

The Use and Misuse of Positron Emission Tomography in Lung Cancer Evaluation

Ching-Fei Chang, MD^a, Afshin Rashtian, MD^b,
Michael K. Gould, MD, MS^{a,c,*}

KEYWORDS

- Non–small-cell lung cancer • Positron emission tomography
- Pulmonary nodules • Mediastinum staging

Positron emission tomography (PET) has been studied for a variety of indications in patients with known or suspected non–small-cell lung cancer (NSCLC). This article discusses the potential benefits and limitations of PET for characterizing lung nodules, staging the mediastinum, identifying occult distant metastasis, determining prognosis and treatment response, guiding plans for radiation therapy, restaging during and after treatment, and selecting targets for tissue sampling (**Table 1**). Evidence from randomized, controlled trials supports the use of PET for initial staging in NSCLC, whereas lower quality evidence from studies of diagnostic accuracy and modeling studies supports the use of PET for characterizing lung nodules. For most other indications in NSCLC, additional studies are required to clarify the role of PET and determine who is most likely to benefit.

In many ways, the history of PET in lung cancer echoes the angst, introspection, and torment of Shakespeare's Hamlet, Prince of Denmark. Although the question "to PET or not to PET?" has been debated extensively, the more pressing concern is how to interpret PET results correctly in light of its performance in various situations.

To the uninitiated, a positive PET scan equals malignancy, and a negative PET scan rules it out, either in regard to the character of the primary lesion or the presence of mediastinal or distant metastasis—but these interpretations are often mistaken. Much like a Shakespearean play, the story of PET is complicated and multilayered, riddled with skeptics and converts, controversial and conflicting data, and shifting realities in which the hero morphs into a villain depending on the circumstances. Therefore, the real question faced by clinicians today is how to interpret the results and avoid misusing them to pursue or withhold potentially curative surgery. As Hamlet would have wisely advised us, "There is nothing either good or bad, but thinking makes it so."

This article presents the key findings from the medical literature regarding the capabilities and fallibilities of PET in lung cancer evaluation, including (but not limited to) characterization of pulmonary nodules and staging in patients with known or suspected NSCLC. The discussion is limited to PET imaging with fluorodeoxyglucose (FDG), recognizing that there is great interest in developing novel tracers for metabolic imaging.

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^a Department of Medicine, Division of Pulmonary and Critical Care Medicine, Keck School of Medicine of USC, 2020 Zonal Avenue, IRD Room 723, Los Angeles, CA 90033, USA

^b Department of Radiation Oncology, Keck School of Medicine of USC, Health Sciences Campus, Los Angeles, CA 90089, USA

^c Department of Research and Evaluation, Kaiser Permanente Southern California, 100 South, Los Robles, Pasadena, CA 91101, USA

* Corresponding author.

E-mail address: michael.k.gould@kp.org

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Table 1
Potential uses of PET imaging in lung cancer

CT Scan Finding:	How Pet May Be Helpful:
Clinical Stage IA (indeterminate pulmonary nodule):	<ol style="list-style-type: none"> 1. Help characterize the nodule as benign or malignant (although a negative result may still require histologic confirmation unless the pretest probability for malignancy is low and active surveillance is acceptable) 2. Help rule out occult metastases to the mediastinum or extrathoracic sites, which may change plans from curative to palliative care 3. Help determine prognosis based on SUV intensity of the primary lesion and identify patients with more aggressive cell behavior who may benefit from adjuvant therapy after curative resection
Clinical Stage IB-IIB:	<ol style="list-style-type: none"> 1. Help downstage or upstage the patient so that more accurate staging can lead to more appropriate care 2. Help assess early response to adjuvant therapy (after first cycle) so that second line or salvage therapy can be offered early without further waste of time, expense, and unnecessary toxicity
Clinical Stage IIIA-IIIIB:	<ol style="list-style-type: none"> 1. Help downstage or upstage the patient so that more accurate staging can lead to more appropriate care 2. Help assess response to induction chemotherapy (if surgical candidate) without the need and risk of re-mediastinoscopy to restage before curative resection 3. Help assess early response to definitive chemo/XRT (if nonsurgical candidate) so that the treatment plan can be changed without waste of time or unnecessary toxicity to the patient 4. Help tailor radiation therapy to provide maximum effect while minimizing toxicity to normal structures
Clinical Stage IV:	<ol style="list-style-type: none"> 1. Potentially downstage the patient if contradictory data are found between CT and PET and a biopsy confirms benign pathologic condition at the M1 site.

The authors hope that the reader will carry away practical learning points that will positively affect their care of lung cancer patients in the future. The approach is skeptical as well as cautiously optimistic. As Shakespeare once said, "Modest doubt is the beacon of the wise," and this should guide the savvy PET-utilizing clinician.

INDICATIONS

In theory, PET can be useful in the evaluation of known or suspected lung cancer in several ways. The three most common indications for PET in lung cancer include

- Characterization of pulmonary nodules
- Staging the mediastinum and identification of occult distant metastasis
- Monitoring for recurrence after completion of treatment.

Over the last decade, there has been a surge of interest in PET scanning for novel indications, including

- Characterization of screening-detected lung nodules

- Assessing response to therapy early during the course of chemoradiation, so that ineffective and potentially toxic regimens can be modified
- Improving prognostication
- Identifying patients with resected NSCLC who are most likely to develop recurrence without additional therapy
- Restaging the mediastinum after neoadjuvant chemoradiation in patients with stage IIIA-N2 disease, to identify candidates who might benefit from surgery
- Confirming and restaging patients with suspected relapse so that aggressive salvage therapy can be planned
- Clarifying the boundaries between tumor and adjacent confounding processes (atelectasis, fibrosis, or postobstructive pneumonia) so that radiation therapy can be more precisely tailored and damage to surrounding structures can be minimized
- Providing a roadmap for high-yield biopsies in the mediastinum by endobronchial ultrasound (EBUS), endoscopic ultrasound (EUS), or mediastinoscopy to expedite staging.

Potentially, the role of PET in NSCLC spans the entire time from diagnosis to death. However, the high cost of PET suggests that its use should be limited to situations in which it is most likely to lead to improved outcomes. In some cases, use of PET may be particularly cost effective, especially if the information provided prevents patients from undergoing unnecessary mediastinoscopy or thoracotomy.¹⁻³ These indications are examined in turn.

HOW PET WORKS

PET is a functional imaging test that detects hypermetabolism in cells as a proxy for the presence of cancer. The tracer 18-FDG is a radio-labeled glucose analog that is selectively taken up by and then accumulates in metabolically active cells because it cannot pass through the complete glycolytic cycle. The trapped 18-fluorine isotope undergoes radioactive decay by releasing a positron, which subsequently collides with an electron to produce two high-energy photons in a so-called annihilation reaction. The photons travel in opposite directions and are detected by a ring scanner and registered when there is coincident detection of counts separated by 180 degrees. The resulting coincidence counts are processed by a computer for display. Modern PET scanners are typically mounted on a single gantry alongside a separate CT scanner, allowing for integration of functional data from PET with more precise anatomic information from CT.

The limitations of FDG-PET imaging primarily stem from the use of hypermetabolism as a proxy for the presence of cancer, although technical factors also play a role. Essentially, PET will miss slow-growing, relatively indolent cancers, and conversely it will detect many nonmalignant active infectious and noninfectious processes that involve recruitment of metabolically active inflammatory cells.

CHARACTERIZATION OF PULMONARY NODULES

Classically, the solitary pulmonary nodule is a well-circumscribed radiographic opacity that measures up to 3 cm in diameter in the lung periphery, without associated lymphadenopathy, atelectasis, or effusion.⁴ The prevalence of malignancy varies widely, depending on the characteristics of the study sample. Before widespread availability of CT scans and PET, surgical resection was (and in some cases remains) the gold standard approach for simultaneous diagnosis and treatment.^{5,6} These days, most nodules are incidentally

detected by CT. In contrast to years past, nodules encountered today are smaller and few are solitary findings.^{7,8} The availability of CT scans, PET, and an expanding menu of nonsurgical biopsy approaches improves the ability to discriminate between patients with benign and malignant nodules, enabling more selective use of surgery in patients with nodules that are most likely to be malignant.

Numerous studies have examined the accuracy of FDG-PET for characterization of focal pulmonary lesions and these studies have been summarized in multiple systematic reviews. In one such review of 40 studies of diagnostic accuracy, the pooled sensitivity and specificity of PET for identifying malignancy in focal pulmonary lesions of any size were 96.8% and 77.8%, respectively. The corresponding likelihood ratios were 4.4 for a positive PET result, and 0.04 for a negative result, suggesting that PET is more useful for excluding than confirming malignancy.⁹ Diagnostic accuracy was similar when the analysis was limited to pulmonary nodules. In a subsequent review of seven prospective studies of diagnostic accuracy, sensitivity ranged from 79% to 100%, and specificity ranged from 40% to 90%, with variability in the latter stemming from study group differences in the prevalence of granulomatous disease, ground glass lesions, and nodules that measured less than 1 cm in diameter.³ Another meta-analysis of 44 studies compared PET, CT, MRI, and single-photon emission computed tomography (SPECT) for identifying malignant lung nodules and found that diagnostic accuracy was similar for PET and SPECT,¹⁰ with likelihood ratios of 5.4 and 0.06 for positive and negative findings, respectively. A prospective study of 344 veterans with newly identified lung nodules reported similar findings.¹¹ For the first time, this study confirmed that accuracy depended on the degree of FDG uptake, with likelihood ratios ranging from 0.03 for “definitely benign results” to 9.9 for “definitely malignant results,” whereas the likelihood ratios were less definitive for “probably benign” (LR 0.15) and “probably malignant” (LR 3.2) results.

Studies of diagnostic accuracy may not capture all of the potential benefits of PET. First, even a false-positive PET result may have some value by alerting the clinician to another active process that requires additional investigation and treatment (eg, endemic mycoses, sarcoidosis). Second, there is some evidence that prognosis is relatively good in patients with false-negative PET results (ie, those with malignant nodules that are minimally or not hypermetabolic), even when surgery is delayed. For example, in one retrospective review of 192 patients with T1N0M0 (stage IA)

lung cancer, prognosis was excellent among nine patients with non-hypermetabolic nodules, despite a mean delay of 27 months (range 3–120 months) until surgery.¹² However, these results were not confirmed in a post hoc analysis of data from a prospective study of diagnostic accuracy.¹³ In this study, 204 patients had malignant nodules, including 10 patients with nodules that were non-hypermetabolic by PET. Differences in 2-year survival between those with hypermetabolic nodules (67%) and those with non-hypermetabolic nodules (80%) were neither confirmed nor excluded (relative risk 0.84, 95% CI 0.61–1.16).

Some proponents argue that PET may also help to identify occult metastasis in patients with nodules that are known or strongly suspected to be malignant, which may be seen in up to 6.3% of patients with clinical stage I tumors.¹⁴ However, the 40% relapse rate in clinical stage I patients who undergo curative resection suggests that the reservoir of occult disease is even deeper, and that the negative predictive value of PET in these patients is limited.

Of note, no randomized, controlled trials have compared strategies for pulmonary nodule management with and without PET. However, several modeling studies have examined the cost-effectiveness of PET for lung nodule management. Two of these studies found that nonselective use of PET was cost-effective^{15,16} while another demonstrated that PET-based strategies were most effective when the pretest probability of malignancy was low to moderate ($\leq 50\%$).¹⁷

In summary, relatively low quality evidence, primarily from studies of diagnostic accuracy, supports using PET in many patients with lung nodules, and PET appears to be most useful (and most cost-effective) for identifying patients with non-hypermetabolic nodules who can be safely managed by active surveillance. However, there are several situations in which PET imaging is probably not indicated, including (1) patients with symptoms, signs, or imaging characteristics that suggest infection; (2) patients with larger (>3 cm) pulmonary mass lesions (of which 90% are malignant); (3) patients with small pulmonary nodules that measure less than 7 to 8 mm in diameter; (4) patients with nodular ground glass opacities; and (5) patients who are not candidates for curative treatment.

CHARACTERIZATION OF SCREENING-DETECTED NODULES

Preliminary results from the National Lung Screening Trial suggest that CT screening may be associated with a 20% reduction in lung

cancer-specific mortality (Data Safety and Monitoring Board Statement Concerning the National Lung Screening Trial, October 28, 2010). If so, there will almost certainly be an explosion in the use of chest CT scans and a corresponding increase in the number of CT-detected pulmonary nodules, especially considering that roughly 25% to 50% of participants in uncontrolled trials of CT screening had one or more nodules detected on the baseline (prevalence) examination and data from the Lung Screening Study indicates that the cumulative probability of false-positive findings is 33% after two rounds of CT screening.^{6,18,19} Given the large numbers of nodules detected by screening and the relatively low prevalence of malignancy in such nodules, the need for an accurate, noninvasive test to distinguish malignant from benign nodules is now even more relevant. Unfortunately, the imperfect ability of PET to characterize subcentimeter nodules potentially limits its utility for this indication.

However, in a recent study of 54 nodules detected by screening as part of the Danish Lung Cancer Screening Trial, the sensitivity and specificity of PET for identifying malignancy were 71% and 91%, respectively.²⁰ In this study, the prevalence of malignancy was 37%, and the mean was 13 mm, but separate results for patients with subcentimeter nodules were not provided. Nevertheless, this study suggests that PET may be helpful for characterizing screening-detected nodules, especially those measuring at least 7 to 8 mm in diameter.

INITIAL STAGING

Although many published studies of diagnostic accuracy have important limitations (eg, small samples, incomplete blinding, suboptimal reference standards), available data strongly suggest that PET is more sensitive than CT scanning for identifying mediastinal lymph node involvement in patients with known or suspected NSCLC. A systematic review and meta-analysis of 44 studies of diagnostic accuracy reported that the sensitivity and specificity of PET for this indication were 74% and 85%, respectively.^{21,22} In the same review, CT scanning was noted to have similar specificity (86%) but substantially lower sensitivity (51%). Another meta-analysis demonstrated that the accuracy of PET depended on the CT findings in that PET results were more likely to be positive (either true-positive or false-positive) when lymph nodes were enlarged, and more likely to be negative (either true-negative or false-negative) when there was no lymph node enlargement.²³ Thus, PET seems to be less sensitive for identifying

metastasis when lymph nodes are not enlarged and less specific when there is lymph node enlargement. The imperfect specificity of PET (especially in patients with enlarged lymph nodes) mandates confirmatory tissue sampling unless there is overwhelming evidence of tumor involvement with bulky, multistation adenopathy.

The availability of mediastinoscopy and newer, nonsurgical methods to sample mediastinal lymph nodes raises the question of if and when PET should be used for mediastinal staging. Indeed, there is a strong case to be made that enlarged nodes on CT should be sampled by invasive methods regardless of the PET results. If so, PET might still be indicated to identify occult distant metastasis, but this is controversial. One prospective study reported that the sensitivity and specificity of PET for identifying extrathoracic metastasis were 82% and 93%, respectively.²⁴ In light of these findings, proponents argue that the prevalence of occult extrathoracic metastasis is high in patients with clinical stage III disease by CT criteria, and that PET is reasonably sensitive for identifying these lesions. Others argue that the negative predictive value of a routine clinical evaluation is sufficiently high to obviate further testing.²⁵ However, there is little disagreement that, because of the test's imperfect specificity, positive extrathoracic findings on PET must be confirmed pathologically unless there is overwhelming evidence of metastasis, as is true in the mediastinum.

There is also disagreement about whether to use PET and/or invasive mediastinal staging in patients with no evidence of lymph node enlargement on CT. Although a full discussion of this debate is beyond the scope of this article, the authors believe that use of PET is reasonable in selected high-risk patients, including patients with primary tumors that are large, centrally-located, or adenocarcinoma by histology, as well as patients with hilar nodal enlargement.^{26,27} However, because these are situations in which the likelihood of malignant mediastinal lymph node involvement is actually increased, many would argue that tissue sampling is mandatory in these patients and that PET is, therefore, superfluous except for the potential to more specifically direct mediastinal biopsies or evaluate for distant metastasis. Of note, EUS may be the preferred approach to identify occult involvement of posterior mediastinal nodes in patients with upper lobe primary tumors.^{28,29}

Part of the reason for PET's limited sensitivity in the mediastinum may be related to micrometastatic foci in normal-sized lymph nodes. Nomori and colleagues³⁰ reported that PET loses its resolution for metastatic foci below 4 mm within

mediastinal lymph nodes. Another group confirmed that the size of the lymph node affects PET sensitivity for malignancy: when the nodes were less than 1 cm, the sensitivity was a dismal 32.4%, but if the nodes were greater than 1 cm, the sensitivity jumped to 85.3%.³¹ Of note, the prognostic significance of occult nodal micrometastasis is uncertain. It is also not clear whether preoperative detection (presumably followed by combined modality therapy) results in better outcomes in these patients, who would otherwise be treated with surgery followed by adjuvant chemotherapy.

Complementary to studies of diagnostic accuracy, several studies have demonstrated that use of PET often results in upstaging or downstaging, relative to CT or conventional staging. In one such prospective study of 105 consecutive patients with NSCLC who were referred for PET imaging (including only 59 patients who were referred for initial staging), PET altered management in 67% of participants by either upstaging to palliative care, downstaging to allow for potentially curative therapy, or changing radiation therapy plans.³² The very high percentage of altered management observed in this study can probably be attributed to selection bias, at least in part. In another study of 153 consecutive patients with newly diagnosed NSCLC from the same group of Australian investigators, 33% of patients were upstaged by PET, 10% were downstaged, and management plans were meaningfully changed in 35%.³³

The highest quality evidence regarding the use of PET for initial staging comes from randomized, controlled trials. No fewer than five randomized trials have examined PET for staging in NSCLC. A European multicenter trial compared conventional staging with conventional staging plus PET in 188 patients with known or suspected NSCLC that was potentially resectable. The primary outcome was the number of futile thoracotomies, defined as surgery for a benign lesion, intraoperative detection of N2, N3, or other stage IIIB disease; exploratory thoracotomy for some other reason; or tumor recurrence or death within 1 year. Similar numbers of patients in both groups underwent nonfutile thoracotomies, although the risk of futile thoracotomy was reduced from 41% in the conventional staging group to 21% in the PET group.¹

These results were subsequently confirmed in two later studies, including a Danish study of 189 patients with NSCLC referred for preoperative staging, 60% of whom had clinical stage III disease. Compared with patients who underwent conventional staging, the risk of futile thoracotomy

was reduced from 52% to 35% in those assigned to staging with integrated PET-CT.³⁴ Another trial performed in Canada enrolled 337 patients with potentially resectable, stage I-III NSCLC and randomized participants to staging with integrated PET-CT or CT plus bone scan. In this study, PET-CT resulted in correct upstaging in 14% of participants, compared with 7% in the CT plus bone scan group, for an absolute reduction of 7% in the risk of unnecessary surgery.³⁵

Two other trials reported less impressive results. In an Australian study of 184 patients with clinical stage I-II NSCLC who were randomized preoperatively to PET or no PET, 16% of patients in the PET group were either upstaged (8%) or downstaged (8%), but few thoracotomies were avoided in either group (4% vs 2%).³⁶ In another multicenter study, from the Netherlands, that compared “up-front” PET with conventional staging in 465 patients with a provisional diagnosis of lung cancer and no overt dissemination, there were fewer mediastinoscopies in the PET group, but the number of staging procedures was similar in the two groups.³⁷

Some have also questioned the validity of recurrence or death within 1 year of surgery as an appropriate outcome in two of the three positive trials. If PET did not detect occult regional or distant metastatic disease in these patients, how can it be responsible for preventing recurrence or death? In addition, none of the studies reported improvements in survival or lung cancer mortality. Thus, the link between more accurate staging and survival has yet to be proved, and probably awaits the development of more effective stage-specific treatments.

Several studies have examined the cost effectiveness of PET for staging in NSCLC. One early study compared conventional staging with CT and mediastinoscopy to conventional staging plus PET and found that PET-based staging reduced costs by \$1154 per patient and increased life expectancy by 3 days.³⁸ Another analysis reported that compared with CT followed by selective mediastinoscopy, a strategy of CT followed by mediastinoscopy (when CT showed enlarged lymph nodes) or PET (when there were no enlarged lymph nodes) cost approximately \$25,000 per life-year gained.³⁹ Another modeling study compared mediastinoscopy alone with PET followed by selective mediastinoscopy and found that for every 100 patients treated, PET plus selective mediastinoscopy resulted in seven fewer futile thoracotomies and saved \$212,800 Australian dollars.⁴⁰ An economic evaluation of data from a randomized, controlled trial of conventional staging versus conventional staging plus PET

reported that PET-based staging was less expensive by approximately €1,300.² However, a cost-minimization study that compared five approaches among patients with enlarged nodes on CT found that PET followed by selective mediastinoscopy was preferred only when the probability of lymph node metastasis was less than 25%. At higher probabilities, EUS-guided fine-needle aspiration (EUS-FNA) followed by negative mediastinoscopy was preferred, provided that the sensitivity of EUS-FNA was at least 75%.⁴¹

In summary, moderate-to-high quality evidence suggests that staging with PET is more accurate than CT, results in substantial upstaging and downstaging, and reduces the risk of futile thoracotomy. However, these benefits have not translated to improvements in survival. Economic evaluations suggest that several different PET-based strategies are either cost-saving or highly cost-effective.

PROGNOSIS

Several studies have confirmed that clinical TNM staging by PET is more strongly associated with prognosis than conventional staging with CT alone.^{33,42} Given that PET is more accurate than CT for initial staging, this should come as no surprise.

Somewhat more controversial is the notion that the degree of FDG uptake in the primary tumor may be independently associated with prognosis. Although intuitively plausible, the correlations between hypermetabolism, growth, metastatic potential, and (ultimately) prognosis might be confounded by other factors, including tumor size and histology. A recent systematic review identified 21 studies that examined the association between primary tumor FDG uptake and survival in patients with NSCLC of any stage, and found that the hazard of death was twice as high when the standardized uptake value (SUV) was above the median value, although the investigators acknowledged that individual patient data would be needed to account for potential confounders.⁴³ Likewise, in another review limited to nine studies of patients with resected stage I NSCLC, higher degrees of FDG uptake in the primary tumor were associated with worse overall or disease-free survival, but differences were statistically significant in only five of the studies.⁴⁴ In a subsequent analysis of data from a prospective study of PET for lung nodule characterization, greater FDG uptake was independently associated with worse prognosis among patients with malignant nodules that were surgically resected, even after adjusting for age, tumor size, histology, and type of resection.⁴⁵

Technical factors may explain differences in study results, at least in part. Published studies of prognosis used heterogeneous methods to perform examinations and measure FDG uptake. Standardization of protocols for acquisition and interpretation of PET images would greatly enhance both the validity and applicability of any results generated from future studies.^{43,46,47}

PREDICTING TREATMENT RESPONSE

Although accurate prognostication is undeniably important to patients, predicting response to treatment is potentially even more valuable. Several studies have examined whether evidence of an early response to treatment by PET predicts longer term response. One such study reported that six of seven patients with advanced NSCLC and evidence of partial response on PET after one cycle of chemotherapy had a best overall response that was at least stable. In contrast, best overall response was stable in only 2 of 11 patients with evidence of progressive disease on early PET. In this study, PET response was not associated with survival.⁴⁸ However, a prospective study of 57 patients with advanced NSCLC found that early metabolic response (defined as a reduction in SUV mean of >20% after the first cycle of chemotherapy) was associated with a significantly longer time to disease progression and more frequent survival to 1 year (44% vs 10%).⁴⁹

Other studies have examined the predictive value of PET following definitive treatment. In a study of 73 patients with NSCLC who underwent PET before and after completing radical radiotherapy or chemoradiotherapy, overall PET response was associated with survival before and after adjustment for performance status, stage, weight loss, and CT response.⁵⁰ Another study from the same group demonstrated that patients with a complete metabolic response had a longer median survival and were less subject to local failure and distant metastasis.⁵¹

Still other studies have used PET to assess response to induction chemotherapy before surgical resection. One study examined early response to induction chemotherapy by performing PET before and after chemotherapy cycles 1 and 3 in 47 patients with stage IIIA-N2 NSCLC.⁵² In this study, both PET stage and various measures of FDG uptake were associated with survival. Another study of 56 patients with NSCLC who received neoadjuvant treatment with either chemoradiation or chemotherapy alone before surgical resection found that an 80% reduction in postinduction maximal SUV (SUVmax) was associated with a complete pathologic response.⁵³

However, two other studies of patients with potentially resectable NSCLC who underwent neoadjuvant therapy found no association between FDG uptake and survival.^{54,55}

One possible confounding factor in these studies is the timing of PET, especially in patients treated with radiation, which can be associated with false-positive findings. In a study of 109 patients treated with neoadjuvant chemoradiation, posttreatment PET was most accurate (compared with pathologic staging) in patients who underwent imaging between 21 and 30 days after the last dose of radiation.⁵⁶

RESTAGING IN NSCLC

Because repeat mediastinoscopy is widely considered difficult and relatively low-yield, an accurate and less invasive option for restaging is highly desirable. Although there is great interest in using EBUS-guided and/or EUS-guided biopsy for this purpose,⁵⁷ these techniques are not yet widely available in community settings. The default method of restaging, until now, has always been CT.

At least in theory, PET has additional advantages over CT for restaging after neoadjuvant therapy or in patients with suspected relapse. Especially in cases in which radiation-induced fibrosis and distortion of intrathoracic structures makes assessment of the original target difficult,^{50,58,59} or in cases of molecular targeted therapy in which the anatomic appearance of the tumor may not change at all,⁶⁰ physiologic assessment of disease activity might prove helpful.

Restaging Following Induction Therapy in Patients with Stage IIIA-N2 Disease

In light of accumulating data suggesting improved outcomes with combined multimodality treatment for patients with stage IIIA NSCLC and nonbulky N2 disease,⁶¹⁻⁶³ the accuracy of PET for identifying complete response following neoadjuvant therapy has been examined in several studies and summarized in two systematic reviews.^{64,65} In one review, the sensitivity and specificity of PET for identifying residual N2 disease were only 64% and 85%, respectively,⁶⁴ suggesting that PET may have limited sensitivity for identifying residual disease in these circumstances.

However, another group reported that the accuracy of PET for restaging the mediastinum varied based on the location of involved lymph nodes, with excellent accuracy in anterior mediastinal nodes and relatively poor accuracy in posterior nodal stations.⁶⁶ This may have important implications for restaging in patients with upper lobe tumors,

which often drain and metastasize to posterior nodes. In addition, the magnitude of reductions in FDG uptake following induction therapy may be more predictive than the categorical presence or absence of FDG uptake, for both the primary tumor and the involved lymph nodes. For example, in a prospective study of 93 patients with stage IIIA (N2) NSCLC who underwent pathologic staging following induction chemoradiotherapy, the sensitivity and specificity of an SUVmax greater than 2.5 for identifying residual N2 disease were 80% and 75%, respectively. Reductions in FDG uptake of at least 75% in the primary tumor and at least 50% in the involved lymph nodes were strongly associated with a "complete response" (and thus survival benefit with surgery).⁵⁷

Restaging in Patients with Suspected Recurrence

Among patients who receive curative treatment for NSCLC, follow-up imaging often reveals suspicious nodules or masses in and outside the lung parenchyma. Although the early detection and treatment of relapses is of uncertain value, it seems that PET identifies relapse with a sensitivity and specificity of approximately 90%.^{67,68} As is true for restaging following induction treatment, PET is often able to distinguish recurrent disease in areas of scarring and posttherapeutic change whereas CT cannot. In one study, PET correctly reclassified CT findings of recurrence in 24% of patients, thus sparing them the potential toxicity associated with unnecessary treatment.⁶⁸

RADIOTHERAPY PLANNING

PET has been studied for several indications related to radiation therapy in patients with NSCLC, including selection of candidates for radical radiotherapy, delineation of radiation therapy volume, and determination of treatment response.⁶⁹

Although many studies have examined the accuracy of PET for mediastinal and distant staging, relatively few studies have used PET stage to determine eligibility for curative radiation treatment. In one prospective study of 167 patients with clinical stage I-III NSCLC by CT scanning who were referred for radical radiation therapy, PET identified occult distant metastasis in 32 patients (19%), including 8% of those with stage I disease, 18% of those with stage II disease, and 24% of those with stage III disease by CT.⁷⁰ By upstaging these patients, PET changed the treatment plan from curative to palliative, possibly reducing treatment toxicity.

Accurate delineation of nodal metastasis is crucial for radiotherapy planning. Because the

negative predictive value of PET for lymph node staging is relatively high, radiation therapy can be designed to target positive nodes selectively. An extreme example of this approach was illustrated in a phase I-II trial of selective mediastinal irradiation based on FDG-PET scan results.⁷¹ In this study, the addition of a PET scan changed nodal stage in 11 of the 44 patients, and only one out of 44 patients treated with the selective approach had an isolated nodal failure. In another study, PET led to an increase in planning target volume to incorporate positive nodal disease in 7 of 11 patients (64%), and the average increase was 19%.⁷² In another study of 73 patients with NSCLC and positive lymph nodes on CT and/or PET who had lymph node metastasis confirmed pathologically, tumor coverage would have improved from 75% with CT to 89% if PET had been used.⁷³

In some cases, radiation volumes determined by PET findings are smaller than those determined by CT, thus enabling delivery of lower doses to surrounding structures, such as the esophagus and heart. This enables the radiation oncologist to deliver a higher dose to the tumor without increasing side effects. Whether this will result in higher cure rates is a matter of ongoing research. In a small, theoretical study, PET results would have led to a reduction in the size or a change in shape of the portal in 12 of 34 patients, including eight patients with obstructive atelectasis that was distinguished from malignancy by PET.⁷⁴ In a subsequent prospective study of 24 patients with stages I-III NSCLC who had three-dimensional conformal radiation therapy, the addition of PET reduced gross tumor volume (GTV) in three patients (14%) and increased GTV in 11 patients.⁷⁵ More recently, GTV was modified by at least 25% in 10 of 19 patients who underwent planning with integrated PET-CT.⁷⁶

Another area of interest is to use PET to monitor response and adjust treatment during the course of radiation therapy. In a small prospective study of 14 patients with stage I-III NSCLC who underwent integrated PET-CT before and midway through radiotherapy, the mean decrease in PET tumor volume was 44%, compared with 26% by CT.⁷⁷ This allowed for meaningful dose escalation and a reduction in the probability of complications. However, another similar study reported only modest dose escalation despite evidence of tumor shrinkage on integrated PET-CT.⁷⁸

As outlined above, PET appears to have a role in designing the radiation field for the mediastinum, as well as distinguishing atelectasis from tumor at the primary site. However, most of the supporting studies were small and uncontrolled. In addition,

PET-defined radiotherapy fields can represent false-positive findings in up to 39% of patients.^{79,80} Thus, positive findings on PET should be confirmed by histology whenever possible. In up to 70% of patients in whom PET scans indicate nodal metastasis, histologic confirmation can be obtained using EUS-FNA.⁸¹ A combination of PET and EUS-FNA therefore holds potential as a minimally invasive approach for defining radiotherapy fields. This may allow for dose escalation to tumor and reduced dose to critical structures and, it is hoped, improved local control.

GUIDANCE FOR DIAGNOSTIC BIOPSY

A promising indication for PET in NSCLC is as a guide to high-yield diagnostic biopsies. By identifying potential intrathoracic and extrathoracic sites of metastatic involvement, PET can streamline the evaluation by helping to target the biopsy site that will establish the highest stage disease. Furthermore, by providing information about the location of potentially involved mediastinal lymph nodes, PET can help to guide the selection of a specific surgical or nonsurgical biopsy procedure. For example, a physician might choose EUS in a patient with hypermetabolic posterior subcarinal or paraesophageal nodes, whereas one would favor anterior mediastinotomy in a patient with isolated para-aortic lymph node involvement.

Systematic sampling of mediastinal nodes with combined EUS and EBUS is emerging as the potential gold standard for mediastinal staging.^{82,83} However, this approach is time consuming and typically requires general anesthesia to keep the patient still and cough-free for a prolonged period of time. Although systematic staging is essential to completely exclude mediastinal involvement, targeted sampling of suspicious N2 or N3 nodes may be all that is necessary to confirm nonresectability in many patients. By identifying nodes that are the most hypermetabolic and/or most easily accessible, PET can facilitate planning for invasive staging.

Although several investigators have alluded to this potential indication for PET in NSCLC,^{14,64,84,85} no data currently exist to confirm or refute whether PET-guided invasive staging is more efficient than systematic staging, making this a ripe target for investigation.

RECENT IMPROVEMENTS IN PET TECHNOLOGY

Integrated PET-CT allows for more precise localization of the specific anatomic structures

responsible for FDG enhancement. Although of questionable value in the characterization of lung nodules, integration of PET and CT images seem to be potentially useful for evaluation of masses abutting the chest wall or mediastinum and for nodal staging. In one study, tumor stage was assigned correctly in 39 of 40 patients by integrated PET-CT, but only in 31 of 40 patients when results of dedicated PET and CT were visually correlated. Similarly, nodal stage was correctly assigned in 31 of 37 patients by integrated PET-CT, compared with 26 of 37 patients by visual correlation. Although widely cited, this small study was limited by incomplete blinding and failure to ascertain final stage in 30% of participants.⁸⁶ In a larger subsequent study of 129 consecutive patients with indeterminate solitary nodules or proven NSCLC, stage assignment by integrated PET-CT was more often correct than staging by dedicated PET alone, but integrated PET-CT was correct only 68% of the time and dedicated PET was correct less than 50% of the time.⁸⁵ It is also important to recognize that the CT portion of most integrated PET-CT scans has inferior image quality compared with that of a standard CT because it is primarily used as an attenuation correction tool and, thus, is subject to breathing and motion artifacts due to a lack of breath-holding.⁸⁷ Therefore, integrated PET-CT does not always obviate a dedicated CT of the chest.

Although integrated PET-CT has been widely adopted in clinical practice, other improvements have not yet been implemented, including standardization of protocols for image acquisition and interpretation so that there is a universally agreed-on fasting time, glucose threshold, delay time between injection of FDG and scanning, and a reproducible method of delineating a region of interest for the measurement of SUVmax. Another advance that has undergone preliminary study is dual-time scanning. With this technique, persistence of FDG uptake on a repeat scan helps, at least in theory, to distinguish malignancy from inflammation.^{88,89}

In all likelihood, the most promising future advances will come from the development of novel tracers for metabolic imaging that are more sensitive or specific for identifying malignancy.

SUMMARY

In the last 2 decades, PET technology has become widely available and PET is now a standard part of the armamentarium for lung cancer diagnosis and staging. However, rational interpretation and use of PET requires careful consideration of the clinical context and the limitations of functional imaging

with a tracer that uses metabolic activity as a proxy for the presence of cancer.

Above all else, it is important to re-emphasize that positive findings on PET, whether in the mediastinum or outside of the thorax, must be confirmed by biopsy before excluding a patient from potentially curative surgical resection, unless there is overwhelming evidence of malignancy. In some cases, absence of FDG uptake in the primary lesion or mediastinum may require confirmatory biopsy as well—especially if the PET-negative primary lesion is in a patient at high-risk for lung cancer, if the mediastinal lymph node size is only mildly enlarged (given that PET is less sensitive in smaller nodes), or if the radiographic presentation has any features that are associated with occult metastasis to the mediastinum (eg, centrally-located tumor, N1 hilar involvement, adenocarcinoma).

Areas of controversy include whether PET should be performed to identify occult metastasis in patients with suspected malignant small pulmonary nodules and whether PET is helpful or redundant for mediastinal staging in patients with clinical stage III disease. Likewise, it is unclear whether PET can identify high risk patients who are more likely to benefit from adjuvant chemotherapy following resection, or whether early detection of recurrence by PET is associated with better response to salvage treatment.

Although clinicians will always be faced with dilemmas of interpreting equivocal findings, PET can still be helpful in patients with known or suspected NSCLC if indications and results are not accepted at face value without additional deliberation. As Shakespeare eloquently put it, “Make not your thoughts your prisons.” Given the rapid pace of technological innovation, the golden age of PET probably lies before us, and the indications will undoubtedly morph and reinvent themselves into clearer recommendations as additional studies are completed and experience accumulates.

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