

Partnerships in Oncology and Radiology: The Role of Radiology in the Detection, Staging, and Follow-up of Lung Cancer

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Key Words. Lung carcinoma • PET • PET/CT • Cancer staging

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the limitations of chest radiographs in detecting lung cancers.
2. Discuss the current status of lung cancer screening.
3. Identify the benefits and limitations of PET/CT in the diagnosis, staging, and follow-up of lung cancer.

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ABSTRACT

In this review, I examine the multifaceted role of radiology in the diagnosis, staging, and management of lung cancer, highlighting new applications and modalities such as computer-aided detection of lung nodules and

positron emission tomography/computed tomography for staging and monitoring response to therapy. Lung cancer screening is also discussed. *The Oncologist* 2006;11:774–779

INTRODUCTION

Lung cancer, the number one cause of cancer-related deaths in U.S. men and women, will claim an estimated 162,460 lives in 2006 and account for about 13% of cancer diagnoses and 28% of all cancer deaths [1].

Radiologic tests, particularly the chest x-ray or chest computed tomography (CT) scan, often provide the first indication that a lung abnormality is present. Imaging-guided biopsy is frequently performed to provide histopathologic confirmation. Relatively recently, combined positron emission tomography and CT (PET/CT) has been shown to improve the diagnostic accuracy of staging lung carcinoma and yields additional information regarding metabolic response to therapy over CT alone. Given the

critical role of radiology in lung cancer diagnosis, staging, and management, it is essential that oncologists understand the contribution and limitations of radiology and be aware of new developments on the horizon.

DETECTION

The clinical signs and symptoms of lung carcinoma are often vague or nonspecific, including cough, chest pain, hoarseness, recurrent pneumonia, and hemoptysis. The chest x-ray, the traditional screening radiology exam for lung nodules/masses, frequently produces false-negative results, particularly in early-stage disease. In a study of 396 chest radiographs of patients with proven lung carcinoma dating from 1992–1995, almost 20% of lung carcinomas

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presenting as nodules were missed at the time of interpretation although were visible in retrospect. The mean diameter of the missed lesion was 1.6 cm. The most common cause of missed cancer was superimposition of a lung nodule with normal anatomic structures such as ribs, hilar structures, and vessels. The border of the nodule also contributed to its detectability, with sharply bordered lesions more visible than those with blurry margins. [2]. Other studies of missed lung carcinoma on conventional chest x-rays demonstrated similar or worse results [3–5]. Centrally located cancers, in particular, tended to be invisible on chest x-rays, even in retrospect, until they had achieved a relatively large size [3].

With the increasing use of picture archiving systems (PACS) in the late 1990s, digital chest radiographs became a reality. The result is a digital image that can be manipulated on a computer screen to enhance contrast, invert the grey scale, magnify, etc. The Radiological Imaging Unification Strategies (RADIUS) chest trial evaluated the factors limiting nodule detectability on digital chest radiographs and found, similar to prior studies of conventional chest films, that the anatomic background is the major imaging component limiting detection of pulmonary nodules [6]. Computer-aided detection (CAD) systems for digital chest radiographs [7], software that subtracts one lung from another to reveal subtle asymmetric opacities [8], and temporal subtraction of prior chest x-rays from the current exam [9] are all topics under investigation to improve the performance of the chest x-ray in detecting lung cancer. However, it is unlikely that technical improvements in the chest x-ray will produce similar lesion detectability to CT.

CT eliminates the problem of reduced detection of lung nodules because of superimposition with normal anatomic structures and has been shown to detect far more lung carcinomas than the chest x-ray [10, 11]. Since its introduction in the mid 1970s, the spatial and temporal resolution of CT has increased by leaps and bounds. Current 64-slice scanners provide images of submillimeter structures and acquire data so quickly that motion artifacts and volume-averaging effects are generally negligible. Several CAD products for lung nodules on CT are commercially available. One recently published trial comparing the performance of radiologists alone with radiologists plus CAD found that the mean sensitivity for the detection of lung nodules on CT rose significantly with the addition of CAD [12, 13]. Several software packages that calculate lung nodule volume are currently available as well and provide more reproducible measurements than manual nodule measurement [14]; this becomes particularly important in the follow-up of pulmonary nodules on serial CT exams in the setting of screening, or following response to therapy in patients with known disease (see below).

SCREENING

Given the fact that patients with small, localized lung cancers without metastatic spread have a relatively high 5-year survival rate of 70% compared with those with more advanced disease and that only 15%–20% of lung cancers are stage I at the time of diagnosis, it makes sense to investigate screening methods for early detection of stage I lung cancers [15]. Prior studies of screening with chest x-rays have yielded disappointing results, with no change in the lung cancer death rate in high-risk patients screened with chest x-rays and sputum cytology every 4 months versus those in a control group [16, 17]. The Early Lung Cancer Action Project (ELCAP), and subsequently the International (I)-ELCAP, has evaluated annual screening low-dose chest CT and chest x-ray in a population of high-risk patients since 1993 [15]. As expected, CT demonstrated a much higher number of lung cancers than did chest x-rays. Preliminary data from these investigations suggest that most screening-detected cancers (80%) are stage I cancers with a surgical cure rate of 70% [18]. The Lung Cancer Screening Study evaluated over 3,000 patients, randomized to either chest x-ray (CXR) or low-dose CT for lung cancer screening; a baseline and 1-year screening exam were performed. Sixty lung cancers were diagnosed, 40 in the CT arm of the study and 20 in the CXR group, with stage I cancers making up almost 50% of the cancers detected using CT [19]. A smaller study of 449 high-risk patients yielded less promising results after 2 years of follow-up, with six lung cancers detected, three of which were unresectable secondary to their central location [20]. Concerns regarding cost, radiation exposure, and the frequency of false-positive findings have been raised [21].

The National Cancer Institute's National Lung Screening Trial, a randomized, controlled, clinical trial of 50,000 subjects is under way to address these issues and is expected to prove the mortality benefit of screening [22].

DIAGNOSIS

Many lung abnormalities (e.g., large nodules or masses discovered by CXR or CT) are considered suspicious enough to prompt immediate biopsy. However, in certain clinical situations, it may be desirable to further characterize a pulmonary nodule by imaging, rather than proceeding immediately to tissue diagnosis. This scenario may be encountered in patients unwilling or hesitant to undergo biopsy, those with underlying lung disease, those at increased risk for biopsy-related complications, and those with multiple pulmonary abnormalities.

Ohtsuka et al. [23] investigated the CT characteristics of primary lung cancers and benign nodules <10 mm in diameter and found that ill-defined margins, spiculation, invasion

of bronchi or vessels, and interval enlargement on follow-up exams (doubling time of 30–360 days) were signs of malignancy. In general, nodules that grow with a doubling time of 30–360 days are considered suspicions and should be biopsied, whereas very rapidly growing nodules (doubling time <1 month) and nodules stable for 24 months (or decreasing in size) are generally indicative of benign processes [24]. Shah et al. [25] found that CAD data helped in the differentiation of benign and malignant pulmonary nodules on CT scans. Other investigators have looked at contrast enhancement characteristics of CT scans and found that a wash-in of contrast of 25 Hounsfield units (HU) or greater, combined with a washout of at least 5 HU, was useful in predicting malignancy [26].

In addition to anatomic imaging, functional characterization of lung nodules with nuclear medicine studies has been extensively investigated. Blum et al. [27] reported characterization of 114 solitary pulmonary nodules (SPNs) and lung masses with a technetium-labeled somatostatin analogue (99mTc-depreotide, Neotect[®], Berlex, Inc., Wayne, NJ) and found the technique to be 97% sensitive and 73% specific for determining a benign versus malignant etiology. The mean size of the lung abnormality in that study was 2.8 cm with a range of 0.8–6 cm. Results with smaller nodules have not been reported. This exam requires only a gamma camera capable of performing single photon emission computed tomography (SPECT) images, and not the dedicated equipment required for PET or PET/CT.

PET with fluorodeoxyglucose (FDG) provides information about metabolism of cells, and since its development in the 1970s, it has grown increasingly important in cancer imaging. The Prospective Investigation of Positron Emission Tomography in Lung Nodules (PIOPILN) study reported a 91% accuracy of PET in differentiating benign and malignant pulmonary nodules; however, the sensitivity decreased from 92% overall to 80% in lesions 7–15 mm in diameter [28]. Herder et al. [29] specifically evaluated the performance of PET in characterizing small SPNs (≤ 10 mm) and reported a sensitivity of 93% and specificity of 77%.

Gould et al. [30] reported a meta-analysis of studies using PET to evaluate focal pulmonary lesions and found an overall sensitivity of 97% and specificity of 78% for nodules 1 cm and larger. Limitations of PET with regard to lesion size have improved with the introduction of combined PET/CT; the multislice CT component improves the spatial resolution of the attenuation—corrected PET images to a practical lower limit of about 6–7 mm. False negatives are known to occur with well-differentiated tumors such as bronchioalveolar carcinoma (which may produce “ground glass” opacities on CT scans) and well-differentiated adenocarcinoma [31,32,33].

STAGING

Lung cancer staging is of the utmost importance, as it will determine the course of treatment to be pursued and is the primary determinant of prognosis. Numerous studies have been published in recent years reporting, initially, the superiority of PET to CT in lung carcinoma staging [34, 35] and, subsequently, the superior accuracy of combined PET/CT to PET or CT alone (see below) [36–38]. Pieterman et al. [35] reported in 2000 that clinical staging with PET upstaged 42 of 102 patients compared with conventional imaging modalities and downstaged 20 patients. The sensitivity and specificity of PET for detecting metastatic mediastinal nodes were 91% and 86%, respectively. PET detected unsuspected distant metastases in >10% of patients [35].

Antoch et al. [36], in a study of 27 patients, found superior T staging (94% accuracy with PET/CT vs. 75% accuracy with either PET or CT alone), superior N staging (93% accuracy for PET/CT vs. 63% for CT and 89% for PET alone), and better detection of distant metastases with PET/CT than with either CT or PET alone. A larger study of 106 patients reported superior T and N staging with PET/CT than with CT alone [37]. Primary tumor staging was correct in 79% of patients using CT versus 86% using PET/CT; the sensitivity, specificity, and accuracy for the detection of lymph node metastases with CT were 70%, 69%, and 69%, respectively, versus 85%, 84%, and 84%, respectively, for PET/CT. Lardinois et al. [38], in a prospective study of 50 patients, found that integrated PET/CT provided additional information in 41% of patients versus separate PET and CT exams, and that the added information led to higher diagnostic accuracy in staging. With respect to tumor stage, CT alone was correct in 58% of patients, PET alone was correct in 40% of patients, and integrated PET/CT was correct in 88% of patients. For nodal staging, CT was correct in 59% of cases, PET was correct in 49% of cases, and combined PET/CT was correct in 81% of cases [38].

Although the accuracy of PET/CT is higher than that of either PET or CT alone, this modality has its limitations, particularly with regard to specificity. Not every FDG-avid lesion is malignant; inflammation, granulomatous diseases (mycobacterial infections, sarcoid), recent surgery, or trauma are only a few of the benign causes of false-positive PET or PET/CT findings [39]. Careful correlation with the clinical findings is a requisite for accurate interpretation of PET/CT results; correlation with additional imaging studies or biopsy may be necessary in some cases.

Magnetic resonance imaging (MRI) is useful in defining the anatomy of superior sulcus tumors with respect to the brachial plexus but otherwise has a limited role in staging locoregional disease [40]. However, because of the normally high uptake of FDG in the brain, MRI is much more

sensitive than PET/CT for detecting metastatic disease to the brain and should be considered in patients with neurologic signs/symptoms or in asymptomatic patients with stage III disease [40–42].

Conflicting results have been published regarding the relative performance of PET in detecting osseous metastatic disease compared with the conventional bone scan, with some authors reporting greater sensitivity and others reporting lower sensitivity than with bone scan [43–46]. Bury et al. [43] reported higher accuracy of PET (96%) than bone scan (66%) for detecting skeletal metastases from lung cancer. Gayed et al. [44] reported lower sensitivity of PET (73%) compared with bone scan (81%) but greater specificity, yielding an overall accuracy of 90% for PET versus 78% for bone scan. Investigators have evaluated PET with tracers other than fluorine-18 FDG for identifying bone metastases. A study of 103 lung cancer patients found an accuracy of 99% for PET with sodium fluoride versus 77% for bone scanning [45]. The American Society of Clinical Oncology guidelines state that bone scanning is optional, but that in patients with a surgically resectable primary tumor, bone lesions discovered on bone scan or PET should be histologically confirmed to be metastatic disease [46].

Staging of small cell lung carcinoma (SCLC) deserves special mention. Although some insurers (notably Medicare/Medicaid) do not cover the use of PET or PET/CT for staging SCLC, evidence is present that there is typically a high degree of FDG uptake in this subtype of lung cancer, both in the primary tumor and in metastatic disease [47–49]. Accurately determining whether limited or extensive disease is present determines treatment. In a study of 42 patients with SCLC, Kamel et al. [47] found that PET findings changed the management in 29% of patients by detecting additional sites of disease unsuspected on CT, demonstrating a lack of FDG uptake in nonspecific findings on CT, and changing the radiation field/radiation volume by better depicting the extent of disease. Blum et al. [49] evaluated 36 patients with SCLC; 33% of patients were upstaged from limited to extensive disease based on the PET results. In patients undergoing restaging PET scans, PET findings were discordant with conventional imaging in 63% of patients. The discordant lesions underwent further evaluation, and PET proved to be accurate in 79% of discordant cases [49]. There is still a relatively small body of literature concerning PET and PET/CT of SCLC (vs. non-small cell lung cancer [NSCLC]), but the published results are promising.

RESTAGING/MONITORING RESPONSE TO THERAPY

Response to treatment (radiation or chemotherapy) has traditionally been assessed with anatomic imaging modalities, primarily CT, with a decrease in the size of a lesion

equating to response. PET provides additional information regarding metabolic response to therapy. Cerfolio et al. [50] reported that the change in FDG uptake, measured by the maximum standardized uptake value (SUV), postchemoradiotherapy, directly correlates with pathologic response and is a more accurate predictor of response than is change in size on CT scans.

Hellwig et al. [51] evaluated 47 patients with advanced NSCLC with PET following induction therapy and correlated the findings with subsequent surgery. All tumors with a maximum SUV ≥ 5.8 contained viable tumor cells at surgery. The median survival time after resection was >56 months for patients with a tumor SUV <4 and only 19 months for tumors with an SUV ≥ 4 [51].

An early report by Hebert et al. [52] in 1996 questioned the effectiveness of PET in differentiating tumor from fibrosis after radiotherapy. A more recent study by Hicks et al. [53] found that postradiation inflammatory changes did not significantly influence PET interpretation; in fact, such changes in irradiated surrounding normal lung correlated with tumor response.

Ichiya et al. [54] examined the FDG uptake in tumors before and after radiation therapy and found that tumors with a high degree of FDG uptake after radiation therapy were more likely to relapse. Similarly, MacManus et al. [55] found that the absence of residual hypermetabolic activity following radical radiotherapy or chemoradiation correlated with a lower relapse rate.

Several investigators have documented a role for PET or PET/CT following surgical therapy of lung carcinoma. In a study of 17 patients postpneumonectomy at high risk for recurrent disease or with suspected residual disease, PET influenced patient management in $>50\%$ of cases by demonstrating a different extent of disease than was noted using CT [56]. Hicks et al. [57] studied the results of PET scans in 63 patients with suspected recurrence after definitive surgical therapy for NSCLC. They found that the PET results significantly impacted patient treatment in 63% of cases and that the presence and extent of recurrent disease on PET were prognostic indicators. A study of PET in 62 patients following surgical therapy of lung cancer found a sensitivity of 93%, specificity of 89%, and accuracy of 92% for identification of recurrent tumor [58].

Post-treatment, false-positive PET uptake can occur from inflammation related to surgery, radiation therapy, or tumor necrosis, related to white blood cells, granulation tissue, and proliferative epithelium [59]. In equivocal cases, serial follow-up PET studies may be useful to document either progressively increasing uptake (recurrent tumor) or stable/decreased activity, corresponding to post-treatment changes.

CONCLUSION

Radiology currently plays an important role in the detection, diagnosis, staging, and follow-up of lung cancer. The increasingly widespread availability of functional imaging (PET, PET/CT) in recent years has provided a more accurate means of assessing stage of disease, following response to therapy, and detecting recurrence after definitive surgical therapy. Lung cancer screening with low-dose CT remains

somewhat controversial, and large ongoing multicenter trials are expected to shed light on the effectiveness of screening in reducing lung cancer mortality.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The author indicates no potential conflicts of interest.

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