000 **Sentinel node identification in clinical stage Ia non–small cell lung cancer by a combined single photon emission computed tomography/computed tomography system**

Hiroaki Nomori, MD, PhD, Koei Ikeda, MD, PhD, Takeshi Mori, MD, PhD,

Shinya Shiraishi, MD, PhD, Hironori Kobayashi, MD, Kazunori Iwatani, MD,

Koichi Kawanaka, MD, PhD, and Toshiaki Kobayashi, MD, PhD, Kumamoto and Tokyo, Japan

SN identification with ^{99m}Tc tin colloid was performed with both SPECT/CT and the gamma probe in 63 patients with lung cancer. SPECT/CT images could identify SNs in segmental and lobar lymph nodes but not in the mediastinum.

Size of Metastatic and Nonmetastatic Mediastinal Lymph Nodes in Non-small Cell Lung Cancer

Koei Ikeda, MD, PhD, Hiroaki Nomori, MD, PhD, Takeshi Mori, MD, Hironori Kobayashi, MD, Kazunori Iwatani, MD, and Kentaro Yoshimoto, MD

Objective: To determine the optimum selection of mediastinal lymph nodes for biopsy in non-small cell lung cancer (NSCLC), lymph nodes with or without metastasis at each mediastinal station were ranked in size in patients with pathological N2 disease.

Methods: Twenty-five NSCLC patients with pathological N2 disease who underwent pulmonary resection with complete mediastinal lymph node clearance were examined. Of 114 mediastinal lymph node stations dissected, 47 had metastases and 67 did not. The sizes of 259 nodes in the 47 positive lymph node stations were measured. Of these 259 nodes, 137 had metastases and 122 did not. The short- and long-axis diameters of the 259 lymph nodes were ranked in each lymph node station.

Results: Mean short- and long-axis diameters of lymph nodes with metastases were significantly greater than those without ($p < 0.001$). In 47 metastatic lymph node stations, the short- and long-axis diameters were greatest in a metastatic node in 44 (94%) and 42 (89%) respectively, whereas in the remaining 3 (6%) and 5 (11%), the second largest but not the largest node was positive. None of the largest lymph nodes with metastasis were smaller than the second largest lymph node at each station. Four of the 10 patients with adenocarcinoma (40%) had metastasis in the second largest but not in the largest node measured by long-axis diameter, a significant difference from one in eight (12.5%) among the squamous cell carcinoma cases ($p = 0.04$).

Conclusion: For mediastinal lymph node biopsy, both the largest and the second largest node at each station should be sampled, especially in adenocarcinoma. If only the largest lymph node is selected, false-negative results will occur at a rate of about 10%.

Key Words: Lung cancer, Mediastinal lymph node, Lymph node stage, Sampling, Biopsy.

(*J Thorac Oncol.* 2006;1: 949–952)

Although intraoperative N-staging has traditionally been conducted according to the surgeon's experience, Gaer and Goldstraw[1] reported that a naked-eye assessment of nodal staging during lung cancer surgery resulted in 11% false-positive and 9% false-negative assessments. Even for preoperative N-staging, mediastinoscopy and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) are reported to have false-negative results,[2–4] which could be attributable to the small size of the biopsy specimens and also to errors in the selection of lymph nodes. Although the largest lymph node is usually selected in mediastinoscopy or EUS-FNA, it has not been confirmed whether the choice of the largest is most appropriate. Thus, it is necessary to consider whether metastasis occurs in the largest lymph nodes. We therefore ranked the sizes of mediastinal lymph nodes with and without metastasis at each nodal station in non-small cell lung cancer (NSCLC) patients with pathological N2 disease.

PATIENTS AND METHODS

Patients

From 1988 to 2005, 420 patients with lung cancer were treated by lobectomy or pneumonectomy with systematic, not lobe-specific, mediastinal lymph node dissection. Of these, 25 patients had mediastinal lymph node metastases (Table 1). Ten patients who underwent neoadjuvant treatment were excluded from the study. Whereas preoperative N-staging was performed by computed tomography (CT) until 2004, positron emission tomography (PET) and EUA-FNA were added for N-staging after 2004. Our treatment strategy for clinical N2 disease was as follows: 1) bulky N2 disease at both superior and inferior mediastinum contraindicated surgery; and 2) N2 disease with multiple affected stations limited to either the superior or inferior mediastinum, or bulky N2 disease at a single station, was treated by neoadjuvant chemoradiotherapy and then surgery.

Pathological Examination

The dissected mediastinal lymph nodes were examined histologically in formalin-fixed paraffin-embedded sections with hematoxylin and eosin (HE) staining. The sections were further examined by immunohistochemical staining with a monoclonal antihuman cytokeratin antibody (DAKO Co., Carpinteria, CA).

TABLE 1. Patient Characteristics

Male	17
Female	8
Mean age (year-old)	63 ± 10
Histological subtype	
Adenocarcinoma	10
Squamous cell carcinoma	8
Adenosquamous carcinoma	2
Large cell carcinoma	4
Mucoepidermoid carcinoma	1
Location of the tumor	
Right upper lobe	11
Right middle lobe	1
Right lower lobe	5
Left upper lobe	6
Left lower lobe	2
Pathological tumor stage	
T1N2M0	6
T2N2M0	13
T3N2M0	3
T4N2M0	3
Total	25

TABLE 2. Lymph Node Nomenclature

N2 Node		N1 Node	
Station	Name	Station	Name
	Superior mediastinal		Hilar
1	Highest mediastinal	10	Hilar
2	Paratracheal	11	Interlobar
3	Pretracheal	12	Lobar
4	Tracheobronchial		
			Intrapulmonary
	Aortic	13	Segmental
5	Botallo	14	Subsegmental
6	Para-aortic		
	Inferior mediastinal		
7	Subcarinal		
8	Paraesophageal		
9	Pulmonary ligament		

Lymph Node Stations

The lymph node nomenclature used was from the lymph node map of Naruke et al,[5] as approved by The Japan Lung Cancer Society (Table 2).

Measurement of Lymph Node Size

The short- and long-axis diameters of all lymph nodes were measured on HE-stained sections and ranked for each lymph node station.

Statistical Analysis

All data were analyzed for significance using two-tailed Student's t tests or χ^2 tests. Differences at $p < 0.05$ were

TABLE 3. Number of Mediastinal Lymph Node Stations with Metastasis in Each Lobe

Lobe	Superior Mediastinum	Inferior Mediastinum (#7)	Total
Right upper lobe	24	2	26
Right middle lobe	0	1	1
Right lower lobe	5	1	6
Left upper lobe	12	0	12
Left lower lobe	1	1	2
Total	42	5	47

TABLE 4. Size of the Lymph Nodes with or Without Metastasis in the Metastatic Lymph Node Stations

	Lymph Nodes		
	With Metastasis	Without Metastasis	p Value
Number	137	122	
Short-axis diameter (mm)			$p < 0.001$
Mean	5 ± 3	3 ± 2	
Range	0.5–18	0.5–11	
Long-axis diameter (mm)			$p < 0.001$
Mean	8 ± 5	5 ± 3	
Range	0.5–33	0.5–19	

accepted as significant. All values in the text and tables are given as mean ± SD.

RESULTS

A total of 114 mediastinal lymph node stations were resected in 25 patients. Of these, 47 stations had metastatic lymph nodes and 67 did not. Whereas 13 of the 25 patients had metastases at a single nodal station, the other 12 had metastases at multiple stations. Table 3 shows the distribution of the 47 metastatic lymph node stations in each lobe. Whereas tumors in the upper lobes had metastases almost in the superior mediastinum, tumors in the right lower lobe did not show the uniform distribution of metastases, that is, four of the five tumors had single-station metastasis in the superior mediastinum, and the remaining one had metastases in both the superior and inferior mediastinum. In the 47 lymph node stations containing metastases, there were 137 lymph nodes with metastases and 122 without (Table 4). Among the 137 metastatic lymph nodes, micrometastasis was found in three (2%) by immunohistochemical examination. The mean short-axis diameter of the lymph nodes with metastasis was 5 ± 3 mm, which was significantly larger than that of those without metastasis (3 ± 2 mm; $p < 0.001$). The mean long-axis diameter of lymph nodes with metastasis was 8 ± 5 mm, which was significantly greater than that of those without metastasis (5 ± 3 mm; $p < 0.001$).

Table 5 shows a ranking of the largest lymph nodes with metastasis at each lymph node station. By short-axis diameter, the largest lymph node had metastases in 44 of the

TABLE 5. Rank of the Size of Lymph Nodes with Metastasis in Each Lymph Node Station

Measured by Short-Axis Diameter	
Largest lymph node	44
Second largest lymph node	3
Smaller than the second one	0
Measured by long-axis diameter	
Largest lymph node	42
Second largest lymph node	5
Smaller than the second	0
Total	47

47 affected lymph node stations (94%). In the remaining three lymph node stations (6%), the largest lymph node was clear of metastasis, but the second largest had metastasis. By long-axis diameter, the largest lymph node had metastasis in 42 of the 47 stations (89%), and in the remaining five lymph node stations (11%), the second largest lymph node was involved, but the largest was not. None of the largest lymph nodes with metastasis were smaller than the second largest one in any of the stations when measuring both the short- and long-axis diameters. Four of 10 patients with adenocarcinoma (40%) had metastasis in the second largest lymph node as measured by long-axis diameter, but not in the largest one, which was more common than in squamous cell carcinoma, where this occurred in one of eight cases (12.5%) ($p = 0.04$).

DISCUSSION

The present study has demonstrated the following points: 1) In pathological N2 disease, approximately 90% of metastases were found in the largest lymph node at its nodal station; 2) approximately 10% of metastasis were in the second largest but not in the largest lymph node of each station; 3) none of the metastatic lymph nodes were smaller than the second largest lymph node of any nodal station; and 4) adenocarcinoma had metastasis in the second largest lymph node, but not in the largest lymph node, more frequently than squamous cell carcinoma. Therefore, examining both the largest and second largest lymph nodes is necessary to reach 100% sensitivity for preoperative and intraoperative mediastinal lymph node staging. However, it should be kept in mind that the present study measured the sizes of lymph nodes in fixed, cut, and stained specimens, which were smaller than their size at the moment of preoperative or intraoperative nodal evaluation. Therefore, the absolute sizes of lymph nodes shown in Table 5 are not applicable to preoperative or intraoperative evaluation of lymph nodes. The present study is concerned with the rank order of sizes of metastatic mediastinal lymph nodes at each nodal station.

It is well known that systematic mediastinal lymph node dissection does not increase postoperative morbidity or mortality.[6,7] However, the recent increase of clinical stage Ia NSCLC has led to increased use of limited lung resection as well as a reduction in mediastinal lymph node dissection. Segmentectomy has been reported to have a similar postoperative prognosis as lobectomy when intraoperative frozen sections of hilar and mediastinal lymph nodes show no

metastasis.[8] Whereas the International Association for the Study of Lung Cancer Staging Committee has determined that the definition of stage p-N0 should be based on the pathological findings of systematic mediastinal lymph node dissection,[9] several authors have proposed lobe-specific mediastinal lymph node dissection for patients with clinical stage Ia NSCLC to minimize surgical damage[10-13]; that is, the dissection of inferior mediastinal lymph node stations could be reduced for upper lobectomy when the hilar and superior mediastinal lymph nodes are negative for metastases, and the dissection of superior mediastinal lymph node stations could be reduced for lower lobectomy when the hilar and inferior mediastinal lymph nodes are negative for malignancy. However, before the final decision is made on both segmentectomy and lobe-specific mediastinal lymph node dissection, a large number of lymph nodes need to be submitted for intraoperative frozen section. To reduce the number of lymph nodes required for this, several authors have proposed intraoperative sentinel lymph node biopsy using radioisotopes.[14-16] However, this necessitates preoperative injection of radioisotopes and intraoperative measurement of the radioactivity of lymph nodes. Based on the results of the present study, we believe that taking the largest and the second largest lymph nodes at each station would provide a sufficient sample of intraoperative frozen sections and would minimize the number of intraoperative frozen sections taken.

Which lymph node stations should be submitted for intraoperative frozen section during lung cancer surgery? In 1999, Naruke et al[10] examined the distribution of lymph node metastasis (i.e., sentinel nodes) in each lobe from data on 1815 patients with T1 NSCLC who had major lung resection with mediastinal lymph node dissection. They concluded that, whereas hilar lymph nodes were usually sentinel nodes in lung cancer, the following mediastinal lymph nodes could be sentinel nodes: #3 and/or #4 in the right upper lobe, #3 and/or #7 in the right middle lobe, #7 in the right lower lobe, #5 and/or #6 in the left upper lobe, and #7 in the left lower lobe. Other authors have reported similar results.[17,18] The present study, however, although showing similar results for the upper lobes of both sides, demonstrated that four of five lung cancers in the right lower lobe had a single metastasis at station #3 or #4. According to our previous study of sentinel node identification using ^{99m}Tc-tin colloid, two of eight NSCLC in the right lower lobe had sentinel nodes in both #4 and #7.[15] We consider that the lymphatic flow from the right lower lobe could partly drain to the superior mediastinum (#3 and #4) along the main bronchus. From the previous report and from the present study, a plan for efficient intraoperative N-staging could be as follows: hilar lymph nodes and lobe-specific mediastinal lymph nodes are dissected;, and the largest and second largest lymph nodes from each station are submitted for intraoperative frozen section. In this way, the number of lymph nodes for frozen section would be minimized.

Although mediastinoscopy and EUS-FNA have been proposed for mediastinal lymph node biopsy, they are known to have false-negative results.[2-4] EUS-FNA is now the least invasive procedure for pathological or cytological diagnosis

of mediastinal lymph nodes, but its sensitivity has been reported to be 65 to 75%, which is lower than that of mediastinoscopy.[2,3] To increase the sensitivity of these biopsy procedures, the present study indicated that both the largest and the second largest lymph nodes should be targeted to reach 100% sensitivity. If only the largest lymph node is selected, the sensitivity will not exceed 90%.

The present study showed that adenocarcinoma may have metastases in the second largest but not in the largest lymph node more frequently than squamous cell carcinoma. It is well known that the pattern of lymph node metastasis is different between adenocarcinoma and squamous cell carcinoma. Ohta et al[19] reported that nodal micrometastasis was detected by immunohistochemistry in 20% of patients with adenocarcinomas 1 to 2 cm in size, whereas it was not found in any patient with squamous cell carcinoma. Mori et al[20] reported that lymph node metastases from adenocarcinoma were of normal size more frequently than those from squamous cell carcinoma. The present study indicated that both the largest and second largest lymph nodes should be examined during N-staging, especially in adenocarcinoma.

Although it has been reported that 20 to 25% of patients with clinical stage I disease have mediastinal lymph node metastasis,[21–23] the present study showed only 35 of 420 patients (8%) with N2 disease. Our procedure for mediastinal lymph node dissection was systematic and yielded 114 nodal stations in 25 patients (4.6 stations per patient) and 259 lymph nodes from the 47 metastatic lymph node stations (5.5 lymph nodes per station). The reason for the low number of patients with N2 disease in the present study is probably attributable to the institutional setting—most of the lung cancers in our patients were found by routine CT examination, resulting in a higher rate of early-stage NSCLC than usual.

The present study showed that an efficient selection of mediastinal lymph nodes for N-staging is obtained by targeting both the largest and the second largest lymph nodes at each station. We believe that the present data are useful not only for intraoperative N-staging but also for preoperative biopsy procedures.

ACKNOWLEDGMENTS

REFERENCES

1. Gaer JAR, Goldstraw P. Intraoperative assessment of nodal staging at thoracotomy for carcinoma of the bronchus. *Eur J Cardiothoracic Surg* 1990;4:207–210.
2. Hermans FH, Van Engelenburg TC, Visser FJ, Thunnissen FB, Termeer R, Janssen JP. Diagnostic yield of transbronchial histology needle aspiration in patients with mediastinal lymph node enlargement. *Respiration* 2003;70:631–635.
3. Annema JT, Veselic M, Versteegh MIM, Willems LNA, Rabe K. Mediastinal restaging: EUS-FNA offers a new perspective. *Lung Cancer* 2003;42:311–318.
4. Freixinet Gilart J, Garcia PG, de Castro FR, Suarez PR, Rodriguez NS,

de Ugarte AV. Extended cervical mediastinoscopy in the staging of bronchogenic carcinoma. *Ann Thorac Surg* 2000;70:1641–1643.
5. Naruke T, Suemasu K, Ishikawa S. Lymph node mapping and curability at various levels of metastasis in resected lung cancer. *J Thorac Cardiovasc Surg* 1978;76:832–839.
6. Lardinois D, Suter H, Hassan H, Rousson V, Betticher D, Ris HB. Morbidity, survival, and site of recurrence after mediastinal lymph node dissection versus systematic sampling after complete resection for non-small cell lung cancer. *Ann Thorac Surg* 2005;80:268–275.
7. Allen MS, Darling GE, Pechet T, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 Trial. *Ann Thorac Surg* 2006;81:1013–1020.
8. Yoshikawa K, Tsubota T, Kodama K, et al. Prospective study of extended segmentectomy for small lung tumors. The final report. *Ann Thorac Surg* 2002;73:1055–1059.
9. Rami-Pora R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: proposed definition. *Lung Cancer* 2005;49:25–33.
10. Naruke T, Tsuchiya R, Kondo H, Nakayama H, Asamura H. Lymph node sampling in lung cancer: how should it be done? *Eur J Cardio Thorac Surg* 1999;16:S17–S24.
11. Asamura H, Nakayama H, Kondo H, Tsuchiya R, Naruke T. Lobe-specific extent of systemic lymph node dissection for non-small cell lung carcinomas according to a retrospective study of metastases and prognosis. *J Thorac Cardiovasc Surg* 1999;117:1102–1111.
12. Okada M, Tsubota N, Yoshimura M, Miyamoto Y, Matsuoka H. Prognosis of completely resected pN2 non-small cell lung carcinomas: what is the significant node that affects survival? *J Thorac Cardiovasc Surg* 1999;118:270–275.
13. Graham ANJ, Chan KJM, Pastorino U, Goldstraw P. Systemic nodal dissection in the intrathoracic staging of patients with non-small cell lung cancer. *J Thorac Cardiovasc Surg* 1999;117:246–251.
14. Liptay MJ, Masters GA, Winchester DJ, et al. Intraoperative radioisotope sentinel lymph node mapping in non-small cell lung cancer. *Ann Thorac Surg* 2000;70:384–390.
15. Nomori H, Horio H, Naruke T, Orikasa H, Yamazaki K, Suemasu K. Use of technetium-99m tin colloid for sentinel lymph node identification in non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2002;124:486–492.
16. Nomori H, Watanabe K, Ohtsuka T, Naruke T, Suemasu K. In vivo identification of sentinel lymph nodes for clinical stage I non-small cell lung cancer for abbreviation of mediastinal lymph node dissection. *Lung Cancer* 2004;46:49–55.
17. Asamura H, Nakayama H, Kondo H, et al. Lobe-specific extent of systemic lymph node dissection for non-small cell lung carcinomas according to a retrospective study of metastasis and prognosis. *J Thorac Cardiovasc Surg* 1999;117:1102–1111.
18. Okada M, Tsubota N, Yoshimura M, Miyamoto Y. Proposal for reasonable mediastinal lymphadenectomy in bronchogenic carcinomas: role of subcarinal nodes in selective dissection. *J Thorac Cardiovasc Surg* 1998;116:949–953.
19. Ohta Y, Oda M, Wu J, Tsunezuka Y, Hiroshi M, Nomura A, et al. Can tumor size be guide for limited surgical intervention in patients with peripheral non-small cell lung cancer? *J Thorac Cardiovasc Surg* 2001; 122:900–906.
20. Mori K, Yokoi K, Saito Y, Tominaga K, Miyazawa N. Diagnosis of mediastinal lymph node metastases in lung cancer. *Jpn J Clin Oncol* 1992;22:35–40.
21. Seely JM, Mayo JR, Miller RR, Muller NL. T1 lung cancer: prevalence of mediastinal node metastases and diagnostic accuracy of CT. *Radiology* 1993;186:129–132.
22. Heavey LR, Glazer GM, Gross BH, Francis IR, Orringer MB. The role of CT in staging radiographic T1N0M0 bronchogenic cancer. *AJR Am. J. Roentgenol.* 1986;146:285–290.
23. Conces DJ, Klink JF, Tarver RD, Moak GD. T1N0M0 lung cancer: evaluation with CT. *Radiology* 1989;170:643–646.

be considered as potentially metastasizing neoplasms. Therefore the benign behavior is probably variable, and the aspects that indicate this behavior need to be clarified.

In summary, the unusual presentation of a benign, clear cell tumor as a large tumor of the lung mimicking malignant behavior in terms of tumor vascularity and local invasion is rare. The need for pneumonectomy for large benign lung tumors is again unusual. The benign behavior is variable, therefore complete surgical resection is probably the best chance to improve survival and quality of life.

References

1. Liebow AA, Castleman B. Benign clear cell tumors of the lung. Am J Pathol 1963;43:13.
2. Gaffey MJ, Mills SE, Zarbo RJ, Weiss LM, Gown AM. Clear cell tumor of the lung. Immnunohistochemical and ultrastructural evidence of melanogenesis. Am J Surg Pathol 1991;15:644–53.
3. Wick MR, Mills SE. Benign and borderline tumors of the lung and pleura. In: Leslie KO, Wick MR, eds. Practical pulmonary pathology a diagnositc approach, 1st ed. Philadelphia: Churchill Livingstone, 2005:713–5.
4. Kung M, Landa JF, Lubin J. Benign clear cell tumor (sugar tumor) of the trachea. Cancer 1984;54:517–9.
5. Alfredo NCS, Flavia SN, Nelson H, Teresa YT. A rare cause of hemoptysis: benign sugar (clear) cell tumor of the lung. Eur J Cardiothorac Surg 2004;25:652–4.
6. Sale GE, Kulander BG. "Benign" clear cell tumor (sugar tumor) of the lung with hepatic metastasis ten years afer resection of pulmonary primary tumor. Arch Pathol Lab Med 1988;112:1177–8.
7. Gaffey MJ, Mills SE, Askin FB, et al. Clear cell tumor of the lung: a clinicopathologic, immunohistochemical and ultrastructural study of eight cases. Am J Surg Pathol 1990;14:248–59.

11C-Acetate and 18F-Fluorodeoxyglucose Positron Emission Tomography of Pulmonary Adenocarcinoma

Masahiro Kaji, MD, PhD, Hiroaki Nomori, MD, PhD, Kenichi Watanabe, MD, PhD, Takashi Ohtsuka, MD, PhD, Tsuguo Naruke, MD, PhD, Keiichi Suemasu, MD, PhD, and Kimiichi Uno, MD, PhD

Department of Thoracic Surgery, Saiseikai Central Hospital, Graduate School of Medicine, Kumamoto University, and Nishidai Clinic, Tokyo, Japan

Positron emission tomography (PET) with 11C-acetate has been recently reported in detection of slow-growing tumors, such as well-differentiated adenocarcinomas of the lung, which are often negative with 18F-fluorodeoxyglucose (FDG) PET. Here we present findings of acetate-PET and FDG-PET in a case of adenocarcinoma that was comprised of peripheral ground glass opacity and solid central components, and was histologically comprised of both a well-differentiated and a moderately-differenti-

ated adenocarcinoma, respectively. Acetate-PET was positive in both components, whereas FDG-PET was only positive in the solid central component. The present case demonstrates the figurative findings of acetate-PET and FDG-PET in lung adenocarcinoma.

(Ann Thorac Surg 2007;83:312–4)
© 2007 by The Society of Thoracic Surgeons

Although positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) has contributed significantly to the diagnosis of lung cancers, well-differentiated adenocarcinomas are well known to frequently be falsely negative with FDG-PET, owing to their low rate of glucose metabolism [1]. Recently, we reported that PET with 11C-acetate (AC) was able to detect well-differentiated adenocarcinomas exhibiting a ground-glass opacity (GGO) appearance more frequently than FDG-PET [2]. Here we present the figurative findings of AC-PET and FDG-PET in a case of lung adenocarcinoma that was comprised of peripheral GGO and solid central components that exhibited the histologic characteristics of both a well-differentiated and moderately-differentiated adenocarcinoma, respectively.

The patient was a 76-year-old woman with adenocarcinoma of the left lung that was detected by a routine annual examination. Computed tomography showed a mass shadow (5.5 × 4.5 cm) that consisted of a peripheral GGO component and a solid central component (Fig 1). The size of the solid central compartment was 4.2 × 1.5 cm. The AC-PET and FDG-PET was conducted according to the following protocol. The AC-PET and FDG-PET demonstrated the following findings: the AC-PET was positive in both the solid and GGO components (Fig 2A) and the FDG-PET was positive in the solid component but negative in the GGO (Fig 2B). A left upper lobectomy with mediastinal lymph node dissection was performed on January 11, 2006. Histologic findings revealed that the peripheral GGO component was a well-differentiated adenocarcinoma and that the solid central component was a moderately-differentiated adenocarcinoma.

The 11C-acetate was produced using an HM-18 cyclotron (Sumitomo Heavy Industries Co, Tokyo, Japan) by proton bombardment of 14N2. The resultant 11CO2 was then reacted with methyl magnesium bromide by a modified method of Pike and colleagues [3]. The AC-PET was performed before FDG-PET on the same day. The dosage of 11C-acetate administered was 125 μCi/kg (4.6 MBq/kg). The PET imaging was performed approximately 10 minutes after the administration of AC using a PosiCam.HZL mPower scanner (Positron Co, Houston, TX). Approximately 30 minutes after AC-PET imaging, fluorine-18 FDG was administered (ie, more than 120 minutes after administration of the AC). The dosage of FDG was 125 μCi/kg (4.6 MBq/kg) for nondiabetic patients and 150 μCi/kg (5.6 MBq/kg) for diabetic patients, as we previously reported [1]. The FDG-PET imaging was performed approximately 45 minutes after administration of the FDG. The cost for one study of AC-PET is less than $100.

Comment

Recent advances in FDG-PET have contributed significantly to the ability to differentiate between benign and malignant pulmonary nodules. However, FDG-PET sometimes provides false-negative findings, particularly for low-grade malignant tumors, such as bronchioloalveolar carcinoma and carcinoid, due to their low glucose metabolism [1, 4]. We previously reported that while FDG-PET did not exhibit false-negative results for squamous cell, large cell, or small cell carcinomas, 60% of well-differentiated adenocarcinomas (1 to 3 cm in size) failed to be identified by FDG-PET [1].

The ^{11}C-acetate has been widely used as a PET tracer for evaluating myocardial oxidative metabolism [5]. Recently AC-PET has been reported to be a useful PET tracer in detecting slow-growing tumors that have failed to be identified by FDG-PET, such as well-differentiated lung adenocarcinomas, well-differentiated hepatocellular carcinomas, and prostate cancers [2, 6, 7].

It is well known that differentiated adenocarcinomas of the lung are often histologically heterogeneous [8] (ie, in the peripheral zone, tumor cells proliferate in a single layer along the alveolar septa, as in bronchioloalveolar carcinomas; whereas in the central zone, tumor cells proliferate in moderately-differentitated or poorly-differentiated papillary structures along with an increase of fibrovascular stroma). Here we present the findings of AC-PET and FDG-PET in a case of adenocarcinoma that consisted of peripheral GGO and solid central components, which exhibited the histologic characteristics of well-differentiated and moderately-differentiated adenocarcinomas, respectively. Although AC-PET was positive in both components, FDG-PET was only positive in the central component of the moderately-differentiated carcinoma, which are typical findings of AC-PET and FDG-PET.
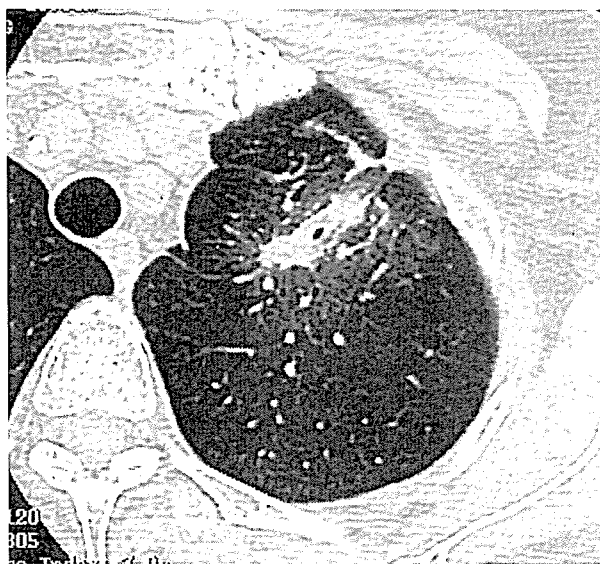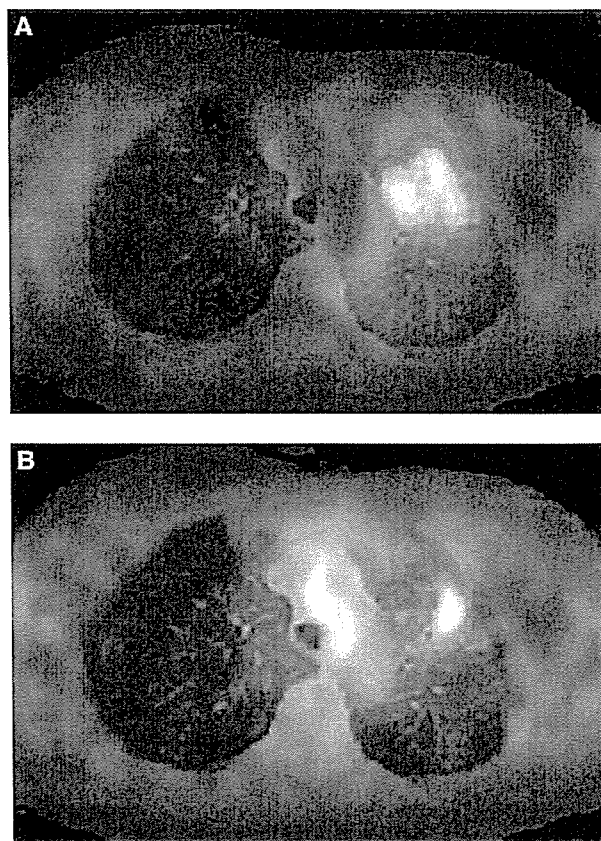

Fig 2. Fusion findings of computed tomography and positron emission tomography. (A) Acetate-positron emission tomography (AC-PET) was positive in both the peripheral ground-glass opacity and the central solid components. (B) The ^{18}F-fluorodeoxyglucose (FDG)-PET was positive in the central solid component but negative in the peripheral ground-glass opacity component.

Our previous investigation demonstrated that 6 of 10 (60%) moderately-differentiated or poorly-differentiated adenocarcinomas were positive with both FDG-PET and AC-PET. Therefore we believe that differentiated adenocarcinomas with GGO images on CT should be examined with AC-PET rather than FDG-PET.

References

1. Nomori H, Watanabe K, Ohtsuka T, et al. Evaluation of F-18 fluorodeoxyglucose (FDG) PET scanning for pulmonary nodules less than 3 cm in diameter, with special reference to the CT images. Lung Cancer 2004;45:19–27.
2. Nomori H, Kosaka N, Watanabe K, et al. ^{11}C-acetate positron emission tomography imaging for lung adenocarcinoma 1 to 3 cm in size with ground-glass opacity images on computed tomography. Ann Thorac Surg 2005;80:2020–5.
3. Pike VW, Eakins MN, Allan RM, et al. Preparation of [1-^{11}C] acetate—an agent for the study of myocardial metabolism by positron emission tomography. Int J Appl Radiat Isot 1982;33:505–12.
4. Nomori H, Watanabe K, Ohtsuka T, et al. Visual and semiquantitative analyses for F-18 fluorodeoxyglucose (FDG) PET scanning in pulmonary nodules 1 to 3 cm in size. Ann Thorac Surg 2005;79:984–8.

Fig 1. Computed tomography showing the lesion composed of the peripheral ground glass opacity and the central solid components.

5. Brown M, Marshall DR, Sobel BE, Bergmann SR. Delineation of myocardial oxygen utilization with carbon-11-labeled acetate. Circulation 1987;76:687–96.
6. C, Yeung DW. C-11 acetate PET imaging in hepatocellular carcinoma and other liver masses. J Nucl Med 2003;44:213–21.
7. Oyama N, Akino H, Kanamaru H, et al. ¹¹C-acetate PET imaging of prostate cancer. J Nucl Med 2002;43:181–6.
8. Shimosato Y, Hashimoto T, Kodama T, et al. Prognostic implications of fibrotic focus (scar) in small peripheral lung cancers. Am J Surg Pathol 1980;4:365–73.

Prolonged Survival Due to Spontaneous Regression and Surgical Excision of Malignant Mesothelioma

John E. Pilling, MRCS, Andrew G. Nicholson, FRCPath, Clive Harmer, FRCP, and Peter Goldstraw, FRCS

Departments of Thoracic Surgery and Pathology, Royal Brompton Hospital, and Department of Oncology, Royal Marsden Hospital, London, United Kingdom

We report a case of malignant pleural mesothelioma with histologically proven spontaneous regression of pleural disease. During a 12-year follow-up there was a single recurrence, which was a lesion in the chest wall at 6 years that was surgically excised. A prominent host response to tumor was seen in both the primary tumor and the recurrence.

(Ann Thorac Surg 2007;83:314–5)
© 2007 by The Society of Thoracic Surgeons

Malignant mesothelioma is an exceptionally aggressive and almost universally fatal neoplasm arising from mesothelial cells that form the serosal lining of the pleural, peritoneal, and pericardial cavities. We report the case of a long-term survivor with malignant pleural mesothelioma (MPM) in which spontaneous regression of the disease has been histologically proven and whose recurrence was controlled with limited surgical excision.

A 58-year-old man presented in 1994 with a 3-month history of chest pain and dyspnea. He was a nonsmoker who had significant occupational exposure to asbestos 16 years previously. Left video-assisted thoracoscopic surgery at another hospital demonstrated a blood stained pleural effusion and tumor nodules infiltrating the posterior parietal pleura. The operative report clearly identified the area of macroscopic disease from which the biopsy was taken. Pleural biopsies showed fibrous thickening with infiltration by a malignant, predominantly epithelioid neoplasm. There were occasional sarcomatoid areas and a prominent inflammatory cell infiltrate. Immunohistochemistry showed a mesothelial phenotype with subsequent diagnosis of MPM. The patient con-

sulted an oncologist, opting for radiological surveillance but no further active treatment at that time.

Five years later he presented with an enlarging, painless chest wall mass 5 cm in diameter overlying the anterior ends of the third to fifth ribs, distant from the previous video-assisted thoracoscopic surgery port sites (Fig 1). A needle biopsy confirmed malignancy and the patient proceeded to a left thoracotomy, multiple pleural biopsies, and chest wall resection with insertion of prosthesis. The chest wall mass was shown to be a completely excised epithelioid MPM in which there was a moderate host inflammatory response (Fig 2). There was a moderately high proliferation index. The mass was arising from the chest wall and was not in continuity with the parietal pleura. It was believed to be a hematogenous metastasis from the original MPM. Both the video-assisted thoracoscopic surgery biopsies and the chest wall lesion were subject to international pathologic review, which confirmed the diagnosis of MPM. Extensive parietal pleurectomy from the region of the previous VATS biopsy in the left paravertebral gutter showed mild fibrosis with no evidence of malignancy. Recovery from the operation was uneventful.

At follow-up 7 years after chest wall resection and 12 years after initial presentation, the patient remains asymptomatic with no radiologic evidence of recurrence. During this time, no adjuvant therapy has been given.

Comment

Survival after diagnosis of MPM is generally poor. Even in those fit for surgical palliation the median survival after surgery is 10 months [1]. Tri-modality therapy (ie, combined radical surgery, radiotherapy and chemotherapy) has had limited success outside of specific subgroups in which patients with epithelioid MPM, negative surgical resection margins, and unaffected extrapleural lymph nodes had a 5-year survival of 46% [2]. Although patients with prolonged survival after very limited treatment have been reported [3], it is extremely rare.
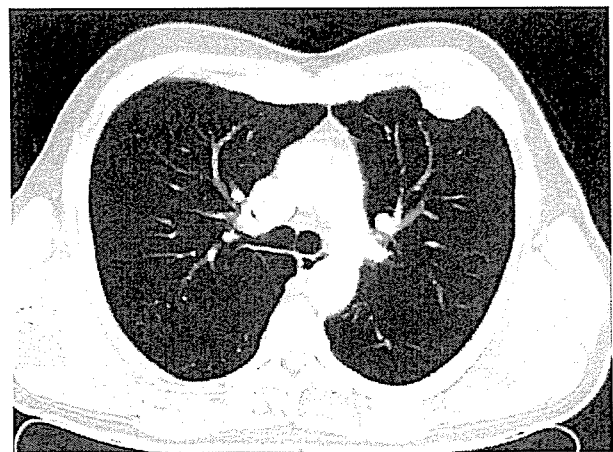
Fig 1. Computed tomographic scan showing chest wall mass at anterior ends of the third to fifth ribs.