PET/CT in treatment response assessment in lung cancer. When should it be recommended?

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Abstract

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. Different treatment options are now possible both for surgical candidates and for those NSCLC patients deemed not suitable for surgery. Despite the treatments available, only a limited number of less advanced stages are potentially curable, with many patients suffering local recurrence or distant metastases.

FDG PET/CT is commonly used in many centers for post-treatment evaluation, follow-up, or surveillance; Nonetheless, there is no clear consensus regarding the indications in these cases.

Based upon the results of a literature review and local expertise from a large lung cancer unit, we built some clinical evidence based recommendations for the use of FDG PET/CT in response assessment. We found that, in general, this is not recommended earlier than 3 months from treatment; however, as described in detail, the correct timing will also depend upon the type of treatment used.
We also present a structured approach in assessing treatment changes when reporting FDG PET/CT, using visual or quantitative approaches.

Introduction:

Lung cancer remains the leading cause of cancer related mortality worldwide (1). NSCLC is the most common type of lung cancer, with adenocarcinoma making up the most frequent histological subtype, followed by squamous cell lung cancer (2). Treatment options vary depending on histological subtype, stage of disease, and the patient's overall fitness and comorbidities.

Advances in lung cancer treatment options have evolved both for surgical candidates (e.g. lobectomy, segmentectomy, wedge-resection, nodulectomy), and for those deemed unsuitable for surgery or inoperable (e.g., conventional radiation therapy, stereotactic body radiation therapy [SABR], radiofrequency ablation, conventional chemotherapy, targeted or immunotherapy treatments). A combination of approaches is also commonly adopted. Despite such advances, only a limited number of stages are considered potentially curable with survival rates declining rapidly with stage, e.g. 5-year survival rate for stage IA NSCLC is 92%, whereas the figure for stage IVB NSCLC is <1% (3,4).

The National Comprehensive Cancer Network (NCCN) suggested CT and clinical evaluation for post treatment surveillance and monitoring treatment response, regardless of stage, type of treatment or cancer molecular type (5,6). The use of 2-deoxy-2-[^{18}F]-fluoro-D-glucose PET/CT (FDG PET/CT) was recommended for initial diagnosis, prior to radiotherapy planning, in cases of significant atelectasis or contraindication to iodinated CT contrast; but it was also recommended that positive findings on FDG PET/CT imaging be confirmed histopathologically (7,8). FDG PET/CT is, however, not recommended in post-treatment evaluation, follow-up, or surveillance. NCCN in fact declared there is a lack of proven benefits on the technique, together with a significant rate of false positive findings, potentially confounding the accurate assessment of response to therapy.

In this expert review, with the help of most updated literature, we aim to provide a synopsis of the current main applications, and experience from a large oncology center in London, of the utility of FDG PET/CT in assessing treatment response. We also describe the main structured approaches in assessing treatment changes when reporting FDG PET/CT.

Clinical based evidence:

Patients with CT findings suspicious for recurrence post-surgery

Post-treatment morphological changes are often challenging to rule out local recurrence, for example a growing soft tissue in the tumor bed, at the bronchial or pulmonary artery stumps, or close to the site of anastomosis. When FDG PET/CT can be performed at postoperative follow-up scan can correctly identify disease in 94% of patients with recurrenceAlthough post-surgical inflammation at the site of surgery can extend between 3-6 months, which represents a window of false positive findings of (9). (Fig.1 a, b)

FDG PET/CT was proven equivalent or superior to clinical examination and chest CT for the detection of loco-regional recurrence. Additionally, the technique can be used to identify distant metastasis with 97–100% sensitivity and 62–100% specificity (7,9,10).

Similarly, to baseline evaluation, a significant role of FDG PET/CT is reserved for the detection of locoregional nodal recurrence, for which the technique shows sensitivity of 75-85% and specificity of 85-90% (11).

In the follow-up, surveillance, and detection of recurrence, He YQ et al. in 2014 studied 1035 recurrent lung cancer cases (both local and distant) in a meta-analysis and showed superior sensitivity and specificity of FDG PET/CT (both at 90%) over conventional CT (78% and 80% respectively) (11).

Other studies demonstrated comparable results suggesting the superiority of FDG PET/CT in identifying extra-thoracic recurrence and distant metastasis, outside the chest CT field of view (12–14). Moreover, Choid et al. showed that FDG PET/CT helped detect recurrent lung cancer in 37% of cases (19 patients) which were not apparent on CT. The majority were found to have intrathoracic findings, as opposed to 7 patients with extra-thoracic findings (15).

Suspicious recurrence or residual disease after radiation treatments:

Fibrotic changes post stereotactic ablative beam radiation (SABR) treatment develops at 6-12 months post completion of therapy and may continue to evolve as low-grade activity over 24 months (16). The onset of FDG PET/CT metabolic activity is documented as early as 6 weeks from starting treatment; however, owing to the high negative predictive value of FDG, absence of focal accumulation at the site of the treatment indicates a favorable response (Fig.2). In this context, FDG activity can guide biopsy site location as recommended by NCCN guidelines for the investigation of equivocal findings (7).

On the other hand, post-radiofrequency ablation (RFA) ground glass opacification decreases after 2-3 months from completing treatment. Hence, FDG PET/CT is not recommended within this window, but focal FDG activity beyond 3 months is suspicious for recurrence (9).

Change in management

FDG PET/CT has shown to influence patients' management in a variable number of cases. Sheikhbahaei et al. conducted a literature review, in which it was reported that 30-80% of patients who underwent imaging 6 months after completing treatment demonstrated a change in treatment(9). This study included re-surgical intervention cases on maintenance therapy (17–19). In a recent review it was postulated that false positive FDG PET/CT findings led to further unnecessarily invasive examinations, although the authors stated that the scans were still able to rule out recurrence and/or metastasis in approximately 25% of patients

(20). Additionally, across different studies amongst patients who had no clinical or radiological suspicion, FDG PET/CT was able to identify 17-48% of residual disease on follow-up scans (11). In a previous study of 2019, similar results were shown by Kendathil and colleagues with significant change in management by using FDG PET/CT, revealing recurrence in clinically non-suspected patients as well as ruling it out in patients with clinical suspicion (7).

Role of FDG PET/CT in response assessment

The recent introduction of new systemic treatments, including targeted agents, anti-angiogenetic drugs and immune checkpoint inhibitors, targeting specific hallmarks of cancer, requires dedicated evaluation.

The selection of cases that would benefit from such a therapeutic approach is currently based on the immunohistochemical (IHC) evaluation of different molecular markers, including EGFR and PD-L1 expression on cyto/histological tumor specimens (21); it is worth mentioning that these are dynamic biomarkers whose expression can potentially be influenced by treatments as well as different tumor microenvironments (e.g., metastatic niches). Recently, FDG PET/CT has been correlated with expression of several predictive biomarkers. FDG PET/CT imaging can act as a virtual biopsy guidance tool to assess several biomarkers at baseline assessments and after treatments (21).

Another key role of FDG PET/CT is in relation to post-treatment evaluation of patients undergoing conventional chemotherapy and targeted treatments. Assessing early features of favorable response to treatment is of immense value to reduced time spent, cost, and toxicities from delivering unproductive therapies (22).

The NCCN recommends performing a CT every 6-12 months in the first 2 years, more frequently if treatment involves chemo +/- radiotherapy, reserving FDG

PET/CT for equivocal CT findings (5). However, CT evaluation based on tumoral size is not only challenging with altered anatomy, but also does not consider potential post-treatment metabolic changes (tumour viability) (Fig. 3).

Certainly, metabolic changes can serve as earlier predictors of treatment response than morphological features. It is known, in fact, that many next generation chemotherapies, have a cytostatic effect, rather that cyto-reductive, with consequent stable appearance in size but changes in the cell viability. Similarly, in lesions with irregular shapes, the evaluation is indeed challenging, and a functional technique provides a better quantitative (and more precise) evaluation of tumor changes. Lastly, in many cases the superiority of PET/CT over conventional CT to detect extra sites of disease in follow up scans is well recognized (Fig.4).

In a study conducted by Toba et al., FDG PET/CT was able to identify disease recurrence after curative intervention in 46 out of 47 patients in 68 out of 69 suspected sites, with 97.9% sensitivity, 97.1% specificity. The imaging correctly identified 7 lesions at the surgical sites (23).

In a meta-analysis of 13 studies of 414 patients, pathological assessment was used as the gold standard to compare the predictive outcome of FDG PET/CT and CT in evaluating adjuvant therapy tumor response. FDG PET/CT was found to be superior with a sensitivity of 83% and a specificity of 84%, compared to 71% and 68% of CT, respectively (24). This was related to accounting for metabolic changes on FDG PET/CT, enabling differentiation between viable tumour from non-viable scarring, fibrosis, or necrotic tissue. Also, volume changes noted on CT may take weeks to months, hindering the use of CT in altering treatment plans (25).

Metabolic assessment of tumor response to treatment: visual, semiquantitative, or quantitative?

Tumor size-based criteria, (i.e., RECIST) is an accurate method for simple use in clinical practice for CT. However, this may incorrectly classify the response assessment in a high percentage of cases (especially when criteria for response is used in interobserver measurements) (26). CT is also unable to identify histopathological response (i.e., viable tumor), with a discordance of 41% (27).

Visual assessment

Aside from RECIST or PERCIST, the Hopkins Criteria are a relatively new structured approach for visual response assessment to treatment in lung cancer, by using a similar approach to that in use for lymphoma(28). A five point visual scoring system comparing tumor uptake of FDG to that of the mediastinal blood pool and liver background metabolic activity is often used to determine the response to treatment. This system also takes in account possible post-treatment inflammation. From 21 different studies, FDG PET/CT was able to identify 70.8-86.7% of cases of residual disease using such a scoring system, with treatment plans altered accordingly (28–30).

Semiquantitative and quantitative measurements

Visual assessment of the metabolic activity of disease is generally adequate for clinical evaluation of PET/CT lung cancer studies; nevertheless, the need for standardization of the methods used to compare studies, particularly in clinical trials evaluating therapeutic effects, and has led to the search for quantitative and semi-quantitative measures. It is beyond the scope of this article to go into each of these parameters in deep detail; rather, we want to give practical information so that clinicians can recognize the differences among the parameters used in standard reporting, and their importance.

Standardized uptake value (SUV), represents a relatively simple computational process of the injected radioactivity within the body; however, there are many technical factors which may influence the actual values obtained. Additional parameters of treatment response criteria have been developed, based on the same theoretical approach as measurement of the SUV, though with refinements. PERCIST (PET response Criteria in Solid Tumors) structure has become widely adopted by the nuclear physician community and is based on the calculation of SUL (standardized uptake value corrected for lean body mass).

The SUL, which represents lean body mass rather than actual patient weight, and SUV peak, which seeks average of the most intense voxels within a relatively small volume of interest (VOI) are promising. The former with the clear advantage acknowledging the possible weight loss occurring in most patients following chemotherapy, which would inevitably impact the measurements with SUV max. The latter was also proposed for PERCIST criteria and aimed to overcome the tendency of isolated intense voxels to influence the result. However, previous studies demonstrated that SUV peak is itself subjected to methodological influences. It is worth mentioning that the uptake of FDG in the tumor and its clearance from the blood and other organs is a dynamic process, and therefore the SUV results are time-dependent and usually increase over time for at least 60 minutes, and then gradually descend (9,31). Accordingly, dynamic scan acquisition protocols have been a focus of studies seeking to evaluate therapeutic response in lung cancer (32).

PET/CT provides the opportunity to evaluate disease burden by using other parameters, such as metabolic tumour volume (MTV) and total lesion glycolysis (a composite parameter that integrates both intensity and volume and is generally calculated by multiply the SUV_{mean} by the MTV). Despite all these interesting concepts, and with many studies proving in some cases a better assessment compared to standardised uptake values, e.g for a better predictor of progression-free survival (24), these parameters often lack standardisation and appropriate and

accurate easy-accessible software of evaluation. Further studies are indeed worth to clarify the exact role of these parameters.

Potential solutions to standardise the measured quantitative values

> Different technical and physiological factors (e.g. different PET camera settings, image reconstruction or data analysis) can influence up to 50% the measured SUV, potentially affecting the reproducibility and accuracy of the standard uptake values (SUV) in oncology FDG PET studies. (REF). Several solutions have been proposed to mitigate these points including Daily quality control (QC). This is essential for the general assessment of image quality including identification of artifacts, and to exclude any detector failure; Calibration or cross-calibration of the PET/CT camera is indispensable to measure the direct calibration of the given camera compared to the department's / institution's dose calibrator (REF,REF). Harmonization strategies (guidelines) have been proposed by the joining international PET/CT accreditation program of European Association of Nuclear Medicine (EANM/EARL[Evaluation and Report Language)] with the intent to systematize different procedures, such as the patient preparation, PET acquisition, reconstruction or therapy assessment (REF)."

Physical and physiological factors ,may affect the reproducibility and accuracy of the standard uptake values (SUV) in oncology FDG PET studies. Different PET camera settings, image reconstruction or data analysis can influence up to 50% the measured SUV (REF). To mitigate this phenomenon, several options should be used in combination. First, daily quality control (QC) is essential to make sure that the PET/CT camera works fine, and to exclude any detector failure (this is usually an automatic procedure). Second, calibration or cross-calibration of the PET/CT camera is indispensable to measure the direct calibration of the given camera compared to the department's / institution's dose calibrator. There are other different dose calibrators on the market which can be ordered from the manufacturer to calculate patient specific tracer avidities and to conduct cross-calibration. Overall, potential discrepancies between the dose calibrator and the PET camera must be monitored to achieve sufficient SUV quantification (REF,REF).

It is also advised to apply EANM/EARL harmonization strategies, which is an international PET/CT accreditation program with an aim to deploy internationally standardised quantitative parameters. These strategies try to systematize different

procedures, such as the patient preparation, PET acquisition, reconstruction or therapy assessment (REF).

Summary

18F-FDG PET/CT was proven through a series of articles to serve as an essential tool for evaluating various aspects of lung cancer and holds a superior function over conventional Chest CT scan in follow-up (FU) imaging. It is worth to remember that FDG is not a specific cancer tracer, therefore might be influenced by inflammatory or reactive changes; thus, the general literature and our clinical practice do recommend to generally conduct FU PET imaging not earlier than 12 weeks after treatments.

In patients treated with RT this time might even be longer (better after 6 months from radiotherapy). However, the intensity of uptake and their distribution are also important visual parameters, since, if the uptake is of low grade and diffusely homogeneous, recurrence is unlikely (high negative predictive value).

In monitoring patients in chemotherapy, interval times of scanning are more controversial, and no definite recommendation can be made. It is indeed true that PET/CT can provide additional information about the therapy (was reported to chng management in a large series of patients), but in most of the cases FDG PET/CT is used when there are unequivocal findings at diagnostic CT which can occur at any time during treatments.

Limitations

The literature search was done to the best of our knowledge by using PubMed and Medline as primary search engines. We searched for English-language papers published between 2010 and Dec.2022 using the following terms combined: PET/CT, ‘18F-FDG PET’ ,’lung cancer’, ‘treatment response’. No proper meta-analysis of these articles was performed but we think this is outside the scope of

the paper which is an expert review of the application of PET/CT in treatment response assessment for lung cancer.

CONCLUSION

FDG PET/CT can serve as a tool for assessing various aspects of lung cancer, as elaborated in this review; and it is proven to be a superior technique over other conventional imaging modalities in demonstrating disease recurrence.
We acknowledge that specific guidelines for the exact timing of when requesting PET/CT is not an easy task, as depending by many different factors, including therapies, stage of disease or concomitant pathologies. Combined efforts with further prospective studies on the appropriateness of the technique will benefit patients' management and will be more cost effective for the healthcare system.

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Ethical standards statement
This article does not contain any studies with human or animal subjects performed by the any of the authors.

Author Contributions
All authors contributed to the study conception and design. All authors read, revised and approved the final manuscript.

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Conflicts of interest:

There are no conflicts of interest.

Figure captions:

Figure 1 a: Postoperative changes in the lung. Patient with RUL lobectomy and suspicious soft tissue at the surgical margins at follow up CT. PET/CT shows intense uptake [SUV max 8.3] at the level of surgical suture adjacent to the bronchial stump (arrow).

Figure 1 b: Postoperative changes in the lung. Similar patient with RUL lobectomy but in this case PET/CT shows no significant uptake at the level of the surgical suture at the right pulmonary hilum.

Figure 2: Patient with previous left upper lobe lobectomy and radiotherapy to the surgical margins due to vascular invasion at histology. CT **(a)** shows an area of fibrotic consolidation with low grade reactive FDG activity [SUV max 2.8] on fused PET/CT image **(b)**.

Figure 3: Patient with metastatic disease under treatment. PET/CT at first follow up (bottom row) demonstrates FDG avid lesion in the left lower lobe (arrow) with focal subcarinal nodal FDG activity (arrowhead). At second follow up (top row) the lesion seems similar in shape but partially covered by some pleural fluid (asterisk). However, the FDG intensity is significantly higher (arrow). The nodal activity has also progressed with now a second focal nodal activity.

Figure 4: PET/CT detecting extra site of disease. Primary lung adenocarcinoma not responding to treatment and demonstrates new, multilevel distant metastases (involving the liver and axial skeleton).

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