has a limited ability to detect brain metastases and dedicated brain imaging using MRI is required to rule out brain lesions. thus [22].

In particular, ***Ohri et al,.*** observed that metabolic tumor volume (MTV) was an independent predictor of overall survival (OS) and loco regional control (LRC) in patients with NSCLC treated with chemo radiotherapy as pre-treatment SUV max was not a predictor[30]. Most studies have been focused on FDG activities ata single-time-point PET scan, either pretreatment or post treatment.

There is evidence that the change of FDG

activity from pre-treatment to post-treatment FDG-PET also provides important prognostic value in patients with NSCLC[28].

PET/CT role in detection of metastatic LNs:

FDG PET can differentiate hyperplastic/reactive nodes from metastatic nodes and is used in the detection of metastasis within normal-sized nodes, so improvement in diagnostic accuracy of imaging for mediastinal nodal disease has been documented.

Though most studies have reported a reasonably high negative predictive value (NPV) of FDG PET for mediastinal disease in the region of 90%, invasive mediastinal staging is still recommended due to the failure of PET to detect disease in about 10% cases [22].

PET/CT role in detection of distant metastatic lesions:

Distant metastases occur in 11%–36% of patients with NSCLC, with common sites including the adrenal glands, liver, brain, bones, and abdominal lymph nodes[31].

FDG PET/ CT for detection of skeletal metastases perform better than bone scintigraphy[22]. The superiority of PET over bone scansis primarily because of its ability to detect both osteolytic and sclerotic metastases unlike bone scan which has a good sensitivity for detecting sclerotic lesions [22].

FDG PET/CT has greater sensitivity and specificity than bone scintigraphy for imaging metastases to the bone marrow, with a positive predictive value of 98% if the finding from PET and CT. PET/CT offers insights into the histology of a lesion under investigation. Previous studies evaluating the preoperative maximum standardized uptake value (SUV max) showed that bronchiolo-alveolar carcinoma and other well-differentiated tumors are less FDG-avid than are squamous cell carcinomas. Such characterizations can also facilitate the differentiation of synchronous primary tumors from metastatic disease, as well as revealing prognostic information beyond what is gathered with CT scan [32-33]. The development of such techniques could of a higher risk of recurrence.

Also, demonstrated that single cell invasion (entire tumor and tumor edge), large nuclear size, and tumor budding were independently associated with an unfavorable OS[34], are concordant [32]. Also it's more accurate methods for the diagnosis of bone metastases than MRI or bone scintigraphy, and FDG PET/CT has a higher diagnostic value than any other method [33].

In the results of a meta-analysis of to

evaluate the diagnostic accuracy of FDG PET/CT for the detection of adrenal metastasis in patients with lung cancer, the pooled sensitivity was 89%, the specificity was 90%, the positive likelihood ratio was 8.5, and the negative likelihood ratio was 0.09[35].

FDG PET can help in characterizing pleural disease by demonstrate tracer uptake in the pleura and is shown to have a high sensitivity and NPV for detecting pleural malignancy[36].

^{18}FDG-PET/CT in NSCLC in relation to clinico-pathological data:

Studies have reported that the EGFR gene can affect GLUT-1 through a downstream pathway, thus further affecting tumor glucose metabolism. As such, differences in EGFR mutation status may lead to differences in tumor glucose metabolism[37]. This may cause patients with different EGFR statuses to show abnormal metabolic indicators on PET/CT[38]. This suggests that the metabolic index calculated from PET/CT may be used as a noninvasive biological marker to indicate EGFR mutation status[39].

Tumor biopsies for the detection of EGFR mutations have limitations. The tumor biopsy location may strongly affect the detection result, and patients' general condition may also restrict wide spread use of biopsies in clinical practice[24].

Therefore, the use of medical imaging as a non-invasive method to obtain information about the tumor phenotype could provide clues to predict mutation status of the EGFR gene and has been investigated in several studies using 18F-FDG PET/CT to predict the mutation status of EGFR in patients with lung adenocarcinoma. Still, the results remain controversial [40]. However, it's worth exploring by using FDG tumor uptake as a predictor of EGFR status[41].

PET/CT is widely used in lung cancer management; its uses include staging at diagnosis, response evaluation after systemic treatment, re-staging after Neoadjuvant treatment, and surveillance after curative resection or stereotactic radiosurgery[42].

Meta-analysis multivariate analysis revealed MTV as a predictor of EGFR mutations, which was not reported in previous studies wherein SUV max was used as a predictor for EGFR mutations[43]. MTV an indicator reflecting the overall metabolic level of the tumor is suitable for predicting the mutation status of EGFR[39].

Lei Zhu, et al found that NSCLC patients with mutated-EGFR had lower SUV max, SUV mean, SUV peak, and SUV ratio measurements based on 18F-FDG PET-CT

than NSCLC patientswith wild-type EGFR suggesting that EGFR-mutated lung adenocarcinomas could be biologically indolent with lower levelsof glucose metabolism than EGFR-wild tumors and these PET-CT parameters could be potentially useful to discriminate the EGFR mutation status in NSCLC patients.[44] Also, **Yang et al** result differently confirmed that the primary tumor SUV max, mediastinal SUV ratio, and liver SUV ratio were all negatively correlated with the EGFR mutation rate. These differences may be because[45] **Y a o et al** found that SUV max of primary tumors and regional lymph nodes didn't seem significantly different between two EGFR status lung adenocarcinomas. However, bone metastasis from EGFR mutant lung adenocarcinoma had lower SUV max than EGFR wild types.[41] **Aydos, et al** found that tumor necrosis rate % did not show any significant correlations with FDG PET parameters (SUV max, TLG and MTV).[46]

Tumor necrosis rates were not also significantly different among the tumor groups. However, among tumor types (adenocarcinoma and SCC) significant differences were present regarding SUV max, TLG with higher values in the SCC group.

CONCLUSIONS:

To extend application of PET/CT in practice, numerous studies have evaluated the possible utility of the semi-quantitative metabolic parameters obtained from ^{18}F-FDG PET/CT images SUV is the most widely investigation. The addition of volumetric parameters including metabolic tumor volume (MTV) and total lesion glycolysis (TLG), which reflect metabolic tumor burden are better prognostic parameters.

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