TABLE 4. Incidence of recurrent disease in the patients with or without VPI as diagnosed with JSS, PE, or either method

Recurrent site	JSS VPI		PE VPI		Either method VPI	
	Present (n = 43)	Absent (n = 100)	Present (n = 18)	Absent (n = 125)	Present (n = 49)	Absent (n = 94)
Local recurrence	12 (28%)*	4 (4%)	4 (22%)	12 (10%)	12 (24%)§	4 (4%)
Carcinomatous pleuritis	7 (16%)†	0	3 (17%)‡	4 (3%)	7 (14%)‖	0
Other sites	5 (12%)	4 (4%)	1 (6%)	8 (6%)	5 (10%)	4 (4%)
Distant metastases	8 (19%)	26 (26%)	7 (39%)	27 (22%)	12 (24%)	22 (23%)

VPI, Visceral pleural invasion; *JSS*, jet stream of saline solution; *PE*, pathologic examination.
*P = .0001.
†P = .0002.
‡P = .04.
§P = .0003.
‖P = .0004.

their distribution were evaluated by means of the log-rank test.[6,7] The Cox proportional hazards models were applied for the multivariate analysis.[8] All data were analyzed with Abacus Concepts, Survival Tools for StatView (Abacus Concepts, Inc, Berkeley, Calif).

Results

Of the 143 tumors evaluated that were located peripherally and suspected of reaching the visceral pleura, 49 (34%) were diagnosed to invade the visceral pleura by means of PE, the JSS method, or both. The diagnosis of VPI was made on the basis of the JSS method in 43 tumors and on the basis of PE in 18 tumors. Twelve tumors were found to have invaded the visceral pleura by means of both the JSS method and PE. The presence of VPI for the 49 resected tumors diagnosed by using the JSS method, PE, or both was considered to be true positive in this study. There were 6 false-negative results with the JSS method and 31 with PE. The sensitivity and accuracy of the JSS method for the diagnosis of VPI were 88% and 96%, respectively. In contrast, the sensitivity and accuracy of PE were 37% and 78%, respectively. The JSS method was significantly more sensitive and accurate than PE for the diagnosis of VPI. Table 1 shows the incidence of VPI as diagnosed with the JSS method and with PE according to pathologic stage. The presence of VPI for 11 (22%) patients with stage IA disease was diagnosed with the JSS method. As shown in Table 2, there was no significant relationship between the extensive N2 involvement and VPI. VPI and a positive finding on intrapleural lavage after a thoracotomy was linked, as shown in Table 3. No positive finding in the intrapleural lavage was found in our series in cases without VPI diagnosed on the basis of either the JSS method or PE. During a more than 5-year observation, we experienced 16 cases of local recurrence (metastases of hilar or mediastinal lymph nodes in 9 cases and carcinomatous pleuritis in 7 cases) and 34 cases of recurrence at distant organs. We defined malignant pleural effusion, pleural dissemination, or both as carcinomatous pleuritis in this study. Although there was no significant difference between the incidence of distant metastases in the patients with VPI and those without VPI, the incidence of local recurrence, especially regarding carcinomatous pleuritis, in the patients with VPI was significantly higher than in those without VPI, as shown in Table 4. Patients who otherwise were classified as having stage I disease had a significantly shorter recurrence-free survival if their VPI was present compared with that in patients with stage I disease without VPI, as shown in Figure 1, *A* (P = .02). All stages of patients with VPI had significantly shorter recurrence-free survivals than the patients without VPI, as shown in Figure 1, *B* (P = .004). As shown in Figure 2, there was also a significant difference between the patients with or without VPI in terms of overall survival (P = .02). In a multivariate analysis model that included sex, age, histologic type, pathologic stage, VPI, and positive cytologic finding on intrapleural lavage, VPI was an independent prognostic factor (P = .03), as were sex (P = .03), age (P = .002), and the stage of the disease ($P < .0001$; Table 5).

Discussion

VPI is a factor of poor prognosis.[1,2] PE alone usually confirms the diagnosis of VPI. However, it remains questionable as to whether a tumor can be considered reliably to have no VPI on the basis of PE findings alone. We previously reported a simple method involving a cytologic examination of cells desquamated from the visceral pleura by using the JSS method, which was significantly more sensitive and accurate than ordinary PE in detecting VPI caused by lung cancer.[3] This is a sequel report about JSS, which is a useful method to detect VPI. This study accumulated over 140 cases, and the follow-up period was sufficient to analyze the relationship between the presence of VPI detected

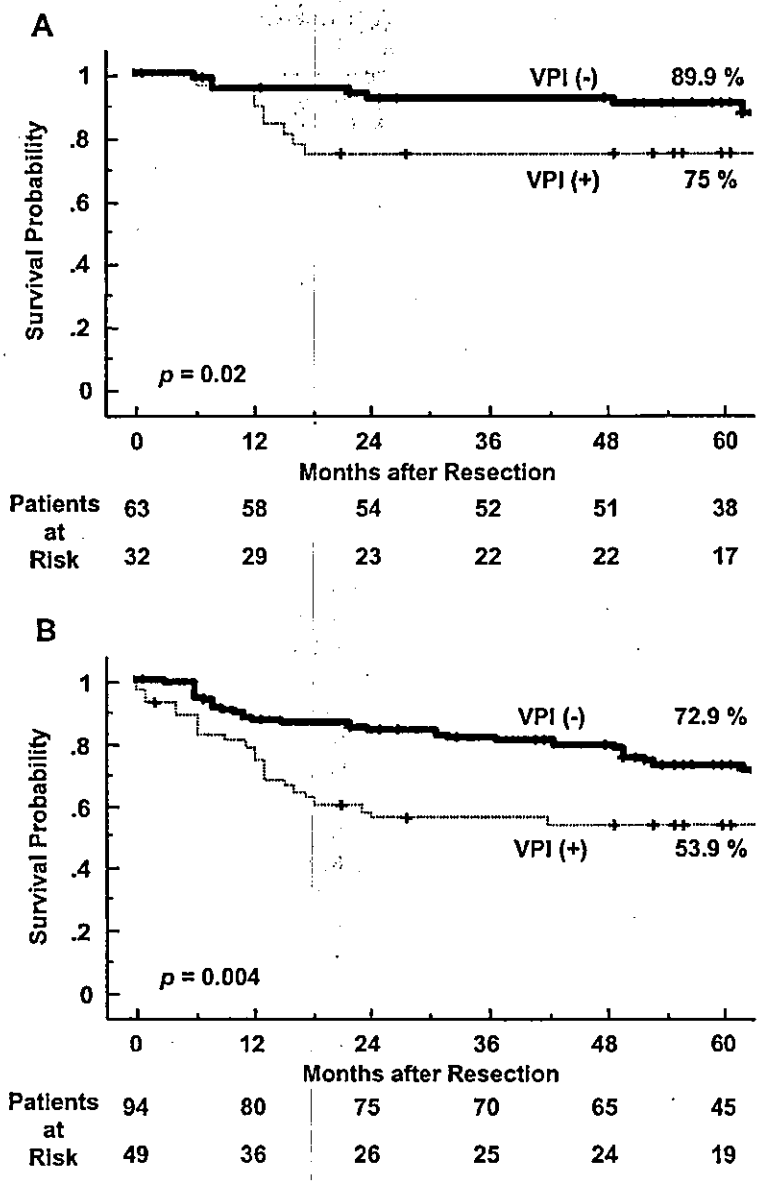

Figure 1. A, Recurrence-free survival in patients with stage I disease with or without VPI, as diagnosed by means of JSS or PE. B, Recurrence-free survival in all stages with or without VPI, as diagnosed by means of JSS or PE.

by means of our method and the prognosis. Bunker and associates[9] reported that an evaluation of VPI by means of hematoxylin and eosin examination alone might be indeterminate, and Verhoeff-Van Gieson elastic stains can be helpful in the diagnosis of VPI. However, there are limitations in making a diagnosis of VPI on the basis of PE alone because the diagnosis of VPI by PE usually is based on 1 or 2 cut slices of the resected tumor. Our findings reconfirmed that the JSS method is significantly more sensitive and accurate than ordinary PE in detecting VPI. The methodology for the JSS after resection for tumor close to the pleura is simple to complete and thus could affect the ultimate staging of patients. Unfortunately, the results are dependent on the ability of the cytologic team, which might not be universally available. Recently, the Cancer and Leukemia Group B trial demonstrated micrometastatic tumor cells in the lymph nodes of patients with stage I NSCLC by using standard and quantitative real-time reverse transcriptase–polymerase chain reaction for carcinoembryonic antigen.[10] Newer molecular techniques like this also might increase the yield of positivity. After our report on the usefulness of the JSS method, Saito and colleagues[11] reported on the diagnosis of

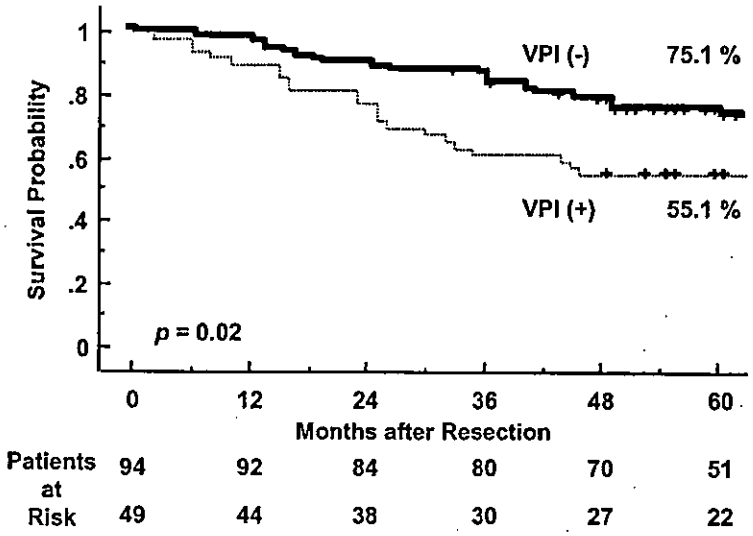

Figure 2. Overall survival with or without VPI, as diagnosed by means of JSS or PE.

VPI by using intraoperative touch cytology. Their method was simple and useful for detecting VPI; however, their follow-up was too short to fully analyze the prognosis. Manac'h and coworkers[2] reported that VPI was associated with a higher frequency of N2 involvement, and cancer-related death was mainly caused by distant metastases rather than local recurrence. Their results support the hypothesis that exfoliated tumor cells are drained through the pleural lymphatics to the mediastinal lymphatic pathways and then into the bloodstream. There was no relationship between the findings of VPI and the N status in our series. The prognosis of patients with positive cytologic findings on intrapleural lavage was poor compared with that in patients with negative findings.[12,13] Therefore they suggested that patients with positive cytologic findings on intrapleural lavage were considered to be in a prestage of carcinomatous pleuritis and thus should be upstaged. It was important that positive cytologic findings on intrapleural lavage were never present in cases without VPI in our series. Ichinose and associates[14] reported that intraoperative intrapleural hypotonic cisplatin treatment was found to effectively suppress the appearance of malignant pleural effusion, pleural dissemination, or both in selected patients who demonstrated positive pleural lavage cytology findings.

Our JSS method in addition to ordinary PE is therefore useful in detecting VPI, which is considered to be one of the causes of local recurrence, especially in patients with carcinomatous pleuritis. VPI is therefore considered to be an important prognostic factor and index for better selecting patients who can most benefit from adjuvant therapy consisting of hypotonic cisplatin treatment.

TABLE 5. Multivariate findings of the recurrence-free survival

Variable	Hazard ratio	95% Confidence interval	*P* value
Sex: female/male	1.96	1.08–3.57	.03
Age*: Elderly (>64 y)/ younger (<64 y)	2.76	1.45–5.24	.002
Histologic type: nonsquamous/squamous	1.44	0.49–4.21	.51
Pathologic stage†:			
IB/IA	3.69	1.19–11.5	.02
II/IA	7.65	2.26–25.9	.001
III/IA	22.0	7.36–65.7	<.0001
VPI	2.15	1.06–4.33	.03
Positive cytologic finding on intrapleural lavage	1.95	0.79–4.83	.15

VPI, Visceral pleural invasion.
*The number of elderly and younger patients was 71 and 72, respectively.
†The pathologic stage of the tumors was IA in 49 patients, IB in 46 patients, II in 17 patients, and III in 31 patients.

We thank Dr Brian T. Quinn for critical comments on the manuscript and Miss Yumiko Oshima for reviewing the patient chart.

References

1. Ichinose Y, Yano T, Asoh H, et al. Prognostic factors obtained by a pathologic examination in completely resected non-small-cell lung cancer. An analysis in each pathologic stage. *J Thorac Cardiovasc Surg*. 1995;110(3):601-5.
2. Manac'h D, Riquet M, Medioni J, et al. Visceral pleura invasion by

non-small cell lung cancer: an underrated bad prognostic factor. *Ann Thorac Surg.* 2001;71(4):1088-93.
3. Ichinose Y, Yano T, Asoh H, et al. Diagnosis of visceral pleural invasion in resected lung cancer using a jet stream of saline solution. *Ann Thorac Surg.* 1997;64(6):1626-9.
4. Sobin LH, Wittenkind C. TNM classification of malignant tumors. New York: Wiley-Liss; 1997.
5. Travis WD, Corrin B, Shimosato Y, et al. International histological classification of tumors. Histological typing of lung and pleural tumors. World Health Organization. 3rd ed. Berlin: Springer Verlag; 1999.
6. Kaplan E, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc.* 1958;53:457-81.
7. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep.* 1966;50(3):163-70.
8. Cox DR. Regression models and life tables. *J R Stat Soc.* 1972;34: 187-220.
9. Bunker ML, Raab SS, Landreneau RJ, Silverman JF. The diagnosis and significance of visceral pleural invasion in lung carcinoma. Histologic predictors and the role of elastic stains. *Am J Clin Pathol.* 1999;112(6):777-83.
10. D'Cunha J, Corfits AL, Herndon JE 2nd, et al. Molecular staging of lung cancer: real-time polymerase chain reaction estimation of lymph node micrometastatic tumor cell burden in stage I non-small cell lung cancer—preliminary results of Cancer and Leukemia Group B Trial 9761. *J Thorac Cardiovasc Surg.* 2002;123(3):484-91.
11. Saito Y, Yamakawa Y, Kiriyama M, et al. Diagnosis of visceral pleural invasion by lung cancer using intraoperative touch cytology. *Ann Thorac Surg.* 2002;73(5):1552-7.
12. Dresler CM, Fratelli C, Babb J. Prognostic value of positive pleural lavage in patients with lung cancer resection. *Ann Thorac Surg.* 1999; 67(5):1435-9.
13. Ichinose Y, Tsuchiya R, Yasumitsu T, et al. Prognosis of non-small cell lung cancer patients with positive pleural lavage cytology after a thoracotomy: results of the survey conducted by the Japan Clinical Oncology Group. *Lung Cancer.* 2001;31(1):37-41.
14. Ichinose Y, Tsuchiya R, Koike T, et al. A prematurely terminated phase III trial of intraoperative intrapleural hypotonic cisplatin treatment in patients with resected non-small cell lung cancer with positive pleural lavage cytology: the incidence of carcinomatous pleuritis after surgical intervention. *J Thorac Cardiovasc Surg.* 2002;123(4):695-9.

World Journal of Surgical Oncology

BioMed Central

Research

Open Access

Multimodal treatment for resectable epithelial type malignant pleural mesothelioma

Ichiro Yoshino*[1], Masafumi Yamaguchi[1], Tatsuro Yokamoto[2], Chie Ushijima[2], Yasuro Fukuyama[2], Yukito Ichinose[2] and Oshihiko Maehara[1]

Address: [1]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan and [2]Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka 811-1395, Japan

Email: Ichiro Yoshino* - iyoshino@surg2.med.kyushu-u.ac.jp; Masafumi Yamaguchi - masafumi@surg2.med.kyushu-u.ac.jp; Tatsuro Yokamoto - tokamoto@nk-cc.go.jp; Chie Ushijima - koromo@pop21.odn.ne.jp; Yasuro Fukuyama - yfukuyama@nk-cc.go.jp; Yukito Ichinose - yichinos@nk-cc.go.jp; Oshihiko Maehara - maehara@surg2.med.kyushu-u.ac.jp

* Corresponding author

Published: 05 May 2004

World Journal of Surgical Oncology 2004, 2:11

Received: 29 September 2003
Accepted: 05 May 2004

This article is available from: http://www.wjso.com/content/2/1/11

Abstract

Background: Malignant pleural mesothelioma is a rare malignancy. The outcome remains poor despite complete surgical resection.

Patients and methods: Eleven patients with histologicaly proven epithelial type malignant pleural mesothelioma undergoing extrapleural pneumonectomy with systemic chemotherapy and/or radiotherapy before and after surgical resection were retrospectively reviewed.

Results: Ten out of 11 patients underwent complete surgical resection, of these 7 patients had stage I disease. Of these 7 patients, 5 are alive without any recurrence, a 2-year survival rate of 80% was observed in this group. There was no operative mortality or morbidity.

Conclusion: Extrapleural pneumonectomy with perioperative adjuvant treatment is safe and effective procedure for epithelial type malignant pleural mesothelioma.

Introduction

Malignant pleural mesothelioma (MPM) is a relatively rare entity among intrathoracic malignancies, as compared with lung cancer, although its prevalence has shown an increase in recent years [1]. Extrapleural pneumonectomy (EPP) is the surgical treatment of choice for MPM that do not extend in to the mediastinum or on to the chest wall, although its survival benefit is still not clear [2]. In a retrospective study of 189 Japanese cases [3], there were no significant differences in survival at 2-years between palliative surgery, such as decortication, and EPP (26% and 30%, respectively). EPP with adjuvant chemotherapy and/or radiotherapy has been reported to be effective against the MPM in its early stages [4,5]. Jaklitsch *et al.*, [6] advocated that EPP plus postoperative chemotherapy using paclitaxel and carboplatin with radiotherapy is effective for MPM if it's of epithelial histology, negative surgical margin, and if extrapleural lymph nodes are negative for metastasis. This study reports on resectable

Table 1: Clinical summary

Case	IMIG stage	BWH stage	Resection	Adjuvant therapy	Recurrence	Survival status/months
1 49 F	III(T3N2M0)	III	Complete	Pre CDDP/Hemithorax RTx	Pericardium	Died 22
2 63 M	III(T3N2M0)	III	Complete	Pre CDDP/Hemithorax RTx	Ipsilateral thorax	Died 30
3 61 M	III(T3N2M0)	III	Incomplete	Pre CDDP/Hemithorax RTx	Ipsilateral thorax	Died 1
4 59 F	III(T1N2M0)	III	Complete	Post CDDP/GEM/UFT	Lung	Dead 28
5 58 M	II(T2N0M0)	I	Complete	Pre CDDP/Hemithorax RTx	None	Alive 28
6 50 M	II(T2N0M0)	I	Complete	Pre CDDP/GEM/VNR	Ipsilateral thorax	Alive 35
7 55 M	II(T2N0M0)	I	Complete	Pre CDDP/GEM/VNR	Pericardium	Died 6
8 66 M	III(T3N0M0)	I	Complete	Pre CDDP/GEM/VNR	None	Alive 15
9 48 M	III(T3N0M0)	I	Complete	Post CDDP/GEM/UFT	None	Alive 32
10 57 M	I(T1N0M0)	I	Complete	Post CDDP/GEM/UFT	None	Alive 39
12 58 M	I(T1N0M0)	I	Complete	Pre CDDP/GEM/VNR	None	Alive 12

IMIG – International mesothelioma Interest group; BWH – Brigham and Women's Hospital; F – Female; M – male; Pre – Pre Operative; Post – Post operativ; CDDP – Cisplatin; RTx – Radiotherapy; GEM – gemcitabine; VNR – Vinorelbine; UFT – Uracil/tegafur

epithelial type MPM with perioperative treatment consisting of radiation and/or chemotherapy.

Patients and methods

Between 1995 and 2002, 10 patients with epithelial type MPM underwent EPP with postoperative or preoperative chemotherapy and/or radiotherapy. The clinical profiles of these patients are detailed in Table 1. The lesions were staged by computed tomographic (CT) scan using International Mesothelioma Interest Group (IMIG) classification. There were 6 stage III, 3 stage II and 1 stage I patient. A bone scan and Magnetic Resonance Imaging (MRI) of the brain were performed if metastasis was suspected. Using the Brigham and Womens Hospital (BWH) staging system of Sugarbaker *et al.* [4], after the surgical resection 6 patients were stage I, in terms of having completely resected primary tumors including chest wall invasion at the biopsy site.

A standard EPP was performed as described earlier [7]. Following a posterolateral incision, extrapleural space was entered from the 5th or 6th rib bed, and dissection was carried superiorly toward the apex, antero- and postero-laterally, and inferiorly toward the diaphragm. During the dissection, port site disease at the chest wall was resected *en block*. Following an antero-medial pericardiotomy, hilar vessels were resected using a mechanical stapler, followed by resection of the main bronchus. The diaphragm was divided from the peritoneum, and EPP was completed. The defects of pericardium and diaphragm were reconstructed with prosthetic patches. A complete mediastinal lymph node dissection was performed in all cases.

In a preoperative adjuvant setting, one course of concurrent chemoradiotherapy using cisplatin (CDDP) (80 mg/m^2, on days 1 and 29) with 40 Gy external beam radiotherapy to the hemithorax [5], was performed in 4 patients (Case 1, 2, 3 and 5) and 2 or 3 courses of chemotherapy using CDDP (40 mg/m^2 on days 1 and 8), gemcitabine (GEM) (800 mg/m^2, on days 1 and 8), and vinorelbine (VNR) (20 mg/m^2, on days 1 and 8) were given at intervals of 3 to 4 weeks in 4 patients (Case 6, 7, 8 and 11) (Table 1). Three patients received 2 courses of postoperative chemotherapy using CDDP (80 mg/m^2, on day 1 and 8), GEM (800 mg/m^2 on days 8 and 15) and UFT (tegafur/uracil) (400 mg/m^2 postoperative on days 1–15) with 3 to 4 weeks interval (Case 4, 9 and 10) (Table 1). One patient received 50 Gy postoperative radiation to the previous thoracic drainage site (Case 10).

Results

Postoperative course of the patients were uneventful, and no morbidity or mortality was experienced. Six patients experienced a relapse in the thorax. One patient underwent resection of the chest wall for recurrence at 12 months after EPP. Other 5 patients (Case 5, 6, 8, 9 and 11) are surviving without any disease. All the survivors had BWH stage I disease, which showed an 80%, 2-year survival. The survival in 4 patients with BWH stage II-III disease was 37% at 2-year. Postoperative chemotherapy was started 2 to 3 months after surgery, and grade 4 neutropenia was observed in all 3 cases, while grade 3 loss of appetite was observed in one. Of the 3 patients who underwent preoperative chemotherapy, a reduction in size of the tumors by 18 to 74% was seen following chemotherapy (Figure 1). Pathological examination of the resected specimens in all 3 cases showed extensive fibrosis with only a small focus of tumor cells (Figure 2). In Case 10, an exploratory thoracotomy was done for suspected recurrence, however, the intrathoracic lesion was found to be a herniated liver from the defect of the reconstructed diaphragm.

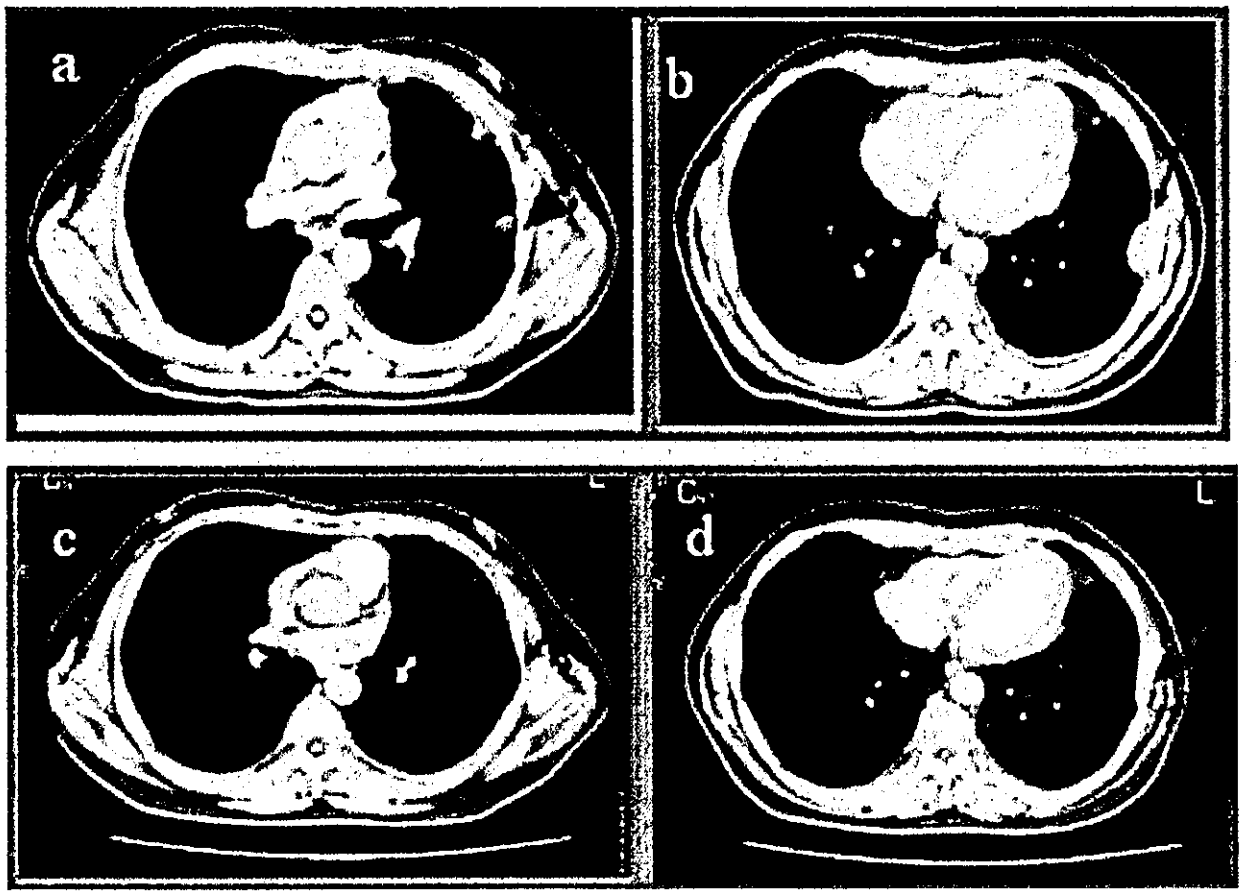

Figure 1
The effect of preoperative chemotherapy using CDDP/GEM/VNR in Case 5: Chest CT before (a, b) and after chemotherapy (c, d). The size of the primary tumors, measured two-dimensionally (arrows) decreased by 74% after chemotherapy.

Discussion

Early stage MPM, especially of the epithelial type, is a disease localized to the hemithorax. Therefore, EPP with or without perioperative adjuvant therapy should be effective, as is shown previously. Sugarbaker *et al.*, [4] reported that the treatment with EPP and adjuvant chemotherapy and hemithorax radiotherapy is effective for select patients with MPM. Nearly 50% of the cases who undergo complete resection of epithelial type MPM survive at 5 years. Rusch *et al.*, [5] showed favorable results with EPP followed by radiation. Survival rate at 5-years for patients with stage I/II IMIG classification was 40% [5].

The aim of the perioperative adjuvant therapy is to control tumor cells located at the front line and the lymphatic system and to sterilize the margin of EPP. However, a therapeutically active modality must be considered from the standpoint of patient benefit and safety. The mortality rates for EPP reported in literature are 3.8% by Sugarbaker *et al.*, [4] and 7.9% by Rusch *et al.*, [5]. In our series, all patients returned to active social life following their treatment, indicating that EPP with perioperative adjuvant therapy is well tolerated. Complete resection of capsulated MPM was achieved in 6 cases that had been designated as BWH stage I. Interestingly, as shown in table 1, BWH stage predicted the prognosis well however IMIG stage failed to do so. This indicated that local therapy for epithelial type MPM might be crucial for staging and prognosis as well.

Sugarbaker *et al.*, [4] started chemotherapy using carboplatin and paclitaxel within 4 weeks after EPP. In our series, chemotherapy was started 2 months after EPP in 4 patients who received CDDP/GEM/UFT. Of the 3 patients

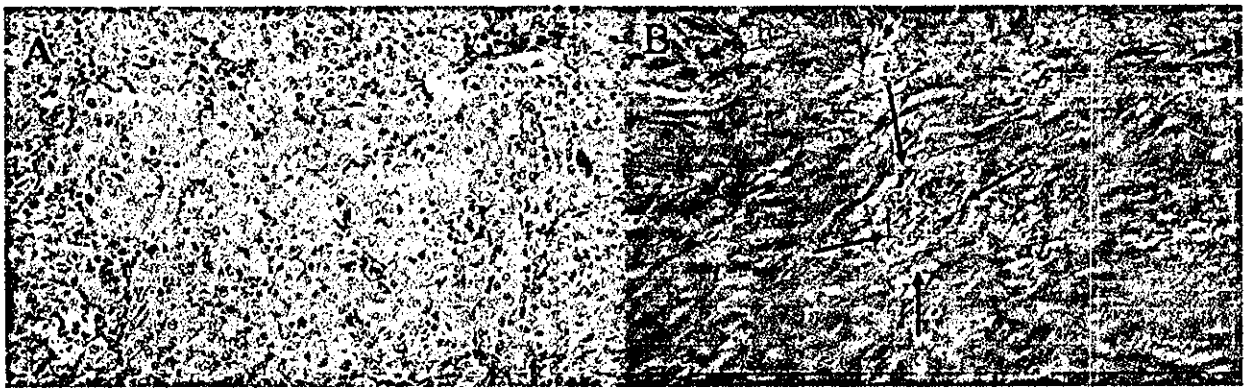

Figure 2
Photomicrograph of case number 5 showing the effect of preoperative chemotherapy. A). Histology of pretreatment biopsy and resected specimen in the above case (× 400, hematoxylin and eosin) B.) Only a small focus of epithelial type mesothelioma cells was found in the resected specimen.

receiving preoperative chemotherapy using CDDP/GEM/VNR, 2 patients received 2 courses and the other received 3 courses. EPP was performed within 5 weeks after cessation of chemotherapy. The clinical and pathological effects were remarkable. Among chemotherapeutic agents, GEM [8] and VNR [9] are reported to be active and the combination of them with CDDP was used in our study. Neutropenia was the main adverse effect of this regimen observed, which reversed with G-CSF. We therefore suggest that preoperative chemotherapy using such active agents followed by EPP is effective and safe procedure. However, this needs to be tested in a randomized controlled trial.

Competing interests
None delcared.

Authors' contributions
IY. Conceived of the study, participated in its design and coordination and drafted the manuscript.

MY. Carried out the literature search and helped in drafting the manuscript.

TO. Participated in the data retrieval and analysis also helped in literature search.

CU. Participated in the design of the study and helped in drafting the manuscript.

YI. Shape the idea for the study, coordinated the study and helped in editing the manuscript.

YM. Helped to shape the idea for the study, coordinated the study and edited the manuscript.

All authors read and approved the final manuscript.

References
1. Connelly RR, Spirtas R, Myers MH, Percy CL, Frameni JF Jr: **Demographic patterns for mesothelioma in the United States.** *J Natl Cancer Inst* 1987, **78**:1053-1060.
2. Harvey JC, Fleischman EH, Kagan AR, Streeter OE: **Malignant pleural mesothelioma: a survival study.** *J Surg Oncol* 1990, **45**:40-42.
3. Takagi K, Tsuchiya R, Watanabe Y: **Surgical approach to pleural diffuse mesothelioma in Japan.** *Lung Cancer* 2001, **31**:57-65.
4. Sugarbaker DJ, Flores R, Jaklitsch MT, Richards WG, Strauss GM, Corson JM, DeCamp MM Jr, Swanson SJ, Bueno R, Lukanich JM, Baldini EH, Mentzer SJ: **Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: Results in 183 patients.** *J Thorac Cardiovasc Surg* 1999, **117**:54-65.
5. Rusch VW, Venkatraman E: **The importance of surgical staging in the treatment of malignant pleural mesothelioma.** *J Thorac Cardiovasc Surg* 1996, **111**:815-826.
6. Jaklitsch MT, Grondin SC, Sugarbaker DJ: **Treatment of malignant mesothelioma.** *World J Surg* 2001, **25**:210-217.
7. Garcia JP, Richards WG, Sugarbaker DJ: **Surgical treatment of malignant mesothelioma.** In *Mastery of cardiothoracic surgery* Edited by: Kaiser LR, Kron IL, Spray TL. Lippincott-Raven, Philadelphia, New York; 1998:230-236.
8. Byrne MJ, Davidson JA, Musk AW, Dewar J, van Hazel G, Buck M, de Klerk NH, Robinson WS: **Cisplatin and gemcitabine treatment for malignant mesothelioma: a phase II study.** *J Clin Oncol* 1999, **17**:25-30.
9. Steele JPC, Shamash J, Evans MT, Gower NH, Tischkowitz MD, Rudd RM: **Phase II study of vinorelbine in patients with malignant pleural mesothelioma.** *J Clin Oncol* 2000, **18**:3912-3917.

Journal of Surgical Oncology 2004;87:134–138

Clinical Patterns and Treatment Outcome of Elderly Patients in Clinical Stage IB/II Non-Small Cell Lung Cancer

TATSURO OKAMOTO, MD, PhD,* RIICHIROH MARUYAMA, MD, FUMIHIRO SHOJI, MD, JIRO IKEDA, MD, TETSUYA MIYAMOTO, MD, TOMOMI NAKAMURA, MD, HIROSHI ASOH, MD, AND YUKITO ICHINOSE, MD
Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan

Background and Objectives: Surgery is a standard treatment in patients with clinical stage IB/II non-small cell lung cancer (NSCLC). We often have difficulty in treating of elderly patients due to their insufficient physiological function. To better manage such elderly patients, the clinical characteristics and prognosis of patients with these stages, who were 75 years of age or older, were reviewed.
Methods: From 1972 to 1999, 112 elderly patients with these stages were treated in our department. These patients comprised 88 men and 24 women. The histological types were 50 adenocarcinomas, 51 squamous cell carcinomas, 8 large cell carcinomas, and 3 adenosquamous carcinomas.
Results: Seventy-four patients (66%) underwent a surgical resection, including 60 surgery alone, 14 combined modality therapy. Radiotherapy, with or without chemotherapy, was given to 30 patients (27%), and chemotherapy alone to 5 (4.5%). In addition, 3 (2.7%) were given no therapy. The survivals of the surgery group at 2 and 5 years are 53% and 21% and those of the radiotherapy group are 35% and 3%, respectively. A multivariate analysis in radiotherapy group shows the predominant prognostic factor to be adenocarcinoma. The 2-year survival of the radiotherapy group in patients with adenocarcinoma is 58%, while that of patients with squamous cell carcinoma is 22%.
Conclusions: These above observations suggest that radiotherapy is an alternative strategy for patients who cannot undergo surgery, especially with adenocarcinoma.
J. Surg. Oncol. 2004;87:134–138. © 2004 Wiley-Liss, Inc.

KEY WORDS: **non-small cell lung cancer; elderly; surgery; radiotherapy**

INTRODUCTION

Lung cancer is the leading cause of cancer deaths in Japan. The elderly population is growing rapidly, and thoracic surgeons and medical oncologists have an increasing chance to treat elderly patients with lung cancer. Surgical resection remains the primary modality for treatment of lung cancer [1], and recent studies have demonstrated that surgery for the elderly patients is still the most effective therapy for stage I/II non-small cell lung cancer (NSCLC) [2,3]. However, elderly patients tend to have lower cardiopulmonary functions and more co-morbidities, and therefore have a higher risk of surgery [4,5]. The careful selection of the candidates for operation is thus necessary for this group of patients. Recently, video-assisted thoracic surgery and limited resection is getting more popular and known as a useful technique for those patients of high risk in early stage NSCLC [6]. However, in clinical stage IB or II, a surgical resection tends to require more extended methods.

The 5-year survival of resected patients in clinical stage IA reaches 70%, however, that in stage IB/II is approximately 35–45% [1]. Although the long-term survival of the patients treated with surgical procedures

*Correspondence to: Tatsuro Okamoto, MD, PhD, Department of Thoracic Oncology, National Kyushu Cancer Center, 3-1-1, Notame, Minami-ku, Fukuoka 811-1395, Japan. Fax: +81-92-551-4585.
E-mail: tokamoto@nk-cc.go.jp
Accepted 17 June 2004
DOI 10.1002/jso.20095
Published online in Wiley InterScience (www.interscience.wiley.com).

has been reported to possibly not be influenced by the patients' age [2], it is often difficult for thoracic surgeons and medical oncologists in practice to determine which treatment modality should be performed for elderly patients with stage IB/II cancer, especially in patients 75 years of age or older. In the present study, we review the initial treatment patterns and outcomes of all the patients who are 75 years of age and older in clinical stage IB, IIA, IIB who were admitted to our department, in order to better manage such patients.

PATIENTS AND METHODS

Between January 1972 and December 1999, 2799 non-small lung cancer patients were admitted to the Department of Thoracic Oncology, National Kyushu Cancer Center. Among them, 390 patients (13.9%) were of 75 years of age or older, and about one-fourth of these patients had clinical stage IB and II disease (112 patients). These patients comprised of 88 men and 24 women. The histological types were 50 adenocarcinomas, 51 squamous cell carcinomas, 8 large cell carcinomas, and 3 adenosquamous carcinomas. The histological analysis of the tumor was based on the WHO classification for cell types [7]. The clinical stage of these patients was determined based on the TNM classification of the Union Internationale Contre Cancer (UICC) [8]. For TNM staging, almost all patients after 1980 underwent a computed tomography (CT) scan of the thorax and upper part of abdomen, and a bone scintigram. A brain CT or MRI was not mandatory unless neurologic symptoms were present. Before 1980, the majority of patients underwent chest roentgenography and conventional tomography and radionuclide scanning of the bone, brain, and liver. Statistical significance was evaluated using the χ^2 test, Fisher's extract test, or the Mann–Whitney test for various clinicopathologic factors. A survival analysis for each categorical variable on overall survival was estimated according to the Kaplan–Meier method. The terminal event was death due to any cause. The statistical significance of the differences between survival curves was evaluated by the log-rank test. The Cox proportional hazards model was applied to the univariate survival analysis. In the multivariate survival analysis, any variables with a *P*-value of less than 0.2 were further analyzed in a stepwise manner. Statistical difference was considered to be significant if the *P*-value was below 0.05.

RESULTS

Treatments

The details of the treatment of the elderly 112 patients are shown in Table I. A surgical resection is the first choice, and if it seems hard to undergo surgery because of low cardiopulmonary functions or poor performance status, we next choose radiotherapy either with or without chemotherapy. Seventy-four patients underwent surgery; 60 patients underwent surgery alone, 14 patients had combined modality therapy. Sixty-eight patients (91.9%) underwent standard lobectomy or more extended treatment, including three sleeve resection of main bronchus. Six patients (8.1%) had a limited resection. A complete resection was done for 72 patients (97.3%); 2 patients did not undergo mediastinal lymph nodes dissection. One patient underwent preoperative chemotherapy, and 6 were given postoperative chemotherapy. One patient had pre- and postoperative radiotherapy, 1 had postoperative radiotherapy alone, 4 had postoperative radiotherapy and chemotherapy, and 1 had preoperative radiotherapy and postoperative chemotherapy. Thirty-eight patients did not undergo surgery. Radiotherapy, with or without chemotherapy, was given for 30 patients, and chemotherapy alone for 5. Three were given no therapy. The reason why patients did not receive a surgical resection was as follows; a poor pulmonary function in 16 patients, a poor performance status in 5, heart disease in 3, avoidance of a pneumonectomy in 2, extended disease at exploratory surgery in 2, chronic renal failure in 1, and double lung cancer in 1. Eight patients refused undergoing surgery on their own volition. In radical radiotherapy, one patient received a total dose of 40 gray, 11 did 50 gray, 17 did 60 gray, and 1 did 80 Gy. In chemotherapy alone, 2 patients received the doublet combination of cisplatin and etoposide, 1 received the triplet regimen of cyclophosphamide, adriamycin, cisplatin (CAP), 1 received CAP plus mitomycin, 1 received adriamycin alone.

We divided these patients into two categories consisting of a surgery group who underwent surgical resection and radiotherapy group who received radiotherapy with or without chemotherapy. The patient characteristics of the two groups were summarized in Table II. There were

TABLE I. Details of the Treatment

	No.	Percent (%)
Surgery		
Total	74	66
Surgery alone	60	53.6
With chemotherapy	7	6.3
With radiotherapy	2	1.8
With chemotherapy and radiotherapy	5	4.5
Radiotherapy		
Total	30	26.8
Radiotherapy alone	20	17.9
With chemotherapy	10	8.9
Chemotherapy alone	5	4.5
No treatment	3	2.7

TABLE II. Comparison of Clinicopathological Characteristics Between the Surgery and Radiotherapy Groups

Category	S (n = 74) N	RT (n = 30) N	P
Age (75 ~ 79, 80 ~ 84, 85~)	58, 13, 3	18, 10, 2	0.147
Gender (Male, female)	55, 19	26, 4	0.169
Histologic type (Ad, Sq, La, Ad-sq)	36, 30, 6, 2	12, 18, 0, 0	0.863
Clinical stage (IB, IIA, IIB)	48, 2, 24	10, 1, 19	0.01
PS (0, 1, 2, 3)	35, 38, 1, 0	1, 23, 5, 1	<0.0001
FEV1/BSA (ml/m^2)	1291 ± 331	989 ± 339	<0.0001

PS, performance status; FEV1, forced expiratory volume in 1 sec; BSA, body surface area; Ad, adenocarcinoma; Sq, squamous cell carcinoma; La, large cell carcinoma; Ad-sq, adenosquamous carcinoma; S, surgery group; RT, radiotherapy group; N, number; *P*, *P*-value.

TABLE III. Comparison of Clinicopathological Characteristics Between the Adenocarcinoma and Squamous Cell Carcinoma Patients in the Radiotherapy Groups

Category	Ad (n = 12) N	Sq (n = 18) N	P
Age (75 ~ 79, 80 ~ 84, 85~)	6, 4, 2	12, 6, 0	0.310
Gender (Male, female)	8, 4	18, 0	0.0085
Clinical stage (IB, IIA, IIB)	4, 1, 7	6, 0, 12	0.800
PS (0, 1, 2, 3)	0, 9, 3, 0	1, 14, 2, 1	0.612
Chemotherapy (+, −)	7, 5	3, 15	0.017
FEV1/BSA (ml/m^2)	1011 ± 355	975 ± 338	0.787

PS, performance status; FEV1, forced expiratory volume in 1 sec; BSA, body surface area; Ad, adenocarcinoma; Sq, squamous cell carcinoma; N, number; *P*, *P*-value.

no significant differences in the gender and histological type. In contrast, there were significant differences in the clinical stage, performance status, and pretreatment forced expiratory volume in 1 sec (FEV 1.0) per body surface area. Radiotherapy tended to be chosen more frequently in the patients with a poor risk, and with advanced disease. Surgery related deaths (death within 30 days after surgery) were found in 2 patients and the mortality rate was 2.7%. Major complications, which required artificial ventilation and the intensive care, were seen in 4 patients (5.4%) and minor complications were seen in 26 patients (35.1%).

Survival

The overall survivals of the two treatment groups are shown in Figure 1. The survivals of the surgery group at 2 and 5 years are 53% and 21% and those of the radiotherapy group are 35% and 3%, respectively. The median survivals times (MST) of both groups were 25 and 15 months. Table III shows a comparison of clinicopathological characteristics between the adenocarcinoma patients and the squamous cell carcinoma patients in the radiotherapy group. There was a significant difference in gender and the use of chemotherapy between the two categories. A univariate survival analysis indicated that adenocarcinoma was a prognostic factor in the radiotherapy group (Table IV); a multivariate analysis using a stepwise method also confirmed that adenocarcinoma was an independent prognostic factor among them Table V.

The survival curve of the radiation group is similar to that of the surgery group until 25 months in adenocarcinoma cases, but it began to decrease after that (Fig. 2A). In contrast, the same tendency was not seen in the squamous cell carcinoma cases (Fig. 2B).

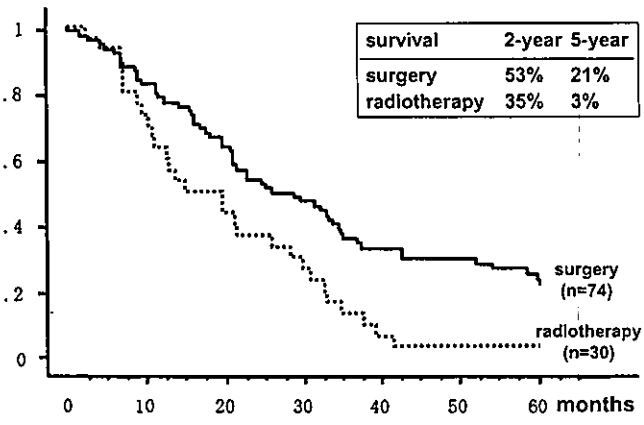

Fig. 1. The overall survival curves of surgery and radiotherapy groups.

DISCUSSION

The proportion of elderly individuals among lung cancer patients is increasing as a consequence of the aging population and the increased life expectancy in Japan. Recent studies demonstrated that surgery is the most effective therapy for early stage NSCLC for the elderly patients [2,9,10]. However, they have a tendency to have more underlying co-morbidities, compared with younger patients. We focused on the elderly population of clinical stage IB and II, and investigated the clinical patterns and treatment outcome, because more extended resection is sometimes required for these cases than those in clinical stage IA, and the treatment choice is often an extremely difficult choice for thoracic surgeons or oncologists.

TABLE IV. Univariate Analysis of Various Prognostic Factors Influencing Survival of Patients Treated With Radiotherapy

		Radiotherapy group			
Variable	Category	N	RR	95% CI	*P*
Age	75～79	18	1		
	80～84	10	0.79	0.36–1.74	0.559
	85～	2	0.71	0.16–3.10	0.645
Gender	Male	26	1		
	Female	4	0.36	0.12–1.12	0.078
Histologic type	Ad	12	1		
	Sq	18	3.1	1.32–7.29	0.010
Clinical stage	IB	10	1		
	II	20	1.21	0.55–2.64	0.634
PS	0/1	24	1		
	2/3	6	0.79	0.32–1.97	0.612
Chemotherapy	No	20	1		
	Yes	10	0.63	0.29–1.32	0.254

PS, performance status; Ad, adenocarcinoma; Sq, squamous cell carcinoma; La, large cell carcinoma; Ad-sq, adenosquamous carcinoma; N, number; RR, relative risk; CI, confidence interval; *P*, *P*-value.

In our department, almost all patients undergo a stress electrocardiogram and respiratory function test, and the patients with heart disease or lower pulmonary function are checked. Patients who are predicted to have a FEV 1.0 per body surface which is less 600 ml/m^2 after surgery, are not indicated to undergo surgical treatment. Since the most frequent reason for no-surgery therapy was low pulmonary function, a significant difference was seen in the pulmonary functions and performance status between the surgery group and radiotherapy group (Table II). From the surgical point of view, more advanced disease is more likely to be treated without operation. In current studies, a pneumonectomy carries a higher mortality rate, especially on the right side. In our series, a pneumonectmy was done for only 1 elderly patient, and a standard lobectomy or bilobectomy were chosen for more than 90% of all patients in the surgery group. In these surgery patients, the co-morbidities were slight higher than in the younger patients, however, the mortality rate 2.7% was similar to that of other reported statistics [2]. These data demonstrate that standard

TABLE V. Multivariate Analysis of Various Prognostic Factors Influencing Survival of Patients Treated With Radiotherapy

		Radiotherapy group	
Variable	Category	RR (95% CI)	*P*
Histologic type	Ad	1	
	Sq	3.10 (1.32–7.29)	0.0096

Ad, adenocarcinoma; Sq, squamous cell carcinoma; RR, relative risk; CI, confidence interval; *P*, *P*-value.

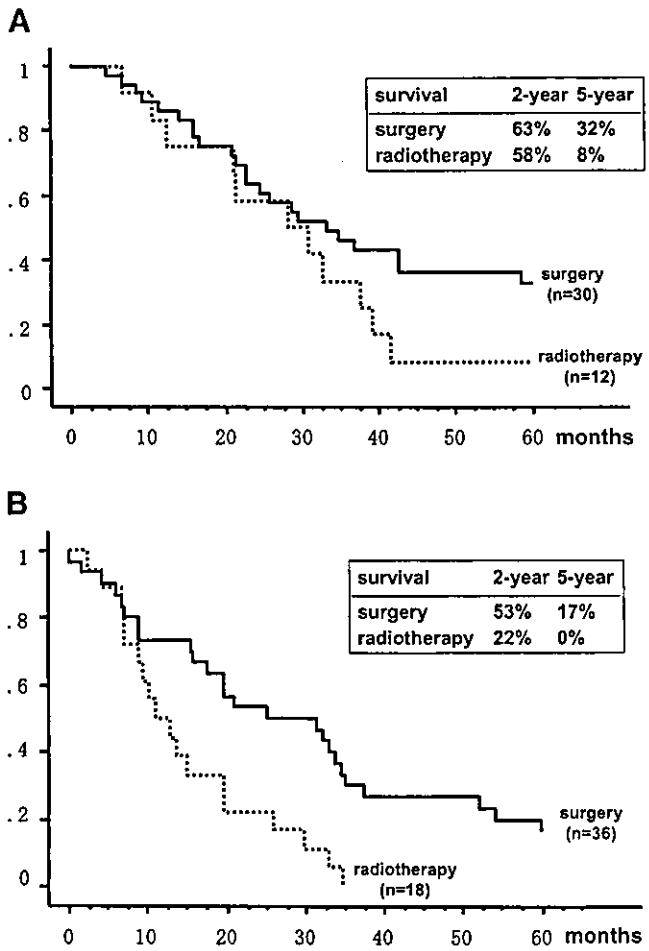

Fig. 2. A: Survival curves of the surgery and radiotherapy groups in the adenocarcinoma. B: Survival curves of the surgery and radiotherapy groups in the squamous cell carcinoma.

surgery, except for a pneumonectomy, is a safe treatment for elderly patients who are carefully selected.

Although there is no evidence from randomized trials to support the use of radical radiotherapy for stage I/II NSCLC, Many non-randomized trials and retrospective studies demonstrated that radiation treatment in stage I/II has a potential for curative treatment, and it is the common concept for most medical oncologists that patients who do not undergo surgical resection in this clinical stage should receive some type of radical treatment [2,11,12]. Radiation is capable of producing MST of 15–33 months and 5-year survivals of 0–42% for patients in stage I/II. Elderly patients can receive radical radiation treatment as safely as younger persons, and the survival results are the same [2,13]. We also use the radical radiotherapy for those who are considered to be inoperable because of insufficient physical function, or those who refuse surgical therapy. The survival of the patients who received radiotherapy in our department was not so good as those of published data. Regarding the causes, patients with stage IIB (63%) and those with low physical functions were the major population.

Many studies have demonstrated the prognostic factors of radiotherapy for early stages, including radiation dose [14], tumor size [15], nodal status [16]. There is only one study that shows the differences in survival based on the histological subtype, however, squamous cell carcinomas are known to have better results [17]. In our present study, patients with adenocarcinoma had a relatively better survival within 2 years of treatment; on the other hand, patients with squamous cell carcinoma had a worse survival. A multvariate survival analysis indicated that adenocarcinoma was the only prognostic factor in the radiotherapy group. The reason for this is unclear, however, one reason for it might be the difference of the biological future between the two histological types; for example, local proliferation of the squamous cell carcinoma is faster than adenocarcinoma. A report of the long-term survivors of NSCLC after radiotherapy shows that among progression free patients at the end of 2 years, 97% of all patients with squamous cell carcinoma survived without any evidence of disease for more than 5 years [18]. This phenomenon might possibly mean that a failure of sufficient disease control in squamous cell carcinoma results in a poor outcome.

CONCLUSIONS

Based on these data, the following conclusion was suggested. Surgery is still the predominant treatment for elderly patients with early stage lung cancer; however, radiotherapy is another preferable strategy for the patients who are unable to undergo surgery because of either a poor physical function or other reason, especially regarding adenocarcinoma patients.

ACKNOWLEDGMENTS

We thank Dr. Brian T. Quinn for critical comments on the manuscript.

REFERENCES

1. Naruke T, Tsuchiya R, Kondo H, et al.: Prognosis and survival after resection for bronchogenic carcinoma based on the 1997 TNM-staging classification: The Japanese experience. Ann Thorac Surg 2001;71:1759–1764.
2. Weinmann M, Jeremic B, Toomes H, et al.: Treatment of lung cancer in the elderly. Part I: Non-small cell lung cancer. Lung Cancer 2003;39:233–253.
3. Smith TJ, Penberthy L, Desch CE, et al.: Differences in initial treatment patterns and outcomes of lung cancer in the elderly. Lung Cancer 1995;13:235–252.
4. Pagni S, McKelvey A, Riordan C, et al.: Pulmonary resection for malignancy in the elderly: Is age still a risk factor? Eur J Cardiothorac Surg 1998;14:40–44.
5. Aoki T, Yamato Y, Tsuchida M, et al.: Pulmonary complications after surgical treatment of lung cancer in octogenarians. Eur J Cardiothorac Surg 2000;18:662–665.
6. Jaklitsch MT, Bueno R, Swanson SJ, et al.: New surgical options for elderly lung cancer patients. Chest 1999;116:480S–485S.
7. Travis WD, Colby TV, Corrin B, et al.: Histological typing of lung and pleural tumors, 3rd edn. World health organization international histological classification of tumors. Berlin: Springer Verlag; 1999.
8. Sobin LH, Wittekind C: International Union Against Cancer, 5th edn. TNM classification of malignant tumors. New York: Wiley-Liss; 1997.
9. Thomas P, Piraux M, Jacques LF, et al.: Clinical patterns and trends of outcome of elderly patients with bronchogenic carcinoma. Eur J Cardiothorac Surg 1998;13:266–274.
10. Pagni S, Federico JA, Ponn RB, et al.: Pulmonary resection for lung cancer in octogenarians. Ann Thorac Surg 1997;63:785–789.
11. Gauden SJ, Tripcony L: The curative treatment by radiation therapy alone of Stage I non-small cell lung cancer in a geriatric population. Lung Cancer 2001;32:71–79.
12. Rowell NP, Williams CJ: Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable): A systematic review. Thorax 2001;56:628–638.
13. Hayakawa K, Mitsuhashi N, Katano S, et al.: High-dose radiation therapy for elderly patients with inoperable or unresectable non-small cell lung cancer. Lung Cancer 2001;32:81–88.
14. Dosoretz DE, Katin MJ, Blitzer PH, et al.: Radiation therapy in the management of medically inoperable carcinoma of the lung: Results and implications for future treatment strategies. Int J Radiat Oncol Biol Phys 1992;24:3–9.
15. Gauden S, Ramsay J, Tripcony L: The curative treatment by radiotherapy alone of stage I non-small cell carcinoma of the lung. Chest 1995;108:1278–1282.
16. Rosenthal SA, Curran WJ, Jr., Herbert SH, et al.: Clinical stage II non-small cell lung cancer treated with radiation therapy alone. The significance of clinically staged ipsilateral hilar adenopathy (N1 disease). Cancer 1992;70:2410–2417.
17. Sibley GS, Jamieson TA, Marks LB, et al.: Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: The Duke experience. Int J Radiat Oncol Biol Phys 1998;40:149–154.
18. Nakayama Y, Hayakawa K, Mitsuhashi N, et al.: Long-term survivors of non-small cell lung cancer after radiation therapy: The significance of histological type. Anticancer Res 1997;17:2769–2773.

Original Article

Necessity of Preoperative Screening for Brain Metastasis in Non-small Cell Lung Cancer Patients without Lymph Node Metastasis

Tomofumi Yohena, MD, Ichiro Yoshino, MD, Masachika Kitajima, MD, Tadashi Uehara, MD, Takanori Kanematsu, MD, Takao Teruya, MD, Jiro Ikeda, MD, and Yukito Ichinose, MD

Background: The exclusion of brain metastasis is important to determine the optimal treatment plan in patients with non-small cell lung cancer (NSCLC). However, a routine examination using magnetic resonance imaging (MRI) for the brain remains controversial in preoperative patients with resectable disease.

Methods: To assess the necessity of routine brain MRI for preoperative patients, a retrospective analysis for a consecutive series of 338 patients with NSCLC was performed. Among the 338 patients, 141 patients who were considered to have potentially resectable diseases through an examination of the chest plus an upper abdominal computed tomography scan and bone radioisotope scan with no neurological symptoms received MRI for examination of brain metastasis.

Results: The incidence of brain metastasis detected by MRI was 2.1% (three of 141) in all patients, 0% (zero of 80) in patients with N0 disease, 5.2% (one of 19) in N1, and 4.7% (two of 42) in N2 cases.

Conclusion: In patients with resectable NSCLC, a brain MRI is not considered to be useful due to the low incidence of asymptomatic brain metastasis. (Ann Thorac Cardiovasc Surg 2004; 10: 347–9)

Key words: non-small cell lung cancer, nodal metastasis, brain metastasis, magnetic resonance imaging

Introduction

The initial staging of non-small cell lung cancer (NSCLC) is essential for determining the appropriate treatment for patients.[1] However, in such patients without any manifestation of distant metastases in a physical examination including a detailed neurologic evaluation and complete blood chemistry study, it remains controversial as to whether or not a full examination should be routinely done. A number of authorities have recommended that an investigation of the most likely sites of metastatic disease such as the bone, brain, liver, and adrenal glands should be restricted to patients with symptoms or signs which suggest metastases.[2-5] Others have, however, suggested that imaging of the adrenal glands, head, bones, and liver, or several combinations thereof should be included in a routine investigation of all patients with lung cancer before a thoracotomy because of the possible existence of silent metastases.[6-12]

Regarding examinations for brain metastases, magnetic resonance imaging (MRI) is reported to have a greater sensitivity and specificity than computed tomography (CT) scans.[13,14] However, we hypothesize that the occurrence of brain metastasis is rare in patients who are considered to have resectable disease. In this retrospective study, we investigated the necessity of performing brain MRI for patients who are considered to have resectable disease based on chest CT, abdominal CT and bone scans as well as a physical examination.

From Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan

Received February 4, 2004; accepted for publication July 30, 2004.
Address reprint requests to Yukito Ichinose, MD: Department of Thoracic Oncology, National Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka 811-1395, Japan.

Patients and Methods

The medical records of all patients who underwent a clinical examination for the staging of NSCLC between April 1996 and December 1998 at National Kyushu Cancer Center, Fukuoka, Japan, were reviewed. The staging protocol during this period consisted of chest CT, radioisotope bone scanning, MRI or CT of the brain, and upper abdominal CT. Among a consecutive series of 338 patients with lung cancer, a total of 280 received brain MRI to evaluate their brain metastases, and the other 58 patients were evaluated by CT. Among the 280 patients, 139 patients were excluded from this study as unresectable cases because of an advanced intrathoracic stage such as T4 (a tumor with either malignant pleural effusion or malignant pericardial effusion, or one that invades either large vessels, the esophagus or vertebral body), cN3 disease, cM1 disease except for brain metastasis, and those considered to have some neurologic symptoms with brain metastasis.

The remaining 141 patients were all considered to have potentially resectable lung cancer, and were subjected to this analysis. The incidence of brain metastasis on MRI was reviewed. They consisted of 98 males and 43 females and their mean age was 63 years (range, 36 to 90 years). Seventy-six patients had T1-2N0, 2 had T3N0, 2 had T4N0, 16 had T1-2N1, 2 had T3N1, 1 had T4N1, 28 had T1-2N2, 12 had T3N2, 2 had T4N2, while 81 were adenocarcinomas (57.4%), 42 were squamous cell carcinomas (29.8%), 9 were small cell carcinomas (6.4%), and 4 were large cell carcinomas (2.8%). All patients had an ECOG performance status ranging from 0 to 2.

Results

The proportion of each TN subset of this cohort is summarized in Table 1. Regarding T3 diseases, seven patients had mediastinal pleural invasion, three chest wall invasion, one pericardium invasion, one direct invasion of another lobe and four invasion of the main bronchus measuring less than 2 cm distal to the carina. All T4 cases had separate nodule (s) in the same lobe of the primary tumor. As for N factor, N0 cases comprised the most common subset (56.7%), followed by N2 (31.0%) and N1 (13.3%).

Three (2.1%) of 141 patients had asymptomatic brain metastasis, one patient in each of the T2N1, T2N2 and T3N2 subsets had asymptomatic brain metastasis and the respective rates were 6.7% (1/15), 5.6% (1/18) and 8.3% (1/12). All three patients had adenocarcinomas. There was no patient whose asymptomatic brain metastasis was detected by MRI among the 76 patients with T1-2N0, four with T3N0-1 and five with T4N0-2.

Table 1. The proportion of evaluated patients and patients with silent brain metastasis as classified according to the presence of T and N factor

	T1	T2	T3	T4
N0	0/37 (0%)	0/39 (0%)	0/2 (0%)	0/2 (0%)
N1	0/1 (0%)	1/15 (6.7%)	0/2 (0%)	0/1 (0%)
N2	0/10 (0%)	1/18 (5.6%)	1/12 (8.3%)	0/2 (0%)

Discussion

The purpose of this study was to determine the value of routine screening for brain metastasis in patients with potentially resectable primary lung cancer. Asymptomatic brain metastasis detected by MRI was observed in three adenocarcinoma patients who had either T2N1, T2N2 or T3N2 disease. There were no patients with brain metastasis who had either a T1 or T4 status while all three patients with the brain metastasis had clinical nodal metastasis. These observations suggested that brain metastasis appeared to be more strongly associated with nodal metastasis than T factor, and with adenocarcinoma.

The present results showed that unless swollen lymph nodes were detected on chest CT, no brain metastasis was detected by MRI. In light of diagnosis for cerebral metastasis, Grant et al.[15] and Bilgin et al.[16] concluded that routine preoperative brain CT can eliminate unnecessary thoracotomies, and The Canadian Lung Oncology Group reported that full investigation including brain CT for all patients including asymptomatic cases may reduce the number of unnecessary thoracotomies.[17] The MRI screening of brain metastasis is more effective for distinguishing asymptomatic brain metastasis than CT.[18] Therefore MRI would eliminate unnecessary thoracotomies.

However, Tanaka et al. reported that routine brain MRI was not recommended due to its cost and its role in increasing the mental duress of the patients, since the examination period is the most stressful time for cancer patients.[19] Concerning the incidence of asymptomatic brain metastasis, Cole et al.[20] advocated that neither MRI nor an enhanced CT scan is indicated for preoperative staging unless some clinical findings are observed. Hochstenbag et al.[21] also reported that the incidence of

brain metastasis was only 3% in NSCLC patients with clinical stage I and II disease before brain MRI screening. In a consensus report of International Association for the Study of Lung Cancer[22] and American Thoracic Society and European Respiratory Society,[23] brain MRI is therefore not considered to be essential for the initial staging of NSCLC.

In conclusion, routine brain MRI is therefore considered to be unnecessary in patients who are considered to have potentially resectable diseases, no distant lesions, and no neurological symptoms.

References

1. Ginsberg RJ, Kris MG, Armstrong JG. Non-small cell lung cancer. In: De Vita VT, Hellman S, Rosenberg SA eds.; Cancer principles and practice of oncology. 5th ed. Philadelphia: Lippincott-Raven, 1997; pp 868–76.
2. Ramsdell JW, Peters RM, Taylor AT, et al. Multiorgan scans for staging lung cancer: correlation with clinical evaluation. *J Thorac Cardiovasc Surg* 1977; **73**: 653–9.
3. Quinn DL, Ostrow LB, Porter DK, et al. Staging of non-small cell bronchogenic carcinoma: relationship of the clinical evaluation to organ scans. *Chest* 1986; **89**: 270–5.
4. Klein JS, Webb WR. The radiologic staging of lung cancer. *J Thorac Imaging* 1991; **7**: 29–47.
5. Kormas P, Bradshaw JR, Jeyasingham K. Preoperative computed tomography of the brain in non-small cell bronchogenic carcinoma. *Thorax* 1992; **47**: 106–8.
6. Chapman GS, Kumar D, Redmond J, et al. Upper abdominal computerized tomography scanning in staging non-small cell lung carcinoma. *Cancer* 1984; **54**: 1541–3.
7. Mintz BJ, Tuhrim S, Alexander S, et al. Intracranial metastases in the initial staging of bronchogenic carcinoma. *Chest* 1984; **86**: 850–3.
8. Heitzman ER. The role of computed tomography in the diagnosis and management of lung cancer: an overview. *Chest* 1986; **89**: 237S–41S.
9. Osada H, Nakajima Y, Taira Y, et al. The role of mediastinal and multi-organ CT scans in staging presumable surgical candidates with non-small cell lung cancer. *Jpn J Surg* 1987; **17**: 362–8.
10. Salvatierra A, Baamonde C, Llamas JM, et al. Extrathoracic staging of bronchogenic carcinoma. *Chest* 1990; **97**: 1052–8.
11. Tornyos K, Garcia O, Karr B, et al. A correlation study of bone scanning with clinical and laboratory findings in the staging of non small-cell lung cancer. *Clin Nucl Med* 1991; **16**: 107–9.
12. Ferrigno D, Buccheri G. Cranial computed tomography as a part of the initial staging procedures for patients with non-small-cell lung cancer. *Chest* 1994; **106**: 1025–9.
13. Sze G, Shin J, Krol G, et al. Intraparenchymal brain metastases: MR imaging versus contrast-enhanced CT. *Radiology* 1988; **168**: 187–94.
14. Yokoi K, Kamiya N, Matsuguma H, et al. Detection of brain metastasis in potentially operable non-small cell lung cancer: a comparison of CT and MRI. *Chest* 1999; **115**: 714–9.
15. Grant D, Edwards D, Goldstraw P. Computed tomography of the brain, chest, and abdomen in the preoperative assessment of non-small cell lung cancer. *Thorax* 1998; **43**: 883–6.
16. Bilgin S, Yilmaz A, Ozdemir F, et al. Extrathoracic staging of non-small cell bronchogenic carcinoma: relationship of the clinical evaluation to organ scans. *Respirology* 2002; **7**: 57–61.
17. The Canadian Lung Oncology Group. Investigating extrathoracic metastatic disease in patients with apparently operable lung cancer. *Ann Thorac Surg* 2001; **71**: 425–33.
18. Hochstenbag MM, Twijnstra A, Wilmink JT, et al. Asymptomatic brain metastases (BM) in small cell lung cancer (SCLC): MR-imaging is useful at initial diagnosis. *J Neurooncol* 2000; **48**: 243–8.
19. Tanaka K, Kubota K, Kodama T, et al. Extrathoracic staging is not necessary for non-small-cell lung cancer with clinical stage T1-2N0. *Ann Thorac Surg* 1999; **68**: 1039–42.
20. Cole FH Jr, Thomas JE, Wilcox AB, et al. Cerebral imaging in the asymptomatic preoperative bronchogenic carcinoma patients: is it worthwhile? *Ann Thorac Surg* 1994; **57**: 838–40.
21. Hochstenbag MM, Twijnstra A, Hofman P, et al. MR-imaging of the brain of neurologic asymptomatic patients with large cell or adenocarcinoma of the lung: does it influence prognosis and treatment? *Lung Cancer* 2003; **42**: 189–93.
22. Feld R, Abratt R, Graziano S, et al. Consensus report pretreatment minimal staging and prognostic factors for non-small cell lung cancer. *Lung Cancer* 1997; **17**(Suppl 1): s3–10.
23. Pretreatment evaluation of non-small-cell lung cancer. *Am J Respir Crit Care Med* 1997; **156**: 320–32.

Original Article

Effects of a Left Ventricular Assist Device on the Myocardium in Ischemia-reperfusion Injury

Satoshi Unosawa, MD

Objective: It is suggested that apoptosis plays a role in heart diseases. The effect of left ventricular assist device (LVAD) on apoptosis at ischemia-reperfusion myocardial injury is unclear. We investigated the effect by assisting the ischemia-reperfusion myocardial injury models with LVAD.
Methods: Twelve swines were divided into two groups: the control group and LVAD group. The diagonal branch of the left coronary artery was occluded and released after 35 min. Reperfusion was performed, and observed for 3 hrs. The LVAD group was assisted by LVAD from 5 min before reperfusion to 3 hrs after it. Cardiac function, coronary flow, and cardiac tissue blood flow were measured. Pathologic assay was performed with terminal deoxynucleotidyl transferase-mediated dUTP in situ nick end labeling (TUNEL) and hematoxylin and eosin (HE) staining. mRNA of Bcl-xL and Bak were measured.
Results: Ejection fraction, cardiac output, and Emax in the LVAD group were improved ($p<0.05$ vs. the control group). There were less necrotic cells in the LVAD group than in the control group. There were more TUNEL positive cells in the LVAD group than in the control group. mRNA of Bcl-xL and Bak in LVAD group were high.
Conclusion: The aggravation of cardiac dysfunction was limited to a minimum in the LVAD group. (Ann Thorac Cardiovasc Surg 2004; 10: 350–6)

Key words: cardiomyocyte apoptosis, left ventricular assist device, ischemia-reperfusion injury, Bcl-2 family

Introduction

Apoptosis is the mechanism of cell death that Kerr et al.[1] researched and advocated by investigating the morphological changes occurring in ischemic hepatic cells. It was thought that there are few apoptotic cell deaths in the myocardial cells, which are the terminally differentiating cells considered to not proliferate generally. As regards apoptosis of myocardial cells in heart diseases, ever since Gottlieb et al.[2] reported the fragmentation of the DNA in the infarcted myocardium of rabbits that had 30 min ischemia and 4 hrs reperfusion, several studies have been described on animal models of myocardial infarction and human autopsies.[3,4] Furthermore, the reports, which suggest that apoptosis plays a role in the causes or the progress of heart diseases such as ischemic cardiac muscle injury and heart failures, have been published consistently.[5,6]

In the field of cardiac surgery, Bartling et al. have reported that apoptosis was decreased by long-period assistance with a left ventricular assist device (LVAD) in end-stage heart failures such as dilated cardiomyopathies etc.[7] Moreover, it has also been reported that apoptosis is caused by cardioplegic arrest.[8] LVAD is the most effective method of assisted circulation, and its clinical effectiveness has been recognized. The effect of LVAD on ischemia-reperfusion myocardial injury has already been demonstrated;[9] however, the details are still unclear. In addition, no study investigating the effect of LVAD on apoptosis in acute ischemia-reperfusion myocardial injury has been conducted.

In this study, we investigated the effect on apoptosis in

From Department of Cardiovascular Surgery, Nihon University School of Medicine, Tokyo, Japan

Received May 19, 2004; accepted for publication September 2, 2004.
Address reprint requests to Satoshi Unosawa, MD: Department of Cardiovascular Surgery, Nihon University School of Medicine, 30-1 Oyaguchi, Kami-machi, Itabashi-ku, Tokyo 173-8610, Japan.

Correlation between computed tomographic findings, bronchioloalveolar carcinoma component, and biologic behavior of small-sized lung adenocarcinomas

Morihito Okada, MD, PhD[a]
Wataru Nishio, MD, PhD[a]
Toshihiko Sakamoto, MD, PhD[a]
Kazuya Uchino, MD[a]
Keisuke Hanioka, MD, PhD[b]
Chiho Ohbayashi, MD, PhD[c]
Noriaki Tsubota, MD, PhD[a]

Objective: Differentiation of bronchioloalveolar carcinoma from other subtypes of lung adenocarcinomas is important in the preoperative assessment of patients. We examined the biologic aggressiveness of small-sized adenocarcinomas according to the pathologically defined bronchioloalveolar carcinoma degree and its correlation with computed tomography findings. In addition, we attempted to predict which patients were suitable for a lesser resection.

Methods: Of 424 consecutive patients who underwent operation for primary lung cancer in the last 3 years, 114 with a histopathologically proven adenocarcinoma 3 cm or less in diameter underwent complete removal of the primary tumor. We examined the characteristics of patients classified into 3 groups based on the proportion of the bronchioloalveolar carcinoma component: 0% to 20% (n = 40), 21% to 50% (n = 38), and 51% to 100% (n = 36). We also investigated the correlation of the bronchioloalveolar carcinoma component with computed tomography findings such as ground-glass opacity (defined as a hazy increase on the lung window) and tumor shadow disappearance rate (defined as the ratio of the tumor area of the mediastinal window to that of the lung window).

Results: Male gender ($P = .0001$), advanced pathologic stage ($P = .001$), larger size of the tumor ($P = .004$), nodal involvement ($P = .04$), pleural invasion ($P = .0003$), lymphatic invasion ($P = .002$), and vascular invasion ($P = .0002$) were observed more often among patients with a smaller proportion of bronchioloalveolar carcinoma. A positive and significant correlation was found between the rate of bronchioloalveolar carcinoma component and ground-glass opacity ($R^2 = 0.488$, $P < .0001$) and tumor shadow disappearance rate ($R^2 = 0.727$, $P < .0001$). As an independent predictor of nodal status, tumor shadow disappearance rate ($P = .015$) and bronchioloalveolar carcinoma component ($P = .015$), as well as tumor size, were significantly valuable, although ground-glass opacity proportion ($P = .086$) was marginally informative.

Conclusions: Small-sized adenocarcinomas with a greater ratio of bronchioloalveolar carcinoma component showed less aggressive behavior. Both tumor shadow disappearance rate and ground-glass opacity ratios, which are obtained preoperatively, were well associated with bronchioloalveolar carcinoma ratios, which are determined postoperatively. Furthermore, tumor shadow disappearance rate had a stronger impact as a predictor of bronchioloalveolar carcinoma component. Preoperative assessment of tumor shadow disappearance rate may be useful to identify patients requiring a less extensive pulmonary resection.

From the Departments of Thoracic Surgery[a] and Pathology,[b] Hyogo Medical Center for Adults, Akashi, Hyogo, Japan, and Department of Surgical Pathology,[c] Kobe University Medical School, Kobe, Hyogo, Japan.

Received for publication March 31, 2003; revisions requested May 27, 2003; revisions received July 29, 2003; accepted for publication Aug 11, 2003.

Address for reprints: Morihito Okada, MD, PhD, Department of Thoracic Surgery, Hyogo Medical Center for Adults, Kitaohji-cho13-70, Akashi City 673-8558, Hyogo, Japan (E-mail: morihito1217jp@aol.com).

J Thorac Cardiovasc Surg 2004;127:857-61

0022-5223/$30.00

doi:10.1016/j.jtcvs.2003.08.048

GTS

The extensive use of computed tomography (CT) scanning for early detection of lung cancer is confronting our approach to surgery. However, there are no definite criteria regarding CT findings that characterize early lung cancers or determine the clinical and tumor biology preoperatively. The increasing number of patients with small-sized lung cancers has led to doubts about whether some of these cancers can be treated with a lesser resection, despite much controversy surrounding the effectiveness of lesser resection as an alternative to lobectomy.[1-6] Approximately one fifth of clinical T1 cancers are linked to nodal involvement,[1,5,7] and the rest have a more inactive biologic performance that should be defined as early cancers. The risks of nodal involvement and subsequent systemic metastases are not completely associated with the size of the tumor. The capacity to differentiate which of these small cancers would have an active or inactive biologic performance is remarkably crucial. Diagnosis of lung cancers at an early stage is important because eradication of small-sized tumors can be accomplished with less loss of tissue. This results in reduced operative complications and loss of pulmonary function. In addition, the procedure is associated with longer survival, and if another tumor is found, the patient would be in better condition to resist a second resection of tissues. The larger the extent of the initial resection, the more restricted the surgical choice for potential subsequent resections.

Ground-glass opacity (GGO), termed as a misty and obscure component in lung attenuation on high-resolution CT (HRCT), seems linked to tumor biology and thereby to the risk of nodal involvement. In particular, cancers 2 cm or smaller, in which the ratio of GGO relative to the whole shadow of the tumor is 50% or greater, are bronchioloalveolar carcinomas (BACs) without nodal involvement.[8-10] In addition, BAC may stand for the preinvasive type of adenocarcinoma often seen at the margin of invasive adenocarcinoma.[1-14] From these findings, we speculated that limited lung resection might be an acceptable approach to the treatment of small BACs. In addition, Takamochi and colleagues[15] proposed a radiologic parameter, namely, the tumor shadow disappearance rate (TDR), designed from tumor shadows on both pulmonary and mediastinal window setting images on CT, as a predictor of N0 disease in patients with an adenocarcinoma. BACs typified by a lepidic growth pattern along the alveoli without invasive areas have an inactive performance and are usually expressed as GGO or tumor shadow disappearance areas on CT. Consequently, the CT characteristics (ie, GGO and TDR) of the tumors must be identified. Notably, the features of these different entities need to be well defined and correlated with preoperative imaging findings and clinical outcomes. Understanding the biologic performance of these small lung cancers preoperatively could also provide clues in selecting patients for limited pulmonary resection. Therefore, we examined the aggressiveness of small-sized pulmonary adenocarcinomas according to the proportion of BAC increase and correlated the proportion of GGO and TDR calculated on the preoperative HRCT with that of BAC components defined on sections of surgical specimens postoperatively. The results of this study can improve our approach to diagnosing and treating small lung adenocarcinomas, which may become an ever more vital portion of thoracic surgical tradition.

Patients and Methods

From January 2000 to December 2002, 424 consecutive patients underwent operation for primary lung cancer with the same surgical team. Of these patients, 114 with a pathologically proven adenocarcinoma 3 cm or less in diameter underwent complete removal of the primary tumor together with ipsilateral hilar and mediastinal lymph nodes. Surgical-pathologic staging was performed according to the New International Staging System for Lung Cancer.[16] This retrospective chart review at our institution was considered exempt research.

Contrast-enhanced HRCT was performed on an Asteion (Toshiba Medical Systems, Tokyo, Japan). All slices with 6-mm spacing were obtained from the apex of the lung to the base. In addition, slices with 2-mm spacing were taken through the nodule. The images were photographed using a window level of −600 Hounsfield units (HU) with a window width of 1700 HU (lung windows) and a level of 25 HU with a width of 350 HU (mediastinal windows). All lesions were completely resected within 1 month after CT. TDR and GGO were assessed by independent observers, and discrepancies in evaluation among the observers were resolved by averaging the values determined by them. The observers quantified the maximum dimension of the tumor (maxD) and the largest dimension perpendicular to the maximum axis (perD) on both the lung and mediastinal windows. As previously reported,[15] TDR was defined as follows:

$$\text{TDR}\,(\%) = \left(1 - \frac{\text{maxD} \times \text{perD on mediastinal windows}}{\text{maxD} \times \text{perD on lung windows}}\right) \times 100$$

The tumors resected surgically were fixed in 10% formalin and embedded in paraffin. The sections including the largest cut were stained with hematoxylin-eosin and elastica van Gieson, and examined histopathologically. Patients were classified into three groups according to the proportion of BAC area relative to the whole tumor, namely, tumors in which the BAC proportion comprised 0% to 20%, 21% to 50%, or 51% to 100%. These estimations were performed by independent pathologists in the same manner as that for CT reviews. The cutoffs of BAC proportion were chosen so that an approximately equal number of patients whose tumors had a low, medium, or high proportion of BAC component were included in each group.

The clinical records of all patients were reviewed for age, sex, pathologic stage, tumor size (T factor), lymph node status (N factor), pleural involvement (P factor), lymphatic invasion (Ly factor), and vascular invasion (V factor). P factors were defined as follows: P0, visceral pleura is not involved by tumor; P1, tumor has

TABLE 1. Clinicopathologic characteristics of patients with lung adenocarcinoma 3 cm or less in diameter in relation to proportion of pathologic BAC

Factors	Overall	Pathologic BAC			*P* value
		0%-20%	21%-50%	51%-100%	
No. of patients	114	40	38	36	
Age, y (mean, range)	64 (39-81)	65 (48-80)	62 (39-81)	64 (40-81)	.2927
Sex					
Male	52	28	18	6	.0001
Female	62	12	20	30	
Pathologic stage					
I	92	26	31	35	.0011
II	8	3	4	1	
III	12	9	3	0	
IV	2	2	0	0	
T factor					
T1	91	27	29	35	.0035
T2	13	5	7	1	
T3	3	3	0	0	
T4	7	5	2	0	
N factor					
N0	98	31	32	35	.0377
N1	8	3	4	1	
N2	8	6	2	0	
P factor					
P0	75	19	24	32	.0003
P1	25	12	9	4	
P2	10	5	5	0	
P3	4	4	0	0	
Ly factor					
Ly (−)	87	25	27	35	.0015
Ly (+)	27	15	11	1	
V factor					
V (−)	90	24	30	36	.0002
V (+)	24	16	8	0	

BAC, Bronchioloalveolar carcinoma.

reached but not invaded the visceral pleura; P2, tumor has invaded the visceral pleura but does not involve the parietal pleura; and P3, tumor has invaded the parietal pleura or the chest wall. In the case of lymphatic and vascular invasion, adenocarcinoma cells were identifiable in the lymphatic and blood vessel lumen, respectively.

The Kruskal-Wallis rank test was performed to investigate the associations between the proportion of BAC component and clinicopathologic factors. We also examined which TDR or GGO ratio correlated more closely with the BAC ratio using a correlation coefficient. To further elucidate the independent variables in relation to the prediction of nodal involvement, we performed multiple logistic regression analyses as multivariate models in which we used categories for sex and continuous variables for age, tumor size, BAC ratio, GGO ratio, and TDR.

Results

The clinicopathologic findings of the patients are summarized in Table 1. Of 114 patients, 52 (46%) were men and 62 were women. The mean age was 64 years (range 39-81 years). The pathologic examination showed stage I disease in 92 patients (81%), stage II in 8 patients, stage III in 12 patients, and stage IV in 2 patients. The two patients with stage IV disease had pulmonary metastases in the other lobe and brain metastasis. T1 and P0 tumors were found in 91 patients (80%) and 75 patients (66%), respectively. Ninety-eight patients (86%) had no nodal involvement, whereas hilar and mediastinal lymph node involvement was discovered in 8 patients (7%). Lymphatic and vascular invasion occurred in 27 patients (24%) and 24 patients (21%), respectively.

A total of 114 patients were divided into 3 groups in relation to the proportion of BAC component: 0% to 20% (n = 40), 21% to 50% (n = 38), and 51% to 100% (n = 36). Table 1 also shows the background factors and pathologic findings of these groups. Although patient distribution by age did not differ ($P = .2927$), there were significant differences among the groups with respect to sex ($P = .0001$), pathologic stage ($P = .0011$), T factor ($P = .0035$), N factor ($P = .0377$), P factor ($P = .0003$), Ly factor ($P = .0015$), and V factor ($P = .0002$). Male gender, advanced pathologic stage, larger tumor size, nodal involvement, pleural invasion, lymphatic invasion, and vascular invasion were