Table 2 Extracorporeal membrane oxygenation (ECMO) equipment used

Equipment	Number of cases
Console	
CAPIOX SP-101	11
Bio-Console 560	1
Stöckert SCP system	1
MERA HAP-31	1
Circuit	
CAPIOX Custom Pack	11
Unknown	3
Oxygenator	
LX or SX	9
BIOCUBE 6000	4
MERA HP Exelungprime	1
Centrifugal pump	
CX-SP45	11
COBE revolution	1
Unknown	2

CAPIOX SP-101, CAPIOX Custom Pack, LX, SX, CX-SP45 (Terumo, Tokyo, Japan), Bio-Console 560 (Medtronic, Minneapolis, MN, USA), Stöckert SCP system (SORIN Group, Germany), MERA HAP-31, MERA HP Exelungprime (Senko Medical Instrument, Tokyo, Japan), BIOCUBE 6000 (NIPRO, Osaka, Japan), COBE revolution (SORIN Group, Italy)

Table 3 Cannula size, approach site, and proximal position for ECMO

Drainage	Number of cases
Size (Fr.)	
18	6
19.5	4
21	3
21.5	1
Approach site	
Femoral vein	14
Proximal position	
Inferior vena cava	10
Right atrium	4
Return	**Number of cases**
Size (Fr.)	
12	1
15	9
16	2
16.5	1
21	1
Approach site	
Right jugular vein	12
Femoral vein	2
Proximal position	
Superior vena cava	8
Right atrium	4
Inferior vena cava	2

severe respiratory failure treated with mechanical ventilation without ECMO for season of 2010–2011 in Japan [8, 9].

In addition, underlying diseases were present in only two patients in this study, and none of the patients had complications involving respiratory, cardiac, or immunological disorders. Anti-influenza drugs had been used in all cases. In particular, during this season, peramivir, a drug for intravenous administration, was newly available on the market and had been used in 11 patients (78.6 %). This drug was used as a more reliable means of treatment than oseltamivir because it is less likely to cause poor absorption via the digestive tract from such problems as vomiting. This finding suggests that the lives of many of these patients could have been saved if appropriate management with ECMO had been applied.

The blood drainage cannula size is considered an important factor for maintaining appropriate flow during ECMO therapy [10]. According to a report from the ECMO Center Karolinska, blood drainage cannulas with sizes between 23 and 29 Fr. were used for patients with a median body weight of 88 kg [5]. In the present study, the drainage cannula size was <20 Fr. in 70 % of the patients, who had a median body weight of 70 kg (range, 51–90 kg) and height of 146–190 cm (estimated from body weight and BMI). According to the previous reports, the achieved ECMO blood flow rates are generally 4–5 l/min [2, 5, 6]. We did not have any ECMO blood flow data in this study, but the cannulas used for these Japanese patients appear to have been too small in diameter. The use of a blood drainage cannula with too small a diameter is more likely to cause adverse events such as inadequate flow (from poor blood drainage flow), hemolysis (due to the need for a sufficiently high pump rotation rate to achieve satisfactory flow), and a hemorrhagic tendency (caused by platelet consumption).

Recently, adverse events arising from ECMO therapy have been clearly decreasing thanks to advances in component technology and techniques [11]. However, in the present study, adverse events associated with ECMO therapy developed in all patients, except for one who died on the first day of this therapy, and the incidence of adverse events was remarkably high compared with that in previous reports [2, 4–7, 11–14]. Among other adverse events, such disorders of the coagulation and fibrinolytic system as massive bleeding, DIC, and thrombus formation, which are complications that require close attention during ECMO therapy [15], developed in most patients. Problems with the equipment and the excessively small diameter of the

Table 4 ECMO therapy

	All cases (14 patients)	Survival group (5 patients)	Non-survival group (9 patients)
Ventilator days before ECMO (days)	5.0 (0.8–8.5)	3.0 (0.5–7.0)	6.0 (0.5–14.0)
Length of ECMO therapy (days)	8.5 (4.0–10.8)	9.0 (6.5–12.5)	8.0 (3.5–11.5)
Number of circuits used	2.0 (1.0–3.0)	2.0 (1.5–2.5)	2.0 (1.0–3.5)
Duration of each circuit (days)	4.0 (3.2–5.3)	5.0 (3.3–6.8)	4.0 (2.1–4.3)

Table 5 Adverse events related to ECMO therapy

Event	Number of cases (%)
Directly related to the ECMO circuit	11 (78.6)
Oxygenator failure	7 (50.0)
Blood clots	4 (28.6)
Oxygenator	3 (21.4)
Other circuit	1 (7.1)
Cannula-related problems	3 (21.4)
Pump head complications	1 (7.1)
Indirectly related to the ECMO circuit	12 (85.7)
Massive bleeding	8 (57.1)
Surgical site bleeding	4 (28.6)
Upper digestive tract hemorrhage	4 (28.6)
Cannulation site bleeding	2 (14.3)
Pulmonary hemorrhage	1 (7.1)
Hemolysis	2 (14.3)
Disseminated intravascular coagulation	10 (71.4)
Venous thrombus	2 (14.3)

cannulas were probably involved in the development of many of the adverse events associated with ECMO therapy in this study. This view is supported by the observation that the duration of each circuit was only 4 days. The life of the oxygenator was extremely short, and this was a major factor in necessitating circuit renewal only 4 days after the start of use. The recommended period of use is only 6 h for the most frequently employed ECMO circuit and oxygenator in Japan, the CAPIOX Custom Pack (Terumo, Tokyo, Japan), according to its package insert (written in Japanese). The cavity of the circuit used in the present study usually had a volume of 500–600 ml. Every time the circuit was renewed, the same volume of blood was lost, and blood transfusion or intravenous fluid infusion was carried out to compensate for the discarded blood. This procedure is a major source of stress for patients. It would appear to be necessary to review the ECMO equipment used in Japan.

Factors that possibly raised the mortality rate following ECMO therapy include central nervous system injury, gastrointestinal or pulmonary hemorrhage, and renal dysfunction [16]. We found, however, no particular differences in any of these factors between the survival and non-survival groups. The maximum SOFA score during treatment was higher in the non-survival group, which reflects the tendency for a more severe disease course in the non-survival group. The only difference between the two groups is that the non-survival group included some patients who were given mechanical ventilation for a period much longer than 7 days before beginning ECMO. When started within 6 days after initiating mechanical ventilation, ECMO therapy offers a high survival rate [3, 6, 10, 11, 17–20]. It is also possible that initiation of ECMO was delayed because Japanese physicians are unfamiliar with this therapy. In addition, it seems that Japanese physicians had not understood or implemented such routine therapeutic strategies as the ELSO guidelines. Instead, a specific form of ventilation that maintained a high average airway pressure, such as APRV, was employed in many cases. Although the setting for mechanical ventilation during ECMO therapy was not sufficiently clear from the data, it appears likely that a high-pressure setting for mechanical ventilation was adopted even during ECMO therapy, and this may be one of the factors responsible for the high mortality rate. It is necessary for physicians to develop a proper understanding of the ECMO treatment strategy.

The survival rate of adults with severe respiratory failure following ECMO therapy is reported to be usually 61 % [15]. It has also been reported that when ECMO therapy is applied to patients with severe respiratory failure, transfer to a central facility, such as an ECMO center, is likely to yield better outcomes [4–6, 11, 12, 14]. During the 2009–2010 season, ECMO therapy was applied to 16 patients with H1N1-related severe respiratory failure in Sweden; 13 (81 %) of these patients were transferred to the ECMO Center Karolinska, and the result was successful weaning from ECMO in all cases [5]. In Italy, establishment of the ECMO network resulted in a high survival rate [6]. Both the effectiveness of ECMO therapy for H1N1-related severe respiratory failure and treating many cases at the central facility were reportedly major factors contributing to the high survival rate [4]. The facilities in Japan have very little experience with ECMO therapy for patients with severe respiratory failure. At most Japanese facilities in the present study, ECMO for severe respiratory failure had been applied to only one or two respiratory failure cases a year or even less frequently; about half of the facilities had no previous experience with this therapy. H1N1-related severe respiratory failure has a high probability of recovery in response to ECMO. Thus, adopting

ECMO therapy should be given due consideration. However, because the number of patients with this condition is not particularly large, transferring patients to central facilities for this therapy is anticipated to improve treatment outcomes because the physicians at such centers can gain experience through dealing with a larger number of cases. ECMO may also be indicated for H5N1 (avian influenza), an outbreak of which is now a great concern. A recent report has shown that ECMO should be performed at centers with high case volumes, established protocols, and clinicians who are experienced in its use [11]. Facilities serving as centers for this therapy should be established in Japan as soon as possible.

The present study has a limitation in that the survey did not cover all patients who received ECMO therapy. According to a report by the Ministry of Health, Labour and Welfare of Japan, there were 15 deaths among the adults who were given ECMO therapy (the number of survivors has not been made public) [21]. In the present study, 9 of the patients died, which would suggest that more than half of all Japanese patients who received ECMO therapy were covered by this survey.

The survival rate for patients with H1N1-related severe respiratory failure following ECMO therapy in the present study was very low. However, this result does not refute the effectiveness of ECMO therapy for H1N1-related severe respiratory failure; the result is instead attributable to the lack of experience and lack of preparedness of Japanese facilities to provide ECMO therapy. To improve the outcomes of ECMO therapy not only in Japan but also in other countries inexperienced with ECMO therapy, efforts should be made along the following lines: (1) supply ECMO equipment suitable for treatment of severe respiratory failure; (2) promote a full understanding of the ECMO treatment strategy by physicians and other medical staff; and (3) transfer patients to central facilities established for this therapy.

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Conflict of interest All authors have no conflict of interest to disclose.

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ORIGINAL ARTICLE

High prevalence of gene abnormalities in young patients with lung cancer

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ABSTRACT

Background: Recently, driver oncogenes in adenocarcinoma of the lung were identified, and several molecular target agents were introduced in the clinical setting. However, there are few reports on the frequency of gene abnormalities in young patients with lung cancer.

Materials and methods: Twelve patients with lung adenocarcinoma aged 40 or younger at Juntendo University Urayasu Hospital or Juntendo University Hospital from July 2004 to March 2010 were analyzed for driver oncogene status including *EGFR* activating mutation, *EML4-ALK* fusion gene, and *K-ras* mutation.

Results: Four patients showed *EGFR* gene mutation. Five out of 7 *EGFR* mutation-negative patients showed positive results for *EML4-ALK* gene fusion. One case whose *EGFR* mutation was indeterminate.

Conclusions: Driver oncogene including *EGFR* mutation and *EML4-ALK* fusion gene was identified in 9 of 12 cases (75%). Examination of gene abnormalities is essential in young patients with non-small cell lung cancer to provide the best treatment.

KEY WORDS Young patients; driver oncogene; lung cancer; *EGFR*; *EML4-ALK*

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Introduction

Many young patients with lung cancer at the time of diagnosis are already advanced stage and therefore result in a poor prognosis (1,2). For patients harboring the *epidermal growth factor receptor* (*EGFR*) gene mutation, *EGFR* tyrosine kinase inhibitors (*EGFR*-TKIs) have been used effectively to prolong progression-free survival and overall survival (3,4). Recently, the powerful driver oncogene, fusion gene of the *anaplastic lymphoma kinase* (*ALK*) with the *echinoderm microtubule-associated protein-like 4* (*EML4*) was identified in non-small cell lung cancer (5). Prolongation of the survival period is expected with the use of the *ALK*-TKI. However, few studies have analyzed the frequency of driver oncogenes in young patients with non-small cell lung cancer aged 40 or younger. Therefore, we performed gene mutation analyses in young patients with lung cancer.

Methods and materials

We retrospectively reviewed medical records of all hospitalized patients with non-small cell lung cancer aged 40 or younger at Juntendo University Urayasu Hospital or Juntendo University Hospital from July 2004 to March 2010. We examined patient background, treatment modalities, and gene abnormalities. First, we examined *EGFR* mutation by performing direct sequencing for tumor biopsy specimens obtained by bronchoscope, resected tumor samples, or cell blocks of bronchoalveolar fluid or pleural effusion. When the *EGFR* mutation was negative, we next performed immunohistochemical analysis [using an intercalated antibody-enhanced polymer (iAEP)] and fluorescence in situ hybridization (FISH) for detection of the *EML4-ALK* fusion protein and gene (6), respectively. In negative cases for both *EGFR* mutation and *EML4-ALK* fusion gene, we analyzed the samples for presence of the *K-ras* mutation. We did not conduct re-evaluation for the *EGFR* gene mutation after recurrence.

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Table 1. Background characteristics of the 12 patients in whom examination was performed for gene abnormalities.

No	Age	Sex	BI	Histology	T	N	M	Stage	PS	EGFR	EML4-ALK	1st line	2nd line	Outcome	Survival time
1	33	m	10	adeno	4	0	1	IV	1	+	n.d.	CBDCA+TXL	Gefitinib	death	1,208 days
2	37	m	800	adeno	4	2	1	IV	1	+	n.d.	Gefitinib	CBDCA+TXL	death	461 days
3	37	m	450	adeno	4	3	1	IV	3	+	n.d.	CBDCA+TXL	Gefitinib	death	379 days
4	39	m	400	adeno	3	3	1	IV	0	+	n.d.	CDDP+PEM	Gefitinib	death	364 days
5	31	f	100	adeno	1	3	0	IIIB	0	±	n.d.	CBDCA+TXL	Gefitinib	alive	2,688+α
6	35	f	0	adeno	4	0	0	IIIB	0	-	+	CBDCA+GEM	PEM	alive	1,456+α
7	37	f	0	adeno	2	1	1	IV	0	-	+	CBDCA+PEM		alive	757+α
8	34	f	0	adeno	4	3	1	IV	2	-	+	CBDCA+TXL	GEM	death	568 days
9	33	m	300	adeno	4	3	1	IV	1	-	+	CBDCA+TXL	CBDCA+PEM	death	175 days
10	35	m	0	adeno	4	3	1	IV	1	-	+	CBDCA+TXL	CBDCA+PEM	death	99 days
11	37	f	0	adeno	2	2	0	IIIA	0	-	-	CBDCA+TXL		alive	365+α
12	36	m	340	non-small	2b	3	1b	IV	1	-	-	CBDCA+TXL		alive	280+α

Abbreviations: BI, brinkman index; PS, performance status; ±, EGFR mutaion indeterminate, but responded to gefitinib; n.d., not done; CBDCA, carboplatin; TXL, pacritaxicel; PEM, pemetrexed; GEM, gemcitabine.

Survival analysis was conducted using the Kaplan-Meier method.

Results

Case profile

We retrospectively studied 12 young patients with non-small cell lung cancer (men, 7; women, 5). The mean age of the patients was 35.3 years (Table 1).

Smoking history

Six patients were smokers. Three out of these patients were heavy smokers over 20 pack pear, and had a long history of smoking. One man and 4 women were non-smokers.

Histology and stage of the disease

All of the patients had non-small cell lung cancer. Eleven patients (91.6%) were diagnosed with adenocarcinoma, while one was with histology not otherwise specified. According to the clinical TMN classification, there were 1 patient with stage IIIA, 2 with stage IIIB cancer; and 9 with stage IV.

Examination of the gene abnormalities

Activating EGFR gene mutations, exon 19 deletion, were detected in 4 cases.

One case whose *EGFR* gene mutations were indeterminate because sample size was not enough for direct sequencing. But she seems to harbor *EGFR* activation mutation because she responded to gefitinib remarkably. Therefore, we considered that she harbored an *EGFR* mutation. Subsequently, we conducted iAEP followed by FISH analyses for 7 patients without *EGFR* mutation to determine EML4-ALK fusion protein and gene. Among 7 patients, 5 patients showed positive for *EML4-ALK* protein or gene. Analysis for the presence of *K-ras* mutation was performed in 2 cases that were negative for both the *EGFR* mutation and the *EML4-ALK* fusion gene. One of the cases was *K-ras* mutation-negative, while the other case was not clear for *K-ras* mutation because of inadequate sample (Figure 1).

Median survival time and survival curve

The patients harboring *EGFR* mutation were treated with gefitinib. The median survival time (MST) was 461 days. The MST for the patients harboring *EML4-ALK fusion gene* was 568 days (Figure 2), because these patients could not be treated *ALK* inhibitors.

Discussion

In this study, all patients were diagnosed as non-small cell lung cancer with advanced stage. Development of metastases without symptoms or prolonged neglect of symptoms could be the reasons for this finding. Gene analysis showed that *EGFR* mutation was clearly identified in 4 of our 12 cases.

The frequency of the EGFR mutation in cases of lung adenocarcinoma has been reported by a previous study (7). There were no significant differences in the frequency for *EGFR* mutation depending on the patient age (8). Five of the 7 *EGFR*-negative cases in our study were detected to have the EML4-ALK fusion gene. According to a previous study, the frequency of the *EML4-ALK* fusion gene is in the range of 1.6% to 8.6% (9-12).

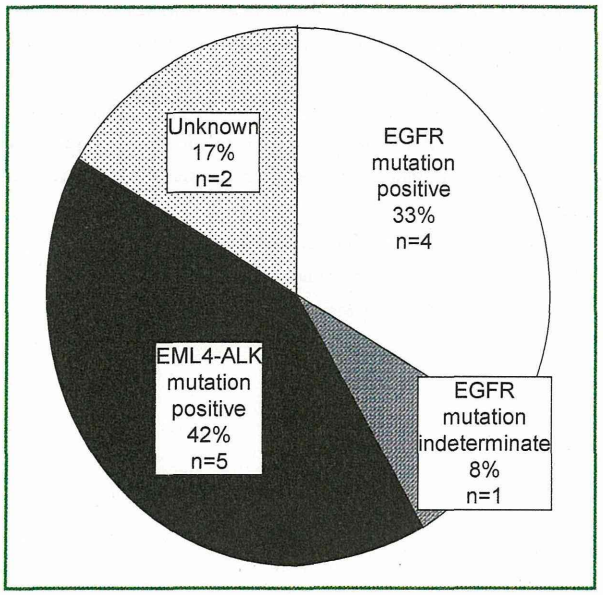

Figure 1. Frequency of gene abnormalities in 12 young patients with lung cancer aged 40 or younger.

The *EML4-ALK* fusion gene is recognized to be associated with the onset of lung cancer in young patients. *EML4-ALK* fusion gene has an exclusive relation with *EGFR* mutation and *K-ras* mutation (13). The frequency for the *EML4-ALK* fusion gene in this study was markedly higher than previous studies. Our sample-size was small, but gene abnormalities were identified in 75% in patients aged 40 and younger with lung cancer. Although all patients with *EGFR* activating mutation were treated with an *EGFR*-TKI, the overall survival was unsatisfactory. Unfortunately, we did not perform a re-examination for the gene abnormalities in the recurrent tumors. One of the potential mechanisms for short survival for these patients could be explained by the fact that 3 patients were heavy smokers, whose *k-ras* could be mutated. Moreover, we could evaluate only one case the *k-ras* status. Furthermore, the overall survival of the patients harboring the *EML4-ALK* fusion gene was also unsatisfactory, probably because *ALK*-TKI was not available at that time for these patients.

The results indicated that driver oncogenes were detected in 75% of our cases and that the frequency of *EML4-ALK* fusion gene was high in the young patients with non-small cell lung cancer. Our finding also suggests that the onset of non-small cell lung cancer in patients aged 40 or younger is more significantly related to gene abnormalities including driver oncogene mutation than to environmental factors.

Conclusions

In this study, we clarified that all 12 patients aged 40 and younger were non-small cell lung cancer and 9 in 12 patients

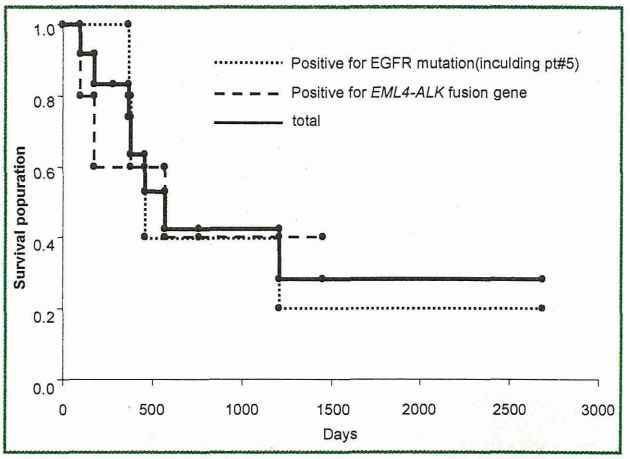

Figure 2. Survival curve of the patients.

were positive for the *EGFR* gene mutation or the *EML4-ALK* fusion gene. Our study revealed that ALK fusion gene affected carcinogenesis by the young patients in efficiency more than previous reports. Therefore, examination of gene abnormalities is especially important in young patients with lung cancer to provide a appropriate treatment modality.

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ORIGINAL ARTICLE

The N-ERC index is a novel monitoring and prognostic marker for advanced malignant pleural mesothelioma

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ABSTRACT

Background: Although N-ERC/mesothelin (N-ERC) is an attractive diagnostic and treatment monitoring biomarker for malignant pleural mesothelioma (MPM), its clinical utility for predicting the prognosis has not yet been clarified. The aim of this study is to investigate whether the serum N-ERC level can accurately predict the outcome in patients with MPM.

Methods: Twenty-six patients with MPM were enrolled. Serum N-ERC level was measured before and after chemotherapy. The N-ERC index was determined by the logarithm of the division of the N-ERC level after two courses of chemotherapy by the prior level.

Results: The median N-ERC index in the partial response (PR) group was significantly lower than that in patients with the stable disease (SD) plus the progressive disease (PD) group. The overall survival in the group whose median N-ERC index was lower than its median value was significantly longer than the group whose median N-ERC index was higher than its median value.

Conclusions: The N-ERC index is therefore considered to be a useful biomarker for predicting not only the chemotherapeutic response, but also the prognosis in patients with advanced MPM.

KEY WORDS Mesothelioma; biomarker; N-ERC index; response; prognosis

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Introduction

Malignant mesothelioma is a rare and highly aggressive disease arising from the serosal surfaces of the pleura and peritoneum. Asbestos exposure is the most common risk factor for malignant pleural mesothelioma (MPM). The incidence of MPM is increasing worldwide due to widespread asbestos exposure. Pemetrexed plus cisplatin chemotherapy has been demonstrated to improve the overall median survival in patients with advanced stage disease (1). The chemotherapeutic response is evaluated by Modified RECIST (2) on computed tomography. However, the determination of the tumor response is not always easy because MPM usually does not form tumors and spread to the pleura. In addition, it tends to be difficult to predict the prognosis after chemotherapy, even though several prognostic biomarkers have been reported. Therefore, new biomarkers are needed that can predict the chemotherapeutic response and prognosis at the time of evaluation of chemotherapeutic response. Although serum mesothelin, osteopontin and soluble mesothelin-related protein (SMRP) have been identified as candidates for diagnostic markers of mesothelioma (3-5), it remains unclear as to which marker is clinically superior (6). In addition, although mesothelin and SMRP have been reported as prognostic markers, no biomarkers that can predict the chemotherapeutic response as well as the prognosis have yet been identified.

We previously reported the renal carcinoma *ERC* gene to be expressed in renal carcinoma of the Eker rat (7). We also identified that ERC is a homolog of human megakaryocyte potentiating factor (MPF)/mesothelin gene (8,9). Rat Erc and the human MPF/mesothelin are functional orthologues.

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We designated this protein as ERC/mesothelin. The ERC/mesothelin gene encodes a 71-kDa precursor protein and the protein is cleaved by a furin-like protease into the 31 kDa N-terminal fragment (N-ERC/mesothelin) and 40 kDa C-terminal fragment (C-ERC/mesothelin) (10,11). We established a novel ELISA assay for the detection of human ERC/mesothelin as previously reported (3,4). The serum N-ERC level is a sensitive marker for early diagnosis of MPM especially in the epithelioid-type of the disease and tends to increase according to the stage of the disease (4). We also reported that since N-ERC values decreased following chemotherapy among PR-responsive patients with MPM, thus N-ERC was a reliable monitoring marker for MPM (12).

In this study, we assessed whether N-ERC is a reliable biomarker, which can not only evaluate the chemotherapeutic response, but also predict the prognosis at the time of the second course of chemotherapy in patients with advanced MPM.

Patients and methods

Between June 2005 and June 2010, twenty-six inoperable patients with histologically confirmed MPM were recruited for treatment with chemotherapy at Juntendo University Hospital. The serum N-ERC levels were measured before (on the same day and just before administering chemotherapy) and following two courses of chemotherapy. All blood samples after two courses of chemotherapy were collected from the patients who were completely relieved from chemotherapeutic adverse effects. Serum specimens were immediately obtained from blood samples and stored in aliquots at –80 °C until analysis. The serum level of N-ERC was measured using the sandwich ELISA kit (Immuno-Biological Laboratories, Ltd., Gunma, Japan) as previously reported (3). The chemotherapeutic assessment was performed using a CT scan with Modified RECIST criteria (2) before and after the two courses of chemotherapy. This study was approved by the Juntendo University Research Ethics Committee. Written informed consent was obtained from all patients enrolled in this study.

Statistical analyses

The N-ERC index was defined as Log_2 (N-ERC value after 2 courses of chemotherapy/N-ERC value prior chemotherapy). In order to analyze the overall survival (OS), survival curves were generated using the Kaplan-Meier method. The OS was calculated from the date of initiation of chemotherapy to the date of death. The statistical analysis was performed with Wilcoxon signed-rank test to compare the N-ERC index between the PR and SD/PD groups. The OS rates were compared using the log-rank test according to the N-ERC index (a group whose N-ERC index is above the median value *vs.* a group whose N-ERC index is below the median value). The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software program version19.0F (SPSS Inc.). Differences between the levels were considered to be statistically significant at $P<0.05$.

Results

The characteristics of the participants enrolled in this study are shown in Table 1. Briefly, 26 patients who were diagnosed with MPM were included, 21 men and 5 women. The median age was 63.8 years (range, 51-78 years). Of 26 patients, 21 were of epithelial type, 4 were sarcomatoid type and 1 was biphasic type. The clinical stage of all patients was as follow: one patient in stage I, 5 in stage II, 8 in stage III and 12 in stage IV. The patient in stage I was inoperable due to an advanced age and a low respiratory function. The chemotherapy regimen is also shown in Table 1. The most frequently used regimen was pemetrexed plus cisplatin. The overall response rate was 19.2% with 5 partial responses (PR), 10 patients with stable disease (SD) and 11 patients with progressive disease (PD).

The average N-ERC level was 21.19 ng/mL (range: 1.58-97.54 ng/mL) before chemotherapy. The median value of the N-ERC index in patients with PR was significantly lower than that in patients with SD/PD (Wilcoxon signed-rank test, $P=0.015$, Figure 1). The overall survival analyses were performed by stratification at a high level (above median) and at a low level (below median) of the N-ERC index. The overall survival in a group whose N-ERC index was below the median level was significantly longer [26.6 months (95% CI, 15.9-37.2 months)] than a group whose N-ERC index was above the median level [10.3 months (95% CI, 5.8-14.1 months)] ($P=0.027$, Figure 2). The causes of mortality for all patients were the underlying disease. In addition, the low N-ERC level group included 4 PR patients, 4 SD patients and 5 PD patients, while the high N-ERC level group included 1PR patient, 6 SD patients and 6 PD patients.

Discussion

Many biomarkers for MPM have been investigated in patients with MPM to aid in making an early diagnosis. For example, Cytokeratin fragment 21-1, TPA, CA15-3, CA19-9 and CEA have been considered to be potential tumor markers for MPM. However, the findings of such studies still remain controversial (6) i.e., the specificity of these biomarkers is quite low. Therefore, many researchers have so far struggled to identify novel biomarkers whose sensitivity and specificity are higher than those of classical markers. Recently, several investigators reported that mesothelin is useful diagnostic biomarkers, with a high sensitivity and specificity, for MPM (5,13).

We previously reported N-ERC to be a sensitive diagnostic