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## LEARNING OBJECTIVES

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

- Describe the advantages of using FDG-PET over traditional cross-sectional imaging modalities for the staging of NSCLC.
- Interpret a surveillance FDG-PET scan after therapy for NSCLC based on pathologic staging performed after initial FDG-PET.
- Recognize possible false positives and false negatives on surveillance FDG-PET after therapy.
- Discuss the current literature and controversies about surveillance FDG-PET after treatment of NSCLC.

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Ms. Bryant and Dr. Cerfolio 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.

## Role of FDG-PET and PET/CT in Detecting Recurrent Non-Small Cell Lung Cancer

By Ayesha Bryant, MSPH, and Robert J. Cerfolio, M.D.

The role of FDG-PET in detection of non-small cell lung cancer is controversial and has not yet been fully explored. Only over the past several years have data shown the usefulness of FDG-PET for evaluation of an indeterminate pulmonary nodule, staging of mediastinal lymph nodes, evaluation of local nodal and distant metastases, and response to chemoradiotherapy<sup>1-7</sup> for patients with NSCLC. FDG-PET is now a widely accepted and readily available radiologic modality for NSCLC in the U.S. and Europe. It is a mandatory staging and diagnostic tool used in the everyday practice of many pulmonologists, oncologists, radiation oncologists, and thoracic surgeons. Its usefulness in the detection and staging of other cancers is also well documented (Table 1).<sup>8</sup>

Some insurance companies have agreed to reimburse the cost of an FDG-PET scan after resection of NSCLC as part of routine surveillance for recurrent disease. Surveillance FDG-PET has also been used in patients who have undergone chemoradiotherapy alone. FDG-PET can be performed alone or via integrated PET/CT using FDG. We have shown the superiority of integrated PET/CT over dedicated PET in a prospective randomized trial<sup>9</sup> for the initial staging of NSCLC. Although other radiopharmaceutical agents have been studied, most of the literature concerns FDG, the workhorse for PET in NSCLC.

### INITIAL FDG-PET AND SUBSEQUENT STAGING

The usefulness of a surveillance FDG-PET scan is contingent on hypervigilance after the initial FDG-PET 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 (maxSUV) of 9. The FDG-PET also finds a suspicious area in the liver, potentially representing M1 disease, with a maximum SUV of 4.5. The possible metastatic site should be cleared by ultrasound-guided biopsy. If that is negative, left upper lobectomy should be performed, even if the pulmonary lesion and the site that possibly harbors cancer have very different maxSUV levels. If the surveillance FDG-PET scan performed three months after resection shows no evidence of local recurrence but



**Figure 1.** Fifty-year-old man had a right lower lobectomy two years prior for a T2N1M0 pathologically staged squamous cell cancer that was completely resected. Patient did not have a complete thoracic lymphadenectomy performed at the time of lobectomy and received no adjuvant therapy. Surveillance chest CT showed a soft-tissue mass near the right lower lobe stump (patient did not have an intercostal muscle flap used to buttress his bronchus at the time of surgery two years earlier) and enlarged (15-mm) paratracheal lymph nodes. Dedicated FDG-PET showed intense uptake in the 2R (maxSUV 7.9), 4R (maxSUV 9.4), 10R (maxSUV 10), 7 (maxSUV 8.6), and 11R (maxSUV 8.8) lymph nodes. No distant metastases were identified.<sup>8</sup> Patient underwent esophageal ultrasound with fine-needle aspirate of the number 7 subcarinal lymph node that confirmed recurrent NSCLC.

again demonstrates a lesion in the liver in the same location and with the same maxSUV, no further investigation is needed, and the patient is spared undue stress. The interpretation of the second FDG-PET scan is enhanced because of the rigors of staging after the initial one.

In contrast, consider the same patient with the same biopsy-proven NSCLC of the left upper lobe nodule with the same maxSUV of the primary lesion of 9. But in this case, the patient is denied surgery because he has an enlarged 1.1-cm subcarinal (number 7) lymph node with a maxSUV of 4.5 and the same lesion in the liver with a maxSUV of 4.5. The patient is never referred for surgical resection because he has “metastatic disease.” Instead, he is offered and undergoes chemoradiotherapy. Three months after the completion of his therapy he is “restaged” by surveillance FDG-PET. How can that scan possibly be interpreted? Was he initially stage IIIa because he had N2 in the subcarinal lymph node, or was he stage IV with M1 disease in the liver? If the primary biopsy-proven site of cancer has a 50% reduction in maxSUV and the other sites do not, does that mean they never harbored cancer and were false positives? The

assumption that the nonbiopsied sites will behave like the biopsied sites is incorrect. Perhaps these sites harbor recalcitrant cancer, or perhaps they were not included in the field of radiation if radiotherapy was used. The poor initial staging has made the surveillance FDG-PET scan essentially uninterpretable and useless.

Patients 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 often are, it may fall under the radar of FDG-PET.<sup>10</sup> 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.<sup>11,12</sup> 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 have shown that FDG-PET is accurate for staging patients with NSCLC.<sup>1,13,14</sup> However, false positives from infections and inflammatory lesions from sources such as tuberculosis granulomas, coccidiomycosis, aspergillosis, histoplasmosis, and silicosis are common. All can result in high uptake values that mimic those of cancer. Histoplasmosis represents a common problem in the southeastern U.S. and along the Mississippi Valley. We reported a larger incidence of false positives in our series<sup>1</sup> than did Gupta and Roberts,<sup>15,16</sup> but most large series report this problem. Obviously, surveillance FDG-PET has the same problem; in fact, it may have 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,<sup>17</sup> determining recurrence is often difficult due to morphological changes, 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 positives, 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.<sup>18</sup> 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.<sup>19</sup> 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,<sup>1</sup> 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, so 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),<sup>20</sup> the periesophageal nodes,<sup>8</sup> and the inferior pulmonary ligament nodes.<sup>9</sup> The accuracy of a postoperative surveillance FDG-PET at each nodal station has never been studied, however. Such a study would be difficult, as the type of therapy alters the results.

Although we recommend and perform a complete thoracic lymphadenectomy in

**TABLE 1. DETECTION AND STAGING OF CANCER BY FDG-PET**

Cancer type	Diagnostic accuracy
Solitary pulmonary nodule	94%
Lung	91%
Head and neck	92%
Colorectal	94%
Melanoma	88%
Lymphoma	97%
Breast	92%
Ovarian	81%
Musculoskeletal	93%
Pancreatic	92%
Metastatic thyroid	100%

all patients at the time of surgery, few surgeons follow this practice, and many patients have residual nodal tissue left in the ipsilateral chest. Furthermore, some patients who undergo a surveillance FDG-PET scan may have been treated only with radiation or chemotherapy and not surgery. If the patient had only radiotherapy, the mediastinal nodes often have a falsely elevated maxSUV secondary to the external-beam radiation. Inoue has shown that postradiotherapy effects can last for up to six months.<sup>21</sup> All these facts need to be carefully considered when interpreting the surveillance FDG-PET studies.

The most important warning, however, is that more chemoradiotherapy is rarely acceptable for a patient who has “recurrent cancer” because FDG-PET shows a “hot node” or a metastatic site. The target that PET provides must be biopsied and should be confirmed or cleared via biopsy unless the risk and/or morbidity of a biopsy is extremely high or likely inaccurate.

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), carcinoid tumors, bronchoalveolar cancer, and well-differentiated adenocarcinoma. If the primary was PET-positive on the initial pretreatment PET, we recommend FDG-PET for surveillance. If it was initially PET-negative, the recurrent cancer may also be negative, and the role of a surveillance PET in these patients is questionable. The cause for the false-negative PET is related to the slower metabolic rate in these lesions compared with other primary lung cancers.<sup>22</sup>

**IDEAL TIMING**

The ideal time to perform a surveillance FDG-PET study is not known; it depends significantly on the treatment that was performed. For example, if a patient has had resection alone, surveillance 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. Frank<sup>23</sup> recommends waiting four to six months to allow inflammatory changes of radiochemotherapy to subside and to provide a more accurate assessment of tumor viability. In our experience, however, a repeat or restaging FDG-PET after neoadjuvant therapy and/or surveillance FDG-PET can be accurately interpreted as early as two weeks following the completion of

**TABLE 2. DETECTION OF RECURRENT NSCLC USING FDG-PET**

First author	Year published	Number of patients	Sensitivity	Specificity
Hicks	2001	59	97%	82%
Lee	2001	196 (13)*	70%	67%
Ukena	2000	41	97%	83%
Bury	1999	129	100%	92%
Inoue	1995	39	100%	61%
Patz	1994	43	97%	100%
Pooled		321	97%	86%

\*Only 13 of 196 patients enrolled in study had a history of NSCLC.

radiotherapy. This is especially true if the initial FDG-PET exam was performed at the same institution and this history is provided to the nuclear radiologist.

Finally, and most provocative, are the growing data that the maxSUV (which is less variable than the mean SUV<sup>24</sup>) 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. Downey reported that in a series of 100 patients, the maxSUV of the pulmonary nodule was a predictor of recurrence and survival in patients who underwent complete resection.<sup>25</sup>

A study by Higashi of 57 patients found that FDG uptake in primary NSCLC was an independent predictor of recurrence, especially in patients with stage I NSCLC.<sup>26</sup> Hicks reported on 59 patients and showed that both the presence ( $p = 0.012$ ) and the extent ( $p < 0.001$ ) of relapse on PET were highly significant prognostic factors.<sup>27</sup>

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 315 patients, we report that the maxSUV via FDG-PET/CT of the pulmonary mass itself is an excellent prognosticator 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, N, and M staging classification.<sup>28</sup>

**SUPPORTING LITERATURE**

The background, reasoning, and potential pitfalls presented above can assist in interpreting current literature on the role of

FDG-PET for detection of recurrent NSCLC. The chance of recurrence in patients with NSCLC is, unfortunately, 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.<sup>29</sup>

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 or quality of life; in fact, some researchers believe that early detection does neither.<sup>30</sup> Despite the lack of research-based evidence, the American Cancer Society guidelines recommend that patients who have undergone “curative resection” should be followed with chest x-rays and CT scans every three to six months during the first year after resection, every six months for the next two years, and yearly after that.

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 the efficacy of repeat FDG-PET for detecting 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.<sup>18</sup>

Inoue found in a 1995 study of 39 patents, all of whom had biopsy-proven recurrence, that the sensitivity and specificity of FDG-PET for detecting recurrent tumors were 100% and 61.5%, respective-

ly.<sup>21</sup> Frank in 1995<sup>31</sup> followed 20 patients for more than four years after treatment for biopsy-proven lung cancer. The sensitivity and specificity of FDG-PET were 100% and 89.3%, respectively, for 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 necrotic tissue caused false-positive results, as did acute inflammation and the presence of reactive mesothelial cells.

Patz and Lowe<sup>32</sup> found in a study of 43 patients that the maxSUV 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 recurrences 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 remain controversial. 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 over CT for detection of 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 radiochemotherapy. The true impact that surveillance FDG-PET will have on survival and disease-free interval, as well as its actual cost-benefit ratio, can be determined only through well-designed prospective multi-institutional trials.

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