University Medical and Dental Hospital, Niigata) for their contributions to this study.

References

[1] Jackman DM, Johnson BE. Small-cell lung cancer. Lancet 2005;366:1385–96.
[2] Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 2002;346:85–91.
[3] Hanna N, Bunn Jr PA, Langer C, Einhorn L, Guthrie Jr T, Beck T, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 2006;24:2038–43.
[4] Lara Jr PN, Natale R, Crowley J, Lenz HJ, Redman MW, Carleton JE, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 2009;27:2530–5.
[5] Turrisi 3rd AT, Kim K, Blum R, Sause WT, Livingston RB, Komaki R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999;340:265–71.
[6] Takada M, Fukuoka M, Kawahara M, Sugiura T, Yokoyama A, Yokota S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 2002;20:3054–60.
[7] Giaccone G, Donadio M, Bonardi G, Testore F, Calciati A. Teniposide in the treatment of small-cell lung cancer: the influence of prior chemotherapy. J Clin Oncol 1988;6:1264–70.
[8] Ardizzoni A, Hansen H, Dombernowsky P, Gamucci T, Kaplan S, Postmus P, et al. Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: a phase II study in patients with refractory and sensitive disease. The European Organization for Research and Treatment of Cancer Early Clinical Studies Group and New Drug Development Office, and the Lung Cancer Cooperative Group. J Clin Oncol 1997;15:2090–6.
[9] Inoue A, Sugawara S, Yamazaki K, Maemondo M, Suzuki T, Gomi K, et al. Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402. J Clin Oncol 2008;26:5401–6.
[10] von Pawel J, Schiller JH, Shepherd FA, Fields SZ, Kleisbauer JP, Chrysson NG, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999;17:658–67.
[11] Perez-Soler R, Glisson BS, Lee JS, Fossella FV, Murphy WK, Shin DM, et al. Treatment of patients with small-cell lung cancer refractory to etoposide and cisplatin with the topoisomerase I poison topotecan. J Clin Oncol 1996;14:2785–90.
[12] Noda T, Watanabe T, Kohda A, Hosokawa S, Suzuki T. Chronic effects of a novel synthetic anthracycline derivative (SM-5887) on normal heart and doxorubicin-induced cardiomyopathy in beagle dogs. Invest New Drugs 1998;16:121–8.
[13] Onoda S, Masuda N, Seto T, Eguchi K, Takiguchi Y, Isobe H, et al. Phase II trial of amrubicin for treatment of refractory or relapsed small-cell lung cancer: Thoracic Oncology Research Group Study 0301. J Clin Oncol 2006;24:5448–53.
[14] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
[15] Jotte R, Von Pawel J, Spigel DR, Socinski MA, O'Brien M, Paschold EH, et al. Randomized phase III trial of amrubicin versus topotecan (Topo) as second-line treatment for small cell lung cancer (SCLC). ASCO Meeting Abstracts 2011;29:7000.
[16] Ettinger DS, Jotte R, Lorigan P, Gupta V, Garbo L, Alemany C, et al. Phase II study of amrubicin as second-line therapy in patients with platinum-refractory small-cell lung cancer. J Clin Oncol 2010;28:2598–603.
[17] Gupta RS, Gupta R, Eng B, Lock RB, Ross WE, Hertzberg RP, et al. Camptothecin-resistant mutants of Chinese hamster ovary cells containing a resistant form of topoisomerase I. Cancer Res 1988;48:6404–10.
[18] Sugimoto Y, Tsukahara S, Oh-hara T, Isoe T, Tsuruo T. Decreased expression of DNA topoisomerase I in camptothecin-resistant tumor cell lines as determined by a monoclonal antibody. Cancer Res 1990;50:6925–30.
[19] Sugimoto Y, Tsukahara S, Oh-hara T, Liu LF, Tsuruo T. Elevated expression of DNA topoisomerase II in camptothecin-resistant human tumor cell lines. Cancer Res 1990;50:7962–5.
[20] Tan KB, Mattern MR, Eng WK, McCabe FL, Johnson RK. Nonproductive rearrangement of DNA topoisomerase I and II genes: correlation with resistance to topoisomerase inhibitors. J Natl Cancer Inst 1989;81:1732–5.
[21] Kotani Y, Satouchi M, Ando M, Nakagawa K, Yamamoto N, Ichinose Y, et al. A phase III study comparing amrubicin and cisplatin (AP) with irinotecan and cisplatin (IP) for the treatment of extended-stage small cell lung cancer (ED-SCLC): JCOG0509. ASCO Meeting Abstracts 2012;30:7003.
[22] Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187–205.

VOLUME 32 · NUMBER 12 · APRIL 20 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Study Comparing Amrubicin Plus Cisplatin With Irinotecan Plus Cisplatin in the Treatment of Extensive-Disease Small-Cell Lung Cancer: JCOG 0509

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Published online ahead of print at www.jco.org on March 17, 2014.

Written on behalf of the Japan Clinical Oncology Group.

Supported in part by Grants No. 23-A-16 and 23-A-18 from the National Cancer Center Research and Development Funds; by Grants-in-Aid for Cancer Research No. 17S-2, 17S-5, 20S-2, and 20S-6 from the Ministry of Health, Labour and Welfare of Japan; and by a contract for periodic safety reports on amrubicin from Dainippon Sumitomo Pharma.

Presented in part at the 49th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 4, 2013.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: UMIN000000720 (registered at University Hospital Medical Information Network Clinical Trials Registry).

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0732-183X/14/3212w-1262w/$20.00

DOI: 10.1200/JCO.2013.53.5153

ABSTRACT

Purpose
This randomized phase III trial was conducted to confirm noninferiority of amrubicin plus cisplatin (AP) compared with irinotecan plus cisplatin (IP) in terms of overall survival (OS) in chemotherapy-naive patients with extensive-disease (ED) small-cell lung cancer (SCLC).

Patients and Methods
Chemotherapy-naive patients with ED-SCLC were randomly assigned to receive IP, composed of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on day 1 every 4 weeks, or AP, composed of amrubicin 40 mg/m^2 on days 1, 2, and 3 and cisplatin 60 mg/m^2 on day 1 every 3 weeks.

Results
A total of 284 patients were randomly assigned to IP (n = 142) and AP (n = 142) arms. The point estimate of OS hazard ratio (HR) for AP to IP in the second interim analysis exceeded the noninferior margin (HR, 1.31), resulting in early publication because of futility. In updated analysis, median survival time was 17.7 (IP) versus 15.0 months (AP; HR, 1.43; 95% CI, 1.10 to 1.85), median progression-free survival was 5.6 (IP) versus 5.1 months (AP; HR, 1.42; 95% CI, 1.16 to 1.73), and response rate was 72.3% (IP) versus 77.9% (AP; $P = .33$). Adverse events observed in IP and AP arms were grade 4 neutropenia (22.5% *v* 79.3%), grade 3 to 4 febrile neutropenia (10.6% *v* 32.1%), and grade 3 to 4 diarrhea (7.7% *v* 1.4%).

Conclusion
AP proved inferior to IP in this trial, perhaps because the efficacy of amrubicin as a salvage therapy was differentially beneficial to IP. IP remains the standard treatment for extensive-stage SCLC in Japan.

J Clin Oncol 32:1262-1268. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide,[1] and small-cell lung cancer (SCLC) accounts for almost 13% of all new cases.[2] More than half of these patients are diagnosed with extensive-disease (ED) SCLC.[3] SCLC refers to a rapidly proliferating tumor that is highly sensitive to chemotherapy. However, rapid emergence of clinical drug resistance has resulted in poor prognosis, with almost all such patients dead within 2 years of initial diagnosis.[3] Thus, there is a need for new and effective therapeutic options for ED-SCLC.

The combination of etoposide and cisplatin (EP) has been standard treatment for ED-SCLC for decades. In 2002, a phase III trial conducted by the Japan Clinical Oncology Group (JCOG 9511) demonstrated the superiority of irinotecan plus cisplatin (IP) over EP for patients with ED-SCLC.[4] Median survival time (MST) and 1-year survival for the IP and EP arms were 12.8 versus 9.4 months and 58.4% versus 37.7%, respectively, but patients in the IP arm experienced a significantly higher proportion of grade 3 to 4 diarrhea. Although two randomized phase III trials have failed to confirm the superiority of IP over EP for chemotherapy-naive patients with SCLC in North America and Australia,[5-7] IP is considered equivalent to EP and one of the standard ED-SCLC regimens in Japan.

Amrubicin is a completely synthetic anthracycline derivative that is converted to an active metabolite, amrubicinol, and it is a potent topoisomerase

II inhibitor.[7] The high degree of therapeutic activity of amrubicin is caused by the selective distribution of amrubicinol, which is 10× to 100× more cytotoxic than its parent compound, amrubicin.[8,9]

A phase II study of amrubicin as single-agent therapy for previously untreated ED-SCLC yielded a response rate (RR) of 76%, complete response (CR) rate of 9%, and MST of 11.7 months,[10] similar to outcomes for platinum-based doublets at the time. Moreover, a phase I/II study of amrubicin plus cisplatin (AP) recommended administration of amrubicin 40 mg/m^2 on days 1, 2, and 3 with cisplatin 60 mg/m^2 on day 1 every 3 weeks. An RR of 87.8% and MST of 13.6 months were demonstrated in the patients treated with the recommended dose.[11] The major toxicity of the AP regimen was hematologic, which was acceptable because of the absence of febrile neutropenia (FN). Moreover, the incidence of grade 3 to 4 diarrhea, a concern with IP, was only 4.9%. Therefore, we believed AP might be a new effective treatment option for ED-SCLC, with a more favorable toxicity profile than IP. We undertook a multicenter, randomized, phase III noninferiority trial of AP compared with IP in previously untreated patients with ED-SCLC.

PATIENTS AND METHODS

Patient Selection

Patients were considered eligible if they met the following criteria: histologically or cytologically demonstrated ED-stage SCLC (defined as ≥ one of following: distant metastasis, contralateral hilar-node metastasis, malignant pleural effusion, pericardial effusion), chemotherapy naive, age 20 to 70 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to1, no prior chemotherapy or radiotherapy for any cancers, and adequate organ function, defined as leukocyte count ≥ 4,000/mm^3, hemoglobin ≥ 9.0 g/dL, platelet count ≥ 100,000/mm^3, total bilirubin ≤ 2.0 mg/dL, AST ≤ 100 IU/L, ALT ≤ 100 IU/L, serum creatinine ≤ 1.5 mg/dL, and partial pressure of arterial blood gas without oxygen inhalation ≥ 70 torr. Patients had normal ECG and were asked to respond to a quality-of-life (QOL) questionnaire before enrollment. Patients were excluded if they had other unrelated invasive malignancies requiring ongoing therapy, serious tumor-related complication, active bacterial or fungal infection, diarrhea, intestinal paralysis or obstruction, evidence of interstitial pneumonia or pulmonary fibrosis on chest x-ray, received or expected to receive long-term treatment (≥ 50 days) with nonsteroidal anti-inflammatory drugs or steroids, serious cardiac disease, serious psychiatric disorder, pregnancy, active gastroduodenal ulcer, or history of myocardial infarction within 12 months. All enrolled patients provided written informed consent to participate in the study.

Treatment Plan

Patients were randomly assigned at a one-to-one ratio to receive either AP or IP. Random assignment was adjusted according to the following stratification factors: ECOG PS, institution, and sex. The IP regimen consisted of four cycles of irinotecan 60 mg/m^2 intravenously (IV) on days 1, 8, and 15 and cisplatin 60 mg/m^2 IV on day 1. Cycle length for this arm was 4 weeks. The AP regimen initially consisted of four cycles of amrubicin 40 mg/m^2 IV on days 1, 2, and 3 and cisplatin 60 mg/m^2 IV on day 1 every 3 weeks. However, because of the high incidence of severe hematologic toxicities, the protocol was revised to reduce the initial dose of amrubicin to 35 mg/m^2 in the AP group after 66% of patients (94 of 142) in the AP arm had been enrolled. The subsequent cycles of both arms were begun if absolute leukocyte count ≥ 3,000/μL, platelet count ≥ 100,000/μL, serum creatinine ≤ 1.5 mg/dL, and treatment-related nonhematologic toxicities (excluding alopecia, weight loss, and hyponatremia) had been resolved to grade ≤ 1. In regard to dose modification, if during the previous course the patient presented with thrombocytopenia (platelet count < 20,000/mm^3) and/or grade 3 nonhematologic toxicity including FN and diarrhea, the dose of irinotecan was reduced by 10 mg/m^2 and the dose of amrubicin by 5 mg/m^2 in the next cycle. The dose of cisplatin was reduced by 20 mg/m^2 for subsequent courses in the event of any of the following toxicities: creatinine > 1.5 to ≤ 2.0 mg/dL, grade 3 nonhematologic toxicity, grade ≥ 2 neuropathy (sensory or motor), and grade ≥ 2 muscle or joint pain. Prophylactic administration of granulocyte colony-stimulating factor was not allowed in the first cycle. After the fourth cycle, initially prophylactic cranial irradiation (PCI) was conducted as per institutional policy. However, because of the report at the 2007 Annual Meeting of the American Society of Clinical Oncology stating that addition of PCI for ED-SCLC responders significantly extended survival,[12] the protocol was revised just 4 months after the start of patient enrollment so that patients with CR or tumor elimination would additionally receive PCI.

Response and Toxicity Evaluations

Baseline evaluation consisted of complete medical history and physical examination, ECG, ECOG PS, complete blood count, blood chemistry, blood gas analysis, computed tomography (CT) scan of the chest, CT or ultrasound of the abdomen, magnetic resonance imaging or CT of the brain, and bone scan or positron emission tomography. During treatment within the study, complete blood count, blood chemistry, and complete physical examination with clinical assessment were performed at least every week. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (version 3). Chest x-ray was performed every cycle during protocol treatment, whether or not there was evidence of progression. All responses were defined according to RECIST (version 1.0). We evaluated patient QOL twice—once at baseline and once after completion of the second course (8 weeks in IP arm, 6 weeks in AP arm after treatment initiation)—using a QOL questionnaire for patients with cancer treated with anticancer drugs (QOL-ACD) and QOL Questionnaire Core 30 (QLQ-C30; diarrhea score). The primary metric used to analyze QOL was a comparison between arms in terms of improvement of physical status score over baseline QOL questionnaire.

End Points

The objective of this randomized phase III study was to establish the noninferiority of AP compared with IP as first-line therapy in patients with ED-SCLC. The primary end point was overall survival (OS). Secondary end points were progression-free survival (PFS), RR, adverse events (AEs), grade 3 to 4 diarrhea, and QOL.

Study Design and Statistical Analysis

This trial was a multicenter randomized trial. The study protocol was approved by the JCOG Protocol Review Committee and the institutional review board of each participating institution.

The trial was designed to achieve at least 70% power to confirm noninferiority of AP compared with IP, with a noninferiority margin of 1.31 in terms of hazard ratio (HR), MST of 12.8 months in both arms, and one-sided α = 0.05. We believed 3 months would be the maximum allowable noninferiority margin in the case of a less-toxic regimen with a different toxicity profile—a profile that we had expected from the phase I/II study. An MST 3 months shorter than that of the IP arm would correspond to an HR of 1.31. The planned sample size was 282 patients, determined by the methods of Schoenfeld and Richter,[13] with 3 years of accrual and 3 years of follow-up. Because of an insufficient accrual rate during the study, the accrual period was revised to 4 years.

An interim analysis was scheduled because of the futility of the trial at the halfway mark of registration. The results from the interim analysis were reviewed by the JCOG Data and Safety Monitoring Committee, and investigators were blinded for the results. After the first interim analysis, the protocol was revised to add second interim analysis after all patients had been registered. Multiplicity for the primary end point was adjusted using O'Brien-Fleming–type alpha spending function.[14] The primary end point—OS—was analyzed using stratified Cox regression analysis with PS (0 *v* 1) and sex (male *v* female) as strata for all eligible patients. Except for the primary analysis, OS and PFS were analyzed using unstratified Cox regression analysis. OS and PFS were estimated using the Kaplan-Meier method. RRs were compared using Fisher's exact test. QOL scores were analyzed using logistic regression with covariate, treatment arm, and QOL scores at baseline. All *P* values are two sided, except for the primary analysis of the noninferiority hypothesis. Statistical analyses were conducted using SAS software (version 9.1 or 9.2; SAS Institute, Cary, NC).

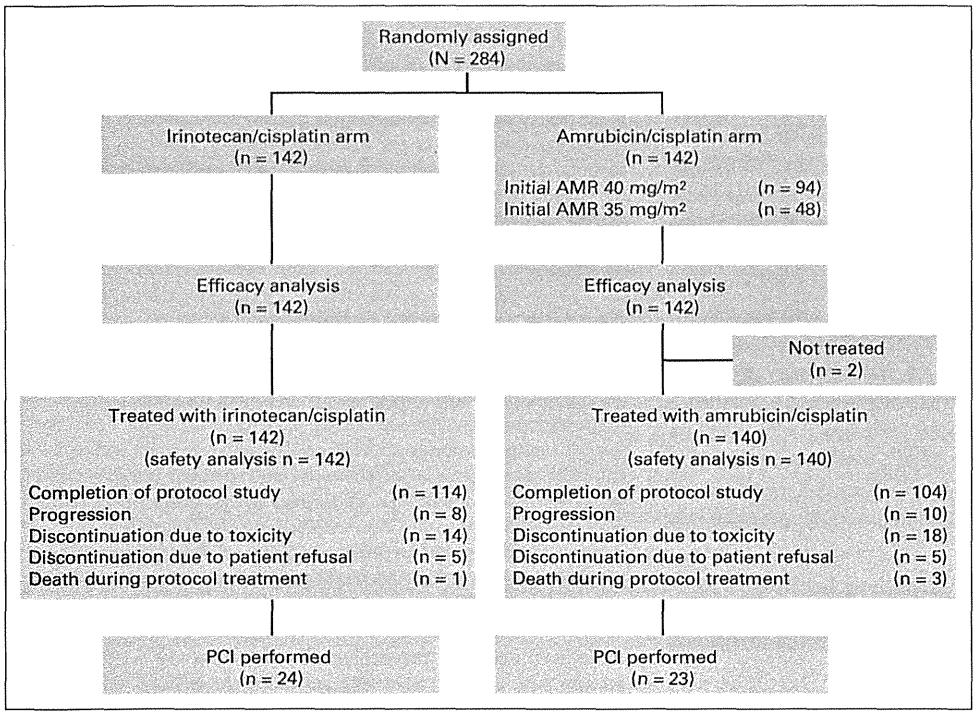

Fig 1. CONSORT diagram. AMR, amrubicin; PCI, prophylactic cranial irradiation.

RESULTS

From May 2007 to December 2010, 284 patients from 35 institutions were enrolled onto the study. All patients were deemed eligible; 142 patients were randomly assigned to the IP arm and 142 to the AP arm (Fig 1). Baseline characteristics were well balanced between the arms (Table 1). All 284 patients were included in the analysis for OS, PFS, and response. Patients who received at least one cycle of study treatment (n = 282) were assessable for toxicity analysis.

Treatment Delivery

Table 2 lists the number of cycles delivered. There were no significant differences between the two arms in treatment delivery. Two patients in the AP arm did not receive any protocol treatment. For the remaining 142 and 140 patients, the proportions receiving the planned four cycles of chemotherapy were 81% and 73.2% in the IP and AP arms, respectively. In the AP arm, 67% (63 of 94) of those who received an initial dose of 40 mg/m^2 completed four cycles, whereas in the AP arm, 85.4% of those who received 35 mg/m^2 completed four cycles; 4.9% (seven of 142) in the IP group and 7% (10 of 142) in the AP group received < two thirds of the planned dose of cisplatin. The interruption rates before protocol completion in the IP and AP arms were 19.7% and 26.8%, respectively; 13.4% and 16.2% of the patients in the IP and AP arms, respectively, had their treatment interrupted because of toxicity. In the IP and AP arms, 24 and 23 patients underwent PCI, respectively.

Toxicity

Table 3 lists grade ≥ 3 major toxicities. The most common grade ≥ 3 AEs in the AP arm were myelosuppression and FN. Diarrhea represented the predominant type of grade ≥ 3 toxicity in the IP arm. Myelosuppression was improved by reducing the initial dose of amrubicin: grade 3 to 4 leukopenia (from 77.2% to 62.5%), neutropenia (from 96.7% to 93.8%), anemia (from 43.5% to 22.9%), thrombocytopenia (from 35.9% to 10.4%), and FN (from 37% to 22.9%).

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	IP Arm (n = 142) No.	IP Arm (n = 142) %	AP Arm (n = 142) No.	AP Arm (n = 142) %
Sex				
Male	120	84.5	119	83.8
Female	22	15.5	23	16.2
Age, years				
Median	63		63	
Range	39-70		29-70	
ECOG PS				
0	78	54.9	80	56.3
1	64	45.1	62	43.7
Measurable lesions				
None	1	0.7	2	1.4
Yes	141	99.3	140	98.6
Smoking status				
Nonsmoker	3	2.1	3	2.1
Smoker	139	97.9	139	97.9
Metastasis (overlapped)				
Lung	9	6.3	14	9.9
Bone	25	17.6	31	21.8
Brain	32	22.5	41	28.9
Liver	35	24.6	45	31.7
Others	68	47.9	64	45.1

Abbreviations: AP, amrubicin plus cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; IP, irinotecan plus cisplatin.

Table 2. Delivered Cycles

No. of Cycles	IP Arm (n = 142) No.	IP Arm (n = 142) %	AP Arm (n = 142) No.	AP Arm (n = 142) %
0	0	0.0	2	1.4
1	7	4.9	8	5.6
2	10	7.0	14	9.9
3	10	7.0	14	9.9
4	115	81.0	104	73.2

Abbreviations: AP, amrubicin plus cisplatin; IP, irinotecan plus cisplatin.

One treatment-related death occurred in the IP arm (resulting from infection), and two occurred in the AP arm (one resulting from infection, and other resulting from pulmonary hemorrhage).

Efficacy

In the first interim analysis, the HR was 1.25 (99.9% CI, 0.28 to 5.59; information time, 0.16). The second interim analysis was conducted after completion of patient accrual based on the data as of May 2011. It showed that the median OS for AP (15.0 months) was much worse than that for IP (18.3 months) and that the HR was 1.41 (96.3% CI, 1.03 to 1.93) in stratified Cox regression. The point estimate of HR in OS for AP to IP exceeded the noninferiority margin (HR, 1.31); therefore, the Data Safety Monitoring Committee recommended early publication because of futility according to the preplanned decision rule that a point estimate of HR of AP to IP exceed the noninferiority margin (HR > 1.31). The Bayesian predictive probability that noninferiority would be shown with statistical significance at the end of this trial was 16.2%. Median PFS was 5.7 (IP) versus 5.2 months (AP; HR, 1.43; 95% CI, 1.13 to 1.82). RR was 72.3% (IP) versus 77.9% (AP; $P = .33$). Even updated analysis, as of May 2012, showed OS to be inferior in the AP arm (17.7 *v* 15.0 months; HR, 1.43; 95% CI, 1.10 to 1.85; Fig 2A). Median PFS was 5.6 (IP) versus 5.1 months (AP; HR, 1.42; 95% CI, 1.12 to 1.80; Fig 2B). The initial dose reduction in amrubicin had no impact on any efficacy results when the dose was reduced to 35 mg (Table 4).

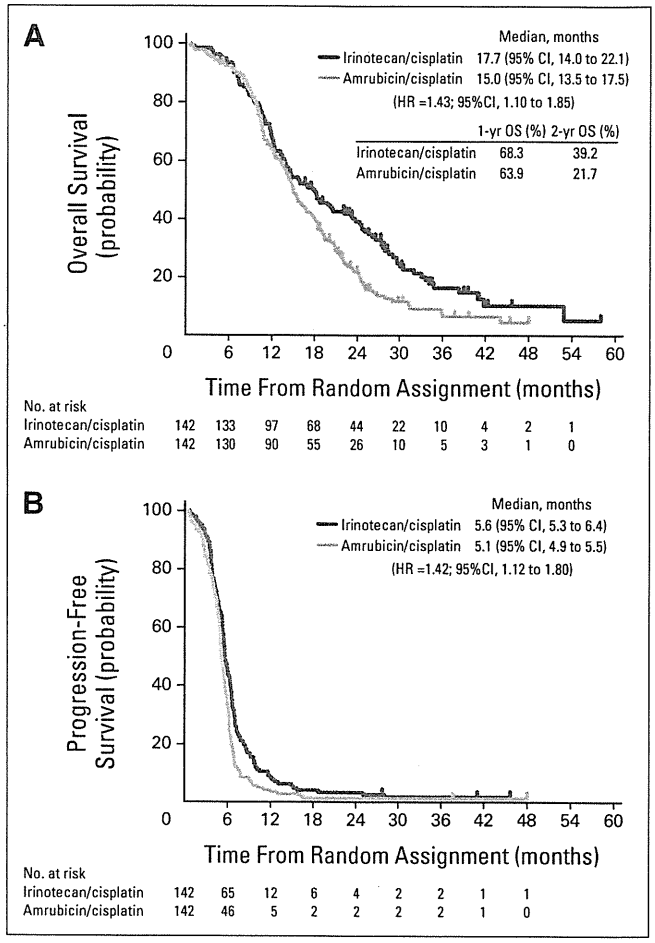

Fig 2. (A) Overall and (B) progression-free survival for intent-to-treat population (n = 284). HR, hazard ratio.

Table 3. Toxicities

Toxicity	Regimen by Grade (%) IP Arm (n = 142)* All	IP Arm 3	IP Arm 4	AP Arm (n = 140)† All	AP Arm 3	AP Arm 4
Hematologic						
Leukopenia	88.7	20.4	2.1	98.6	46.4	25.7
Neutropenia	95.8	35.9	22.5	99.3	16.4	79.3
Anemia	85.9	16.9	6.3	91.4	23.6	12.9
Thrombocytopenia	12.0	1.4	0.7	59.3	15.7	11.4
Nonhematologic						
FN	10.6	9.9	0.7	32.1	31.4	0.7
Fatigue	61.3	3.5	0.7	64.3	3.6	0.0
Nausea	78.9	6.3	0.0	79.3	4.3	0.0
Vomiting	37.3	3.5	0.0	34.3	2.1	0.0
Diarrhea	63.4	7.7	0.0	26.4	1.4	0.0
Hyponatremia	74.6	14.8	4.9	79.3	15.7	6.4
Cardiovascular events	0.0	0.0	0.0	0.0	0.0	0.0

Abbreviations: AP, amrubicin plus cisplatin; FN, febrile neutropenia; IP, irinotecan plus cisplatin.
*One treatment-related death (0.7%).
†Two treatment-related deaths (1.4%).

The QOL questionnaire was completed in most cases: 282 of 284 patients at baseline and 272 patients at the end of the second course. The proportion of improvement in physical status in terms of QOL—the primary metric used to analyze QOL—was 37.1% in the IP arm versus 31.7% in the AP arm (odds ratio, 0.72; 95% CI, 0.43 to 1.22; $P = .23$). There was no significant difference in QOL improvement.

Poststudy Treatment

Table 5 summarizes poststudy treatment. Overall, 93.7% of IP-arm patients and 92.1% of AP-arm patients received additional therapy; 89.4% of patients in the IP arm and 87.1% of those in the AP arm received second-line chemotherapy, whereas 59.2% of those in the IP arm and 62.1% of those in the AP arm received third-line chemotherapy, indicating no substantial difference in the percentage receiving poststudy treatment. Nonetheless, 61 and 34 patients in the IP arm were administered single-agent amrubicin in their second- or third-line therapy, respectively. These figures are higher than those observed in the AP arm.

Table 4. Summary of Survival and Response

Survival/ Response	Before Amrubicin Dose Revision		After Amrubicin Dose Revision	
	IP Arm (n = 97)	AP Arm (n = 94)	IP Arm (n = 45)	AP Arm (n = 48)
ORR				
No.	72 of 97	70 of 93*	30 of 44*	39 of 47*
%	74.2	75.3	68.2	83.0
PFS				
Median	6.0	5.3	5.4	5.0
95% CI	5.5 to 6.6	4.9 to 5.7	4.8 to 6.4	4.7 to 5.7
OS				
Median	17.7	14.9	18.0	15.6
95% CI	13.9 to 22.1	13.1 to 16.8	12.2 to NE	12.4 to 20.7

Abbreviations: AP, amrubicin plus cisplatin; IP, irinotecan plus cisplatin; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
*One patient excluded because of no measurable lesions.

DISCUSSION

The outcomes in our study did not satisfy the primary end point, showing OS in the AP arm to be significantly inferior to that in the IP arm. The MST for AP was favorable (15 months), reproducing the outcomes obtained in the phase I/II study. The MST for IP was approximately 5 months beyond that shown in JCOG 9511. AP may simply be inferior to IP in the first line in that the platinum–topoisomerase I inhibitor partnership between cisplatin and irinotecan may be more synergistic. Although there was only a 0.5-month difference in median PFS, the IP arm displayed a much longer MST (ie, postprogression survival of IP arm was longer); two conceivable reasons for this are the advancements in support therapy and the influence of poststudy treatment.

Table 5. Poststudy Therapy

Chemotherapy	Second Line		Third Line	
	IP Arm (n = 127)	AP Arm (n = 122)	IP Arm (n = 84)	AP Arm (n = 87)
IP	7	10	0	3
Irinotecan	3	24	7	19
Cisplatin, irinotecan, and etoposide	10	13	2	2
Carboplatin plus irinotecan	1	4	0	9
Irinotecan plus other	0	1	3	4
Amrubicin	61	2	34	12
AP	0	4	0	1
Carboplatin plus amrubicin	1	0	0	0
Cisplatin plus etoposide	9	11	4	1
Carboplatin plus etoposide	22	29	25	24
Etoposide	1	0	0	0
Carboplatin, etoposide, and other	0	1	0	0
Topotecan	12	23	6	5
Carboplatin	0	0	0	1
Carboplatin plus other	0	0	1	4
Other	0	0	2	2

Abbreviations: AP, amrubicin plus cisplatin; IP, irinotecan plus cisplatin.

The incidence of the greatest toxicity concern in JCOG 9511, grade 3 to 4 diarrhea, was 7.7% in this study (16.0% in JCOG 9511). The incidence of diarrhea was lower, which was most likely the result of advances in support therapy. That said, the impact of poststudy treatment should garner the most attention as a reason for the inability to demonstrate survival extension or noninferiority in our study.

Analysis of subsequent therapies administered in this study revealed that ultimately, two thirds of all patients in the IP arm received single-agent amrubicin as a subsequent therapy. There was no difference between the two arms in terms of the percentage of patients who received subsequent therapies, suggesting that amrubicin, used in a large percentage of patients in the IP arm as postprotocol therapy, contributed to an extension in OS.

Several studies have examined the use of amrubicin as secondary treatment for SCLC.[15-18] A phase II study by Inoue et al[15] comparing amrubicin with topotecan, considered to be standard secondary treatment, indicated the possibility that amrubicin might be superior to topotecan. A phase III study conducted by Jotte et al[16] did not show any significant difference between topotecan and amrubicin as second-line chemotherapy in terms of OS (MST: amrubicin, 9.2 months; topotecan, 9.9 months; HR, 0.89; 95% CI, 0.73 to 1.06); however, outcomes with amrubicin were significantly better in terms of RR and PFS, and OS was better in subanalysis only among patients experiencing refractory relapse (MST: amrubicin, 6.2 months; topotecan, 5.7 months; HR, 0.77; 95% CI, 0.79 to 1.0; $P = .047$). Although topotecan is the most evidence-based second-line therapy for SCLC,[19,20] amrubicin has come into widespread use in Japan as a result of many reports on its use among Japanese patients (ie, RR and PFS compare favorably, and survival is quite respectable).

Amrubicin is a topoisomerase II inhibitor, suggesting that it may not be effective in patients for whom etoposide (also topisomerase II inhibitor) or EP has failed. Irinotecan is a topoisomerase I inhibitor, and amrubicin may be effective in those for whom IP has failed (unlike in those for whom EP has failed). Accordingly, the possibility remains that the frequent use of amrubicin in poststudy treatment may have extended survival even beyond that expected. This may be a reason why IP therapy showed significantly better survival than AP therapy in our study. In this phase III trial, AP proved to be inferior to IP, but the results seen here do not negate the activity of this agent in SCLC and perhaps underscore the particular value of amrubicin as second- or third-line therapy in this setting.

The AP arm showed reproducible, favorable survival in the form of 15-month MST and noninferiority to EP in a phase III study conducted in China (MST: AP, 11.79 months; EP, 10.28 months),[21] suggesting that AP is rather effective. However, considering that hematotoxicity and FN, even after reduction of the dose to 35 mg/m^2, were relatively serious, and considering the excellent effect of amrubicin monotherapy in relapse treatment, we are unable to recommend AP as standard first-line therapy for ED-SCLC. Therefore, IP therapy showed favorable OS and toxicity profile, indicating, as expected, its continuing presence as one of the standard first-line therapies for ED-SCLC in Japan.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** Miyako Satouchi, Nippon Kayaku; Tomohide Tamura, Daiichi Sankyo, Bristol-Myers Squibb **Research Funding:** Toyoaki Hida, Nippon Kayaku **Expert Testimony:** None **Patents, Royalties, and Licenses:** None **Other Remuneration:** None

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REFERENCES

1. Siegel R, Naishadham D, Jemal A: Cancer statistics, 2012. CA Cancer J Clin 62:10-29, 2012
2. Govindan R, Page N, Morgensztern D, et al: Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: Analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 24:4539-4544, 2006
3. Shepherd FA, Crowley J, Van Houtte P, et al: The International Association for the Study of Lung Cancer lung cancer staging project: Proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. J Thorac Oncol 2:1067-1077, 2007
4. Noda K, Nishiwaki Y, Kawahara M, et al: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 346:85-91, 2002
5. Lara PN Jr, Natale R, Crowley J, et al: Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: Clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 27:2530-2535, 2009
6. Hanna N, Bunn PA Jr, Langer C, et al: Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 24:2038-2043, 2006
7. Lara PN Jr, Chansky K, Shibata T, et al: Common arm comparative outcomes analysis of phase 3 trials of cisplatin + irinotecan versus cisplatin + etoposide in extensive stage small cell lung cancer: Final patient-level results from Japan Clinical Oncology Group 9511 and Southwest Oncology Group 0124. Cancer 116:5710-5715, 2010
8. Noguchi T, Ichii S, Morisada S, et al: Tumor-selective distribution of an active metabolite of the 9-aminoanthracycline amrubicin. Jpn J Cancer Res 89:1061-1066, 1998
9. Morisada S, Yanagi Y, Noguchi T, et al: Antitumor activities of a novel 9-aminoanthracycline (SM-5887) against mouse experimental tumors and human tumor xenografts. Jpn J Cancer Res 80:69-76, 1989
10. Yana T, Negoro S, Takada M, et al: Phase II study of amrubicin in previously untreated patients with extensive-disease small cell lung cancer: West Japan Thoracic Oncology Group (WJTOG) study. Invest New Drugs 25:253-258, 2007
11. Ohe Y, Negoro S, Matsui K, et al: Phase I-II study of amrubicin and cisplatin in previously untreated patients with extensive-stage small-cell lung cancer. Ann Oncol 16:430-436, 2005
12. Slotman B, Faivre-Finn C, Kramer G, et al: Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 357:664-672, 2007
13. Schoenfeld DA, Richter JR: Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. Biometrics 38:163-170, 1982
14. Lan KKG, DeMets DL: Discrete sequential boundaries for clinical trials. Biometrika 70:659-663, 1983
15. Inoue A, Sugawara S, Yamazaki K, et al: Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402. J Clin Oncol 26:5401-5406, 2008
16. Jotte R, Von Pawel J, Spigel DR, et al: Randomized phase III trial of amrubicin versus topotecan (Topo) as second-line treatment foer small cell lung cancer. J Clin Oncol 29:453s, 2011 (suppl; abstr 7000)
17. Onoda S, Masuda N, Seto T, et al: Phase II trial of amrubicin for treatment of refractory or relapsed small-cell lung cancer: Thoracic Oncology Research Group Study 0301. J Clin Oncol 24:5448-5453, 2006
18. Jotte R, Conkling P, Reynolds C, et al: Randomized phase II trial of single-agent amrubicin or topotecan as second-line treatment in patients with small-cell lung cancer sensitive to first-line platinum-based chemotherapy. J Clin Oncol 29:287-293, 2011
19. O'Brien ME, Ciuleanu TE, Tsekov H, et al: Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol 24: 5441-5447, 2006
20. von Pawel J, Schiller JH, Shepherd FA, et al: Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 17:658-667, 1999
21. Sun Y, Cheng Y, Hao X: Result of phase III trial of amrubicin/cisplatin versus etoposide/cisplatin as first-line treatment for extensive small cell lung cancer. J Clin Oncol 31:459s, 2013 (suppl 15; abstr 7507)

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GLOSSARY TERMS

Topoisomerase I: An enzyme that acts on the topology of native DNA by changing the supercoiled structure of DNA. Topoisomerase I makes a nick in one DNA strand, twists it around the other, and religates the nicked strand.

Topoisomerase II: An enzyme that catalyzes the ATP-dependent transport of one segment of DNA duplex through another DNA duplex. Topoisomerases change the topology of DNA by controlling the essential functions of separating intertwined daughter chromosomes.

Acknowledgment

We thank the patients and their families for participating in this trial; Shunichi Negoro, MD, for encouraging and supporting this trial; Tomoko Kazato and Mieko Imai for data management; and Junki Mizusawa for statistical analysis support from the Japan Clinical Oncology Group Data Center.

Appendix

Overall survival (OS) was defined as the time from random assignment to death resulting from any cause and censored at the last follow-up date. Progression-free survival (PFS) was defined as the interval from random assignment to diagnosis of progression or death resulting from any cause and censored at the last date on which progression-free status was evaluated.

The response rate was the proportion of patients evaluated as having a complete or partial response as overall response among all eligible patients with evaluable lesions. Proportion of grade 3 to 4 diarrhea was defined the number of patients who experienced at least one grade 3 to 4 diarrhea event by Common Terminology Criteria for Adverse Events (version 3) from the first day of protocol treatment to 30 days after protocol treatment. Quality of life was compared in terms of a proportion of patients whose quality-of-life scores improved during protocol treatment.

CIs for OS and PFS proportions were estimated using Greenwood's formula, and those of median OS and median PFS were estimated using the method of Brookmeyer and Crowley. Hazard ratios were estimated using Cox regression.

Interactive CardioVascular and Thoracic Surgery 18 (2014) 329–334
doi:10.1093/icvts/ivt500 Advance Access publication 18 December 2013

Tumour standardized uptake value on positron emission tomography is a novel predictor of adenocarcinoma *in situ* for c-Stage IA lung cancer patients with a part-solid nodule on thin-section computed tomography scan†

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Received 2 June 2013; received in revised form 20 August 2013; accepted 29 August 2013

Abstract

OBJECTIVES: Adenocarcinoma *in situ* (AIS), which is considered to be pathologically non-invasive in the new International Association for the Study of Lung Cancer/the American Thoracic Society/the European Respiratory Society classification, might be present in patients who show a part-solid nodule on thin-section computed tomography (CT) scan.

METHODS: Between 2008 and 2011, 556 clinical Stage IA (c-Stage IA) lung cancer patients underwent pulmonary resection. For all the patients, the findings obtained by preoperative thin-section CT were reviewed and categorized as pure ground-glass nodule (GGN), part-solid nodule or pure-solid nodule based on the findings on thin-section CT, i.e. based on the consolidation/tumour ratio (CTR). A part-solid nodule was defined as a tumour with $0 < CTR < 1.0$, which indicated focal nodular opacity that contained both solid and GGN components. All the patients were evaluated by positron emission tomography (PET), and the maximum standardized uptake value (SUVmax) was recorded. Several clinicopathological features were investigated to identify predictors of AIS in clinical Stage IA lung cancer patients with a part-solid nodule radiologically, using multivariate analyses.

RESULTS: One-hundred and twelve c-Stage IA lung cancer patients showed a part-solid appearance on thin-section CT. Among them, AIS was found in 10 (32%) of the tumours with $0 < CTR \leq 0.5$, in contrast to 3 (5%) with $0.5 < CTR < 1.0$. According to multivariate analyses, SUVmax and CTR significantly predicted AIS in patients with a part-solid nodule ($P = 0.04$, 0.02). The mean SUVmax of the patients with AIS was 0.57 (0–1.6). Moreover, in the subgroup of part-solid nodule with a SUVmax of ≤1.0 and a CTR of ≤0.40, which were calculated as cut-off values for AIS based on the results for a receiver operating characteristic curve, 6 (40%) patients with these criteria showed a pathological non-invasive nature, even patients with a part-solid nodule.

CONCLUSIONS: Among c-Stage IA adenocarcinoma with a part-solid nodule on thin-section CT scan, an extremely low level of SUVmax could reflect a pure GGN equivalent radiologically and AIS pathologically. The preoperative tumour SUVmax on PET could yield important information for predicting non-invasiveness in patients with a part-solid nodule.

Keywords: Lung cancer • Part-solid nodule • Adenocarcinoma *in situ* • Positron emission tomography

INTRODUCTION

Lung cancer is the most common cause of major cancer and mortality worldwide [1]. Adenocarcinoma is the most common histological subtype of lung cancer in most countries and accounts for approximately half of all lung cancers. Moreover, recent developments in imaging technology and the widespread use of thin-section computed tomography (CT) for screening have made it possible to detect small-sized lung cancers [2, 3]. Most of these are peripherally located adenocarcinoma of the lung, and several authors have reported that lung cancers with a wide area of ground-glass nodule (GGN) on thin-section CT scan have a good prognosis, and in most cases, their pathological features are minimally invasive [4–7]. Thus, these tumours are considered to be feasible candidates for limited surgical resection, as revealed by the prospective JCOG 0201 study in Japan [8]. Nonetheless, there are still some discrepancies between CTR and the degree of pathological behaviour in patients with early stage lung cancer.

On the other hand, the maximum standardized uptake value (SUVmax) on positron emission tomography (PET) with F-18 fluorodeoxyglucose (^{18}F-FDG) is a promising modality for predicting

†Presented at the 21st European Conference on General Thoracic Surgery, Birmingham, UK, 26–29 May 2013.

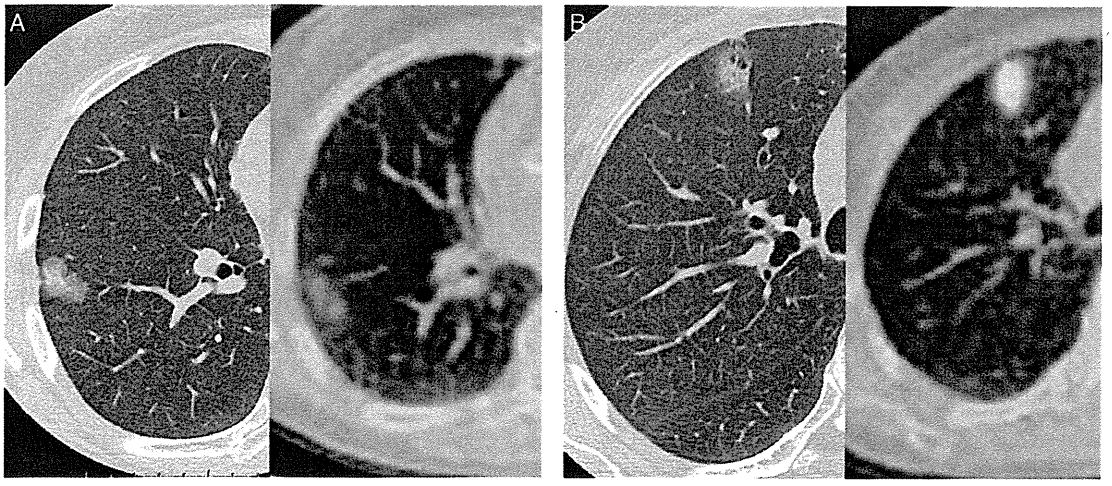

Figure 1: Thin-section CT scan and PET–CT reveal lung adenocarcinoma with a radiologically part-solid appearance and a wide range of grades of malignancy. (**A**) shows low-grade malignancy based on SUVmax on PET–CT. In contrast, (**B**) shows high-grade malignancy based on PET–CT despite the findings of thin-section CT.

the prognosis and invasiveness of lung adenocarcinoma [9, 10]. Lung adenocarcinoma with a radiologically part-solid appearance exhibits a wide range of grades of malignancy (Fig. 1). To predict the biological behaviour of a part-solid nodule, preoperative findings with PET and thin-section CT must be correlated with the pathological features of these lesions, since these observations could provide more precise clues regarding proper treatment strategies for small adenocarcinoma with a part-solid appearance. In the current retrospective study, we focused on the relationships between SUVmax on PET, CTR on thin-section CT scan in clinical Stage IA (c-Stage IA) lung cancer with a part-solid nodule and its pathological invasiveness, especially regarding adenocarcinoma *in situ* (AIS), to develop criteria for identifying candidates for limited surgical resection by predicting pathological non-invasiveness in patients with a part-solid nodule.

MATERIALS AND METHODS

This protocol was approved by the ethics committee at our institute. All the patients provided their written informed consent before trial enrolment.

Between January 2008 and December 2011, 556 c-Stage IA lung cancer patients underwent pulmonary resection at our institute. For all the patients, the findings of preoperative CT were reviewed by the authors (A.H., T.M. and K.S.). A contrast-enhanced CT scan was performed to evaluate the entire lung for preoperative staging. The size of the tumours was determined preoperatively based on the findings of thin-section CT scan. In addition, all tumours were subsequently evaluated to estimate the extent of GGN with a thin-section CT scan with 2 mm collimation. The lung was photographed with a window level of −500 to −700 H and a window depth of 1000–2000 H as a 'lung window'. The solid component was defined as an area of increased opacification that completely obscured the underlying vascular markings. Ground-glass nodule was defined as an area of a slight, homogeneous increase in density that did not obscure the underlying vascular markings. According to the radiological findings on thin-section CT, tumours were divided into three groups: pure GGN, part-solid nodule and pure-solid nodule based on the ratio of the maximum diameter of consolidation to the maximum tumour diameter (consolidation/tumour ratio, CTR). According to thin-section CT findings, pure GGN was defined as a tumour of CTR = 0, pure-solid nodule was defined as a tumour of CTR = 1.0 and part-solid nodule was defined as a tumour of 0 < CTR < 1.0, which indicated focal nodular opacity that included both solid and GGN components. The pure GGN and pure-solid nodule groups were excluded from this study.

With regard to PET–CT scanning, 112 patients underwent a PET–CT scan at the Yotsuya Medical Cube (Tokyo, Japan). The technique used for ^{18}F-FDG-PET/CT scanning at the Yotsuya Medical Cube was as follows. All patients were asked to fast for at least 6 h before ^{18}F-FDG injection to minimize their blood insulin level and normal tissue glucose uptake. The subjects were injected intravenously with 3.5 MBq/kg of ^{18}F-FDG, and static emission images were obtained 60 min after injection. Image acquisition was performed using a Discovery ST PET/CT scanner (GE Medical Systems, Waukesha, WI, USA). After CT image acquisition, emission scanning was performed from the head to the mid-thighs in six bed positions. The acquired PET data were reconstructed to volumetric images with a 2D-OSEM algorithm (2 iterations/15 subsets) incorporating a CT-based attenuation correction.

All PET–CT images were interpreted by one or two experienced nuclear medicine radiologists. A workstation (Xeleris; Elegems, Haifa, Israel) was used for image display and analysis, and the SUVmax of the primary tumour was obtained.

With regard to pathological evaluations, the histological subtype of lung adenocarcinoma was determined according to a new international multidisciplinary classification published by Travis *et al.* [1] under the sponsorship of the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS). Adenocarcinoma *in situ* (one of the lesions formerly known as bronchioloalveolar carcinoma (BAC)) was defined as a localized small (≤3 cm) lung adenocarcinoma with growth restricted to neoplastic cells along pre-existing alveolar structures (i.e. lepidic growth), which lacked stromal, vascular or pleural invasion.

Ultimately, 112 patients showed c-Stage IA lung cancer with a 'part-solid' appearance on thin-section CT scan. All the patients were evaluated by PET, and the SUVmax was recorded. The medical record of each patient was reviewed with regard to

gender, sex, pack-year smoking, clinical T-status (c-T1a vs c-T1b), radiological pleural involvement, presence of air bronchogram in the tumour, serum carcinoembryonic antigen level (ng/ml, the cut-off value in our institute is 3.0) and SUVmax on PET. The relationships between these factors and pathological status were investigated to identify significant predictors of AIS in c-Stage IA patients with a part-solid nodule on thin-section CT scan. Fisher's exact test or χ^2 test was used to compare two factors. Univariate and multivariate analyses were used to identify the clinical factors that predicted AIS in c-Stage IA part-solid lung cancer. Furthermore, a receiver operating characteristic (ROC) curve for predicting AIS was generated using SPSS Statistics 20 (SPSS, Inc.) by plotting sensitivity vs 1-specificity for various thresholds of several clinical factors. Regarding the way to select the optimal cut-off value from the ROC curve, we calculated the distance between the point (0, 1) and each observed cut-off point on the ROC curve. The optimal cut-off value was obtained from the point at which the distance is minimum. A multivariate analysis was performed by logistic regression analysis using SPSS Statistics 20 (SPSS, Inc.). Forward and backward stepwise procedures were used to determine the combination of factors that were essential for predicting the prognosis. Statistical analysis was considered to be significant when the probability value was <0.05.

RESULTS

There were 112 c-Stage IA lung cancer patients who showed a part-solid appearance on thin-section CT scan. Forty-one patients were male and 71 were female. The patients ranged in age from 35 to 86 years, with an average of 66 years. Pathologically, all of them were adenocarcinoma. Among them, AIS was found in 13 (12%) patients with a part-solid nodule on thin-section CT scan. Conversely, postoperative nodal involvement was found in 3 (3%) of these patients (2 in N1 station and 1 in N2 station). The overall characteristics of c-Stage IA lung adenocarcinoma patients with a part-solid nodule are summarized in Table 1. AIS was found in 10 (32%) tumours with $0 < CTR \leq 0.5$, in contrast to 3 (5%) with $0.5 < CTR < 1.0$ ($P < 0.01$). Regarding the relationship between AIS and the SUVmax value on PET, all patients with AIS showed a SUVmax of ≤2.0 ($P = 0.02$).

According to a multivariate analysis in c-Stage IA lung cancer patients with a part-solid nodule on thin-section CT scan, the following factors significantly predicted AIS pathologically: preceding malignancies, CTR and SUVmax level ($P = 0.04$, 0.02 and 0.04; Table 2). The mean SUVmax and mean CTR of the patients with AIS were 0.57 (0–1.6) and 0.47 (0.30–0.85), respectively.

Regarding SUVmax on PET and CTR on thin-section CT scan, the ROC curve revealed that the optimal cut-off value for predicting AIS in patients with a part-solid nodule was a SUVmax of 1.0 (area under the curve 0.728; standard error 0.057) (Fig. 2) and a CTR of 0.40 (area under the curve 0.702; standard error 0.075) (Fig. 3), respectively. These cut-off values yielded a sensitivity of 0.692 and a specificity of 0.677 for SUVmax, and a sensitivity of 0.769 and a specificity of 0.697 for CTR. Based on these results, in the subgroup with a part-solid nodule with both a SUVmax of ≤1.0 and a CTR of ≤0.40, 6 (40.0%) of the 15 patients with these criteria showed AIS, i.e. a pathological non-invasive nature, even patients with a part-solid nodule. Moreover, by combining these predictors, we identified subgroups with different frequencies of pathological lymphatic vessel invasion (LVI) among c-Stage IA lung cancer with a part-solid appearance on thin-section CT scan

Table 1: Results of univariate analysis for predictors of AIS in clinical Stage IA lung cancer patients with a part-solid nodule

Clinical factors	No. of patients	No. of patients with AIS (%)	*P*-value*
Total	112	13 (12)	
Gender			
Male	41	3 (7)	0.28
Female	71	10 (14)	
Age (years)			
≥70	33	2 (6)	0.24
<70	79	11 (14)	
Pack-year smoking			
≥20	26	2 (8)	0.48
<20	86	11 (13)	
Clinical T-status			
c-T1a	66	12 (18)	<0.01
c-T1b	46	1 (2)	
Pleural involvement			
Absent	59	9 (15)	0.20
Present	53	4 (8)	
Air bronchogram			
Absent	30	6 (20)	0.09
Present	82	7 (9)	
Preceding malignancies			
Absent	101	10 (10)	0.09
Present	11	3 (27)	
CEA			
≤3	77	9 (12)	0.97
>3	35	4 (11)	
CTR			
≤0.35	13	3 (23)	0.16
>0.35	99	10 (10)	
≤0.40	26	7 (27)	<0.01
>0.40	86	6 (7)	
≤0.45	33	9 (27)	<0.01
>0.45	79	4 (5)	
SUVmax			
≤1.0	43	9 (21)	0.02
>1.0	69	4 (6)	
≤1.5	63	11 (17)	0.03
>1.5	49	2 (4)	
≤2.0	81	13 (16)	0.02
>2.0	31	0 (0)	

AIS: adenocarcinoma *in situ*; CEA: carcinoembryonic antigen; CTR: consolidation/tumour ratio; SUV: standardized uptake value.
**P*-value in χ^2 test or Fisher's exact test.

Table 2: Results of multivariate analysis for predictors of AIS in clinical Stage IA lung cancer patients with a part-solid nodule

Variable	Odds ratio	95% Confidence interval	*P*-value*
Preceding malignancies	0.16	0.03–0.96	0.04
CTR	4.97	1.26–19.62	0.02
SUVmax	4.32	1.05–17.68	0.04

AIS: adenocarcinoma *in situ*; CTR: consolidation/tumour ratio; SUV: standardized uptake value.
**P*-value in logistic regression analysis.

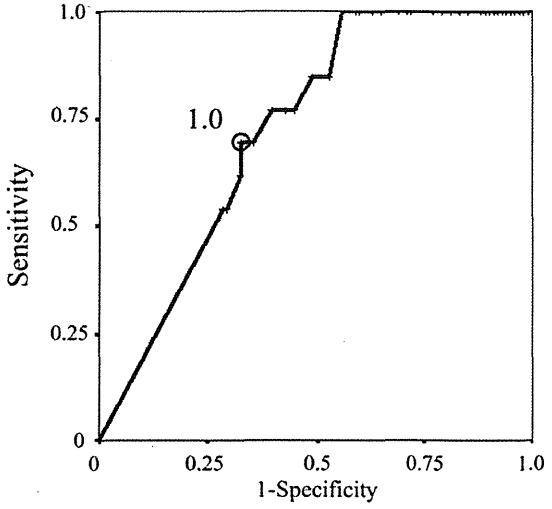

Figure 2: The ROC curve of SUVmax on PET for the prediction of AIS in clinical Stage IA lung cancer patients with a part-solid nodule, with a cut-off value of 1.0.

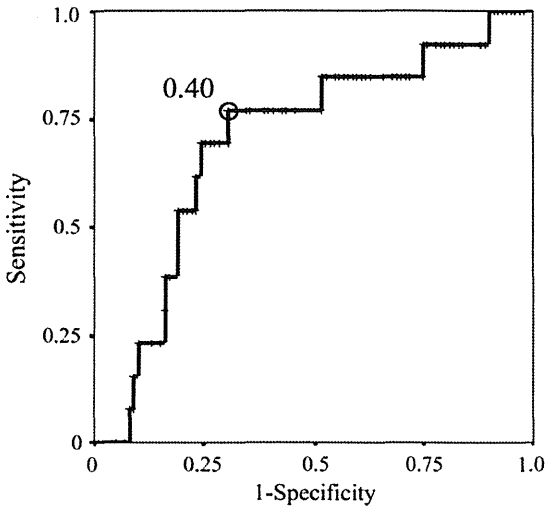

Figure 3: The ROC curve of CTR on thin-section CT scan for the prediction of AIS in clinical Stage IA lung cancer patients with a part-solid nodule, with a cut-off value of 0.40.

(Table 3). The results showed that none of the patients with a part-solid nodule who showed both a SUVmax of ≤1.0 and a CTR of ≤0.40 had LVI. On the other hand, ~26% of patients with c-Stage IA lung cancer with a part-solid nodule who did not have either of these predictors had LVI.

DISCUSSION

Recently, limited surgical resection has been actively indicated for multiple primary lung cancers and/or very early lung cancers that are located peripherally and show a GGN appearance on thin-section CT scan. Based on rapid advances in clinical, radiological, pathological and molecular aspects of lung adenocarcinoma, a new international multidisciplinary classification was published in

Table 3: Probability of the presence of lymphatic vessel invasion in patients with clinical Stage IA lung cancer patients with a part-solid nodule

Subgroups	No. of patients	No. of patients with LVI (%)	*P*-value*
Total number	112	19 (17)	
Presence of SUVmax ≤ 1.0 and CTR ≤ 0.40			
with both factors	15	0 (0)	0.02
with either factors	39	4 (10)	
with neither factors	58	15 (26)	

LVI: lymphatic vessel invasion; CTR: consolidation/tumour ratio; SUV: standardized uptake value.
*P-value in χ^2 test.

2011 under the sponsorship of IASLC/ATS/ERS [1]. In this classification, AIS is a newly defined concept that refers to a localized non-invasive adenocarcinoma with lepidic growth, which lacks stromal, vascular or pleural invasion. Adenocarcinoma *in situ* is best demonstrated typically as a pure GGN on thin-section CT, but is sometimes seen as a part-solid or occasionally a pure-solid nodule (Fig. 4). Since several studies have demonstrated that AIS with pure lepidic growth was associated with 100% disease-free survival [11–14], the ability to predict non-invasiveness in c-Stage IA lung cancer patients with a part-solid nodule could be important for identifying appropriate surgical treatments.

Notably, a prospective trial of the Japan Clinical Oncology Group, JCOG 0201 [8], revealed proper candidates for limited surgery based on the results of radiological findings to predict non-invasive lung cancer, which was defined as an adenocarcinoma of 2 cm or less with a CTR of ≤0.25. This indicates a significant correlation between CTR and pathological findings. The prognostic significance of a solid part in small-sized GGN adenocarcinoma has already been addressed in the literature [15, 16]. Nonetheless, as indicated in this study, there are still some discrepancies between CTR and the degree of pathological behaviour in patients with early stage lung cancer. Lung adenocarcinoma with a part-solid appearance has a wide range of pathological characteristics, since the solid part on thin-section CT scan represents various features, such as collapse of the alveoli, the subsequent formation of an active fibrotic focus and the proliferation of cancer cells [15, 17]. Actually, delayed loco-regional recurrence after limited resection has been reported even for GGN adenocarcinoma [18].

On the other hand, a previous report suggested that a higher SUVmax may indicate aggressive malignant behaviour in small-sized adenocarcinoma, which was independent of the *in situ* components pathologically [19–21]. An elevated SUVmax on PET reflects cellular proliferation and the aggressiveness of the primary lung cancer; however, the sensitivity of PET for AIS is usually very low due to the lower metabolic activity of cancer cells and the likelihood that they will escape detection with the use of FDG [22]. Therefore, the efficacy of PET for predicting the biological features of small-sized adenocarcinoma, especially AIS, remains unclear. However, this disadvantage of FDG-PET for detecting very early lung cancer could provide more important information. By combining the latest radiological imaging of CTR on thin-section CT scan and SUVmax on PET, more precise clues for predicting a pathological non-invasive nature can be obtained for

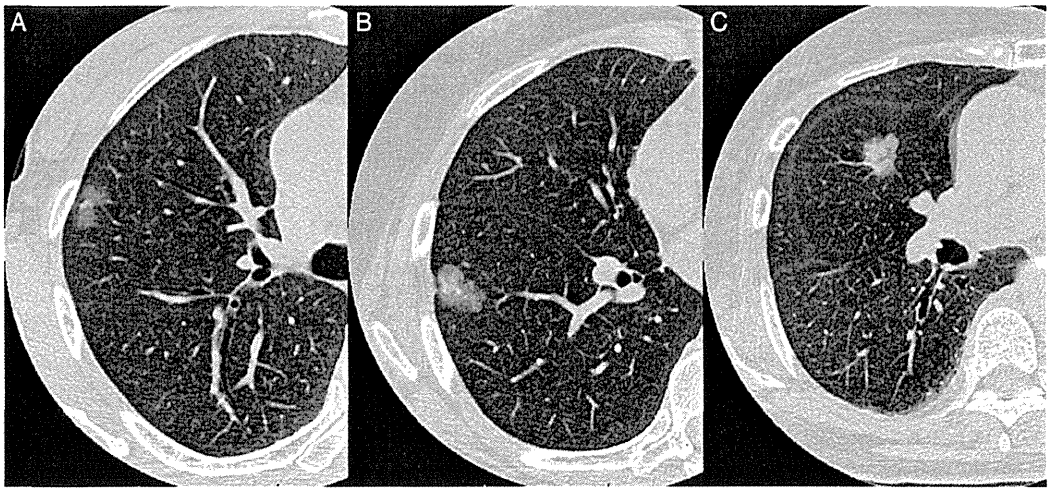

Figure 4: Adenocarcinoma *in situ* is sometimes seen radiologically as a part-solid nodule or occasionally as a pure-solid nodule. The CTRs are: (**A**) 0.31, (**B**) 0. 40 and (**C**) 0.85.

lung cancer patients with part-solid lesions, and this could aid in the selection of appropriate candidates for sublobar resection.

According to the present results in 112 part-solid lung adenocarcinoma patients of c-N0 status, both CTR on thin-section CT scan and the SUVmax level on PET of primary tumours were significantly correlated with AIS, i.e. pathologically non-invasive, by a multivariate analysis. Our results showed that, if they had both a SUVmax of ≤1.0 and a CTR of ≤0.40, even patients with radiologically part-solid tumours had an extremely high incidence of AIS (40%). Furthermore, LVI was never found in patients who had both a SUVmax of ≤1.0 and a CTR of ≤0.40, even if they had a part-solid nodule. On the other hand, if patients had neither of these predictors, we found an extremely high incidence of LVI (26%) in c-Stage IA lung cancer with a part-solid nodule. Our results suggest that limited surgical resection could be an effective therapy for these patients with a SUVmax of ≤1.0 and a CTR of ≤0.40, due to the significantly non-invasive nature of these cancers. Thus, our findings regarding the combination of CTR on thin-section CT and SUVmax on PET more accurately reflect the pathological nature of lung cancer with a part-solid appearance. These findings may be applicable to a specific surgical approach, such as a sublobar resection for early stage lung cancer, the extent of lymph node dissection and the treatment of multiple small-sized lung cancers. In addition, these findings to predict AIS in patients with a part-solid nodule could be used more effectively in our daily practice when we continue the close observation for small-sized lung cancer with GGN predominance as well as selecting appropriate operative modes.

Basically, it is certain that AIS is found in patients with a pure GGN on thin-section CT scan, and the information about the relationship between pure GGN and AIS is an interesting matter. In contrast, AIS is found very occasionally in patients with a part-solid nodule [1]. Actually, we encounter AIS in resected patients with lung cancers showing part-solid nodules on thin-section CT scan. The important point is that 100% disease-free survival is expected if AIS is completely resected. Moreover, lung adenocarcinoma with a radiologically part-solid appearance exhibits a wide range of grades of malignancy. So it is worth investigating the clinical predictors of AIS in patients with part-solid nodules on thin-section CT scan. These data would be informative for deciding the appropriate treatment strategies of part-solid nodules.

The improved quality of CT images and the frequent application of CT examinations in screening programmes have enhanced the capability to detect small-sized lung cancers, which has raised surgical issues that do not yet have definitive answers. Lobectomy has been recommended as a standard surgical procedure [23], even for small-sized lung cancers, since lymph node metastasis can be found in ~15% of lung cancers that are 2 cm or smaller [24, 25]. Nevertheless, our radiological criteria that combine thin-section CT and FDG-PET could be used more precisely to predict pathological non-invasiveness for patients with a part-solid appearance. These patients would be feasible candidates for limited surgical resection, such as wide wedge resection or segmentectomy. In the future, however, whether or not limited surgical resection is an appropriate therapy for lung cancers with a GGN appearance on thin-section CT could be strictly based on the results of three randomized trials (JCOG 0802 and JCOG 0804 in Japan and CALGB 140503 in North America).

This study was limited by a short median follow-up period. And the number of patients with AIS was relatively small, because our cohorts were composed by c-Stage IA lung adenocarcinoma with a 'part-solid' appearance on thin-section CT scan. Further investigations are warranted in the future. Moreover, c-Stage IA lung adenocarcinoma is a heterogeneous cohort. Basically, AIS reveals pure GGN radiologically [1]. On the other hand, like some radiological findings we indicated in this study, we encounter AIS that presents sometimes a part-solid or occasionally a solid nodule in our daily practice. Actually, lung adenocarcinoma with a radiological part-solid appearance exhibits a wide range of grade of malignancies. Generally, radiological part-solid lesions reveal excellent prognosis. Nonetheless, there are some discrepancies among CTR, SUVmax and pathological status. To predict the biological behaviour of a part-solid nodule, preoperative findings with PET and thin-section CT must be correlated with pathological features of these lesions. So in this study, we aimed to predict AIS in c-Stage IA lung cancer patients with a part-solid appearance on thin-section CT scan, since these observations could provide more precise clues regarding proper treatment strategies for small-sized adenocarcinoma with a part-solid appearance. In contrast, regarding c-Stage IA pure-solid lung cancer, the most important topic is the appropriate operative strategy for resectable

NSCLC <2 cm in size [25]. From this point, a Phase III trial as to the feasibility of segmentectomy for lung cancer 2 cm or less in size is now ongoing in Japan (JCOG 0802) and the USA. But historically, lung cancers with a pure-solid appearance on thin-section CT scan are considered to be of invasive nature with a high incidence of nodal involvement of >20%, despite their small size [5, 25]. Regarding the proper indication of segmentectomy for pure-solid lung cancer, some controversies are still surrounded such as possible high local recurrence rate and insufficiency of interlobar lymph node dissection in patients who underwent segmentectomy. So the study to investigate radiological features for negative nodal involvement and to elucidate the candidate for limited surgery even in patients with radiologically pure-solid lung cancer is warranted. Therefore, in the future, we have to address the identification of the clinical and radiological factors to stratify the prognosis of c-Stage IA lung cancer patients. Further studies are needed.

In conclusion, the radiological diagnosis of non-invasive lung cancer using the CTR on thin-section CT scan and SUVmax on PET correlated well with pathological AIS. Our results support the notion that limited surgical resection is an effective therapy even for lung cancers with a part-solid appearance, in patients who have both a SUVmax of ≤1.0 and a CTR of ≤0.40.

Funding

This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare, Japan.

Conflict of interest: none declared.

REFERENCES

[1] Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y *et al.* International association for the study of lung cancer/American thoracic society/European respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244–85.

[2] Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM *et al.* Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395–409.

[3] Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763–71.

[4] Suzuki K, Asamura H, Kusumoto M, Kondo H, Tsuchiya R. 'Early' peripheral lung cancer: prognostic significance of ground glass opacity on thin-section computed tomographic scan. Ann Thorac Surg 2002;74:1635–9.

[5] Suzuki K, Kusumoto M, Watanabe S, Tsuchiya R, Asamura H. Radiologic classification of small adenocarcinoma of the lung: radiologic-pathologic correlation and its prognostic impact. Ann Thorac Surg 2006;81:413–9.

[6] Takamochi K, Nagai K, Yoshida J, Suzuki K, Ohde Y, Nishimura M *et al.* The role of computed tomographic scanning in diagnosing mediastinal node involvement in non-small cell lung cancer. J Thorac Cardiovasc Surg 2000; 119:1135–40.

[7] Kodama K, Higashiyama M, Yokouchi H, Takami K, Kuriyama K, Mano M *et al.* Prognostic value of ground-glass opacity found in small lung adenocarcinoma on high-resolution CT scanning. Lung Cancer 2001;33:17–25.

[8] Suzuki K, Koike T, Asakawa T, Kusumoto M, Asamura H, Nagai K *et al.* A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). J Thorac Oncol 2011;6: 751–6.

[9] Vansteenkiste J, Fischer BM, Dooms C, Mortensen J. Positron-emission tomography in prognostic and therapeutic assessment of lung cancer: systematic review. Lancet Oncol 2004;5:531–40.

[10] Nair VS, Barnett PG, Ananth L, Gould MK. PET scan ^{18}F-fluorodeoxyglucose uptake and prognosis in patients with resected clinical stage IA non-small cell lung cancer. Chest 2010;137:1150–6.

[11] Noguchi M, Morikawa A, Kawasaki M, Matsuno Y, Yamada T, Hirohashi S *et al.* Small adenocarcinoma of the lung. Histologic characteristics and prognosis. Cancer 1995;75:2844–52.

[12] Koike T, Togashi K, Shirato T, Sato S, Hirahara H, Sugawara M *et al.* Limited resection for noninvasive bronchioloalveolar carcinoma diagnosed by intraoperative pathologic examination. Ann Thorac Surg 2009; 88:1106–11.

[13] Watanabe S, Watanabe T, Arai K, Kasai T, Haratake J, Urayama H. Results of wedge resection for focal bronchioloalveolar carcinoma showing pure ground-glass attenuation on computed tomography. Ann Thorac Surg 2002;73:1071–5.

[14] Sakurai H, Dobashi Y, Mizutani E, Matsubara H, Suzuki S, Takano K *et al.* Bronchioloalveolar carcinoma of the lung 3 centimeters or less in diameter: a prognostic assessment. Ann Thorac Surg 2004;78:1728–33.

[15] Suzuki K, Yokose T, Yoshida J, Nishimura M, Takahashi K, Nagai K *et al.* Prognostic significance of the size of central fibrosis in peripheral adenocarcinoma of the lung. Ann Thorac Surg 2000;69:893–7.

[16] Breathnach OS, Kwiatkowski DJ, Finkelstein DM, Godleski J, Sugarbaker DJ, Johnson BE *et al.* Bronchioloalveolar carcinoma of the lung: recurrences and survival in patients with stage I disease. J Thorac Cardiovasc Surg 2001;121:42–7.

[17] Shimosato Y, Suzuki A, Hashimoto T, Nishiwaki Y, Kodama T, Yoneyama T *et al.* Prognostic implications of fibrotic focus (scar) in small peripheral lung cancers. Am J Surg Pathol 1980;4:365–73.

[18] Yoshida J, Ishii G, Yokose T, Aokage K, Hishida T, Nishimura M *et al.* Possible delayed cut-end recurrence after limited resection for ground-glass opacity adenocarcinoma, intraoperatively diagnosed as Noguchi type B, in three patients. J Thorac Oncol 2010;5:546–50.

[19] Okada M, Nakayama H, Okumura S, Daisaki H, Adachi S, Yoshimura M *et al.* Multicenter analysis of high-resolution computed tomography and positron emission tomography/computed tomography findings to choose therapeutic strategies for clinical stage IA lung adenocarcinoma. J Thorac Cardiovasc Surg 2011;141:1384–91.

[20] Nakayama H, Okumura S, Daisaki H, Kato Y, Uehara H, Adachi S *et al.* Value of integrated positron emission tomography revised using a phantom study to evaluate malignancy grade of lung adenocarcinoma: a multicenter study. Cancer 2010;116:3170–7.

[21] Miyasaka Y, Suzuki K, Takamochi K, Matsunaga T, Oh S. The maximum standardized uptake value of fluorodeoxyglucose positron emission tomography of the primary tumour is a good predictor of pathological nodal involvement in clinical N0 non-small-cell lung cancer. Eur J Cardiothorac Surg 2013;44:83–7.

[22] Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. JAMA 2001;285:914–24.

[23] Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615–22; discussion 622–23.

[24] Asamura H, Nakayama H, Kondo H, Tsuchiya R, Shimosato Y, Naruke T. Lymph node involvement, recurrence, and prognosis in resected small, peripheral, non-small-cell lung carcinomas: are these carcinomas candidates for video-assisted lobectomy? J Thorac Cardiovasc Surg 1996;111: 1125–34.

[25] Hattori A, Suzuki K, Matsunaga T, Fukui M, Kitamura Y, Miyasaka Y *et al.* Is limited resection appropriate for radiologically 'solid' tumor in small lung cancers? Ann Thorac Surg 2012;94:212–5.

Journal of Surgical Oncology 2014;109:179–183

Does the Mode of Surgical Resection Affect the Prognosis/Recurrence in Patients With Thymoma?

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Background: Among the various controversies in the treatment strategies for patients with thymoma, the optimal mode of resection needs to be defined. To explore whether or not the mode of resection affects the prognosis/recurrence in patients with thymoma, we evaluated the treatment outcome of patients with resected thymoma.

Methods: One hundred seventy-three nonmyasthenic patients with stage I or II resected thymoma were studied. Patients were divided into two groups: a thymomectomy (resection of thymoma without total thymectomy) group (n = 100) and a thymothymomectomy (resection of thymoma with total thymectomy) group (n = 73). The differences in the clinicopathological characteristics and prognosis between the two groups were examined.

Results: Myasthenia gravis developed postoperatively in three patients (3%) in the thymomectomy group and in 6 (8%) in the thymothymomectomy group. The 5- and 10-year overall survival rates in the thymomectomy group were 96.7% and 92.2%, and those in the thymothymomectomy group were 94.0% and 86.2%, respectively ($P = 0.755$). Two patients (2%) in the thymomectomy group and 4 (5%) in the thymothymomectomy group experienced recurrence.

Conclusions: There was no difference in prognosis/recurrence between the two groups. Thymothymomectomy might not always be necessary for nonmyasthenic patients with stage I or II thymoma.

J. Surg. Oncol. 2014;109:179–183. © 2013 Wiley Periodicals, Inc.

KEY WORDS: **thymoma; surgery; thymomectomy; thymothymomectomy**

INTRODUCTION

Surgical resection is considered to be the mainstay of treatment for thymoma. With regard to the extent of resection, recent guidelines and reviews have recommended complete en-bloc resection of the tumor with the entire thymus gland (thymothymomectomy) [1–4]. Among several approaches for the surgical treatment of thymoma, median sternotomy is the most appropriate, since it can be difficult to easily and precisely perform thymothymomectomy through other approaches [5–7].

These surgical methods are standard treatment for thymoma with myasthenia gravis (MG), but the usefulness and necessity of these surgical methods for thymoma without MG have not been fully evaluated [8–10]. In fact, there has never been a prospective study on the surgical treatment of thymoma. Furthermore, several reports have shown that total thymectomy (thymothymomectomy) has not been performed in every patient with thymoma [11–13]. Therefore, as some authors have pointed out [13–15], the optimal surgical treatment for thymoma without MG remains unclear.

Most recently, Tseng et al. [16] compared the surgical results in early-stage nonmyasthenic thymoma patients who underwent thymomectomy with and without extended thymectomy and concluded that thymomectomy without thymectomy is justified in early stage nonmyasthenic thymoma patients. Further investigations are needed to evaluate their findings.

To explore whether or not the mode of resection affects the prognosis/recurrence in patients with thymoma, we evaluated the surgical outcome of nonmyasthenic patients with resected stage I or II thymoma.

METHODS

Patients and Clinical Evaluation

We reviewed the records of 219 patients who underwent resection for thymoma at the National Cancer Center Hospital in Tokyo, Japan, between January 1962 and December 2011. Of these 219 patients, those with stage III (n = 26) or stage IV (n = 17) thymoma were excluded. Among patients with stage I or stage II thymoma, three patients who had MG preoperatively were also excluded. The remaining 173 nonmyasthenic patients who had stage I or II thymoma were included in this study. The patients were divided into two groups: a thymomectomy group (n = 100) and a thymothymomectomy group (n = 73). With regard to the mode of resection, thymomectomy was defined as resection of thymoma leaving residual thymic tissue behind; thymothymomectomy was defined as resection of thymoma with the entire thymus as well as mediastinal fatty tissue between both phrenic nerves. There was indeed a trend for performing thymomectomy or thymothymomectomy. Before the 1980s, thymomectomy was performed in almost all patients with thymoma. From the early 1980s to the mid 1990s, thymothymomectomy through median sternotomy was mainly performed. After the introduction of VATS in the 1990s, thymomectomy by VATS was sometimes performed for patients with thymoma smaller than 5 cm. Over the past 10 years, thymomectomy by VATS or through an anterolateral mini-thoracotomy has been a standard procedure for nonmyasthenic patients with radiologically non-invasive thymoma smaller than 5 cm. Complete resection (R0) was defined as no macroscopic/microscopic residual tumor. Incomplete resection was defined as evident microscopic (R1)/macroscopic (R2) residual tumor.

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Received 28 June 2013; Accepted 23 October 2013

DOI 10.1002/jso.23499

Published online 19 November 2013 in Wiley Online Library (wileyonlinelibrary.com).

TABLE I. Characteristics of the Patients

Characteristic	Thymomectomy (n = 100)	Thymothymomectomy (n = 73)	*P*
Age (years)	57.7 ± 13.1	55.1 ± 12.5	0.108
Gender			0.453
Male	33 (33%)	29 (40%)	
Female	67 (67%)	44 (60%)	
Tumor size (cm)			0.094
Mean	5.7 ± 2.7	6.3 ± 2.4	
Range	1.2–16.0	1.5–17.0	
ITMIG stage			0.303
I	46 (46%)	27 (37%)	
II	54 (54%)	46 (63%)	
WHO histologic type			0.912
A	12 (12%)	9 (12%)	
AB	53 (53%)	40 (55%)	
B1	17 (17%)	9 (12%)	
B2	16 (16%)	14 (20%)	
B3	2 (2%)	1 (1%)	

ITMIG, International Thymic Malignancies Interest Group.

We defined recurrence as any evidence of tumor recurrence detected either by imaging or by pathologic examination during follow-up. The site of recurrence was defined according to the International Thymic Malignancies Interest Group (ITMIG) recommendation as either local (anterior mediastinum), regional (intrathoracic recurrence not contiguous with thymus or previous thymoma), or distant disease [17].

Histologic Type and Stage

In this retrospective study, the histologic type of thymoma was determined according to the WHO (2004) histologic classification, which includes six histologic subtypes for thymoma: Type A, B, AB, B1, B2, and B3 [18]. The tumor stage was determined according to the ITMIG stage classification [19], which can be summarized as follows: *Stage I*, grossly and microscopically encapsulated (i.e., the tumor has not spread beyond the thymus); *Stage II*, the thymoma invades beyond the capsule (outer boundary of the thymus) and into the nearby fatty tissue or the pleura (outer covering of the lung); *Stage III*, macroscopic invasion of neighboring organs; *Stage IVA*, pleural or pericardial dissemination; and *Stage IVB*, hematogenous or lymphatic dissemination.

Statistical Analyses

The associations between variables in each group were analyzed by either a Chi-square test or Mann–Whitney and Wilcoxon tests. Overall survival was defined as the time from the date of surgery to the date of death from any cause. Disease-free survival was defined as the time from the date of surgery to the date of the first recurrence of thymoma or death from any cause. Freedom-from-recurrence was defined as the time from the date of surgery to the date of the first recurrence. The survival curves were estimated by the Kaplan–Meier method, and the differences in survival were tested by the log-rank test. Reported *P* values were two-sided and those less than 0.05 were considered to indicate statistical significance. Statistical analyses were performed with the SPSS 11.0 statistical software program (Dr. SPSS II for Windows, standard version 11.0, SPSS, Inc., Chicago, IL).

RESULTS

The clinicopathological backgrounds of the two groups are summarized in Table I. There was no significant difference in age, sex ratio, tumor size, histologic subtype, or stage between the two groups.

With regard to the surgical approach, median sternotomy, anterolateral thoracotomy, or video-assisted thoracotomy (VATS) was planned based on the tumor size, location of the disease, and the presence or absence of invasion to neighboring structures. In the thymomectomy group, 58 patients (58%) underwent anterolateral thoracotomy, 41 (41%) underwent VATS, and 1 (1%) underwent median sternotomy. In the thymothymomectomy group, 72 patients (99%) underwent median sternotomy, and 1 (1%) underwent VATS.

None of the patients in either group received preoperative therapy. One patient (1%) in the thymomectomy group received postoperative radiation therapy at 50 Gy. Two patients in the thymothymomectomy group received postoperative radiation therapy: 1 at 40 Gy and 1 at 50 Gy.

MG developed postoperatively in 3 patients (3%) in the thymomectomy group and in 6 (8%) in the thymothymomectomy group. The clinical characteristics of these nine patients with postoperative myasthenia gravis are summarized in Table II. Of these nine patients, eight patients were treated with anti-cholinesterase or steroids and improved. The clinical course of the other one patient was unknown.

The mean follow-up time was 9 years (range: 0.1–32 years) in the thymomectomy group and 9 years (range: 0.1–23 years) in the thymothymomectomy group. Overall survival curves according to the mode of resection are shown in Figure 1. The 5- and 10-year survival rates in the thymomectomy group were 96.7% and 92.2%, and those in the thymothymomectomy group were 94.0% and 86.2%, respectively, and the difference between the two groups was not statistically significant (log-rank test, $P = 0.755$). Figure 2 shows the disease-free survival curves. The 5- and 10-year survival rates in the thymomectomy group were 95.4% and 90.8%, and those in the thymothymomectomy group were 92.5% and 83.6%, respectively, and the difference between the two groups was not statistically significant (log-rank test, $P = 0.371$). The freedom-from-recurrence curves are shown in Figure 3. The 5- and 10-year freedom-from-recurrence rates in the thymomectomy group

TABLE II. Clinical Characteristics of the Patients With Postoperative Myasthenia Gravis

Patient	Gender	Age	Size (cm)	Mode of resection	WHO histologic type	Stage	Interval (months)	Recurrence
1	Female	63	8.0	Thymomectomy	AB	II	3	None
2	Female	73	6.5	Thymomectomy	B1	I	12	None
3	Male	29	7.0	Thymothymomectomy	A	I	18	None
4	Female	63	4.8	Thymomectomy	B2	II	24	None
5	Female	72	7.0	Thymothymomectomy	AB	II	44	None
6	Female	58	6.0	Thymothymomectomy	B2	II	50	None
7	Female	51	6.0	Thymothymomectomy	AB	II	60	None
8	Female	28	11.0	Thymothymomectomy	B2	II	72	Local
9	Female	62	7.0	Thymothymomectomy	AB	I	102	None

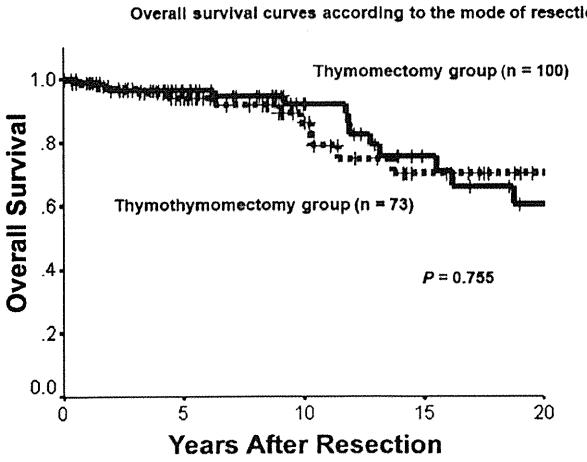

Fig. 1. Overall survival curves for the thymomectomy and thymothymomectomy groups.

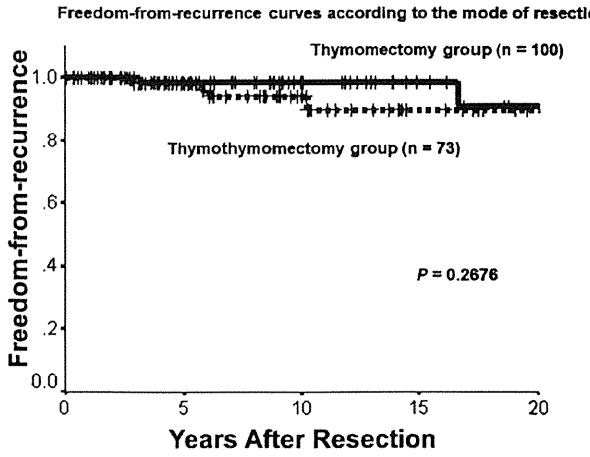

Fig. 3. Freedom-from-recurrence curves for the thymomectomy and thymothymomectomy groups.

were 98.7% and 98.7%, and those in the thymothymomectomy group were 98.5% and 94.1%, respectively, and the difference between the two groups was not statistically significant (log-rank test, $P = 0.266$). Two patients (2%) in the thymomectomy group and 4 (5%) in the thymothymomectomy group experienced recurrence. The sites of initial recurrence in the thymomectomy group were local in one patient and distant in 1, and those in the thymothymomectomy group were local in 1, regional (pleural dissemination) in 1, and distant in 2. The details of the patients with recurrence are shown in Table III. Only one (1%) patient in the thymomectomy group had a local recurrence, and the details have been described previously [20].

During the follow-up period, 16 deaths occurred in the thymomectomy group. Of these, 6 died of another malignancy, 2 of pneumonia, 2 of heart disease, 1 of renal failure, and 5 of unknown causes. In contrast, 11 deaths occurred in the thymothymomectomy group. Of these, 3 died of another malignancy, 2 of heart disease, 1 of pneumonia, 1 of brain disease, and 4 of unknown causes. None of the patients died of thymoma-related causes.

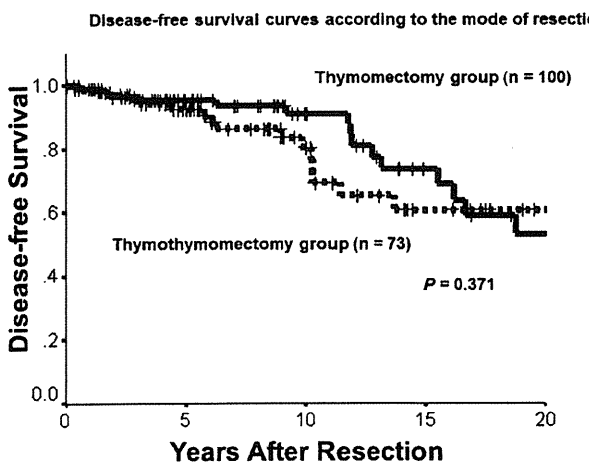

Fig. 2. Disease-free survival curves for the thymomectomy and thymothymomectomy groups.

DISCUSSION

In 1936, Blalock performed the first trans-sternal thymectomy for a 19-year-old woman with MG and a thymic tumor [21]. Since then, his landmark resection has been a standard surgical procedure for patients with thymoma. Median sternotomy is thought to be the most suitable approach, and other approaches can prove challenging for total thymectomy (thymothymomectomy) [5–7]. Therefore, complete surgical resection of the entire thymus gland through median sternotomy is strongly recommended for the resection of thymoma [2–4].

However, these recommendations were established based on retrospective cohort studies, and there have never been any prospective trials that focused on prognostic differences between thymomectomy and thymothymomectomy. Furthermore, with regard to the mode of resection in several previous reports, total thymectomy (thymothymomectomy) was not performed in every patient with thymoma [11–13], especially in those without MG.

To date, there has been only one study on the mode of resection for thymoma [22], and the authors concluded that limited thymectomy (thymomectomy) that avoided total thymectomy (thymothymomectomy) can be indicated for stage I or II thymoma. In our previous report, there was no difference in survival between patients who underwent total thymectomy (thymothymomectomy) and those who underwent thymomectomy [20]. Since then, thymomectomy by VATS or through an anterolateral mini-thoracotomy has been the standard procedure for nonmyasthenic patients with radiologically non-invasive thymoma smaller than 5 cm in our institution. As several authors have mentioned, the optimal mode of resection for thymoma without MG remains controversial [13–15]. Most recently, Tseng et al. compared the surgical results in early stage nonmyasthenic thymoma patients who underwent thymomectomy with and without extended thymectomy. They concluded that thymomectomy without thymectomy, through thoracotomy or VATS, is justified in early-stage nonmyasthenic thymoma patients [16]. Their findings need to be verified.

Meanwhile, it is not yet clear why thymothymomectomy should be performed in nonmyasthenic patients with thymoma. We think that there are at least three arguments for the necessity of thymothymomectomy in patients with thymoma.

The first argument is the occurrence of MG after the resection of thymoma. Several authors have stated that the prevention of postoperative MG is the most important rationale behind the necessity for thymothymomectomy in every patient with thymoma [23,24]. In fact, in

TABLE III. Clinicopathologic Features of the Patients Who Had Tumor Recurrence

Patient	Gender	Age	Size (cm)	Mode of resection	WHO histologic type	Stage	Site	Interval to recurrence from operation	Treatment for recurrent tumors	Outcome
1	F	36	8.5	Thymomectomy	A	I	Local	16 years	Resection	Alive at 32 years
3	F	58	7.0	Thymomectomy	AB	II	PM	3 years	Resection	Alive at 19 years
4	F	28	11.0	Thymothymomectomy	B2	II	Local	6 years	Resection and RT	Alive at 11 years
2	M	59	10.0	Thymothymomectomy	A	I	PM	3 years	Resection and CT	Alive at 9 years
5	M	47	5.5	Thymothymomectomy	B3	II	PM	10 years	Resection	Alive at 20 years
6	F	46	8.5	Thymothymomectomy	B2	II	PD	6 years	Resection	Alive at 16 years

PM, pulmonary metastasis; PD, pleural dissemination; CT, chemotherapy; RT, radiation therapy.

the present study, MG developed in six patients (5%) after thymomectomy, but this incidence was not as high as that in the thymothymomectomy group (8%). Kondo and Monden [25] and Sun et al. [26] examined the frequency of postoperative MG according to the mode of resection and concluded that total thymectomy (thymothymomectomy) did not prevent postoperative MG. Furthermore, for the treatment of postoperative MG, the remnant thymus can be removed by complete (extended) thymectomy via median sternotomy. Thus, from the perspective of preventing postoperative MG, thymothymomectomy is not always necessary for nonmyasthenic patients with thymoma.

The second argument is the possibility of an increase in the rate of local recurrence in the remnant thymus gland. In several previous reports, the rate of local recurrence after the resection of thymoma was less than 5% [20,27–31]. In this study, only one patient (1%) in the thymomectomy group experienced local recurrence. If we consider its indolent nature, when the tumor is completely encapsulated, it should be possible to achieve curative resection by only thymomectomy.

The third argument is the presence of multiple thymomas, especially those that are microscopic. Suzuki and colleagues reviewed 16 patients with multiple thymomas [32]. Of these patients, 14 had macroscopic multiple thymomas. The remaining two patients had both a macroscopic tumor and a microscopic tumor. One patient had two tumors that measured 23 and 2 mm in diameter. The other patient had two tumors that measured 58 and 0.5 mm in diameter. None of the patients in the present study had a microscopic tumor. The incidence of patients who have both a macroscopic and a microscopic thymoma seems to be extremely low. Furthermore, we repeatedly emphasize that metachronous thymoma can be resected by complete thymectomy after thymomectomy. Hence, thymothymomectomy may not be appropriate for all patients with thymoma based on the potential for multiple thymomas.

This study has several limitations, including its retrospective nature and the long observation period (almost 50 years). In addition, the mode of resection was determined depending on the tumor size, location of the tumor, the presence or absence of invasion to neighboring structures, and each surgeon's decision at the time of the procedure. Furthermore, similar to several previous reports [16,22], this study included a relatively small number of patients. Thus, the findings in all of these studies should be tested and validated in a larger population.

There was no difference in prognosis/recurrence between the thymomectomy and thymothymomectomy groups, although there might be a selection bias regarding the mode of surgical resection. To precisely define the role of the surgical mode of resection on the prognosis of patients with thymoma, a prospective study might be necessary.

CONCLUSION

Patients with thymomectomy had an outcome equivalent to that in patients with thymothymomectomy. The results of the present study suggest that thymothymomectomy might not always be necessary as the surgical mode for nonmyasthenic patients with stage I or II thymoma.

REFERENCES

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology—Thymomas and thymic carcinomas. V. 2. 2013. Available at: http://www.nccn.org/professionals/physician_gls/PDF/thymic.pdf.
2. Falkson CB, Bezjak A, Darling G, et al.: The management of thymoma: A systematic review and practice guideline. J Thorac Oncol 2009;4:911–919.
3. Tomaszek S, Wigle DA, Keshavjee S, et al.: Thymomas: Review of current clinical practice. Ann Thorac Surg 2009;87: 1973–1980.
4. Girard N, Mornex F, Van Houtte P, et al.: Thymoma: A focus on current therapeutic management. J Thorac Oncol 2009;4: 119–126.
5. Block MI: Thymic tumors, Chapter 63. In: Peason FG, Ginsberg RJ, Cooper JD, et al., editors: Thoracic surgery. New York: Churchill Livingstone; 2002;pp. 1682–1710.
6. Thomas CR, Wright CD, Loehrer PJ: Thymoma: State of the art. J Clin Oncol 1999;17:2280–2289.
7. Wilkins EW, Jr., Grillo HC, Scannell JG, et al.: Role of staging in prognosis and management of thymoma. Ann Thorac Surg 1991;51:888–892.
8. Masaoka A, Monden Y, Nakahara K, et al.: Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485–2492.
9. Wilkins EW, Jr., Castleman B: Thymoma: A continuing survey at the Massachusetts General Hospital. Ann Thorac Surg 1979;28:252–256.
10. Katz RI, Joseph WL, Mulder DG: Surgery of the thymus. Ann Thorac Surg 1968;6:591–605.
11. Regnard J-F, Magdeleinat P, Dromer C: Prognostic factors and long term results after thymoma resection: A series of 307 patients. J Thorac Cardiovasc Surg 1996;112:376–384.
12. Blumberg D, Port JL, Weksler B, et al.: Thymoma: A multivariate analysis of factors predicting survival. Ann Thorac Surg 1995;60:908–913.
13. Maggi G, Casadio C, Cavallo A, et al.: Thymoma: Results of 241 operated cases. Ann Thorac Surg 1991;51:152–156.
14. Koppitz H, Rockstroh JK, Schüller H, et al.: State-of-the-art classification and multimodality treatment of malignant thymoma. Cancer Treat Rev 2012;38:540–548.
15. Venuta F, Rendina EA, Anile M, et al.: Thymoma and thymic carcinoma. Gen Thorac Cardiovasc Surg 2012;60:1–12.
16. Tseng YC, Hsieh CC, Huang HY, et al.: Is thymectomy necessary in nonmyasthenic patients with early thymoma? J Thorac Oncol 2013;8:952–958.
17. Huang J, Detterbeck FC, Wang Z, et al.: Standard outcome measures for thymic malignancies. J Thorac Oncol 2011;6:S1691–S1697.
18. Travis WD, Brambilla E, Mueller-Hermelink HK, et al.: Pathology and genetics of tumors of the lung pleura, thymus and heart. Lyon: IARC Press; 2004.

19. Diagnosis, Staging, & Classification [the International Thymic Malignancies Interest Group Web site]. Available at: http://www.itmig.org/. Accessed June 1, 2013.
20. Nakagawa K, Asamura H, Matsuno Y, et al.: Thymoma: A clinicopathologic study based on the new World Health Organization classification. J Thorac Cardiovasc Surg 2003;126:1134–1140.
21. Blalock A, Mason MF, Morgan HJ, et al.: Myasthenia gravis and tumors of the thymic region: Report of a case in which the tumor was removed. Ann Surg 1939;110:544–561.
22. Onuki T, Ishikawa S, Iguchi K, et al.: Limited thymectomy for stage I or II thymomas. Lung Cancer 2010;68:460–465.
23. Weissberg D, Goldberg M, Pearson FG: Thymoma. Ann Thorac Surg 1973;16:141–147.
24. Soutter L, Sommers S, Relman AS, et al.: Problems in the surgical management of thymic tumors. Ann Surg 1957;146:424–438.
25. Kondo K, Monden Y: Myasthenia gravis appearing after thymectomy for thymoma. Eur J Cardiothorac Surg 2005;28:22–25.
26. Sun XG, Wang YL, Liu YH, et al.: Myasthenia gravis appearing after thymectomy. J Clin Neurosci 2011;18:57–60.
27. Zisis C, Rontogianni D, Tzavara C, et al.: Prognostic factors in thymic epithelial tumors undergoing complete resection. Ann Thorac Surg 2005;80:1056–1062.
28. Bedini AV, Andreani SM, Tavecchio L, et al.: Proposal of a novel system for the staging of thymic epithelial tumors. Ann Thorac Surg 2005;80:1994–2000.
29. Rena O, Papalia E, Maggi G, et al.: World Health Organization histologic classification: An independent prognostic factor in resected thymomas. Lung Cancer 2005;50:59–66.
30. Wright CD, Wain JC, Wong DR, et al.: Predictors of recurrence in thymic tumors: Importance of invasion, World Health Organization histology, and size. J Thorac Cardiovasc Surg 2005;130:1413–1421.
31. Kondo K, Monden Y: Therapy for thymic epithelial tumors: A clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003;76:878–884.
32. Suzuki H, Yoshida S, Hiroshima K, et al.: Synchronous multiple thymoma: Report of three cases. Surg Today 2010;40:456–459.