



Staging Work-up for Early Lung Cancer: The More the Better?

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The initial staging work-up is a crucial step in patients with newly diagnosed non-small cell lung cancer (NSCLC) to provide the appropriate treatment and assess the prognosis. The stage of NSCLC is determined by TNM system which is based on the location and extent of the primary tumor (T), the status of lymph nodes (N), and the distant metastasis (M). To apply local treatment of surgery or radiotherapy which has the potential opportunity of cure, it is very important to exclude metastasis. At the time of first presentation, occult metastases can be present in up to 30% of NSCLC patients, especially in adrenal gland and liver¹. Because the positron emission tomography/computed tomography (PET/CT) has been proven to be very useful to detect these unsuspected distant and lymph node metastases and to improve the diagnostic accuracy since its introduction, it becomes one of the essential diagnostic modalities in initial staging for lung cancer. PET/CT is currently recommended in pretreatment evaluation of lung cancer regardless of its stage by National Comprehensive Cancer Network (NCCN) guidelines.

In the article of this issue of the *Tuberculosis and Respiratory Diseases* (TRD), Song et al.² addressed the necessity of PET/CT and brain magnetic resonance imaging (MRI) in the staging of ground-glass nodular lung adenocarcinoma. They found that the chest computed tomography (CT) did not differ from the combined modality of PET/CT and brain MRI for

determination of overall stage (94.6% vs. 90.5%; kappa value, 0.712) in the analysis of 74 ground-glass nodules of less than 3 cm in diameter in 72 patients.

Actually, the addition of PET/CT to the conventional methods could alter the treatment in 20%–30% of patients with NSCLC, mostly by upstaging³. According to the PLUS multi-center randomized trial, additional PET/CT prevented unnecessary surgery in almost half of patients⁴. Two more randomized trials also showed that the use of PET/CT for preoperative staging significantly reduced the unnecessary thoracotomy^{5,6}. Notably, Maziak et al.⁶ found that PET/CT was superior to conventional staging for disease at all stages although the greatest benefit was seen at higher stages. Even in stage IA, 5 of 81 patients (6%) were correctly upstaged by PET/CT⁶. Although we could not see detailed data according to stage in the study by Fischer et al.⁵, PET/CT reduced the frequency of futile thoracotomy in stage IA–IIB. Based on these, NCCN guidelines recommend PET/CT for initial staging work-up even in stage I. Therefore, it is too early to accept the conclusion of study by Song et al.² as it is. The problem is that the numbers of enrolled patients in all studies mentioned above do not seem to be enough to draw a clear conclusion, especially in stage IA.

In changing a viewpoint, why does the use of PET/CT in stage IA matter? Aside from the high cost of PET/CT, the incorrect upstaging by PET/CT requires additional investigation, often invasive procedures. Maziak et al.⁶ showed eight false-positive cases by PET/CT of which the abnormal sites were adrenals, pituitary, tonsils, contralateral lung, and mediastinal nodes. Confirmatory imaging or biopsy was needed as expected. In the study of Song et al.², incidental fluoro-2-deoxy-D-glucose uptake on PET/CT was found in seven thyroid glands, two adrenal glands, one colon, and one 4R lymph node. None of them was related to lung cancer although it required more tests. The relatively high false positivity and the low risk of missing metastasis may warrant the advocate of no need of PET/CT, particularly in stage IA NSCLC.

Taken together, it is true to say that it's not conclusive at present. We should wait for results of larger, well-designed, randomized, prospective studies to have a correct answer.

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Brain is one of the most frequent sites of metastasis from lung cancer. Brain MRI is the diagnostic choice to detect brain metastasis because of its better performance than cranial CT⁷. The prognosis of patients with brain metastasis is generally poor⁸ even though patients with oligo-metastasis to brain and otherwise operable stage lung cancer would benefit from aggressive treatment of both lesions⁹. The detection of multiple brain metastases before treatment enables to avoid unnecessary local therapy to primary site such as surgery or definitive radiotherapy. Therefore, it is important to know the exact status of brain metastasis before making a decision on how to treat.

However, the necessity of brain MRI in preoperative work-up in asymptomatic patients with early stage (especially stage I) lung cancer has been a long debate because of the low incidence of brain metastasis in those patients¹⁰ and the high cost of imaging. Actually, silent brain metastasis could be detected preoperatively by brain MRI in 2%–5% of patients with potentially operable NSCLC^{7,10}. But, the actual incidence of brain metastasis seems to be much lower in stage I NSCLC. Among 643 patients with stage IA in the National Lung Screening Trial, 77 patients (12%) received at least one brain imaging study. There was no intracranial metastasis¹¹. In addition, Yohena et al.¹⁰ could not detect any metastatic brain lesion in 80 patients with stage I NSCLC. Hence, the routine use of brain MRI is not recommended in stage IA and optional in stage IB by NCCN guidelines. Accordingly, Song et al.² also could not find out brain metastasis in all of enrolled patients by brain MRI. At present, it seems like there is no argument over the needlessness of brain MRI during work-up for stage IA NSCLC.

Song et al.² in this issue of TRD addressed one of unsolved questions in the diagnosis of NSCLC. Although the conclusion suggested by authors should be regarded with caution because of the limitations of the study and the previous contradictory results of others, we expect that more clear answers will come out in the near future through this kind of efforts.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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