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Guidelines for the role of FDG-PET/CT in lung cancer management

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Summary Fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) and PET/computed tomography (FDG-PET/CT) is regarded as a standard of care in the management of non-small-cell lung carcinoma (NSCLC) and is a useful adjunct in the characterization of indeterminate solitary lung nodules (SLN), and pre-treatment staging of NSCLC, notably mediastinal nodal staging and detection of remote metastases. FDG-PET/CT has the ability to assess locoregional lymph node spread more precisely than CT, to detect metastatic lesions that would have been missed on conventional imaging or are located in difficult areas, and to help in the differentiation of lesions that are equivocal after conventional imaging. Increasingly FDG-PET/CT is employed in radiotherapy planning, prediction of prognosis in terms of tumor response to neo-adjuvant, radiation and chemotherapy treatment. Evidence is accumulating of usefulness of PET/CT in small cell lung cancer.

Introduction

Positron emission tomography (PET) has dramatically changed oncological imaging practice by using a variety of radionuclides. PET enables in vivo characterization and measurement of biological processes at cellular and molecular levels. The most readily available radiopharmaceutical is 2-[18F]-fluoro-2-deoxy-D-glucose (FDG), where fluorine-18 (18F) is a positron-emitter giving rise to high-energy photons, and FDG is a glucose analog employed as a tracer of glucose transport and metabolism. The rate of cellular glycolysis is reflected by the degree of FDG uptake and that can be determined from imaging data with correction for attenuation of photons by body tissues. The relatively low specificity of FDG-PET and the difficulty in localizing the

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activity identified by FDG-PET imaging have elicited efforts to integrate FDG-PET with other morphological imaging techniques. Hereby a PET/CT was introduced offering a combination of morphological and molecular/cellular imaging. FDG-PET and FDG-PET/CT have a better sensitivity than CT alone in the detection of locoregional cancer spread and distant metastases in patients with NSCLC and small cell lung cancer (SCLC). FDG-PET/CT is regarded as a standard of care in the management of non-small-cell lung carcinoma (NSCLC) and small cell lung cancer (SCLC). It is a useful adjunct in the characterization of indeterminate solitary pulmonary nodule (SPN), and pre-treatment staging of NSCLC, notably mediastinal nodal staging and detection of remote metastases. FDG-PET/CT is more precise than CT in its ability to assess locoregional lymph node spread. It can detect metastatic lesions that would have been missed on conventional imaging or are located in difficult anatomical areas, and helps in the differentiation of lesions that are equivocal after conventional imaging. Increasingly FDG-PET/CT is employed in radiotherapy planning, prediction of prognosis in terms of tumor response to neo-adjuvant, radiation and chemotherapy treatment. Evidence is accumulating of usefulness of PET/CT in small cell lung cancer. In this review we will discuss the role of PET/CT in the diagnosis and management of lung cancer.

The solitary pulmonary nodule (SPN)

Christensen et al. compared CT enhancement of SPN vs. 18 FDG. They examined 42 SPNs with both CT and PET scanning. CT was positive for a peak enhancement of more than 15 HU in all malignant nodules and 12 benign nodules (sensitivity 100%, specificity 29%, PPV 68% and NPV 100%). PET studies were positive by semi-quantitative analysis where the Standardized uptake value (SUV) was greater than 2.5 in 21 out of 25 malignant SPNs and 3 of the 17 benign SPNs (sensitivity 84%, specificity 82%, PPV 88% and NPV 78%). The study concluded that PET had much higher sensitivity, and is preferable to CT in characterizing indeterminate SPNs. However, CT remains useful and is the first choice imaging because of the high NPV, convenience and cost [1].

Fletcher et al. concluded in their paper that definitely and probably benign SPNs on PET and CT strongly predicted benign lesions. However, such results were 3 times more common with PET. Definitely positive PET scans were much more predictive of malignancy than were these results on CT. A malignant final diagnosis was approximately 10 times more likely than a benign lesion when PET results were rated definitely malignant [2].

A meta-analysis [3] found a consistently high sensitivity (80—100%) of FDG-PET for identifying a malignant SPN, whereas specificity was lower and more variable across studies (40—100%).

Staging lung cancer

Fischer et al. conducted a randomized study to evaluate the clinical effect of PET—CT on preoperative staging of NSCLC. The study concluded that the use of PET—CT for preoperative staging of NSCLC reduced both the total number of thoracotomies and the number of futile thoracotomies but did not affect overall mortality [4].

FDG-PET is a useful adjunct in NSCLC TNM staging. The usefulness of FDG-PET mainly lies in nodal staging and distant metastatic survey. Defining malignant involvement of mediastinal lymph nodes eventually determines operability of the lung cancer. Several meta-analyses on the performance of CT reported a pooled sensitivity from 51% to 61% and specificity from 77% to 86%, whereas PET had significantly better performance with a pooled sensitivity from 74% to 85% and specificity from 85% to 91% [5—7]. The performance of PET was also influenced by the presence or absence of lymph node enlargement [8]. When there were enlarged nodes, PET's sensitivity and specificity operated at 91% and 78% respectively. The performance of imaging in lung cancer is summarized in Table 1.

FDG-PET is highly sensitive at identifying distant metastases except metastases to the brain owing to the fact that the brain gray matter has high FDG uptake normally. The rate of discovering unanticipated metastases by PET often varied between 10% and 20% of cases, and that increased with the clinical stages, for example in one study, the rates were 8%, 18% and 24% in patients with stage I, II and III diseases, respectively [10,11].

The impact of PET on staging has shown, an up-stage in 16—41%, and down-stage in 6—20% of patients [10,12,13]. Two multi-centric trials have shown that the use of PET could reduce unnecessary thoracotomies in up to 20% of patients with suspected or proven NSCLC [14,15].

The American College of Chest Physicians (ACCP) Clinical Practice Guidelines recommends the use of FDG-PET for mediastinal and extra-thoracic staging in patients with clinical stage IB to IIIB in lung cancer being treated with curative intent. The usefulness of PET-CT is not clear in clinical stage IA. However, it should be considered in patients with

Table 1 Performance of imaging in the staging of lung cancer.

	Sensitivity %	Specificity %	NPV %	PPV %	References
Initial evaluation of the mediastinum					
CT	47—54	84—88	47—96	30—95	[7,32]
PET	50—89	77—90	50—100	43—100	[7,32]
PET/CT	47—89	60—100	85—99	37.5—100	[33,34,16]
Evaluation of extrathoracic metastases					
CT	18	98	89	71	[33]
PET	50—79	75—100	89	75	[33]
PET/CT	92	98	98	89	[33]
Restaging of the mediastinum					
CT	59	62	53	66	[34]
PET	71	69	64	75	[34]
PET/CT	77	92	75	93	[34]

Modified from Ref. [35].
Positive predicted value (PPV); negative predicted value (NPV).

clinical 1A lung cancer being treated with curative intent [7].

Although PET is useful in staging NSCLC, there is a false-positive rate in 15—20% and false-negatives rate of 9—28% [7]. The false positive results are primarily due to infective or inflammatory conditions. False negative results may accrue due to low-grade or slow-growing tumors, or small lesions. A positive result from PET-CT needs histopathological confirmation as no patient should be denied potentially curative treatment based on imaging alone in other hand, patients with negative integrated PET-CT can be operated upon without invasive mediastinal staging [8]. The ACCP guidelines [9,16] recommend invasive confirmation of the radiographic stage, regardless of whether a PET finding is positive or negative in the mediastinal nodes, for patients with (a) discrete mediastinal lymph node enlargement, or (b) with a radiographically normal mediastinum and a central tumor or N1 lymph node enlargement. Therefore, a positive PET—CT serves as an indication for further invasive testing. The ACCP guidelines also recommend histological confirmation of mediastinal nodes for patients with a peripheral clinical stage I tumor with a positive mediastinal nodes uptake [9,16]. Guidelines from the European Society of Thoracic Surgeons [17] additionally recommend invasive staging when the primary tumor shows low FDG uptake such as in a bronchioloalveolar carcinoma.

Accurate and fast staging of small-cell lung cancer (SCLC) is mandatory when choosing treatment, but current staging procedures are time consuming and lack sensitivity. Fischer et al. conducted the first prospective study on 29 consecutive patients to assess the role of PET/CT compared with CT, bone scintigraphy and immunocytochemical assessment of bone marrow biopsy of patients with SCLC. PET/CT restaged 17% of the patients. The sensitivity for accurate staging of patients with extensive disease was the following: for standard staging 79%, PET 93% and PET/CT 93%. Specificity was 100%, 83% and 100%, respectively. The authors concluded that FDG-PET/CT can simplify and perhaps even improve the accuracy of the current staging procedure in SCLC [18].

Another useful role of PET/CT is to guide biopsy for difficult cases when CT fails to distinguish lung mass from post-obstructive pneumonitis.

Radiotherapy planning

FDG-PET/CT is increasingly used for radiotherapy planning in patients with non-small-cell lung carcinoma. PET/CT is now preferable for radiotherapy planning in NSCLC rather than CT alone. Integration of PET/CT in radiotherapy planning may improve patient outcome although studies that are more clinical are required to arrive at a definite conclusion [19]. PET/CT planning for target volumes in radiotherapy of NSCLC is different from the treatment volumes [20]. The percentage of changes recorded, by PET/CT ranges from 27% to 100% [20]. This change may be related to the exclusion of atelectasis or inclusion of PET-positive nodes. Target volumes calculated by PET/CT when compared to CT also greatly reduce the inter-observer variability. PET/CT may also provide improved therapeutic ratio when compared with conventional CT. Grgic et al. found significantly better fusion of PET and planning CT can be reached with PET acquired in the radiotherapy position [21]. The best intra-individual fusion results are obtained with the planning CT performed during mid-breath hold

[21]. However, the methodology for incorporating PET technique in radiotherapy planning continues to be refined [22]. Ceresoli et al. in their study suggest that FDG/PET should be integrated in conformal radiotherapy of mediastinal elective node irradiation techniques, as it improves target volume delineation without a major increase in predicted toxicity [23].

Treatment response

A major issue with treatment response and ultimate prognosis in NSCLC has until recently been dependent on morphologic information provided by standard chest radiography and CT. Unfortunately, these imaging techniques cannot reliably distinguish necrotic tumor or fibrotic scar from residual tumor tissue [24]. Response evaluation with radiography and CT does not correlate well with histopathological response, and tumor response is determined more by residual tumor aggressiveness than by its size/volume [25].

Many studies have shown the sensitivity and specificity of PET for assessing histopathological response of NSCLC ranging between 81% and 97%, and 64% and 100%, respectively [26]. Thus, FDG-PET/CT is regarded as a predictor of treatment response and a prognosticator [27]. FDG-PET/CT has also been used in pre-operative assessment of prognosis of NSCLC [28]. The standard uptake values (SUV) of NSCLC measured pre-operatively correlates with tumor doubling times and on a multivariate analysis, was an independent predictor of disease relapse and death [29,30]. Huang et al. have shown that SUV and metabolic tumor volume (MTV) changes from two serial FDG-PET/CT scans, before and after initial chemoradiotherapy, allow prediction of the treatment response in advanced NSCLC [31].

Summary: role of PET/CT

- PET/CT or PET are indicated for evaluation of mediastinum or for metastasis at initial evaluation for patient with resectable with curative intent in tumor stage IA—IIIB [16,35]
- If there is no distal metastasis then a Positive mediastinal lymph nodes by PET need cytological confirmation by biopsy [16,35]
- Surgical treatment can be done in operable patient if PET scan is negative. However, surgical cytohistological confirmation is necessary if [16,35]
  1. Significant mediastinal lymph nodes enlargement (smallest diameter is >15 mm on CT)
  2. A central tumor (middle 1/3 of the hemithorax)
  3. There is suspicion for N1
  4. The tumor has low SUVmax

Appendix A. Committee members

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