

# Monitoring and management of lung cancer patients following curative-intent treatment: clinical utility of 2-deoxy-2-[fluorine-18]fluoro-d-glucose positron emission tomography/computed tomography

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**Abstract:** A large number of studies have demonstrated that 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) is superior to conventional modalities for the diagnosis of lung cancer and the evaluation of the extent of the disease. However, the efficacy of PET/CT in a follow-up surveillance setting following curative-intent treatments for lung cancer has not yet been established. We reviewed previous papers and evaluated the potential efficacy of PET-CT in the setting of follow-up surveillance. The following are our findings: 1) PET/CT is considered to be superior or equivalent to conventional modalities for the detection of local recurrence. However, inflammatory changes and fibrosis after treatments in local areas often result in false-positive findings; 2) the detection of asymptomatic distant metastasis is considered to be an advantage of PET/CT in a follow-up setting. However, it should be noted that detection of brain metastasis with PET/CT has some limitation, similar to its use in pretreatment staging; 3) additional radiation exposure and higher medical cost arising from the use of PET/CT should be taken into consideration, particularly in patients who might not have cancer after curative-intent treatment and are expected to have a long lifespan. The absence of any data regarding survival benefits and/or improvements in quality of life is another critical issue. In summary, PET/CT is considered to be more accurate and sensitive than conventional modalities for the detection of asymptomatic recurrence after curative-intent treatments. These advantages could modify subsequent management in patients with suspected recurrence and might contribute to the selection of appropriate treatments for recurrence. Therefore, PET/CT may be an alternative to conventional follow-up modalities. However, several important issues remain to be solved. PET/CT in a follow-up surveillance setting is generally not recommended in clinical practice at the moment.

**Keywords:** lung cancer, follow-up surveillance, FDG-PET/CT

## Introduction

Periodic examinations, including physiologic and radiographic examinations, are usually performed to detect recurrence after curative-intent treatment, and these examinations are commonly referred to as follow-up surveillance. However, the efficacy of 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) in a follow-up surveillance setting following curative-intent treatments for lung cancer has not yet been established. In this review, we survey previous papers and evaluate the potential efficacy of FDG-PET/CT in the setting of long-term follow-up surveillance. We first briefly summarize the current

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imaging examinations used for diagnosis or pretreatment staging of lung cancer and conventional follow-up modalities performed after curative-intent treatment. We then review the efficacy of FDG-PET/CT in a follow-up surveillance setting following curative-intent treatments.

## Conventional imaging examinations used for diagnosis and pretreatment staging of lung cancer

Imaging modalities including CT, magnetic resonance imaging (MRI), bone scintigraphy, and abdominal ultrasonography are used for the diagnosis of lung cancer and the evaluation of disease extent. CT is fast and painless and has high spatial resolution, providing excellent morphologic information.<sup>1,2</sup> The sensitivity and specificity of CT for the diagnosis of lung cancer have been reported as 50%–90% and 60%–90%, respectively.<sup>3,4</sup> MRI creates images using a magnetic field and pulses of radiowave energy, providing information regarding the lesion structure different from that obtainable using CT; MRI is more frequently used to detect brain abnormalities.<sup>5</sup> Combining these modalities can provide a more accurate diagnosis of lung cancer and a more accurate evaluation of the disease extent.

## History of FDG-PET or FDG-PET/CT

PET was initially used as a research tool for brain function studies and the assessment of cardiac metabolism.<sup>6–8</sup> PET using FDG has been applied in patients with neoplasms. Neoplastic tissues have a much higher rate of glucose consumption than normal tissue or benign lesions. FDG-PET can visualize glucose metabolism, enabling the whole body, excluding the brain, to be examined in a noninvasive manner in addition to enabling the differentiation of malignant and benign lesions with high accuracy.<sup>9–13</sup> Furthermore, FDG uptake is reportedly correlated with the tumor response to chemotherapy/radiotherapy and patient outcome.<sup>14–16</sup> Using advanced computer technology, FDG-PET has been integrated with CT and merged as an examination that can provide not only a differential diagnosis between neoplasms and normal tissues but also an accurate location of the lesions.<sup>17–19</sup> Because of these advantages, FDG-PET or FDG-PET/CT has quickly spread and is now used worldwide for the diagnosis of malignancies and the evaluation of the disease extent. Recently, new radiotracers such as <sup>18</sup>F-fluorothymidine or <sup>68</sup>Ga-Alfatide II have also been studied. <sup>18</sup>F-fluorothymidine is an indicator of proliferation, and <sup>68</sup>Ga-Alfatide II is a marker of neovascularization, and these radiotracers reflect different aspects of malignancy from FDG.<sup>20,21</sup> PET/CT using new radiotracers might be available in the future.

## PET/CT for the diagnosis and staging of lung cancer

### Diagnosis of lung cancer

A large number of studies have demonstrated that PET/CT is more accurate than CT for the diagnosis of lung cancer, with a sensitivity of ~95% and a specificity of 80%.<sup>22,23</sup> In contrast, false-positive results are often obtained for inflammatory or granulomatous lesions.<sup>24</sup> Furthermore, false-negative results can occur in subcentimeter lung cancer or in adenocarcinoma in situ, even those that are >1 cm.<sup>25,26</sup>

### Evaluation of disease extent

#### Mediastinal lymph node metastasis

The approximate sensitivity and specificity of CT for the detection of mediastinal lymph node metastasis were reportedly 50%–70% and 65%–85%, respectively, while the corresponding values for PET/CT were 75%–85% and 85%–90%, respectively.<sup>27,28</sup> Thus, PET/CT is significantly superior to CT for the diagnosis of mediastinal lymph node metastasis.<sup>29–32</sup> However, false-positive results were observed in some patients with anthracosilicosis or inflammatory diseases.

#### Distant metastasis

The most common sites of metastasis are bones, the adrenal gland, the liver, and the brain. Several studies have demonstrated that PET/CT is superior or equal to conventional modalities for the detection of distant metastasis.<sup>32,33</sup> However, the ability of PET/CT to detect brain metastasis is significantly limited because of the high level of glucose consumption in the brain, and enhanced MRI remains the gold standard for the detection of brain metastasis.<sup>34–36</sup>

Overall, PET/CT is considered to be superior to conventional modalities for the diagnosis of lung cancer and the evaluation of disease extent. Pieterman et al<sup>32</sup> reviewed previous studies and compared PET with CT in terms of sensitivity and specificity and reported that the use of PET for preoperative staging resulted in a different staging from that determined using conventional modalities in 27%–62% of patients. Upstaging because of the detection of unexpected metastasis using PET was frequently observed. Schrevels et al<sup>37</sup> reported that unknown metastases were found using PET in 5%–29% of patients with negative conventional staging, and such PET/CT findings could influence a patient's subsequent management, potentially contributing to an improved outcome.

Thus, a large number of studies have demonstrated the superiority of PET/CT over conventional modalities, but most of these studies focused on the efficacy of PET/CT

in a pretreatment work-up setting; only a few addressed the efficacy of PET/CT in a follow-up surveillance setting. Therefore, we reviewed papers discussing the use of PET/CT in a follow-up surveillance setting following curative-intent treatments and evaluated the potential efficacy and advantage of PET/CT in this setting.

## Current recommendations for follow-up surveillance following curative-intent treatment: how often and which modalities?

Follow-up surveillance is usually performed after curative-intent treatment. The purpose of follow-up surveillance is to detect recurrences and disease progression at an early stage to institute adequate treatment in an attempt to improve the survival duration and quality of life. However, an adequate follow-up schedule outlining when and which examinations should be performed after curative-intent treatment has not yet been established. Furthermore, whether aggressive searches for asymptomatic recurrences through periodic examinations contribute to an improvement in survival has not yet been confirmed. No recent studies have addressed the cost effectiveness of postoperative follow-up examinations, and only the few investigators who had previously evaluated them had questioned the benefit of such examinations in cancer patients from the viewpoints of efficacy and cost effectiveness.<sup>38–40</sup> On the other hand, some investigators have reported that the survival duration is longer in patients with recurrences detected during the asymptomatic stage than in those with recurrences diagnosed after the onset of

symptoms, and that follow-up is useful for the detection of asymptomatic recurrences.<sup>41,42</sup>

Under these circumstances, several medical societies have individually designed follow-up surveillance guidelines for patient care after curative-intent treatments for lung cancer. While some variations in follow-up modalities and the frequencies of their use exist among the guidelines, all the guidelines recommend the use of chest CT (Table 1).<sup>43–46</sup> In contrast, none of the guidelines recommends the use of PET/CT in a follow-up surveillance setting.

## PET/CT in a follow-up surveillance setting

We reviewed studies that used PET/CT as a follow-up examination after curative-intent treatment.

### Local recurrence

#### Post resection

The major issue concerning the use of PET/CT in a post-operative follow-up setting might be the various inflammatory changes that can develop locally after resection, such as in the mediastinum or at the surgical margin, since these changes often cause a high FDG uptake and result in false-positive findings. Inflammatory changes gradually disappear after resection, but Kanzaki et al<sup>47</sup> reported that inflammatory changes were the main reason for false-positive findings even when the PET/CT examinations were performed 6 months after resection. Choi et al<sup>13</sup> also reported a false-positive rate of 13.4% for PET/CT in a postoperative follow-up setting.

**Table 1** Follow-up surveillance guidelines recommended by medical societies

|                      | Time after resection (month) |   |    |    |     |    |    |    |    |    |    |    |    |
|----------------------|------------------------------|---|----|----|-----|----|----|----|----|----|----|----|----|
|                      | 6                            | 9 | 12 | 15 | 18  | 21 | 24 | 30 | 36 | 42 | 48 | 54 | 60 |
| NCCN                 |                              |   |    |    |     |    |    |    |    |    |    |    |    |
| Physical examination | •                            |   | •  |    | •   |    | •  |    | •  |    | •  |    | •  |
| (Enhanced) CT        | (•)                          |   | •  |    | (•) |    | •  |    | •  |    | •  |    | •  |
| ACCP                 |                              |   |    |    |     |    |    |    |    |    |    |    |    |
| Physical examination | •                            |   | •  |    | •   |    | •  |    | •  |    | •  |    | •  |
| Radiograph or CT     | •                            |   | •  |    | •   |    | •  |    | •  |    | •  |    | •  |
| ESMO                 |                              |   |    |    |     |    |    |    |    |    |    |    |    |
| Physical examination | •                            |   | •  |    | •   |    | •  |    | •  |    | •  |    | •  |
| (Enhanced) CT        |                              |   | •  |    |     |    | •  |    | •  |    | •  |    | •  |
| ACR                  |                              |   |    |    |     |    |    |    |    |    |    |    |    |
| Physical examination | •                            | • | •  | •  | •   | •  | •  | •  | •  | •  | •  | •  | •  |
| Chest radiograph     | •                            | • |    | •  | •   | •  |    | •  |    | •  |    | •  |    |
| CT                   |                              |   | •  |    |     |    | •  |    | •  |    | •  |    | •  |

**Note:** (•) indicates optional.

**Abbreviations:** NCCN, National Comprehensive Cancer Network; CT, computed tomography; ACCP, American College of Chest Physicians; ESMO, European Society for Medical Oncology; ACR, American College of Rheumatology.

## Post radiotherapy

The evaluation of local recurrence after radiotherapy is more complicated in patients than after resection, since the main tumor and/or lymph nodes are still present after radiation and are likely to be affected by inflammation and/or fibrosis.<sup>48,49</sup> Several studies have used PET/CT as a follow-up modality after stereotactic radiotherapy and reported difficulty in diagnosing recurrences based on FDG values observed at a single time point.<sup>50-52</sup> Mohammed et al<sup>53</sup> conducted a systematic review and reported that recurrences should be suspected if sequential opacity enlargement and a standardized uptake value of  $\geq 5$  were observed on repeated PET/CT examinations.

## Postdefinitive chemoradiotherapy

Several studies have evaluated the efficacy of PET/CT after definitive chemoradiotherapy, but the intent of these studies was to investigate the use of PET/CT as an indicator of tumor response to treatment or as a predictor of patient survival, rather than as a follow-up modality.<sup>54-56</sup>

## Distant metastasis

The ability to detect distant metastasis in a follow-up setting is considered to be an advantage of PET/CT compared to the conventional follow-up modalities. However, it should be noted that although brain is the frequent site of metastasis, detection of brain metastasis with PET/CT has limitation, similar to its use in pretreatment staging.

Another advantage of PET/CT is its ability to detect asymptomatic second malignancies not only in the lung but also in other organs. Although PET/CT has some limitations as for health screening examinations, such as false positives and the difficulty to detect early cancer such as early gastric cancer or cervical cancer, PET/CT can screen almost the whole body noninvasively. The detection rate for a second malignancy using PET/CT in patients after resection has been reported to be ~3% during the follow-up period.<sup>13,57,58</sup>

PET/CT is equivalent or superior to conventional follow-up modalities for the detection of local recurrence and is superior for the detection of distant metastasis in a follow-up setting. Keidar et al<sup>59</sup> prospectively evaluated the impact of PET/CT on the subsequent management in patients with suspected recurrent lung cancer. They reported that the PET/CT findings potentially modified the subsequent management (ie, eliminated the need for previously planned diagnostic procedures, resulted in the initiation of a previously unplanned treatment, or changed the previously planned therapeutic approach) in 29% of the patients. Similarly,

Ebright et al<sup>60</sup> reported that PET/CT enhanced the detection of local recurrence after stereotactic radiotherapy and might have influenced decisions regarding subsequent treatments performed for recurrence.

In contrast, Takenaka et al<sup>61</sup> compared standard radiologic examinations (enhanced whole-body CT and bone scintigraphy) and PET/CT prospectively and reported that there was no difference between them in terms of sensitivity, specificity, and accuracy for the detection of recurrence. Choi et al<sup>13</sup> also performed a cohort study of 358 patients in whom enhanced chest CT examinations were performed every 6 months and PET/CT was performed annually for 5 years after resection, and concluded that PET/CT seemed to be superior to chest CT but that PET/CT could fail to detect small or hypometabolic recurrences.

## Potential disadvantages or issues associated with the use of PET/CT in a follow-up surveillance setting

### Radiation exposure

The radiation exposure from a single PET/CT examination is ~11 mSV (PET = 4 mSV and CT = 7 mSV). The exposure from a high-resolution CT examination is ~7 mSV, while that of low-dose CT is 2 mSV and that of chest radiography is 0.05 mSV. Thus, radiation exposure from PET/CT is higher than that from conventional modalities.<sup>13,62</sup> Brenner and Hall<sup>63</sup> have warned that radiation exposure caused by medical examinations is associated with the risk of cancer. Excess radiation exposure from follow-up examinations should therefore be taken into consideration, especially in patients who might not be in a cancer-burdened state and are expected to have long life spans after curative-intent treatment.

### Cost implications

The medical cost of PET/CT is ~US \$850 (=100,000 Yen), while that of chest radiography is \$20, of plain chest CT is \$150, of enhanced brain MRI is \$250, and of bone scintigraphy is \$400 under the current medical environment in Japan. While the medical cost of PET/CT might vary among countries, it is usually much more expensive than other examinations. Choi et al<sup>13</sup> evaluated the additional medical cost caused by false-positive findings from PET/CT examinations and reported that 33 out of 247 patients (13.4%) had undergone unnecessary examinations including needle biopsy, MRI, and bronchoscopy because of false-positive findings from a PET/CT examination. Thus, the issue of medical cost should also be taken into consideration when evaluating the efficacy of follow-up examinations using PET/CT.

## Survival benefit

Another critical issue that might need to be discussed is the survival benefit and/or improvement in the quality of life arising from a PET/CT examination. A number of studies have evaluated the accuracy of PET/CT for the detection of recurrence and have demonstrated the superiority of PET/CT over conventional modalities.<sup>13,47,57,58</sup> None of these studies, however, evaluated the survival benefit and/or improvement in quality of life after follow-up with PET/CT, and the significance of PET/CT follow-up after curative-intent treatment remains unknown.

## Availability

The last critical issue is the availability of PET/CT. This modality has spread widely throughout the world. As of 2015, 1,570 and 466 PET/CT setups are active in US and Japan.<sup>64</sup> However, not all patients can access PET/CT, since it is available only at select institutes, such as university hospitals and cancer centers. It is, therefore, difficult to recommend PET/CT as a standard follow-up modality for use in general clinical practice.

## Summary of the applications of PET/CT in a follow-up surveillance setting

1. PET/CT is considered to be superior to conventional modalities for the detection of asymptomatic recurrences, although false-positive results in local areas are often problematic.
2. PET/CT can modify the subsequent management that is performed in patients with suspected recurrences and might contribute to the appropriate selection of subsequent treatments.
3. Whether the use of PET/CT and the detection of asymptomatic recurrences in a follow-up setting improves the survival and/or quality of life of patients after curative-intent treatment has not yet been determined.
4. Both the radiation exposure and medical costs associated with PET/CT are higher than those of conventional follow-up modalities.

## Current status of PET/CT for follow-up surveillance

According to the advantages described earlier, PET/CT could potentially become an alternative to conventional follow-up modalities after curative-intent treatment. However, several important issues remain to be solved, such as availability, the limitation of detection of brain metastasis, as well as unknown

survival benefits and medical cost. In particular, performing repeated examinations without evidence of survival benefit in patients who might not have recurrence is questionable, taking its high medical cost into consideration. Considering these issues, it is premature to recommend PET/CT as a follow-up examination after curative-intent treatment in clinical practice at the moment.

## In the future

1. Patient populations who are at high risk for recurrence and might receive a benefit from PET/CT are to be identified.
2. The number of times to perform PET/CT, either once or twice, as well as their most efficient timing during the follow-up period is to be identified.

If these issues are solved, PET/CT will be accepted as one of the standard follow-up modalities after curative-intent treatment for lung cancer.

## Disclosure

The authors report no conflicts of interest in this work.

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