evaluate the variables identified as significant predictors of survival.

Results

Table 1 summarizes the clinical characteristics of the 29 patients. The study population consisted of 25 men and 4 women, with a median age at diagnosis of 60.5 years. Most (25/29; 89 %) patients had neurologic symptoms, including headaches, ataxia, and paralysis. Fifteen patients had a solitary brain metastasis and 14 had multiple (two to five) metastatic lesions.

The pulmonary resection procedure was lobectomy for 27 patients and pneumonectomy for 2 patients. Pathological T1 disease was diagnosed in 7 patients, T2 disease in 12, T3 disease in 7, and T4 disease in 3. Lymph node metastasis was found in 14 patients, as N1 disease in 4 and N2 disease in 10. The histopathologic subtype was adenocarcinoma in 19 patients and other subtypes in 10. Eighteen of the patients received preoperative or postoperative chemotherapy. The other patients did not receive adjuvant chemotherapy because their performance status was poor. The therapeutic modalities used to treat brain metastasis included brain surgery only in 12 patients, brain surgery plus whole brain radiotherapy (WBRT) in 12 patients, and stereotactic radiosurgery (SRS) in 5 patients.

The median follow-up time from surgery for the primary lesion was 9.6 months (range 3–107 months) and the 5-year overall survival rate was 20.6 % (Fig. 1). In this series, recurrence developed in 23 patients: intrathoracically in 8, intracranially in 7, and at other distant sites in 15. Six patients had multiple metastases and 7 patients had intracranial recurrence. Of these seven patients, five underwent craniotomy followed by WBRT and two received SRS only. One patient died of aspiration pneumonia 4 months after undergoing pulmonary resection.

Table 2 summarizes the results of univariate regression analysis, according to which a high CEA level, large tumor size, and mediastinal lymph node involvement significantly affected survival after treatment. The median overall survival was 7.3 months for the patients with a high CEA level vs. 20.6 months for those with a normal CEA level; 6.2 months for the patients with mediastinal lymph node involvement vs. 16.6 months for those without mediastinal lymph node involvement; and 8.2 months for the patients with tumors larger than 5 cm in size vs. 16.2 months for those with a smaller tumor These differences were significant ($p < 0.05$). Figure 2 shows the Kaplan–Meier survival plots generated from curves stratified according to the CEA level, tumor size, and lymph node status. Multivariate analysis also revealed that these factors significantly affected the 5-year survival (Table 3). Age, sex, histological tumor type, the number of brain metastases and the presence of symptoms caused by brain metastasis did not significantly affect the survival. Analysis of the relationship between several factors and disease-free survival (DFS) revealed that in addition to the prognostic factors, a high CEA level and large tumor size were possible risk factors for recurrence (Tables 4, 5).

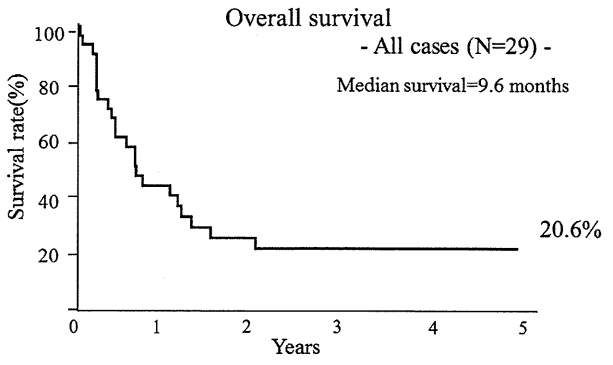

Fig. 1 Kaplan–Meier survival curves for the entire cohort

Table 2 Results of univariate analysis of the prognostic factors for survival

	Cases	HR	*p* value	Median survival (months)
Gender				
Male/female	25/4	1.61	0.12	8.3/16.3
CEA (ng/ml)				
<5.0/≥5.0	14/15	10.3	0.01	20.6/7.3
Tumor size				
<5 cm/≥5 cm	19/10	4.37	0.03	16.5/8.2
pN				
N0 or N1/N2	19/10	4.63	0.03	16.6/6.2
Histologic type				
Ad/others	19/10	1.27	0.38	8.8/9.8
Brain metastasis				
Single/multiple	15/14	1.11	0.77	8.8/9.4
Symptoms from brain tumor				
Yes/no	25/4	1.09	0.29	8.9/9.7
Perioperative chemotherapy				
Any/none	18/11	0.82	0.36	8.9/8.8
Treatment date				
~ 1999/2000 ~	13/16	0.78	0.37	9.6/13.1

HR hazard ratio

Postoperative recurrence developed in 23 of the 29 patients. The site of the first recurrence was extracranial in 8 (26 %) patients, intracranial in 7 (24 %) and other in 15 (52 %). Table 6 outlines the relationships between the prognostic factors and recurrence rates. The rate of

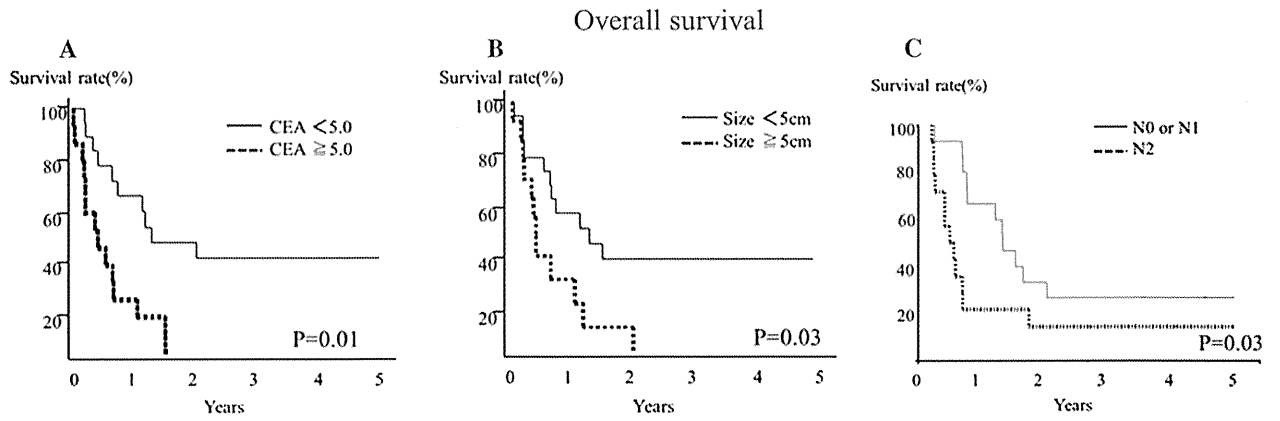

Fig. 2 **a** Kaplan–Meier survival curves for the patients with brain metastasis according to the CEA level (**a**), tumor size (**b**), and lymph node status (**c**)

Table 3 Results of multivariate analysis of the prognostic factors for survival

Factor	Odds ratio (95 % CI)	*p* value
CEA (ng/ml)		
<5.0/≥5.0	3.451 (1.336–8.915)	0.01
Tumor size		
<5 cm/≥5 cm	4.279 (1.591–11.504)	0.01
pN		
N0 or N1/N2	2.890 (1.027–8.139)	0.04

CI confidence interval

Table 4 Results of univariate analysis of risk factors for recurrence

	Cases	*p* value	Median DFS (months)
Gender			
Male/female	25/4	0.16	4.2/13.2
CEA (ng/ml)			
<5.0/≥5.0	14/15	0.01	6.3/1.9
Tumor size			
<5 cm/≥5 cm	19/10	0.03	5.1/2.1
pN			
N0 or N1/N2	19/10	0.05	5.3/2.3
Histologic type			
Ad/others	19/10	0.11	3.7/4.0
Brain metastasis			
Single/multiple	15/14	0.50	5.7/3.7
Symptoms from brain tumor			
Yes/no	25/4	0.54	3.7/5.3
Perioperative chemotherapy			
Any/none	18/11	0.25	4.6/2.9

DFS disease-free survival

intracranial recurrence was significantly higher in the patients with a high CEA level than in those with a normal CEA level. In turn, the rate of intrathoracic recurrence was

Table 5 Results of multivariate analysis of risk factors for recurrence

Factor	Odds ratio (95 % CI)	*p* value
CEA (ng/ml)		
<5.0/≥5.0	3.834 (1.395–10.532)	0.01
Tumor size		
<5 cm/≥5 cm	4.058 (1.415–11.552)	0.01
pN		
N0 or N1/N2	2.454 (0.849–7.032)	0.09

CI confidence interval

Table 6 Patterns of postoperative recurrence

Factor	Recurrence	Type of recurrence		
		Intracranial	Extracranial	Others
CEA (ng/ml)				
<5.0/≥5.0	8 (57 %)/15 (100 %)	1 (7 %)/6 (40 %)	3 (21 %)/5 (33 %)	6 (44 %)/9 (60 %)
Tumor size				
5 cm/≥5 cm	14 (73 %)/9 (90 %)	6 (26 %)/2 (20 %)	3 (16 %)/5 (50 %)	9 (47 %)/6 (60 %)
pN				
N0 or N1/N2	14 (73 %)/9 (90 %)	4 (20 %)/3 (30 %)	5 (26 %)/3 (30 %)	8 (43 %)/7 (70 %)
Total	23 (79 %)	7 (24 %)	8 (26 %)	15 (52 %)

significantly higher in the patients with a large tumor than in those with a smaller tumor. The rate of extracranial and extrathoracic recurrence was higher in the patients with mediastinal lymph node metastasis than in those without mediastinal lymph node metastasis. Finally, the rate of extracranial recurrence tended to be higher among all groups of patients with unfavorable prognostic factors than in those without unfavorable prognostic factors.

Discussion

After more than a decade of research, the treatment of stage IV NSCLC patients with synchronous brain metastasis continues to be debated. The development of brain metastasis is usually a fatal event in the natural history of NSCLC. The median overall survival of patients who undergo resection of brain metastases from lung cancer is 4–7.7 months [15]; however, several reports have indicated that the survival of patients with a single synchronous brain metastasis from NSCLC was significantly improved by resection of both the lung and brain tumors [16]. In a surgical series, Billing and colleagues argued that patients with synchronous brain metastasis and lung cancer without nodal involvement should be treated with dual resection if medically fit [8]. Although it is intuitively apparent that some patients will benefit from aggressive treatment of brain metastasis, it remains unclear which patients should be treated and how.

Synchronous brain and lung resection series are generally very few in number. Torre et al. [17] reported a series of 27 patients with synchronous single brain metastasis from lung cancer, in which the overall 5-year survival rate was 15 %. Similar results were achieved with bifocal surgery and WBRT in a study reported by Rossi et al. [18], of 40 patients with single brain lesions, in which the overall 5-year survival rate was 12.5 %.

Several investigators have studied promising prognostic factors for NSCLC patients with a single brain metastases. Iwasaki et al. [19] reported that the serum CEA level is a significant prognostic factor for these patients. In their study, the 5-year survival of patients with a high CEA level was 0 vs. 39.6 % for those with a normal CEA level. Similarly, in our study, the 5-year survival of patients with a high serum CEA level was also 0 vs. 38 % for those with a normal serum CEA level ($p = 0.01$). Moreover, postoperative recurrence developed in only 8 (57 %) of the 14 patients with a normal CEA level vs. all of those with a high CEA level. Considering the relationship between the CEA level and the recurrence rate, elevation of the serum CEA level may indicate the potential for recurrence. This may explain why the CEA level is an independent prognostic factor for these patient groups.

Bonnette et al. [9] argued that the histology of the cancer affects the survival of patients treated with resection for solitary brain metastases, finding that patients with adenocarcinoma had significantly longer survival than those with squamous or large cell carcinoma ($p = 0.019$). In contrast, Mussi et al. [20] found that patients with squamous cell carcinoma had longer survival than those with adenocarcinoma. In our cohort, we were unable to demonstrate significant differences between the survival of patients with adenocarcinoma vs. that of those with other histological types. This study targets a unique population. In our group, the tumors exhibited a high level of metastatic potential regardless of the histological type, which may explain why the histological type did not affect the survival.

In recent years, the use of an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) against brain metastasis has become an important issue, with several authors reporting its high efficacy against brain metastasis in NSCLC patients harboring an activating EGFR mutation [21, 22]. In our institution, patients with adenocarcinoma have been routinely screened for mutations in the EGFR gene since 2004 and we anticipate that more patients will be treated with EGFR-TKI in the future. Thus, the prognosis of this study's cohort will be affected by the prevalence of tyrosine kinase inhibitors.

We found tumor size to be another prognostic factor of survival in this series, with 5-year survival rates of 0 vs. 37 % for patients with large tumors (>5 cm) vs. those with smaller tumors (<5 cm; $p = 0.03$). To the best of our knowledge, no previous reports have demonstrated a relationship between tumor size and prognosis. We also found lymph node status to be a prognostic factor for survival in this series, with 5-year survival rates of 27 vs. 10 % for patients with pathological N0 or N1 disease vs. those with mediastinal lymph node metastasis ($p = 0.03$). This finding is consistent with the results of previous studies evaluating the surgical treatment of pulmonary and brain metastatic tumors [8, 17, 18]. Billing et al. [8] reported that among patients treated with surgery for primary lung cancer and synchronous brain metastasis, the 5-year survival of those with N0 disease was 35 %, whereas no patients with lymph node involvement (N1 and N2) survived longer than 3 years ($p = 0.001$). In the present study, of the 10 patients with mediastinal lymph node metastasis (pathological N2), only 1 survived without recurrence for longer than 5 years. All of the remaining nine patients with pN2 disease suffered recurrence and none survived for 5 years. Considering this result, it is reasonable to conclude that patients with cN2 disease should not undergo aggressive treatment against both lung and brain tumors.

Our search of the literature found a few reports on the differences in outcomes of patients with single vs. those with multiple brain metastases. The majority of published series analyzed the outcomes of patients with single brain metastases, although Detterbeck et al. [23] reported that the number of brain metastases may not play a significant role, as long as it is small. We also did not find a significant difference in the survival of patients with single vs. those with multiple brain lesions in the present series. Of the 15 patients with a single brain metastasis, 2 (12 %) suffered intracranial recurrence and 9 (60 %) suffered extracranial recurrence. In contrast, of the 14 patients with multiple brain metastases, 5 (37 %) suffered intracranial recurrence

and 9 (65 %) suffered extracranial recurrence. There was little difference in the rate of extracranial recurrence between these two groups. In comparison with the management of intracranial recurrence, we were unable to effectively control intrathoracic and other organ recurrence in either group, which may account for the fact that there were no differences observed between these two groups. In contrast, among all groups of patients with unfavorable prognostic factors, the rate of extracranial recurrence tended to be higher than that in those without unfavorable prognostic factors (Table 6). Our results suggest that patients with synchronous brain metastasis and a primary tumor that can be both resected completely, or irradiated with SRS, should be considered as candidates for curative bifocal treatment, even if there is more than one brain metastasis.

Locoregional or distant recurrence developed in 23 of the 29 patients in this series and 1 patient died of aspiration pneumonia 4 months after undergoing pulmonary resection. As 15 patients suffered postoperative recurrence in distant organs, excluding intracranial lesions, such patients may require more aggressive adjuvant chemotherapy, although it has been debated whether perioperative chemotherapy improves the survival of NSCLC patients with synchronous brain metastasis. Most series reported in the literature do not document any improvements in survival with adjuvant chemotherapy. We also did not observe any differences in overall survival following the administration of perioperative chemotherapy, possibly because most of these patients were unable to receive sufficient chemotherapy due to their decreased quality of life after treatment for the brain tumors. However, given the high potential for postoperative recurrence in this cohort, these patients may benefit from perioperative chemotherapy, if this is feasible.

In conclusion, local control and improved survival rates can be achieved by aggressive surgical treatment of the primary tumor and synchronous brain metastasis in some NSCLC patients with stage IV brain metastasis. Although this study has several limitations such as a long interval, changed treatment for brain metastasis, and the availability of EGFR-TKI, our retrospective analyses have some practical implications. This study suggests that surgical resection may be beneficial for a select group of patients with a normal CEA level, a small primary tumor (<5 cm), and a node-negative status.

Conflict of interest Takashi Kanou and his co-authors have no conflicts of interest.

References

1. Quint LE, Tummala S, Brisson LJ, Francis IR, Krupnick AS, Kazerooni EA, et al. Distribution of distant metastases from newly diagnosed non-small cell lung cancer. Ann Thorac Surg. 1996;62(1):246–50.
2. Sorensen JB, Hansen HH, Hansen M, Dombernowsky P. Brain metastases in adenocarcinoma of the lung: frequency, risk groups, and prognosis. J Clin Oncol. 1988;6(9):1474–80.
3. Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. Int J Radiat Oncol Biol Phys. 1999;43(4):795–803.
4. Rodrigus P, de Brouwer P, Raaymakers E. Brain metastases and non-small cell lung cancer. Prognostic factors and correlation with survival after irradiation. Lung Cancer. 2001;32(2):129–36.
5. Takeshima H, Kuratsu J, Nishi T, Ushio Y. Prognostic factors in patients who survived more than 10 years after undergoing surgery for metastatic brain tumors: report of 5 cases and review of the literature. Surg Neurol. 2002;58(2):118–23 discussion 123.
6. Granone P, Margaritora S, D'Andrilli A, Cesario A, Kawamukai K, Meacci E. Non-small cell lung cancer with single brain metastasis: the role of surgical treatment. Eur J Cardiothorac Surg. 2001;20(2):361–6.
7. Burt M, Wronski M, Arbit E, Galicich JH. Resection of brain metastases from non-small-cell lung carcinoma. Results of therapy. Memorial Sloan-Kettering Cancer Center Thoracic Surgical Staff. J Thorac Cardiovasc Surg. 1992;103(3):399–410 discussion 410–391.
8. Billing PS, Miller DL, Allen MS, Deschamps C, Trastek VF, Pairolero PC. Surgical treatment of primary lung cancer with synchronous brain metastases. J Thorac Cardiovasc Surg. 2001; 122(3):548–53.
9. Bonnette P, Puyo P, Gabriel C, Giudicelli R, Regnard JF, Riquet M, et al. Surgical management of non-small cell lung cancer with synchronous brain metastases. Chest. 2001;119(5):1469–75.
10. Chidel MA, Suh JH, Greskovich JF, Kupelian PA, Barnett GH. Treatment outcome for patients with primary nonsmall-cell lung cancer and synchronous brain metastasis. Radiat Oncol Investig. 1999;7(5):313–9.
11. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet. 2004;363(9422):1665–72.
12. Endoh H, Yamamoto R, Satoh Y, Kuwano H, Nishizawa N. Risk analysis of pulmonary resection for elderly patients with lung cancer. Surg Today. 2013;43(5):514–20.
13. Okamoto T, Iwata T, Mizobuchi T, Hoshino H, Moriya Y, Yoshida S, et al. Surgical treatment for non-small cell lung cancer with ipsilateral pulmonary metastases. Surg Today. 2013;43(10): 1123–8.
14. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol. 2007;2(8):706–14.
15. Penel N, Brichet A, Prevost B, Duhamel A, Assaker R, Dubois F, et al. Prognostic factors of synchronous brain metastases from lung cancer. Lung Cancer. 2001;33(2–3):143–54.
16. Magilligan DJ Jr, Duvernoy C, Malik G, Lewis JW Jr, Knighton R, Ausman JI. Surgical approach to lung cancer with solitary cerebral metastasis: 25 years' experience. Ann Thorac Surg. 1986;42(4):360–4.
17. Torre M, Barbieri B, Bera E, Locicero S, Pieri Nerli F, Belloni PA. Surgical therapy in lung cancer with single brain metastasis. Eur J Cardiothorac Surg. 1988;2(5):336–9.
18. Rossi NP, Zavala DC, VanGilder JC. A combined surgical approach to non-oat-cell pulmonary carcinoma with single cerebral metastasis. Respiration. 1987;51(3):170–8.

19. Iwasaki A, Shirakusa T, Yoshinaga Y, Enatsu S, Yamamoto M. Evaluation of the treatment of non-small cell lung cancer with brain metastasis and the role of risk score as a survival predictor. Eur J Cardiothorac Surg. 2004;26(3):488–93.
20. Mussi A, Pistolesi M, Lucchi M, Janni A, Chella A, Parenti G, et al. Resection of single brain metastasis in non-small-cell lung cancer: prognostic factors. J Thorac Cardiovasc Surg. 1996; 112(1):146–53.
21. Park SJ, Kim HT, Lee DH, Kim KP, Kim SW, Suh C, et al. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation. Lung Cancer. 2012;77(3):556–60.
22. Bartolotti M, Franceschi E, Brandes AA. EGF receptor tyrosine kinase inhibitors in the treatment of brain metastases from non-small-cell lung cancer. Expert Rev Anticancer Ther. 2012;12(11): 1429–35.
23. Detterbeck FC, Jones DR, Kernstine KH, Naunheim KS. Lung cancer. Special treatment issues. Chest. 2003;123(1 Suppl):244S–58S.

Thin-section CT findings in peripheral lung cancer of 3?cm or smaller: are there any characteristic features for predicting tumor histology or do they depend only on tumor size?

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Thin-section CT findings in peripheral lung cancer of 3 cm or smaller: are there any characteristic features for predicting tumor histology or do they depend only on tumor size?

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Abstract

Background: Ground-glass opacity (GGO) is reported to be characteristic to lepidic growth of neoplasm in subsolid nodules. In solid nodules of lung cancer, however, there is no characteristic feature to be reported.

Purpose: To study if there are any thin-section CT findings characteristic to tumor histology or if they are only related to tumor size in solid nodules of the lung cancer.

Material and Methods: This study included 106 solid peripheral lung cancers of 3 cm or smaller (56 adenocarcinomas, 33 squamous cell carcinomas, and 17 small cell carcinomas) in which 16-slice CT with 1 mm collimation was performed before surgery. Six morphologic findings (presence or absence of lobulation, coarse spiculation, air bronchogram, cavity, pleural tag, and pleural-based lesion) and four measurements (ratio of the greatest transverse and vertical diameter to the shortest transverse diameter and density of lobulation and coarse spiculation) on thin-section CT images were evaluated. Density of lobulation (coarse spiculation) was defined as the ratio of lobulation (coarse spiculation) number to the greatest transverse diameter of a nodule.

Results: Air bronchogram ($P < 0.01$) was the only significant factor for predicting lung adenocarcinoma. The prevalence of air bronchogram was significantly greater in adenocarcinoma than in squamous cell carcinoma ($P < 0.01$) or small cell carcinoma ($P < 0.01$). As the tumor size advanced, significantly positive linear trends were seen in the prevalence of lobulation ($P < 0.01$), coarse spiculation ($P < 0.01$), and pleural tag ($P < 0.01$), and the mean values of density of lobulation ($P < 0.01$) and coarse spiculation ($P < 0.01$), while the significant negative linear trend was seen in the ratio of vertical diameter to the shortest transverse ($P = 0.02$).

Conclusion: Air bronchogram on thin-section CT is characteristic feature of solid adenocarcinoma of the lung. However, other thin-section CT findings are irrelevant to tumor histology and related only to tumor size.

Keywords
Lung neoplasms, air bronchogram, computed tomography, CT findings

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Introduction

According to recent global cancer statistics, lung cancer is the most common form of cancer and the leading cause of cancer death (1). As for the histology of lung cancer, adenocarcinoma, which accounts for 38.5% of

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all lung cancer, has become the most common histologic type, largely due to an increase in adenocarcinoma with lepidic growth, which usually shows ground-glass opacity (GGO) (2,3). Lepidic growth is defined as a growth restricted to neoplastic cells along pre-existing alveolar structures, lacking stromal, vascular, or pleural invasion (3). The advance of multislice computed technology has made it possible to detect small GGO nodules that were probably missed when only chest X-ray or thick-section computed tomography (CT) was available. This may partly explain the higher prevalence of adenocarcinoma among lung cancer in recent years (4).

Prognosis and treatment methods for patients with lung cancer depend on the results of histological examination of pulmonary carcinomas (5,6). It is therefore important to predict a likely histological classification of lung cancer with a non-invasive procedure, such as thin-section CT. If the lesion is neoplastic, GGO is related to tumor cell replacement or lepidic growth of the neoplasm. For this reason, GGO has been documented as characteristic of adenocarcinoma (7–14). There are several reports (15–18) on the evaluation of the prevalence of thin-section CT findings for the histology of individual cases of lung cancer, including squamous cell carcinoma, small cell carcinoma, large cell carcinoma, and adenosquamous carcinoma. To the best of our knowledge, however, there are no reports of studies which systematically investigated the prevalence of thin-section CT findings in relation to lung cancer subtypes.

The purpose of this study was to examine if any characteristic thin-section CT findings can predict tumor histology and if such features are related only to tumor size.

Material and Methods

This retrospective study was approved by our institutional review board and written informed consent for CT scans was obtained from all participants.

Subjects

We reviewed the medical and radiological records of patients who had been pathologically diagnosed with lung cancer which had been detected as solitary solid pulmonary nodules ($\leq$3 cm) on thin-section CT at our institution between January 2008 and October 2012. Patients were enrolled only if (a) preoperative, continuous thin-section CT scans of the chest were performed; (b) the nodules were surgically resected; and (c) findings of pathologic examination of the resected lung specimens were available. Histological diagnoses made by a pathologist with 20-year experience in surgical pathology (YT).

CT technology and image analysis

All scans were performed with a 16-slice CT scanner (Aquilion 16; Toshiba, Tokyo, Japan) in helical mode from the apex to the lung base. Technical parameters were: tube voltage, 120 kVp; X-ray tube current, 240–300 mA; rotation speed, 0.5 s; collimation, 1 mm; matrix, 512 × 512; bone reconstruction algorithm. Images were evaluated with the aid of a monitor at a window level of −600 HU and a window width of 1200 HU.

Without knowledge of the histologic diagnosis, two radiologists (BJ and ST, with 5 and 30 years of experience in chest radiology, respectively) independently evaluated the thin-section CT findings including presence or absence of lobulation, coarse spiculation, air bronchogram, cavity, pleural tag, or pleural-based lesion (Fig. 1). The following definitions were used for these findings. Lobulation: irregular undulation of the nodule margin; coarse spiculation: the presence of 2 mm or thicker strands extending from the nodule margin into the lung parenchyma without reaching the pleural surface; air bronchogram: a pattern of air-filled (low-attenuation) bronchi against a background of an opaque (high-attenuation) air-less lung; cavity: an air-filled space, seen as a lucency or low-attenuation area within a pulmonary nodule; pleural tag: as a linear or triangular strand originating from the nodule surface and reaching the pleural surface; pleural-based lesion: a nodule adhering to the pleura and with the diameter of the interface more than half that of the nodule. The final interpretation was based on a consensus of the two radiologists.

Also, both radiologists independently measured the greatest transverse, the shortest transverse, and the vertical diameter of each nodule and calculated the density of lobulation and coarse spiculation, the ratio of the greatest transverse and vertical diameter to the shortest transverse diameter. Density of lobulation (coarse spiculation) was defined as the ratio of lobulation (coarse spiculation) number to the greatest transverse diameter of a nodule. Averaged values of measurements were used for analyses in this study.

Statistical analysis

A kappa or Bland-Altman analysis was performed to assess the inter-observer agreement (19). Chi-square test or Kruskal-Wallis test was used for comparing three groups of data. The discriminant factors for subtypes of lung cancer were examined by means of discriminant analysis. A P value <0.05 was considered to be significant. All of the statistical calculations were performed with SPSS software (PASW Statistics 18; SPSS Inc., Chicago, IL, USA).

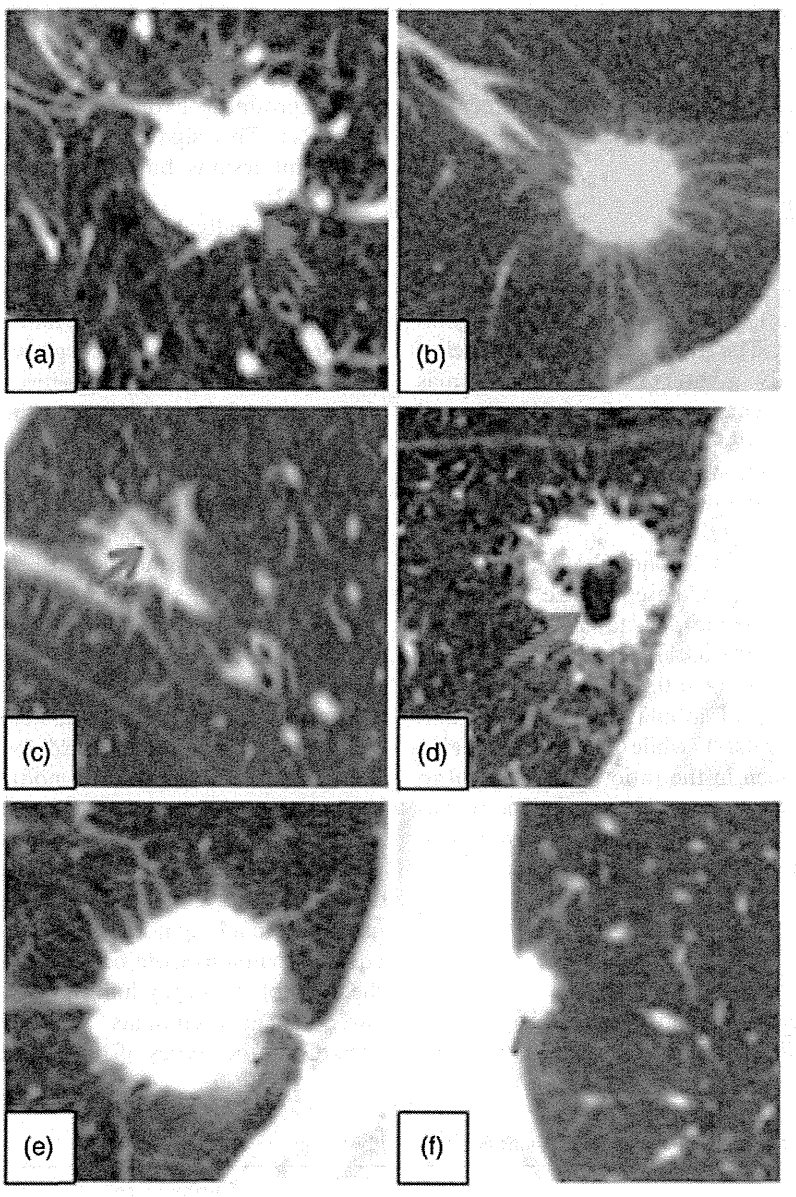

Fig. 1. Thin-section CT findings. (a) Lobulation; (b) coarse spiculation; (c) air bronchogram; (d) cavity; (e) pleural tag; (f) pleural-based lesion.

Results

Between January 2008 and October 2012, 331 patients underwent surgery at our hospital for primary lung cancers consisting of 258 adenocarcinomas, 38 squamous cell carcinomas, 17 small cell carcinomas, three large cell carcinomas, and 15 other lung carcinomas. Thin-section CT scans were available for 164 adenocarcinomas, 33 squamous cell carcinomas, and 17 small cell carcinomas. Of them, 52 nodules with pure GGO and 56 nodules with mixed GGO were excluded. Eventually, 106 solid pulmonary nodules (56 adenocarcinomas, 33 squamous cell carcinomas, and 17 small cell carcinomas) from 106 consecutive patients (76 men and 30 women; mean age, 67 ± 9.5 years) were included in this study.

Agreement between two observers

The kappa values for the two radiologists were 0.61 for lobulation, 0.72 for coarse spiculation, 0.78 for air bronchogram, 0.76 for cavity, 0.90 for pleural tag, and 0.94 for pleural-based lesion, indicating a moderate to excellent agreement (20). The 95% confidence

intervals (CI) of Bland-Altman analysis for the greatest transverse, the vertical, and the shortest transverse diameter were [−2.3, 6.3], [−3.4, 3.9], and [−2.8, 5.3], respectively, which represents an acceptable agreement between the measurements by the two radiologists.

Thin-section CT findings

Comparisons of thin-section CT findings of each histological examination of the lung cancer (Table 1) showed that air bronchogram ($P < 0.01$) was the only significantly different factor. The prevalence of air bronchogram was significantly greater in adenocarcinomas than in squamous cell carcinomas ($P < 0.01$) or small cell carcinomas ($P < 0.01$). The discriminant analysis showed air bronchogram was the discriminant factor for adenocarcinoma of the lung (classification function coefficient: 2.374; $P = 0.001$).

Thin-section CT findings for nodule size (Table 2) showed that, as the tumor increased in size, significant positive linear trends became detectable in the prevalence of lobulation ($P < 0.01$), coarse spiculation ($P < 0.01$) and pleural tag ($P < 0.01$), as well as in the mean values of density of lobulation ($P < 0.01$) and coarse spiculation ($P < 0.01$), while a significant negative linear trend was seen in the ratio of the vertical to the shortest transverse diameter ($P = 0.02$). The prevalence of adenocarcinoma, squamous cell carcinoma, and small cell carcinoma was unrelated to tumor size ($P = 0.224$).

Discussion

Characteristic thin-section CT findings of histology of lung cancer indicated that air bronchogram was the only significant factor for identification of adenocarcinoma in our study. The "air bronchogram" sign is a pattern of air-filled (low-attenuation) bronchi against a background of opaque (high-attenuation) airless lung (21). This sign can be seen in both benign and malignant lesions but shows a preference for malignancy (22).

Pathologically, lung cancer originates from the bronchial epithelium and has two major growth types: a replacement tumor growth of alveolar lining cells, and a compressive or destructive tumor growth (23). In the compressive or destructive growth type, tumor cells with a substantial proliferation and accumulation shape the endobronchial tumor tissue and this causes occlusion of the bronchus. In the replacement growth type, tumor cells creep outward and extend by way of alveolar pores along the alveolar wall and alveolar septa, eventually producing the air bronchogram sign. Therefore, air bronchogram can be seen more often in tumors with predominant replacement or lepidic growth than in tumors with predominant expansive growth (Fig. 2).

Several articles (24–26) have focused on the clinical aspects of air bronchogram and confirmed this sign was characteristic of adenocarcinoma. For example, Kuriyama et al. studied 40 nodules, 20 adenocarcinomas, and 20 benign lesions, with a diameter of <2 cm and found that the prevalence of air bronchogram was 65% in adenocarcinomas but only 5% in benign lesions (24). They concluded the air bronchogram sign in a lung nodule was useful for differentiating adenocarcinomas from benign lesions. However, size of their sample was only half of ours, and they only compared adenocarcinomas with benign lesions, thus excluding other types of lung cancer.

Table 1. Relationship between thin-section CT findings and tumor histology.

	Adenocarcinoma ($n = 56$)	Squamous cell carcinoma ($n = 33$)	Small cell carcinoma ($n = 17$)	*P* value
Prevalence (%)				
Lobulation	68%	85%	82%	0.153
Coarse spiculation	45%	45%	47%	0.984
Air bronchogram	29%	3%	0%	0.001
Cavity	21%	30%	6%	0.139
Pleural tag	63%	52%	53%	0.548
Pleural-based lesion	30%	24%	18%	0.549
Measurement (mean ± SD)				
Density of lobulation	0.21 ± 0.18	0.25 ± 0.18	0.23 ± 0.16	0.634
Density of coarse spiculation	0.06 ± 0.09	0.05 ± 0.07	0.06 ± 0.07	0.638
Ratio of the greatest to the shortest transverse	1.31 ± 0.28	1.26 ± 0.21	1.21 ± 0.13	0.257
Ratio of vertical to the shortest transverse	1.33 ± 0.42	1.19 ± 0.25	1.14 ± 0.32	0.107

In addition, characteristic thin-section CT findings have also been explored for other histological studies of lung cancer with a limited number of patients (only 12–27 patients in each study) (15–18). According to these reports, the prevalence of lobulation, coarse spiculation, cavity, pleural indentation, and air bronchogram varied in squamous cell carcinoma, small and large cell carcinoma, and adenosquamous carcinoma. However, the prevalence of thin-section CT findings based on lung cancer subtypes was not investigated systematically in these studies.

Thin-section CT findings for nodule size in our study showed a significant positive linear trend in the prevalence of lobulation, coarse spiculation, pleural tag, or density of notch and coarse spiculation, but a negative linear trend in the ratio of vertical to the shortest transverse diameter. As far as we know, there is nothing in the literature about this finding.

Tumor cells feature heterogeneous differentiation and growth rates in the margin of the tumor, which is surrounded by heterogeneous tissue structures. As the tumor cells grow, the heterogeneity of the micro-environment within and around the tumor becomes more and more significant, resulting in an increase in the prevalence of lobulation (27). In addition, due to a desmoplastic response, coarse fibrotic strands radiating from the tumor margin invade the lung and form coarse spiculation or pleural tag. This phenomenon may also be secondary to direct tumor extension along interstitial planes or a consequence of lymphangitic spread of the tumor (28). With the tumor enlargement resulting in a more manifest response, the prevalence of observed coarse spiculation and pleural tag increases. Density of lobulation and coarse spiculation can share the same principle with the lobulation and coarse spiculation. The gradual changes in the ratio of the vertical to the shortest transverse diameter indicate that the tumor is becoming rounder as it grows. Although coarse spiculation was reported to be related to the risk of malignancy (29), it was found to be unrelated to lung cancer subtypes in this study.

Our study demonstrated that thin-section CT was useful for histologically distinguishing adenocarcinoma from other peripheral solid lung cancer because the

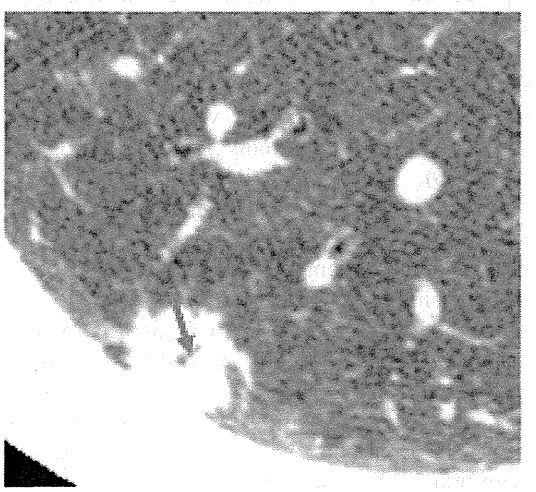

Fig. 2. Adenocarcinoma with air bronchogram in a 65-year-old woman. Thin-section CT demonstrated a solid nodule of 15 mm with air bronchogram (arrow). Pathology confirmed it was non-mucinous minimally invasive adenocarcinoma without lymphatic or vascular invasion.

Table 2. Relationship between thin-section CT findings and tumor size.

	≤1.0 cm ($n=9$)	>1.0 cm and ≤2.0 cm ($n=59$)	>2.0 cm and ≤3.0 cm ($n=38$)	*P* value
Prevalence (%)				
Lobulation	23%	68%	100%	<0.001
Coarse spiculation	11%	31%	76%	<0.001
Air bronchogram	0%	24%	8%	0.045
Cavity	11%	25%	18%	0.518
Pleural tag	44%	49%	74%	0.041
Pleural-based lesion	11%	27%	29%	0.542
Measurement (mean ± SD)				
Density of lobulation	0.05 ± 0.09	0.18 ± 0.18	0.33 ± 0.18	<0.001
Density of coarse spiculation	0.02 ± 0.07	0.04 ± 0.07	0.10 ± 0.09	<0.001
Ratio of the greatest to the shortest transverse	1.24 ± 0.09	1.33 ± 0.32	1.23 ± 0.14	0.128
Ratio of vertical to the shortest transverse	1.36 ± 0.20	1.33 ± 0.44	1.12 ± 0.25	0.021

presence of air bronchogram on thin-section CT is characteristic of solid adenocarcinoma of the lung. The prognosis of patients with non-small cell lung carcinoma (NSCLC) is better than that of patients with small cell lung cancer (SCLC), and those with NSCLC, while the prognosis of adenocarcinoma with GGO is better than that of NSCLC with a different histology (2). From a pathological point of view, nodules with air bronchogram can represent an intermediate form in the development from GGOs to pure solid lesions. The presence of air bronchogram can therefore be considered as a favorable prognostic factor. Furthermore, if the hypothesis can be confirmed that prognosis of peripheral lung cancer with air bronchogram is not worse than that of nodular GGO or adenocarcinoma of <2 cm, peripheral lung cancer with air bronchogram can be treated with minimally invasive thoracic surgery (MITS), which has the usual advantages of less invasive approaches for patients with lung cancer (30).

We are able to demonstrate that thin-section CT can provide important information for predicting the histology of lung cancer, as well as the prognosis and appropriate treatment methods for patients with peripheral solid lung cancer. Thin-section CT is also useful for reaching a rational histological diagnosis for patients with lung cancer who are not candidates for surgical resection or who are not willing to undergo surgery. To the best of our knowledge, ours is the first report of a systematic evaluation of thin-section CT findings based on histological findings of lung cancer. We were able to confirm that bronchogram is characteristic of solid adenocarcinoma, while other thin-section CT findings are irrelevant for tumor histology and related only to tumor size.

There are a few limitations to our study. First, no patients with large cell carcinoma or adenosquamous carcinoma were included in our study so that the spectrum of disease was not complete. However, such carcinomas actually rarely encounter in a clinical setting. Second, our study was retrospective, which may have resulted in a sampling bias. Third, we could not make a prognostic analysis of air bronchogram for patients with peripheral lung cancer because of our limited clinical data.

In conclusion, air bronchogram on thin-section CT is a characteristic feature of solid adenocarcinoma of the lung. However, other CT findings, including lobulation, coarse spiculation, cavity, pleural tag, density of lobulation, and coarse spiculation, in addition to the ratio of the vertical to the shortest transverse diameter, were found to be unrelated to tumor histology and related only to tumor size.

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References

1. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277–300.
2. SEER cancer statistics review, 1975–2008. See http://seer.cancer.gov/csr/1975_2008/results_merged/sect_15_lung_bronchus.pdf
3. Travis WD, Brambilla E, Noguchi M, 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;6:244–285.
4. Ko JP. Lung nodule detection and characterization with multi-slice CT. J Thorac Imaging 2005;20:196–209.
5. Ettinger DS, Bepler G, Bueno R, et al. Non-small cell lung cancer clinical practice guidelines in oncology. J Natl Compr Canc Netw 2006;4:548–482.
6. Johnson BE, Crawford J, Downey RJ, et al. Small cell lung cancer clinical practice guidelines in oncology. J Natl Compr Canc Netw 2006;4:602–622.
7. Goo JM, Park CM, Lee HJ. Ground-glass nodules on chest CT as imaging biomarkers in the management of lung adenocarcinoma. Am J Roentgenol 2011;196:533–543.
8. Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008;246:697–722.
9. Kuriyama K, Seto M, Kasugai T, et al. Ground-glass opacity on thin-section CT: value in differentiating subtypes of adenocarcinoma of the lung. Am J Roentgenol 1999;173:465–469.
10. Aoki T, Tomoda Y, Watanabe H, et al. Peripheral lung adenocarcinoma: correlation of thin-section CT findings with histologic prognostic factors and survival. Radiology 2001;220:803–809.
11. Tsuchiya R. Implication of the CT characteristics of subcentimeter pulmonary nodules. Semin Thorac Cardiovasc Surg 2005;17:107–109.
12. Park CM, Goo JM, Lee HJ, et al. Nodular ground-glass opacity at thin-section CT: histologic correlation and evaluation of change at follow-up. Radiographics 2007;27:391–408.
13. Godoy MC, Naidich DP. Subsolid pulmonary nodules and the spectrum of peripheral adenocarcinomas of the lung: recommended interim guidelines for assessment and management. Radiology 2009;253:606–622.
14. Lee HY, Lee KS. Ground-glass opacity nodules: histopathology, imaging evaluation, and clinical implications. J Thorac Imaging 2011;26:106–18.
15. Akata S, Yoshimura M, Nishio R, et al. High-resolution computed tomographic findings of small peripherally located squamous cell carcinoma. Clin Imaging 2008;32:259–263.
16. Hashimoto M, Miyauchi T, Heianna J, et al. Accurate diagnosis of peripheral small cell lung cancer with

computed tomography. Tohoku J Exp Med 2009;217:217–221.
17. Oshiro Y, Kusumoto M, Matsuno Y, et al. CT findings of surgically resected large cell neuroendocrine carcinoma of the lung in 38 patients. Am J Roentgenol 2004;182:87–91.
18. Yu JQ, Yang ZG, Austin JH, et al. Adenosquamous carcinoma of the lung: CT-pathological correlation. Clin Radiol 2005;60:364–369.
19. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res 1999;8:135–160.
20. Blum A, Feldmann L, Bresler F, et al. Value of calculation of the kappa coefficient in the evaluation of an imaging method. J Radiol 1995;76:441–443.
21. Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008;246:697–722.
22. Naidich DP, Sussman R, Kutcher WL, et al. Solitary pulmonary nodules: CT-bronchoscopic correlation. Chest 1988;93:595–598.
23. Takashima S, Maruyama Y, Hasegawa M, et al. CT findings and progression of small peripheral lung neoplasms having a replacement growth pattern. Am J Roentgenol 2003;180:817–826.
24. Kuriyama K, Tateishi R, Doi O, et al. Prevalence of air bronchograms in small peripheral carcinomas of the lung on thin-section CT: comparison with benign tumors. Am J Roentgenol 1991;156:921–924.
25. Kui M, Templeton PA, White CS, et al. Evaluation of the air bronchogram sign on CT in solitary pulmonary lesions. J Comput Assist Tomogr 1996;20:983–986.
26. Choi JA, Kim JH, Hong KT, et al. CT bronchus sign in malignant solitary pulmonary lesions: value in the prediction of cell type. Eur Radiol 2000;10:1304–1309.
27. Zwirewich CV, Vedal S, Miller RR, et al. Solitary pulmonary nodule: high-resolution CT and radiologic-pathologic correlation. Radiology 1991;179:469–476.
28. Meziane MA, Hruban RH, Zerhouni EA, et al. High resolution CT of the lung parenchyma with pathologic correlation. Radiographics 1988;8:27–54.
29. Shimada Y, Yoshida J, Hishida T, et al. Predictive factors of pathologically proven noninvasive tumor characteristics in T1aN0M0 peripheral non-small cell lung cancer. Chest 2012;141:1003–1009.
30. Rocco G, Internullo E, Cassivi SD, et al. The variability of practice in minimally invasive thoracic surgery for pulmonary resections. Thorac Surg Clin 2008;18:235–247.

Thymoma Patients With Pleural Dissemination: Nationwide Retrospective Study of 136 Cases in Japan

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Background. Thymoma is a rare mediastinal tumor with relatively slow growth. However, advanced-stage cases with pleural dissemination are occasionally encountered. The outcome of surgical resection for thymomas with pleural dissemination has not been clearly determined.

Methods. We retrospectively investigated the clinical records of 2,835 patients with thymic epithelial tumors that were treated from 1991 to 2010 in 32 institutions that participated in the Japanese Association for Research on the Thymus. In this study, we analyzed the clinicopathologic factors and prognosis of thymoma patients with pleural dissemination who underwent surgical resection.

Results. The thymomas with pleural disseminations numbered 148 cases (5.2% in the 2,835 thymic epithelial tumors). Surgical resection was performed in 136 cases. Pathologic Masaoka stages were classified as IVA (n = 118) and IVB (n = 18). In Masaoka stage IVA disease, the small number of disseminated pleural nodules (10 or fewer) was related to the curative resection. The prognosis was also better in these cases than in those with greater than 10 disseminated pleural nodules (certified during the operation; $p = 0.0057$). Patients who underwent macroscopic total resection of disseminated nodules had a better prognosis than those with residual tumors ($p = 0.037$). In stage IVA cases with complete resection (n = 42), the efficacy of adjuvant chemotherapy, radiotherapy, or both was not demonstrated.

Conclusions. Macroscopic total resection of tumors appears to be a promising prognostic factor in Masaoka stage IVA thymomas. The number of disseminated pleural nodules correlated with resectability.

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Thymoma is a rare mediastinal tumor, and because its progression is relatively slow, a large number of patients and long (>5 years) follow-up are required to determine the effect of any treatment. In the treatment for thymoma, only complete surgical resection has been considered as potentially curable [1, 2]. For the early-stage cases, there is no doubt that surgical resection is the treatment of choice. For the cases with pleural dissemination, there is a lack of consensus on treatment strategy, and complete surgical resection is generally considered difficult. Multimodality therapy (surgery, chemotherapy, and radiation) has been used for advanced thymomas. However, the efficacy of chemotherapy and radiotherapy for advanced or recurrent thymomas has not been determined [3–7]. In addition, it is difficult to plan clinical trials because of the rarity of thymomas with pleural dissemination.

The progression pattern for thymoma is different from that for tumors of other organs, which metastasize by lymphogenous or hematogenous routes. Thymomas often recur locally or as pleural dissemination. To improve survival, adjuvant therapies including preoperative or postoperative chemotherapy and radiotherapy for advanced thymomas have been suggested. However, the efficacies of adjuvant chemotherapy and radiotherapy have been controversial [1, 8–13].

In this retrospective study, the clinicopathologic factors and the prognosis of thymoma with pleural dissemination were studied using the data from multiple centers of the Japanese Association for Research on the Thymus for evaluating the efficacy of surgical resection and multimodality therapy.

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Patients and Methods

Patients

A retrospective review of clinical records was conducted at 32 institutions that participated in the Japanese Association for Research on the Thymus. The present study was approved by the Institutional Review Board of Nagoya City University Hospital and other institutions, and individual patient consent was not required for this retrospective study. There were 2,835 thymic epithelial tumors collected that were treated between 1991 and 2010. They included 2,423 thymomas, 306 thymic carcinomas, 64 neuroendocrine carcinomas, and 42 unknown thymic epithelial tumors.

In this study, 148 thymoma patients with pleural dissemination were extracted. They included 128 and 20 patients in Masaoka stages IVA and IVB, respectively. To clarify the efficacy of surgical resection, 12 patients who underwent biopsy only were excluded. We used the most recent revision of the World Health Organization histologic TNM classification and stage grouping of thymic epithelial tumors in 2004 [14] and the Masaoka staging system [15, 16]. In cases with disseminated pleural nodules (stage IVA) or lymph node involvement (stage IVB), if all of the pleural nodules or involved lymph nodes were completely resected, the operation was considered a macroscopically complete resection (MCR).

Statistical Analysis

Survival curves were analyzed by the Kaplan-Meier method and univariate log-rank test. Overall survival was calculated from the date of surgery to death. Disease-free survival was calculated from the date of surgery to the date of identification of the recurrent disease or death for any cause. The frequency distributions between groups were tested with the χ^2 test. Significance was defined as a probability value of less than 0.05. All of the data were analyzed with EZR software [17].

Results

The 136 patients ranged in age from 23 to 83 years, with a mean age of 52. They consisted of 51 men and 85 women. Using World Health Organization histopathologic classification of the tumors [12], thymomas were diagnosed as

Table 1. Prognostic Factors in Thymoma With Pleural Dissemination (n = 136)

Factor	Subgroup	Numbers	5-Year Survival	10-Year Survival	Log-Rank Test *p* Value
Sex	Male	51	87.3%	68.2%	0.572
	Female	85	81.3%	59.8%	
Age	≤60 y	95	89.3%	60.5%	0.462
	>60 y	41	68.4%	68.4%	
PS	0	98	83.8%	62.8%	0.823
	≥1	33	84.5%	57.1%	
WHO classification	A, AB, B1	31	73.1%	53.3%	0.371
	B2, B3	105	86.0%	65.4%	
Extrapleural pneumonectomy	−	128	85.3%	62.5%	0.633
	+	8	70.0%	70.0%	
MG	−	97	79.4%	58.0%	0.125
	+	39	92.6%	71.9%	
Adjuvant chemotherapy	−	93	84.5%	62.3%	0.690
	+	43	82.2%	62.2%	
Adjuvant radiotherapy	−	75	83.5%	60.6%	0.759
	+	61	81.9%	62.2%	
Adjuvant chemoradiotherapy	−	120	82.8%	61.7%	0.515
	+	16	84.8%	60.6%	
Preoperative Masaoka stage	I–III	27	87.0%	77.3%	0.173
	IVa, IVb	75	83.7%	56.6%	
Maximal tumor size	≤70 mm	68	85.1%	63.0%	0.762
	>70 mm	60	86.0%	60.8%	
Number of pleural dissemination	1–10	64	84.2%	80.2%	0.090
	≥11	35	85.0%	52.2%	
Resectability	MCR	46	82.6%	82.6%	0.064
	MRT	86	83.2%	53.9%	
Postoperative Masaoka stage	IVA	118	86.7%	62.5%	0.255
	IVB	18	67.8%	59.4%	

MCR = macroscopic complete resection; MG = myasthenia gravis; MRT = macroscopic residual tumor; PS = performance status; WHO = World Health Organization.

type A (n = 2), type AB (n = 8), type B1 (n = 21), type B2 (n = 62), and type B3 (n = 43). The preoperative clinical staging showed the following composition of patients: 5 in stage I, 8 in stage II, 14 in stage III, 76 in stage IVA, 12 in stage IVB, and 21 unknown. Associated complications were myasthenia gravis (n = 39), pure red cell aplasia (n = 10), and Sjögren's syndrome (n = 1). Median follow-up duration for the 136 patients was 4.4 years.

Thymoma With Pleural Dissemination

Clinical and pathologic data of the 136 patients are shown in Table 1. Briefly, B2 and B3 thymomas were the main types and made up 77.2% of the total. Tumor resection was performed in 128 patients (94.1%), and only 8 patients underwent extrapleural pneumonectomy (5.9%). Resectability was not high as reflected by only 46 cases that were evaluated as MCR (33.8%), and adjuvant chemotherapy, radiotherapy, or both were often selected. There were no standard therapeutic courses as adjuvant therapy, and the therapeutic course after surgery was decided by each institution.

In the present study, no relationship was detected between clinicopathologic factors and the prognosis in the 136 cases with pleural dissemination (Table 1). The 5-year survival of the thymomas with pleural dissemination was 83.5%. In the analysis of numbers of disseminated pleural nodules, the cases with 10 or fewer tended to have a better prognosis (Fig 1A; $p = 0.090$). Also in the analysis of resectability, the MCR cases tended to show a better prognosis (Fig 2A; $p = 0.064$). The number of disseminated pleural nodules was correlated with resectability ($p = 0.0016$). Extrapleural pneumonectomy was performed in 8 patients. One patient had a recurrence 30 months after surgery and died 50 months after surgery. One patient died 14 days after surgery because of heart failure. Three patients were alive without recurrence, and 3 patients were alive with recurrent tumor.

Thymoma With Pleural Dissemination Without Systemic Metastasis or Lymph Node Involvement (Pathologic Masaoka Stage IVA)

In the next step, prognosis of the patients with postoperative Masaoka IVA disease was analyzed (Table 2). Masaoka IVB disease was excluded because it is no longer a local disease. The 5-year survival of the thymomas in stage IVA was 86.7%. The cases with 10 or fewer pleural nodules had a better prognosis than those with 11 or

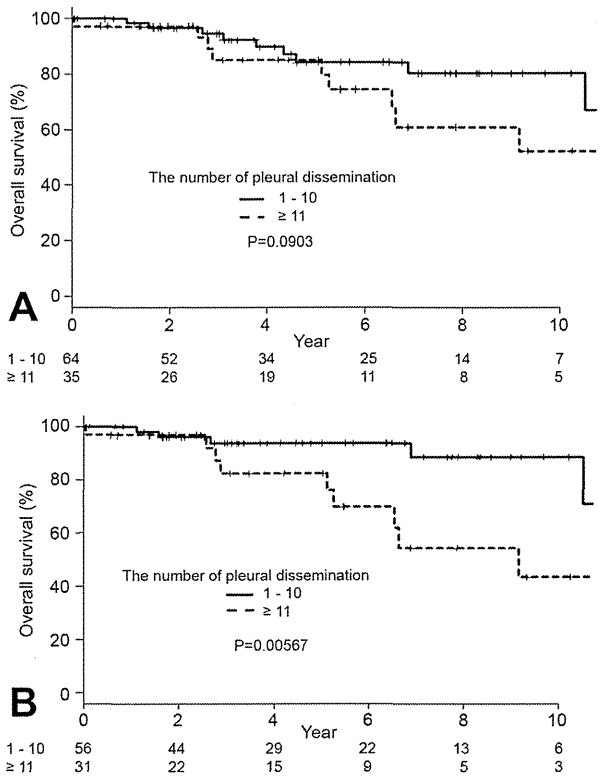

Fig 1. (A) Overall survival of thymoma with pleural dissemination divided by the number of pleural dissemination (n = 136; p = 0.090). (B) Overall survival of Masaoka stage IVA thymoma with pleural dissemination divided by the number of pleural dissemination (n = 118; p = 0.0057).

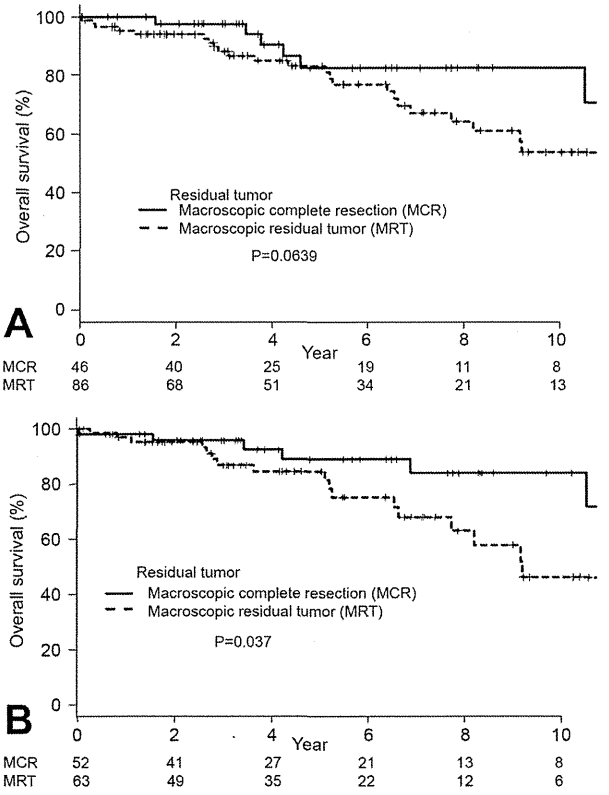

Fig 2. (A) Overall survival of thymoma with pleural dissemination divided by the macroscopic complete resection (MCR) or macroscopic residual tumor (MRT; n = 136; p = 0.064). (B) Overall survival of Masaoka stage IVA thymoma with pleural dissemination divided by the macroscopic complete resection or macroscopic residual tumor (n = 118; p = 0.037).

Table 2. Prognostic Factors in Thymoma With Pleural Dissemination (Masaoka Stage IVA, n = 118)

Factor	Subgroup	Numbers	5-Year Survival	10-Year Survival	Log-Rank Test p Value
Sex	Male	46	85.5%	63.9%	0.894
	Female	72	87.6%	62.4%	
Age	≤60 y	81	92.7%	57.0%	0.742
	>60 y	37	71.3%	71.3%	
PS	0	87	86.6%	63.0%	0.783
	≥1	27	90.7%	54.9%	
WHO classification	A, AB, B1	27	88.3%	64.4%	0.948
	B2, B3	91	86.0%	62.7%	
Extrapleural pneumonectomy	−	110	89.5%	62.7%	0.497
	+	8	70.0%	70.0%	
MG	−	83	84.5%	58.0%	0.268
	+	35	91.3%	71.5%	
Adjuvant chemotherapy	−	83	85.9%	62.3%	0.611
	+	35	89.1%	64.3%	
Adjuvant radiotherapy	−	65	90.0%	62.0%	0.633
	+	53	83.3%	60.9%	
Adjuvant chemoradiotherapy	−	103	87.4%	64.5%	0.987
	+	15	83.6%	55.7%	
Preoperative Masaoka stage	I–III	21	95.0%	79.2%	0.123
	IVa, IVb	75	83.3%	55.8%	
Maximal tumor size	≤70 mm	63	89.4%	64.1%	0.744
	>70 mm	49	88.1%	54.6%	
Number of pleural dissemination	1–10	56	93.6%	88.4%	0.0057
	≥11	31	82.3%	43.3%	
Resectability	MCR	52	88.6%	88.6%	0.037
	MRT	63	84.5%	46.3%	

MCR = macroscopic complete resection; MG = myasthenia gravis; MRT = macroscopic residual tumor; PS = performance status; WHO = World Health Organization.

more (Fig 1B; $p = 0.0057$). The cases that had all of the pleural nodules resected (MCR) had a better prognosis than those with residual tumors (Fig 2B; $p = 0.037$). The number of disseminated pleural nodules correlated with resectability ($p = 0.00065$).

Thymoma With Pleural Dissemination With Systemic Metastasis or Lymph Node Involvement (Pathologic Masaoka Stage IVB)

The cases with Masaoka IVB disease (Table 3) were analyzed to determine the efficacy of the surgical resections that were performed. The 5-year survival of the thymomas in stage IVB was 67.8%. In stage IVB patients, those with type A, AB, or B1 had a poorer prognosis than those with type B2 or B3 ($p = 0.027$), but this analysis was based on a very small number (n = 4) of type A, AB, or B1 patients. Other clinicopathologic factors did not affect the prognosis of stage IVB thymoma patients with pleural dissemination (Table 3).

Adjuvant Therapy for Masaoka Stage IVA Thymoma With No Macroscopic Residual Tumor

The overall survival and disease-free survival of patients who had adjuvant chemotherapy, adjuvant radiotherapy, or adjuvant chemoradiotherapy were not better than patients who did not undergo postoperative adjuvant therapy (Fig 3; $p = 0.477$, $p = 0.366$).

Comment

A large-scale retrospective analysis was conducted of thymoma patients with pleural dissemination. The therapeutic strategy and prognostic factors for thymomas with pleural dissemination have not been determined. Surgical resection has been recommended as the principal treatment, and completeness of resection is considered to be the most important determinant of long-term survival in thymomas. However, in thymoma cases with pleural dissemination, complete surgical resection of disseminated pleural nodules is difficult. In this study 136 thymomas with pleural disseminations were investigated for the relationship between clinicopathologic factors and prognosis. We have demonstrated the importance of complete surgical resection of tumors even in cases with disseminated nodules in Masaoka IVA disease. There was an interaction between the numbers of disseminated pleural nodules and resectability in Masaoka IVA disease. This interaction was not found in Masaoka IVB disease. It is difficult to determine the number of disseminated nodules by preoperative imaging because our patients

Table 3. Prognostic Factors in Thymoma With Pleural Dissemination (Masaoka Stage IVB, n = 18)

Factor	Subgroup	Numbers	5-Year Survival	10-Year Survival	Log-Rank Test *p* Value
Sex	Male	5	100%	100%	0.054
	Female	13	56.6%	45.3%	
Age	≤60 y	13	74.1%	63.5%	0.871
	>60 y	5	40.0%	40.0%	
PS	0	11	70.1%	58.4%	0.883
	≥1	6	62.5%	62.5%	
WHO classification	A, AB, B1	4	0%	0%	0.027
	B2, B3	14	85.1%	74.5%	
Extrapleural pneumonectomy	−	18	67.6%	59.1%	−
	+	0	−	−	
MG	−	14	55.9%	55.9%	0.227
	+	4	100%	75.0%	
Adjuvant chemotherapy	−	10	77.1%	61.7%	0.617
	+	8	57.1%	57.1%	
Adjuvant radiotherapy	−	10	60.0%	60.0%	0.690
	+	8	75.0%	62.5%	
Adjuvant chemoradiotherapy	−	17	65.5%	56.2%	0.460
	+	1	100%	100%	
Preoperative Masaoka stage	I–III	6	66.7%	66.7%	0.707
	IVa, IVb	10	67.5%	54.0%	
Maximal tumor size	≤70 mm	5	60.0%	60.0%	0.611
	>70 mm	12	77.1%	64.3%	
Number of pleural dissemination	1–10	8	43.8%	43.8%	0.100
	≥11	4	100%	100%	
Resectability	MCR	3	33.3%	33.3%	0.340
	MRT	14	76.6%	65.7%	

MCR = macroscopic complete resection; MG = myasthenia gravis; MRT = macroscopic residual tumor; PS = performance status; WHO = World Health Organization.

included many who were diagnosed with diseases in clinical stages I to III (20 of 94; 21.3%). Yano and colleagues [3] also reported the discrepancy between the numbers of disseminated nodules that were diagnosed preoperatively and those counted intraoperatively.

The present data demonstrated that the prognosis of thymoma patients with stage IVA disease is not as dismal as expected (Figs 1, 2). When the dissemination is found during the operation, it is suggested that the operation be continued and the nodules resected if there are 10 or fewer disseminated nodules. The appropriateness of using the number of 10 nodules should be determined by prospective studies. Yano and colleagues [18] reported that a small number of recurrent lesions of thymoma showed better prognosis. The number of disseminated nodules may be a prognostic factor in Masaoka IVA disease.

Some authors have stated that extrapleural pneumonectomy was effective for complete resection of pleural dissemination [19–21]. In this study 8 patients underwent extrapleural pneumonectomy, but the 5-year survival was only 70%. Although extrapleural pneumonectomy may be an option for thymoma cases with pleural dissemination, the procedure should be limited because of the high operative mortality and the low postoperative quality of life.

In the cases of thymoma patients in Masaoka stage IV disease, no significant improvement in overall survival and disease-free survival was noted for patients who were treated with postoperative radiation, chemotherapy, or both compared with those without adjuvant therapy. Although a variety of chemotherapeutic regimens such as adjuvant chemotherapy after surgery for thymoma have been reported, there is no standard chemotherapeutic protocol for thymoma [9–11]. Thymoma is a rare tumor, and advanced stages of thymoma are much rarer. Even in the present relatively large-scale study, efficacy of adjuvant therapy could not be demonstrated. A prospective, worldwide, randomized, controlled trial of chemotherapy or radiotherapy for advanced thymoma is eagerly awaited.

The present study has several limitations, other than the small number of advanced-stage patients. During the two decades of this study, newer surgical devices and techniques have been introduced including thoracoscopic surgery and robotic surgery. Chemotherapeutic agents, apparatuses for radiotherapy, and radiographic imaging technologies have also been improved. The chemotherapeutic agents and regimens, as well as devices and techniques, varied by the period and among the institutions.

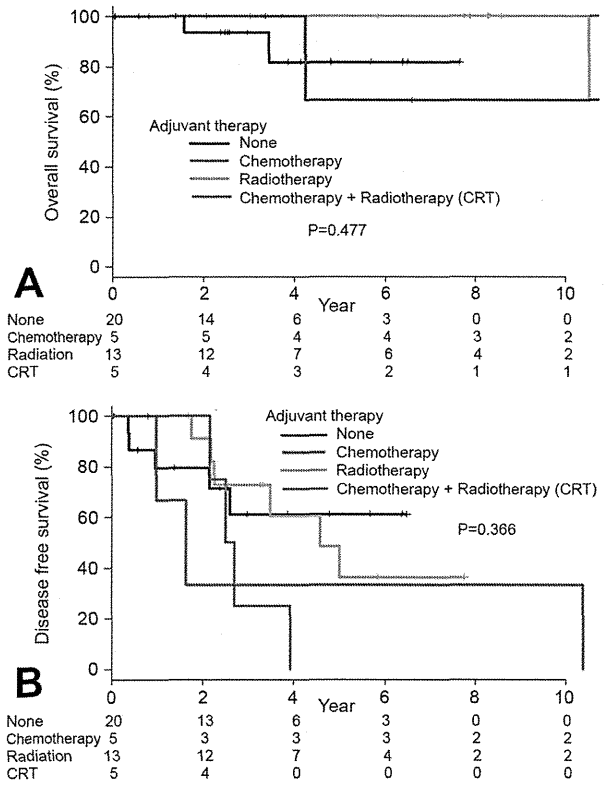

Fig 3. (A) Overall survival of Masaoka stage IVA thymoma with macroscopic complete resection divided by the adjuvant therapy (none, chemotherapy, radiotherapy, or chemoradiotherapy [CRT]; n = 42; p = 0.477). (B) Disease-free survival of Masaoka stage IVA thymoma with macroscopic complete resection divided by the adjuvant therapy (none, chemotherapy, radiotherapy, or chemoradiotherapy; n = 42; p = 0.366).

In conclusion, resection of disseminated pleural nodules of thymoma appears to be an acceptable therapeutic option for Masaoka stage IVA diseases.

References

1. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003;76:878–85.
2. Regnard JF, Magdeleinat P, Dromer C, et al. Prognostic factors and long-term results after thymoma resection: a series of 307 patients. J Thorac Cardiovasc Surg 1996;112:376–84.
3. Yano M, Sasaki H, Yukiue H, et al. Thymoma with dissemination: efficacy of macroscopic total resection of disseminated nodules. World J Surg 2009;33:1425–31.
4. Kim ES, Putnam JB, Komaki R, et al. Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. Lung Cancer 2004;44:369–79.
5. Lucchi M, Ambrogi MC, Duranti L, et al. Advanced stage thymomas and thymic carcinomas: results of multimodality treatments. Ann Thorac Surg 2005;79:1840–4.
6. Haniuda M, Miyazawa M, Yoshida K, et al. Is postoperative radiotherapy for thymoma effective? Ann Surg 1996;224:219–24.
7. Uematsu M, Yoshida H, Kondo M, et al. Entire hemithorax irradiation following complete resection in patients with stage II–III invasive thymoma. Int J Radiat Oncol Biol Phys 1996;35:357–60.
8. Ogawa K, Uno T, Toita T, et al. Postoperative radiotherapy for patients with completely resected thymoma: a multi-institutional, retrospective review of 103 patients. Cancer 2002;94:1405–13.
9. Utsumi T, Shiono H, Kadota Y, et al. Postoperative radiation therapy after complete resection of thymoma has little impact on survival. Cancer 2009;115:5413–20.
10. Sugie C, Shibamoto Y, Ikeya-Hashizume C, et al. Invasive thymoma: postoperative mediastinal irradiation, and low-dose entire hemithorax irradiation in patients with pleural dissemination. J Thorac Oncol 2008;3:75–81.
11. Venuta F, Rendina EA, Longo F, et al. Long-term outcome after multimodality treatment for stage III thymic tumors. Ann Thorac Surg 2003;76:1866–72.
12. Lucchi M, Melfi F, Dini P, et al. Neoadjuvant chemotherapy for stage III and IVA thymomas: a single-institution experience with a long follow-up. J Thorac Oncol 2006;1:308–13.
13. Yokoi K, Matsuguma H, Nakahara R, et al. Multidisciplinary treatment for advanced invasive thymoma with cisplatin, doxorubicin, and methylprednisolone. J Thorac Oncol 2007;2:73–8.
14. Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. World Health Organization classification of tumours. Pathology and genetics of tumours of the lung, pleura, thymus and heart. Lyon: International Agency for Research on Cancer Press; 2004:146–51.
15. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485–92.
16. Yamakawa Y, Masaoka A, Hashimoto T, et al. A tentative tumor-node-metastasis classification of thymoma. Cancer 1991;68:1984–7.
17. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452–8.
18. Yano M, Sasaki H, Moriyama S, et al. Number of recurrent lesions is a prognostic factor in recurrent thymoma. Interact Cardiovasc Thorac Surg 2011;13:21–4.
19. Wright CD. Pleuropneumonectomy for the treatment of Masaoka stage IVA thymoma. Ann Thorac Surg 2006;82:1234–9.
20. Ishikawa Y, Matsuguma H, Nakahara R, et al. Mulimodality therapy for patients with invasive thymoma disseminated into the pleural cavity: the potential role of extrapleural pneumonectomy. Ann Thorac Surg 2009;88:952–7.
21. Yang HC, Yoon YS, Kim HK, et al. En bloc extended total thymectomy and extrapleural pneumonectomy in Masaoka stage IVA thymomas. J Cardiothorac Surg 2011;6:28.

INVITED COMMENTARY

Okuda and colleagues [1] report on a relatively large number of patients with Masaoka stage IVA thymoma (136) who had resection of their tumor and the pleural implants. These rare patients were accumulated from a national Japanese database, The Japanese Association for Research on the Thymus, which covered 32 institutions over 19 years to produce this number of patients, further emphasizing just how uncommon this

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CASE REPORT Open Access

Primary papillary carcinoma of the thymus with invasion into subcutaneous tissue through the sternum

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Abstract

Thymic carcinoma is a rare malignant neoplasm. We present a Japanese case of papillary carcinoma of thymus in a 64-year-old man that invaded into subcutaneous tissue penetrating the sternum. We describe the clinical and pathologic features of this extremely rare thymic epithelial tumor, with disease-free survival at three years of follow-up.

Keywords: Thymus, Cancer, Sternum, Surgery, Chest wall

Background

Thymic carcinoma is a rare tumor. The most common histological subtype of thymic carcinoma is squamous cell carcinoma, and adenocarcinoma is extremely rare. We report the case of a 64-year-old Japanese man with thymic papillary carcinoma. In this case, the tumor invaded into subcutaneous tissue by penetrating the sternum with osteolytic change.

Case presentation

A 64-year-old Japanese man presented with bulging of the anterior chest wall for 3 months duration. On examination, a round mass was palpable with tenderness and redness, and fixed in the upper mid- sternum. The patient had undergone wedge resection of the right upper lobe due to a spontaneous pneumothorax when he was young. Computed tomographic (CT) scan showed a 7.5 × 5.5 × 7.2 cm mass in anterior mediastinum invading into subcutaneous fat tissue through the sternum with bone destruction (Figure 1a and b). On fluorine-18-fluorodeoxyglucose (FDG)-positron emission tomography (PET), abnormal FDG uptake was observed only in the mediastinal mass with a maximum standardized uptake ratio of 15.0. Serum carcinoembryonic antigen (CEA) was remarkably elevated to be 2047.2 ng/ml but other tumor markers (AFP, beta-HCG, SCC), anti-acetylcholine receptor antibody, and an alkaline phosphatase were negative. The tumor was diagnosed to be carcinoma by fine-needle aspiration, but the definitive histology could not be determined.

The patients underwent enbloc resection of the tumor through a midline incision over the sternum and a right collar incision. The tissue around the tumor was mobilized in a circumferential manner, and an upper half of the sternum including terminal 3–5 cm of the clavicle and the upper three ribs on the right side, medial end of the left clavicle, and adjacent subcutaneous tissue and the skin. The great vessels and the pericardium were free from the tumor. Because upper lobes of both lungs were adherent to the mediastinal pleura at the tumor site, wedge resections were performed. Regional lymph node exploration revealed no nodal involvement of the tumor cells. The sternal defect was not reconstructed. The postoperative course was uneventful and the patient was discharged on the 14th day after surgery. Paradoxical respiratory movement of the chest was not observed. Serum CEA level returned to normal 3 months after surgery.

Macroscopic examination of the tumor penetrating the sternum was not encapsulated but showed a vaguely infiltrative border with extension into mediastinal tissue and subcutaneous fat (Figure 2a). Histological examination revealed that the tumor cells proliferate in papillary clusters separated by fibrovascular septa (Figure 2b and c).

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