The Role of PET in the Evaluation, Treatment, and Ongoing Management of Lung Cancer

Kevin Stephans, MDa,c,*, Anton Khouri, MDb,c, Mitchell Machtay, MDa,b

[18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) has gained a major role in the evaluation and treatment of lung cancer over the past two decades. Over that time span PET and treatment techniques have both evolved substantially. While technical changes in PET and PET/computed tomography (CT) have improved accuracy and reliability, the evolution toward increasingly targeted and intensive treatment has increased the reliance upon imaging for radiation treatment. This article seeks to review the current role of PET in the evaluation and treatment of lung cancer with radiation.

DIAGNOSIS

The FDG PET imaging has attained a central role in both the evaluation of new pulmonary lesions and the staging of lung cancer. A meta-analysis of 40 prospective studies suggested a sensitivity of 96.8% and specificity of 77.8%1 for FDG-PET in the evaluation of a new lung nodule. This finding makes PET an excellent frontline study, even prior to pathologic diagnosis of lung cancer. FDG-PET is extremely useful in guiding the need for biopsy, given that PET-negative lesions are rarely malignant and therefore can typically be followed clinically. Most PET false-negative lung cancers are bronchioloalveolar cell lung carcinomas. These lesions have unique CT characteristics and are typically low grade with a slow-growth pattern demonstrating progression over only long intervals, therefore the urgency of diagnosis may be less. As the specificity of FDG-PET is only 77.8%,1 biopsy confirmation of malignancy remains vital. Biopsy offers confirmation of malignancy justifying treatment, as well as histology, which is critical. For example, small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC) may be treated very differently despite otherwise identical presentation.

Combining PET with CT allows the potential for integrated imaging, which should improve sensitivity by eliminating from consideration areas of increased standardized uptake value (SUV) with no associated CT changes. The specificity of PET/CT might be greater than the 77.8% reported for PET alone in the aforementioned meta-analysis.

This work was done independently of any grant or research funding.

a Department of Radiation Oncology, Cleveland Clinic, 9500 Euclid Avenue, T28, Cleveland, OH 44195, USA
b Department of Radiation Oncology, University Hospitals/Case Western Reserve University, 11100 Euclid Avenue, Cleveland, OH 44106, USA
c Case Comprehensive Cancer Center, Wean 152, 11100 Euclid Avenue, Cleveland, OH, USA
* Corresponding author. Department of Radiation Oncology, Cleveland Clinic, 9500 Euclid Avenue, T28, Cleveland, OH 44195.
E-mail address: stephak@ccf.org

PET Clin 6 (2011) 265–274
doi:10.1016/j.cpet.2011.05.003
1556-8598/11/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
though comparative data at this point are limited. Some investigators have even suggested that combining CT and PET features may even give some insight into tumor histology; this may take on further interest with the future availability of additional PET radio tracers.

An important exception to the requirement for tissue diagnosis comes in medically inoperable patients with highly suspected NSCLC. Biopsy may be high risk in patients with extremely poor lung function or in those with history of contralateral pneumonectomy, and otherwise unreliable in patients with small but PET-positive lesions located in areas where access is technically challenging. Such patients are typically treated based on radiographic criteria, which may vary by institution. To consider empiric treatment, a lesion is required to be both increasing in size on serial CT over a 6-week to 3-month interval, and positive on FDG-PET with an SUV of greater than 3.0. The numbers of patients treated in this manner are small and the population is heterogeneous, making reliable analysis of these criteria difficult. However, the fact that the rate of future distant metastasis is comparable in a series of stage I patients treated with histologic versus radiographic characteristics suggests these criteria are reasonable.

**STAGING**

Once a biopsy diagnosis is reached, FDG-PET/CT is the gold standard for noninvasive staging. PET offers substantial improvements in both mediastinal and distant staging over CT criteria alone, and is the standard of care for all patients with newly diagnosed NSCLC.

**Mediastinal Staging**

According to a recent meta-analysis the addition of PET to standard CT increases the sensitivity for the detection of mediastinal nodal involvement from 61% to 85%, while specificity is improved from 79% to 90%. Of interest, when CT demonstrated enlarged mediastinal lymph nodes PET was more sensitive (100%), but less specific than at baseline (78%). Conversely, when CT showed no nodal enlargement, sensitivity was near baseline at 82% and specificity 93%. This finding has important treatment planning implications: enlarged but PET-negative nodes therefore are unlikely to contain disease (as PET was 100% sensitive in this series), whereas small but PET-positive nodes are very likely to be malignant. Given the association of target size and PET SUV measurement, both of these conclusions are logical, and have important implications for both staging and treatment planning.

Even after PET, patients who are surgical candidates frequently proceed to additional staging by mediastinoscopy prior to the final selection of treatment modality. The ACOSOG Z0050 trial investigated the correlation of CT, PET, and mediastinoscopy in 303 potentially resectable patients with NSCLC. PET detected microscopic N2 nodal disease in 58% of patients. However, as sensitivity was only 61% and negative predictive value 87%, the ability of PET to detect microscopic N2 disease appears to be modest. In addition, a Cleveland Clinic review of 87 patients with pathologic stage IIIA NSCLC by mediastinoscopy reported that 38% of pN2+ patients had no previous abnormal PET findings in the mediastinum. Other reports suggest higher accuracy of PET, including a recent Korean report of 750 NSCLC patients who were mediastinal node negative by CT and PET criteria and who underwent mediastinoscopy. Only 6.8% of these patients were found to have N2 disease on mediastinoscopy, though an additional 8.5% were later found to have N2 disease on final surgical dissection after completion of neoadjuvant therapy. A similar Japanese study suggested an 11% (24 out of 224) incidence of mediastinoscopy-detected microscopic N2 disease present in NSCLC patients who were node negative by PET. Of note, most metastases were small, with two-thirds being less than 4 mm. Multivariate analysis identified adenocarcinoma, tumors located in upper or middle lobe, tumor size larger than 3 cm, and maximum SUV of primary tumor greater than 4.0 g/mL as significant risk factors for microscopic nodal metastasis. An Irish review by Al-Sarraf and colleagues demonstrated a 16% incidence of microscopic N2 disease in PET-negative patients, and identified central tumors, right upper lobe tumors, and PET-positive uptake in hilar (N1) nodes as significant risk factors for undetected microscopic N2 disease. Based on the aforementioned studies the incidence of PET false-negative mediastinal nodes ranges substantially, from 10% to as much as 40%. For this reason mediastinoscopy remains clinically indicated for most patients undergoing surgical resection. Conversely, for patients with locally advanced NSCLC undergoing chemoradiation (as well as medically inoperable stage I NSCLC) mediastinoscopy, an invasive procedure that would delay the start of radiotherapy is not typically performed. The standard staging system for these patients is based on PET. Additional mediastinal staging tools such as endobronchial ultrasound sampling, magnetic resonance (MR) imaging, or MR spectroscopy are currently under investigation as a supplement to PET in these patients. Despite
the high sensitivity and specificity of PET, findings which do not fit clinical context or expectations should be investigated further (Fig. 1).

Despite some limitations in the detection of microscopic disease, PET remains an important supplement to mediastinoscopy. Limitations to mediastinoscopy include variation in the number of nodes sampled by individual surgeons as well as access only to a limited number of mediastinal nodal stations. This is illustrated in a Danish randomized trial of 189 patients to mediastinoscopy with or without preceding PET/CT. The accuracy of nodal staging was improved from 85% to 95% with the addition of PET/CT.

For locally advanced NSCLC patients treated with chemoradiation, as well as stage I medically inoperable NSCLC, mediastinoscopy has not been part of the standard staging with target volumes primarily based on CT, PET, and clinical judgment. The accuracy of staging in this population has been less well studied, with no large cooperative group trials, and is inherently more challenging because of the absence of pathologic confirmation accompanying resection in surgical series. Data assessing the accuracy of staging for nonsurgical patients is therefore based primarily on outcomes, that is, patterns of failure.

The overall limited prognosis of many of these patients, due to comorbidities in the medically inoperable stage I population, and progressive disease in the locally advanced chemoradiation population, makes accurate assessment of staging difficult in these settings. Preradiation PET staging alone appears to be justified in stage I NSCLC because isolated nodal failure is less than 5% despite treatment to the primary site alone.

In the locally advanced population, precise staging of the mediastinum has been historically less important because of the widespread use of comprehensive elective nodal radiation. However, mediastinal staging is becoming a topic of greater interest, with modernly tailored fields and selective dose escalation. This trend is discussed in greater detail in the section on treatment planning. The difference between PET and mediastinoscopy staging is important to consider when comparing outcomes of surgical and nonoperative series.

**Distant Staging**

In addition to improvements in mediastinal nodal staging, PET has substantial impact on treatment choices by improving systemic staging. In the ACOSOG Z0050 trial, 6.3% of patients were

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**Fig. 1.** A 84 year old male with biopsy proven left upper lobe adenocarcinoma with SUV 9.1 (A). PET shows increased uptake throughout mediastinum (B, C), and bilateral hilum (C) with SUV at all stations between 4.5 and 6.1, highest uptake in R10. Because of clinically unusual picture of small primary with diffuse mediastinal and even contralateral hilar uptake pathological verification was sought by endobronchial ultrasound guided sampling revealing benign lymphatic tissue and calcified granulomas at all stations. Patient was treated with stereotactic radiation to left upper lobe primary for presumed stage IB NSCLC (48 Gy in 4 fractions) and is disease free at 18 months. While PET SUV >5 is highly specific clinically atypical results should be verified pathologically.
found to have extracranial distant metastasis not seen on previous CT staging at the time of PET scan. A meta-analysis of more than 1000 patients suggested a sensitivity of 94% and specificity of 97% in the detection of distant metastasis. Overall there was a 12% rate of detection of distant metastasis, and a change in the therapeutic plan for 18% of patients (in some cases CT-diagnosed metastasis were excluded) through the use of PET rather than conventional imaging. PET is excellent at detecting metastasis in otherwise normal-appearing soft tissue (liver, adrenals, omentum, and upper abdominal nodes) as well as in the evaluation of otherwise benign enlargements such as adrenal adenomas and bone islands (Fig. 2). The detection of metastasis also increases with increasing stage. MacManus and colleagues found a 7.5% incidence of metastasis in stage I NSCLC, increasing to 18% in stage II and 24% in stage III. As PET is poor at detecting brain metastasis because of high background metabolism in the gray matter, dedicated brain imaging (contrast-enhanced CT or magnetic resonance imaging (MRI)) is recommended as a supplement to PET by National Comprehensive Cancer Center guidelines for asymptomatic stage II and higher NSCLC, and is optional for patients with asymptomatic stage I disease (recommended for all patients with central nervous system symptoms). PET is also more accurate than bone scintigraphy in evaluation for bone marrow metastasis. The only setting where bone scintigraphy may be preferred (in combination with serum alkaline phosphatase) is in previously established stage IV disease where PET is not otherwise needed and bone scintigraphy may be more cost effective. The same seems to be true for SCLC, where PET appears to be equally accurate as CT plus bone scintigraphy and bone marrow analysis, though with more limited data.

In summary, FDG-PET is recommended for the staging of all patients with a new diagnosis of lung cancer, and has been shown to be cost effective because of its ability to more appropriately select therapeutic choices, which is particularly true in the age of dose-escalated radiotherapy with elimination of elective nodal radiation. This aspect will increase the importance of the staging PET scan, discussed in greater detail below. For patients under evaluation for surgical therapy, mediastinoscopy should supplement PET findings prior to thoracotomy, as microscopic nodal metastasis may be missed by PET in 10% to 40% of cases.

PROGNOSIS

In a systematic review of 13 studies comprising 1474 patients with NSCLC, increasing maximum SUV on FDG-PET was found to be prognostic as a continuous variable for lower overall survival, though no clear cutoff was identified. This result has been confirmed individually in patients undergoing surgical resection for a range of NSCLCs, stage I NSCLC, and chemoradiation for locally advanced NSCLC. Of note, the only two studies looking at stereotactic radiation for stage I NSCLC did not find a correlation between maximum pretreatment SUV and local control, distant failure, or overall survival. A third study including a large number of stage I NSCLC patients was also inconclusive. The critical unanswered question is whether the mechanism for the relationship of maximal pretreatment SUV to affect overall survival is through the inability to control local disease, or rather a higher potential for distant metastasis (or perhaps both). Insight into this would...
allow for appropriate escalation of therapy, with either additional local therapy or the addition of systemic therapies in appropriately selected patients.

One major limiting confounding factor in answering this question is that because of respiratory motion and other measurement factors, larger tumors will have higher maximum SUV values than similarly active smaller tumors. Tumor size is a known risk factor for both nodal and distant metastasis, and this association between size and SUV may not always be controlled for adequately. For example, in the analysis by Ikushima and colleagues from M.D. Anderson, tumor SUV strongly predicted for local control, distant metastasis, and overall survival in a series of 149 patients with locally advanced NSCLC treated with chemoradiation. When tumor size alone was corrected, this association weakened substantially. On multivariate analysis of patients receiving integrated PET/CT, SUV was not significant for any outcome measure.

The lack of correlation of pretreatment tumor SUV to outcomes after stereotactic radiation is also of interest given its frequent correlation for other treatment modalities; this may simply be due to limited numbers of patients and follow-up in this series. Other potential explanations include the possibility that the extremely dose-escalated treatment overcomes radioresistance. In addition, perhaps the inclusion of low-grade, poorly marginated tumors (which may be more challenging to target), particularly in series including patients without biopsy confirmation, introduces the possibility of bimodal distribution of SUV-related outcomes.

Overall it is well established that, in general, tumors with high pretreatment maximum SUV on FDG-PET have inferior prognosis; however, the mechanisms for this are not well established, and there may be differences among disease stages and treatment modalities.

**TREATMENT PLANNING**

FDG-PET imaging has significant implications for treatment volumes, particularly in the setting of locally advanced NSCLC. The impact of improved disease targeting should continue to increase in the newer era of dose-escalated, image-guided radiation to smaller, more precise treatment fields, as this will emphasize the importance of accuracy in field design.

For medically inoperable stage I NSCLC, PET will rarely change treatment fields, outside of the impact on initial staging, as most lesions are well defined given the clear boundary between an isolated pulmonary nodule and surrounding air. Aside from occasional demonstration of clear invasion into the mediastinum, the boundary between tumor and either mediastinum or chest wall is typically more clearly seen on CT or MR imaging. The primary role of PET in delineation of target volumes for stage I NSCLC is in the differentiation of tumor from occasional downstream atelectasis, particularly with larger lesions.

Medically inoperable stage II NSCLC is a relatively uncommon and poorly defined entity. As such, a standard of care does not truly exist and the concept of elective nodal radiation is poorly defined in this context. The primary lesion and ipsilatera lateral hilar nodal regions clearly will be targeted. The use of at least some elective mediastinal nodal radiation is relatively common, given the association of PET-positive hilar nodes to mediastinal micrometastasis. Other previously identified risk factors are tumor size larger than 3 cm, upper or middle lobe tumors, central tumors, primary tumor SUV greater than 4, and adenocarcinoma histology. The final decision on field size and mediastinal radiation in these patients is frequently a compromise, weighing the risk factors for mediastinal disease against the patient’s overall performance as well as medical comorbidities that prohibited surgery in the first place. Consideration should be given to mediastinoscopy or endobronchial ultrasound sampling in appropriate patients.

In stage III NSCLC, evidence for improved overall survival with dose escalation is mounting. An analysis of data from 7 randomized Radiation Therapy Oncology Group (RTOG) trials demonstrated total radiation dose to be strongly correlated with both local control and overall survival. Each 1-Gy increase in biological equivalent dose was associated with a 4% relative improvement in survival and 3% improvement in local control. Furthermore, a randomized Chinese trial of standard dose radiation with elective nodal coverage versus escalated radiation dose to involved disease alone demonstrated an improvement in 2-year overall survival from 26% to 39% in favor of escalated dose to the involved target volume only. At the same time, toxicity-related breaks in treatment have been shown to have a deleterious effect on survival. As clinical recurrence in areas of omitted elective nodal radiation has been documented to be rare, there is a strong movement to dose-escalated radiation to involved nodes only, with consideration of elective coverage only to the highest risk mediastinal nodes, to maximize dose while minimizing toxicity. PET is thus a critical tool in identification of the true involved target volume, and has been demonstrated to affect treatment volumes in many stage III patients, changing the electively targeted volume from CT alone along
with the corresponding volume of normal lung and esophagus irradiated in the majority of patients (Fig. 3). RTOG 0515, a recent prospective multicenter cooperative group phase 2 trial, demonstrated a 10% reduction in treatment volumes when adding PET information to CT contours with a corresponding trend to decrease in median lung dose, without significant change in the number of involved nodes or median esophageal dose. Only one patient (2%) had developed an out-of-field elective nodal failure with 12.9-month median follow-up.

PET-guided selective nodal radiation with consideration of escalation of radiation dose is the current standard of care for locally advanced NSCLC based on the aforementioned results.

ADAPTIVE TREATMENT

The concept of adaptive replanning during treatment to adjust for changes in tumor size is most common in head and neck cancer. This concept has gained popularity for this site for two reasons: the observed rapid treatment response of some large neck lymph nodes involved with squamous cell carcinoma; and the resultant change in dosimetry to both normal structures and tumor, due to treatment to a small area of the body with changing surface dimensions and close association of critical tissue. The importance of this concept may be slightly less in lung cancer because of the far lesser extent of changes in surface anatomy during therapy. Nevertheless, with local control rates not much more than 50% even with dose-escalated therapy, there may be room for further escalation and volume reduction. Two studies of volume changes with mid-treatment PET scan after 5 to 6 weeks of radiation, with the goal of reduced volume high-dose boost, have demonstrated modest reductions in full-dose radiation target volume by 20% to 44%, though the expected benefit in normal tissue complications averaged only 2%. This is a novel and interesting concept, which at this point remains experimental and requires further study.

RESPONSE ASSESSMENT

The significance of posttreatment imaging changes in NSCLC can be extremely complicated because of the common presence of postradiation fibrosis, atelectasis, and inflammatory changes during the standard follow-up interval. Furthermore, the modest rate of local control, even with modern dose-escalated radiation, provides rationale for consideration of further intensification of therapy if local failure, or at least poor response, can be identified early (Fig. 4). This concept has led to interest in the role of PET in response assessment. A prospective Australian study by MacManus and colleagues suggested a much more powerful correlation of outcome to PET metabolic response versus CT response. At a median of 70 days post treatment 2-year overall survivals of 61%, 34%,

Fig. 3. A 58 year old male with stage IIIa squamous cell carcinoma with mediastinoscopy positive level 7 and 4L nodes. Treated with definitive chemotherapy and radiation to 70 Gy with weekly carboplatin and paclitaxel followed by consolidation chemotherapy. PET scan was critical in defining target volume for high-dose radiation given surrounding lung collapse. Internal target volume in yellow created from PET + 4D CT scan then expanded to planning target volume (not shown).
20%, and 18% were noted respectively for patients with a metabolic complete response, versus partial response, stable disease, or progressive disease. Furthermore, metabolic complete response was much more common than CT complete response (47% vs 14%), with poor concordance between PET and CT responses. Inflammatory changes were also noted in normal tissue, and appeared to correlate positively with the degree of metabolic tumor response, suggesting linkage between normal tissue radiosensitivity and tumor response. Rosenzweig and colleagues likewise demonstrated improvement in local control of 83% compared with 23% for patients with 4-month postradiation tumor SUV of less than 3.5 versus SUV greater than 3.5. Decreases in maximum SUV during and just after treatment have also been shown to correlate with improved survival for both induction chemotherapy and chemoradiation. A large prospective multi-institutional trial of PET response to chemoradiation (ACRIN 6668/RTOG 0235) has recently been completed, with results pending. These data will help further establish the role of PET in the early postradiation response assessment, and likely will serve as a springboard for further attempts to improve outcome.

Although the field of stereotactic radiation (SBRT) for NSCLC is relatively new, early data are available regarding PET response to treatment. These data are of increased interest to SBRT given the high incidence of postradiation inflammatory changes, which can be very intense, prolonged, and easily mistaken for tumor progression. As part of a prospective pilot study, 14 patients treated to 60 Gy in 3 fractions underwent repeat PET at 2, 26, and 52 weeks after SBRT. While maximum SUVs generally decreased over time, the median was higher at 52 weeks than at 26 weeks. Six patients with maximum SUV remaining above 3.5 had no evidence of local progression with further follow-up (the only patient...

Fig. 4. A 78 year old male with stage IIIB NSCLC of the right upper lobe s/p combined chemoRT (A). 20 months post treatment possible enlargement in post-treatment effect on CT noted, PET verified increased metabolic activity and biopsy demonstrated recurrent NSCLC without evidence of distant metastasis. Treated with salvage stereotactic radiation to 50 Gy in 5 fractions after creating ITV from PET and 4DCT which was expanded by 5 mm to create PTV in blue (B). Stereotactic treatment plan, ITV in purple, PTV in blue, dose as per table (C).
with a persistently rising SUV had repeat biopsy negative for disease, but died shortly thereafter of infection, limiting further follow-up data. A similar study from Georgetown evaluating 20 patients demonstrated some mild individual elevations in maximum SUV, though the average decreased from 6.2 to 2.3. At 18 to 24 months, however, controlled tumors showed a narrow range of SUVs (1.5 to 2.8), whereas a single confirmed local failure exhibited an SUV of 8.4. Additional data will be derived from RTOG 0618, which is a prospective multi-institutional trial of stereotactic body radiation therapy (SBRT) in medically operable patients and includes post-treatment PET evaluation for identification of patients for surgical salvage. Further investigation is needed, although early results suggest occasional early reactive increase in SUV but long-term declines in controlled patients. Thus any patient with a persistently elevated or increasing SUV should be evaluated and given the potential for salvage therapy. Elevated SUV alone, however, should not be automatically assumed to represent recurrence/progression, and repeat biopsy is strongly recommended. Assessment of post-SBRT PET response will gain increasing importance as a trigger for biopsy and/or surgical salvage with increasing use of SBRT in medically operable early-stage NSCLC.

NOVEL DIRECTIONS

FDG-PET is well established. However, a host of other PET radiotracers that are analogues to thymidine, methionine, choline, annexin V, as well as proliferative and hypoxic markers, plus a variety of other cellular activity markers are under further investigation. These agents may help clarify the biological blueprint of tumors to identify prognosis, give insight into tumor histology, predict toxicity and, more significantly, lead to novel methods of treatment selection and targeted therapies. Along with mapping of tumor DNA and protein, as well as MR spectroscopy, novel PET analogues represent the horizon of individualized tumor therapy, though substantial prospective assessment is required before the clinical impact can be confirmed and realized.

SUMMARY

PET is central to the diagnosis and staging of lung cancer. The transition to dose-escalate radiation with increasingly selective nodal radiation has made the accurate characterization of nodal status critical to successful treatment. Although mediastinoscopy increases the detection of microscopic nodal metastasis to a greater extent than PET alone, treatment failure in omitted elective nodal areas is rare with PET-guided modern chemoradiation. New horizons for PET scanning include the ability to potentially allow for early detection of salvageable poor treatment responses or local recurrence, as well as to improve the molecular blueprint of tumors with novel tracers to assist with treatment selection and delivery of targeted therapy. The role of PET imaging in the management of lung cancer is likely to continue to increase in the future.

REFERENCES


