TABLE 6. Patients who were converted to major lung resection

Patient No.	Age/sex	Histologic type	Planned segmentectomy	SN with metastasis	Converted procedure	Pathologic TNM
1	70/M	Ad	Apical segment of RLL	No. 13	Lobectomy	T1 N1 M0
2	72/M	Ad	Apical segment of RLL	No. 11	Lobectomy	T2 N1 M0
3	80/M	Ad	Posterior apical segment of LUL	No. 5	Upper division segmentectomy	T1 N2 M0

SN, Sentinel node; *Ad*, adenocarcinoma; *RLL*, right lower lobe; *LUL*, left upper lobe.

Therefore, to determine the intraoperative indication for segmentectomy without using SN identification, not only hilar lymph nodes but also lobe-specific mediastinal lymph nodes should be submitted for intraoperative frozen section diagnosis. The SN identification can target the lymph nodes among those.

The identification rate of SNs was 83% in the present study, as it was in the data of previous reports by several authors, that is, 63% to 82%.[12-14] We[14] previously reported the results of SN identification in 104 patients with clinical stage I NSCLC. Of the 104 patients, 15 patients had N1 or N2 disease. Although SN could be found to have metastases during the operation in 13 (87%) of those 15 patients, it produced false negative results in the remaining 2 patients. One of the 2 patients had T2 tumor and metastasis in the No. 12 nodal station, and the other had T1 tumor and metastasis in the No. 14 nodal station, which could not be identified as SN by our procedure because of its intrapulmonary location. We therefore believe that SN could be identified by our procedure in most of the patients with T1 N0 M0 NSCLC.

Although it has been reported that 20% to 25% of patients with clinical stage I disease have mediastinal lymph node metastasis,[22,23] the present study showed only 3 (6%) of 52 patients with N1 or N2 disease. Our procedure for lymph node dissection was systematic and then yielded 6 ± 1.8 nodal stations and 12.5 ± 6 lymph nodes to be dissected per patient. The low number of patients with N1 or N2 disease in the present study is probably due to the institutional setting; that is, most lung cancers in our patients were found by routine CT examination, resulting in a higher rate of early-stage NSCLC than usual.

The Lung Cancer Study Group study in 1995 (the only prospective randomized trial of lobectomy versus limited resection for T1 N0 NSCLC) reported that limited resection was inferior to lobectomy regarding death rate and local recurrence.[1] However, the study included a significant number (33%) of wedge resections in the limited resection group and did not analyze the results of segmentectomy. In addition, compared with clinical staging in 1995 when the Lung Cancer Study Group study was reported, it is now more accurate because of improved CT and FDG-PET technology. Therefore, a prospective randomized trial of lobectomy versus segmentectomy should be performed for c-T1 N0 M0 NSCLC. The SN navigation segmentectomy, which can target lymph nodes for intraoperative frozen section diagnosis, is a reasonable procedure for determining the final indication of segmentectomy.

GTS

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Three Cases of Multiple Thymoma with a Review of the Literature

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Three cases of patients with synchronous multiple thymoma are reported. Two patients had two thymomas each and the remaining patient had three. The thymomas in each patient all displayed similar histological findings, of which the WHO histological classification were type B2, A and B1, respectively. With a modified Masaoka staging system, the thymomas were determined to be stages II-1 and I in patient 1, one of stage III and two of stage I in patient 2, and two of stage II-1 in patient 3. We reviewed nine reported cases of multiple thymoma in which histological findings were provided and discuss whether they developed from multi-centric origin or from intra-thymic metastasis.

Key words: thymoma – multiple developments – multi-centric development – recurrence

INTRODUCTION

Although it is well known that multiple thymoma can develop in a single patient, its actual incidence is very low. Also it remains controversial whether the cases represent disease of multi-centric origin or intra-thymic metastasis. To address this issue, we present three cases of patients with multiple thymoma and also review the reported cases of which histological findings have been provided (1–8).

MATERIALS AND METHODS

From 1981 to 2005, 96 patients with thymoma were treated by thymo-thymomectomy in the Department of Thoracic Surgery of Kumamoto University Hospital. Of these, three patients (3.1%) had multiple thymomas. The histological type of each thymoma was classified according to the World Health Organization (WHO) classification system (9). The tumor stage was classified by a modified Masaoka classification (10).

CASE REPORT

Patient 1

A 69-year-old male with ocular type myasthenia gravis (MG) was admitted to our hospital for surgical treatment of an anterior mediastinal tumor. The serum level of anti-acethylcholine receptor antibody (AchR Ab) was elevated to 8 nmol/l (normal level < 0.2 nmol/l). Computed tomography (CT) showed a well-defined mass bounded on the ascending aorta (Fig. 1). Thymo-thymomectomy was performed via median sternotomy. While pathological examination diagnosed the tumor as type B2 thymoma 23 × 12 mm in size, pathological examination revealed another type B2 thymoma 2 × 2 mm in size located within the same lobe (Fig. 2). While the intra-operative findings showed no invasion of the main tumor, microscopic invasion into the surrounding thymic tissue was obserbed, i.e. the tumor stage was II-1. The patient is now alive without recurrence of thymoma and with complete remission of MG 5 years after surgery.

Patient 2

A 74-year-old male without MG was admitted to our hospital for surgical treatment of an anterior mediastinal tumor. The serum AchR Ab level was within normal limits. CT revealed a small, ill-defined mass bounding on the ascending aorta (Fig. 3). The intra-operative findings revealed invasion of the tumor into the right middle lobe of the lung and also two additional tumors within the right thymic lobe. A thymo-thymomectomy was performed with wedge resection of the right middle lobe. Pathological diagnosis was type A thymoma in all three of the tumors, the respective sizes were 58 × 35, 24×7 and 10 × 8 mm. The patient was treated with post-operative radiotherapy (50 Gy). He is now alive without recurrence of thymoma 10 months after surgery.

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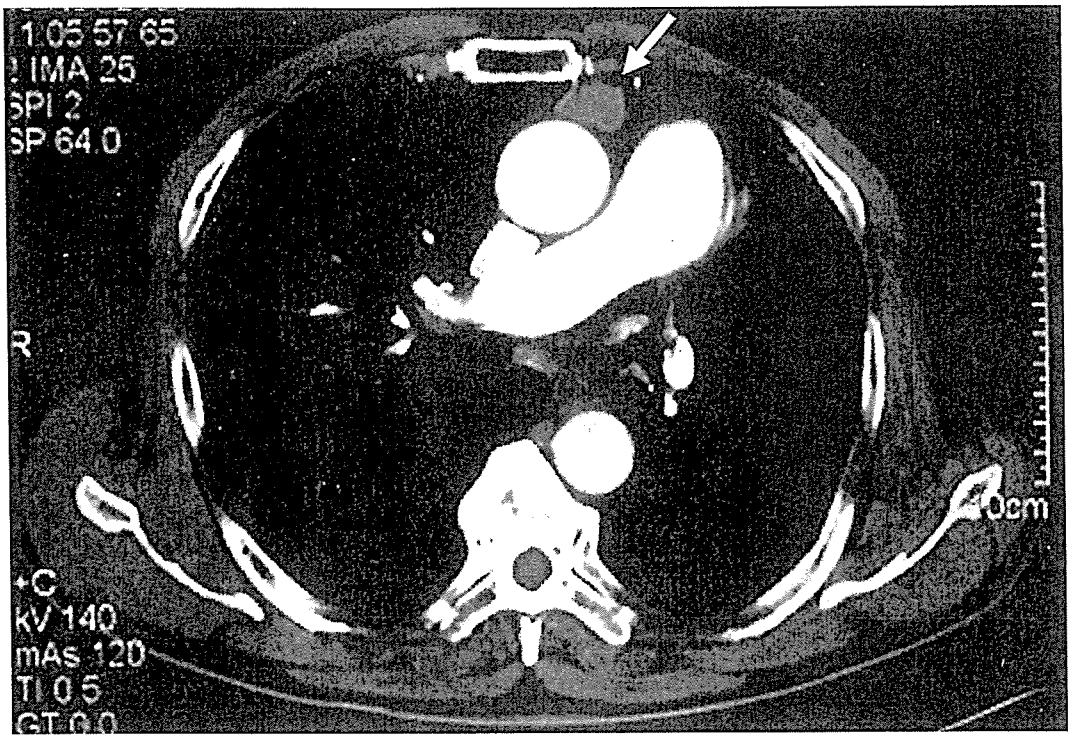

Figure 1. Case 1. Computed tomogram (CT) showing well-defined mass (arrow) bound on the ascending aorta.

PATIENT 3

A 46-year-old male with ocular type MG was admitted to our hospital for surgical treatment of an anterior mediastinal tumor. The serum level of AchR Ab was elevated to 9.5 nmol/l. Computed tomography revealed a well-defined mass on the left upper side of the anterior mediastinum. Thymothymomectomy was performed via median sternotomy. During the operation, another tumor was found within the right lower thymus. The sizes of the two tumors were 22 × 15 and 15 × 8 mm, respectively. Pathological diagnosis was type B1 thymoma in both tumors. While intra-operative findings did not show any invasion by the tumors, pathological examination revealed microscopic invasion into the surrounding thymic tissue in both, i.e. both

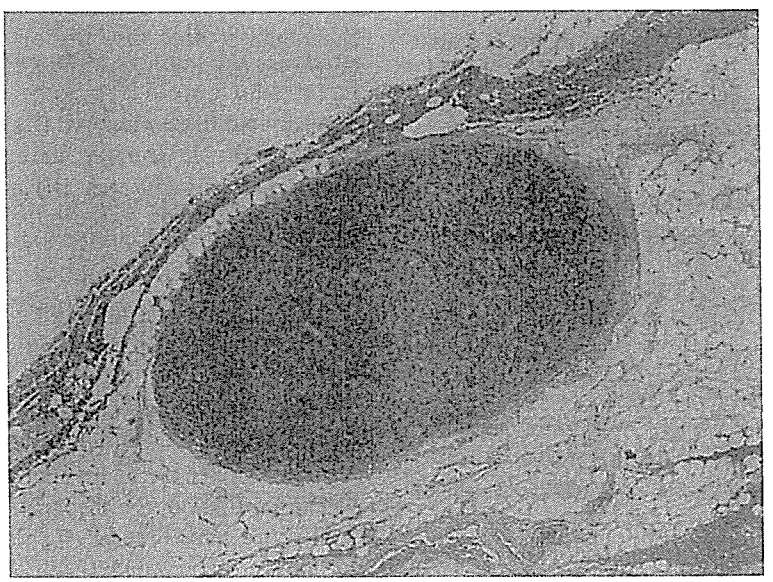

Figure 2. Case 1. A small thymoma existing in the thymic tissue.

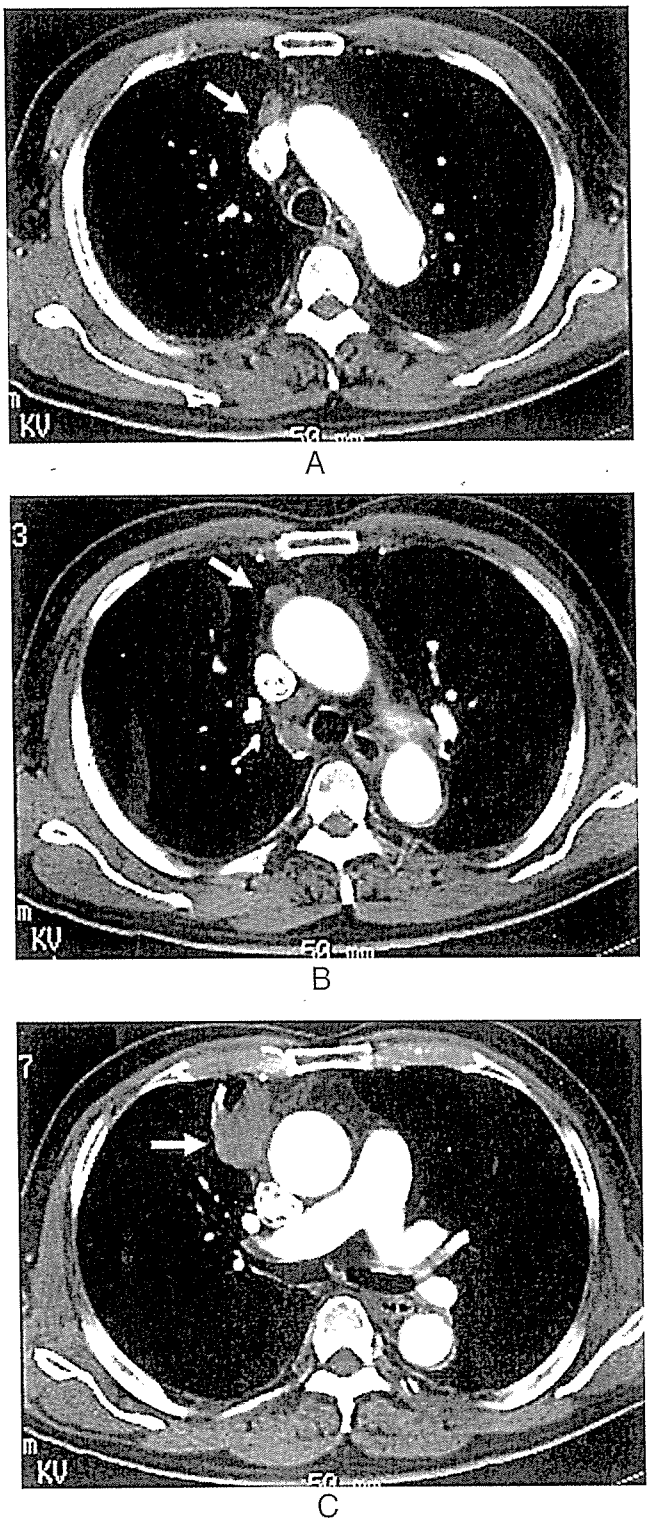

Figure 3. Case 2. CT showing homogenous anterior mediastinal tumor (arrow); one was on the superior vena cava (A), another was on the ascending aorta (B), and last one invaded into the lung (C).

were stage II-1. The patient is now alive without recurrence of thymoma and with complete remission of MG, 6 years after surgery.

DISCUSSION

Multiple thymoma is a well-known phenomenon, but its occurrence is very rare. Bernatz et al. reported just three out of 138 (2.2%) thymomas to be multiple (11). Jaretzky et al. reported one (1.1%) multiple thymoma out of 95 cases of thymoma (12). However, these reports did not describe any histological differences between the multiple thymomas documented. In 1990, Nomori et al. reported one case of multiple thymoma and suggested the possibility of intra-thymic metastasis rather than multi-centric development based on histological, morphometrical and immunohistochemical findings (1). Since their report, nine cases with multiple thymoma have been reported with their histological findings provided (1–8). We reviewed these reports and present their respective clinicopathological characteristics in Table 1. Histological subtypes of thymoma by WHO classification were judged from the histological findings included in each report (9). The characteristics are as follows: (i) mean age was 57 $\pm$ 11-year-old (range: 28–81); (ii) there were eight males and four females; (iii) the numbers of thymomas were two in 11 patients, and three in one; (iv) of the total of 25 thymomas, three (12%) could be histologically classified as type A, 13 (52%) as type B1, eight (32%) as type B2, and one (4%) as type B3; (v) histological findings of the multiple thymomas in each patient were similar in 10 patients (83%), while the remaining two (17%) displayed different subtypes; (vi) the difference in tumor size between the thymomas in each patient was such that the smaller ones were usually larger than 25% of the main ones, except for case numbers 1 and 10, which displayed a greater than 10 times size difference between the tumors. Of the 25 thymomas, 20 were stage I (80%), three stage II-1 (12%), and the remaining two were stage III (8%).

It is controversial whether cases of multiple thymomas represent multi-centric origin or intra-thymic metastasis. From the characteristics of the 12 cases in Table 1, multicentric development is suggested by the following characteristics: (i) the number of thymomas were usually less than three, which would be surprising if the source were in intra-thymic dissemination; (ii) there is little size difference between the thymomas in each case, except for case numbers 1 and 10; and (iii) most of the thymomas were stage I, which are essentially unable to spread into the thymic tissue.

However, the possibility of intra-thymic metastasis might be suggested by the finding that each of 10 patients (83%) were found to have similar histological characteristics in their thymomas. While it cannot be concluded at this point whether multiple thymomas are derived from multi-centric development or intra-thymic metastasis, we favor the former hypothesis because of the analysis presented above. While we cannot rule out the theory of intra-thymic metastasis, we believe that most multiple thymomas develop from identical tumor genesis events in each patient, thus resulting in the similar histological findings.

Table 1. Reported cases with multiple thymoma of which histological findings are described

	References/cases	Age/sex	Thymomas		Maximum diameter (mm)	Stage (Modified Masaoka)	Myasthenia gravis
			Number	Histological type*			
1	Nomori et al. 1990 (1)	28/F	2	B2 and B2	70 and 1.5	I and I	+
2	Takeuchi et al. 1997 (2)	74/F	2	B1 and B1	90 and 83	I and I	−
3	Okada et al. 1998 (3)	37/F	2	B1 and B1	55 and 35	I and I	−
4	Okada et al. 1998 (3)	70/M	2	B2 and B2	50 and 24	I and I	−
5	Gotoh and Yokoi 2000 (4)	57/F	2	B1 and B1	39 and 32	I and I	−
6	Hirai et al. 2001 (5)	42/M	2	B1 and B2	40 and 30	I and I	−
7	Ishibashi et al. 2003 (6)	47/M	2	B1 and B1	60 and 25	I and I	+
8	Nonami and Moriki 2004 (7)	81/F	2	B1 and B1	80 and 25	I and I	−
9	Yoneda et al. 2004 (8)	44/M	2	B2 and B3	64 and 60	I and III	−
10	The present cases	69/M	2	B2 and B2	23 and 2	II-1 and I	+
11	The present cases	74/M	3	A, A and A	40, 24 and 10	III, I and I	−
12	The present cases	46/M	2	B1 and B1	22 and 15	II-1 and II-1	+

M, male; F, female.
*WHO classification judged from the histological findings written in each report.

Denzinger et al. reported clonality analysis of multi-focal bladder tumors by examining the loss of heterozygosity (LOH) and fluorescence *in situ* hybridization (FISH) (13). However, it has not been clarified whether these chromosomal losses of primary tumors in epithelial tumors are also preserved in metastatic sites or not. In addition, while Inoue et al. reported the difference of LOH and FISH among histological types of thymoma by using micro-dissection or culture of thymoma-epithelial cells (14), thymoma is generally hard to examine by LOH and FISH owing to many lymphocytes among the thymoma-epithelial cells. Therefore, it is difficult to examine whether the multiple thymomas in our report are from multi-centric origins or metastasis by the clonality analysis, such as the LOH or FISH method.

Finally, it is reported that local recurrence sometimes takes place after resection of non-invasive thymomas (15–17). Maggi et al. reported that two of 133 (1.4%) encapsulated thymomas had recurred after surgery (16). Because these could be recurrences from small or even tiny thymoma remnants in thymic tissue, we recommend an extensive thymectomy even for stage I thymoma.

Conflict of interest statement

None declared.

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CHEST

Original Research

LUNG PATHOLOGY

Impalpable Pulmonary Nodules With Ground-Glass Opacity*

Success for Making Pathologic Sections With Preoperative Marking by Lipiodol

Koei Ikeda, MD, PhD; Hiroaki Nomori, MD, PhD; Takeshi Mori, MD; Hironori Kobayashi, MD; Kazunori Iwatani, MD; Kentaro Yoshimoto, MD; and Ko-ichi Kawanaka, MD

Background: **The developments in high-resolution CT scanning have increased the chance of detecting small bronchioloalveolar carcinoma (BAC) or atypical adenomatous hyperplasia (AAH) that appears as a ground-glass opacity (GGO). However, these lesions are not only difficult to localize during surgery, but they are also hard to make pathologic sections of because they are usually impalpable. Here, we report a method of making pathologic sections for impalpable GGO lesions.**

Methods: **Twenty-nine impalpable GGO lesions < 1 cm in size were marked by 0.4 to 0.5 mL of lipiodol under CT scan before surgery. The lesions were resected under C-arm fluoroscopy. The radiopaque areas marked by lipiodol within the formalin-fixed specimens were cut serially under conventional fluoroscopy for pathologic examinations.**

Results: **The mean (± SD) size of the lesions was 0.5 ± 0.2 cm (range, 0.2 to 1 cm), and the mean depth from the pleural surface was 1.6 ± 1.4 cm (range, 0.2 to 6 cm). The mean number of sections submitted for pathologic examinations was 2.3 ± 1.7 per lesion (range, 1 to 7 per lesion). While 11 of the 29 lesions (38%) were invisible even on the cut surface of the specimens, all were demonstrated in hematoxylin-eosin sections. The pathologic diagnosis was BAC in 17 lesions, AAH in 10 lesions, and organized pneumonia in 2 lesions. The use of lipiodol did not affect the pathologic findings.**

Conclusions: **The use of fluoroscopy to cut sections from resected specimens after preoperative marking with lipiodol was useful for making pathologic sections of impalpable GGOs < 1 cm in size.**

(CHEST 2007; 131:502–506)

Key words: lung cancer; pathology lung cancer; thoracic surgery

Abbreviations: AAH = atypical adenomatous hyperplasia; BAC = bronchioloalveolar carcinoma; GGO = ground-glass opacity

The development of high-resolution CT scanning has allowed the frequent detection of small ground-glass opacity (GGO) lesions in the lung. Because a percutaneous or transbronchial biopsy of such lesions is often difficult, thoracoscopic surgical techniques have been used in diagnostic excisional biopsies as well as in therapeutic resections. Because small GGO lesions cannot usually be palpated or

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visualized during surgery, several marking techniques have been reported for localization during thoracoscopic surgery, such as those using a dye,[1–3] colored collagen,[4] barium,[5,6] lipiodol,[7,8] microcoil,[9] and hook wire.[10,11] However, even if the lesions are successfully resected, it is still difficult to make pathologic sections of small GGO lesions because they usually cannot be palpated in the resected specimens. In addition, small bronchioloalveolar carcinoma (BAC) and atypical adenomatous hyperplasia (AAH) are sometimes hard to visualize on the cut surface of the resected specimens. This requires many pathologic sections to be made, which is time-consuming and expensive. To resolve these issues, we have performed preoperative marking with lipiodol for impalpable GGO lesions and have made pathologic sections under fluoroscopy, enabling the pathologic diagnosis to be made in all cases. Here, we report on the technique and the results of using it in detail.

Materials and Methods

Eligibility

The CT scan-guided lipiodol marking was approved by the ethics committee of Kumamoto University Hospital in April 2005. Written informed consent was obtained from all patients after they had discussed the risks and benefits of the procedure with the surgeons. Nodules that were potentially difficult to localize during surgery, or difficult to see or palpate on the cut surface of the resected specimens, such as GGO lesions or small nodules situated at a considerable depth from the pleural surface, were candidates for the procedure.

Patients

The nodules that were thought to be difficult to localize under thoracoscopy, such as GGO lesions, nodules situated at a considerable depth from the pleural surface, and nodules < 1 cm in size, were candidates for lipiodol marking. Between May 2005 and June 2006, preoperative lipiodol marking was performed under fluoroscopic CT scanning (AREX-T2310R1; Toshiba; Tokyo, Japan) on 60 nodules in 43 patients. Of these, 29 nodules in 18 patients were impalpable even in the specimens from patients who had undergone resection, who served as subjects in the present study (Table 1). All of the nodules were incidentally detected on CT scan and had no solid component on multidirection CT scans (BRILLIANCE 64; Philips; Amsterdam, the Netherlands), which usually scanned the lesions with 0.5 to 1 mm thickness. All of the nodules were clearly visible, round GGOs < 1 cm in size, which were suspicious for BAC. Of the 29 lesions, 14 accompanied other resectable non-small cell lung cancers, 9 were part of multiple GGOs < 1 cm in size, and the remaining 6 were single GGOs. The mean (± SD) size of the lesions was 0.5 ± 0.2 cm (range, 0.2 to 1 cm), and their mean distance from the pleural surface was 1.6 ± 1.4 cm (range, 0.2 to 6 cm).

Marking Technique

The procedure used for marking was as follows: lesions were usually marked 1 day before surgery under fluoroscopic CT scanning (AREX-T2310R1; Toshiba). Patients were placed on the CT scan table in a suitable position (*ie*, supine or prone). After administering local anesthesia to the thoracic wall, 0.4 to 0.5 mL of lipiodol (Lipiodol Ultrafluid; Laboratorie Guerbet; Aulnay-Sons-Bois, France), which is generally used as a contrast medium for lymphatic vessels, was injected into the nodules under fluoroscopic CT scan guidance (Fig 1).

Table 1—*Clinicopathologic Characteristics of Impalpable Pure GGO Nodules < 1 cm in Size

Characteristics	Values
Size, cm	0.5 ± 0.2 (0.2–1)
Distance from visceral pleura, cm	1.6 ± 1.4 (0.2–6)
Accompanied lesions	
Lung cancer	14
Multiple GGO lesions	9
None (single GGO)	6
Location	
Right upper	9
Right middle	0
Right lower	5
Left upper	7
Left lower	8
Operative procedure	
Wedge resection	23
Segmentectomy	6
Total	29

*Values are given as mean ± SD (range) or No.

Resection Technique

For resection of the marked nodules, a C-arm-shaped fluoroscopic unit was used to detect the radiopaque nodules, which were grasped using a ring-shaped forceps under fluoroscopy in multiple projections. For the deeply situated nodules, segmentectomy was performed. Successful resection of the nodule was finally confirmed by viewing the radiopaque nodule within the resected specimen under C-arm fluoroscopy.

Making the Cut Surface of the Resected Specimen

The resected specimens were inflated and fixed with a syringe of formalin using a thin needle. Intraoperative diagnoses of frozen specimens were not conducted. Formalin-fixed specimens were then viewed under fluoroscopy. The radiopaque area marked by lipiodol was cut serially at 5-mm intervals under fluoroscopy (Fig 2). The sections including the radiopaque area were submitted for pathologic examinations (Fig 3).

Results

All of the nodules could be marked on the CT scan images before surgery. Pneumothorax occurred in seven patients (39%), two of whom (11%) required drainage. No other complications were associated with the lipiodol marking. All of the 29 nodules could be successfully localized during surgery and completely resected. The surgical procedures used were wedge resection for 23 nodules and segmentectomy for 6 nodules.

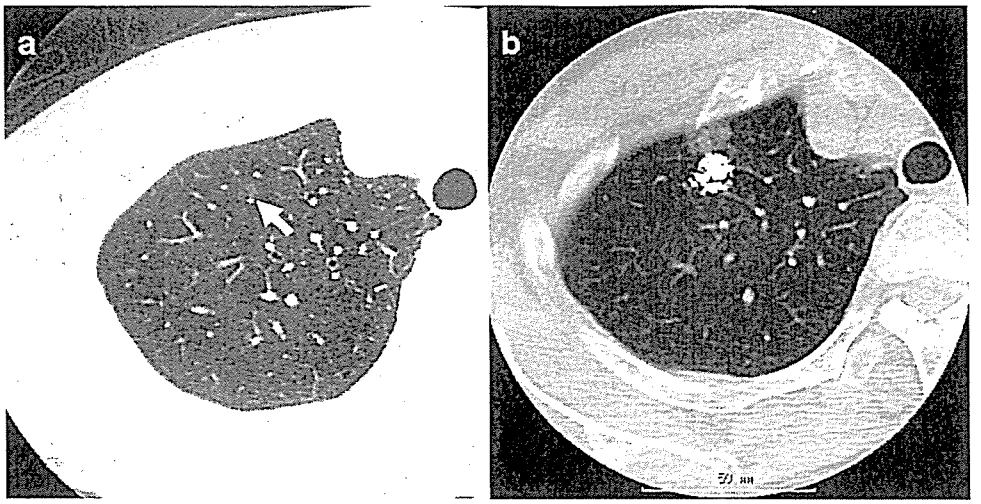

FIGURE 1. *Left, a*: GGO lesion 7 mm in size in the right apical segment (indicated by an arrow). *Right, b*: the lesion is marked with lipiodol.

All of the radiopaque nodules within the resected specimens could be seen distinctly on fluoroscopy even after formalin fixation. The mean number of sections submitted for pathologic examination was 2.3 ± 1.7 sections per lesion (range, 1 to 7 sections per lesion). While 11 of the 29 nodules (38%) could not be seen macroscopically on the cut surface of the sections, all could be seen microscopically and diagnosed pathologically (Table 2).

Pathologic diagnosis was BAC in 17 nodules, AAH in 10, and organized pneumonia in 2. Lipiodol did not affect the pathologic findings. Of the 17 BAC lesions, 6 accompanied the other lung cancers, 7 were part of multiple BAC or AAH lesions, and 4 were single lesions. Of the 10 AAH lesions, 5 accompanied the other lung cancers, and the other 5 were part of multiple BAC or AAH lesions. Of the two lesions with organized pneumonia, one accompanied another lung cancer and the other one accompanied a BAC lesion.

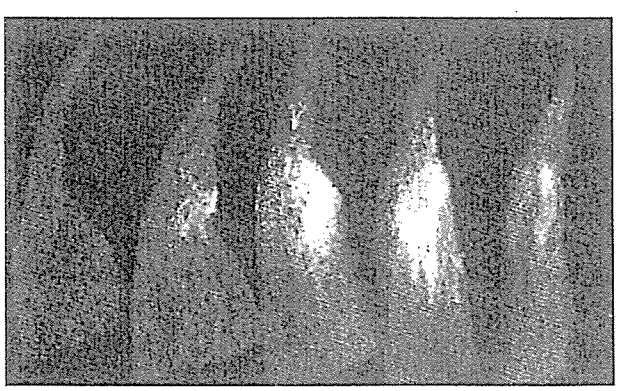

FIGURE 2. Serially cut sections including radiopaque area marked by lipiodol.

DISCUSSION

While the lipiodol-marking procedure is useful for localizing and resecting small pulmonary nodules,[7] it is still difficult to make pathologic sections that include the pulmonary nodules from the resected specimens. This is made particularly difficult by the fact that GGOs < 1 cm in size are generally impalpable. In addition, AAH and BAC lesions < 1 cm in size remain hard to visualize on the cut surface of sections, even after formalin fixation. This requires many pathologic sections to be made, which is time-consuming and expensive. However, the present method enables pathologic sections to be made that include impalpable GGO lesions, which could not only reduce the number of pathologic sections required but also could allow a definitive pathologic diagnosis.

While many small GGO lesions have been found recently by high-resolution CT scans, the management of such lesions remains controversial.[12,13] Small GGO lesions are generally observed initially by CT scanning. Even if a nodule is subsequently discovered to be a BAC, this approach would not miss the chance of surgical cure because it would remain within the T1N0M0 stage during the follow-up period until it grew to 2 cm in size.[14–16] However, for GGOs with CT scan findings that are highly suspicious for BAC, such as those that are round and dense, it would be desirable to perform a surgical biopsy rather than a follow-up for the following reasons: (1) follow-up for at least several years would be necessary because of the slow growth of BAC lesions,[17] which not only causes patients psychological stress but also entails the expense of follow-up CT scans; (2) while BAC lesions < 2 cm in size could

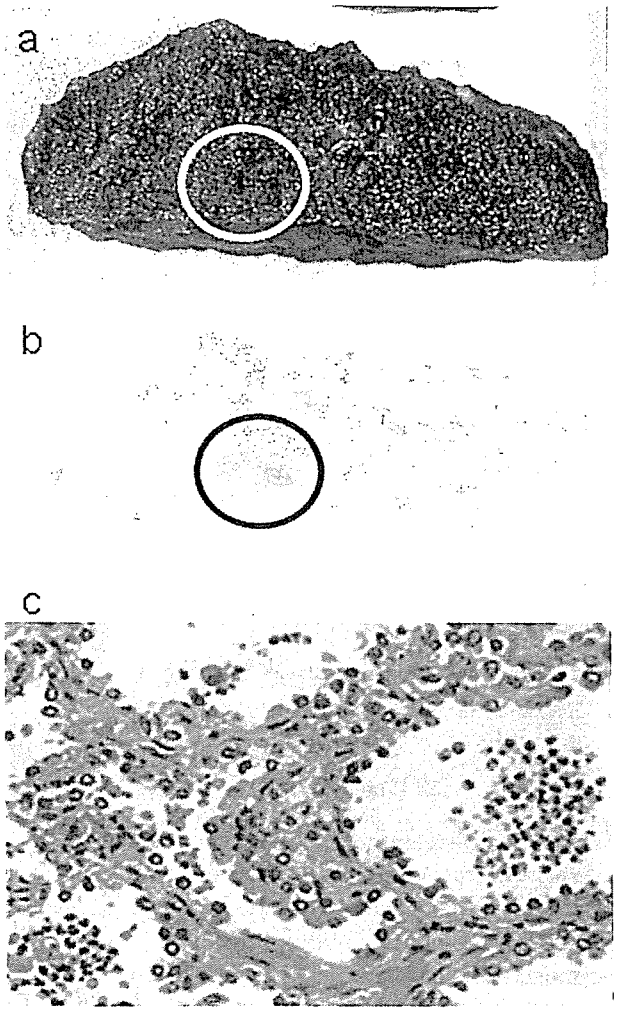

FIGURE 3. *Top, a*: the cut surface of the radiopaque area (indicated by a circle), where the lesion cannot be seen. *Middle, b*: the hematoxylin-eosin-stained section of the same section (the lesion is indicated by a circle). *Bottom, c*: the microscopic findings of the hematoxylin-eosin-stained section (×100), which is histologically diagnosed as BAC.

be cured by limited lung resection, follow-up might result in tumors increasing in size and becoming more aggressive. This could miss the chance of a cure by limited resection and increase the need for lobectomy.[18,19] In addition, CT scan examinations before surgery for general lung cancers sometimes detect other small GGOs, and it is then necessary to understand whether these are double lung cancers or intrapulmonary metastases. Of the 29 GGO lesions in the present study, 17 were BAC lesions and 12 were nonmalignant lesions, including 10 AAH lesions. The 17 lesions with BAC could be cured by limited resection. Of the 12 nonmalignant lesions, 6 were resected with their associated lung cancers, which enabled accurate TNM staging. The remaining six nonmalignant lesions were resected along with their associated BAC or AAH lesion < 1 cm in size; in this latter scenario, pathologic diagnosis could be made and follow-up could be discontinued for a considerable time. We therefore think that a positive surgical biopsy finding is acceptable for GGO lesions with CT scan findings that are highly suspicious of BAC or is accompanied by other lung cancers, even if those were < 1 cm in size.

Table 2—*Macroscopic Findings and Pathologic Diagnosis of the Nodules*

Pathologic Diagnosis	Macroscopic Finding		Total
	Visible	Nonvisible	
BAC	10	7	17
AAH	7	3	10
Organizing pneumonia	1	1	2
Total	18	11	29

Several marking methods have been reported for the localization of small pulmonary nodules. These include the hook-wire technique,[10,11] microcoil,[9] barium marking via bronchoscopy or percutaneous injection,[5,6] percutaneous injections of dyes,[1–3] colored collagen,[4] and lipiodol.[7,8] Because the general dye substances are water soluble, it is impossible to localize the dye-marked lesions after formalin fixation. The microcoil is under phase I study and has not been available in routine use.[9] The barium is seen as a lesion in the hematoxylin-eosin-stained sections and also causes an inflammatory change of the lung tissue, which might make a pathologic diagnosis difficult. The hook-wire technique has been reported to cause massive air embolism,[20,21] which had led to its prohibition in Japan. The lipiodol that was used in the present study not only stays at an injected site even after formalin fixation due to its insolubility in water but also never affects the pathologic findings of the injected site. We therefore think that lipiodol could be one of the optimal markers for not only localizing GGO lesions but also making pathologic sections from resected specimens.

The only complication of lipiodol marking in the present study was pneumothorax in seven patients (39%), two of whom (11%) required drainage. This arose due to the insertion of the needle into the lung but not due to the lipiodol itself. Although we have never encountered air embolisms during percutaneous needle insertion into the lung, the risk of this complication has been reported to be 0.02 to 0.07%.[20] In addition, lipiodol itself poses a potential risk of embolism because it is insoluble in water. We therefore take the following precautions: (1) prior to the injection of lipiodol, the syringe is withdrawn to confirm that blood has not flowed backward; (2) a

minimum amount of lipiodol, up to 0.5 mL, is injected; and (3) lipiodol is injected under fluoroscopic CT scanning to confirm that it does not enter vessels during injection. While there have been no reports of embolism due to lipiodol itself, patients should be informed of the potential risk. Moreover, the procedure should be performed with an awareness of the risk of embolism due to air or lipiodol.

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The distribution of parenchyma, follicles, and lymphocyte subsets in thymus of patients with myasthenia gravis, with special reference to remission after thymectomy

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Drs Ikeda, Mori, and Nomori (*left to right*). The bronze statue is Dr Shibasaburo Kitasato.

Objective: We sought to examine the distribution of parenchyma, follicles, and lymphocyte subsets in the thymus of patients with myasthenia gravis and to identify determinants of remission after thymectomy.

Methods: Sixty patients with myasthenia gravis who underwent thymectomy were examined. The thymus was divided into upper, middle, and lower parts. The upper part was defined as the superior horn, the lower part as the inferior horn, and the middle part as tissue located between the 2 horns. The percentage of parenchyma was measured morphometrically. The degree of follicular hyperplasia was classified into 5 grades. The densities of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes were classified into 5 grades. The remission of myasthenia gravis after thymectomy was examined with those variables in each part of the thymus.

Results: The middle part had the highest percentage of parenchyma, the highest grade of follicular hyperplasia, and the highest density of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes among the 3 parts ($P < .001$-$.05$). The grades of follicular hyperplasia in the middle and lower parts were significantly higher in patients with improvement of myasthenia gravis than in those without ($P < .05$). The densities of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes in the cortex of the middle part were significantly higher in patients with improvement than in those without improvement ($P < .01$-$.05$).

Conclusions: The thymus has a heterogeneous distribution of parenchyma, follicles, and lymphocyte subsets. The middle part had the largest parenchyma, the highest grade of follicular hyperplasia, and the highest densities of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes among the 3 parts of the thymus. The grade of follicular hyperplasia and the density of these lymphocyte subsets are predictive of improvement in myasthenia gravis after thymectomy.

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The grade of follicular hyperplasia (FH) in the thymus has been reported to be a significant factor for predicting remission of myasthenia gravis (MG) after thymectomy.[1-4] However, it has not been determined whether the distribution of parenchyma and follicles is uniform in the thymus. If these distributions are not uniform, the part of the thymus that is most appropriate for predicting remission of MG after thymectomy requires clarification. To examine these issues, we studied the following: (1) the thymus was divided into the upper, middle, and lower parts; (2) the percentage of parenchyma, grade of FH, and density of lymphocyte subsets in each part were investigated; and (3) the relationship between those variables and the remission of MG after thymectomy was analyzed.

Materials and Methods

One hundred six consecutive patients with MG were treated with extended thymectomy from 1997 through 2004 at the Department of Thoracic Surgery of Kumamoto University Hospital.

Abbreviations and Acronyms
FH = follicular hyperplasia
MG = myasthenia gravis

Of the 106 patients, 60 were available for pathological examination of the upper, middle, and lower parts of the thymus (Table 1). We studied these 60 patients retrospectively. All 60 patients had an extended thymectomy or extended thymothymomectomy through a median sternotomy.

The thymus was divided into 3 parts (ie, upper, middle, and lower; Figure 1). The upper part of the thymus was defined as the bilateral superior horns. The lower part was defined as the bilateral inferior horns. The middle part was defined as the tissue between the upper and lower parts. After fixation with formalin, these 3 pieces were usually sliced at intervals of 10 mm, resulting in an average of 16 tissue blocks (range, 5-55) submitted for pathological examination in each patient.

The percentage of parenchyma in each part of the thymus was measured by using the following method: (1) a hematoxylin and eosin–stained section was viewed under a macro lens and was displayed on the screen of a 3CCD digital color camera-computer system (FX380, Olympus Co); (2) the image of the whole of the selected section was outlined with a mouse on the screen, including both the parenchyma and adipose tissue, and the data were processed by using a computer, which calculated the total area; (3) the area of parenchyma was likewise calculated; and (4) the percentage of parenchyma was derived from the area of parenchyma divided by the total area.

The degree of FH of the thymus was classified into 5 grades according to the classification of the MG study group of the Ministry of Health and Welfare of Japan in 1977: grade 0, involuted thymus; grade I, accumulation of lymphocytes in the distended medulla; grade II, 1 follicle in 1 section; grade III, 2 to 4 follicles in 1 section; and grade IV, more than 5 follicles in 1 section or more than 1 follicle in each lobule.

An immunohistochemical analysis of lymphocytes using markers for CD3, CD4, and CD8 (Nichirei Co) was performed in each part. The density of lymphocyte subsets stained with these markers was classified into 5 grades: grade 0, no positive cells; grade I, scattered positive cells, grade II, fewer than half positive cells; grade III, more than half positive cells; and grade IV, almost all lymphocytes positive.

TABLE 1. Patient characteristics

Male/female sex	16/44
Mean age, range (y)	51 ± 18 (13–80)
Grade of MG (Osserman)	
I	6
II	32
III	20
IV	2
Thymoma/nonthymoma	19/41
Outcome of operation	
A	10
B	40
C	9
D	0
E	1

MG, Myasthenia gravis.

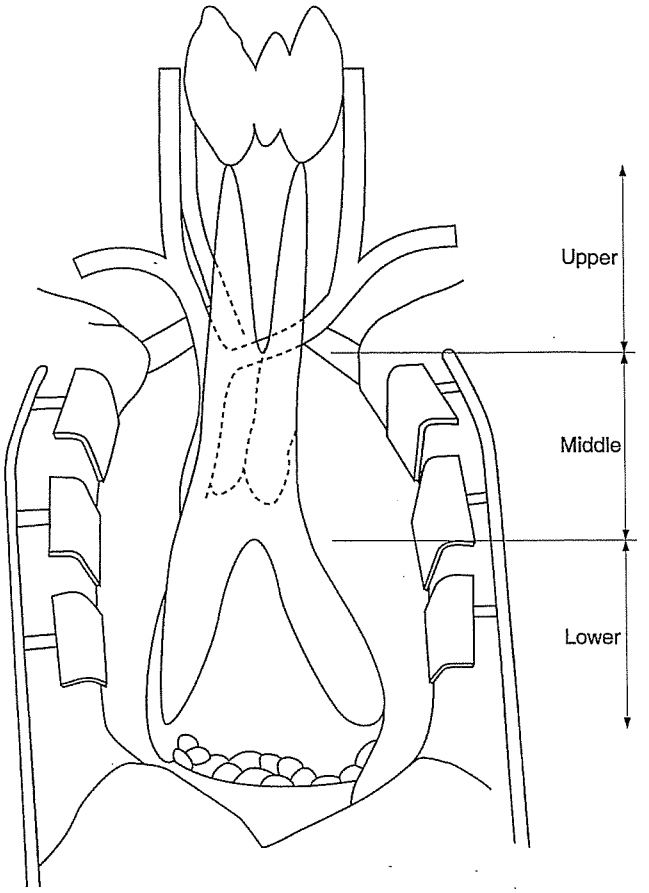

Figure 1. Definition of upper, middle, and lower parts of the thymus in the present study.

The postoperative outcome was obtained from hospital records or by means of telephone contact with a validated questionnaire. The investigation was approved by the institutional committee in 2005. The outcome of MG after thymectomy was classified from A to E: A, no symptoms and without medication; B, improvement and reduction in medication; C, no change; D, symptoms worse; and E, death caused by MG.

Differences in the percentage of parenchyma among parts of the thymus were analyzed by using paired Student *t* tests. Differences in the grade of FH and density of lymphocyte subsets in each part of the thymus were analyzed by using Wilcoxon signed-rank tests. Differences in the percentage of parenchyma between patients with and without improvement after thymectomy were analyzed with *t* tests. Differences in the grade of FH and the density of lymphocyte subsets between the patients with improvement and those without improvement were analyzed by using Mann–Whitney *U* tests. The Bonferroni test was used to determine

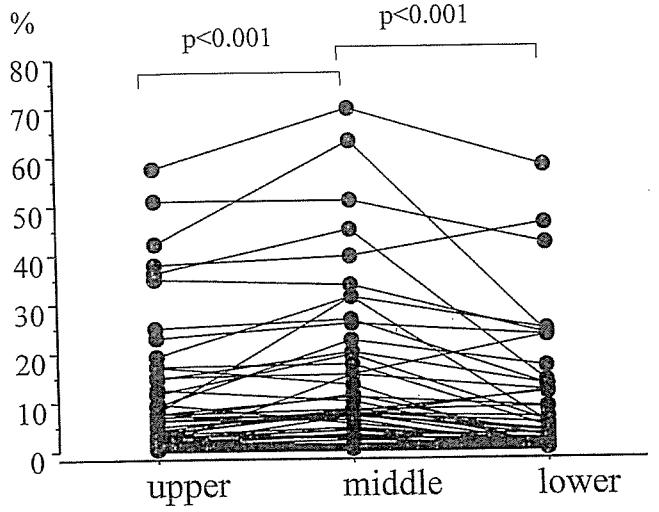

Figure 2. Percentage of parenchyma in each part of the thymus.

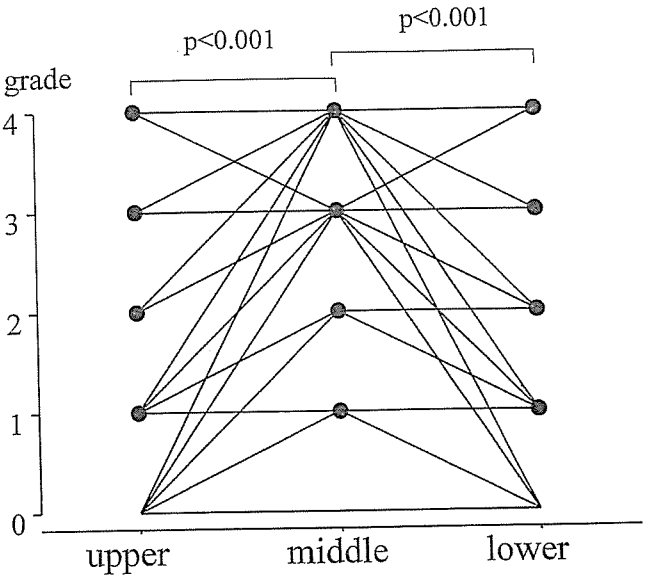

Figure 3. Grades of follicular hyperplasia in each part of the thymus.

significance for comparisons among the 3 parts. All values in the text and tables are presented as means ± standard deviation.

Results

The average of the total area of the upper, middle, and lower parts of the thymus was 4.2 ± 3.3, 7.6 ± 4.3, and 5.8 ± 4.3 cm^2, respectively. The average area of parenchyma was 0.3 ± 0.5, 0.8 ± 1.2, and 0.4 ± 0.7 cm^2 in the upper, middle, and lower parts of the thymus, respectively. As a result, the average percentage of parenchyma was 9.2% ± 13.1%, 11.8% ± 15.7%, and 7.5% ± 12.0% in the upper, middle, and lower parts of the thymus, respectively (Figure 2). The percentage of parenchyma in the middle part of the thymus was significantly greater than in either the upper or lower parts ($P < .001$).

The average grade of FH was 1.6 ± 1.5, 2.7 ± 1.7, and 1.4 ± 1.6 in the upper, middle, and lower parts of the thymus, respectively (Figure 3). The grade in the middle part was significantly higher than in the upper or lower parts ($P < .001$).

The distributions of densities of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes in the cortex and medulla of each part of the thymus are summarized in Table 2. Although the density of $CD3^+$ lymphocytes was significantly higher in the medulla than in the cortex of each part ($P < .0001$), the densities of $CD4^+$ and $CD8^+$ lymphocytes were significantly higher in the cortex than in the medulla of each part ($P < .0001$). In the cortex the densities of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes were significantly higher in the middle part than in the upper or lower parts ($P < .001$-$.05$), except for difference in density of $CD3^+$ lymphocytes between the upper and middle parts. In the medulla the densities of $CD4^+$ lymphocytes were significantly higher in the middle part than in the lower parts ($P < .05$).

The mean follow-up period after thymectomy was 49 ± 28 months. A postoperative status of A was seen in 10 patients, B in 40 patients, C in 9 patients, and E in 1 patient. The patient with a postoperative status of E was a 79-year-old woman who died of a myasthenic crisis 49 months after thymectomy. Figure 4 shows the percentage of parenchyma of each part of the thymus in 50 patients with improvement (A and B) and 10 patients without improvement (C, D, and E), showing no significant difference between the 2 groups ($P = .16$, .09, and .12, respectively).

Figure 5 shows the grades of FH of each part of the thymus in patients with and without improvement. Although the grade of FH in the middle and lower parts was significantly higher in patients with improvement than in

TABLE 2. Distribution of density of lymphocyte subsets in the thymus

	Density of lymphocyte subsets		
	$CD3^+$	$CD4^+$	$CD8^+$
Cortex			
Upper	1.5 ± 0.8	1.6 ± 0.9†	2.0 ± 0.8†
Middle	1.5 ± 0.7*	2.1 ± 1.0†	2.4 ± 0.8†
Lower	1.2 ± 0.8*	1.6 ± 1.1†	2.0 ± 1.1*
Medulla			
Upper	1.9 ± 0.6	1.2 ± 0.8	0.8 ± 0.5
Middle	2.0 ± 0.7	1.3 ± 0.7*	0.9 ± 0.5
Lower	1.8 ± 0.9	1.1 ± 0.8*	0.8 ± 0.5

Upper, Upper part of the thymus; *Middle*, middle part of the thymus; *Lower*, lower part of the thymus. *$P < .05$; †$P < .01$; ‡$P < .001$.

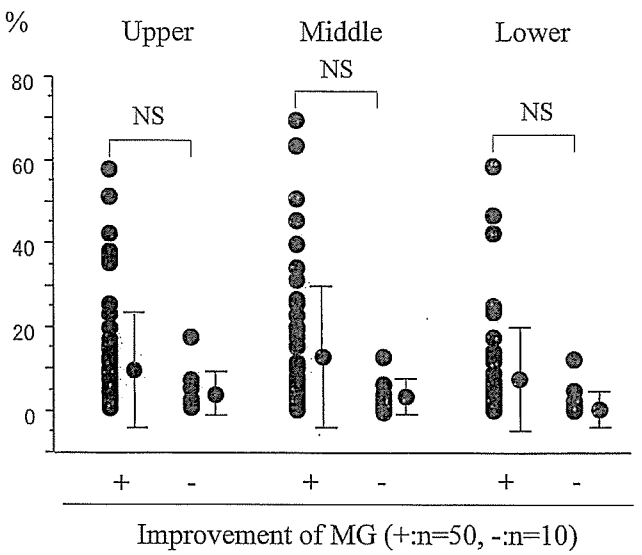

Figure 4. Differences in percentage of parenchyma in each part of the thymus between patients with and without improvement of myasthenia gravis after thymectomy. *NS*, Nonsignificant; *MG*, myasthenia gravis.

those without (P = .026 and .044, respectively), that in the upper part did not show a significant difference (P = .16).

The densities of $CD3^+$, $CD4^+$ and $CD8^+$ lymphocytes in the cortex and medulla of each part of the thymus in patients with improvement and in those without are summarized in

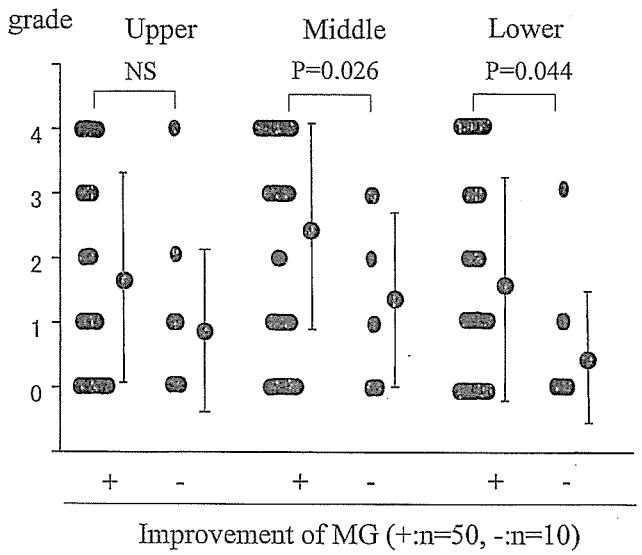

Figure 5. Differences in grade of follicular hyperplasia in each part of the thymus between patients with and without improvement of myasthenia gravis after thymectomy. *NS*, Nonsignificant; *MG*, myasthenia gravis.

TABLE 3. Density of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes in each part of the thymus in patients with and without improvement of myasthenia gravis after thymectomy

	Improvement of MG (+/−)		
	Density of:		
	$CD3^+$	$CD4^+$	$CD8^+$
Cortex			
Upper	1.6/0.9*	1.8/0.9†	2.1/1.7
Middle	1.6/0.9†	2.2/1.4*	2.5/1.7*
Lower	1.8/1.1	1.7/1.0	2.1/1.8
Medulla			
Upper	2.0/1.5*	1.3/0.8	0.8/0.6
Middle	2.1/1.6	1.4/0.7†	0.9/0.7
Lower	1.8/1.5	1.1/0.7	0.8/0.7

Upper, Upper part of the thymus; *Middle*, middle part of the thymus; *Lower*, lower part of the thymus. *$P < .05$, †$P < .01$.

Table 3. The results in the cortex were as follows: (1) although the densities of $CD3^+$ lymphocytes in the upper and middle parts were higher in patients with improvement than in those without (P = .012 and .003, respectively), the difference in the lower part was not significant (P = .8); (2) although the densities of $CD4^+$ lymphocytes in the upper and middle parts were higher in patients with improvement than in those without (P = .006 and .015, respectively), the difference in the lower part was not significant (P = .8); and (3) although the density of $CD8^+$ lymphocytes in the middle part was higher in the patients with improvement than in those without improvement (P = .014), the differences in the upper and lower parts were not significant (P = .1 and .4, respectively). In the medulla (1) the density of $CD3^+$ lymphocytes in the upper part was higher in patients with improvement than in those without (P = .012), but the differences in the middle and lower parts were not significant (P = .054 and .3, respectively); (2) the density of $CD4^+$ lymphocytes in the middle part was higher in patients with improvement than in those without (P = .007), but the differences in the upper and lower parts were not significant (P = .07 and .13, respectively); and (3) the density of $CD8^+$ lymphocytes did not show significant differences between patients with improvement and those without in any of the 3 parts (P = .2, .2, and .7, respectively). Thus the differences in density of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes between patients with improvement and those without improvement were most significant in the cortex of the middle part of the thymus.

Pathological differences of thymus (eg, thymic hyperplasia, involuted thymus, and thymoma) did not affect the above results.

Discussion

The present study revealed 3 main points: (1) the middle part of the thymus had the highest percentage of paren-

chyma, the highest grade of FH, and the highest densities of lymphocyte subsets of the 3 parts; (2) the grades of FH in the middle and lower parts showed significant correlations with remission of MG after thymectomy, although that in the upper part did not; and (3) the densities of $CD3^+$, $CD4^+$ and $CD8^+$ lymphocytes in the cortex of the middle part showed the greatest correlation with remission of MG after thymectomy, whereas those in the other parts showed less correlation.

The distribution of parenchyma, follicles, and lymphocyte subsets in the thymus has not been previously reported. The present study examined the differences of the percentage of parenchyma, grade of FH, and densities of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes in the upper, middle, and lower parts of the thymus and revealed that the middle part had significantly higher values of these variables than the other parts. Therefore we conclude that the middle part of the thymus is the most representative area for examining parenchyma, follicles, and lymphocyte subsets.

It has been reported that patients with MG with FH of the thymus have higher remission rates after thymectomy than those without,[1-4] but other authors have disputed this.[5,6] The present study showed that the grades of FH in the middle and lower parts of the thymus were higher in patients with improvement than in those without improvement, although the grades in the upper part did not show a significant difference. Therefore to predict the outcome after thymectomy from the grade of FH, the middle or lower part is more appropriate than the upper part.

The present study has shown that the thymus has a heterogeneous distribution of parenchyma, follicles, and T-cell subsets. The middle part had the largest parenchyma, the highest grade of FH, and the highest density of T-cell subsets. Both the grade of FH and density of T-cell subsets in the middle part had significant correlation with improvement of MG after thymectomy. The middle part of the thymus is therefore the most representative area not only for histopathological examination but also for predicting improvement of MG after thymectomy.

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Original Article

The Efficacy of Epidural Analgesia after Video-Assisted Thoracoscopic Surgery: A Randomized Control Study

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Purpose: Video-assisted thoracoscopic surgery (VATS) is known to reduce the severity of pain after surgery. However, it has not yet been established whether epidural anesthesia/analgesia (EA) is necessary after VATS. We therefore conducted a randomized control study to examine whether or not EA is necessary for pain control after VATS.

Patients and Methods: Forty-six patients undergoing VATS were randomly allocated to one of 2 groups: 24 who were given EA after the procedure (EA group) and 22 who were not (NEA group). Patients in the EA group received a continuous infusion of fentanyl and bupivacaine via an epidural catheter for 2 days after VATS. The degree of postoperative pain was assessed on the total dose of additional analgesics administered, a visual analog scale (VAS), a verbal pain score at rest (VPS-R) and on movement (VPS-M), from the day of surgery to the 2nd postoperative day (2 POD).

Results: Additional use of rectal diclofenac sodium and intramuscular pentazocine was more frequent in the NEA group than in the EA group ($p<0.05$). The VAS, VPS-R, and VPS-M scores were significantly lower in the EA group than in the NEA group at 0 POD, from 0 to 1 POD, and from 0 to 2 POD, respectively ($p<0.0001$–0.05). Stepwise regression analysis revealed that EA was a significant independent variable of VPS-R and VPS-M from 0 to 1 POD ($p<0.05$). However, the incidence of nausea/vomiting in the EA group was 29%, which was more frequent than in the NEA group (5%) ($p<0.05$).

Conclusion: While EA causes nausea/vomiting in some patients, it is effective for pain control until 1 POD after VATS, especially for pain on movements. (Ann Thorac Cardiovasc Surg 2006; 12: 313–8)

Key words: epidural anesthesia, video-assisted thoracoscopic surgery, pain control

Introduction

The application of video-assisted surgery has not only provided the benefit of minimal invasion but has also revolutionized operative procedures and postoperative management. Video-assisted thoracoscopic surgery (VATS) requires only a small skin incision and no rib retraction. This causes minimal damage to the thoracic wall, resulting in a decrease in postoperative pain, postoperative pulmonary dysfunction, and postoperative morbidity and mortality.[1–6] The application of VATS has led to a change in postoperative management, especially in pain control.[7,8]

There is no precise data on how many patients receive epidural anesthesia/analgesia (EA) following thoracic surgery. In 2004, Wu et al. reported the effect of postop-

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erative EA following surgery in medicare patients.[9] Out of 68,723 patients analyzed, 3,796 patients underwent thoracic surgery. Fifty percent of these patients had postoperative epidural usage following thoracic surgery (1,899 patients). EA has emerged as the preferred pain control. While EA has been used after thoracic surgery, it is debatable whether VATS patients would require EA because of the lower severity of postoperative pain in comparison with open thoracotomy.[1,4,6] However, it has not been clarified whether EA is necessary after VATS. To address this issue, we examined the pain score and side effects of EA in post-VATS patients using a randomized control study.

Patients and Methods

Patient entry and randomization

This study was approved by the ethics committee of Kumamoto University Hospital in August 1999. Patients who were scheduled to undergo lobectomy or partial lung resection by VATS at Kumamoto University Hospital from September 1999 to September 2001 were enrolled. Exclusion criteria included emergency cases, American Society of Anesthesiology (ASA) risk grade over III, and contraindication for EA.

At the time of entry, the patients received an explanation about the study by both an anesthesiologist and a surgeon before the operation, and a written informed consent was obtained from them. Patients who agreed to participate were randomly allocated using envelopes to one of 2 groups: an EA group and an NEA group.

Anesthesia and postoperative pain control

All patients received premedication with an intramuscular injection of atropine sulfate 0.25–0.5 mg and midazolam 0.06 mg/kg. In the operating room, epidural catheters of patients in the EA group were placed in Th5/6 or Th6/7 level before induction of general anesthesia. General anesthesia was induced with intravenous thiamylal sodium (4–6 mg/kg) and vecuronium bromide (0.1 mg/kg). Anesthesia was maintained with isoflurane, air and oxygen. Vecuronium bromide was occasionally given for muscle relaxation as required. Neither narcotics nor epidural anesthesia were used during surgery.

Immediately after surgery, patients in the EA group were given a single injection of 5 ml of 0.25% bupivacaine hydrochloride via the epidural catheter, followed by continuous infusion of 80 ml of 0.25% bupivacaine hydrochloride (90 ml in patients over 70 years old) and 1 mg of fentanyl citrate (0.5 mg in patients over 70 years old) using a balloon infuser at a rate of 2.0 ml/h. If adequate postoperative pain relief could not be achieved, additional analgesics were administered in both groups. The total dose of each additional analgesic was compared between the 2 groups.

Assessment of postoperative pain

Each patient was interviewed by anesthesiologists, who were not included by the authors in this study, every night from the day of surgery (0 POD) to the 2nd postoperative day (2 POD). The patients were asked to indicate their degree of postoperative pain on a visual analog scale (VAS) ranging from 0 mm (no pain) to 100 mm (extreme pain) on a 100-mm line drawing.[10] The verbal pain score at rest (VPS-R) was graded from 0 to 3 (0 = no pain, 1 = slight pain, 2 = moderate pain without analgesics, 3 = pain requiring analgesics). The verbal pain score on movement (VPS-M) was graded from 0 to 2 (0 = no pain on movement, 1 = pain on coughing and moving but controlled, 2 = pain on coughing or moving and not controlled).[11] The requirement for additional analgesics was examined from 0 to 2 POD. Postoperative symptoms, complications, and side effects related to EA were examined.

Operative procedure

VATS lobectomy was undertaken via one access port (12 mm) and one lateral utility thoracotomy (6 cm) without a rib retractor. Mediastinal lymph node dissection was performed routinely with VATS lobectomy. Partial lung resection was undertaken via 3 surgical ports (12 mm) for benign pulmonary nodules or bronchiolo-alveolar cell carcinomas less than 10 mm in diameter. A 28F intercostal drain was inserted through an access port incision in each patient. These drains were removed when the underlying lung was fully expanded with no residual air leak.

Statistical analysis

The χ^2 test and Fisher's exact test were used to compare discrete variables. Stepwise forward analysis was performed, with drop in VPS-R and VPS-M as dependent variables. Factors considered among the independent variables included EA, age, sex, ASA, the duration of surgery, and the duration of chest tube drainage. Statistical significance was assumed at $p<0.05$. All analysis was performed using StatView software (version 5.0, SAS Institute Inc., Cary, NC, USA). All values in the text and tables are given as mean±SD (standard deviation).

Table 1. Patient classification

	EA group	NEA group
Number	24	22
Age (years)	64.4±12.3	62.4±9.9
BMI (kg/m^2)	22.9±3.2	22.9±2.7
Sex (M/F)	11/13	10/12
Duration of surgery (min)	170.7±94.8	172.0±96.5
Partial resection/lobectomy	10/14	10/12
ASA I/II/III	8/13/3	9/12/1
Chest tube drainage over 2 POD	13	12

BMI, body mass index; M, male; F, female; ASA, risk grade according to criteria set down by American Society of Anesthesiology; POD, postoperative day; EA, epidural anesthesia; NEA, non-EA.

Table 2. Number of patients required additional analgesia

Drug	Route of administration	Number of patients		p value
		EA group	NEA group	
Diclofenac sodium	Rectally	16	22	0.0040
Pentazocine	im	3	16	<0.0001
Loxoprofen sodium	Orally	6	9	0.3480

im, intramuscularly; EA, epidural anesthesia; NEA, non-EA.

Table 3. Total dose of diclofenac sodium and pentazocine per patient

Drug	EA group	NEA group	p value
Diclofenac sodium (mg)	44.8±44.2	109.1±93.7	0.0040
Pentazocine (mg)	1.9±5.1	20.5±18.7	<0.0001

EA, epidural anesthesia; NEA, non-EA.

Results

Forty-six patients were enrolled. There were 24 patients in the EA group and 22 patients in the NEA group (Table 1). There were no significant differences in age, body mass index (BMI), sex, duration of surgery, extent of surgery (partial resection or lobectomy) or ASA score between the 2 groups.

Most of the patients needed additional analgesics postoperatively until 2 POD. Rectal suppositories of diclofenac sodium, intramuscular injection of pentazocine, and oral loxoprofen sodium were commonly used in each group (Table 2). Rectal diclofenac sodium and intramuscular pentazocine were needed more frequently in the NEA group than in the EA group ($p<0.05$). Total doses of diclofenac sodium and pentazocine per patient were also higher in the NEA group than in the EA group ($p=0.0040$ and $p<0.0001$, respectively)(Table 3).

Pain scores assessed by VAS, VPS-R and VPS-M are shown in Figs. 1–3. The mean VAS scores in the NEA and EA groups were 35.3±28.6 and 18.7±25.5 at 0 POD, 29.6±20.5 and 21.6±19.1 at 1 POD, and 20.1±20.6 and 12.7±14.0 at 2 POD, respectively (Fig. 1). The mean VAS score in the EA group was significantly lower than that in the NEA group at 0 POD ($p=0.045$), but there was no significant difference at 1 and 2 POD. The mean VPS-R scores in the NEA and EA groups were 1.41±1.01 and 0.54±0.88 at 0 POD, 1.00±0.05 and 0.50±0.72 at 1 POD, and 0.73±0.83 and 0.38±0.58 at 2 POD, respectively (Fig. 2). The difference between the 2 groups was significant at 0 and 1 POD ($p=0.003$ and $p=0.046$, respectively). At 0 POD, VPS-R grade 0 (no pain at rest) was seen in 16 patients of the EA group (67%) and 4 of the NEA group (17%), while VPS-R grade 3 (pain requiring analgesics) was seen in one patient of the EA group (4%) and 4 of the NEA group (18%). At 1 POD, VPS-R grade 0 was seen in 15 patients of the EA group (63%) and 8 of the NEA group (36%), while grade 3 was

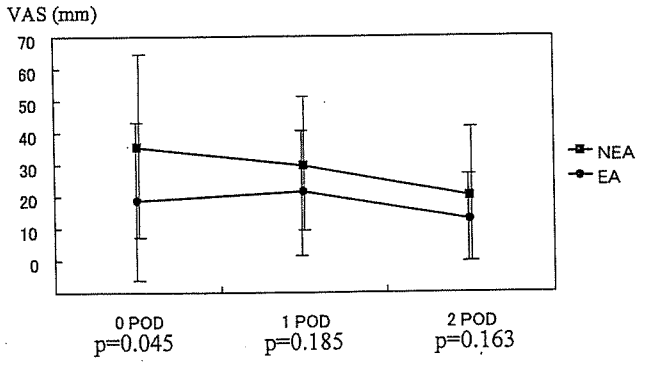

Fig. 1. Mean VAS score after VATS.
VAS, visual analogue scale; VATS, video-assisted thoracoscopic surgery; EA, epidural anesthesia; NEA, not EA; POD, postoperative day.

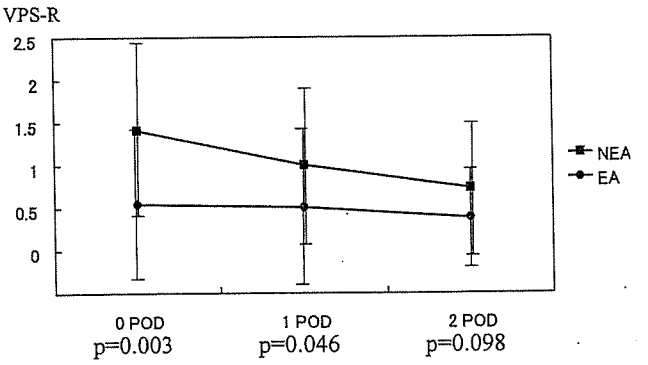

Fig. 2. Mean VPS-R score after VATS.
VPS-R, verbal pain score at rest; VATS, video-assisted thoracoscopic surgery; EA, epidural anesthesia; NEA, not EA; POD, postoperative day.

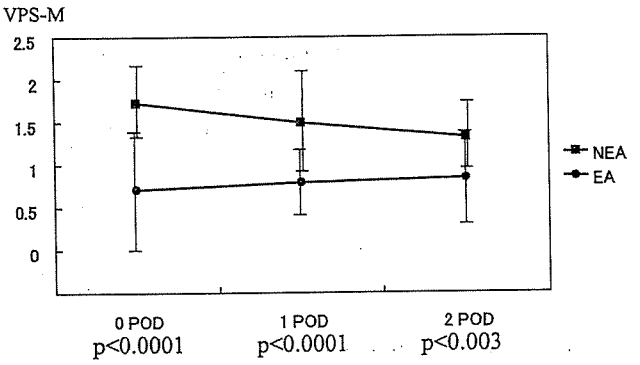

Fig. 3. Mean VPS-M score after VATS.
VPS-M, verbal pain score on movement; VATS, video-assisted thoracoscopic surgery; EA, epidural anesthesia; NEA, not EA; POD, postoperative day.

seen in none of the EA group (0%) and one of the NEA group (5%). The mean VPS-M scores in the NEA and EA groups were 1.73±0.46 and 0.71±0.69 at 0 POD, 1.50±0.60 and 0.79±0.42 at 1 POD, and 1.32±0.48 and 0.83±0.57 at 2 POD, respectively (Fig. 3). The difference between the 2 groups was significant from 0 to 2 POD ($p<0.0001$).

Table 4 presents the result of stepwise regression analysis, showing that EA was only one independent predictor of VPS-R at 0 and 1 POD ($p=0.0033$ and 0.0462). However, there was no predictor of VPS-R at 2 POD. With VPS-M, there were a few independent predictors at 0–2 POD, i.e. EA from 0 to 2 POD, ASA risk grade at 0 POD and the duration of surgery (DOS) at 2 POD ($p<0.0001$ and 0.0017).

Table 5 shows the incidence of EA-related side effects and complications after surgery. Seven patients in the EA group (29%) suffered nausea or vomiting, of which the frequency was higher than in the NEA group (1 patient, 5%)($p<0.05$). All patients who complained of nausea or vomiting were over 60 years old. While one patient in the NEA group had air leakage for more than 7 days after VATS, none of the other patients in both groups suffered any postoperative complications. EA was discontinued in 3 patients because of nausea or vomiting, but there were no incidences of marked hypotension in any of the patients in the EA group.

Discussion

In thoracic surgery, adequate control of acute postoperative pain is known to decrease postoperative morbidity and mortality and result in a lower incidence of chronic postsurgical pain.[12,13] For this reason, thoracic surgeons have pursued both minimally invasive surgery and better management of postoperative pain. VATS represents the ultimate minimally invasive surgery, and results in a significant reduction in postoperative pain.[14] EA and systemic opioids have been commonly used for postoperative analgesia. It is necessary to establish the most suitable type of pain management after VATS.[15]

There has been clinical debate about which analgesic techniques provides the most effective postoperative pain control, i.e., intravenous or epidural opioids, epidural or paravertebral local anesthetics with or without opioids, patient controlled analgesia (PCA) or continuous injection, cryoanalgesia, transcutaneous electrical nerve stimulation (TENS), or non-steroidal anti-inflammatory drugs