Table 1. Surgical Procedures

Procedure and Characteristic	Result
Thoracotomy	
Median sternotomy/posterolateral	7/33
Blood loss, range (mean)	120–1,350 mL (604 mL)
Operation time, range (mean)	150–811 min (451 min)
Lung resection	
Lobectomy/pneumonectomy	19/21
Bronchoplasty	
Bronchial sleeve/carinal resection	5/15
Surgical margin	
Macroscopic complete resection	33 (82.5%)
Microscopic complete resection	28 (70%)
Time for cross-clamp, range (median)[a]	10–44 (33 min)

[a] Cross-clamp was performed in 7 patients. No neurologic complications were observed.

dal strategy in clinical trial setting. Postoperative treatment was performed in 7 patients. Chemotherapy was performed for 1 patient and radiotherapy for 6 patients. Histologic typing of resected lung carcinoma resulted in 17 adenocarcinomas, 15 squamous cell carcinomas, 4 large cell carcinomas, and 4 other histologic types. The maximum tumor dimension ranged from 1.8 to 11 cm, with a mean of 5.6 cm. No patients were pathologically classified as stage I, 5 were classed as stage IIB, 6 as stage IIIA, 26 as stage IIIB, and 3 as stage IV. As to T factor, T4 disease was found in 26 patients, and mediastinal lymph node metastases were found in 27 patients.

Surgical Procedures

Lung carcinoma was resected through a median sternotomy in 7 patients (18%) and through a right thoracotomy in 33 patients (82%; Table 1). A median sternotomy approach was used mainly for making an intraoperative shunt between the left brachiocephalic vein and the right atrium. If the shunt is patent, combined resection of the SVC can be performed more simply because a cross-clamp of the SVC is safely performed. A right thoracotomy in the fourth or fifth intercostal space was usually used to access the tumor. Through this approach we could easily access the lung and mediastinum including the SVC system. The only disadvantage of this approach is the difficulty of accessing the left brachiocephalic vein. Pneumonectomy was performed in 21 patients (53%) and lobectomy in 19 patients (47%). Bronchoplasty procedures were necessary in 20 patients (50%), and sleeve pneumonectomy was performed in 15 of these patients (75%). Surgical margin was negative macroscopically and microscopically in 33 patients (83%) and 28 patients (70%), respectively. As to the adjuvant therapy, among 12 patients with incomplete resection, 3 could not undergo adjuvant therapy because of postoperative major complications. Another patient did not undergo adjuvant therapy because of disseminated tumor cells. Two patients were considered to have minimum positive margin and we did not perform adjuvant therapy. In all, 6 patients with incomplete resection underwent adjuvant therapy. All of them had postoperative radiotherapy, and 2 long-term survivors underwent postoperative radiotherapy of 45 and 50 Gy.

Type of Vascular Reconstructions

The total number of reconstructions was 44. The SVC pathway was reconstructed with two vascular grafts in 4 patients (10%). No patients had clinical features of SVC syndrome preoperatively. The SVC system was totally and partially resected in 11 patients (28%) and 29 patients (72%), respectively. For all of the former patients, a replacement with vascular grafts was performed. For the latter patients, autologous pericardial patch was used in 8patients, and running direct suture was performed in 21patients. Replacement of the SVC or brachiocephalic vein was performed with Gore-Tex bypass grafts (W.L. Gore & Associates, Inc, Naperville, IL). The size of the grafts ranged from 10 to 14 mm for the reconstruction for the SVC, and 10 to 12 mm for the left brachiocephalic vein. Resection and reconstruction of the SVC system is a major technical challenge because of possible detrimental effects of clamping a patent vessel. A venous catheter in the lower limbs is usually necessary for maintaining volume during clamping. We performed a partial clamp of the SVC system in 19 patients (48%), and a cross-clamp in 7 patients (18%). Among the 7 patients who underwent cross-clamping, just 1 patient underwent total replacement of the SVC. In the remaining 6 patients, we performed a direct running suture of the SVC in 3 patients, and pericardial patch in 3 patients. Therefore total replacement of the SVC was performed using extraluminal shunt in most cases. The time for cross-clamping ranged from 10 to 44 minutes, with a median of 33 minutes. Postoperative neurologic complications were not observed. For the other patients vascular shunts were used to reduce the harmful effect of clamping the SVC. Intraluminal shunts were used in 3 patients, and extraluminal shunts in 12 patients. When total replacement of the SVC is necessary, we preferred making shunts to reduce the potential risk of cross-clamping of the SVC. Vascular patency was evaluated with computed tomography with contrast enhancement in most patients. Postoperative anticoagulant therapy was not always adopted at our institute.

Clinicopathologic Factors and Statistic Analyses

The medical record of each patient was examined as to several prognostic factors. To investigate the impact on survival, the following conventional clinicopathologic factors were studied retrospectively: age (continuous variables), sex (men versus women), histologic type of tumor (squamous cell carcinoma versus others), pathologic T factors (T1 to T3 versus T4), pathologic N status (pN0 to pN1 versus pN2 to pN3), type of reconstruction of the SVC (graft versus other methods), patterns of SVC involvement (direct extension by primary tumor versus by lymph nodes), and curability of the surgical resection (incomplete versus complete). The definition for incom-

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plete resection is as follows: (1) positive histologic margin, and (2) disseminated disease. We had 1 patient with disseminated disease, and the disseminated tumor cells were diagnosed pathologically, not noticed during surgical resection. These factors were entered into univariate analyses to determine which clinicopathologic factors have a greater impact on the 5-year survival rate. The median follow-up period for living patients was 67 months. The length of survival was defined as the interval in months between the day of surgical resection of lung carcinoma and the date of overall death or the last follow-up. An observation was censored at the last follow-up when the patients were alive. The survival rates were calculated by the Kaplan-Meier method, and univariate analyses were performed by means of the log-rank test on StatView 5.0 (SAS Institute, Inc, Cary, NC) with a PCV-RX75 (Sony, Inc, Tokyo, Japan) [9]. Statistical analysis was considered to be significant when the probability value was less than 0.05.

Results

Vascular Patency, Surgical Morbidity, and Mortality

For patients undergoing cross-clamping of the SVC, the time for complete obstruction ranged from 10 to 44 minutes, with a median of 33 minutes. No perioperative complications caused by the clamping, such as neurologic deficit, were observed. As regards vascular patency, there were no early prosthesis thromboses in our series. However, there were two vascular occlusions (5%) with a median follow-up period for patency of the graft of 67 months. One occlusion occurred as a result of a locoregional recurrence of lung cancer 9 months after surgery, and the other was caused by a thrombosis 13 months after surgery. Postoperative major morbidity and 30-day mortality were 40% (n = 16) and 10% (n = 4), respectively. There were three bronchopleural fistulas with one postoperative death, three major pneumonias with one fatal sequence, 4 patients with thoracic empyema, 3 patients with postoperative bleeding, one fatal bronchoarterial fistula, and one fatal Mallory-Weiss syndrome. Among 16 patients with major complications, 11 patients underwent bronchoplastic procedures. Furthermore, 8 patients underwent sleeve pneumonectomy.

Prognostic Factors

The overall 5-year survival rate for 40 resected lung cancer patients was 24% with the median follow-up period for living patients of 67 months (7 patients were actual 5-year survivors). Univariate analyses revealed no significant prognostic factors except the patterns of involvement of the SVC system. The 5-year survival rate of patients with SVC invasion by direct tumor extension (n = 25) was 36% and those with SVC invasion by metastatic lymph nodes (n = 15) was 6.6%, and this difference was statistically significant (p = 0.05, log-rank test; Fig 1).

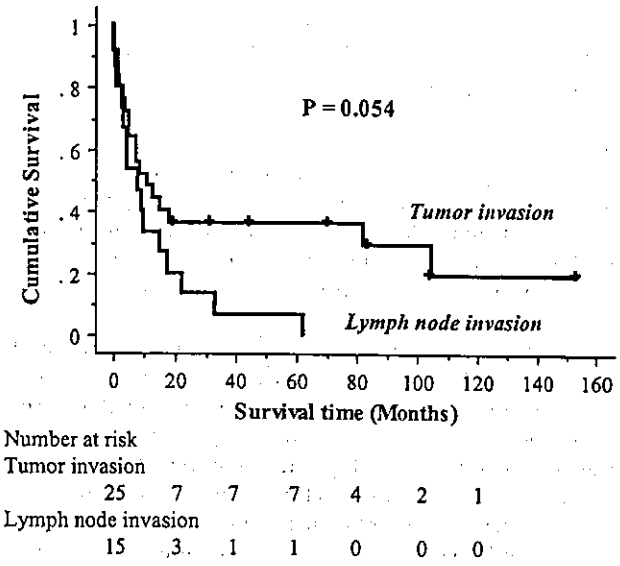

Fig 1. Survival by the patterns of involving the superior vena cava system for patients with lung cancer who underwent combined resection of the superior vena cava. A significant difference was observed (p = 0.05, log-rank test).

Comment

Inasmuch as a distant failure is frequently observed, the indication of surgery for T4 disease, to date, remains controversial. Chemoradiotherapy is considered to be a standard for stage IIIB lung cancer, and the 5-year survival rate is reported to be approximately 15% [10, 11]. However, locoregional control is not sufficient after chemoradiotherapy, and local recurrence rate is reported as 17% at 1 year [12]. Although the persistence of viable cells after chemoradiotherapy is considered as one of the poor prognostic indicators, surgery successfully salvaged this population [6, 13–15]. Surgical resection for patients with viable tumor cells in a residual tumor after chemoradiotherapy offered approximately 28% long-term survival. However, one of the major concerns of salvage surgery is mortality and morbidity owing to the difficulty of procedures required for resection of T4 disease. As regards the SVC, there have been a few reports dealing with the prognosis and feasibility of surgical resection. Therefore, we attempted to clarify the outcome of combined resection of the SVC system for lung carcinoma.

Considering the surgical indication for lung cancer involving the SVC, the possibility of good prognosis with low postoperative complications would be key, and the most important thing is the selection of patients who will benefit from surgical resection. Although some prognostic factors, such as the degree of SVC involvement, have been reported, controversies still remain [7]. Our results showed the pattern of SVC involvement to be a significant prognostic factor. The prognoses were compared between patients with SVC invasion by metastatic lymph nodes (n = 15) and those with SVC invasion by a direct tumor extension (n = 25), and the survival difference was significant (5-year survival rate: 6.6% versus 36%; p =

0.05). This is the major finding from our study. Interestingly, nodal status (N0 to N1 versus N2 to N3) was not a significant prognostic factor. That is to say, if a lung cancer is centrally located and involves the SVC directly, the prognosis of the patients would be relatively promising. In contrast, if a tumor is located peripherally and metastatic lymph nodes involve the SVC, the prognosis would be dismal. These are the unique and important prognostic factors, and they should be taken into consideration in planning for surgery or a clinical trial for T4 lung cancer.

Our results confirmed reported surgical mortality and morbidity for T4 lung cancer surgery. The rate of postoperative complications appears to be higher than previous reports [1–3, 6, 7, 16]. Right side pneumonectomy is often associated with postoperative complications, and in our series right pneumonectomies were performed in more than half of patients. Furthermore, among them 15 patients underwent right side sleeve pneumonectomy. This is a possible explanation for the relatively high rate of postoperative morbidity and mortality.

We prefer using an extraluminal shunt, rather than an intraluminal shunt, when complete SVC clamping is needed. Median sternotomy is the easy way to make a temporary shunt between the left brachiocephalic vein and the right atrium. If the bypass remains patent during clamping of the SVC, the risk to the central nervous system would decrease. We had no choice but to perform cross-clamping of the SVC in 7 patients. The time for cross-clamping ranged from 10 to 44 minutes, with a median of 33 minutes. Postoperative neurologic complication was not observed in our series. The time of brain damage onset has been a topic of debate. According to experimental data, approximately 60 minutes of clamping was well tolerated in animal models [17]. Although the definitive report for human models has not been reported, we consider up to 30 minutes of clamping would be tolerable. However, to avoid possible damage to the brain, rapid reconstruction is mandatory.

Postoperative thromboembolic disorder is relatively rare in our country. Therefore, an intraoperative or postoperative regimen of anticoagulation therapy is not always adopted. We experienced no cases with early occlusion of the graft, but two cases with chronic graft occlusion. One of these patients had intrathoracic recurrent disease, and the other had thrombosis in the graft. The number of vascular reconstructions for the latter patient was two. A graft with a small lumen (8 mm in diameter) was used for the first bypass between the left brachiocephalic vein and the right atrium. The second graft with a lumen of 12 mm in diameter was placed between the right brachiocephalic vein and the proximal stump (near the heart). We believe that the risk of occlusion of grafts depends on the number of reconstructions or the caliber of the lumen of the grafts. Two vascular reconstructions would be vulnerable to vascular occlusion, and a small-caliber prosthesis would also lead to vascular troubles. As a rule, we prefer isolated reconstruction of the SVC system with a large-lumen prosthesis.

Because distant failure is the most frequent site of postoperative recurrence, surgery for T4 disease should be performed in multimodal strategy in principle. Considering the indication for SVC resection, direct involvement of the vessel by the primary tumor would be the best situation. When the primary tumor is located peripherally and mediastinal lymph nodes involve the SVC system, the prognosis would be dismal. This criterion for SVC resection should be taken into consideration for future clinical trials dealing with T4 lung cancer.

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DISCUSSION

DR FRANK C. DETTERBECK (Chapel Hill, NC): I am a little bit unclear about that slide where you showed no difference between T stages. Are not all of these tumors T4 if they involve the superior vena cava (SVC)? Or are some not counted as T4 if there was nodal involvement into the SVC?

My second question is, how would you evaluate a patient preoperatively? If you find N2 or mediastinal lymph node involvement, do you think that patient should nevertheless undergo surgery, or is that a contraindication to surgical resection?

DR SUZUKI: Thank you for your comments. Among 40 patients, 26 had T4 disease. Those tumors invaded the SVC system. The remaining 14 patients had T2 or T3 disease. For those patients, the SVC system was resected because of nodal invasion. Furthermore, in some cases surgical T4 was restaged to pathologic T3 disease. Surgical findings are not always correct considering pathologic examination.

As to preoperative evaluation, if clinical N2 nodes are found, we do not recommend surgery alone. Mediastinoscopy is recommended, and, if positive for cancer cells, chemoradiotherapy will be planned. However, if nodal status is marginal and the nodes are involved by the primary tumor, surgical resection might be considered. Distant failure is dominant in this population, and systemic treatment is mandatory in principle.

As to the T4 disease, we have 26 patients with T4 disease. Other patients have T3. That is because it is difficult to evaluate the invasiveness of the tumor to the SVC intraoperatively, so we sometimes have to resect the SVC for T3 disease.

For the second question, usually now we are performing mediastinoscopy for clinical N2 status patients. Those surgeries were performed after 1990 or 1995. We used to perform surgical resection for clinical N2 disease, as you know, in Japan. So we diagnosed N2 in a patient based on the computed tomographic (CT) findings, the same criteria as you used.

DR WICKII VIGNESWARAN (Maywood, IL): What percentage of patients had preoperative chemoradiation in your group? Obviously, the other question is, the T1 and T2 patients who have the nodal involvement of the SVC, should they undergo surgical resection?

DR SUZUKI: Preoperative chemoradiotherapy was performed on 3 patients. They are not included in any clinical trial. The chemoradiotherapy was performed in practice.

DR VIGNESWARAN: Would it be logical to downstage some of these patients before going for surgical resection?

DR SUZUKI: I did not evaluate that point.

DR SULAIMAN HASAN (Charleston, WV): I enjoyed your presentation. I have two questions.

What graft material did you use? The other question obviously has to do with what you would do today if you had, say, N2 disease on mediastinoscopy. Would you stent some of these vena cavae or would you still do surgery on them or would you radiate them?

DR SUZUKI: We used Gore-Tex grafts. For the second question, now we do not perform surgery alone for clinical N2 disease. Chemoradiotherapy is the standard. But only for selected patients, after chemoradiotherapy or after chemotherapy, a surgical resection will be performed.

DR STEVEN R. DEMEESTER (Los Angeles, CA): What size Gore-Tex graft do you recommend?

DR SUZUKI: Probably I would recommend 12 mm to 14 mm for the reconstruction of the SVC. Probably this is smaller than you use in the United States. This is probably related to the size of the body in Japan and the United States.

DR DOMINIQUE GRUNENWALD (Paris, France): That was an excellent presentation, Dr Suzuki.

You reported an excellent patency of your reconstruction. What is your policy regarding anticoagulation therapy and what is the length of your treatment?

DR SUZUKI: Actually we rarely have patients with postoperative thromboembolic disease compared with the United States or European countries. So actually we do not always adopt postoperative anticoagulant therapy, only for selected patients.

DR DAVID V. SABORIO (Brooklyn, NY): This was a very provocative paper, but I have a couple of comments. First, the CT scan you presented shows a very large tumor with clear invasion of mediastinal structures. I would probably not offer surgery as initial therapy to a patient with such findings on CT scan. So I would like to know whether that CT scan was taken after neoadjuvant therapy and before surgery or before neoadjuvant therapy was started. Second, if you currently perform surgery on patients with such advanced tumors on CT scan and for your paper to be more convincing, you would have to tell us what percentage of patients in your institution get thoracotomies and are found to be nonresectable.

DR SUZUKI: Could you repeat the first question?

DR DEMEESTER: He was interested in what percentage had neoadjuvant therapy and were the CAT scans done before or after neoadjuvant therapy.

DR SUZUKI: Usually we do not perform surgery alone for such a patient. We usually perform preoperative chemotherapy or preoperative chemoradiotherapy or chemoradiotherapy alone.

DR SABORIO: And what is the percentage of patients in your institution who get thoracotomies and are found to be unresectable?

DR SUZUKI: About 5%, I think.

DR BENNY WEKSLER (Rio de Janeiro, Brazil): I have noticed, and you may correct me if I am wrong, that you had 4 empyemas in 40 patients, which is 10%, and this seems a little high. Maybe you can comment on that. Also, what do you do when you get empyema with a Gore-Tex graft in the vena cava?

DR SUZUKI: Actually, compared with reported papers, the postoperative surgical mortality is relatively high. Probably this is because of the rate of pneumonectomy. Three pneumonectomies were performed in 15 patients. That is why our postoperative surgical mortality is relatively high. And if the patient has empyema postoperatively, probably we would perform an open-window method to prevent additional reinfection intrathoracically.

DR DEMEESTER: Were there any problems with the graft with that?

DR SUZUKI: No, I do not think so, but some people have postoperative bleeding.

DR KESHAUDAS PAHUJA (Stoughton, MA): I enjoyed the paper.

I have a couple of questions. What do you do with the phrenic nerve? Do you always sacrifice that or do you try to preserve it, and what are the consequences of that?

Second, did you have any incidence after pneumonectomy of pulmonary edemas in your cases?

DR SUZUKI: What is the question?

DR RICHARD H. FEINS (Rochester, NY): What do you do with the phrenic nerve, or what does the pathologist do with the phrenic nerve?

DR DEMEESTER: Do you always remove the phrenic nerve with the surgery?

DR SUZUKI: The phrenic nerve?

DR FEINS: The phrenic nerve that runs along the cava, does that go en bloc with your resection? You do not preserve the phrenic nerve?

DR SUZUKI: We sometimes preserve the phrenic nerve, but sometimes we will resect the phrenic nerve when we resect the lung cancer.

DR PAHUJA: Did you most of the time try to preserve it or did you try to resect it most of the time?

DR SUZUKI: Pardon me?

DR FEINS: Do you try to preserve it or do you resect it most of the time?

DR SUZUKI: If we see the tumor invade or if it is just adjacent to the phrenic nerve, we almost always resect the phrenic nerve.

DR FEINS: Why do you find it necessary to replace the innominate vein, or do you? The innominate vein, is it truly necessary to do anything with that, the left innominate vein?

DR SUZUKI: Sometimes we just leave the left side innominate vein. We prefer isolated vascular reconstruction for this.

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Management of Primary Malignant Germ Cell Tumor of the Mediastinum

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Background: Primary mediastinal malignant germ cell tumors (GCTs) are rare and have a worse prognosis than their gonadal counterparts. Although multimodality treatment is a standard therapeutic strategy in mediastinal GCTs, the clinical implications of surgical intervention remain unclear.

Methods: Forty-eight patients with primary mediastinal malignant GCT who were treated at the National Cancer Center Hospital, Tokyo, from 1962 to 2002 were studied retrospectively with regard to their histology and clinical profile.

Results: Mediastinal GCT occurred predominantly in young males, with a mean age of 28.8 years at the time of diagnosis. There were 46 males (96%) and two females (4%). Histologically, seven patients (15%) were diagnosed as having pure seminoma and 41 (85%) had nonseminomatous GCT. Treatment consisted of surgery alone in nine patients, surgery followed by chemotherapy in two, and chemotherapy followed by surgery in 20. The other 17 patients received chemotherapy and/or radiotherapy without surgery. Of these latter 17 patients, 14 developed progressive disease and three were followed up with a sustained partial response. Among the 31 patients who underwent surgery, complete resection was performed in 27 (87%) and incomplete resection was performed in four (13%). Twelve (41%) patients had elevated serum tumor marker levels preoperatively. Among the 20 patients who received preoperative chemotherapy, viable cells were found in the resected specimen in six (30%). With regard to tumor recurrence in patients with surgical intervention, the preoperative serum tumor marker levels and the presence of viable cells in the resected specimen were significantly associated with recurrence. There was no significant association between surgical curability and recurrence. The 5-year overall survival rate in all 48 patients was 45.5%.

Conclusions: Surgical intervention for mediastinal GCT may be needed to remove a chemotherapy-refractory tumor or to assess the pathological response to chemotherapy to determine the indications for further chemotherapy.

Key words: mediastinum – mediastinal neoplasms – germ cell tumor – tumor markers

INTRODUCTION

Although the most common location for malignant germ cell tumors (GCTs) is the gonads, they can also arise in extragonadal regions such as the mediastinum, retroperitoneum and pineal gland (1). It has been speculated that they occur in such unusual locations due to the abnormal migration of germ cells during embryogenesis (2,3). The histologic characteristics of extragonadal tumors are similar to those of gonadal GCTs, and both are chemosensitive. The mediastinum is the most common site of primary extragonadal GCTs (4). Primary malignant GCTs of the mediastinum account for 1–6% of all mediastinal tumors (5–8). Primary extragonadal GCTs, especially primary mediastinal tumors, are considered to have a poor prognosis (9–16). Although they have similar histologic features, mediastinal GCTs are clinically and biologically distinct from their testicular counterparts.

Malignant GCTs are closely related to serum tumor markers, especially alpha-fetoprotein (AFP) and/or the beta subunit of human chorionic gonadotropin (HCG). Measurement of these serum tumor markers is important in diagnosis of the disease, and in the management and follow-up of patients with GCTs.

Chemotherapy for malignant GCTs has become standard practice since the introduction of cisplatin-based combination

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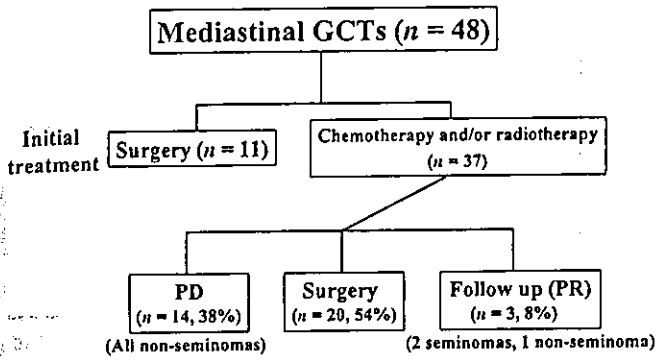

Figure 1. Treatment summary for 48 patients with mediastinal germ cell tumor. GCT, germ cell tumor; PD, progressive disease; PR, partial remission.

chemotherapy in the late 1970s (11,17–19). High-dose chemotherapy with peripheral blood stem cell transplantation (PBSCT) has also been used for refractory tumors (20–22). Patients with these tumors have not usually been considered as candidates for primary surgery because of the presumed systemic nature of the disease. Thus, all resections for GCTs have been performed as 'salvage surgery', which is considered to be the resection of residual tumor after a partial response to induction chemotherapy or an operation at the time of relapse after a complete response to chemotherapy (23). Although salvage surgery is performed with the intent to remove chemotherapy-resistant disease, to assess the pathological response to chemotherapy in the resected specimen and to guide additional chemotherapy, the clinical significance and indications of salvage surgery in the treatment of mediastinal GCTs remain unclear.

Several issues must be addressed in the management of malignant GCT: preoperative normalized serum tumor marker levels, the relationship between prognosis and the presence of persistent viable cells in post-chemotherapy resected specimens, the significance of the completeness of resection and the operative risk, especially after high-dose chemotherapy with PBSCT. Due to the rarity of GCTs arising in the mediastinum, there have been few reports on the clinical outcome after therapeutic challenge for this type of tumor in a large population.

This report describes our experience with managing patients with mediastinal GCT.

PATIENTS AND METHODS

PATIENTS

In the 41-year period from 1962 through 2002, 48 patients with malignant GCT of the mediastinum were treated at the National Cancer Center Hospital, Tokyo. Three patients were referred to us after surgical resection of the tumor as the initial treatment of choice at another institute. The clinicopathological characteristics of these 48 patients were examined in this retrospective study. The patients were considered to have primary mediastinal GCT when a bulky anterior mediastinal mass was present in the absence of any clinically detectable testicular or ovarian masses at any time during the course of the disease (24). The diagnosis of mediastinal GCT was defined clinicopathologically in all patients. Serum tumor markers, especially AFP and/or HCG, were measured preoperatively in 29 patients.

TREATMENT

The treatments used in the 48 patients with mediastinal GCTs are summarized in Fig. 1. All patients who received chemotherapy initially or postoperatively were treated with a regimen containing cisplatin. The chemotherapy regimen used in each case was one of those sequentially developed throughout the study period at our institute for the management of germ cell tumors. Mainly, the patient was treated with either a combination of cisplatin and etoposide (PE) or a combination of cisplatin, bleomycin and etoposide (BEP), whether for seminomatous or non-seminomatous GCT. The PE chemotherapy consisted of intravenous cisplatin (120 mg/m^2) and intravenous etoposide (100 mg/m^2) given on days 1–5. The BEP chemotherapy consisted of intravenous cisplatin (20 mg/m^2 of body-surface area) given daily for 5 days, intravenous bleomycin (30 U) given on days 2, 9 and 16, and intravenous etoposide (100 mg/m^2) given on days 1–5. The patients received two to four courses of the chemotherapy given at 3-week intervals. Of these 48 patients, 23 received multimodality treatment while 25 received only one form of treatment, such as chemotherapy, surgery or radiotherapy. Thirty-four patients received chemotherapy, 11 received radiotherapy and 31 underwent surgery. Three patients received high-dose combination chemotherapy with PBSCT: one underwent high-dose chemotherapy following the initial chemotherapy and surgical resection, and the others underwent the initial high-dose chemotherapy followed by surgical resection.

Based on previous reports (3,13,25), the response criteria were defined as follows: complete remission (CR) was recorded when serum tumor markers normalized and complete resolution of tumor masses occurred. CR was also documented when resection of a residual mass revealed only necrosis. Partial remission (PR) was defined as a >50% decrease in bidimensional tumor measurements and ≥50% decline in serum tumor markers. A radiological increase in tumor dimensions or an elevation of marker levels indicated progressive disease (PD).

Operative reports were reviewed and the curability of resection (complete resection or incomplete resection) and outcome (mortality and morbidity) were recorded. Complete resection was defined as no macroscopic or microscopic residual tumor, and incomplete resection was defined as evident macroscopic or microscopic residual tumor. Operative death was defined as any death within 30 days of the operation or during hospitalization. Preoperative serum tumor markers, AFP and HCG, were defined as normal or elevated on the basis of marker values collected before the operation and approximately 4–6 weeks from the date of the last chemotherapy.

Post-chemotherapy resected specimens were categorized as follows. Specimens that showed the histological appearance of

Table 1. Symptoms at presentation

Symptom	No. of patients (%)
Chest radiograph abnormality (asymptomatic)	12 (25)
Chest pain	18 (38)
Cough	11 (23)
Back pain	5 (10)
Bloody sputum	1 (2)
Fever	1 (2)

GCTs such as embryonal carcinoma, yolk sac carcinoma, immature or mature teratoma, choriocarcinoma or seminoma were regarded as having viable cells. Specimens that included only necrosis, based on histologic findings of necrotic debris without any viable cells, were regarded as having no viable cells.

Statistics

A chi-square test was used to compare the frequencies among different groups. Survival curves were estimated by the Kaplan–Meier method using the date when treatment began as the starting point and the date of recurrence, death or last follow-up as the endpoint. A P-value of <0.05 was considered statistically significant.

RESULTS

Clinical Findings

Malignant GCT of the mediastinum occurred predominantly in young adults, with a mean age of 28.8 years at the time of diagnosis (range, 13–68). There was a male preponderance: 46 (96%) males and two (4%) females. Thirty-six (75%) of the 48 patients showed a symptom that could be related to the tumor at the initial examination. These symptoms were non-specific and resulted from the expanding tumor encroaching on surrounding structures (Table 1). The remaining 12 (25%) patients were asymptomatic and the tumors were found based on evidence of an anterior mediastinal mass on a routine chest radiograph. Klinefelter syndrome was also found in a 13-year-old patient with an immature teratoma.

Diagnosis and Histology

The histologic diagnosis of these 48 malignant GCTs was confirmed in resected specimens taken by thoracotomy (13 patients, 27%), incisional biopsy of the tumor (six patients, 13%), percutaneous needle biopsy (27 patients, 56%), or autopsy (two patients, 4%). Although biopsy specimens were taken in the two autopsy cases, they were not of diagnostic significance. The histologic subtype could not be determined in one patient because of total necrosis of the resected tumor after cisplatin-based chemotherapy, and, therefore, no histologic type could be specified. However, since the pre-chemotherapy serum tumor markers were markedly elevated, a diagnosis of non-seminomatous GCT was made. Seven patients (15%) were diagnosed as having pure seminoma and 41 (85%) had non-seminomatous GCT, containing non-seminomatous elements.

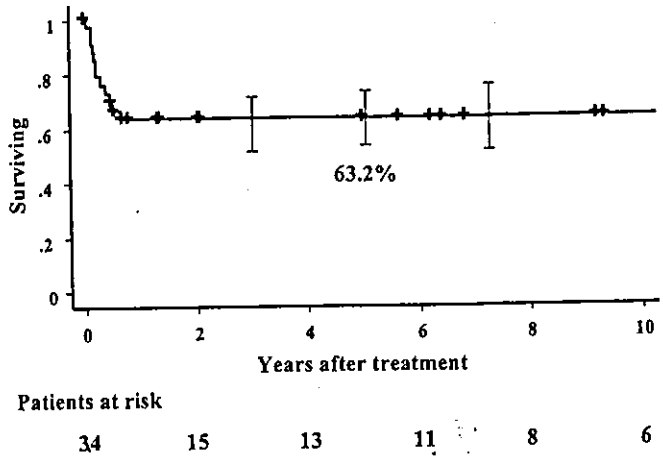

Figure 2. Relapse-free survival in 34 patients, excluding 14 who developed progressive disease after initial chemotherapy. The 5-year relapse-free survival rate was 63.2%. Bars indicate 95% confidence intervals.

Treatment and Response

Among these 48 patients, nine underwent surgical resection alone. Two patients underwent surgical resection followed by chemotherapy and 20 patients received chemotherapy followed by surgical resection. Seventeen patients received chemotherapy and/or radiotherapy without surgery. Of these latter 17 patients, 14 developed PD and three were followed up with sustained PR. With regard to the initial treatment, 11 patients underwent surgical resection and 37 received chemotherapy and/ or radiotherapy. Among these latter 37, 14 (38%), all of whom had non-seminomatous lesions, developed PD, and 20 (54%) were followed by surgery with PR. The remaining three patients (8%) (one was diagnosed as having non-seminomatous lesion and two were seminoma) were followed up without surgical resection because of sustained good PR (tumor measured 3 cm or less in diameter on CT).

For the 31 patients who underwent surgical resection, complete resection was performed in 27 patients (87%) and incomplete resection was performed in four (13%). Twelve (41%) of the 29 patients whose serum tumor markers were measured had elevated tumor markers prior to resection. Nine of these 12 patients had elevated AFP and five had elevated HCG. Both tumor markers were elevated in only two patients. In the remaining 17 patients (59%), serum tumor markers were within the normal range.

Among the 20 patients who received preoperative chemotherapy, six (30%) had viable cells in the resected specimen and 14 (70%) had no viable cells.

Prognosis

The median follow-up period was 6.5 years. The 5-year relapse-free survival rate in 34 patients, excluding the 14

Table 2. Relapse-free patients with preoperative elevated serum tumor marker levels

Patient	Age (years)	Preoperative treatment	Histology	Viable cells	Postoperative treatment	Prognosis (years)
1	24	Chemo	Non-seminoma	Negative	High-dose	6.2, alive, NED
2	16	Chemo	Non-seminoma	Negative	None	6.8, alive, NED
3	17	None	Non-seminoma	–	Chemo	0.7, dead, NED

Chemo, conventional chemotherapy; Viable cells, viable cells present in the resected specimen; High-dose, high-dose chemotherapy with PBSCT; NED, no evidence of disease.

patients who developed PD after initial chemotherapy, was 63.2% (Fig. 2). Among the 29 patients whose preoperative serum tumor markers were measured, 17 had normal serum tumor marker levels and two (12%) of these had recurrence. The remaining 12 had elevated levels and nine (75%) of these had recurrence. Thus, the prevalence of recurrence in patients with preoperative elevated serum tumor markers was significantly higher than that in patients with preoperative normal serum tumor markers ($P = 0.001$). In the three patients with preoperative elevated serum tumor markers who had no recurrence (Table 2), the histological diagnosis was non-seminomatous GCT. Two of these three patients received chemotherapy followed by surgery and had no viable cells in their resected specimens, and one of these two received postoperative high-dose chemotherapy with PBSCT because of pulmonary disseminated disease on CT. These two patients both survived relapse-free for more than 5 years. The other patient underwent initial surgery followed by chemotherapy. This patient was lost on the 285th postoperative day due to secondary malignancy (acute leukemia).

Among the 31 surgical resections, there were 27 complete resections and four incomplete resections. Among the 27 complete resections, there were 10 cases (37%) with recurrence and 17 (63%) without recurrence. On the other hand, there were two cases (50%) with recurrence and two (50%) without recurrence in the four incomplete resections. There was no significant difference between curability and recurrence ($P = 0.633$).

With regard to the relationship between recurrence and the presence of viable cells in the resected specimen (Table 3), among the 20 patients who underwent preoperative treatment (chemotherapy and/or radiotherapy), six had viable cells and 14 had no viable cells. Four (67%) of the six patients with viable cells, all of whom had been diagnosed as having non-seminoma, had recurrence. Two (14%) of the 14 patients (five seminomas, nine non-seminomas) with no viable cells had recurrence. There was a significant difference between recurrence and the presence of viable cells in the resected specimen ($P = 0.018$).

The 5-year overall survival rate in the 48 patients was 45.5% (Fig. 3). Among the 23 deaths following treatment, 21 were caused by either recurrence or progression of the disease (tumor-related death). The remaining two patients were lost on the 7th and 285th postoperative days because of multiple organ failure due to disseminated intravascular coagulation (DIC) and secondary malignancy (acute leukemia), respectively. Surgical mortality and morbidity are shown in Table 4. Among the 31 patients who underwent surgical resection, there was one (3%) operative death caused by DIC. Postoperative morbidity was found in 13% of patients.

Table 3. Relationship between recurrence and the presence of viable cells in the resected specimen

Histology	Viable cells ($n = 20$)	
	Positive	Negative
Seminoma ($n = 5$)	0/0 (–)	0/5 (0%)
Non-seminoma ($n = 15$)	4/6 (67%)	2/9 (22%)
Total*	4/6 (67%)	2/14 (14%)

*$P = 0.018$.

DISCUSSION

Although the general histologic and serologic characteristics of mediastinal malignant GCTs are similar to those of testicular GCTs, mediastinal GCTs have been reported to have a worse prognosis than gonadal GCTs (15,16). Furthermore, the clear differences in clinical behavior suggest that these tumors are biologically distinct. Some investigators have proposed that

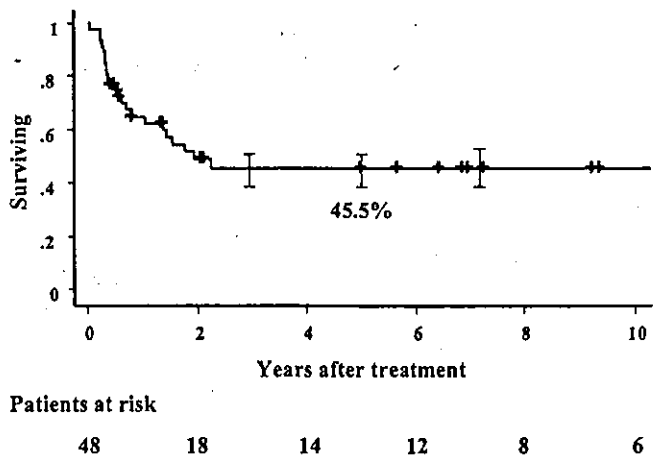

Figure 3. Survival in all 48 patients with primary mediastinal germ cell tumor. The 5-year overall survival rate was 45.5%. Bars indicate 95% confidence intervals.

Table 4. Operative mortality and morbidity

Mortality and morbidity	No. of patients (%)
Operative death	1 (3%)
Postoperative morbidity	4 (13%)
Wound infection	2
Empyema	1
DIC	1

DIC, disseminated intravascular coagulation.

mediastinal GCTs arise from cells of a different embryologic origin than testicular primaries (10). Others have suggested that the poor outcome of treatment for mediastinal GCTs reflects the advanced stage of the disease usually present at the time of diagnosis and that there is little intrinsic difference between mediastinal and gonadal GCTs with respect to their response to chemotherapy (26). However, the reasons for the observed differences in the clinical characteristics and behavior of mediastinal GCT are unknown. In addition, some reports have suggested that patients with Klinefelter syndrome have a slightly increased predisposition of having mediastinal GCT (27,28). One patient (2%) in the present study had Klinefelter syndrome. The pathogenesis of the association between mediastinal GCT and Klinefelter syndrome remains unclear.

With regard to the treatment of mediastinal malignant GCTs, the current consensus is that initial systemic chemotherapy should be followed by aggressive complete resection of all macroscopic residual tumor when necessary (4,18,24,29–31). As in most series, patients treated with this approach had a superior outcome to those treated with initial resection, even though these tended to be smaller tumors. Our study also ended in disaster for the prognosis. Nine of the 11 patients who underwent surgery as initial treatment had recurrence (distant organ) within one year after surgery, three of whom received adjuvant chemotherapy; the remaining two were survivors for more than 10 years, one of whom received adjuvant chemotherapy and the other, diagnosed as having immature teratoma, underwent only surgery for treatment. However, the clinical implications of surgical resection in the multimodality treatment of mediastinal GCTs are not yet clear.

The management of patients with elevated serum tumor marker levels after chemotherapy is controversial. The degree of the elevation of serum tumor markers, especially AFP and HCG, plays a crucial role in defining the outlook (6,15,16,32,33). In the present study, patients with preoperative normal tumor marker levels had significantly better survival than those with preoperative elevated tumor marker levels. Surgical resection for patients whose markers have not normalized with chemotherapy is usually futile (4,6,34–36). Dulmet and colleagues also stated that normalizing serum tumor marker levels before surgical resection was a significant favorable prognostic factor (7). On the other hand, Vuky and associates found a tendency for shorter survival in patients with elevated and increasing tumor markers compared to patients with normal or elevated-but-declining markers before surgical resection (37). In our series, two patients with chemo-refractory marker-elevated GCTs achieved a prolonged relapse-free status with salvage surgery and they had no viable cells in the resected specimens. These two patients had elevated, but markedly declining, marker levels before surgical resection. In addition, both these two patients had no viable cells in the resected specimens pathologically. These might be due to a half-life of tumor markers and the possibility of a few viable cells besides sections examined microscopically in spite of the diagnosis of no viable cells. Thus, selected patients, such as patients with elevated but declining marker levels before surgery, might be considered as candidates for surgery (33,38).

The histopathologic findings of post-chemotherapy resected specimens are important prognostically (30,33,37). The presence of persistent GCT in the resected specimen is a poor prognostic factor. In the present study, four (67%) of six patients with viable cells in the resected specimen had recurrent disease despite the resection of persistent GCT, whereas two (14%) of 14 patients with no viable cells had recurrence. One definite purpose of surgery is careful evaluation of the tumor after chemotherapy to see whether or not any viable cells remain. Further chemotherapy in the adjuvant setting may be considered in patients who show viable tumor. On the other hand, patients with residual tumor such as mature teratoma are commonly found because of the histological heterogeneity of GCTs. Residual teratomas must be completely removed, since they can compress or invade surrounding mediastinal structures, and dedifferentiation into carcinoma is possible (39).

In the present study, histology influenced the treatment outcome. Patients with pure seminoma achieved a high pathological CR rate and an excellent prognosis (5-year survival rate, 100%). Several reports have confirmed the good prognosis of mediastinal pure seminoma compared with non-seminomatous

Table 5. Three patients who received high-dose chemotherapy with PBSCT

Patient	Age (years)	Initial treatment	Histology	Viable cells	Postoperative treatment	Prognosis (years)
1	24	Chemo	Non-seminoma	Negative	High-dose	6.2, alive, NED
2	27	High-dose	Non-seminoma	Positive	None	1.9, dead, WD
3	21	High-dose	Non-seminoma	Positive	None	0.8, dead, WD

Chemo, conventional chemotherapy; High-dose, high-dose chemotherapy with peripheral blood stem cell transplantation; Viable cells, viable cells present in the resected specimen; NED, no evidence of disease; WD, with disease.

GCTs (7–9,13,15,29,31,40–42). The Southeastern Cancer Study Group reported excellent sustained remissions with initial chemotherapy in all patients with mediastinal seminomas (19). In our study, five patients with seminoma, who received chemotherapy followed by surgery, all had CR without any viable cells in the resected specimen. Motzer and colleagues proposed that close observation without surgery is possible for seminoma patients with a post-chemotherapy residual tumor of 3 cm or less in diameter because none of the patients with a residual tumor of this size had viable cells in the resected specimen (43). In the present study, two patients with pure seminoma also had sustained post-chemotherapy good PR (tumor size, 3 cm or less in diameter on CT) without tumor relapse. On the other hand, GCTs could have a mixed histology, with both seminomatous and non-seminomatous components (40). Accordingly, elevated serum tumor markers in patients with GCT might indicate a non-seminomatous component even if biopsied specimens reveal only pure seminoma. A diagnosis of seminoma based on small biopsy specimens should be considered clinically as well as histopathologically.

High-dose chemotherapy was introduced to improve the outcome in patients with refractory GCTs, based on the fact that the response rate of non-seminomatous GCT increases with the intensification of chemotherapy (21,22). Some reports have suggested that high-dose chemotherapy with PBSCT may have curative potential in refractory GCTs (22,44). In the present study, three patients were treated with high-dose carboplatin and etoposide with PBSCT (Table 5). All three patients underwent surgical intervention. Two of them received two or more regimens of conventional chemotherapy prior to high-dose chemotherapy followed by surgery, with viable cells in the resected specimens. Ultimately, both died of relapse disease in less than 2 years. The other patient received high-dose chemotherapy for disseminated disease (lung disease) after conventional chemotherapy followed by reduction surgery, and remains free of disease at 74 months. Some investigators have proposed that the use of high-dose chemotherapy with PBSCT does not produce durable remission in patients with refractory mediastinal GCT with a poor prognosis (45,46). The efficacy of high-dose chemotherapy, in conjunction with surgical resection when necessary, in the treatment of refractory mediastinal GCTs must be further evaluated.

In conclusion, surgical resection for mediastinal GCT may be required to remove chemotherapy-refractory tumor for local control or assess the pathological response to chemotherapy. Although whether a gross chemotherapy refractory tumor includes pathologically viable cells or not is unknown, if there are any, it might lead to a hotbed of local relapse, which can life-threateningly compress mediastinal structures such as the heart, aorta and superior vena cava. The presence of viable cells in the resected specimen may suggest a necessity for additional chemotherapy because of the presumed systemic nature of the disease. On the other hand, patients with preoperative elevated increasing tumor marker levels and/or progressive disease after initial chemotherapy are no longer candidates for surgery for local control because of their extremely poor prognosis. However, the clinical implications and indications of surgical resection must be investigated further. Additionally, more appropriate and effective therapeutic strategies are needed in the treatment of patients with mediastinal GCT to achieve better survival rates.

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Inflammatory myofibroblastic tumor of the lung

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Abstract

Objective: Inflammatory myofibroblastic tumor (IMT) is a rare disease that usually occurs in the lung. Recently, several reports have suggested that IMT is a true neoplasm rather than a reactive lesion. In this retrospective study, we reviewed clinicopathological characteristics and prognoses for all patients with surgically resected IMT of the lung at our institute. **Methods:** From January 1985 to December 2002, nine patients had surgical intervention for IMT of the lung at the National Cancer Center Hospital, Tokyo. The resected lesions were studied histologically, immunohistochemically, and ultrastructurally. Follow-up was complete in all patients and varied from 3 months to 16 years 2 months (median, 6 years 2 months). **Results:** These nine patients included five men and four women. They ranged in age from 25 to 66 years. Seven patients were asymptomatic. The two symptomatic patients had problems including cough, hemoptysis, and dyspnea. For all these patients, the diagnostic procedure was surgical excision. The resected tumor size ranged from 1.0 to 4.0 cm in diameter. Histologically, a variety of inflammatory and spindle cells were observed. The spindle cells corresponded ultrastructurally to myofibroblasts or fibroblasts. With the exception of one patient who had spontaneous resolution of a recurrent tumor, there was no recurrence in these patients, and all of them are in good health. **Conclusions:** Histopathologically, IMT is characterized by myofibroblasts that are mixed with chronic inflammatory cells, including plasma cells, lymphocytes, and histiocytes. Surgical resection, when possible, can be chosen as the treatment. Complete resection leads to excellent survival.

Keywords: Lung pathology; Surgery; Survival; Inflammatory pseudotumor; Pulmonary neoplasm

1. Introduction

Inflammatory myofibroblastic tumor (IMT) is a rare disease that usually occurs in the lung. IMT has been described by various terms because of its variable cellular components, which includes plasma cell granuloma, inflammatory pseudotumor, xanthogranuloma, and fibrous histiocytoma [1–18]. The notion of IMT being a reactive lesion or a neoplasm was controversial [18]. However, this entity has been characterized by not variable chronic inflammatory cells but myofibroblasts, and the recent cytogenetic studies have suggested that IMT is a true neoplasm [14–16]. There is little information on the clinicopathological features because IMT is rare and its terminology was confusing.

To examine the clinicopathological characteristics and prognosis, we reviewed a set of patients with surgically resected IMT of the lung.

2. Material and methods

2.1. Patients

Between January 1985 and December 2002, nine patients had surgical intervention for IMT of the lung at the National Cancer Center Hospital, Tokyo. These patients comprised 0.18% of 4893 patients who had thoracic surgical procedures at our institute during the same period. The clinical characteristics of these patients are shown in Table 1. Preoperative work-up included laboratory examinations, fiberoptic bronchoscopy, chest radiograph, and computed tomographic (CT) scans. Follow-up was complete in all

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Table 1
Clinical characteristics of patients with inflammatory myofibroblastic tumor

Case	Sex/age	Symptom	Location	Tumor size (cm)	Mode of operation	Prognosis after surgery
1	F/59	None	HLN	2.5	Extirpation	16 years 2 months, alive
2	F/41	None	LLL	1.0	Lobectomy	13 years 9 months, alive
3	F/58	Cough/ Hemoptysis	RIB	2.0	Bilobectomy	1 year 4 months, alive
4	M/25	None	LUL	2.2	Segmentectomy	2 years 3 months, alive
5	M/49	None	LUL	3.6	Segmentectomy	9 years 6 months, alive
6	M/66	None	LUL	3.5	Segmentectomy	6 years 6 months, alive
7	M/47	Cough/ Dyspnea	LMB	4.0	Segmental bronchial resection	6 months, alive
8	M/26	None	LLL	3.0	Segmentectomy	5 years 2 months, alive
9	F/30	None	RUL	3.2	Lobectomy	3 months, alive

HLN, hilar lymph node; LLL, left lower lobe; RIB, right intermediate bronchus; LUL, left upper lobe; LMB, left main bronchus; RUL, right upper lobe.

patients and ranged from 3 months to 16 years 2 months (median, 6 years 2 months).

2.2. Pathological and ultrastructural evaluations

In each case, the tissue was fixed in 10% buffered formalin, processed routinely, and embedded in paraffin. Sections 4 μm thick, were cut and then stained with hematoxylin and eosin. Each section was also evaluated immunohistochemically. Immunohistochemical staining was accomplished by the labeled streptavidin-biotin method using an LSAB kit (Dako Corporation, Carpinteria, CA). Primary antibodies against various antigens were used in this study: vimentin (V10 clone; Dako; 1:200), cytokeratin (CAM5.2 clone; Becton Dickinson, San Jose, CA; 1:100), cytokeratin (AE1/AE3 clone; Dako; 1:125), desmin (Dako; 1:500), smooth muscle actin (1A4 clone; Dako; 1:100), CD34 (My10 clone; Becton Dickinson; 1:100), S100 protein (Dako; 1:2000), and epithelial membrane antigen (Dako; 1:100).

Small fresh fragments of tumor tissue in four cases (cases 3, 4, 7 and 9) were fixed in 2.5% glutaraldehyde, post-fixed in 1% osmium tetroxide, and embedded in epoxy resin. After contrasting with uranyl acetate and lead citrate, ultrathin sections were examined with a transmission electron microscope.

3. Results

3.1. Clinical findings

These nine patients included five men and four women. They ranged in age from 25 to 66 years, with a mean age of 44.6 years. Seven patients were asymptomatic and were found to have pulmonary nodules on routine chest radiography (Fig. 1). One of these patients (case 6) was clinically suspected of pulmonary metastasis. This was pointed out during postoperative follow-up of a right nephrectomy for renal cell carcinoma that the patient had undergone 5 years before. The two symptomatic patients had problems including cough, hemoptysis, and dyspnea. The preoperative laboratory results were within normal limits for eight patients, but one patient (case 5) had a C-reactive protein (CRP) rate of 9.4 mg/dl and a white blood cell (WBC) count of 10,000/μl. These findings returned to normal within 10 days after operation. All patients underwent a fiberoptic bronchoscopy preoperatively. Six patients did not have any bronchial abnormality. One (case 1) had a stenosis of the right basal bronchus. The other two had an endobronchial tumor. One patient (case 7) with an endobronchial tumor had complete atelectasis of the left lung (Fig. 2). Chest CT showed a solitary, well-circumscribed nodule or mass in all patients. A definitive diagnosis of IMT was not made in any of the patients, although all patients had undergone transbronchial biopsy or transthoracic needle biopsy for diagnosis preoperatively. The spindle cells and inflammatory cells in small biopsied specimen, even if they were taken by biopsy, were useless for

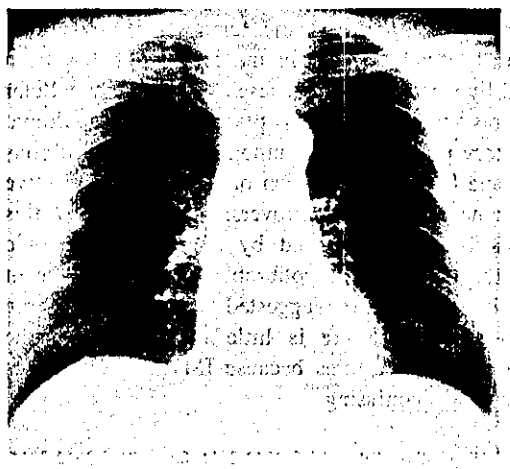

Fig. 1. Chest radiograph shows a well-defined mass in the left lung (case 5).

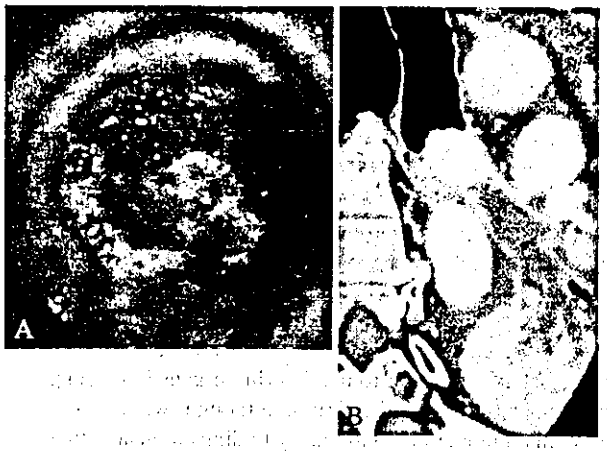

Fig. 2. This patient (case 7) had complete atelectasis of the left whole lung. Bronchoscopy shows a polypoid lesion, which almost completely occluded the left main bronchus (A). Chest CT on the coronal view shows a well-circumscribed enhanced mass with occlusion of left main bronchus (B).

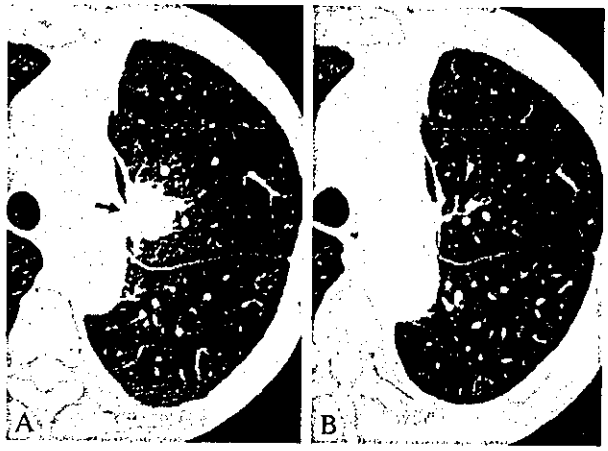

Fig. 3. On the CT findings, one patient (case 6) suffered from margin relapse, which developed adjacent to resected staple line (arrow), 4 years after initial resection (A). About 8 months later, spontaneous resolution of the tumor has been observed (B).

the definitive diagnosis because they followed a variety of lesions such as inflammation or malignancy. One patient (case 6) had an erroneous diagnosis of adenocarcinoma by aspiration cytology, because the cytologic findings showed atypical epithelial-like cells with lymphocytes and histiocytes. For all these patients, the diagnostic procedure was surgical excision. Although an intraoperative frozen section was done for the tumor in all cases, the confirmed diagnosis could not be made. However, all the tumors were regarded as low-grade malignancy because of low nuclear atypia and infrequent mitosis. The extent of surgical excision was as follows: segmentectomy in four patients, segmental bronchial resection in one, lobectomy in two, bilobectomy with bronchoplasty in one, and extirpation in one. Complete resection of the tumor was accomplished in eight patients (89%). One patient (case 7) had a pathological residual tumor in the submucosal tissue of the left main bronchus. None of the operations resulted in death. On the follow-up CT one patient (case 6) had a suspected recurrent tumor developing adjacent to the resected line four years after the initial resection, although this tumor was not evaluated histologically. Interestingly, spontaneous resolution of this tumor has been observed (Fig. 3). In the other eight patients, no recurrence of IMT occurred. All of the patients have remained healthy.

3.2. Pathological and ultrastructural findings

The resected tumor size ranged from 1.0 to 4.0 cm in the greatest diameter, with a mean of 2.8 cm. For gross appearance, most of the tumors were well-circumscribed masses without fibrous capsules and yellow to whitish in color on cut section.

Microscopically, the lesions consisted of a variety of inflammatory and mesenchymal cells, including plasma cells, histiocytes, lymphocytes, and spindle cells. All of the tumors showed interlacing fascicles, or a storiform pattern of spindle cells and an admixture of diverse inflammatory cells (Fig. 4A). The spindle cells had low cellular atypia and no mitotic activity (Fig. 4B). Blood vessel invasion was identified in one instance (case 4).

Immunohistochemically, most of spindle cells in all nine cases showed diffuse and strong reactivity for vimentin. All tumors exhibited reactivity for smooth muscle actin (Fig. 5). The staining was diffuse in eight of nine cases (89%) and focal in one (11%). One tumor exhibited focal staining for desmin. All tumors were negative for cytokeratins, CD34, S100 protein, and epithelial membrane antigen.

Ultrastructurally, two tumors (cases 3 and 9) out of four contained a varying proportion of myofibroblastic cells, as well as fibroblastic cells with a prominent Golgi apparatus

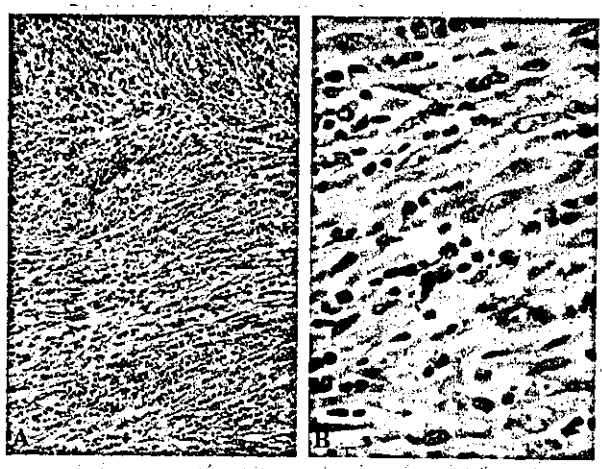

Fig. 4. Photomicrographs show an inflammatory myofibroblastic tumor. The lesion is composed of spindle cells arranged in interlacing fascicles, with admixed diverse inflammatory cells (A). The spindle cells have low cellular atypia and no mitotic activity, and the inflammatory cells are mature (B). (both, hematoxylin-eosin; A, original magnification 100 ×, B, original magnification 400 ×).

Fig. 5. Immunohistochemically, the spindle cells of the lesion show diffuse and strong reactivity for smooth muscle actin (immunohistochemistry for smooth muscle actin, original magnification 200 ×).

and well developed rough endoplasmic reticulum (RER). The myofibroblastic tumor cells were recognized by the presence of an often well developed branching RER and primarily peripheral bundles of actin microfilaments with interspersed fusiform densities (Fig. 6). Subplasmalemmal attachment plaques, focal basal lamina-like material, and micropinocytotic vesicles were present to variable degrees in these cells. The other tumors consisted of fibroblastic and histiocytic cells with lysosomes and lipid droplets.

4. Discussion

IMT of the lung is rare, and its incidence is reported to be 0.04–1% of all tumors of the lung [1,3]. Although IMT can grow at a wide variety of other sites [19,20], it usually arises within the lung [1]. Concerning the age of patients at diagnosis, the mean age of 44.6 years in this study was relatively older than those reported previously [4,5,7,10,17]. According to previous reports, most of the patients were under 40 years old, with a mean age of 27–50 years. There was no predominance of either sex. The precise etiology of IMT of the lung is still unknown. Although a history of prior pulmonary infection in some patients with IMT has been pointed out [4], this type of patient was not found in the present study. Patients with IMT usually are asymptomatic, with a solitary nodule or mass detected by routine chest roentgenogram [5]. Endobronchial growth of IMT has only rarely been observed [2,6,7], with a prevalence of between 0 and 12%. In this study we had a relatively high prevalence (two of nine, or 22%) of patients with endobronchial growth of IMT. On the other hand, it has been known that IMT carries a risk of extension to neighboring organs [1,4,9,11], in particular to the mediastinum, although we did not observe this. Preoperative laboratory findings indicated that only one patient (11%) with a solitary pulmonary mass had an elevated CRP rate and WBC count, and the IMT appeared to have no connection with these laboratory findings [3,4]. The preoperative diagnosis of IMT is seldom confirmed, and small biopsied specimens are generally considered insufficient for diagnosis because of the predominance of inflammatory cells.

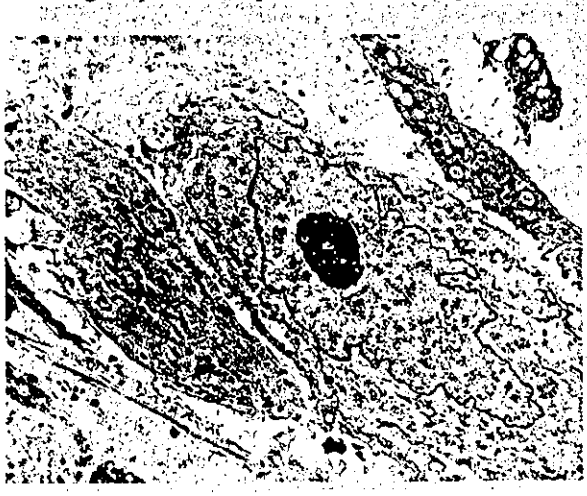

Fig. 6. Ultrastructurally, the myofibroblastic tumor cell is recognized by the presence of a well developed branching RER and primarily peripheral bundles of actin microfilaments with interspersed fusiform densities.

Pathologically, IMT is composed of a variable inflammatory and mesenchymal cellular mixture including plasma cells, histiocytes, lymphocytes, and spindle cells. Therefore, depending on the predominant cellular components, many synonyms for this disease have been described. In 1990, Pettinato and colleagues referred to this entity as IMT because the bulk of the lesion invariably consisted of not specific inflammatory cells, but proliferative myofibroblasts and fibroblasts [17]. Most of the spindle cells were myofibroblasts, which showed immunohistochemical staining for vimentin and smooth muscle actin, and consistent ultrastructural features. The spindle cells commonly have low cellular atypia and no mitotic activity. Inflammatory cells are mature and have no cellular atypia, and do not show monoclonal proliferation [3,17,18]. IMT occasionally invades bronchi or blood vessels [8,18]. We treated one patient (11%) with IMT who showed blood vessel invasion (case 4). However, it is doubtful that these are truly the tumor infiltrations, because the existing histologic architecture of the lung can also be destroyed by infiltration of only inflammatory cells. Furthermore, distant metastases from IMT are hardly ever reported. The differential diagnosis of IMT is multifarious because of its variable cellular admixture. It includes malignant lymphoma, lymphoid hyperplasia, pseudolymphoma, plasmacytoma, malignant fibrous histiocytoma, sarcomatoid carcinoma of the lung, sclerosing hemangioma, sarcoma, and/or nodular chronic pneumonitis. These lesions can be differentiated by careful attention to cellular atypia, necrosis, mitotic activity, immunoreactivity, or clonality [1,9,18]. IMT of the lung also has the histologic resemblance to the fibromas of the parietal or visceral pleuras. The fibromas shows short fascicles or haphazard fashion of spindle cells with few inflammatory cells, whereas IMT shows interlacing

fascicles or a storiform pattern of spindle cells and an admixture of diverse inflammatory cells [21].

Although the notion of IMT being a reactive lesion or a neoplasm had been controversial, IMT has been recently thought of as a neoplasm rather than a reactive lesion because of clonal chromosomal abnormalities [15], chromosomal rearrangements involving the ALK receptor tyrosine-kinase locus region (chromosome band 2p23) [16], or DNA aneuploidy in IMT [14]. IMT usually grows locally and slowly. Therefore, taking into account these histopathologic and biological findings, IMT may be regarded as low-grade malignancy or benign tumor.

Surgical resection is recommended as the treatment of choice. Cerfolio and colleagues reported that the residual tumor became enlarged in 60% of patients who had incomplete resection [1]. They advocated the importance of initial complete resection of the tumor. Surgical removal usually fills the role of both diagnosis and treatment. The effectiveness of radiotherapy, chemotherapy, or steroids is uncertain [1,12]. The spontaneous regression of IMT has been reported only infrequently [9]. Likewise, we cared for one patient with spontaneous regression of the recurrent tumor, although this was not confirmed histologically. The causes of these remissions are unknown. The outcome after resection is usually excellent, and all of the patients in this study have also remained well over the longer term. However, long-term follow-up is necessary because of reported cases of recurrences many years after resection [2,22].

In conclusion, IMT of the lung is rare. Histopathologically, IMT is characterized by myofibroblasts that are mixed with chronic inflammatory components, consisting of plasma cells, lymphocytes, and histiocytes. Surgical resection, when possible, is recommended as the treatment of choice. The outcome after complete resection is excellent.

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Grade of Stromal Invasion in Small Adenocarcinoma of the Lung

Histopathological Minimal Invasion and Prognosis

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Abstract: The pathologic features of invasion such as stromal disruption and pleural/vascular involvement have been shown to be of prognostic value in adenocarcinoma. However, the relationship between the degree of invasion, histologic subtype of adenocarcinoma, and prognosis remains unclear. We retrospectively studied 380 peripheral adenocarcinomas of ≤2.0 cm in diameter with regard to histology and clinical profiles. Their degree of invasive growth was classified into four grades as follows according to the structural deformity and its location in the adenocarcinoma lesion: Grade 0 had a pure bronchioloalveolar growth pattern and no evidence of stromal invasion. Grade 1 had stromal invasion in the area of bronchioloalveolar growth. Grade 2 had stromal invasion localized on the periphery of a fibrotic focus. Grade 3 had stromal invasion into the center of a fibrotic focus. The clinicopathological data were obtained from medical records. The distribution of the histologic grade of invasion was as follows: grade 0 in 85 tumors (22%), grade 1 in 37 (10%), grade 2 in 46 (12%), and grade 3 in 212 (56%). This histologic grade of invasion was closely related to other indicators of tumor spread. Vascular/lymphatic permeation was seen in none of grade 0, in 1 lesion each of grade 1 and grade 2, and 144 (68%) of grade 3. Lymph node metastasis was seen in 57 (27%) lesions of grade 3 but not in grades 0, 1, or 2. The 5-year disease-free survival rates were 100%, 100%, 100%, and 59.6% for tumors with grade 0, grade 1, grade 2, and grade 3 invasion, respectively. Tumors with grade 1 and grade 2 invasion, like tumors with grade 0 invasion (bronchioloalveolar carcinoma), showed an excellent prognosis. Therefore, tumors with grade 1 and grade 2 invasion could be considered "minimally invasive" or "early" adenocarcinomas.

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Key Words: adenocarcinoma, pathology, prognosis, early cancer, lung

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Because of the advent of high-resolution computed tomography (CT) and the consequent availability of more detailed images and screening programs, small lung cancers are being found more often.[12] Most of these have an adenocarcinoma histology and arise in the periphery of the lung parenchyma.[1] It has also been repeatedly reported that lymph node metastasis is found in approximately 20% of peripheral adenocarcinomas, even if the tumor diameter is small, such as <2.0 cm.[2,11,13,15,17,22]

On the other hand, another histologic category of adenocarcinoma, bronchioloalveolar carcinoma (BAC), has also been discussed with regard to its histologic features and prognosis.[5,6,8,14,23] This subcategory is classified as a subtype of adenocarcinoma, which histologically shows a unique replacing growth pattern of tumor cells along the alveolar wall. According to radiologic studies by high-resolution CT, the replacing growth pattern of adenocarcinoma cells seen in BAC presents as a focal, hazy increase in attenuation called "ground-glass opacity."[3] Radiologic-pathologic studies have demonstrated that the ground-glass opacity appearance represents patent alveolar spaces and the preservation of bronchial and vascular margins.[16,18]

In the recently revised histologic classification of lung and pleural tumors by the World Health Organization (WHO),[29] adenocarcinomas have been classified into five histologic subtypes: BAC, acinar, papillary, solid with mucin, and adenocarcinoma with mixed subtypes. The WHO classification describes BAC as a form of adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular, or pleural invasion. Accordingly, BAC is the only subtype without any invasive features. Obviously, an excellent prognosis can reasonably be expected for noninvasive BACs, and invasive features seen in adenocarcinoma are thought to be

prognostic. However, the relationship between the degree of pathologic invasion and prognosis has not yet been clarified.

In this retrospective study, we histopathologically graded the degree of invasion and explored the relationship between invasion and the prognosis of patients with adenocarcinoma, which might contribute to establishing the concept of "curable" lung cancer.

MATERIALS AND METHODS

Patients

For the 8-year period from January 1993 to December 2000, a total of 1045 pulmonary resections were performed for adenocarcinoma of the lung at the National Cancer Center Hospital, Tokyo. These comprised 60% of all resections for primary lung carcinomas performed during the same period (1738 resections). Among these 1045 adenocarcinomas, 384 tumors were ≤2.0 cm in diameter and located in the periphery of the lung parenchyma. Three cases with a past history of resection for other lesions and one case with preoperative treatment were excluded from this study. A total of 380 peripheral adenocarcinomas of ≤2.0 cm in diameter (36%) were studied to explore the relationship between the degree of invasive growth and prognosis. Clinicopathologic information was obtained by reviewing the medical chart in detail with regard to age, sex, mode of resection, recurrence, and survival. The surgical and postsurgical stages were determined according to the TNM system of the UICC.[26] The backgrounds of these 380 patients are summarized in Table 1. The patients ranged in age from 23 to 89 years with an average of 61.3 years. A total of 182 patients (48%) were male and 198 patients (52%) were female. Most of the patients (98%) underwent complete resection. As the mode of surgical resection, at least lobectomy was performed in 83%.

TABLE 1. Characteristics of Patients With Small Adenocarcinoma

Characteristic	Data
No. of patients	380
Age (years)	
Mean	61.3
Range	23–89
Gender	
Male	182 (48%)
Female	198 (52%)
Operative mode	
Pneumonectomy/lobectomy	314 (83%)
Segmentectomy/partial	66 (17%)
Lymph node dissection	
Mediastinohilar	227 (60%)
Hilar only/none	153 (40%)
Curability of surgery	
Complete	373 (98%)
Incomplete	7 (2%)
Histologic subtype by the WHO classification	
BAC	85 (22%)
Acinar	4 (1%)
Papillary	7 (2%)
Solid with mucin	27 (7%)
Mixed subtypes	257 (68%)
Pathologic stage	
IA	312 (82%)
IB	6 (1%)
IIA	21 (6%)
IIB	5 (1%)
IIIA	22 (6%)
IIIB/IV	14 (4%)

WHO, World Health Organization; BAC, bronchioloalveolar carcinoma.

Pathologic Evaluations

The resected specimens were routinely fixed with 10% formalin after lung inflation by intubation from the bronchus and embedded in paraffin. The entire nodules were blocked for histologic examination. Each of the specimens, including the largest cut surface of the tumor, was cut into 3-μm-thick sections. Sections of the tumor were stained by hematoxylin and eosin, periodic acid-Schiff, and elastica, and then examined by light microscopy. The histologic subtype was determined according to the WHO classification as BAC, acinar, papillary, solid with mucin, or adenocarcinoma with mixed subtypes. We strictly assigned a diagnosis of BAC for noninvasive tumors as defined by the WHO classification, where it is defined as "an adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular or pleural invasion." In this study, histopathological "invasion" was defined when the tumor cells were arranged in acinic/papillotubular structures or solid nests in a fibroblastic stroma, often accompanied by collagenization, and when the alveolar structures were no longer discernible (Fig. 1).[7,29] To categorize the degree of invasive growth in adenocarcinoma, four grades (0-3) were defined according to the location of the above-mentioned invasive features in adenocarcinoma lesions (Table 2). Lesions that were defined as having grade 0 invasion were consistent with BAC by the WHO classification. Typical histologic findings in each grade of invasion are shown in Figures 2 to 5. The following histopathologic findings were also evaluated in the same slides; tumor size (maximum tumor dimension), the size of the fibrotic focus within the tumor, degree of pleural involvement, vascular/lymphatic permeation, lymph node involvement, and pathologic stage. The size of the fibrotic focus was measured at the maximum dimension of the tumor after the fibrotic focus was diagnosed histologically in a low-power

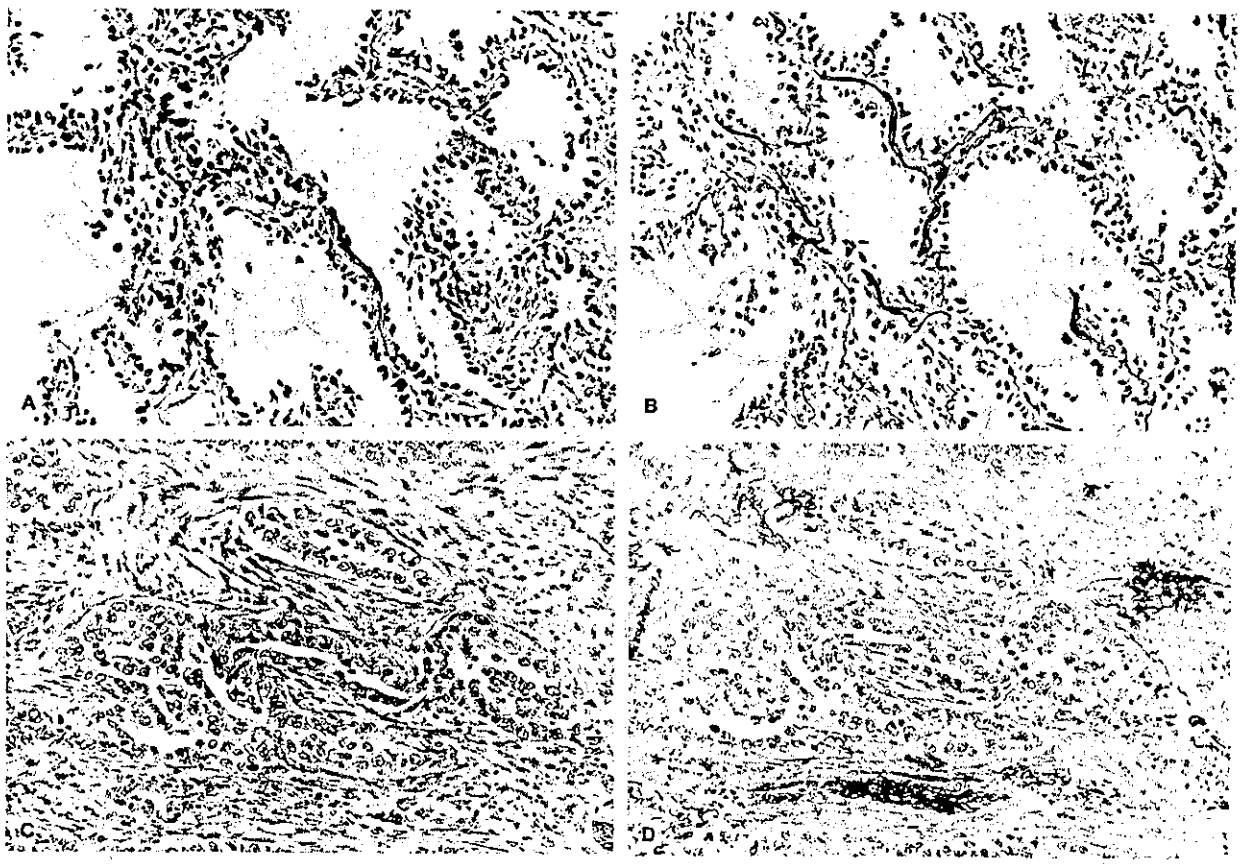

FIGURE 1. Features of histologic noninvasion (A, B) and invasion (C, D) in adenocarcinoma lesions. A and B, The tumor shows a pure bronchioloalveolar growth pattern and no evidence of stromal invasion. The elastic fiber framework is preserved. C and D: The tumor cells are arranged in acinic/papillotubular structures in a fibroblastic stroma, and the elastic framework is disrupted. The elastic stain highlights the elastic framework. Hematoxylin and eosin staining (A, C) and Elastica staining (B, D): original magnification ×200.

view as previously reported.[27] Pleural involvement was classified as positive when the tumor was exposed on the pleural surface or when the tumor invaded the parietal pleura or chest wall. Vascular and lymphatic permeation was evaluated based on the presence of identifiable tumor cells in the blood vessel lumen or lymphatic lumen, respectively.

TABLE 2. Histologic Grade of Invasion in Adenocarcinoma

Grade	Description
0	Pure bronchioloalveolar growth pattern and no evidence of stromal invasion
1	Stromal invasion in the area of bronchioloalveolar growth
2	Stromal invasion localized on the periphery of a fibrotic focus
3	Stromal invasion into the center of a fibrotic focus

Statistics

To compare the frequencies among different groups, a χ^2 test or Tukey's significant difference test was used. Survival curves were estimated by the Kaplan-Meier method using the date of resection as the starting point and the date of recurrence or last follow-up as the end point. Deaths by causes other than lung cancer were considered censored. Survival curves were compared by the log-rank test. A P value of less than 0.05 was considered statistically significant.

RESULTS

Pathologic Findings

The distribution of histologic grade of invasion (grade 0-3) was as follows: 85 (22%) in grade 0, 37 (10%) in grade 1, 46 (12%) in grade 2, and 212 (56%) in grade 3. The pathologic characteristics of each grade are summarized in Table 3. The histologic grade of invasion defined in this study was closely