

# DISCUSSIONS IN

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PET



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I M A G I N G

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## LEARNING OBJECTIVES

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

- Describe the fundamental approach of imaging use in small cell lung cancer.
- Summarize the usefulness of PET or PET/CT imaging compared with conventional methods.
- Explain the role of FDG-PET or PET/CT in evaluation of SCLC.
- Describe the potential role of PET or PET/CT in management of SCLC.

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Dr. Pandit-Taskar and Dr. Larson 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 profession service.

## PET and PET/CT in Small Cell Lung Cancer

By Neeta Pandit-Taskar, M.D., and Steven M Larson, M.D.

Lung carcinoma is a leading cause of cancer death in men and women in the U.S. While most lung cancers are non-small cell tumors, about 10% to 20% are small cell (SCLC), with slightly higher incidence in women than in men. SCLC is associated with poor prognosis, with an average two-year survival rate of less than 10%. Patients are usually symptomatic at diagnosis; 30% to 40% report dyspnea and chest pain. Only 4% to 5% of SCLC cases are detected as solitary pulmonary nodules.<sup>1</sup> Thus, SCLC differs markedly from non-small cell lung carcinoma (NSCLC) in biologic behavior and clinical course. It is associated with rapid growth, and almost two-thirds of patients have metastatic disease at presentation.

Early diagnosis and accurate staging are key to planning appropriate treatment. SCLC is staged as limited or extensive disease. Limited disease is localized enough to be included in a radiation port, while extensive disease includes distant metastases. Initial stage is the most important prognostic factor for survival. Age at diagnosis and performance status have also been independently linked to prognosis.

Surgery has a restricted use in management of SCLC, as only a few patients with limited disease may be eligible. Chemotherapy is the primary form of treatment for both stages, and radiation is included for patients staged with limited disease. The

response to initial treatment is usually good, with almost 80% of patients showing a major response. About 20% of patients with limited disease can be cured with proper therapy, while others will eventually have recurrence. The overall median survival for SCLC is only 10 to 14 months, longer for those with limited disease than for extensive disease.<sup>1</sup>

SCLC starts within the thorax, often near the mediastinum, and rapidly spreads to the lymph

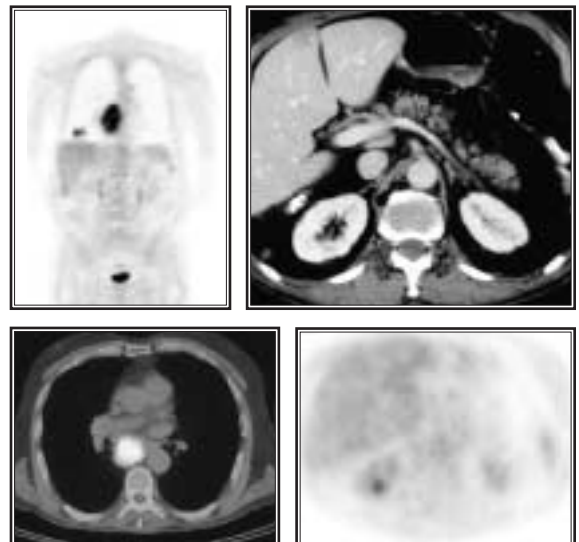


Figure 1. 81-year-old man with SCLC for initial staging. PET/CT shows uptake in right lung and mediastinum. CT shows lesion in liver. PET/CT allows accurate fusion to exclude disease in liver and adrenals. Disease is confined to left hemithorax.

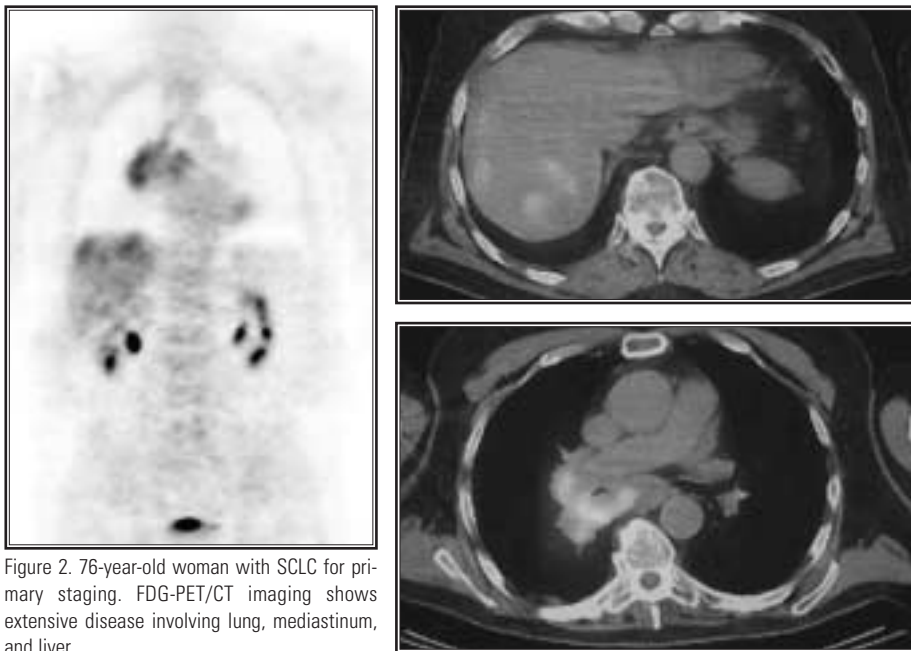


Figure 2. 76-year-old woman with SCLC for primary staging. FDG-PET/CT imaging shows extensive disease involving lung, mediastinum, and liver.

nodes, skeleton, brain, bone, liver, and adrenals. Staging is based on biopsy confirmation, rather than major surgery, and must be augmented by standard workup including chest radiography, CT scanning, thoracoscopy/mediastinoscopy, MR imaging, bone scans, and bone marrow biopsy.

Imaging plays a critical role not only in initial diagnosis but also in staging by establishing the correct extent of disease. Chest x-ray is useful for screening, while lesions are also detected on CT scans performed for evaluation of symptoms.<sup>2</sup> CT scanning has an established role in initial diagnosis and staging in the chest and mediastinum. Diagnosis of lymph node involvement by CT scans is considered reasonably accurate, except that diagnosis is based on the size of lesions, and nodes that are not significantly enlarged are categorized as benign. The accuracy for detection of metastatic lymph nodes and invasion in the mediastinum is reported to be between 50% and 82%.<sup>3</sup> Tumor recurrence and residual disease post-treatment are often difficult to assess by CT alone due to the alterations in the anatomic structures and other changes associated with surgery or radiation in postsurgical and postradiation treated cases. Accuracy in distinguishing tumor necrosis versus residual tumor is low.

Bone scanning, routinely used for staging and establishing disease to bones, is an easy and cost-effective method that provides complementary information to bone marrow biopsy. About 30% to 40% of evaluated patients can show disease on bone scans. Bone scan and bone marrow biopsy may not entirely corre-

late, however. It is likely that each identifies an independent pattern of osseous metastases, and both procedures should be performed. Serial bone scans can also be used to evaluate the course of disease, and improvement or worsening in follow-up scans may be associated with nonbony tumor response or progression, respectively, 70% of the time.<sup>4,5</sup>

Various radiopharmaceuticals, including thallium-201 chloride and indium-111 octreotide, have been used for evaluation of SCLC without success.<sup>6,7</sup> Scanning with 18-fluorodeoxyglucose (FDG) PET uses a physiologic method for evaluation of tumor that is based on increased metabolic activity and uptake of glucose by tumor cells. It has the ability to detect active sites of tumor tissue and plays an established role in diagnosis and staging of many cancers.

FDG-PET scanning is now routinely used in NSCLC for staging, restaging, and assessment of therapy. It is highly sensitive and accurate in distinguishing benign from malignant lesions for evaluation of solitary nodules and in staging of mediastinal disease. It is useful in distinguishing N0/N1 disease from N2/N3 disease and helps in obviating invasive procedures such as mediastinoscopy and thoracotomy by identifying N3 disease. It has also been found to be more cost-effective for follow-up and has prognostic value in imaging lung cancer patients on treatment.<sup>8</sup>

Combination scanning with PET and CT has added a new dimension to cancer imaging, and the number of sites with PET/CT has grown rapidly in last two years. The combination scanner allows faster imaging by preclud-

ing the need for slower transmission images and by integrating the CT images with PET images. CT images provide an anatomic map and are used for attenuation correction. Combined scanning allows easier, more accurate fusion of images and overcomes the drawbacks of time-consuming retrospective fusion through software and the inaccuracies inherent in fusing disparate image data sets. PET/CT has resulted in better diagnosis, staging, and restaging in a variety of cancers.<sup>9</sup>

Increased glucose metabolic activity and uptake of FDG in SCLC makes it possible to evaluate these tumors using PET.<sup>10</sup> Although experience with PET is more limited in SCLC than in NSCLC, recent studies have found PET and PET/CT to be useful. PET/CT is likely to be more sensitive and specific in evaluation of the mediastinum, with its complex anatomy and close proximity of vasculature and nodal stations, and of adrenal lesions and liver by accurate localization of FDG-avid foci.

### BENEFITS IN STAGING

Establishing limited disease by excluding extrathoracic disease would indicate treatment with radiation and chemotherapy as opposed to only chemotherapy for extensive disease. Accurately mapping the extent of thoracic disease is also important to delineating an appropriate radiation port. Since CT assessment is based on size criteria, even in patients with normal nodes (<1 cm) on CT, about 10% to 15% may have disease. Treatment failure may occur if these lesions are not identified. FDG-PET can help identify active tumors by their tracer avidness even if the lymph nodes are not enlarged. Recent studies have shown high sensitivity and specificity for PET and PET/CT in SCLC (Figures 1 and 2).

Initial studies in a small number of patients have shown a potential role for FDG in the staging of SCLC and high uptake of the tracer in the primary cancer.<sup>11</sup> Schumacher et al compared PET/CT and CT in 13 patients, showing overall benefits for PET, which detected more sites than CT and led to a change in staging in seven patients (limited to extensive disease).<sup>12</sup> PET detected all primary and metastatic sites with sensitivity as high as 97% to 100% and 83% agreement with conventional staging.

In a large study, FDG-PET caused a stage migration in 14 of 120 patients, correctly upstaging 10 patients to extensive disease and downstaging four. FDG-PET was significantly superior to CT in the detection of extrathoracic lymph node involvement (sensitivity 100% versus 70%, specificity 98% versus 94%) and distant metastases (sensitivity 98% versus 83%, specificity 92% versus 79%).<sup>13</sup> Overall, in

various studies, FDG-PET upgraded limited disease to extensive disease in 8% to 11% patients.<sup>13-15</sup>

- *Assessment of appropriate patients for surgery.* Selected cases with limited stage SCLC are likely to undergo surgical resection followed by platinum-based chemotherapy (T1/T2 tumors). PET imaging can help identify such candidates by accurate staging that complements the information of CT scanning and can localize otherwise undetected tumor sites for surgical biopsy or in cases with carcinoid or other mixed histology tumors. FDG-PET imaging can provide more accurate and precise thoracic versus extrathoracic staging, leading to better identification of patients who are eligible for surgery.

- *Evaluation of bone metastasis.* Distant metastasis is very common in patients with SCLC. Autopsies in patients with advanced disease show that only 4% have disease confined to the thorax, while the remainder have metastatic disease outside the thoracic cavity. Bone metastases may be present in 27% to 41% of patients and in 9% to 13% as a single site of metastatic involvement.<sup>1</sup> While large studies evaluating PET imaging for bone lesions in SCLC are lacking, some studies have found FDG-PET more useful and sensitive as compared with bone scans in a small number of cases. A study by Schumacher et al that evaluated FDG-PET for staging found it more sensitive for evaluation of bone metastasis than bone scan in three of 10 patients with bone disease.<sup>12</sup> More data are needed to firmly establish this conclusion.

- *Evaluation of brain metastasis.* Brain metastasis occurs in about 10% to 14% of patients with SCLC and may occur as a single site of metastatic disease in 4% to 6% of patients.<sup>1</sup> MRI with gadolinium enhancement is the method of choice for assessing the brain in patients with SCLC. FDG is known to accumulate in high concentration in the brain, limiting evaluation of brain tumors. FDG is not sensitive in diagnosing brain lesions and is not recommended for routine evaluation of brain metastasis. In a number of studies in which patients were evaluated for metastatic disease, brain metastases were not correctly diagnosed.

Other PET tracers that normally do not accumulate in the brain may be more helpful in evaluation of brain metastasis, but there are presently no concrete data to support their use in SCLC. In a study by Brink et al evaluating FDG-PET for staging, FDG was significantly less sensitive than cranial MRI/CT in the detection of brain metastases, with a sensitivity of 46% versus 100% and specificity of 97% versus 100%.<sup>13</sup> FDG-PET imaging has been used in other tumors to identify post-treatment changes from residual tumor in brain or evaluation of recurrent disease, especially when MRI shows subtle change or is equivocal due to the associated post-treatment changes. Similar use in SCLC has yet to be explored, however. FDG-PET's ultimate usefulness in clinical practice and management may be limited by this disease's aggressive clinical course and the lack of alternative therapeutic options.

- *Paraneoplastic syndromes (PNS).* SCLC can also present as paraneoplastic syndrome, and it can account for approximately 75% of the tumors associated with syndrome of inappropriate secretion of antidiuretic hormone. A study using FDG-PET imaging in patients with PNS showed that in eight of 20 patients, FDG-PET was able to localize disease sites and direct biopsy, which was ultimately useful in establishing histologic diagnoses of SCLC. FDG-PET could be a useful diagnostic test for evaluating patients with PNS, especially when conventional imaging fails to identify the tumor and guide biopsies.<sup>16</sup>

## RECURRENT DISEASE AND PROGNOSIS

Many initial PET studies included patients scanned for recurrent disease or restaging. FDG-PET has been shown to be highly sensitive in detection of recurrent disease and restaging.<sup>17</sup>

PET has also been shown to be of prognostic value in SCLC. We evaluated 62 scans in 46 patients with SCLC. In 54 scans that were done for residual or recurrent disease, there was avid uptake of tracer by the tumors. FDG-PET showed high sensitivity in detection of recurrent and residual disease. We correlated PET positivity and SUV as predictors of outcome.

All patients with negative scans had better long-term survival as compared with the FDG-positive cases. Limited disease patients showed a greater statistically significant difference than extensive disease patients.<sup>17</sup>

In another study by Blum et al, PET-CR (complete remission) was shown to confer longer median time to progression (13.7 months) as compared with patients with no CR (9.7 months).<sup>18</sup>

We feel that FDG-PET can help in cases in which evaluation of residual disease is equivocal by other methods due to therapy effect and can provide prognostic information so that further therapies can be suitably managed.

## CHANGE IN MANAGEMENT

PET imaging has played an important role in management of many cancers. In various tumors, it has been used to assess early

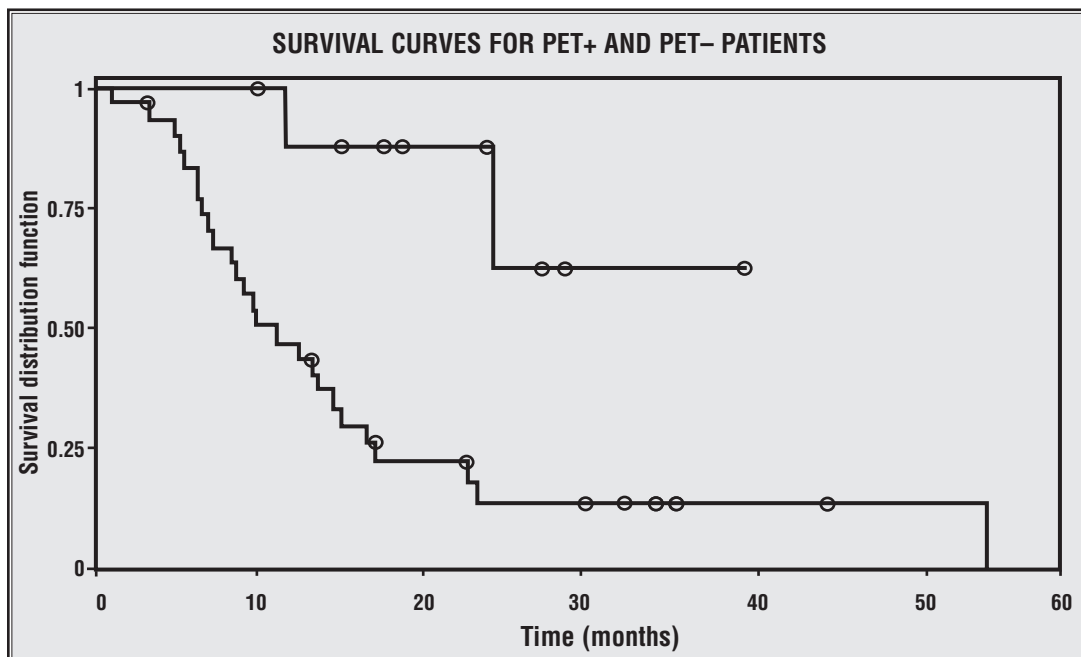


Figure 3. Kaplan Meier curve for the PET+ and PET- patients. There is statistically significant difference between number of patients surviving in the PET- and in the PET+ group ( $p = 0.0108$ , log-rank test).

response to treatment and has led to change in treatment. It has also shown promising results and impact in management of radiation therapy planning (RTP). Studies in NSCLC have shown its potential in identifying the viable extent of tumors and definition of gross and treatment target volumes for RTP. The functional information provided by PET has often led to alterations in treatment planning, changing the size and/or direction of radiation portals. Overall, FDG-PET helped achieve better targets by inclusion of lesions otherwise missed by other imaging modalities.<sup>19</sup>

It is important to ask if the higher sensitivity of FDG-PET imaging and improved results in staging in SCLC also lead to any change in management. Recent studies have specifically addressed this issue, and data support PET's usefulness in management of SCLC. Blum et al studied 36 consecutive SCLC patients who underwent 47 PET studies for either staging (n = 11), restaging after therapy (n = 21), or both (n = 4). FDG-PET upstaged 33% of patients from limited to extensive disease and was confirmed accurate in 11 (79%) sites by follow-up. Restaging PET influenced management in 13 cases (52%).<sup>18</sup>

In another study in 42 patients, PET results changed the patient's management in 12 cases (29%), and in eight patients (19%) changed the RT plan, which was either canceled or modified in radiation field and vol-

ume. PET also helped to exclude extensive disease in a patient, permitting surgical resection, and helped alter the chemotherapy plan in three patients. In five patients (12%), PET excluded malignancy, as the suspicious lesions found with conventional cross-sectional imaging did not take up F-18 FDG.<sup>20</sup>

Bradley et al identified unsuspected regional nodal metastasis in six (25%) of 24 patients, and the RTP was significantly altered to include the PET-positive/CT-negative nodes within the high-dose region in each of these patients.<sup>15</sup>

### OTHER TRACERS

SCLC expresses neuroendocrine markers, and dihydroxyphenylalanine (DOPA) is known to accumulate in neuroendocrine tumors. Imaging of SCLC using 3,4-dihydroxy-6-(18)F-fluoro-phenylalanine (F-18 DOPA) was attempted and compared with FDG-PET and other conventional imaging procedures. F-18 DOPA PET was less sensitive than FDG-PET and standard imaging procedures in the staging of SCLC. There was no clear relation between F-18 DOPA uptake and positivity of neuroendocrine markers on immunohistochemistry. F-18 DOPA does not appear to be useful for staging or treatment evaluation in SCLC. It is possible that F-18 DOPA uptake may reflect better differentiation of the tumor and possibly a better

prognosis.<sup>21</sup> However, this needs to be established in a larger study.

### CONCLUSION

SCLC is a clinically challenging tumor that has a high rate of recurrence and a low cure rate. Initial staging is critical for management and has prognostic value. FDG-PET or PET/CT imaging allows detection of active tumor and appears to be useful in SCLC. It is highly sensitive and accurate in detection of disease and initial staging. It appears to have significant impact on management of SCLC patients by altering staging and radiation plan. Semiquantitative estimates like SUVmax and PET positivity provide prognostic information that can be useful in guiding therapy in patients.

In selected cases where other imaging is equivocal or difficult due to anatomic alterations, FDG-PET can be useful for evaluating recurrent or residual disease.

The lack of newer or alternate therapies has limited its use in clinical practice of management of SCLC. As the search for new therapies is ongoing, assessment of physiologic response using FDG-PET may be useful in monitoring treatment effectiveness.

It appears likely that PET/CT will play an increasing role in management of SCLC patients in staging, assessment of treatment response, and radiation therapy planning in limited stage disease.

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