Annals of Nuclear Medicine Vol. 19, No. 5, 393–398, 2005

Should mediastinoscopy actually be incorporated into the FDG PET strategy for patients with non-small cell lung carcinoma?

Katsumi HAYASHI, Katsumi ABE, Fuzuki YANO, Sadahiro WATANABE, Yoshie IWASAKI and Shigeru KOSUDA

Department of Radiology, National Defense Medical College

Background: Incorporating mediastinoscopy (MS) into the PET-based strategy for non-small cell lung carcinoma (NSCLC) patients might be cost-effective because MS can allow unnecessary thoracotomies to be avoided. The objective of our study was to assess the cost-effectiveness of incorporating MS into a PET strategy for NSCLC patients. ***Methods:*** To determine life expectancy (LE), quality adjusted life years (QALY), and the incremental cost-effectiveness ratio (ICER), a decision-tree sensitivity analysis was designed for histopathologically confirmed NSCLC patients with M0 disease, based on the three competing strategies of chest CT only vs. PET + CT vs. PET + CT + MS. A simulation of 1,000 NSCLC patients was created using baselines of other relevant variables in regard to sensitivity, specificity, mortality, LE, utilities and cost from published data. One-way sensitivity analyses were performed to determine the influences of mediastinal metastasis prevalence on LE, QALY and ICER. ***Results:*** The LE and QALY per patient in the CT only strategy, PET + CT strategy and PET + CT + MS strategy were 4.79 and 4.35, 5.33 and 4.93 and 5.68 and 5.33 years, respectively, with a 20% prevalence of mediastinal metastasis. The ICERs were ¥906.6 × 10^3 (US$7,555)/QALY/patient at a 20% mediastinal metastasis prevalence, and ¥2,194 × 10^3 (US$18,282)/QALY/patient at a 50% prevalence, but exceeded ¥5,280 × 10^3 (US$44,000)/QALY/patient at 80%. ***Conclusions:*** Our study quantitatively showed the CT + PET + MS strategy in place of the PET + CT strategy in managing NSCLC patients to be cost-effective. MS should be incorporated into the PET + CT strategy for NSCLC patients except in those highly suspected of having mediastinal disease on chest CT or PET.

Key words: lung cancer, diagnosis and staging, mediastinoscopy, positron emission tomography (PET)

INTRODUCTION

ACCURATE MEDIASTINAL STAGING of patients with non-small cell lung carcinoma (NSCLC) is crucial because mediastinal metastasis (N2, N3 disease), in general, indicates an ominous prognosis and precludes surgical cure. Patients with mediastinal lymph node metastasis have an average 5-year survival of approximately 10%, as opposed to 50% for patients without mediastinal lymph node metastasis.[1,2]

Positron emission tomography (PET) is superior to CT for mediastinal staging of NSCLC. Mean sensitivity and specificity were 0.79 ± 0.03 and 0.91 ± 0.02, for PET and 0.60 ± 0.02 and 0.77 ± 0.02 for CT, respectively.[3] However, the positive predictive value of PET for mediastinal disease is approximately 65%,[4–6] while the negative predictive value of PET for mediastinal disease is reportedly greater than 95%.[6,7] More accurate procedures are needed to confirm nodal metastasis in order to avoid missing NSCLC patients potentially curable with thoracotomy among those with false positive nodes on 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) PET. Pretreatment practice

Received November 30, 2004, revision accepted May 9, 2005.

This paper was presented at the 51st annual meeting of the Society of Nuclear Medicine (Philadelphia, Pennsylvania, June 21, 2004).

For reprint contact: Shigeru Kosuda, M.D., Department of Radiology, National Defense Medical College, 3–2 Namiki, Tokorozawa 359–8513, JAPAN.

E-mail: nucleark@me.ndmc.ac.jp

guidelines for NSCLC patients have been formulated,[8–10] but routine clinical practice remains variable.

While PET shows accuracy in detecting mediastinal metastasis and is being used nationwide in Japan, mediastinoscopy (MS) has yet to be established as having a role in histopathologically determining mediastinal node status. In general, pulmonologists and thoracic surgeons in Japanese hospitals do not perform MS, or perform it less often in NSCLC patients, probably because MS is an invasive and expensive procedure. However, introducing MS into the PET-based diagnostic and therapeutic strategy for NSCLC patients might be cost-effective because MS allows some increase in the number of curative thoracotomies and improves life expectancy (LE) of NSCLC patients.

The objective of our study was to assess the cost-effectiveness of incorporating MS into an FDG PET strategy for NSCLC patients.

MATERIALS AND METHODS

The study was built upon, revised, and expanded the analyses performed in our previously published reports on the cost-effectiveness of whole-body FDG PET in the management of patients with NSCLC.[11,12] To determine LE, quality adjusted life years (QALY) and the incremental cost-effectiveness ratio (ICER), a decision-tree sensitivity analysis was designed for NSCLC patients, based on the three competing strategies of chest CT only vs. a combination of chest PET and chest CT without MS (PET + CT) vs. a combination of chest PET, chest CT, and MS (PET + CT + MS). The ICER was defined as follows: the subtraction of cost-effectiveness ratios (cost/QALY/patient) in the PET + CT strategy from those in the PET + CT + MS strategy at each mediastinal metastasis prevalence examined.

We assumed all NSCLC patients to be free of M1 disease and to have been histopathologically confirmed as having NSCLC. The ratio of N2 only to N3 was assumed to be 3 to 2, when multiple mediastinal lymph node metastases were present.[13]

A chest CT only strategy and a PET + CT strategy that modeled dependence upon chest contrast CT and chest FDG PET, respectively, were designed (Figs. 1, 2). With these strategies, only patients whose CT or PET studies were negative for N2 and N3 disease underwent thoracotomy. By contrast, patients with N2 or N3 disease on chest CT or PET studies were precluded from thoracotomy and underwent chemoradiotherapy instead.

In the PET + CT + MS strategy, patients with negative findings in the mediastinum on PET imaging were precluded from MS because of the high NPV of PET for mediastinal disease. On the other hand, only patients with positive mediastinal disease findings on PET underwent MS as part of the strategy because the PPV is inferior to the NPV in diagnosing mediastinal disease. Patients with

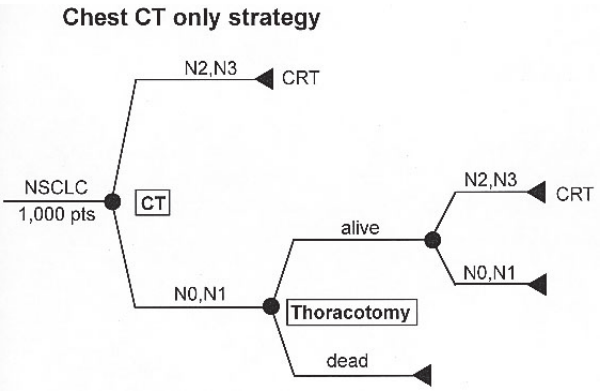

Fig. 1 Decision-tree for the CT only strategy in a simulation of 1,000 NSCLC patients with M0. Note that NSCLC patients with N2, N3 disease, who are misdiagnosed as N0, N1 disease on CT, end up undergoing unnecessary thoracotomy. NSCLC patients with N0, N1 disease, who are misdiagnosed as N2, N3 disease on CT, end up missing curative thoracotomy. CRT = chemoradiotherapy.

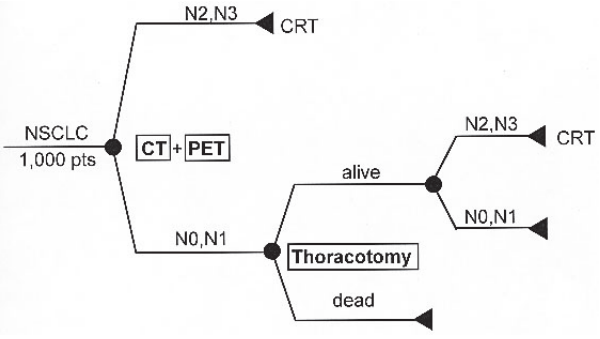

Fig. 2 Decision-tree for the PET + CT strategy in a simulation of 1,000 NSCLC patients with M0. Note that unnecessary and noncurative thoracotomies decrease in the PET + CT strategy because some NSCLC patients with N2, N3 disease, who are misdiagnosed as N0, N1 disease in the CT only strategy, are correctly diagnosed due to the high NPV of PET studies. CRT = chemoradiotherapy.

N2 or N3 disease in MS were precluded only from thoracotomy and underwent chemoradiotherapy, while patients without N2 and N3 disease and those with minimal N2 disease in MS underwent potentially curable thoracotomies because intranodal involvement in a single lymph node was established at mediastinal dissection[14] (Fig. 3). The role of induction therapy was not considered.

A simulation of 1,000 patients with NSCLC was created using baselines of other relevant variables, in regard to sensitivity, specificity, mortality, LE, utilities and cost, from published data.[11,12,15–21] The authors reviewed the published articles to determine eligibility. Articles selected for inclusion fulfilled the following criteria: (1) assessment of the diagnostic performance of FDG PET and CT for the detection of mediastinal node metastases from NSCLC, (2) comparison of imaging results with

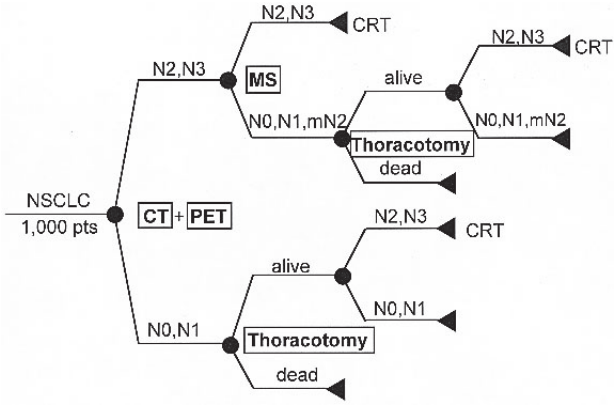

Fig. 3 Decision-tree for the PET + CT + MS strategy in a simulation of 1,000 NSCLC patients with M0. Note that the N0, N1, mN2 arm is correctly diagnosed by MS. CRT = chemoradiotherapy. MS = mediastinoscopy.

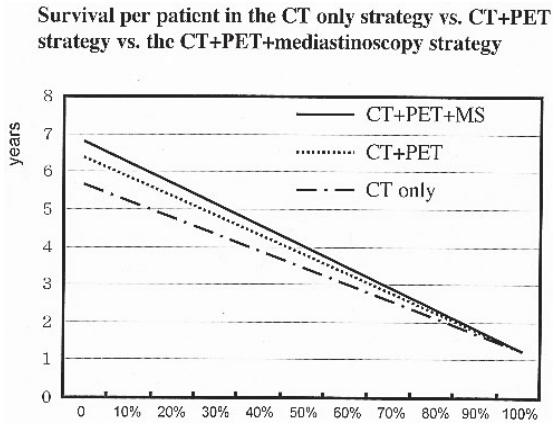

Fig. 4 Results of the one-way sensitivity analysis for mediastinal node metastasis prevalence values ranging from 0% to 100% on the life expectancy (years) per patient in the CT only strategy, PET + CT strategy, and PET + CT + MS strategy.

Table 1 Baseline of all relevant variables used in the decision trees. The variables were cited from the published references

Prevalence of lung cancer	100%
Prevalence of m. metastasis	0%–100%
Sensitivity for detecting m. metastasis in CT	60%
Specificity for detecting m. metastasis in CT	77%
Sensitivity for detecting m. metastasis in PET	79%
Specificity for detecting m. metastasis in PET	91%
Sensitivity for detecting m. metastasis in MS	90%
Specificity for detecting m. metastasis in MS	100%
Mortality (%)	
PET	0
CT	0.0025
Thoracotomy	3.0
Mediastinoscopy	0
Life expectancy (yr)	
N0, N1 patients with surgical cure	7.0
N0, N1 patients with CRT	2.0
N2 patients with CRT	1.45
N2 patients with surgical cure plus RT	1.62
N3 patients with CRT	0.8
Cost (yen)	
CT with contrast	35,800
FDG PET	80,300
Thoracotomy	1,600,000
MS	377,000
Health-state utilities	
Postoperative state	0.95
Radiotherapy	0.70
Chemoradiotherapy	0.60
Death	0.00

pathological diagnoses, (3) reporting of sufficient results with sensitivity, specificity, and accuracy, (4) use of established diagnostic criteria for abnormal test results. Sensitivities and specificities for the diagnosis of mediastinal disease were assumed to be 60% and 77%, for CT, 79% and 91%, for PET, and 90% and 100%, for MS, respectively[3–12] (Table 1). One-way sensitivity analyses were performed to determine the influences of mediastinal metastasis prevalence on LE (years), QALY (years), and ICER (¥ or US$).

The medical examination costs in Japanese yen were based on revised established insurance reimbursement system bills. Overhead costs and extra costs related to examinations were not included in the current study. The cost in U.S. dollars was calculated at a yen-to-dollar conversion rate of ¥120 to $1.

The present value is expressed as $PV = C/(1 + r)^t$, where PV is the present value, C is the amount of money paid, r is the risk-adjusted discount rate, and t is the time period after which future costs are to be paid. Future costs and outcomes in our series were discounted 3%.

RESULTS

Figures 4 and 5 show the sensitivity analysis for mediastinal metastasis prevalences, ranging from 0% to 100%, on the LE (years) and QALY (years) for the three strategies. The PET + CT + MS strategy yielded the longest survival and best QALY across the prevalences, followed by the PET + CT strategy. However, the differences among the three strategies diminished as the mediastinal metastasis prevalence increased. The LE and QALY per patient in the CT only, PET + CT, and PET + CT + MS strategies were 4.79 and 4.35, 5.33 and 4.93 and 5.68 and 5.33 years, respectively, at a 20% prevalence of mediastinal metastasis. However, the LE and QALY per patient in the CT only, PET + CT, and PET + CT + MS strategies were 2.11 and 1.69, 2.24 and 1.79 and 2.38 and 1.98 years, respectively, at an 80% mediastinal metastasis prevalence. Figure 6 shows the ICEF (¥) for mediastinal metastasis prevalence, ranging from 0% to 100%, on the PET + CT strategy vs. the PET + CT + MS strategy. The ICER values increased as the mediastinal prevalence increased. The ICER values were ¥906.6×10^3 (US$7,555)/QALY/

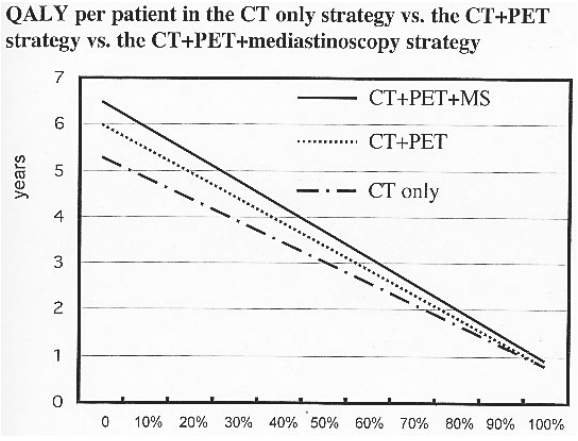

Fig. 5 Results of the one-way sensitivity analysis for mediastinal node metastasis prevalence values ranging from 0% to 100% on the QALY (years) per patient in the CT only strategy, PET + CT strategy, and PET + CT + MS strategy.

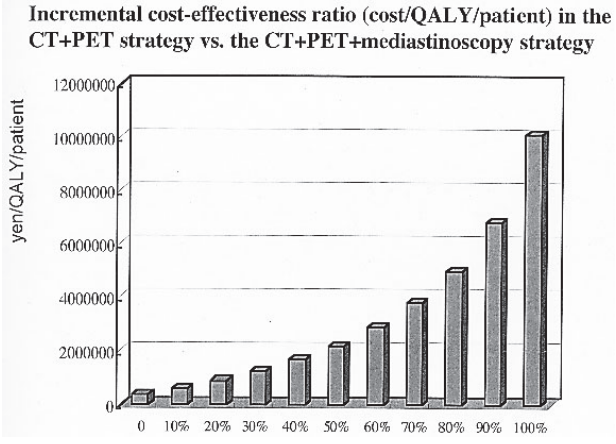

Fig. 6 The ICEF (¥) for mediastinal node metastasis prevalence values, ranging 0% to 100%, on the PET + CT strategy vs. PET + CT + MS strategy.

patient at a 20% mediastinal metastasis prevalence, and ¥1,294 × 10^3 (US$18,282)/QALY/patient at a 50% prevalence, but exceeded ¥5,280 × 10^3 (US$44,000)/QALY/patient at 80%. When the PET + CT + MS strategy was compared to the CT only strategy, the ICER values were ¥573.1 × 10^3 (US$4,776)/QALY/patient at a 20% mediastinal metastasis prevalence, ¥1,051 × 10^3 (US$8,757)/QALY/patient at 50%, and ¥2,580 × 10^3 (US$21,498)/QALY/patient at 80%.

DISCUSSION

In patients with a bulky mass or multilevel nodal involvement on CT or MR imaging, the assessment of N stage is not difficult. Central necrosis or extranodal cancer extension is highly suggestive of lymph node metastasis. In general, however, CT and MR imaging are limited in depicting small node metastasis, since both modalities provide predominantly morphological information. McLoud et al. reported that 13% of nodes measuring <1.0 cm in evaluated patients with lung cancer were metastatic while one third of nodes 2–4 cm in diameter were benign.[22] Because of the limitations of size criteria in predicting lymph node status, pathologic confirmation is essential for true staging.

FDG PET, which has provided metabolic information and accurate staging in patients with NSCLC, is significantly more accurate than chest CT for demonstration of mediastinal nodal metastases.[3] However, with smaller nodal metastases the sensitivity of PET is decreased. Micrometastasis, which is defined as a metastasis measuring 2 mm or less in greatest dimension, cannot be demonstrated by PET.[23] In nodes with inflammatory or granulomatous disease, the specificity of PET is also decreased.[24–27] FDG PET, particularly when fused with CT, has a growing role in detecting the presence of disease in lymph nodes which appear normal with CT alone. Using pathological findings as the gold standard, the accuracy for N-staging was 94% for PET/CT, 89% for PET, and 64% for CT ($p < 0.05$).[28]

Owing to the aforementioned limitation, patients with positive mediastinal nodes on PET images should undergo a confirmatory procedure such as MS or bronchial biopsy before an attempt at curative thoracotomy is abandoned. MS has one great advantage over CT, MR imaging, and FDG PET, namely it provides a histopathological diagnosis of mediastinal nodes. Indications for MS reportedly include a serum CEA level >5.0 ng/d*l* and a largest primary tumor dimension >20 mm. However, MS should be avoided in NSCLC patients with a bulky mass or multilevel nodal involvement on CT and/or MR imaging.

Cervical mediastinoscopy is currently the best procedure for assessing the right and left paratracheal, pretracheal, right and left tracheobronchial, and subcarinal nodes. The subaortic and aortopulmonary window nodes can be reached by anterior mediastinoscopy. Video-assisted MS, if feasible, combined with video-assisted thoracoscopy, provides a wider view of the mediastinum with far fewer complications. The aforementioned techniques were considered in our study.

Several studies have attempted to identify the best strategy for staging the mediastinum in NSCLC patients.[15,29–31] However, these studies were designed and based, not on PET but on chest CT. FDG PET is now widely employed in Japan for cancer screening and staging. MS has been performed less frequently in Japan because it incurs additional costs and risks. Performing MS, not routinely but selectively based on the PET strategy, in NSCLC patients would be cost-effective since MS allows an increase in the number of curative thoracotomies and improves LE of NSCLC patients.

In our series, we principally compared the outcomes and cost-effectiveness of the two mediastinal staging

strategies, i.e., the newly developed PET-based strategy without and with MS for NSCLC patients. The mortalities, subsequent treatments and survivals associated with each strategy were included in the current study. Furthermore, to rigorously demonstrate cost-effectiveness and calculate QALY and ICER, we used a reference-based, decision-tree analysis, including revised Japanese insurance reimbursement system bills and discounting of costs and outcomes.

The LE difference between the CT only and PET + CT strategies was +0.54 years/patient, and that between the PET + CT and PET + CT + MS strategies was +0.35 years/patient at a 20% mediastinal metastasis prevalence, which is similar to the mediastinal metastasis prevalence of NSCLC patients with T1 and early stage T2. The QALY differences were greater than the survival differences. Since the estimated number of NSCLC cases in Japan for 2002 was 36,000,[32] the PET + CT + MS strategy would annually yield an increased LE of approximately 13,000 years for all Japanese NSCLC patients, as compared to the PET + CT strategy.

Our results show the PET + CT + MS strategy to yield the longest LE and best QALY among the three strategies, i.e., CT only, PET + CT and CT + PET + MS, though these differences among the strategies diminished as the mediastinal metastasis prevalence increased. From the economic standpoint, the ICER values in the PET + CT vs. the PET + CT + MS strategy were favorable with costs of ¥906.6 × 10^3 (US$7,555)/QALY/patient at a 20% mediastinal metastasis prevalence and of ¥2,194 × 10^3 (US$18,282)/QALY/patient at a 50% prevalence in NSCLC patients. The ICER values were much lower than the ¥6,000 × 10^3 (US$50,000)/QALY/patient obtained with the routine CT-based MS strategy without PET.[15] In our series, however, the ICER exceeded ¥5,280 × 10^3 (US$44,000)/QALY/patient at an 80% mediastinal metastasis prevalence. The CT + PET + MS strategy probably requires less than an 80% mediastinal metastasis prevalence. While a PET study and an MS procedure are generally expensive, the ICER values dropped by approximately half when the PET + CT + MS strategy vs. the CT only strategy was compared to the PET + CT + MS strategy vs. the PET + CT strategy.

Study limitations: The study may be criticized because a strategy of CT + MS was not explored. But MS after chest CT is actually performed less frequently by Japanese surgeons. The hypothesis of our study is based on the exclusion of thoracotomy for N2/3 patients. However, clinical treatment strategy always changes according to the up-to-date results, i.e., preoperative chemotherapy followed by resection.

The accuracy for FDG PET to diagnose mediastinal disease is variable. A few PET centers have accuracies lower than those we cited from the references, indicating the inadequacy to stage the mediastinum.[33,34] PET accuracy in detecting mediastinal nodal metastasis depends on patient population with active inflammatory or granulomatous nodes, or definition of node metastasis (eg, abnormal lymph node uptake exceeding that of mediastinal blood pool). In our series, we assumed a brand-new, dedicated PET camera or PET/CT, interpreters with greater training and experience, superior data acquisition, and histopathologically confirmed NSCLC in the primary lesion.

An accomplished surgeon may feel that all NSCLC patients who are considered for operation should have mediastinoscopy regardless of PET findings.[33,34] However, most nuclear medicine physicians, particularly Japanese ones, view the staging of lung cancer from a different perspective because mediastinoscopy is an invasive and expensive study.[35]

In conclusion, our study quantitatively showed the CT + PET + MS strategy, in place of the CT + PET strategy in managing NSCLC patients, to be cost-effective. However, the CT + PET + MS strategy appears to require a less than 80% mediastinal metastasis prevalence. MS should be incorporated into the FDG PET strategy for patients with NSCLC, except those highly suspected of having mediastinal disease on chest CT or PET.

ACKNOWLEDGMENT

We are very grateful to Yoshio Hohshito, NMT, for his expert assistance in the preparation of this manuscript.

REFERENCES

1. Mountain CF. Value of the new TNM staging system for lung cancer. *Chest* 1989; 96 (Suppl 1): 47S–49S.
2. Kadri MA, Dussek JE. Survival and prognosis following resection of primary non-small cell bronchogenic carcinoma. *Eur J Cardiothorac Surg* 1991; 5: 132–136.
3. Dwamena BA, Sonnad SS, Angobaldo JO, Wahl RL. Metastases from non-small cell lung cancer: Mediastinal staging in the 1990s-Meta-analytic comparison of PET and CT. *Radiology* 1999; 213: 530–536.
4. Vansteenkiste JF, Stroobants SG, Dupont PJ, De Leyn PR, De Wever WF, Verbeken EK, et al. FDG PET scan in potentially operable non-small cell lung cancer: do anatometabolic PET-CT fusion images improve the location of regional lymph node metastases? The Leuven Lung Cancer Group. *Eur J Nucl Med* 1998; 25: 1495–1501.
5. Magnani P, Carretta A, Rizzo G, Fazio G, Vanzlli A, Lucignani G, et al. FDG/PET and spiral CT image fusion for mediastinal lymph node assessment of non-small cell lung cancer patients. *J Cardiovasc Surg* 1999; 40: 741–748.
6. Pieterman RM, van Putten JWG, Meuzelaar JJ, Mooyaart EL, Vaalburg W, Koeter GH, et al. Preoperative staging of non-small-cell lung cancer with positron emission tomography. *New Eng J Med* 2000; 343: 254–261.
7. Farrell MA, McAdams HP, Herndon JE, Patz EF Jr. Non-small cell lung cancer: FDG PET for nodal staging in patients with Stage I disease. *Radiology* 2000; 215: 886–890.

8. Fergusson RJ, Gregor A, Dodds R, Kerr G. Management of lung cancer in South East Scotland. *Thorax* 1996; 51: 569–574.
9. Herder GJ, Verboom P, Smit EF, van Velthoven PC, van den Bergh JH, Colder CD, et al. Practice, efficacy and cost of staging suspected non-small cell lung cancer: a retrospective study in two Dutch hospitals. *Thorax* 2002; 57: 11–14.
10. Guyatt GH, Cook DJ, Griffith LE, Miller JD, Todd, TR, Johnston MR, et al. Surgeon's assessment of symptoms suggesting extrathoracic metastases in patients with lung cancer. *Ann Thoracic Surg* 1999; 68: 309–315.
11. Kosuda S, Ichihara K, Watanabe M, Kobayashi H, Kusano S. Decision-tree sensitivity analysis for cost-effectiveness of chest FDG-PET in patients with a pulmonary nodule (non-small-cell lung carcinoma) in Japan. *Chest* 2000; 117: 346–353.
12. Abe K, Kosuda S, Kusano S. Medical economics of whole-body FDG PET in patients suspected of having non-small cell lung carcinoma—Reassessment based on the revised Japanese national insurance reimbursement system. *Ann Nucl Med* 2003; 17: 649–655.
13. Albain KS, Rusch VW, Crowley JJ, Rice TW, Turrisi AT 3rd, Weick JK, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. *J Clin Oncol* 1995; 13: 1880–1892.
14. DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer principles and practice of oncology, 5th edn.* Philadelphia; Lippincott-Raven Publishers, 1997.
15. Esnaola NF, Lazarides SN, Mentzer SJ, Kuntz KM. Outcome and cost-effectiveness of alternative staging strategies for non-small-cell lung cancer. *J Clin Oncol* 2002; 20: 263–273.
16. Crino L, Scagliotti GV, Ricci S, De Marinis F, Rinaldi M, Gridelli C, et al. Gemcitabine and cisplatin versus mitomycin, ifosfamide, and cisplatin in advanced non-small-cell lung cancer: A randomized phase III study of Italian Lung Cancer Project. *J Clin Oncol* 1999; 17: 3522–3530.
17. Johnstone DW, Byhardt RW, Ettinger D, Scott CB. Phase III study comparing chemotherapy and radiotherapy with preoperative chemotherapy and surgical resection in patients with non-small-cell lung cancer with spread to mediastinal lymph nodes (N2); final report of RTOG 89-01. Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 2002; 54: 365–369.
18. Jett JR, Scott WJ, Rivera MP, Sause WT. Guidelines on treatment of stage IIIB non-small cell lung cancer. *Chest* 2003; 123 (1 Suppl): 221S–225S.
19. Albain KS, Crowley JJ, Turrisi AT 3rd, Gandara DR, Farrar WB, Clark JI, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. *J Clin Oncol* 2002; 20: 3454–3460.
20. Sawabata N, Ohta M, Maeda H, Takeda S, Hirano H, Okumura Y, et al. Prognostic significance of persistent mediastinal metastasis following induction therapy in large (> or = 2 cm) N2 or N3 non-small cell lung cancer. *Jpn J Thorac Cardiovasc Surg* 2003; 51: 123–129.
21. Tsushima Y, Aoki J, Endo K. Whether and under what conditions FDG-PET might be cost-effective in evaluating solitary pulmonary nodules depicted on lung cancer screening in Japan. *Nippon Acta Radiologica* 2003; 63: 390–398.
22. McLoud TC, Bourgouin PM, Greenberg RW, Kosiuk JP, Templeton PA, Shepard JA, et al. Bronchogenic carcinoma: analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling. *Radiology* 1992; 182: 319–323.
23. Ferlito A, Rinaldo A. Controversies in the treatment of N0 neck in laryngeal cancer: Neck dissection, no surgery or sentinel lymph node biopsy? *ORL* 2000; 62: 287–289.
24. Lewis PJ, Salama A. Uptake of fluorine-18-fluorodeoxyglucose in sarcoidosis. *J Nucl Med* 1994; 35: 1647–1649.
25. Larson SM. Cancer or inflammation? A holy grail for nuclear medicine. *J Nucl Med* 1994; 35: 1653–1655.
26. Lee J, Aronchick J, Alavi A. Accuracy of F-18 fluorodeoxyglucose positron emission tomography for the evaluation of malignancy in patients presenting with new lung abnormalities: a retrospective review. *Chest* 2001; 120: 1791–1797.
27. Lowe VJ, Fletcher JW, Gobar L, Lawson M, Kirchner P, Valk P, et al. Prospective investigation of positron emission tomography in lung nodules. *J Clin Oncol* 1998; 16: 1075–1084.
28. Antoch G, Freudenberg L, Nemat A, Beyer T, Bockisch A. Preoperative staging of non-small cell lung cancer with dual modality PET/CT imaging: a comparison with PET and CT. *J Nucl Med* 2003; 44: 172p.
29. Malenka DJ, Colice GL, Jacobs C, Beck JR. Mediastinal staging in non-small cell lung cancer. *Med Decis Making* 1989; 9: 231–242.
30. Eddy R. Cost-effectiveness of CT compared to mediastinoscopy in the preoperative staging of lung cancer. *J Can Assoc Radiol* 1989; 40: 189–193.
31. The Canadian Lung Oncology Group. Investigation for mediastinal disease in patients with apparently operable lung cancer. *Ann Thorac Surg* 1995; 60: 1382–1389.
32. The Statistical Information Department of the Welfare & Labor Ministry in Japan. *The vital statistics of Japan in 2002.* The Welfare Statistics Association Press, Tokyo, 2004.
33. Gonzalez-Stawinski GV, Lemaire A, Merchant F, O'Halloran E, Coleman RE, Harpole DH, et al. A comparative analysis of positron emission tomography and mediastinoscopy in staging non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2003; 126: 1900–1904.
34. Kernstine KH. Positron emission tomography with 2-[^{18}F]fluoro-2-deoxy-glucose: can it be used to accurately stage the mediastinum in non-small cell lung cancer as an alternative to mediastinoscopy? *J Thorac Cardiovasc Surg* 2003; 126: 1700–1703.
35. Hayashi K, Abe K, Sakaguchi C, Kawauchi T, Kosuda K. Questionnaires on mediastinoscopy for mediastinal FDG uptake in patients with non-small cell lung carcinoma—analysis in the institutions without a PET system. *Jpn J Clin Radiol* 2005; 50: 281–289.