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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe the role of PET/CT in the indeterminate lung nodule.
- Review the role of PET/CT in assessment of the staging and the malignant potential of non-small cell lung cancer.
- Discuss the role of PET and PET/CT in evaluating the response of a patient with non-small cell lung cancer to neoadjuvant chemotherapy and radiation.
- Compare the advantages and disadvantages of CT, PET, and PET/CT.

The Role of PET and PET/CT in Evaluating and Staging Patients with Non-Small Cell Lung Cancer

By Robert James Cerfolio, M.D., and Ayesha S. Bryant, MSPH

Lung cancer kills more people in the U.S. each year than the second, third, and fourth most common cancers (breast, colon, and prostate) combined. Eighty percent of lung cancers are non-small cell lung cancer (NSCLC). Treatment, which depends on the stage, will be the focus of this report.

The involvement of cancer in metastatic sites (M1) and/or regional mediastinal (N2 or N3) or hilar lymph nodes (N1) is the determinant of the stage and hence the treatment. The traditional methods for staging patients with NSCLC or with an indeterminate nodule include CT scans of the chest and upper abdomen, bone scans, and MR or CT scans of the brain.

Suspicious M1 lesions and N3, N2, or N1 lymph nodes discovered by these tests are biopsied to prove or disprove the presence of cancer. Lymph nodes are biopsied using minimally invasive procedures such as mediastinoscopy, video-assisted thoracoscopy (VATS), and esophageal

ultrasound with fine-needle aspiration.

In addition to these imaging modalities, whole-body PET scans using fluorine-18 FDG have been used in the last few years to stage patients with NSCLC. Even more recently, integrated PET/CT scanners have been developed that further enhance the ability to localize potentially metastatic M1 cancer and pinpoint N1 disease. A number of large studies that have examined these issues have demonstrated the superiority of integrated PET/CT over PET alone for staging patients with NSCLC.

INDETERMINATE PULMONARY NODULES

The incidence of the "indeterminate nodule" is rising, probably because more patients are getting chest CT scans after trauma, as a screening modality, and even as part of a routine yearly physical exam. Further investigation is often needed when a pulmonary nodule is truly indeterminate (i.e., it is

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Dr. Cerfolio and Ms. Bryant have no significant financial arrangement or affiliation with any manufacturer of any pharmaceutical or medical device and are not affiliated in any manner with any provider of any commercial medical or healthcare professional service.

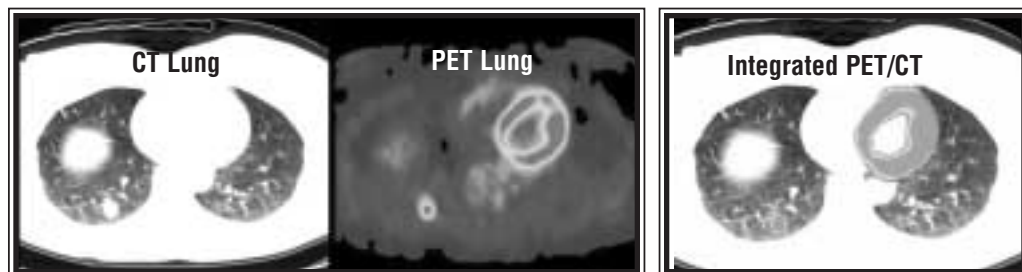


Figure 1. 56-year-old woman with indeterminate nodule of right lower lobe. Pathological examination revealed a T2N0M0 adenocarcinoma.

Summary of Results of FDG-PET Literature Search for Lung Cancer

	Sensitivity	Specificity	Accuracy
Diagnosis	96%	73%	90%
Staging*	83%	91%	82%
Recurrence	98%	92%	96%
Monitoring response to chemotherapy	94%	90%	96%

* Management change in 37% patients

new when compared with old chest x-rays or is noncalcified).

If the nodule is 5 to 6 mm or greater, dedicated PET and PET/CT are powerful tools that help further characterize its nature.¹ Several studies have shown PET to have a sensitivity of 91% to 97% and a specificity of 78% to 88% for predicting the pathologic nature of nodules that are indeterminate on x-ray and CT.^{2,3} Similarly, we evaluated 130 patients and found the mean standard uptake value (SUV) on integrated FDG-PET/CT to be highly predictive (publication pending). We found that nodules with an SUV of less than 2.5 have only a 12% chance of being malignant; indeterminate nodules with a mean SUV between 2.5 and 3.5 have a 67% chance of being malignant; and those with a mean SUV of 3.5 or greater have a 97% chance of being malignant.

Figure 1 shows images of a 56-year-old woman with an indeterminate nodule in the right lower lobe. Chest CT showed a noncalcified spiculated 1.7 x 1.4-cm nodule in the posterior basal segment of the right lower lobe. Integrated FDG-PET/CT revealed an intensely hypermetabolic area in the right lower lobe with a maximum SUV of 8 and a mean SUV of 4.7 in an area of 1.9 x 1.4 cm. The patient underwent thoracotomy, lobec-

tomomy, and complete thoracic lymphadenectomy. Pathology showed a T2N0M0 moderately differentiated adenocarcinoma.

Figure 2 shows a PET/CT image of a 59-year-old man with a left upper lobe mass. Integrated PET/CT showed mildly increased F-18 FDG uptake in the location of the left upper nodule with a maximum SUV of 3.2 and a mean SUV of 2.5. The patient desired resection despite our recommendation for careful follow-up. Postoperative pathology showed benign inflammatory pathology with mixed plasma cell and granulomatous component.

As these two cases illustrate, mean SUVs are important predictors that can help guide treatment. But the question arises whether SUVs are translatable from one center to another. If one of these patients had a PET scan on a different machine at another PET center and the SUVs were completely different, the power of these studies would obviously be limited. Because SUVs can vary for several reasons, including the amount of F-18 FDG injected and the time between injection and image production, some have referred to the term “standard uptake value” as an oxymoron. It is not standardized at all, although work is under way to make it as standardized as possible.

We believe that SUVs from integrated PET/CT are more similar from machine to machine than those from PET alone. This is probably because some PET examinations are performed not on dedicated scanners but

on coincidence cameras or cameras with lens thickness greater than 5/8 of an inch. In contrast, integrated PET/CT machine are more similar to one another.

SUV AS INDEPENDENT PREDICTOR OF MALIGNANCY POTENTIAL

If the indeterminate nodule is found to be malignant by biopsy or is large and highly suspicious of malignancy on CT and PET, the stage of the patient determines the treatment. Many studies have shown that PET is accurate in the staging of patients with NSCLC.⁴⁻⁶ Its superiority over CT for assessing N1 and N2 disease is well documented. FDG-PET seems to be less accurate at the subcarinal and lower paratracheal lymph node stations than at other N2 stations.

Figure 3 shows a 69-year-old woman with a small nodular area in the left anterior lateral hemidiaphragm on chest CT. An integrated FDG-PET/CT shows an intensely hypermetabolic area in the left lung base laterally (maximum SUV = 9.3, mean SUV = 3.5, area = 3 x 1.5 cm). A well-defined focal area of intensely increased uptake is noted in the left lower paratracheal (station 4L), aortopulmonary (station 5), hilar (station 10L), and interlobar (station 11L) lymph nodes. The left hilar lymph node had a maximum SUV = 10.9, mean SUV = 4.2, area = 1.5 x 1.8 cm. Minimally invasive VATS with biopsies revealed moderately differentiated adenocarcinoma metastatic to the aortopulmonary lymph node.

The clinical import of knowing about N2 disease prior to surgical resection is well documented in reports by Roth and Rosell^{7,8} that show a survival advantage if patients with N2 disease undergo neoadjuvant treatment prior to pulmonary resection. PET thus allows these suspicious lymph nodes to be targeted and biopsied directly via the

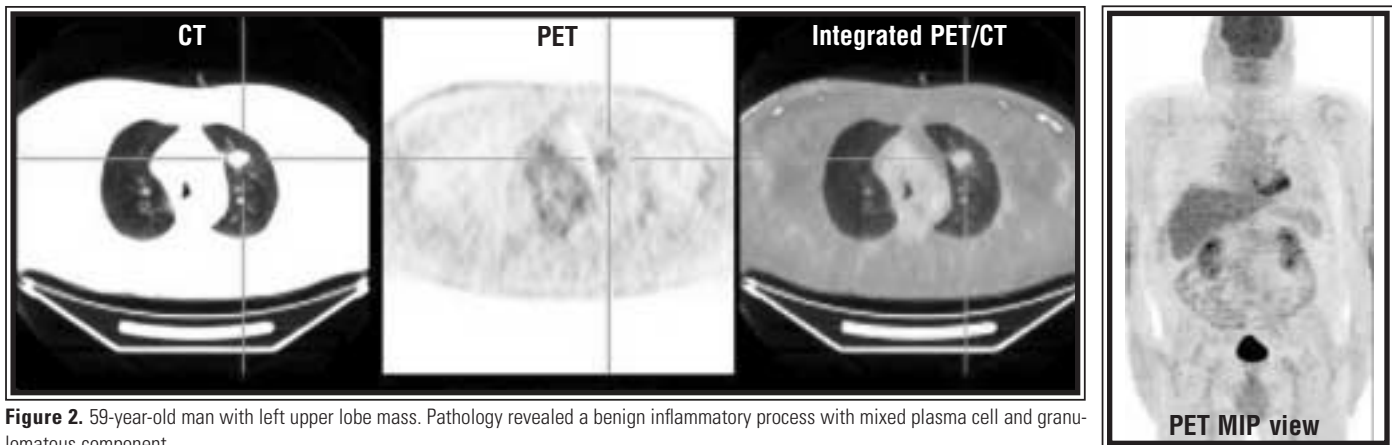


Figure 2. 59-year-old man with left upper lobe mass. Pathology revealed a benign inflammatory process with mixed plasma cell and granulomatous component.

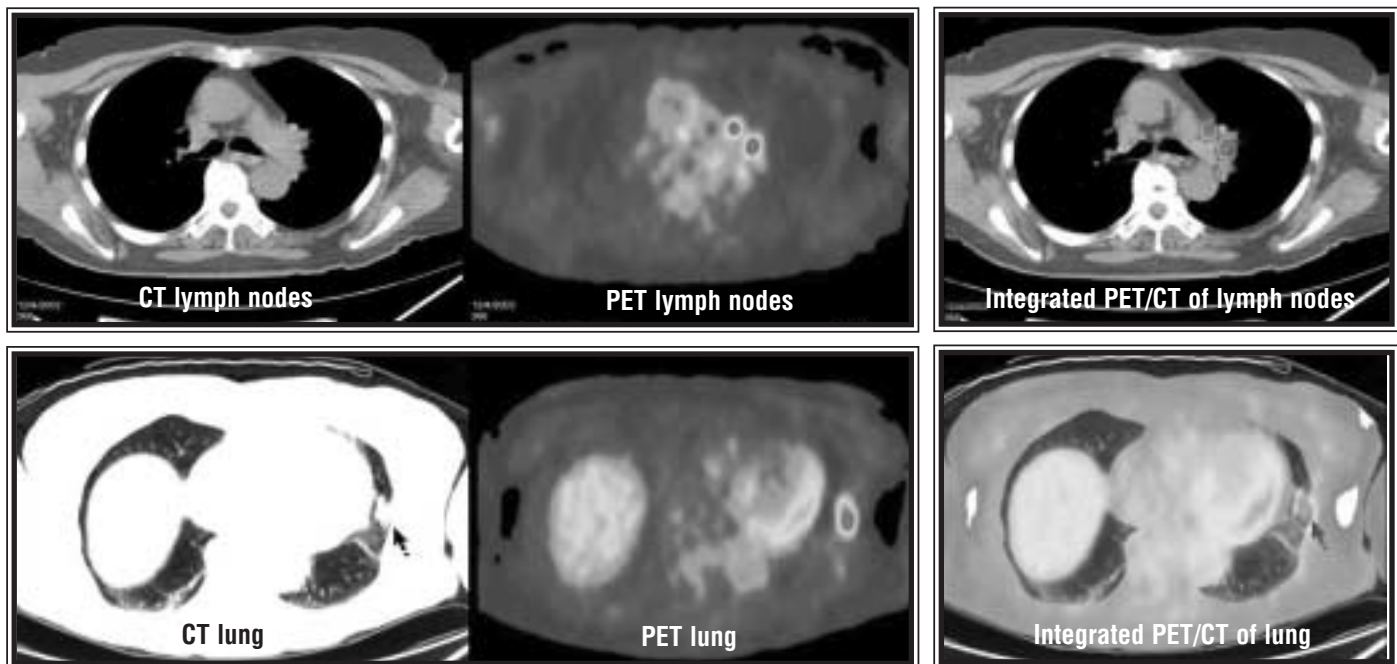


Figure 3. 69-year-old woman with a small nodular pleural thickening along the left anterior lateral hemidiaphragm on chest CT. Pathology from VATS revealed moderately differentiated adenocarcinoma and metastatic adenocarcinoma in aortopulmonary lymph node.

best minimally invasive operation. This affords the patient the chance to undergo neoadjuvant therapy and perhaps enjoy improved survival.

Unfortunately, many patients with unsuspected M1 disease undergo thoracotomy. For this reason, some surgeons routinely perform numerous tests such as bone scans, brain scans, and liver ultrasound, even in asymptomatic patients, to rule out M1 disease. The advantages that PET offers over the multi-test method are well documented. Crespo-Jara reported in 1999 that PET had 83% sensitivity for detecting bone metastases. PET revealed more lesions than did bone scanning, independent of the type of cancer or location of bone involvement.

In an extremely important prospective randomized multicenter trial presented at the American Association for Thoracic Surgery meeting in May 2003 (publication pending), Reed and colleagues showed that dedicated PET using FDG-18 was a better predictor of the stage of patients with NSCLC than conventional methods alone. The study enrolled 271 patients from many major centers in the U.S.

Similarly, we showed in a recently published paper that FDG-PET scanning enables improved patient selection prior to surgery for patients with NSCLC.⁹ It is more sensitive and has a higher negative predic-

tive value than CT for N1 and N2 lymph nodes. False positives are common when using FDG-PET, however. Some infections and inflammatory lesions, such as tuberculous granulomas, coccidioidomycosis, aspergillosis, and histoplasmosis, can result in high uptake values that mimic those of a neoplasm. We found a larger number of false positives than were found in a series reported by Gupta and Roberts.^{10,11} This may be due to the higher prevalence of histoplasmosis in the southeastern U.S. A positive FDG-PET scan means only that tissue biopsies are indicated. Interestingly, other studies have shown that PET is more accurate than CT for detecting cancers in other organs as well.

Finally, and most provocatively, we have found that the SUV of a lung nodule may be an independent predictor of its malignant potential and stage. In this study (publication pending), we found that PET/CT with F-18 FDG of the pulmonary mass itself is an excellent prognosticator of the malignant potential, lymphovascular invasion, and degree of differentiation of a patient's NSCLC (see table). This is true regardless of the lymph node status. If additional multicenter trials confirm these data, it is possible that use of neoadjuvant therapy may be based on the SUVs of the lung nodule as well as its stage as determined by biopsy of regional lymph nodes.

PATIENT RESPONSE TO CHEMO/RADIATION THERAPY

More and more patients are undergoing neoadjuvant therapy prior to surgical resection for advanced stages of NSCLC. Moreover, several prospective randomized trials are evaluating the use of preoperative chemotherapy for patients with early-stage lung cancer, including stage Ib, IIa, and IIb disease and stage III disease that is N2 negative. Because patients who do not respond to neoadjuvant therapy rarely benefit from surgical resection, the oncologist and surgeon must decide if the patient has responded to the treatment. Studies have shown that the reduction of metabolic activity after chemotherapy correlates with the final outcome of therapy.¹²

Other studies have demonstrated that PET and PET/CT are valuable noninvasive ways to evaluate a patient's response to chemotherapy as well as to monitor for recurrence.^{13,14} Because repeat mediastinoscopy has significant risk, these studies have powerful implications. We have shown that repeat PET had 100% accuracy in assessing this response for paratracheal lymph nodes.¹⁵

The true power of PET is best illustrated when a baseline PET scan is taken and tissue biopsies subsequently confirm what is and is not cancer. After the patient has completed neoadjuvant therapy, a repeat

PET is performed on the same machine. We have found this second PET to be an extremely accurate restaging tool. Moreover, studies have shown that the change in the SUV on PET may be a predictor of the amount of cellular death,¹² and we are currently evaluating this response in patients.

Repeat PET, or even better, PET/CT, after neoadjuvant therapy may thus become a standard tool to assess patient response to a certain neoadjuvant therapy, to help select appropriate patients for surgical resection, and to direct different, continued, or varied chemotherapeutic regimens with or without addition of radiotherapy.

PET/CT SUPERIOR TO PET

The term PET/CT can be misconstrued. Integrated PET/CT has been shown in two prospective randomized trials to be superior to PET alone (with a recent CT scan used for visual correlation of PET with CT) for staging patients with NSCLC. PET offers superior metabolic information, but it has only limited spatial resolution and anatomic landmarks^{16,17} when compared with CT. Additionally, FDG is taken up by muscles,

and inflammatory processes can be mistaken for a malignant process.^{18,19} CT lacks the molecular activity that PET demonstrates, but it provides excellent anatomical information. Visual correlation of PET and CT is also inaccurate. Integrated PET/CT allows anatomic definition to be added to help assess molecular ambiguity. And improved localization with PET/CT enables the radiologist to clearly distinguish areas of normal physiological tracer uptake from regions of increased metabolic activity.

Some institutions use software that fuses CT and PET images. The problem with this technique is that patients move or the scans may have to be performed on separate days. Performing PET and CT studies simultaneously on an integrated system overcomes these limitations of retrospective comparison of individual images, eliminates the need for postacquisition image alignment, and avoids the imprecision to which it leads.

Three series have examined the efficacy of PET/CT versus PET and CT alone. In two prospective studies, PET/CT provided additional information in 41% of patients (20/49) as compared with visual correlation of PET and CT individually.^{20,21} The third

study showed a reduction in the number of false positives (from three to none) and false negatives (from 16 to two) compared with PET alone.²² We reported at the Southern Thoracic Surgical Association meeting in November 2003 that PET/CT is superior to PET alone for evaluation of the T, N, and M status of patients with NSCLC. This study examined 150 patients in a prospective, blinded fashion. Unlike other studies, all patients underwent definitive biopsies. We found that integrated PET/CT had a higher accuracy than PET alone for the T, N, and M status of patients with NSCLC.

The future of PET and PET/CT is bright. Its application can extend beyond the diagnosis and staging of lung cancer. Its ability to stage patients with other cancers has been demonstrated. The majority of work with PET and PET/CT has been done with F-18 FDG. As new radiopharmaceutical isotopes enter the clinical arena, each must be studied and its accuracy at each specific station must be assessed. We must be willing to perform prospective randomized trials and in multi-institutional studies to help answer these important questions.

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REFERENCES

- Hanley KS, Rubins JB. Classifying solitary pulmonary nodules. New imaging methods to distinguish malignant, benign lesions. *Postgrad Med* 2003;114(2):29-35.
- Pitman AG, Hicks RJ, Binns DS, et al. Performance of sodium iodide based (18)F-fluorodeoxyglucose positron emission tomography in the characterization of indeterminate pulmonary nodules or masses. *Br J Radiol* 2002;75(890):114-121.
- Coleman RE. PET in lung cancer staging. *Q J Nucl Med* 2001;45(3):231-234.
- Gupta NC, Graeber GM, Rogers JS II, Bishop HA. Comparative efficacy of PET with FDG computed tomographic scanning in preoperative staging of non-small cell lung cancer. *Ann Surg* 1999;229:286-291.
- Van Tinteren H, Hoekstra OS, Smit EF, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomized trial. *Lancet* 2002;359:1388-1393.
- Cerfolio RC, Buddhwardan O, Bryant AS, et al. The role of FDG-PET scan in staging patients with non-small cell cancer. *Ann Thorac Surg* 2003;76:861-866.
- Roth JA, Atkinson EN, Fossella F, et al. Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *Lung Cancer* 1998;21(1):1-6.
- Rosell R, Gomez-Codina J, Camps C, et al. Pre-resectional chemotherapy in stage IIIA non-small-cell lung cancer: a 7-year assessment of a randomized controlled trial. *Lung Cancer* 1999;26(1):7-14.
- Nakamoto Y, Osman M, Wahl RL. Prevalence and patterns of bone metastases detected with positron emission tomography using F-18 FDG. *Clin Nucl Med* 2003;28(4):302-307.
- Gupta NC, Graeber GM, Bishop HA, et al. Comparative efficacy of positron emission tomography with fluorodeoxyglucose in evaluation of small, intermediate and large lymph node lesions. *Chest* 2000;117:773-778.
- Roberts, PF, Follette DM, von Haag D, et al. Factors associated with false-positive staging of lung cancer by positron emission tomography. *Ann Thorac Surg* 2000;70:1154-1160.
- Weber WA, Petersen V, Schmidt B, et al. Positron emission tomography in non-small-cell lung cancer: prediction of response to chemotherapy by quantitative assessment of glucose use. *J Clin Oncol* 2003;21(14):2651-2657.
- Weber WA, Petersen V, Schmidt B, et al. Positron emission tomography in non-small-cell lung cancer: prediction of response to chemotherapy by quantitative assessment of glucose use. *J Clin Oncol* 2003;21(14):2651-2657.
- Dimitrakopoulou-Strauss A, Strauss LG, Rudi J. PET-FDG as predictor of therapy response in patients with colorectal carcinoma. *Q J Nucl Med* 2003;47(1):8-13.
- Cerfolio RJ, Ojha B, Mukerjee S, et al. Positron emission tomography scanning with 2-fluoro-2-deoxy-d-glucose as a predictor of response of neoadjuvant treatment for non-small cell carcinoma. *Thorac Cardiovasc Surg* 2003;125(4):938-944.
- Klaff V, Hicks RG, MacManus MP, et al. Clinical impact of (18) FDG positron emission tomography in patients with non-small-cell lung cancer: a prospective study. *J Clin Oncol* 2001;19:111-118.
- Pitterman RM, Van Putten JW, Meuzelarr JJ, et al. Preoperative staging of non-small cell lung cancer with positron-emission-tomography. *New Engl J Med* 2000;343:254-261.
- Cook GJR, Maisey MN, Fogelman I. Normal variants, artifacts and interpretative pitfalls in PET imaging with 18-flouro-deoxyglucose and carbon-11 methionine. *Eur J Nucl Med* 1999;26:1363-1378.
- Engel H, Steinhart H, Buck A, et al. Whole body PET: physiological and artifactual fluorodeoxyglucose accumulations. *J Nucl Med* 1996;37:441-446.
- Steinert HC, von Schulthess GK. Initial experience using a new integrated in-line PET/CT system. *Br J Radiol* 2002;75:S36-S38.
- Lardinois D, Weder W, Hany TF, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography-computed tomography. *New Engl J Med* 2003;348(25):2500-2507.
- Kaiser, CP. PET/CT fusion proves its worth. *Diagnostic Imaging*, Nov 2001, diagnosticimaging.com.



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M03JS007JAN • Release: Jan 2004 • Expiration: Jan 2007
Reviews Scheduled: Jan 2005 and Jan 2006

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