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FDG-PET in the Evaluation of Solitary Pulmonary Nodules and the Staging of Lung Cancer

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*Lung cancer is the l*eading cause of cancer death for both men and women in the United States, killing more people than breast, prostate, colon, and pancreas cancers combined: Fully 85 percent of patients who develop lung cancer die from it.

Since peaking in 1984, the U.S. age-adjusted lung cancer incidence has decreased by more than 19 percent in men of all ages combined, with decreases since 1970 exceeding 40 percent among men less than age 55 years. Among women, rates continued to increase until recently and are now showing signs of leveling off. These trends largely reflect changes in smoking prevalence, which began to decline first among men and only later among women. Because 85 to 90 percent of lung cancer is attributable to smoking, lung cancer rates will continue to decline only if smoking prevalence declines further.

More women have died from lung cancer than from breast cancer

The scope of the problem, however, remains enormous:

1. Lung cancer is the leading cause of cancer death for both men and women and kills more patients than the next five most common cancers combined. Among men it accounts for more deaths than the next four causes of cancer death combined (prostate, colon and rectum, pancreas, leukemia), and among women it causes more deaths than breast cancer. Fully 85 percent of patients who develop lung cancer die from it.
2. In 2001, an estimated 169,500 Americans will be diagnosed with lung cancer. Lung cancer represents 13 percent of all incident cancers annually in the United States and 29 percent of all cancer deaths.
3. Although lung cancer mortality rates began to decline in 1990 for men (about 1.7 percent per year) and the 1-year relative survival rate for lung cancer overall has increased from 34 percent in 1975 to 41 percent in 1996, mortality rates for women continued to increase at least until 1998.
4. Since the 1980s, more women have died from lung cancer than from breast cancer-previously the major cause of cancer deaths in women
5. Even patients with the earliest surgical stage (T1N0) have disseminated disease between 15 and 30 percent of the time.
6. Although the link to tobacco is the clearest etiologic relationship for a human cancer, the development of lung cancer in persons who have never smoked and in former smokers and the failure of the majority of heavy smokers to develop the disease are poorly understood. The complex inter-relationships among genetic, molecular, and other biologic processes in modulating the carcinogenic response to tobacco smoke need to be

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further explored.

7. Chemotherapy, surgery, and radiation therapy have had a modest effect on patient outcomes, but these are more often expressed as improvements in "time to progression" or short-term survival than as overall survival. The mechanisms of resistance to drug and radiation therapy are poorly understood.
8. Despite significant progress, the molecular events underlying the development of lung cancer are largely unknown.
9. No chemopreventive agent has been shown to be effective in the prevention of lung cancer, and there is often brisk debate about whether there are any proven means of diagnosing lung cancer early.

PET improves on the accuracy of current methods of pre-treatment staging in cancer patients

Role of PET-FDG: The major clinical problems in lung cancer in which PET can assist include the identification of lung cancer in early stages when survival rates are higher and the correct staging of lung cancer for developing appropriate treatment strategies. Inherent in the process of early identification of lung cancer is the correct characterization of solitary pulmonary nodules. At present, only a small percentage of such nodules can be correctly characterized as confidently benign or malignant by chest radiography and CT. Most nodules remain indeterminate and the patient may unnecessarily be subjected to a tissue sampling procedure for diagnosis. An unacceptably high percentage of such indeterminate nodules continue to be discovered to be benign following a diagnostic surgical procedure.

The finding of a solitary pulmonary nodule (SPN) on a chest radiograph is a common problem in pulmonary medicine. SPNs are seen in 0.09 to 0.2% of chest radiographs (about 1 in 500 chest radiographs) and are caused by a variety of conditions, ranging from benign granulomas to lung cancer. Because solitary nodules are often malignant and because 5-yr survival after resection of a solitary bronchogenic carcinoma is 40 to 80%, it is important to promptly identify malignant nodules to ensure optimal treatment.

SPNs are caused by a variety of benign and malignant pro-cesses. Of the benign lesions, 80% are caused by infectious granulomas, 10% are caused by hamartomas, and the remaining 10% are caused by a variety of rarer disorders including noninfectious granulomas and other benign tumors.

The incidence of malignancy in SPN varies in different series considerably based on the definition of SPN used (e.g., 1 to 6 cm), selection criteria of patients (e.g., all surgical patients), as well as the referral pattern of the study center. The incidence of malignancy therefore ranges from 10 to 68% in the literature.

The percentage of malignancy, however, may decrease as the increasing use of CT imaging results in many smaller nodules being detected. Often, these tiny CT-detected nodules are simply dismissed, without further diagnostic evaluation, as not being clinically relevant. This, however, may not be appropriate, because recent reports suggest a higher than previously suspected percentage of these small nodules are malignant. Primary lung carcinoma rates of 38% have been reported among patients undergoing thoracoscopic biopsies for nodules less than 1 cm and a prevalence rate of 6.4% was found among those undergoing lung volume reduction surgery for emphysema. Additionally, in a recently completed CT screening study, the overall prevalence of high-risk patients with small nodules was 22%, with nearly 10% of these patients with nodules showing malignancy. Although a higher percentage of

these small nodules are benign, the fact that a considerable number of them are malignant has led to reassessment of diagnostic strategies and also created renewed interest in screening for lung cancer.

Once a pulmonary nodule is discovered, the possibility of its being malignant becomes an immediate concern because lung cancer is one of the most virulent of all cancers with a very low overall 5-year survival of approximately 10% to 15%. This statistic has not improved significantly for over 40 years despite considerable improvement in surgical techniques and the availability of other therapeutic options. The most hopeful note regarding this illness remains early detection, diagnosis, and treatment because true stage I lung cancers have a significantly better chance of survival, estimated to be 70% or higher. It appears that the smaller the malignancy when treated, the greater the survival advantage.

One major role of PET in lung cancer is to provide a reliable method for characterizing such indeterminate nodules with subsequent avoidance of need for invasive surgical procedure or CT-guided biopsy. A recent meta analysis published in the literature this year confirms the high sensitivity of FDG-PET in the characterization of solitary pulmonary nodules resulting in very useful negative predictive values and good likelihood ratios. The table below illustrates the excellent performance of FDG-PET compared to CT as reported by two recent articles in the literature.

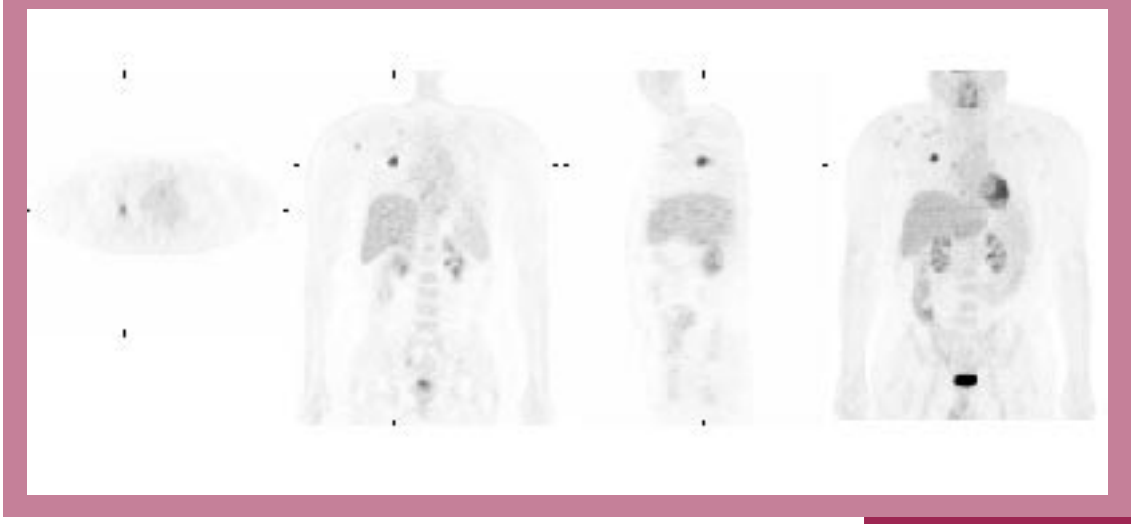
	FDG-PET	CT
Sensitivity	*92% [1] (97%)[2]*	*90%*
Specificity	*90% [1] (78%)[2]*	*65%*

[1] Lowe et al. J Clin Oncol. 1998;16: 1075-1084
[2] Gould et al. JAMA 2001;285:914-924

Another major role of PET in lung cancer is to improve on the accuracy of current methods for pre-treatment staging. At least two large studies published in the recent literature document the superior performance of FDG-PET over CT in staging. In using PET in this manner, important consideration needs to be given to the conditional performance of PET (sensitivity and specificity depending on the results of CT).

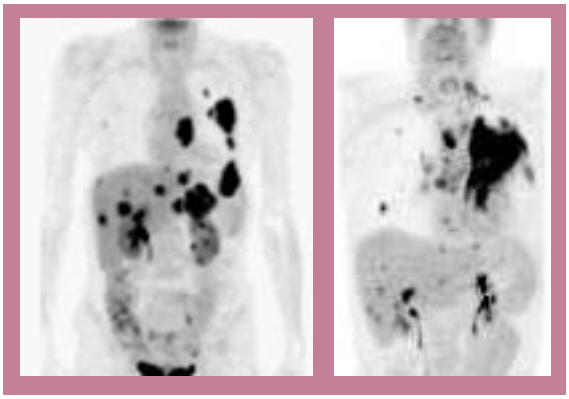
	FDG-PET	CT/MRI
Sensitivity	*92%[1]91% (± 9)[2]*	*52%/48%75% (± 15)[2]*
Specificity	*90% [1]86% (± 8) [2]*	*69%/64%66% (± 11)[2]*

[1] Bury et al. Eur Respir J 1997; 10: p 2529-2534 [2] Pieterman et al NEJM 2000; 343: p



75 year old male with persistent cough. Smoker for 30 years. FDG-PET study showed hypermetabolic nodule in right mid-lung strongly consistent with malignancy. CT result was indeterminate.

[Below] Two examples of advanced stage (Stage IV) non-small cell cancer of the lung imaged with FDG-PET are shown. PET is particularly helpful in assessing the "N" component of the TNM staging/classification criteria and often upstages a patient from "resectable" to a non-resectable (Stage IIIB or Stage IV) category.



References

Patients are able to relax comfortably while undergoing PET examinations.

August 2001. http://osp.nci.nih.gov/prg_assess/prg/lungprg/lung_rpt.htm

Lowe VJ, Fletcher JW, Gobar L, Lawson M, Kirchner P, Valk P, Karis J, Hubner K, Delbeke D, Heiberg EV, Patz EF, Coleman RE. Prospective investigation of positron emission tomography in lung nodules. [Multicenter Study]. Journal of Clinica Oncology. 16(3):1075-84, 1998 Mar.

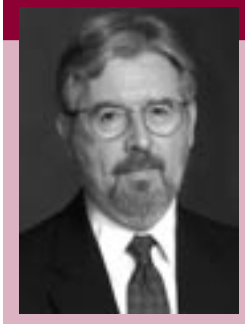
Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emmission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. [Meta-Analysis] JAMA. 285(7):914-24, 2001 Feb 21.

Bury T, Dowlati A, Paulus P, Corhay JL, Hustinx R, Ghaye B, Radermecker M, Rigo P. Whole-body 18FDG positron emission tomography in the staging of non-small cell lung cancer. European Respiratory Journal 10(11):2529-2534, 1997 Nov.

Pieterman RM, van Putten JW, Meuzelaar JJ, Mooyaart EL, Vaalburg W, Koeter GH, Fidler V, Pruim J, Groen HJ. Preoperative staging of non-small-cell lung cancer with positron emission tomography. New England Journal of Medicine 343(4):254-61, 2000 Jul 27.

Ost D, Fein A: Evaluation and Management of the Solitary Pulmonary Nodule. Am J Respir Crit Care Med Vol 162. pp 782-787, 2000.

Yankelevitz DF, Henschke CI: Small Solitary Pulmonary Nodules. Rad *Clinics North America . Vol 38. No. 3, May 2000.*



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James Fletcher, M.D., is currently a member of the Board of Directors and Chairman of the PET Education Committee of the Academy of Molecular Imaging; and a member of the House of Delegates and Chairman of the PET Education Committee for the Society of Nuclear Medicine.He is also the Chair of the Cooperative Studies Research Project on Role of FDG-PET in Evaluation of Solitary Pulmonary Nodules and Lung Cancer, a multi-institutional, 5-year research project sponsored by the Research Service of the Department of Veterans Affairs, with a $5,000,000 operational budget. He is the coordinator and participates in numerous professional educational symposia discussing clinical applications of Positron Emission Tomography.

Dr. Fletcher is interested in advancing the role of Positron Emission Tomography and Nuclear Medicine in Molecular Imaging to understand molecular basis of disease. He also conducts translational research involving novel radiolabeled biologic probes and ligands to support new drug discovery and development and is currently developing clinical applications for combined modality or dual imaging systems using contemporaneous computed tomography and positron emission tomography (CT/PET) “fusion imaging.”

Dr. Fletcher's has served as a Professor of Medicine and Radiology and the Director of the Division of Nuclear Medicine and PET at Saint Louis University School of Medicine. His previous professional activities include serving as President and Chairman of the Board of Directors of the Society of Nuclear Medicine; Chairman of the Board of Directors of the American Board of Nuclear Medicine; a Member of the ACGME Residency Review Committee for Nuclear Medicine; and the National Program Director for Nuclear Medicine of the Department of Veterans Affairs

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