for post testing and Reader Evaluation. E 100% and 89.3%, respectively, for an sensitivity and specificity of FDG-PET were for biopsy-proven lung cancer. The sen-


7. Strauss LG. Sensitivity and specificity of FDG-PET in eval-
ung of malignancy in patients present-
ing M1 disease, with a maximum SUV of 4.5. Br Thorac Cardiovasc Surg 1999;54:370-

193.


1791.

12. Coleman RE. PET in lung cancer stag-

13. Dhital K, Saunders CA, Seed PT, et al. Comparative efficacy of positron emission tomography in evaluating patients for pul-

monary malignancies. J Nucl Med 2001;42:773-

778.


555.

15. Gupta NC, Graeber GM, Bishop HA, et al. PET and PET/CT imaging of malignancies in patients presenting with NSCLC. Curr Oncol Rep 2003;5:370-

193.


794.

17. Frank A, Lefkowitz D, Jaeger S, et al. Accuracy of 18F-fluorodeoxy-

D-glucose positron emission tomography for the eval-
ung of malignancy in patients present-
ing M1 disease, with a maximum SUV of 4.5. Br Thorac Cardiovasc Surg 1999;54:370-

193.


1027.


1472.

23. Frank A, Lefkowitz D, Jaeger S, et al. PET and PET/CT imaging of malignancies in patients presenting with NSCLC. Curr Oncol Rep 2003;5:370-

193.


1472.


1472.


3260.


3260.


3260.


794.


3260.


3260.


3260.


3260.


3260.


3260.


3260.
Patient with NSCLC who have been resected and/or treated sometimes return with a new nodule in the lung. Because almost all patients have previous CT scans for comparison, the determination of whether or not it is new is usually straightforward. This lesion, if malignant, is considered metastatic cancer and not a second primary if it appears within 24 months of the first pulmonary resection. Unfortunately, if the nodule is less than 6 mm in size, which they typically are, it may fall under the radar of FDG-PET. FDG-PET is quite sensitive (91% to 97%) and specific (78% to 88%) for larger nodules, but biopsy is again required prior to any treatment.

The repeat FDG-PET, like the initial PET scan, only provides targets for biopsy. It does not confirm or rule out the presence or absence of cancer.

FALSE POSITIVES AND FALSE NEGATIVES

Many studies point out that FDG-PET is accurate for staging patients with NSCLC.11,12 However, false positives from infections and inflammatory processes such as tuberculosis granulomas, coccidiodomycosis, aspergillosis, histoplasmosis, and silicosis are common. They result in high uptake values that mimic those of cancer. Histoplasmosis represents a common problem in the U.S. and along the Mississippi Valley. We reported a larger incidence of false positives in our series than did Gupta and Roberts,12,15 but most large series report this problem. Obviously, surveillance FDG-PET has the same problem as the initial PET scan, but more of a problem because of the treatment the patient received.

While recent trials have found FDG-PET highly accurate for detection of breast cancer, determining recurrence is often difficult due to the inflammatory responses, necrotic tumor, or fibrotic scar tissue from recurrent tumor, resulting in false-positive results. Understanding the physiological and benign causes of FDG uptake is therefore important for accurate interpretation of FDG-PET scans.

Various mechanisms that may contribute to false positive results, such as uptake macrophages, can influence FDG-PET in detection of recurrent NSCLC. Cellular repair mechanisms by which macrophages replace tumor cells and thus enhance FDG uptake are often found in patients who have received radiation and chemotherapy. Postirradiation pneumonitis has also been linked to increased FDG uptake. A study of 89 patients conducted by Lowe in 1998 demonstrated that the rate of FDG accumulation in inflammatory cells differs from that of tumor cells. Thus, technical improvements in emission acquisition time may be able to decrease the false positive rate attributed to active infection by differentiating it from cancer.

In our report on 400 patients, we showed that FDG-PET scanning improved patient selection prior to surgery for patients with NSCLC. The accuracy varied at different thoracic lymph node locations, however. Similarly, after resection, lymph nodes are often “hot” or suspicious on the surveillance FDG-PET scan, but the accuracy at each lymph node station must be taken into account. We found that the initial FDG-PET scan is most accurate at the high paratracheal nodes (2L and 2R), the subcarinal node, the mediastinal lymph nodes, and the inferior pulmonary ligament nodes. The accuracy of a postoperative surveillance PET scan varies from station to station and varies at different thoracic lymph node stations. The initial FDG-PET scan is most accurate at the high paratracheal nodes. If the patient has received chemotherapy and radiotherapy, the initial FDG-PET scan is most accurate at the high paratracheal nodes.

Clinicians, of course, worry more about false negatives than false positives. False negatives can occur in patients with recurrent small nodules (less than 6 to 8 mm in size), pleural mesothelioma, recurrent cancer, and well-differentiated adenocarcinoma. If the primary was PET-positive on initial imaging, we recommend FDG-PET for surveillance. If it was PET-negative, the recurrent cancer needs to be biopsied to determine if the patient is a surveillance PET in these patients is questionable. The cause for the false-negative rate can be explained in three categories.

IDEAL TIMING

The ideal time to perform a surveillance FDG-PET is not known, it depends significantly on the treatment that was performed. For example, if a patient has had surgery and radiation therapy, the FDG-PET is probably easy to interpret after six weeks. But if a patient has had chest irradiation as part of the treatment, false positives can be present for a longer time.

Frank9 recommends waiting four to six months for a more accurate PET scan due to changes in chemotherapeutic drug dosages. If a patient received chemotherapy to subside and to provide a more accurate assessment of tumor viability. In our experience, however, patients with highgrade adenocarcinoma, metastases, and FDG-PET results should be repeated after six weeks following the completion of radiation therapy. This is especially true if the initial FDG-PET exam was performed at the same institution.

Finally, and most provocative, are the growing data that the maxSUV (which is less variable than the mean SUV) represents a tumor’s “in vivo virulence” or an objective measure of its biologic aggressiveness. Identifying a high-risk group of patients who are more likely to recur may help determine the best frequency of surveillance.

A study by Higushi et al. of 57 patients found that FDG uptake in primary NSCLC was an independent predictor of recurrence, especially for patients with T3N1 NSCLC. Hicks reported on 59 patients and showed that both the presence (p = 0.012) and the extent (p < 0.001) of FDG uptake were highly significant prognostic factors.

Perhaps patients who have a primary lung mass with a maxSUV greater than 10 might deserve closer surveillance after resection. Similarly, in our soon-to-be-published study of 118 patients, we reported that the maxSUV via FDG-PET/CT of the pulmonary mass itself is an excellent prognostic indicator of the malignant potential, lymphovascular invasion, and degree of differentiation of a patient’s NSCLC, as well as a better predictor of recurrence and survival than the current T and N classification.

SUPPORTING LITERATURE

The background, reasoning, and potential pitfalls presented here are an important foundation for understanding current literature on the role of FDG-PET for detection of recurrent NSCLC. The chance of recurrence in patients with stage IIIA NSCLC with an excellent resection is high despite complete resection. The five-year survival rate for patients with pathologic stage (not clinical stage) Ia, Ib, II, and IIIA NSCLC is 67%, 57%, 47%, and 23%, respectively.10

Approximately half of patients with a history of resected NSCLC present with a recurrent tumor. No randomized trial has ever shown that early detection of recurrent NSCLC positively affects a patient’s length of life or quality of life; in fact, some researchers believe that early detection does not improve survival.14

Table 2 summarizes some of the studies that have evaluated the efficacy of FDG-PET for detection of recurrent NSCLC. Bury et al. studied 129 patients with NSCLC (60 with a previous history of NSCLC) and determined that FDG-PET can detect recurrent or residual NSCLC. In this study, however, only 50% of the patients had pathologically proven biopsies. The authors found the sensitivity and specificity of repeat FDG-PET for detecting recurrent cancer to be 100% and 92%, respectively, compared with only 71% and 95% for CT.15

In a review of a 1995 study of 39 patients, all of whom had biopsy-proven recurrence, that the sensitivity and specificity of FDG-PET were 100% and 61.5%, respectively...
FDG-PET is not known; it depends on the type of therapy alters the results.

The ideal time to perform a surveillance FDG-PET study is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.

FDG-PET is not known; it depends on the type of therapy alters the results.
ly. Frank in 1995 followed 20 patients for more than four years assessing for biopsy-proven lung cancer. The sensitivity and specificity of FDG-PET were 100% and 88.9% respectively with an overall accuracy of 92.5%, sensitivity and specificity with CT were 67% and 85%, for an accuracy of 82%. All 20 patients were biopsied. Radiation pneumonitis and the accumulation of macrophages around the biopsy site did not affect the detection of positive results, as did acute inflammation and the presence of reactive mesothelial cells.

Patr and Lowe found in a study of 43 patients that the mass SUV on FDG-PET can help distinguish between recurrence and fibrosis. In Table 2, a pooled data analysis for studies that have at least 35 patients indicates that local recurrence of previously treated lung carcinomas (an example of which is shown in the figure) can be detected by FDG-PET with an average sensitivity of 97% and a specificity of 86%.

### CONCLUSIONS

The role-FDG-PET plays in patients with NSCLC is well documented, it is a vital part of staging. In contrast, its role in detecting recurrent NSCLC and its impact as a surveillance tool remains undefined. The interpretation of the surveillance FDG-PET scan is only as good as the staging performed after the initial FDG-PET scan done prior to therapy. But significant evidence supports the superiority of FDG-PET for CT detection for both recurrent local and distal NSCLC. This has led many insurance companies to reimburse the cost of surveillance FDG-PET. It is difficult to demonstrate the effect of careful follow-up in patients with any type of cancer. However, FDG-PET already plays an important role in the planning and direction of adjuvant radiotherapy. The true impact that surveillance FDG-PET will have on survival and disease-free survival, as well as its actual cost-benefit ratio, can be determined only through well-designed prospective multi-institutional trials.

---

**References**


---

**Initial FDG-PET and CT Imaging**

The usefulness of a surveillance FDG-PET scan is contingent on hypervigilance after the initial FDG-PET scan exam. All suspicious locations on the first PET scan should have been biopsied or further investigated (MR imaging for bone and brain and biopsies for all other nodal or possible metastatic sites). We firmly believe that the value of the repeat FDG-PET study depends largely on the choice of targets to be biopsied after the first PET scan. Interpretation is easier and more useful if all suspicious sites have been confirmed or cleared prior to initial therapy (surgery or chemo-radiotherapy). A serious conundrum exists if this is not done. Patients with NSCLC must be pathologically staged, not clinically staged.

An example is a patient who has biopsy-proven NSCLC in the left upper lobe, which has a maximum standard uptake value (mSUV) of 9. The first FDG-PET also finds a suspicious area in the liver, potentially representing a metastasis. If that is negative, left upper lobeectomy should be performed, even if the pulmonary lesion and the suspicious lesionobar has very different SUVs (max SUV levels). If the surveillance FDG-PET scan performed three months after resection shows no evidence of local recurrence but...