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Prognostic significance of metabolic response by positron emission tomography after neoadjuvant chemotherapy for resectable malignant pleural mesothelioma

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Background: To select optimal candidates for extrapleural pneumonectomy (EPP), we retrospectively evaluated the usefulness of metabolic response by fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) after neoadjuvant chemotherapy to predict prognosis for patients with resectable malignant pleural mesothelioma (MPM) who underwent EPP in a multicenter study.

Patients and methods: We carried out high-resolution CT (HRCT) and FDG-PET/CT before and after neoadjuvant platinum-based chemotherapy on 50 patients with clinical T1–3 N0-2 M0 MPM who underwent EPP ± postoperative hemithoracic radiotherapy. A decrease of ≥30% in the tumor maximum standardized uptake value (SUV_{max}) was defined as a metabolic responder. The radiologic response using the modified RECIST or metabolic response and surgical results were analyzed.

Results: The median overall survival (OS) from diagnosis was 20.5 months. Metabolic responders significantly correlated to OS with median OS for metabolic responders not reached *versus* 18.7 months for non-responders. No correlation was observed between OS and radiologic response with median OS for radiologic responders and non-responders. Based on the multivariate Cox analyses, decreased SUV_{max} and epithelioid subtype were significantly

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independent factors for OS.

Conclusions: The metabolic response after neoadjuvant chemotherapy is an independent prognostic factor for patients with resectable MPM. Patients with metabolic responder or epithelioid subtype may be good candidates for EPP.

Key words: extrapleural pneumonectomy, malignant pleural mesothelioma, metabolic response, neoadjuvant chemotherapy, positron emission tomography

introduction

Malignant pleural mesothelioma (MPM) is an uncommon tumor characterized by locally aggressive behavior which leads to a fatal prognosis, but its incidence has increased in recent times within industrialized nations including Japan [1–4]. The optimal management of resectable MPM continues to be an ongoing topic of debate with general agreement in regard to poor disease control by any single-modality therapy [5]. The current standard for possible cure of the disease has shifted to a multidisciplinary approach combining extrapleural pneumonectomy (EPP) with chemotherapy and/or radiotherapy. Because of the difficulty in administering adjuvant chemotherapy after EPP, we conducted trimodality therapy with neoadjuvant chemotherapy followed by EPP and hemithoracic radiotherapy [6]. Several studies have been reported on trimodality therapy, such as chemotherapy followed by EPP and radiotherapy for resectable T1–3 N0-2 M0 MPM, in which the median survival from the start of chemotherapy or from registration ranged from 14.0 to 25.5 months [7–11]. The MARS feasibility trial, which failed to meet the primary end-point of assigning 50 patients to EPP or non-EPP after induction chemotherapy within 1 year, suggested that EPP within the trimodality therapy offers no benefit and possibly harms the patients, with median survival from randomization of 14.4 months for the EPP group and 19.5 months for the non-EPP group [12]. Currently, the role of neoadjuvant chemotherapy followed by EPP for resectable MPM is controversial, and we need the selection criteria for those patients most likely to benefit from EPP after neoadjuvant chemotherapy. In unresectable MPM, early response evaluation by 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) rather than by computed tomography (CT) is a promising method to predict the patient survival outcome [13]. To our knowledge, there are no data available using FDG-PET/CT in regard to metabolic response after neoadjuvant chemotherapy for resectable MPM. The purpose of this multicenter study was to evaluate the usefulness of metabolic response by FDG-PET/CT after neoadjuvant chemotherapy in predicting prognosis for patients with resectable MPM who underwent EPP.

patients and methods

We enrolled 73 patients with clinical T1–3 N0-2 M0 malignant pleural mesothelioma who were scheduled for multimodality therapy comprising neoadjuvant platinum-based chemotherapy followed by EPP and postoperative hemithoracic radiotherapy. Patients were staged according to the system developed by the International Mesothelioma Interest Group [14] at two institutions (Hyogo College of Medicine and Hiroshima University) between 1 January 2004 and 31 December 2011. Among these patients, we excluded those who had not undergone EPP ($n = 11$) and those for whom the FDG-PET/CT data before or after neoadjuvant chemotherapy were lacking ($n = 12$). Ultimately, 50 patients were enrolled in this retrospective study (Figure 1). We obtained appropriate approval for this multicenter study from the Institutional Review Board of each institution, which waived the requirement for informed consent from individual patients for this retrospective review from a prospective database.

Patients were eligible for trimodality therapy if they had a histologically confirmed diagnosis of MPM, including all subtypes and clinical T1–3 N0-2 M0 disease considered to be completely resectable; no prior treatment with chemotherapy, surgery, or radiotherapy for the disease; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; a predicted postoperative forced expiratory volume in 1 s of >1000 ml; and adequate bone marrow, hepatic, renal, cardiac and respiratory function. Patients were staged with high-resolution CT (HRCT) scanning of the chest and abdomen, brain magnetic resonance imaging or CT, and FDG-PET/CT.

Neoadjuvant chemotherapy consisted of three or four cycles of cisplatin-based chemotherapy followed by HRCT and FDG-PET/CT restaging. Cisplatin (Nippon Kayaku Co., Ltd., Tokyo, Japan) plus pemetrexed was predominantly used for neoadjuvant chemotherapy. A surgery was carried out 3–6 weeks after the end of chemotherapy.

EPP was defined as an en bloc resection of the lung, pleura, pericardium, and diaphragm without entering the pleural cavity. Partial or no removal of the pericardium or diaphragm was sometimes carried out for a parietal pleural tumor separable from the pericardium or diaphragm. Previous biopsy sites were removed with limited chest wall resection.

Adjuvant hemithoracic radiotherapy was carried out within 12 weeks of surgery. Patients received three-dimensional conformal radiotherapy using a linear accelerator for 6–20 MV photon energies. A total dose of 54 Gy was delivered in 30 fractions of 1.8 Gy/day. The target volume included the hemithorax and chest wall incisions.

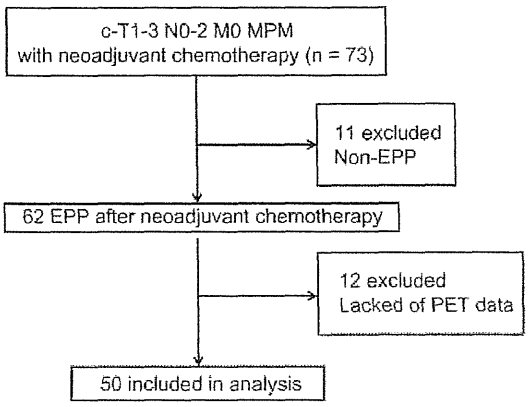

Figure 1. Flow chart of patients in the study.

Postoperatively, all patients underwent a physical examination every 3 months, and CT of the chest and abdomen every 6 months.

HRCT

HRCT was carried out at baseline before neoadjuvant chemotherapy, and repeated after neoadjuvant chemotherapy. Chest images were obtained using 16-row multidetector CT independent of subsequent FDG-PET/CT examinations. High-resolution images of tumors were acquired using the following parameters: 120 kVp, 200 mA, section thickness 1–2 mm, pixel resolution 512 × 512, scanning time 0.5–1.0 s, and a high spatial reconstruction algorithm with a 20 cm field of view and mediastinal (level, 40 HU; width, 400 HU) window setting.

FDG-PET/CT

FDG-PET/CT imaging was carried out at baseline before neoadjuvant chemotherapy, and repeated after neoadjuvant chemotherapy. Patients fasted for at least 4 h before being intravenously injected with 3.7 MBq/kg of FDG, and they then rested for about 1 h before being scanned. Blood glucose was measured before tracer injection to ensure a level of <150 mg/dl, and patients with blood glucose ≥150 mg/dl during FDG-PET/CT image acquisition were excluded. All the patients were assessed using an integrated FDG-PET/CT scanner, either Discovery ST16 (GE Healthcare) or GEMINI GXL (Philips Medical Systems). An unenhanced CT image of a 2–4 mm thick section that matched the PET images was obtained from the head to the pelvic floor of each patient using a standard protocol. Immediately after CT, PET covered the identical axial field of view (2–4 min per table position depending on the condition of the patient and scanner performance). Both PET and CT studies proceeded with normal tidal breathing. All PET images were reconstructed using an iterative algorithm with CT-derived attenuation correction using Fourier rebinning followed by ordered-subset expectation maximization. A maximum standardized uptake value (SUV_{max}) was established by drawing regions of interest (ROI) around the primary tumor on attenuation-corrected FDG-PET images and calculated using the dedicated software of the PET/CT scanner based on the following formula: $SUV_{max} = [C(\mu C_i/ml)/ID(\mu C_i)]/w$, where C is defined as activity at a pixel within the tissue identified by ROI and ID is defined as the injected dose/kg body weight (w). We adopted SUV_{max} in the present analysis because it is less variable than the mean SUV in terms of measurements [15].

response evaluation

Radiologic response was assessed by HRCT after completion of neoadjuvant chemotherapy using unidimensional measurement of pleural thickness perpendicular to the chest wall or mediastinum and modified RECIST criteria [16].

The metabolic response on FDG-PET/CT was measured after completion of neoadjuvant chemotherapy adjusted to modified RESICT criteria [16]. Complete resolution of FDG uptake within the tumor volume so that it was indistinguishable from the surrounding normal tissue was considered as a complete response (CR). A partial response (PR) was defined as a reduction of ≥30% in tumor FDG uptake. An increase in tumor SUV_{max} of ≥20% within the ROI defined on the baseline scan, or the appearance of new FDG uptake in another region, was classified as progressive disease (PD). Stable disease (SD) was classified as an increase in tumor SUV_{max} of <20% or a decrease of <30%.

statistical analysis

Data are presented as numbers (%) or mean ± standard deviation unless otherwise stated. Overall survival (OS) was calculated as the time (in days) from diagnostic biopsy until death from any cause; patients who were alive on the date of the most recent follow-up were censored on that date. The duration of OS was analyzed using the Kaplan–Meier method. The differences in OS were assessed using the log-rank test. To assess the potential independent effects of decreased SUV_{max} on OS, we carried out multivariate analyses using the Cox proportional hazards model using variables with a P value of <0.1 in the univariate analyses; $P < 0.05$ was considered statistically significant. Data were statistically analyzed using SPSS software (version 10.5, SPSS Inc., Chicago, IL).

Table 1. Patient characteristics

All cohort patients ($n = 50$)	
Age (year)	61.6 ± 7.6
Sex	
Male	45 (90%)
Female	5 (10%)
Side	
Left	26 (52%)
Right	24 (48%)
Clinical stage	
I	17 (34%)
II	16 (32%)
III	17 (34%)
Histology	
Epithelioid	38 (76%)
Biphasic	10 (20%)
Sarcomatoid	2 (4%)

results

The characteristics of the 50 study patients are summarized in Table 1. The mean follow-up period after diagnosis was 18.6 ± 13.5 months. The chemotherapy regimen was cisplatin plus pemetrexed in 47 (94%) patients and cisplatin, CPT-11, and doxorubicin (adriamycin) (Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan) in 3 (6%) patients. Patients received three to four cycles of neoadjuvant chemotherapy (3.3 ± 1.1 cycles).

According to modified RECIST criteria, 20 (40%) patients had an objective response [1 CR and 19 PR], 28 (56%) were classified as SD and 2 (4%) had PD (Table 2).

FDG-PET/CT measurement identified 14 (28%) responders (1 CR and 13 PR), 20 (40%) patients with SD, and 16 (32%) patients with PD.

Table 2. Discrepancies between the radiologic and metabolic responses

	Metabolic response				Total
	CR	PR	SD	PD	
Radiologic response					
CR		1			1 (2%)
PR	1	9	4	5	19 (38%)
SD		3	16	9	28 (56%)
PD				2	2 (4%)
Total	1 (2%)	13 (26%)	20 (40%)	16 (32%)	50

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

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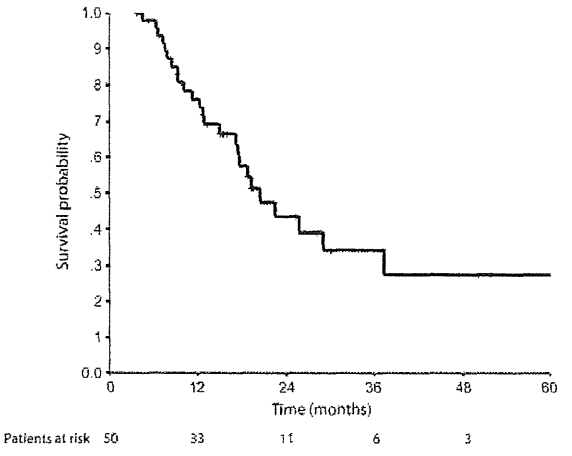

Figure 2. Cumulative overall survival (OS) of all 50 patients (median, 20.5 months; 95% CI, 15.0–26.0 months).

All 50 patients underwent EPP. A complete macroscopic resection of the tumor (R0 or R1 resection) was achieved in 48 (96%) patients. Two (4%) patients had gross residual disease (R2 resection) remaining on the chest wall. One patient died after surgery (aortic hemorrhage), with a postoperative 30-day mortality rate of 2.0%. Major complications occurred in 16 (32%) patients including diaphragmatic hernia ($n = 4$), bronchopleural fistula ($n = 3$), intrathoracic hemorrhage ($n = 2$), empyema ($n = 2$), respiratory failure ($n = 2$), chylothorax ($n = 1$), cardiac hernia ($n = 1$), and heart failure ($n = 1$).

A total of 29 (58%) patients completed adjuvant hemithoracic radiation after EPP.

The median OS for all 50 patients was 20.5 months [95% confidence interval (CI), 15.0–26.0 months], with a 3-year OS rate of 34.2% from diagnosis (Figure 2).

No correlation was observed between OS and radiologic response with median OS for radiologic responders of 25.7 months ($n = 20$; 95% CI, 14.5–37.0 months; 3-year OS rate,

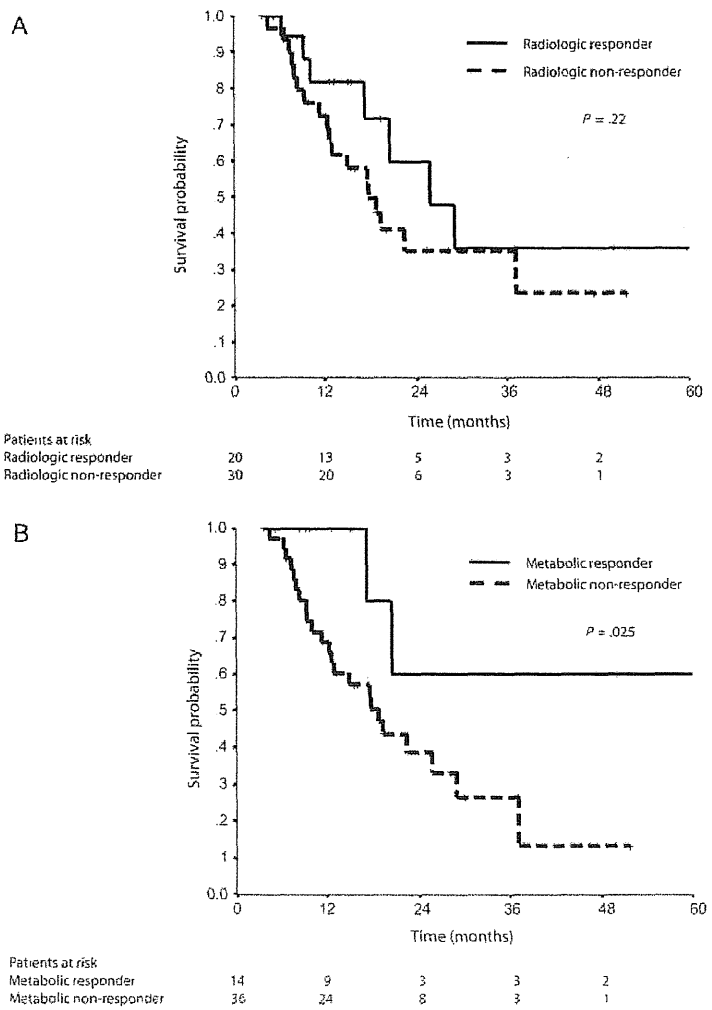

Figure 3. Overall survival (OS) by (A) radiologic response and (B) metabolic response. No significant difference was observed between the radiologic responders and the non-responders ($P = 0.22$); a significant difference was observed between the metabolic responders and the non-responders ($P = 0.025$).

Table 3. Univariate and multivariate analyses of overall survival (OS)

	HR	95% CI	*P* value
Univariate analyses			
Age	1.05	0.98–1.12	0.13
Sex: male	0.74	0.22–2.49	0.63
Side: right	0.71	0.31–1.61	0.41
Histology: epithelioid	0.43	0.17–1.11	0.08
c-Stage: III	1.53	0.67–3.51	0.31
Tumor shrinkage (ratio)	0.34	0.98–1.20	0.09
Decrease of SUV_{max} (ratio)	0.82	0.70–0.97	0.02
Multivariate analyses			
Model 1			
Histology: epithelioid	0.39	0.12–1.22	0.11
Tumor shrinkage (ratio)	0.46	0.14–1.54	0.21
Model 2			
Histology: epithelioid	0.36	0.14–0.97	0.04
Decrease of SUV_{max} (ratio)	0.80	0.67–0.95	0.01

SUV_{max}, maximum standardized uptake value; HR, hazard ratio; CI, confidence interval.

35.8%) versus 17.7 months ($n = 30$; 95% CI, 12.8–22.6 months; 3-year OS rate, 35.1%) for non-responders ($P = 0.22$, Figure 3A). In contrast, metabolic responders significantly correlated to OS with median OS for metabolic responders not reached ($n = 14$; 3-year OS rate, 60.0%) versus 18.7 months ($n = 36$; 95% CI, 13.3–24.2 months; 3-year OS rate, 26.5%) for non-responders ($P = 0.025$, Figure 3B). The OS of patients with epithelioid subtype ($n = 38$; median OS, 22.4 months; 95% CI, 13.7–31.1 months; 3-year OS rate, 39.4%) was better than for those with non-epithelioid subtype ($n = 12$; median OS, 14.9 months; 95% CI, 9.4–20.4 months; 3-year OS rate, 0%, $P = 0.072$).

Univariate analysis of the OS in all patients included the variables such as age, sex, location (side), histology, clinical stage, tumor shrinkage by HRCT, and SUV_{max} decrease by FDG-PET/CT (Table 3). Epithelioid histology, tumor shrinkage, and SUV_{max} decrease were potentially associated with a long OS ($P < 0.1$). Multivariate analysis that included histology and tumor shrinkage (model 1), or histology and SUV decrease (model 2) showed that epithelioid histology [hazard ratio (HR) 0.36; 95% CI, 0.14–0.97; $P = 0.04$] and SUV_{max} decrease (HR 0.80; 95% CI, 0.67–0.95; $P = 0.01$) were independent prognostic factors for OS (Table 3).

discussion

The median OS from diagnosis for all cohort patients in this study was 20.5 months, which is similar to the reported range of 18.0–27.5 months for subsets of patients undergoing EPP after neoadjuvant chemotherapy [7–12]. In the MARS trial, the median OS of the non-EPP arm from the start of treatment was about 23.1 months [12]. The median OS of EPP patients for unselected resectable MPM is not always better than that of non-EPP patients. In a systematic review of EPP outcomes, the 30-day mortality rates ranged from 0% to 11.8%, and the perioperative morbidity rates ranged from 22% to 82% [17]. Although the 30-day mortality and morbidity rates were both relatively low (2% and 32%, respectively) in the current study, the median OS was not satisfactory. To avoid futile surgery with high mortality and morbidity, we need the criteria for selection of patients with potentially resectable MPM who may benefit from EPP.

The current study demonstrated that decreased SUV_{max} as evaluated by FDG-PET/CT after neoadjuvant chemotherapy is an independent prognostic factor for patients with resectable MPM who underwent EPP. In patients with MPM who underwent EPP, decrease in SUV_{max} was more useful in predicting prognosis than tumor shrinkage on HRCT by modified RECIST. Radiographically, MPM is difficult to evaluate, given the nonradical and inconsistent pattern of growth and response to treatment. Although the RECIST criteria have been developed and have become widely accepted and used in clinical trials, the application of these criteria in MPM could be variably interpreted by different investigators, and this may lead to unsatisfactory results [18]. Modified RECIST has now been developed to avoid difficult and ambiguous situations concerning the interpretation in clinical trials, and this successfully distinguished between the responders and the non-responders in regard to survival parameters [16]. However, measuring the tumor thickness of resectable MPM is sometimes more difficult than that of unresectable bulky MPM because the thickness of resectable MPM tumors is often subcentimeter. We failed to distinguish between the responders and the non-responders in regard to OS using the modified RECIST in this study. In unresectable MPM, it was reported that a significant correlation between the metabolic response as evaluated by PET assessment after two cycles of pemetrexed-based chemotherapy and the patient outcome as measured by time to progression (TTP) was observed, whereas the radiologic response assessed by CT scanning was not predictive of improved TTP [13]. The findings of our study in regard to resectable MPM are consistent with those of the above study on unresectable MPM [13]. This is the first paper to describe the significance of metabolic response for resectable MPM using FDG-PET/CT.

The cut-off value of SUV_{max} decrease in defining the metabolic response is important in clinical practice. Although a 20%–25% decrease in tumor FDG uptake is a widely accepted definition in patients undergoing palliative chemotherapy, higher threshold values seem more appropriate for neoadjuvant therapy [19]. Therefore, at the cut-off value of 30% for metabolic response used in this study, there was a significant difference in OS between the metabolic responders and the non-responders. Regardless of the cut-off value, SUV_{max} decrease as a continuous variable was an independent prognostic factor for OS, which indicates the importance of metabolic response in predicting the survival in patients with resectable MPM who underwent EPP. Considering the satisfactory 3-year OS rate of 60% for metabolic responders, a cut-off value of 30% seems to be suitable to define metabolic responders who may benefit from EPP.

There were some discrepancies between the radiologic response and the metabolic response. Nine (18%) radiologic responders were defined as metabolic non-responders, whereas three (6%) radiologic non-responders were defined as

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metabolic responders. Overall, 14 (28%) metabolic responders may have been good candidates for EPP.

Epithelioid subtype is well known as a prognostic factor in patients with MPM [20–22]. In our analysis, it was an independent factor for OS, and patients with this subtype had a better prognosis than those with the non-epithelioid subtype.

The limitations of our study include the relatively small number of patients, the retrospective nature of the study, and no comparison with pleurectomy/decortication (P/D) or nonsurgical patients. One of the controversies surrounding the treatment of resectable MPM is whether EPP is more effective than less extensive operations such as P/D [20, 23]. The survival of metabolic responders who underwent P/D or who did not undergo surgery is unknown in our study. Randomization to surgery versus no surgery after induction chemotherapy is very difficult in patients with resectable MPM [12].

One of the limitations of this multicenter study in regard to the use of PET is the wide variation in SUV among institutions. Many factors such as preparation procedures, scan acquisition, image reconstruction, and data analysis can affect the SUV. Using the metabolic response, which is the ratio of change in SUV_{max}, one can minimize the effect of SUV_{max} discrepancies among institutions.

In conclusion, the epithelioid subtype and metabolic response after neoadjuvant chemotherapy are both independent prognostic factors for patients with resectable MPM who underwent EPP. Patients with a metabolic response or epithelioid subtype may be suitable candidates for EPP after neoadjuvant chemotherapy. Further confirmation in a large cohort is required.

disclosure

The authors have declared no conflicts of interest.

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ORIGINAL ARTICLE – TRANSLATIONAL RESEARCH AND BIOMARKERS

Circulating Tumor Cells (CTCs) in Malignant Pleural Mesothelioma (MPM)

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ABSTRACT

Purpose. To investigate the diagnostic and prognostic value of circulating tumor cells (CTCs), a potential surrogate of micrometastasis, in malignant pleural mesothelioma (MPM).

Methods. We prospectively evaluated CTCs in 7.5 mL of peripheral blood sampled from patients with a suspicion of MPM. A semiautomated system was used to capture CTCs with an antibody against the epithelial cell adhesion molecule.

Results. Of 136 eligible patients, 32 were finally diagnosed with nonmalignant diseases (NM), and 104 had MPM. CTCs were detected in 32.7 % (34 of 104) of MPM patients but in only 9.4 % (3 of 32) of NM patients ($P = 0.011$). The CTC count was significantly higher in MPM patients than in NM patients ($P = 0.007$), and a receiver operating characteristic (ROC) curve analysis showed an insufficient capability of the CTC test in discrimination between MPM and NM, with an area under ROC curve of 0.623 (95 % confidence interval, 0.523–0.723; $P = 0.036$). Among MPM patients, CTCs were more frequently detected in patients with epithelioid subtype (39.7 %, 31 of 78) than in those with nonepithelioid subtypes (11.5 %, 3 of 26; $P = 0.016$). Positive CTCs (CTC count ≥ 1) were a significant factor to predict a poor prognosis among epithelioid patients (median overall survival, 22.3 months for positive CTCs vs. 12.6 months for negative CTCs; $P = 0.004$) and not in nonepithelioid patients ($P = 0.649$). A multivariate analysis showed that positive CTCs were a significant and independent factor to predict a poor prognosis (hazard ratio, 2.904; 95 % confidence interval, 1.530–5.511; $P = 0.001$) for epithelioid MPM patients.

Conclusions. CTC was a promising marker in diagnosis and prediction of prognosis in MPM, especially in epithelioid MPM.

Malignant pleural mesothelioma (MPM) is a highly aggressive malignant tumor of the pleura associated with asbestos exposure.[1–3] The gold standard for the diagnosis is histologic examination, which usually needs invasive procedures such as core-needle biopsy or video-assisted thoracoscopic biopsy.[3,4] Such invasive procedures are not feasible for mass screening for an asbestos-exposed high-risk population or may not be performed for patients with poor performance status (PS). Accordingly, it is clinically important to develop and establish noninvasive diagnostic procedures to accurately predict and/or exclude the diagnosis of MPM. A number of noninvasive markers have emerged and have been evaluated, in accordance with recent advances in the understanding of molecular and

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biological characteristics of MPM.[5,6] Among them, serum soluble mesothelin-related protein is the most promising diagnostic marker in discrimination of MPM from nonmalignant (NM) diseases or from other malignant diseases.[5] However, the use of soluble mesothelin-related protein in daily clinical practice is not recommended, because no prospective validation study has confirmed the diagnostic performance.[4,5,7] MPM is a uniformly fatal disease with a median survival time of 4–12 months, because there is no established treatment modality for the cure.[2,8–10] In addition to the lack of effective treatment options, a lack of useful clinical indicators predicting prognosis and/or response to treatment may contribute to the poor prognosis.[5]

Circulating tumor cells (CTCs) are tumor cells that have shed from a primary tumor and circulate in the peripheral blood. Recent experimental and clinical studies have shown that CTCs can be detected not only in late-stage malignant tumors with apparent distant metastases, but also in early-stage diseases, and that the CTC test can be a potentially useful clinical marker in the diagnosis of and decision-making for malignant tumors.[11] The CellSearch system (Veridex LLC, Raritan, NJ, USA), a semiautomated system for quantitative evaluation of CTCs, has been recently developed. In it, CTCs are immunomagnetically captured with an antibody against the epithelial cell adhesion molecule (EpCAM).[12] The most important advantage of the CellSearch system is reproducibility across different laboratories, which is validated by a prospective multicenter study in metastatic breast cancer.[13] On the basis of accumulating data supporting the accuracy and precision in evaluating CTCs, the CTC test using the CellSearch system has been approved in the United States by the Food and Drug Administration for monitoring blood from metastatic breast and colon cancer patients.[14–16] In addition, several clinical studies have shown that the CTC test is potentially useful in the diagnosis and therapy of other malignant tumors, such as prostate cancer.[17–20] In MPM, however, no previous study has been reported about the incidence of CTCs, and its clinical significance remains unknown. Thus, in the present study, we prospectively examined the diagnostic performance and prognostic value of the CTC test in MPM.

METHODS

Study Design

Patients who presented at the Hyogo College of Medicine Hospital to receive a pleural biopsy with a suspicion of MPM on computed tomography (CT) and positron emission tomography scanning were eligible. All patients provided written informed consent before enrollment.

A 7.5-mL peripheral blood sample from each patient was used for the CTC test. Complete clinical data including history, physical examination, and laboratory and radiographic studies were also collected. For all patients, pleural biopsy was performed, and a final pathologic diagnosis was established. For patients with MPM, whole-body CT as well as brain CT or magnetic resonance imaging were routinely conducted to evaluate tumor progression. Clinical (c-) stage was determined according to the current tumor-node-metastasis (TNM) classification as determined by the International Mesothelioma Interest Group.[21] This study was approved by the Institutional Review Board of Hyogo College of Medicine.

Evaluation of CTCs

Blood samples drawn into the CellSave tube containing cell preservatives (Veridex LLC, Raritan, NJ, USA) were maintained at room temperature and were processed within 72 h after collection. CTCs were isolated from peripheral blood by using the CellSearch system (Veridex LLC), and the number of CTCs was determined according to the manufacturer's protocol.[12] In brief, epithelial cells that were captured using ferroparticles coupled to an anti-Ep-CAM antibody were separated in a magnetic field, and the enriched samples were then stained with 4′,6-diamidino-2-phenylindole (DAPI) and anti-cytokeratin–phycoerythrin. Contaminated white blood cells were excluded by negative selection for CD45. Stained cells were then analyzed on a florescent microscope by using the Cell Track Analyzer II (Veridex LLC). The criteria for each cell to be defined as a CTC were as follows: round to oval morphology, a visible DAPI-positive nucleus, positive cytokeratin staining in the cytoplasm, and negative staining for CD45. All evaluations were performed by two authors (K.Y. and F.T.; both completed the Cell Interpretation Proficiency Assessment managed by the Veridex LLC for identification of CTCs) independently without knowledge of the clinical characteristics of patients.

Statistics

Counts were compared by the Chi-square test. Continuous data were compared by using Student's t test if the distribution of samples was normal or by using nonparametric tests (Mann–Whitney U-test for comparison between 2 groups and Kruskal–Wallis test for comparison among 3 or more groups) if the sample distribution was asymmetrical.

The diagnostic performance of CTCs was assessed by constructing a receiver operating characteristic (ROC) curve and was evaluated by calculating the area under each ROC curve (AUC-ROC).[22] An AUC-ROC = 1 denotes

perfect discrimination of a test, whereas an AUC-ROC equal to 0.5 denotes complete lack of discrimination of a test. *P* values were calculated for the difference between each AUC-ROC and 0.5 (completely useless test).

Survival curves were generated by using the Kaplan–Meier method, and the differences were assessed by the log-rank test. Cox's regression model was used for a multivariate analysis of prognostic factors.

For each test, two-sided *P* values less than 0.05 were considered statistically significant. All statistical manipulations were performed by using the SPSS for Windows software system (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Characteristics

From September 2007 to July 2010, 139 consecutive patients were enrolled in the study. Pleural biopsy was performed and final pathologic diagnosis was established in all patients; 3 patients were excluded because the biopsy specimen showed pleural disseminated adenocarcinoma of the lung. Of 136 eligible patients, 32 were finally diagnosed pathologically with NM pleural diseases, and the other 104 had MPM. Most MPM patients presented with advanced disease, and most had the epithelioid subtype (Fig. 1; Table 1 in Appendix).

The incidence of patients with good PS (Eastern Cooperative Oncology Group 0 or 1) was significantly higher in NM disease; there was no difference in any other patient characteristic. Most patients had a history of asbestos exposure (Table 1 in Appendix).

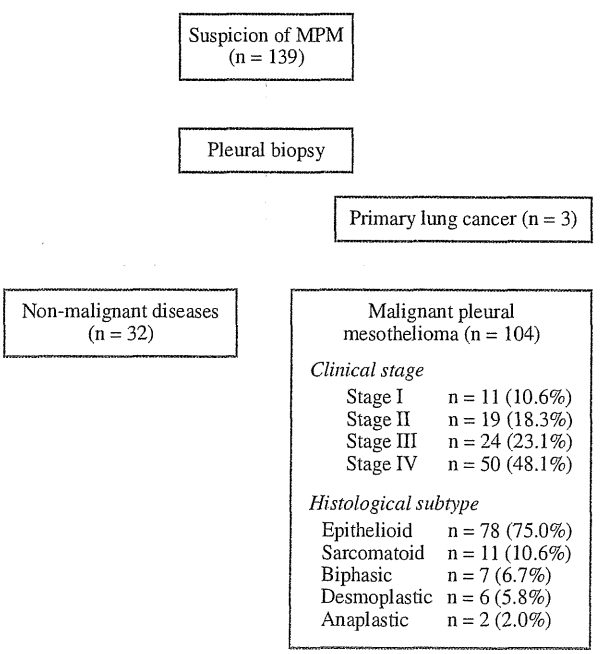

FIG. 1 Flowchart of diagnosis of patients enrolled in the study from September 2007 through July 2010

Chemotherapy using pemetrexed with or without platinum agents (cisplatin or carboplatin) was performed in 80 (76.9 %) of 104 MPM patients; after chemotherapy, extrapleural pneumonectomy was performed in only 6 patients (6.7 %).

CTCs in MPM and NM Patients

CTCs were identified in the peripheral blood of 3 (9.4 %) NM patients, and the CTC count was 1 in all 3 patients. CTCs were identified in the peripheral blood of 34 (32.7 %) patients with MPM, and MPM patients had a significantly higher CTC count than patients with NM (Fig. 2a).

The AUC-ROC for CTC count for discrimination between primary MPM and NM patients was 0.623, and the difference from 0.5 reached statistical significance ($P = 0.036$; Fig. 2b). When a cut-off point for the diagnosis of MPM was 1, that is, patients with 1 or more CTCs were judged as MPM patients, the sensitivity and specificity were 32.7 and 90.6 %, respectively.

CTCs in MPM Patients

CTCs were more frequently detected and the CTC count was also higher in patients with epithelioid-subtype MPM (Fig. 3a), as well as in advanced-stage patients (Fig. 3b). Univariate analyses revealed that poor PS, nonepithelioid histology, advanced clinical stage, and no chemotherapy were significantly associated with a poor prognosis (Table 2 in Appendix).

CTC-negative patients seemed to have a better overall survival than CTC-positive patients, but the difference did not reach statistical significance (median overall survival, 12.7 and 7.6 months, respectively; $P = 0.160$; Fig. 4a). However, when analyzed only in epithelioid patients, the CTC test provided a statistically significant prognostic value (median overall survival, 22.3 and 12.6 months, respectively; $P = 0.004$; Fig. 4b), and a multivariate analysis also indicated that positive CTCs were a significant and independent factor to predict a poor prognosis (hazard ratio, 2.904; 95 % confidence interval, 1.530–5.511; $P = 0.001$; Table 4 in Appendix).

DISCUSSION

The present study is the first clinical study on CTCs in MPM. First, we assessed the diagnostic value of the CTC test in patients with a suspicion of having MPM and

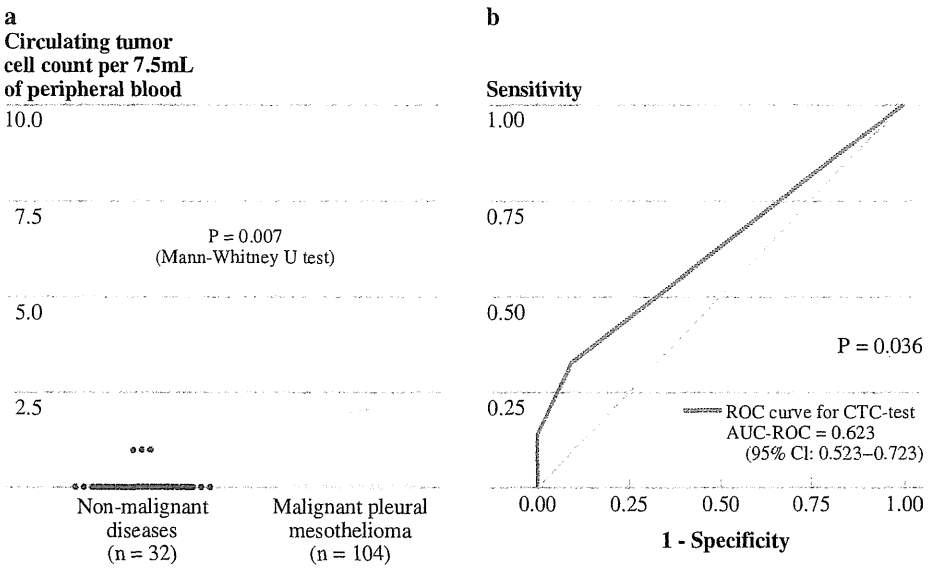

FIG. 2 **a** Distribution of CTC count in patients with NM diseases and in patients with MPM, **b** ROC curves for the CTC test to discriminate malignant pleural mesothelioma from nonmalignant diseases. The AUC-ROC is calculated, and the *P* value for testing the significance of difference from 0.5 (lack of discrimination) is indicated. The sensitivity and specificity of the CTC test at the cut-off value of CTC = 1 were 32.7 and 90.6 %, respectively

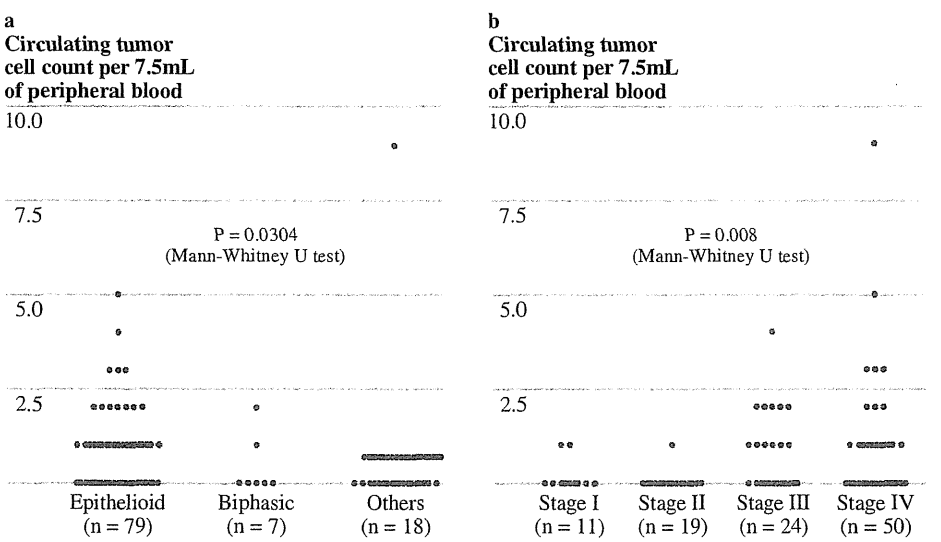

FIG. 3 **a** Distribution of CTC count in patients with MPM according to histologic subtype, **b** distribution of CTC count in patients with MPM according to clinical stage

showed that the CTC count was significantly higher in MPM patients than in NM patients. The ROC curve analysis showed that the CTC test provided a significant diagnostic capability in discrimination of MPM from NM diseases with an AUC-ROC of 0.623 ($P = 0.036$), thus suggesting that the CTC test is a promising noninvasive marker in the diagnosis of MPM. When the cut-off value of CTC-count was 1, the sensitivity and specificity were 32.7 and 90.6 %, respectively, and the positive predictive value and negative predictive value were 91.9 and 29.3 %, respectively. Alternatively, when a cut-off point of 2 was adopted, the specificity reached 100 % with no false-positive case, but the sensitivity decreased to 13.5 %. These results have indicated that the CTC test is characterized by low sensitivity and negative predictive value as well as high specificity and positive predictive value. Accordingly, the CTC test may be useful not for MPM screening, but for selection of patients who should receive invasive examinations such as video-assisted thoracoscopic biopsy after screening with more sensitive tools such as SMRP test.

Here, attention should be paid to the fact that some patients (9.4 %, 3 of 32 patients) were finally diagnosed with NM diseases, whereas one tumor cell was identified in the peripheral blood. These results are similar as those in a previous study showing that up to 3 CTCs were detected in a small subset of healthy volunteers or NM patients.[12] Such "false-positive" cases may be classified into "true" false-positive cases or "false" false-positive cases. A "true" false-positive result, indicating that patients without any malignant tumor are judged to have a malignant tumor according to the CTC test, can be brought about by several

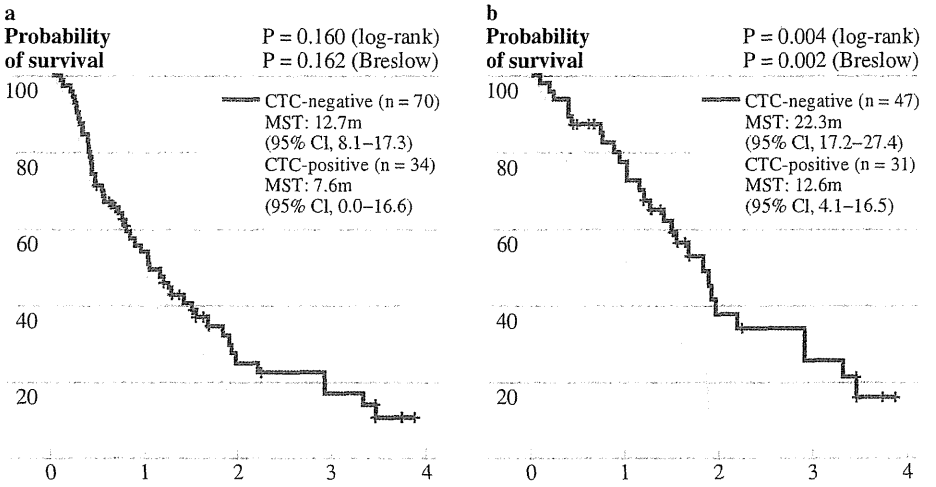

FIG. 4 **a** Survival curves according to CTC count in all MPM patients, **b** survival curves according to CTC count in epithelioid-type MPM patients. *MST* mean survival time

factors: contamination of epithelial cells in blood samples due to a variety of technical issues such as inappropriate blood sampling, false-positive staining of contaminated nonepithelial cells for cytokeratin/DAPI during sample processing, or inappropriate judgment in identification of CTCs by researchers. A "false" false-positive result can occur when detected CTCs originate from a clinically undetectable malignant tumor. An individual reason for 3 false-positive cases in the present study remains unclear, and careful long-term follow-up to watch for the development of malignant tumors should be performed. In fact, in one of the 3 false-positive cases, MPM had developed 2 years after initial pleural biopsy, which might indicate that "positive CTC" at the time of initial pleural biopsy was not "false-positive" but "true-positive."

The most important issues of the CTC test in the diagnosis of MPM were the low sensitivity (32.7 %) and the low negative predictive power (29.3 %). The CellSearch system used in the present study is the only commercially available detection system for detection and identification of CTCs, and the accuracy and reproducibility have been established. However, many previous studies have shown that the most critical issue in the use of the CellSearch system is its low sensitivity for detecting CTCs in other malignant tumors.[17,19] Recently, a novel microfluidic platform for detecting CTCs (the CTC chip) has been developed. This CTC chip consists of an array of 78,000 microposts coated with anti-EpCAM antibodies, and CTCs are captured by interaction of these cells with the EpCAM-coated microposts under laminar flow conditions. The CTC chip may provide a higher sensitivity in identification of CTCs, because a pilot study showed that CTCs were detected in most blood samples taken from patients with a variety of malignant tumors, including lung, prostate, pancreatic, breast, and colon cancer.[23] The most important reason for the low sensitivity in detecting CTCs in MPM was that the CellSearch system can principally capture tumor cells expressing EpCAM. Most malignant tumors of epithelial origin express EpCAM, and such tumor cells circulating in the blood can be captured with the CellSearch system. However, mesothelioma, originating from mesothelium that does not express EpCAM, may not express EpCAM. In fact, our preliminary study of immunohistochemical staining with an anti-EpCAM antibody showed that only 11 of 21 MPM tumors showed positive EpCAM expression and that EpCAM expression was exclusively observed in epithelioid-type MPM.[24] These results explain the reason for low sensitivity in detection of CTCs in MPM patients, especially in patients with nonepithelioid subtypes, in the present study. Thus, to improve the sensitivity, it is essential to develop novel systems of EpCAM-independent detection of CTCs.

Next, we showed a trend of increase in CTC count along with tumor progression. However, even in stage IV diseases, CTCs were detected in only 19 (38 %) of 50 MPM patients; when analyzed according to histologic subtypes, CTCs were detected in 48.6 % (18 of 37) of epithelioid cases, but in only 7.7 % (1 of 13) of nonepithelioid cases. These results also indicate that the CellSearch system provided an insufficient sensitivity in detection of CTCs in MPM, especially in nonepithelioid subtypes.

Finally, we showed that positive CTCs were a significant factor to predict a poor prognosis in epithelioid MPM, but not in nonepithelioid MPM. There was no difference in mode of therapy, which may influence prognosis between CTC-negative and CTC-positive patients; in fact,

pemetrexed-based chemotherapy was performed in most patients (74.3 % of CTC-positive patients and 82.4 % of CTC-negative patients, respectively; $P = 0.460$). In addition, a multivariate analysis revealed that positive CTCs were an independent prognostic factor. These results suggest that a poor prognosis in CTC-positive patients was not influenced by a difference in mode of therapy.

We did not show a significant prognostic value of c-stage, which was established as a strong prognostic factor in many other malignant tumors. In MPM, a prospective study conducted by the European Organization for Research and Treatment (EORTC) also revealed that c-stage was not a significant prognostic factor.[25] The EORTC study significant factors that predicted a poor prognosis were as follows: poor PS, high white blood cell count, probable or possible histologic diagnosis, male sex, and sarcomatoid subtype. The EORTC prognostic model is now widely accepted and used in clinical practice.[2,7,26] These results not only indicate limitations of conventional imaging in evaluation of c-stage in MPM, but also suggest that the current TNM system does not correctly represent the extent of tumor progression. To establish the prognostic performance of the CTC test, future validation studies are warranted.

In conclusion, the CTC test is a promising noninvasive diagnostic test in discrimination between MPM and NM. In addition, the CTC test provided significant prognostic information in epithelioid MPM. Future validation studies should be conducted to establish its clinical value.

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APPENDIX

See Tables 1, 2, 3 and 4; Fig. 5.

TABLE 1 Characteristics of patients with nonmalignant diseases and with malignant pleural mesothelioma (September 2007–July 2010)

Variable	Nonmalignant disease		Malignant pleural mesothelioma		*P*
	No. of patients	%	No. of patients	%	
Total patients	32	100	104	100	
Sex					
Female	3	9.4	21	20.2	0.194
Male	29	90.6	83	79.8	
Age (year)					
Median	69.5		67.0		
Mean ± SE	67.7 ± 1.6		66.7 ± 0.9		0.601
Range	41–80		50–87		
ECOG PS					
0–1	29	90.6	73	70.2	0.020
2–4	3	9.4	31	29.8	
Side of disease					
Left	11	34.4	46	44.2	0.413
Right	21	65.6	58	55.8	
Smoking habit					
Never	4	15.6	28	26.9	0.242
Smoker	27	84.4	76	73.1	
Pack-years of smokers					
Median	52.5		45.0		
Mean ± SE	55.7 ± 7.5		48.3 ± 4.2		0.398
Asbestos exposure					
No or unknown	4	12.5	7	6.7	
Yes	28	87.5	97	93.3	0.286

ECOG Eastern Cooperative Oncology Group

TABLE 2 Univariate analysis of prognostic factors for malignant pleural mesothelioma patients

Variable	No. patients	Overall survival (months)			HR		
		Median	95 % CI	*P* value	HR	95 % CI	*P*
Sex							
Male	83	9.6	4.9–14.3	0.637	1		
Female	21	14.9	6.0–23.8		0.878	0.512–1.508	0.638
Age (years)							
Lower (<67)	50	15.4	7.8–23.0	0.087	1		
Higher (≥67)	54	7.6	3.3–11.9		1.482	0.942–2.330	0.089
PS							
0–1	73	17.5	13.2–21.8	<0.001	1		
2–4	31	4.8	4.0–5.6		3.541	2.196–5.710	<0.001
Side							
Right	58	14.6	10.5–18.6	0.541	1		
Left	46	9.6	5.0–14.2		1.150	0.734–1.802	0.542
Smoking							
Never	28	13.8	10.0–17.7	0.948	1		
Smoker	59	11.4	7.4–15.5		0.984	0.599–1.614	0.948
Asbestos exposure							
No/unknown	7	12.4	0–27.1	0.785	1		
Yes	97	12.6	8.4–16.8		1.381	0.532–2.210	0.798
Histologic subtype							
Epithelioid	78	17.5	12.6–22.4	<0.001	1		
Nonepithelioid	26	5.0	4.1–6.0		2.705	1.683–4.612	<0.001
c-Stage							
Stage I	11	19.5	7.8–31.1	0.025	1		
Stage II	19	15.4	10.0–20.8				
Stage III	24	18.2	12.0–24.5		1.376	1.082–1.750	0.009
Stage IV	50	5.7	3.8–7.5				
Chemo							
Not performed	24	5.7	3.5–7.8	0.003	1		
Performed	80	14.6	11.8–17.4		0.488	0.299–0.797	0.004
EPP							
Not performed	97	11.3	8.1–14.8	0.058	1		
Performed	7	22.7	1.1–44.3		0.28	0.069–1.144	0.076
CTC							
Negative	70	12.7	8.1–17.3	0.160	1		
Positive	34	7.6	0–16.6		1.407	0.871–2.271	0.163

EPP extrapleural pneumonectomy, *HR* hazard ratio, *CI* confidence interval, *Chemo* chemotherapy

TABLE 3 Multivariate analysis of prognostic factors for MPM patients (all histology)

Variable	HR	95 % CI	*P*
Sex			
Male	1		
Female	0.657	0.227–1.899	0.438
Age (years)			
Lower (≤67)	1		
Higher (>67)	0.904	0.566–1.654	0.904
ECOG PS			
0–1	1		
2–4	3.221	1.608–6.452	0.001
Side			
Right	1		
Left	0.923	0.529–1.610	0.778
Smoking			
Never	1		
Smoker	0.900	0.353–2.294	0.900
Asbestos exposure			
No or unknown	1		
Yes	1.520	0.552–4.186	0.418
Histology			
Epithelioid	1		
Non-epithelioid	5.583	2.955–10.551	<0.001
Clinical stage			
Stage I–III	1		
Stage IV	1.099	0.609–1.983	0.753
Chemotherapy			
No	1		
Yes	0.668	0.365–1.223	0.191
EPP			
No	1		
Yes	0.923	0.088–1.711	0.211
CTC			
Negative	1		
Positive	2.343	1.362–4.030	0.002

ECOG Eastern Cooperative Oncology Group; *EPP* extrapleural pneumonectomy; *HR* hazard ratio, *CI* confidence interval

TABLE 4 Multivariate analysis of prognostic factors for malignant pleural mesothelioma patients (epithelioid-type patients only)

Variable	HR	95 % CI	*P*
Sex			
Male	1		
Female	1.876	0.396–8.878	0.423
Age (years)			
Lower (≤67)	1		
Higher (>67)	1.155	0.634–2.104	0.639
ECOG PS			
0–1	1		
2–4	3.388	1.460–7.862	0.004
Side			
Right	1		
Left	1.156	0.608–2.196	0.659
Smoking			
Never	1		
Smoker	2.391	0.544–10.505	0.248
Asbestos exposure			
No or Unknown	1		
Yes	2.581	0.691–9.635	0.158
Clinical stage			
Stage I–III	1		
Stage IV	1.161	0.546–2.471	0.699
Chemotherapy			
No	1		
Yes	0.526	0.254–1.089	0.084
EPP			
No	1		
Yes	0.402	0.051–3.135	0.384
CTC			
Negative	1		
Positive	2.904	1.530–5.511	0.001

ECOG Eastern Cooperative Oncology Group, *EPP* extrapleural pneumonectomy, *HR* hazard ratio, *CI* confidence interval

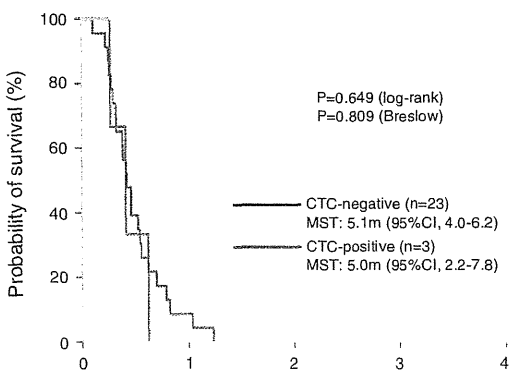

FIG. 5 Survival curves according to CTC count in nonepithelioid-type MPM patients

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The role of surgical cytoreduction in the treatment of malignant pleural mesothelioma: Meeting summary of the International Mesothelioma Interest Group Congress, September 11-14, 2012, Boston, Mass

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The treatment of all solid tumors, including malignant pleural mesothelioma (MPM), is dependent on (1) macroscopic complete resection and (2) treatment of micrometastatic disease. The role of surgery in the treatment of MPM has been the subject of debate after the recent publication of the Mesothelioma and Radical Surgery (MARS) I trial.[1] The International Mesothelioma Interest Group (IMIG) met from September 11 through 14, 2012, in Boston, Mass. During this meeting, more than 500 participants representing all the involved specialty groups met in multiple comprehensive sessions to review, critique, and extend the state of knowledge regarding the role of surgery, including both extended pleurectomy/decortication (P/D) and extrapleural pneumonectomy (EPP), in the treatment of MPM.

Some of the deficiencies of the MARS I trial, which was published a year ago in *Lancet Oncology*, were discussed in multiple sessions of the IMIG meeting. The editorial that accompanied the publication articulated numerous shortcomings of the trial.[2] The MARS I trial was designed as a pilot feasibility trial, the result of which was negative in that it failed to demonstrate the feasibility of randomly allocating patients to surgery versus no surgery. Nevertheless, the publication contained an analysis of tertiary end points, including survival, which was based on the small pilot cohort, representing fewer than 10% of the required sample size for an adequately powered between-arm comparison as published by the MARS trialists. Protocol compliance was also poor in that 6 of 26 patients in the no EPP group underwent off-protocol surgery, whereas only 16 of 24 patients in the EPP group actually underwent EPP.

Quality control of the surgery in the MARS trial, if undertaken, was not reported. Intent-to-treat morbidity (11/24; 46%) and mortality (3/24; 13%), and more strikingly, EPP-associated morbidity (11/16; 69%) and mortality (3/16; 19%), were much higher than reported in the literature. The chemotherapy regimens applied were uncontrolled. Neither final histologic type nor disease stage was reported for the patients who underwent surgery, leaving an open question as to whether these patients, who demonstrated survival inferior to most previous reports, may have had disproportionate N2 or nonepithelial disease. Conversely, the reported 19-month median survival among chemotherapy-only (no EPP) patients was clearly anomalous when compared with a vast prospective literature. The long-term outcome of the study cohort remains unknown, because the overall survival analysis was truncated at 18 months, whereas the quality of life data were reported to 24 months. These deficiencies make drawing any conclusions from MARS I regarding the therapeutic efficacy of EPP impossible.

The patterns of failure in MPM were reaffirmed at the 2012 IMIG meeting. Dr Elizabeth H. Baldini, in reference to her previous work, presented a contemporary group of patients and demonstrated essentially the same distribution of recurrence as originally reported, which is primarily local.[3] Six institutional series from the US, Europe, and Japan involving macroscopic complete resection by EPP or P/D in the setting of multimodality treatment of MPM were presented at the meeting.[4-9] These reports were discussed in detail in light of previous literature to date. Median survival ranged from 25 to 37 months for patients with epithelial disease and negative extrapleural lymph nodes. Operative mortality ranged from 0% to 2%.

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On behalf of the International Association for the Study of Lung Cancer (IASLC), Dr Valerie Rusch presented a preliminary analysis of the IASLC staging project, which has since been published in the November 2012 issue of the *Journal of Thoracic Oncology.*[10] In the IASLC worldwide registry of patients with all stages of epithelial MPM, the analysis showed 19-month median survival among 1359 patients undergoing surgical resection (P/D or EPP). Moreover, patients undergoing EPP for early-stage disease demonstrated survival superior to that of all other subgroups, a median of 40 months. On the basis of the current literature and the IASLC report, it was concluded by IMIG members that surgery, whether P/D or EPP, with the goal of obtaining a macroscopic complete resection should be performed in the multimodality treatment of MPM. In particular, it was agreed that the type of cytoreductive procedure should be selected on the basis of disease distribution, institutional experience, and surgeon preference and experience. Furthermore, it was collectively decided that these operations should be performed by surgeons who have achieved morbidity and mortality within the scope of the current literature.

After much discussion in multiple forums and settings with surgeons, medical oncologists, radiation oncologists, epidemiologists, and basic scientists, the attendees of the 2012 IMIG meeting reached agreement on the following points:

- Surgical macroscopic complete resection and control of micrometastatic disease play a vital role in the multimodality therapy of MPM, as is the case for other solid malignancies.
- Surgical cytoreduction is indicated when macroscopic complete resection is deemed achievable.
- The type of surgery (EPP or P/D) depends on clinical factors and on individual surgical judgment and expertise.
- All patients with the diagnosis of MPM should be initially evaluated in a multidisciplinary setting, including medical oncology, radiation oncology, and surgery.
- Clinical staging (lymph node sampling, positron emission tomography, magnetic resonance imaging) should be performed before therapy.
- The histologic subtype should be identified by tissue biopsy before initiation of therapy.

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Visceral Pleural Invasion Classification in Non–Small-Cell Lung Cancer in the 7th Edition of the Tumor, Node, Metastasis Classification for Lung Cancer: Validation Analysis Based on a Large-Scale Nationwide Database

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Objective: In the 7th tumor, node, metastasis (TNM) classification, visceral pleural invasion (VPI) is defined as invasion beyond the elastic layer, including invasion to the visceral pleural surface, and T1 tumors with VPI are upgraded to T2a. To validate this, we analyzed the survival of non–small-cell lung cancer patients from a nationwide database and evaluated the prognostic impact of VPI.

Methods: The clinicopathological characteristics and prognosis of 4995 patients who were included in the registry study of the Japanese Joint Committee of Lung Cancer Registry were retrospectively analyzed with a special interest in the prognostic impact of VPI. These patients underwent surgery in 2004 and were pathologically staged as T1a-3N0. VPI was defined as including PL1 and PL2 according to the 7th TNM Classification, but the Japanese Joint Committee of Lung Cancer Registry did not collect data regarding staining or how extensively VPI was evaluated in each participating institution.

Results: The survival differences were statistically significant between PL0 and PL1, PL1 and PL2, as well as PL2 and T3. There were no significant survival differences between T1a with VPI and T1b without VPI, or between T1a with VPI and T2a without VPI. There were no significant survival differences between T1b with VPI and T2a without VPI, or between T1b with VPI and T2b without VPI. There were no significant survival differences between T2a with VPI and T2b without VPI, or between T2b with VPI and T2b without VPI. T3 showed significantly worse prognosis than T2a with VPI and T2b with VPI.

Conclusions: In addition to the current TNM classification recommendations, in which T1 tumors with VPI are upgraded to T2a, T2a tumors with VPI should be classified as T2b.

Key Words: TNM classification, NSCLC, visceral pleural invasion

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Visceral pleural invasion (VPI) of lung cancer has been known to be a poor prognostic factor.[1-10] In the 7th edition of the tumor, node, metastasis (TNM) classification for lung cancer, pleural invasion status is classified as follows: PL0, tumor within the subpleural lung parenchyma or superficial invasion into the pleural connective tissue beneath the elastic layer; PL1, tumor invasion beyond the elastic layer; PL2, tumor invasion to the pleural surface; and PL3, tumor invasion into any part of the parietal pleura.[11,12] Although the current TNM classification does not describe a survival difference between PL1 and PL2[11,12], VPI is defined to include PL1 and PL2. Tumors of 3 cm or less (T1a and T1b) with VPI (PL1 and PL2) are upgraded to T2a, whereas tumors greater than 3 and 7 cm or less (T2a and T2b) with VPI remain unchanged as T2.[13] These recommendations—to upgrade the T-classification according to VPI status—were based on the results of five retrospective studies[1,3,8,14] and not on the large-scale data accumulated by the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Project.[11]

In 2009, 253 Japanese institutions submitted information to the Japanese Joint Committee of Lung Cancer Registry (JJCLCR) regarding the outcome and clinicopathologic profiles of patients who had undergone surgical resection for primary lung cancer in the year 2004.[15] We retrospectively analyzed the survival of almost 5000 patients with pulmonary non–small-cell lung cancer (NSCLC) without node involvement from this registration to evaluate the impact of VPI on survival, and we

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propose incorporating VPI into T-status classification in the forthcoming TNM classification of the Union for International Cancer Control (UICC) staging system.

PATIENTS AND METHODS

Patient Cohort

As described previously, the JJCLCR performed a nationwide retrospective registry study in 2010 on the outcome and clinicopathologic profiles of resected primary lung neoplasms in Japan.[15] Only primary lung cancers that had been resected in 2004 at certified teaching hospitals in Japan, with a follow-up period of at least 5 years, were considered eligible for the registration. The committee received the registered data of 11,663 patients from 253 teaching hospitals. The registry questionnaire included the following items: (1) demographic background, (a) date of registry, (b) sex, (c) birth month and year, and (d) date of diagnosis; (2) preoperative status, (a) Eastern Cooperative Oncology Group performance status, (b) preoperative comorbidity, (c) smoking status, and (d) status of serum tumor markers (CEA, SCC or CYFRA, SLX and NSE, or Pro-GRP); (3) clinical T factors, (a) tumor size, (b) extent of invasion to the main bronchus, (c) pleural invasion, (d) intrapulmonary metastasis, (e) status of pleural effusion, (f) extent of atelectasis, and (g) status of invaded organ; (4) clinical N factor (status of removal of and metastasis to each lymph node); (5) clinical M factor (metastasized organ); (6) type of surgery, (a) induction therapy, (b) extent of lung resection, (c) place of tumor origin, (d) extent of lymph node removal, (e) gross curative status, (f) status of residual tumor, (g) lavage cytology findings, and (h) combined resection; (7) postoperative morbidity; (8) tumor histology; (9) adjuvant therapy; (10) pathological T factors, (a) tumor size, (b) extent of bronchial involvement, (c) pleural invasion, (d) intrapulmonary metastasis, (e) status of pleural effusion, (f) pleural dissemination, (g) status of atelectasis, and (h) status of invaded organ; (11) pathological N factor (status of removal of and metastasis to each lymph node); and (12) pathological M factor (metastasized organ). The extent of resection (exploratory, R0, R1, or R2) was also registered. Although the Japan Lung Cancer Society also recommends using not only hematoxylin and eosin (HE) staining but also elastic staining such as Victoria-blue van Gieson staining in VPI evaluation, the JJCLCR did not collect data regarding staining or how extensively VPI was evaluated in each participating institution. Diseases were staged based on the 7th edition of the UICC TNM classification.[11,12] Histopathologic classifications were described according to World Health Organization criteria.[16] Recurrent or multiple lung cancers were not included in the registration.

Of the 11,663 patients, 4995 patients (42.8%) underwent pulmonary resection (lobectomy or greater) and systematic mediastinal lymph node dissection for pathologically T1aN0, T1bN0, T2aN0, T2bN0, or T3N0 NSCLC. All these patients had curative resection, which was defined as complete removal of the ipsilateral hilar and mediastinal lymph nodes together with the complete resection of the primary tumor. Patients who had induction chemotherapy, radiotherapy, or both, and patients with evidence of residual tumor at the surgical margin, malignant effusion, interlobar invasion, or distant metastasis, verified intraoperatively or by means of postoperative pathologic examination were excluded from this study.

Statistical Analysis

Pleural invasion status was classified according to the 7th edition of the UICC TNM classification[11-13]: PL0, tumor within the subpleural lung parenchyma or superficial invasion into the pleural connective tissue beneath the elastic layer; PL1, tumor invasion beyond the elastic layer; PL2, tumor invasion to the pleural surface; and PL3, tumor invasion into any part of the parietal pleura. In the following descriptions, T-classification is determined excluding VPI status, but PL3 tumors are classified as T3.

First, we analyzed the overall survival of PL0, PL1 and PL2 or T3 patient groups. Second, defining VPI to include PL1 and PL2, we analyzed the overall survival of the pT1a patient groups with or without VPI, pT1b with or without VPI, pT2a with or without VPI, and pT2b with or without VPI or T3. The follow-up period was defined as the time from the date of surgery to the most recent follow-up examination. The survival period was defined as the number of months from the day of surgery to the day of death from any cause. Survival curves were estimated using the Kaplan-Meier method. Differences in survival were tested using the log-rank test. A p value of less than 0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using software packages (SAS version 9.1.3 [SAS Institute, Inc., Cary, NC], SPSS version 19 [IBM Corp., New York, NY]).

This study was approved by the institutional review board of Osaka University Medical Hospital, where the office of JJCLCR is located, on August 13, 2009 (approval no. 09124).

RESULTS

Patient Characteristics and Visceral Pleural Invasion

Table 1 shows the patient characteristics. There were 2981 men and 2014 women, aged 15 to 90 years (median, 67 years). The extent of pulmonary resection was pneumonectomy (n = 65), bilobectomy (n = 122), and lobectomy (n = 4808). The histological types were adenocarcinoma (n = 3638), squamous cell carcinoma (n = 1028), adenosquamous carcinoma (n = 84), large-cell carcinoma (n = 149), and other histological types (n = 96).

Survival Differences

The overall 5-year survival rates for PL0 (n = 3606), PL1 (n = 727), PL2 (n = 219), and T3 (n = 443) patients were 87%, 77%, 69%, and 54%, respectively. There were significant survival differences between PL0 and PL1 ($p < 0.001$), between PL1 and PL2 ($p = 0.023$), and between PL2 and T3 ($p < 0.001$) patients (Fig. 1).

The survival curves stratified by T and VPI status are shown in Figure 2*A*. Figure 2*B* shows the survival impact of VPI on T1a tumors. Although T1a tumors with VPI had a

TABLE 1. Patient Characteristics

Characteristics	No. of Patients (%)				
	VPI Factor of T1/T2 Cases				
	PL0	PL1	PL2	T3	Total
Age, yr					
Median (range)	67 (15–89)	68 (31–90)	68 (30–85)	69 (34–83)	67 (15–90)
Sex					
Men	2034 (56)	466 (64)	142 (64)	339 (77)	2981 (60)
Women	1572 (44)	261 (36)	77 (36)	104 (23)	2014 (40)
Surgery					
Lobectomy	3477 (96)	706 (97)	215 (98)	410 (93)	4808 (96)
Bilobectomy	95 (3)	12 (2)	3 (1)	12 (3)	122 (2)
Pneumonectomy	34 (1)	9 (1)	1 (1)	21 (5)	65 (1)
Histology					
Adenocarcinoma	2743 (76)	505 (70)	168 (77)	222 (50)	3638 (73)
Squamous cell carcinoma	660 (18)	168 (23)	37 (17)	163 (37)	1028 (21)
Adenosquamous carcinoma	55 (2)	14 (2)	2 (1)	13 (3)	84 (2)
Large-cell carcinoma	81 (2)	32 (4)	7 (3)	29 (7)	149 (3)
Others	67 (2)	8 (1)	5 (2)	16 (4)	96 (2)
Tumor diameter, cm					
<2	1558 (43)	199 (27)	40 (18)	29 (7)	1826 (37)
2.1–3	1125 (31)	215 (30)	72 (33)	71 (16)	1483 (30)
3.1–5	805 (22)	252 (35)	81 (37)	130 (29)	1268 (25)
5.1–7	118 (3)	61 (8)	26 (12)	72 (16)	277 (6)
≥7.1–	–	–	–	141 (32)	141 (3)
Total	3606	727	219	443	4995

VPI status was defined according to the 7th edition of the tumor, node, metastasis classification for lung and pleural tumors.
VPI, visceral pleural invasion

significantly poorer prognosis than T1a tumors without VPI ($p < 0.001$), there were no significant survival differences between T1a tumors with VPI and T1b tumors without VPI ($p = 0.083$) or T2a tumors without VPI ($p = 0.221$).

Figure 2*C* shows the survival impact of VPI on T1b tumors. Although T1b tumors with VPI had a significantly poorer prognosis than T1b tumors without VPI ($p = 0.001$), there were no significant survival differences between T1b

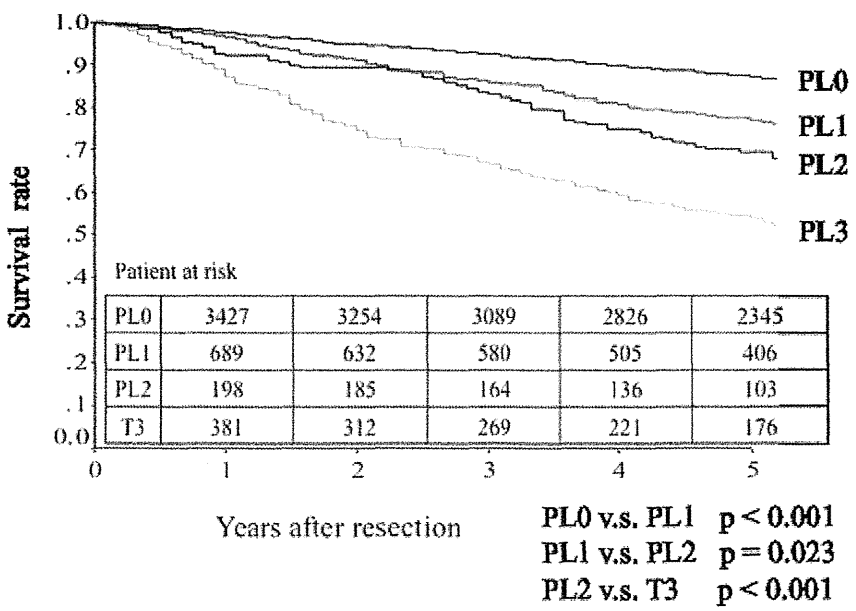

FIGURE 1. Overall survival curves of PL0, PL1, PL2, and T3 patients.