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Multimodality therapy for thymoma patients with pleural dissemination

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ABSTRACT

Background: Although multidisciplinary treatment is recommended for patients with advanced stage and recurrent thymoma, a detailed treatment strategy remains controversial. We have performed a multimodality therapy of induction chemotherapy (CAMP therapy: cisplatin, doxorubicin, and methylprednisolone) combined with surgery for those patients. We now conducted a retrospective study for investigating results of this multimodality therapy for thymoma patients with pleural dissemination.

Patients and Methods: Between 2003 and 2017, 201 patients underwent surgical resection for thymomas. Twenty-six of them received induction CAMP therapy followed by surgery, and 19 of them with pleural dissemination were enrolled in this study. Those cohort were divided into 2 groups by employing surgical procedures: extrapleural pneumonectomy (EPP) group (n = 10) and resection of plural dissemination (RPD) group (n = 9).

Results: The median age of all patients was 49 years old. Based on the WHO classification, histological diagnoses of those thymomas were as follows: Type B1 (n = 1), Type B2 (n = 13), and Type B3 (n = 5). Seven patients were complicated with myasthenia gravis (MG). Clinical stage of the 13 primary cases based on the Masaoka classification were stage IV, and the remaining six cases had recurrent pleural

dissemination after surgery. Partial response in induction CAMP therapy was obtained in 78.9% (n = 15) of the patients. Adverse events (Grade 4) occurred in 2 patients (10.5%). Postoperative complications (Grade 4) were observed in 2 patients (10.5%). In all of the enrolled patients, the five-year overall survival rate (5Y-OS) and 5-year progression-free survival rate (5Y-PFS) were 76.7% and 55.1%, respectively. In the EPP group, 5Y-OS and 5Y-PFS were 83.3% and 83.3%, respectively, and in the RPD group, 70.0% and 29.6%, respectively.

Conclusions: Multidisciplinary treatment using induction CAMP therapy and surgical resection for thymoma patients with pleural dissemination was effective and feasible. Because of the low recurrent rate of disease, those young patients with good cardiopulmonary function and well controlled MG might be a good indication for EPP.

Introduction

Thymoma is a thymic neoplasm that grows relatively slowly and generally responds to surgical resection, chemotherapy and radiotherapy [1]. For patients with stage I and II thymoma, primary resection is recommended. On the other hand, multidisciplinary treatment is required for patients with advanced stage and recurrent thymoma [2]. However, detailed treatment strategies including chemotherapy regimen and optimal surgical procedures remains controversial.

Patients with thymoma are often complicated with associated diseases such as myasthenia gravis (MG), pure red cell aplasia, hypo-gammaglobulinemia and so on [3]. Therefore, although it is considered that radical resection is needed for advanced stage and recurrent thymoma to achieve R0 resection, sometimes it could not be acceptable to choose radical resection but palliative resection. Surgeons must choose well-balanced surgical treatment for those complicated patients.

We have performed a multimodality therapy including induction chemotherapy (CAMP therapy: cisplatin, doxorubicin, and methylprednisolone) combined with surgery for patients with advanced stage and recurrent thymoma [4, 5]. We now conducted a retrospective study for investigating results of the multimodality therapy for thymoma patients with pleural dissemination, including patients complicated with

MG.

Patients and Methods

Between 2003 and 2017, two hundred and one consecutive patients with thymoma underwent surgical resection at Nagoya University Hospital. Twenty-six of them received induction chemotherapy followed by surgery, and 19 among of them patients with pleural dissemination were enrolled in the current study. All information on radiological and pathological variables was collected from the medical records. This retrospective study protocol was approved by the institutional review boards of the university hospital. Pathological staging was based on the Masaoka staging system [6], and histological classification was according to the World Health Organization (WHO) classification [7].

Therapeutic strategy

The chemotherapy regimen consisted of cisplatin (20 mg/m^2 per day, continuous infusion on days 1 through 4), doxorubicin (40 mg/m^2 intravenously on day 1), and methylprednisolone (1000 mg/day intravenously on days 1 through 4 and 500 mg/day intravenously on days 5 and 6) (CAMP therapy) [5]. Treatment cycles were repeated

every 21 to 28 days. Surgical resection was attempted after three or four cycles of the chemotherapy. Our concepts of surgical procedures for those patients after induction chemotherapy were as follows; for selected young patients whose cardiopulmonary function was sufficient to undergo pneumonectomy, a thymectomy combined with extrapleural pneumonectomy (EPP) was performed. Patients were examined stress electrocardiogram, echocardiography, pulmonary functional test and pulmonary perfusion scintigraphy for investigating whether pneumonectomy was tolerable. When it was concluded that a patient could tolerate pneumonectomy, it was also thought that the patient could tolerate EPP. For patients complicated with MG, when their general condition was stable with/without low dose of steroid and/or pyridostigmine, we considered that the patients were also acceptable for receiving EPP. None of the patients were treated with immunosuppressive agents prior to EPP. The limit age of performing EPP was under 70-year-old. For patients whose general and/or disease condition was not indicated for EPP, a thymectomy and resection of the visible disseminated nodules in the pleural cavity were performed. Those 19 patients were divided into 2 groups by employed surgical procedures: EPP with or without thymectomy (EPP) group (n = 10), and resection of plural disseminated nodules with or without thymectomy (RPD) group (n = 9).

Follow-up and evaluation

The patients were followed up every 1 to 3 months for 2 years after completion of the multimodality therapy and every 6 months thereafter. All patients were followed up until August 2018, and the median follow-up period for surviving patients was 59.7 months (16.1 – 184.2 months). The patients were evaluated with computed tomography (CT) and positron emission tomography (PET)/CT before and after induction chemotherapy. Response for induction chemotherapy was evaluated according to RECIST criteria [8]. Adverse events associated with chemotherapy and surgical treatments were evaluated using common terminology criteria for adverse events (CTCAE version 4.0).

Statistical analysis

Overall survival was measured from the first day of treatment at our hospital for advanced and recurrent thymoma until death from any cause or the last date of follow-up. Progression-free survival was measured from the first day of treatment until progression of disease or death from any cause or the last date of follow-up. Overall and progression-free survival curves were calculated by the Kaplan-Meier estimation

method using a log-rank test. All statistical analyses were performed with R 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The patients' characteristics were summarized in Table 1. Seven of the 19 patients were complicated with MG. Clinical stage of the 13 primary cases was IV, and the remaining six were recurrent cases of pleural disseminations after surgical treatment. Half of the patients received 4 courses or more of induction CAMP therapy. Responses for CAMP chemotherapy were as follows; PR (n = 15; 78.9%) and SD (n = 4; 21.1%) (Fig. 1). Adverse events (Grade 3 and 4) by CAMP therapy occurred in 10 patients (Table 2). Postoperative complications (G3 and G4) were observed in 4 patients (Table 3).

In all of the enrolled patients, 5-year (5Y-OS) and 10-year (10Y-OS) overall survival rates were both 76.7% (Fig. 2A), and 5-year (5Y-PFS) and 10-year (10Y-PFS) progression-free survival rates were 55.1% and 45.9%, respectively. In the EPP group, the 5Y- and 10Y-OS rates were both 83.3% (Fig. 2C), and 5Y- and 10Y-PFS rates were both 83.3% (Fig. 2D). In the EPP group, one patient died from respiratory failure without recurrence 53 months after surgery. In the RPD group, 5Y- and 10Y-OS rates

were both 70.0%, and 5Y- and 10Y-PFS rates were 29.6% and 14.8%, respectively (Fig. 2F). In the RPD group, the OS rate was high despite the low PFS rate. All those recurrent sites were pleural cavity. Table 4 showed a summary of those recurrent patients in the RPD group, which indicated that customized and suitable treatments were performed for each patient with steroid therapy and/or radiation therapy.

Discussion

For patients with early stage thymoma, surgical resection is considered the mainstay of therapy, nevertheless the standard treatment strategy for advanced stage and recurrent thymoma patients has not been established. Because complete resection of those advanced thymoma was occasionally difficult to achieve, various trials of treatment strategy have been enforced. Thereafter, multimodality therapy with induction chemotherapy followed by surgical resection is nowadays widely accepted as a feasible treatment strategy and is considered to promise long-term survivals [4, 9].

The reasons why multidisciplinary treatment using induction chemotherapy should be needed for patients with advanced stage and recurrent thymoma including complicated with pleural dissemination were considered as below; increasing macroscopic complete resection rates, gaining safety surgical margin by tumor

regression, controlling pleural and pericardial dissemination, and scarring of tumors.

Although no standard combination chemotherapy for thymomas has been established, several regimens have been introduced [5, 10, 11, 12]. Yokoi et al. reported their experience of chemotherapy for patients with advanced stage thymomas [5]. The regimen consisted of cisplatin, doxorubicin and methylprednisolone called CAMP. The response rate was 92.9%, the 5- and 10-year overall survival rates were both 80.7%, and the major adverse events associated with CAMP therapy was only acceptable neutropenia. They concluded that CAMP therapy was highly effective for advanced stage thymomas, and the multidisciplinary therapy including this chemotherapy justifiable for the initial treatment of patients with advanced stage and recurrent thymoma. Our current study also used this regimen prior to surgery and showed the feasibility and safety of this multidisciplinary treatment.

Hence macroscopic complete resection of the tumors might be a promising good prognosis in stage IVa thymomas [3, 13, 14], we considered that EPP was an ideal approach in selected relatively young patients with adequate cardiopulmonary function and well managed MG by medications when complicated. The induction CAMP therapy might assist the EPP procedure to achieve complete resection, and OS and PFS rates were excellent in the EPP group from the results of this study. Actually, several patients

were reported with long disease-free survivals over 20 years which received the same treatment strategy [5]. We believe that complete resection after induction CAMP therapy was one of the effective treatment strategies for young thymoma patients with pleural dissemination. It has been reported that the number of disseminated nodules is one of the prognostic factors for thymoma patients [15]. In the current study, almost all patients had over ten pleural nodules, and it was difficult to count the correct number of nodules. We considered that patients with several nodules were suitable for RPD and the other patients were indication for EPP.

On the other hand, some patients with pleural disseminations were not indicated for radical resection of EPP because of aging, insufficient cardiopulmonary conditions and/or complications (e.g. MG, hypo-gammaglobulinemia, and pure red cell aplasia). For those patients, we performed induction CAMP therapy followed by resection of visible pleural nodules, and as a result the PFS rate was low despite the high OS rate. This reason was that customized and suitable therapy might be performed after recurrence of disease for each case with steroid therapy, radiation therapy, and/or surgical resection. In other words, they were forced to receive some repeated treatments after recurrences, resulting in their long-term prognoses. Those recurrent diseases progress gradually but finally patients die of disease or deterioration of the general

condition because of loss of tolerance for any treatments. In Table 4, all recurrent patients except one in the RPD group did not receive surgical treatment. Although we suppose that surgical treatment is effective for RPD recurrent patients, in this series there were a few tolerable cases for repetitive surgical treatments. We consider that recurrent patients without tolerability for surgery are indicative for re-CAMP or radiation therapy.

Among the total enrolled patients of the current study, OS rates were almost equivalent in comparison with previous studies [15, 16, 17]. However, the PFS rate in our EPP group was as high as the OS rate, while in the RPD group the OS rate was also high but the PFS rate was very low. There were a very few reports of PFS rates after multidisciplinary treatments for advanced stage thymoma, and then our results could not be comparable with other cohorts. Therefore, we consider our results might be the basis for comparison with future investigations.

In conclusion, multidisciplinary treatment using induction CAMP therapy and surgical resection for thymoma patients with pleural dissemination was effective. Because of the low recurrent rate of disease, patients with pleural disseminated nodules, who are young and well managed for their status of MG and had sufficient cardiopulmonary function, might be a good indication for EPP.

Conflict of interest: The authors have declared that no conflict of interest exists.

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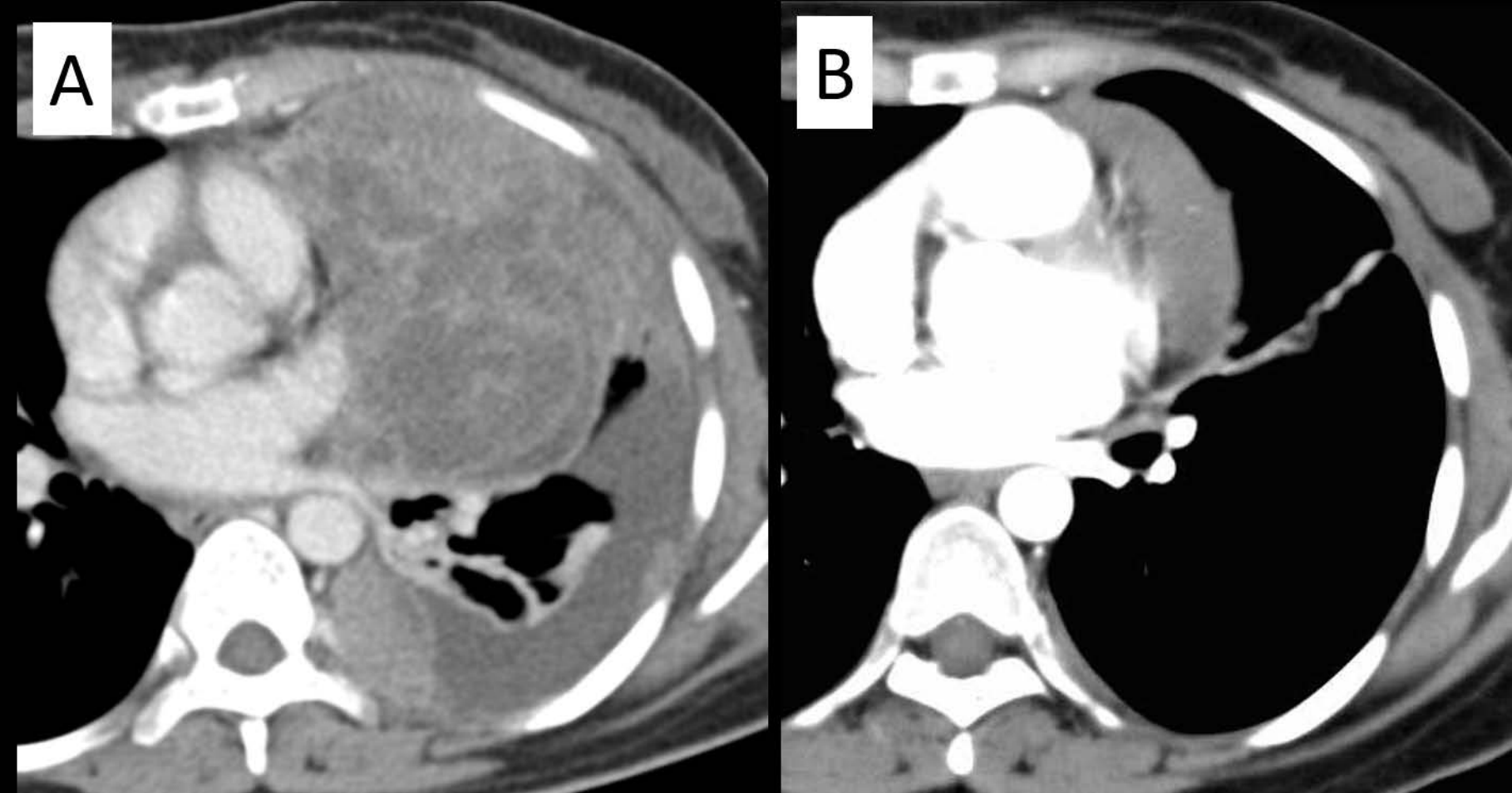
Figure legends

FIGURE 1. A; Chest computed tomography shows primary thymic mass and pleural nodules in the left thoracic cavity in 32-year old female before treatment. B; Chest computed tomography shows the left thoracic cavity after induction CAMP therapy. The primary thymic mass and pleural nodules were dramatically reduced. Thereafter she received an extrapleural pneumonectomy (EPP), and the tumor histology was B2 thymoma. The patient is now alive with disease 65 months after EPP, which chest wall recurrence was under control with radiotherapy.

FIGURE 2. 2A-B; Overall survival and progression-free survival curves of all if the enrolled patients. 2C-D; Overall survival and progression-free survival curves of patients received an extrapleural pneumonectomy after induction CAMP therapy. 2E-F; Overall survival and progression-free survival curves of patients received a resection of disseminated pleural nodules after induction CAMP therapy.


A
B

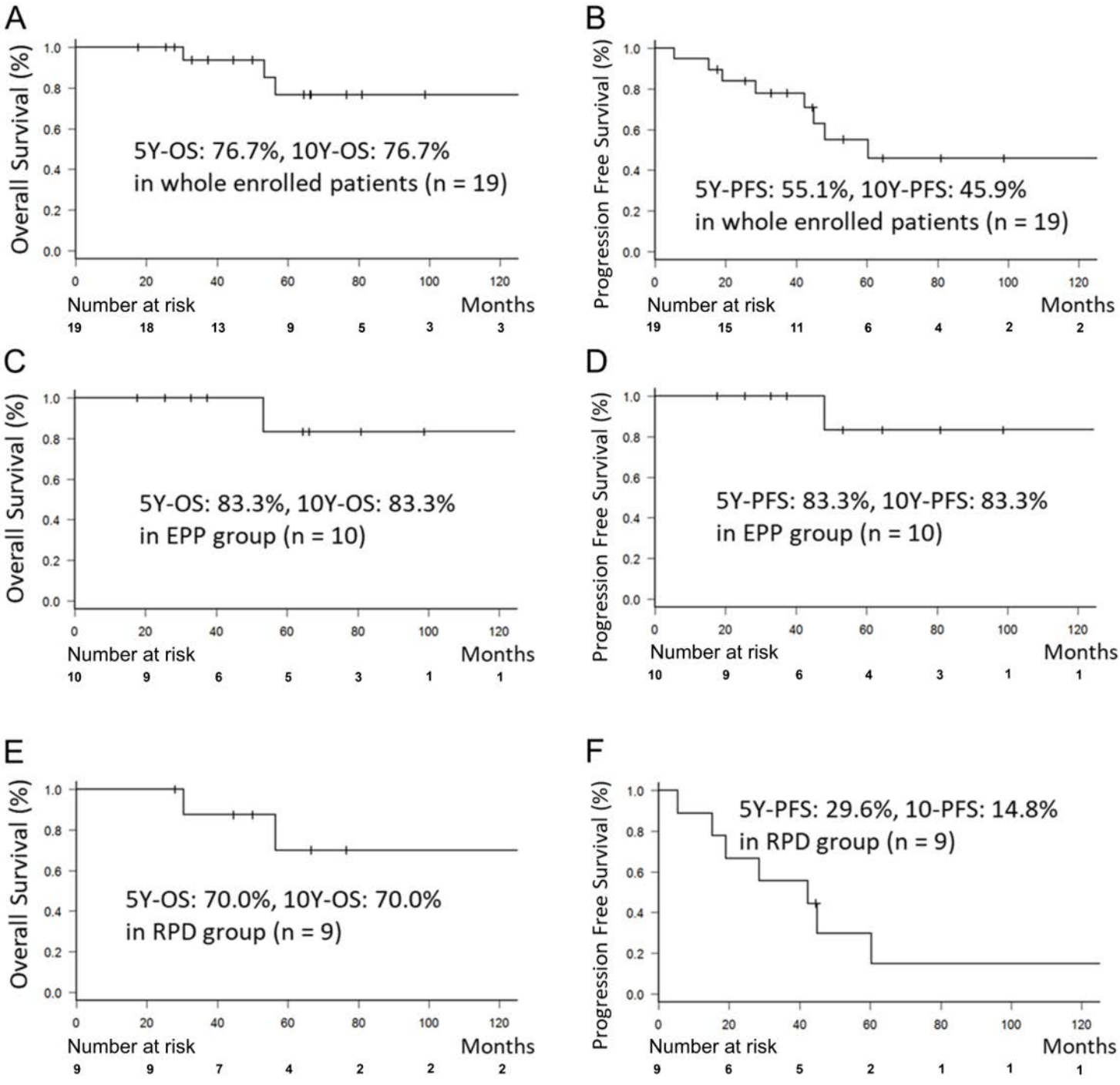

A
Overall Survival (%)
1.0
0.8
0.6
0.4
0.2
0.0
5Y-OS: 76.7%, 10Y-OS: 76.7%
in whole enrolled patients (n = 19)
0 20 40 60 80 100 120
Number at risk
Months
19 18 13 9 5 3 3
B
Progression Free Survival (%)
5Y-PFS: 55.1%, 10Y-PFS: 45.9%
in whole enrolled patients (n = 19)
19 15 11 6 4 2 2
C
5Y-OS: 83.3%, 10Y-OS: 83.3%
in EPP group (n = 10)
10 9 6 5 3 1 1
D
5Y-PFS: 83.3%, 10Y-PFS: 83.3%
in EPP group (n = 10)
10 9 6 4 3 1 1
E
5Y-OS: 70.0%, 10Y-OS: 70.0%
in RPD group (n = 9)
9 9 7 4 2 2 2
F
5Y-PFS: 29.6%, 10-PFS: 14.8%
in RPD group (n = 9)
9 6 5 2 1 1 1

Table 1. Patients Characteristics

Characteristic	All patients (n = 19)	*EPP group (n = 10)	**RPD group (n = 9)
Age, years (median)	49	49	52
(range)	(32 - 70)	(32 - 60)	(42 - 70)
Sex			
Male	11	4	7
Female	8	6	2
Associated disease			
#MG	7	2 (under control)	5
None	12	8	4
Histology (WHO classification)			
B1	1	1	
B2	13	6	7
B3	5	3	2
Disease status			
Primary	13	8	5
Recurrent	6	2	4
Number of courses of performed chemotherapy			
1 course	3	2	1
2 courses	1	1	
3 courses	5	2	3
4 courses or more	9	5	4
Response for ##CAMP therapy			
PR	15	7	8
SD	4	3	1

*EPP: extrapleural pneumonectomy, **RPD: resection of pleural dissemination. #MG: myasthenia gravis, ##CAMP therapy: regimen consisted of cisplatin, doxorubicin, and methylprednisolone

Table 2. Toxicities by induction CAMP chemotherapy

Events	Grade 3	Grade 4	% of patients with toxicities ≥ G3
Neutropenia	4	1	26.3
Pneumonia	1	1	10.5
Dehydration	2	-	10.5
Nausea	1	-	5.3
Varicella-zoster	1	-	5.3

Table 3. Postoperative complications

Events	Grade 3	Grade 4	% of patients with adverse events ≥ G3
Bleeding	-	1 (EPP[#])	5.3
Heart failure	-	1 (EPP[#])	5.3
MG* crisis	1 (RPD**)	-	5.3
Paralytic ileus	1 (RPD**)	-	5.3
Massive pleural effusion	1 (RPD**)	-	5.3

*MG: myasthenia gravis, **RPD: resection of pleural dissemination group

[#]EPP: extrapleural pneumonectomy group

One RPD patient has 2 complications; MG crisis and paralytic ileus

Table 4. Summary of recurrent patients in the RPD* group (n = 7)

Cases	Associated disease	Recurrent site	Treatment after recurrence	Survival (months)	Status
1	MG**	Pleura	RT*** × 2 times	28	AWD^{+}
2	-	Pleura	Re-RPD	50	AWD^{+}
3	-	Pleura	PSL$^{\#}$	67	AWD^{+}
4	MG**	Pleura	PSL + TAC$^{\#\#}$	77	AWD^{+}
5	MG**	Pleura	RT × 5 times	179	AWD^{+}
6	MG**	Pleura	RT × 2 times + Steroid pulse therapy	31	DOD^{++}
7	-	Pleura	Observation	56	DOD^{++}

*RPD; resection of pleural dissemination, **MG: myathsenia gravis, ***RT: radiation therapy, $^{\#}$PSL: prednisolone, $^{\#\#}$TAC; tacrolimus, $^{+}$AWD; alive with disease, $^{++}$DOD; dead of disease

Steroid therapy was initially used mainly for MG, not recurrent tumors. As a result, steroids often served as a disease suppressor.