TABLE 1 continued

Characteristic	Variable	Low BMI ($n = 35$)	Normal BMI ($n = 177$)	High BMI ($n = 31$)	*P* value	
					L vs. N	N vs. H
pN	0	13 (37.1)	95 (53.7)	13 (41.9)	0.25	0.62
	1	13 (37.1)	40 (22.6)	8 (25.8)		
	2	7 (20.0)	32 (18.1)	7 (22.6)		
	3	2 (5.7)	10 (5.6)	3 (9.7)		
pStage	0	1 (2.9)	4 (2.3)	1 (3.2)	0.011	0.24
	IA	5 (14.9)	68 (38.4)	7 (22.6)		
	IB	0	8 (4.5)	1 (3.2)		
	IIA	8 (22.9)	15 (8.5)	4 (12.9)		
	IIB	4 (11.4)	29 (16.4)	6 (19.4)		
	IIIA	7 (20.0)	25 (14.1)	3 (9.7)		
	IIIB	3 (8.6)	15 (8.5)	4 (12.9)		
	IIIC	7 (20.0)	13 (7.3)	4 (12.9)		
	IV	0	0	1 (3.2)		
Histologic grade	G1	10 (28.6)	40 (22.6)	8 (25.8)	0.18	0.75
	G2	15 (42.9)	61 (34.5)	12 (38.7)		
	G3	2 (5.7)	38 (21.5)	4 (12.9)		
	Unknown	8 (22.9)	38 (21.5)	7 (22.6)		
Residual disease	R0	27 (77.1)	165 (93.2)	28 (90.3)	0.012	0.26
	R1	2 (5.7)	3 (1.7)	2 (6.5)		
	R2	6 (17.1)	9 (5.1)	1 (3.2)		
Postoperative CT	Present	7 (20.0)	39 (22.0)	11 (35.5)	0.79	0.11

BMI body mass index, *CT* chemotherapy, *CRT* chemoradiotherapy, *dCRT* definitive chemoradiotherapy, *CVD* cerebrovascular diseases, *TT* transthoracic esophagectomy, *ILE* Ivor-Lewis esophagectomy, *TH* transhiatal esophagectomy, *L* low BMI, *N* normal BMI, *H* high BMI

cited as possible mechanisms through which diabetes may stimulate tumor growth.[18]

Obesity also has the potential to contribute to tumor progression through the upregulation of insulin signaling and chronic inflammation with altered regulation of cytokines and adipokines, including tumor necrosis factor alpha, interleukin-6, fatty acid synthase, resistin, leptin, and adiponectin.[19,20] Insulin-like growth factor (IGF) signaling is known to be associated with progression of esophageal cancer cells and mediates 5-fluorouracil chemoresistance.[21–23] Leptin is overexpressed in obese subjects and has been identified as a growth factor for cancers arising from the gastrointestinal epithelium.[20] To understand how high BMI negatively affects prognosis, it is necessary to investigate the effect of obesity on such signals or molecules. We are planning in vitro assay to evaluate the effect of different glucose concentration on the proliferation and the insulin-signaling in esophageal cancer cells. In addition, effect of antidiabetics or IGF targeting agents should be assessed in ESCC cell lines.[24]

Recently, FDG PET has become a useful tool to estimate the extent of certain tumors.[25] The rationale for the use of FDG-PET is based on the enhanced glucose metabolism of malignant tumor cells. Increased FDG uptake has been documented also in ESCC, suggesting the increased glucose metabolism in this tumor.[26] We have previously reported that glucose transporter type 1 (Glut 1) was overexpressed in esophageal cancer compared to the normal esophageal epithelium and the expression correlated with the FDG accumulation.[27] These findings suggest that enhanced glucose metabolism may have an important role in the progression of ESCC. Although we compared maximum standardized uptake values (SUV) among the groups stratified by BMI, no difference was found among the groups (data not shown). Simple comparison of SUV may not make sense to evaluate the glucose metabolism because blood sugar levels affect the SUV.

Definitions of obesity vary among countries. Japan Society for the study of obesity defines a BMI $\geq$25 kg/m^2 as obesity, while a BMI of $\geq$28 mg/m^2 is defined as obesity in China and a BMI between 25 and 30 mg/m^2 is diagnosed as overweight in Western countries. Therefore, results of this study cannot be generalized to different populations and should be validated according to the different definitions.

This study has several limitations. First, this study was a retrospective study conducted at a single institute, and the case number was limited. Obese patients with higher number of underlying comorbidities may have excluded from surgery and recommended definitive chemoradiotherapy without surgery. In order to exclude the possibility, we investigated BMIs of patients listed in our

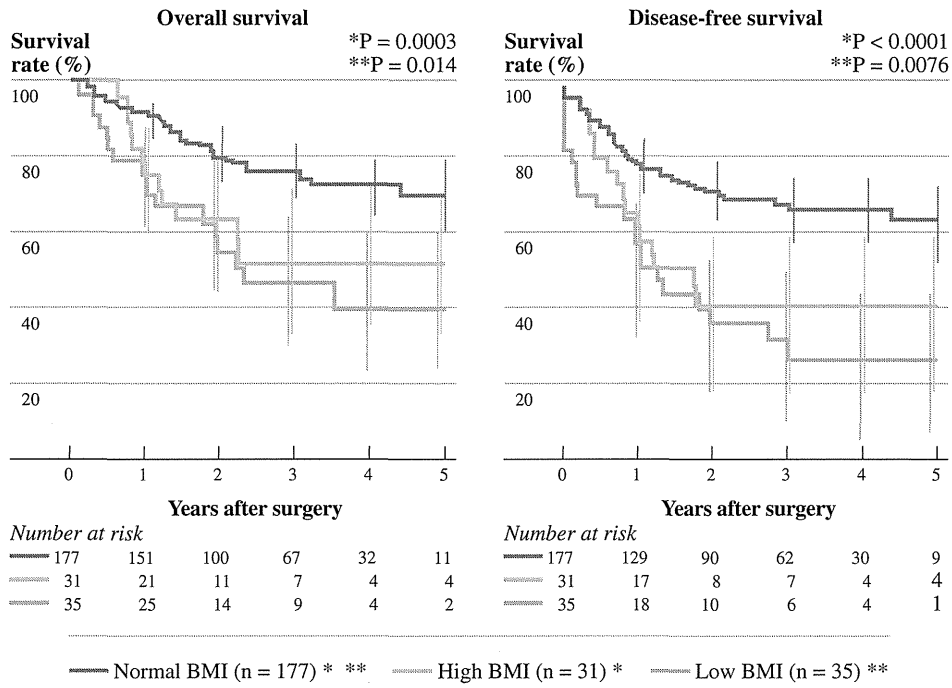

FIG. 1 Overall and disease-free survival, stratified by BMI. The median follow-up period was 25.7 months. Significantly worse overall and disease-free survival rates were observed in both the low and high BMI groups, compared to the normal BMI group

TABLE 2 Characteristics of patients who underwent esophagectomy in the propensity score-matching cohort

Characteristic	Variable	Normal BMI (n = 27)	High BMI (n = 27)	P value
Propensity score		0.86 ± 0.06	0.86 ± 0.06	0.33
Age (years)	Mean ± SD	69.1 ± 7.8	67.1 ± 7.2	0.24
Sex	Male	24 (88.9)	24 (88.9)	0.68
	Female	3 (11.1)	3 (11.1)	
BMI	Mean ± SD	22.0 ± 2.0	26.6 ± 1.1	<0.0001
Location	Upper/middle	18 (66.7)	18 (66.7)	0.75
	Middle	9 (33.3)	9 (33.3)	
cT	1/2	15 (55.6)	18 (66.7)	0.58
	3/4	12 (44.4)	9 (33.3)	
cN	0	13 (48.1)	12 (44.4)	1.00
	1–3	14 (51.9)	15 (55.6)	
cStage	I/II	16 (59.3)	17 (63.0)	1.00
	III	11 (40.7)	10 (37.0)	
Neoadjuvant treatment	Present	11 (40.7)	12 (44.4)	1.00
Comorbidity	Present	7 (25.9)	8 (29.6)	0.72
Postoperative complication	Present	18 (66.7)	18 (66.7)	0.75
No. of retrieved nodes		40.4 ± 18.8	41.6 ± 18.4	0.81
Residual tumor	R0	25 (92.6)	24 (88.8)	1.00
	R1/2	2 (7.4)	3 (11.2)	
Postoperative CT	Present	5 (18.5)	9 (33.3)	0.29

BMI body mass index, *CT* chemotherapy

chemoradiotherapy database, and found that percentage of high BMI patients who underwent definitive chemoradiotherapy was very similar to that of the high BMI group in this study. A large cohort is needed to confirm the result. Second, the follow-up period of 25.7 months may not be long enough. However, given that more than 86 % of

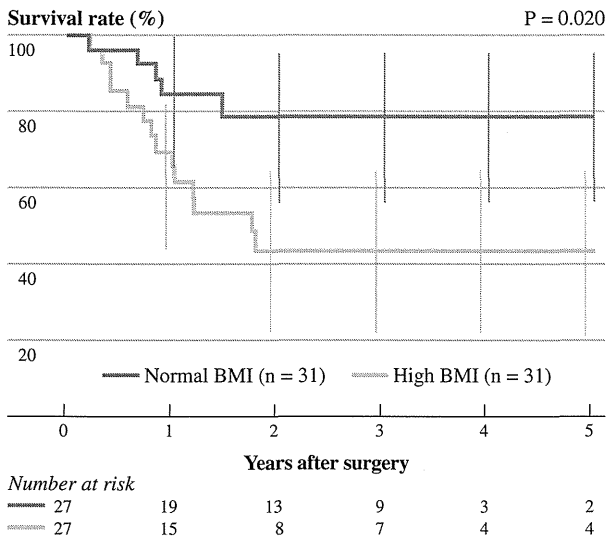

FIG. 2 Disease-free survival in the propensity score-matching cohort. Significantly worse survival rates were observed in high BMI group in comparison with the normal BMI group

TABLE 3 Multivariate analysis of disease-free survival in the propensity score-matching cohort

Characteristic	Variable	HR	95 % CI	*P* value
Age		1.006	0.933–1.084	0.88
Sex	Male	6.188	1.243–30.80	0.026
Location	Upper or middle	0.953	0.340–2.676	0.93
pStage	III, IV	11.110	3.690–33.45	<0.0001
Postoperative morbidity	Present	0.896	0.233–3.454	0.87
BMI group	H (vs. N)	2.949	1.132–7.683	0.027
Propensity score		0.001	2.09E-8–33.45	0.87

HR hazard ratio, *CI* confidence interval, *BMI* body mass index, *N* normal BMI, *H* high BMI

recurring tumors appear within 2 years after esophagectomy, the great difference in prognosis for normal and high BMI groups (Fig. 1) will not diminish over a longer follow-up period.[28] Third, we currently have no data supporting the hypothesis that tumors in overweight patients are more aggressive than those in patients with normal BMI. Further analysis on the expression levels of glucose metabolism-related molecules, such as IGF, leptin and Glut 1, is required to clarify the molecular basis of relationship between obesity and cancer.

In conclusion, both undernutrition and overweight were associated with poor prognosis of squamous cell carcinoma of the esophagus, due to different mechanisms. Advanced tumors are the reason for poor prognosis in patients with low BMI, while biological aggressiveness of tumors is possibly the reason for poor prognosis in patients with high BMI. Although further analysis is required to clarify the influence of overweight on the biological features of ESCC, glucose metabolism may be a therapeutic target for ESCC.

CONFLICT OF INTEREST The authors declare no conflict of interest.

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Preoperative Neutrophil-to-Lymphocyte Ratio Is a Predictor of Survival After Hepatectomy for Hepatocellular Carcinoma

A Retrospective Analysis

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Objective: To clarify the prognostic value of the preoperative blood neutrophil-to-lymphocyte ratio (NLR) in patients undergoing hepatectomy for hepatocellular carcinoma (HCC).

Background: Although a high NLR has been reported to be a predictor of poor survival in patients with various cancers, it has not been extensively examined in patients with HCC.

Methods: This retrospective study enrolled 958 patients who underwent hepatectomy without preoperative therapy for HCC from 1996 to 2009. Clinicopathological parameters, including NLR, were evaluated to identify predictors of overall and recurrence-free survival after hepatectomy. Univariate and multivariate analyses were performed, using the Cox proportional hazards model. The best cutoff was determined with time-dependent receiver operating characteristic curve. To determine the mechanism of NLR elevation, immunohistological examination using CD163 staining was performed in 150 patients.

Results: Univariate and multivariate analyses showed that NLR was an independent prognostic factor in overall and recurrence-free survival. The best cutoff of NLR was 2.81, and 238 of 958 patients (24.8%) had NLR of more than 2.81. The 5-year survival rate after hepatectomy was 72.9% in patients with NLR less than 2.81 and 51.5% in those with NLR 2.81 or more ($P < 0.0001$). CD163-positive cell counts were significantly higher in tumors in the group with NLR 2.81 or more than in the group with NLR less than 2.81 ($P = 0.0004$).

Conclusions: Our results show that NLR is an independent predictor of survival after hepatectomy in patients with HCC. Accumulation of tumor-associated macrophages in the tumor is associated with a high NLR.

Keywords: blood neutrophil-to-lymphocyte ratio, hepatocellular carcinoma, liver resection, prognosis, tumor-associated macrophage

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Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide.[1] Hepatic resection is considered to be the treatment of choice for solitary lesions in patients with noncirrhotic livers or with Child-Pugh–grade cirrhosis, indicating well-preserved liver function.[2] However, the 5-year overall survival rate after hepatic resection is only 50% to 70%.[3–5]

The most significant factor affecting survival is the high postoperative recurrence rate. The reasons for this high recurrence rate remain unclear and seem to be complex and multifactorial.[6,7] One of the important causes of recurrence is metachronous carcinogenesis, caused by hepatic inflammation.[8] Another cause is the malignant potential of cancer cells. Pathological examination shows that microscopic portal vein invasion and intrahepatic metastasis are prognostic factors for survival.[9] Tumor-associated macrophages (TAMs) have been shown to have tumor-promoting effects, with a high density of TAMs in the tumor reported to be associated with a poor prognosis.[10,11] High serum *des*-γ-carboxy prothrombin level and expression of focal adhesion kinase have also been reported to reflect a high malignant potential in HCC.[12,13]

There is increasing evidence that increased systemic inflammation correlates with poorer cancer-specific survival in various cancers.[14–18] Recent studies have shown that the host's inflammatory response to cancer and/or the systemic effects exerted by the cancer cells lead to upregulation of the inflammatory process, predisposing the cancer to proliferation and metastasis through the inhibition of apoptosis, promotion of angiogenesis, and repair of DNA damage.[19,20] The presence of a systemic inflammatory response can be detected by the elevation of the C-reactive protein (CRP) level[21] and neutrophil-to-lymphocyte ratio (NLR)[22]. A high serum CRP level has been shown to be associated with portal vein invasion of cancer cells, and some reports have indicated that a high preoperative serum CRP level is associated with early recurrence of HCC and poorer survival after hepatic resection.[23] A high NLR has been reported to be a predictor of poor survival after hepatic resection, radio-frequency ablation, transarterial chemoembolization, and liver transplantation for HCC.[24–27] To our knowledge, only one relatively small study of fewer than 100 patients by Gomez et al[24] has reported that the preoperative NLR was a prognostic indicator of survival after hepatic resection for HCC.

This study aimed to evaluate the relationship between systemic inflammation and focal infiltration of inflammatory cells, represented by the preoperative NLR and TAMs, and outcome after hepatic resection in 958 patients in 3 high-volume centers in Japan.

METHODS

Patients

From January 1996 to December 2009, a total of 422 patients at the Second Department of Surgery, Kyushu University, 253 patients at the Department of Surgery, Hiroshima Red Cross Hospital, and 316 patients at the Department of Surgery, Iizuka Hospital, underwent hepatic resection for HCC. Thirty-three patients who underwent

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preoperative therapy, such as transarterial chemoembolization, radiofrequency ablation, or percutaneous ethanol injection, were excluded, and the remaining 958 patients (689 males, 269 females) were enrolled in this study. The mean age of patients was 67 years.

Curative resection was defined as complete macroscopic removal of the tumor and was performed in 874 patients (91.2%). Of these, 591 patients (61.7%) were seropositive for hepatitis C antibody (HCV-Ab), 161 (16.8%) were seropositive for hepatitis B surface antigen (HBs-Ag), 204 (21.3%) were seronegative for both HCV-Ab and HBs-Ag, and 5 (0.5%) were seropositive for both HBs-Ag and HCV-Ab. Of the 422 patients who underwent hepatic resection in Kyushu University, 150 consecutive patients who underwent resection from January 1997 to March 2005 were selected for immunohistological examination using CD163 staining.

Prognostic Factors in Overall and Recurrence-Free Survival After Hepatectomy

Neutrophil-to-lymphocyte ratios of all the patients in this study were calculated on the basis of preoperative blood value. Univariate analysis in overall survival and recurrence-free survival was performed, using the Cox proportional hazards model. The overall survival was evaluated in all the 958 patients, and the recurrence-free survival was evaluated only in 874 patients who underwent curative resection. The following variables were examined with respect to overall survival and recurrence-free survival rate: age, sex, serum albumin level, indocyanine green retention rate at 15 minutes (ICGR15), tumor size, serum α-fetoprotein (AFP) level, portal vein thrombus, number of tumors, TNM stage according to the Liver Cancer Study Group in Japan[28] (I or II vs III or IV), and curative resection (resection without remnant tumors). In the analysis of recurrence-free survival, variable: curative resection was excluded, because postoperative recurrence was defined only in the patients without remnant HCC who underwent curative resection. The contiguous variables were entered into the model.

The best cutoff of NLR was determined by receiver operating characteristic curve. The recurrence pattern of HCC was compared between patients with the best cutoff value of NLR. The recurrence pattern was defined as nodular ($\leq$3 nodules), multiple (>3 nodules), and extrahepatic metastasis (metastasis to organs other than the liver), as previously described.[29]

Follow-up Strategy and Recurrence Pattern

After discharge, all patients underwent monthly screening for recurrence, using ultrasonography and tumor markers such as AFP, and 6-monthly computerized tomography scanning. If recurrence was suspected, additional investigations such as hepatic angiography were performed.

Immunohistochemical Examination

Sections of resected specimens were fixed in 10% buffered formalin, embedded in paraffin, and stained using the Envision+ system and DAB kit (DAKO, Grostrup, Denmark). Immunohistochemical staining was performed using CD163 antibodies (10D6, 1:200; Novocastra). Sections were pretreated before being incubated with primary antibodies in a microwave oven for 20 minutes. Serial sections were stained and examined by 2 pathologists (Y.M. and S.A.). The total number of cells with cytoplasmic or membrane staining in 3 high-power fields was counted.

Statistical Analysis

All data are expressed as the mean ± standard deviation. Independent χ^2 tests were used to compare categorical variables. Continuous variables were compared using unpaired t tests. Survival curves were analyzed using the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards model was used for univariate and multivariate analyses. The best cutoff of NLR was determined by time-dependent receiver operating characteristic curve.[30] Adjustment for covariates and the Cox proportional hazards model was conducted using JMP software (SAS Institute, Cary, NC) on a Windows computer. P values of less than 0.05 were considered statistically significant.

RESULTS

NLR as an Independent Prognostic Factor

The statistically significant prognostic factors identified by univariate analyses are shown in Table 1. Indicators of poor liver function, such as low serum albumin level and high ICGR15, were identified as significant predictors of poor prognosis. Among tumor-related factors, large tumor size, high AFP level, presence of portal vein thrombus, multiple tumors, advanced clinical stage, and noncurative resection were identified as predictors of poor prognosis. Furthermore, NLR was also identified as a predictor of prognosis. Multivariate analyses identified low serum albumin level, large tumor size, high NLR level, presence of portal vein thrombus, multiple tumors, and advanced clinical stage as independent predictors of poor prognosis (Table 2).

The statistically significant factors in recurrence-free survival identified by univariate analyses are shown in Table 3. Indicators of poor liver function, such as low serum albumin level and high ICGR15, were identified as significant predictors of poor prognosis. Among tumor-related factors, large tumor size, high AFP level,

TABLE 1. Univariate Analyses of Factors in Relation to Overall Survival, Using the Cox Proportional Hazards Model

Prognostic Variables	Hazard Ratio	P	95% CI
Age	1.226	0.4145	0.993–1.018
Sex	1.964	0.6105	0.821–1.400
Albumin	7.813	<0.0001	0.271–0.457
ICGR15, %	3.274	0.0011	1.007–1.030
Tumor size	8.527	<0.0001	1.117–1.193
AFP	5.608	<0.0001	1.000–1.000
Portal vein thrombus	7.666	<0.0001	0.194–0.378
Multiple	5.520	<0.0001	0.375–0.627
Stage (I + II)	8.150	<0.0001	0.292–0.471
NLR	3.716	0.0002	1.022–1.074
Curative resection	2.392	0.0168	0.445–0.923

TABLE 2. Multivariate Analyses of Factors in Relation to Overall Survival, Using the Cox Proportional Hazards Model

Prognostic Variables	Hazard Ratio	P	95% CI
Albumin	6.779	<0.0001	0.279–0.495
NLR	3.745	0.0002	1.027–1.088
Tumor size	3.736	0.0002	1.036–1.122
Portal vein thrombus	3.445	0.0006	0.315–0.728
Stage (I + II)	2.603	0.0092	0.467–0.898
Multiple	2.211	0.0270	0.512–0.960
ICGR15	1.532	0.1254	0.997–1.022
Curative resection	1.044	0.2967	0.534–1.211
AFP	1.000	0.5100	1.000–1.000
Age	1.003	0.6721	0.990–1.016
Sex	1.058	0.6947	0.797–1.405

presence of portal vein thrombus, multiple tumors, and advanced clinical stage were identified as predictors of poor prognosis for recurrence-free survivals. Furthermore, NLR was also identified as a predictor of tumor recurrence. Multivariate analyses identified high AFP levels, low serum albumin level, high IGGR15, high NLR level, and presence of portal vein thrombus as independent predictors of tumor recurrence (Table 4).

Selection of the Best Cutoff Point for NLR

The best cutoff of NLR was determined for postoperative prognosis, using time-dependent receiver operating characteristic curve. An NLR of 2.81 was the best cutoff point for operative prognosis. All the patients were divided into 2 groups: a low (<2.81) NLR group (n = 720) and a high (≥2.81) NLR group (n = 238).

Prognostic Comparisons of the Low and High NLR Groups

The overall survival rates of patients in the low and high NLR groups are shown in Figure 1. The overall 1-, 3-, and 5-year survival rates were 95.5%, 83.9%, and 72.9% in the low (<2.81) NLR group and 87.1%, 68.9%, and 51.5% in the high (≥2.81) NLR group, which was a significant difference ($P < 0.0001$). The mean survival time was 8.0 ± 0.23 years in the low NLR group and 6.1 ± 0.38 years in the high NLR group.

The recurrence-free survival rates of patients in the low and high NLR groups are shown in Figure 2. The recurrence-free survival rate was significantly higher in the low NLR group than in the high NLR group ($P = 0.0272$).

Comparison of tumor recurrence patterns between the groups is shown in Table 5. Considering those patients with recurrence,

TABLE 3. Univariate Analyses of Factors in Relation to Recurrence Free Survival, Using the Cox Proportional Hazards Model

Prognostic Variables	Hazard Ratio	*P*	95% CI
Age	1.002	0.6467	0.993–1.011
Sex	1.121	0.2622	0.919–1.366
Albumin	3.928	<0.0001	0.546–0.817
ICGR15, %	3.603	0.0003	1.007–1.024
Tumor size	1.452	0.1465	0.991–1.063
AFP	6.271	<0.0001	1.000–1.000
Portal vein thrombus	2.659	0.0078	0.452–0.887
Multiple	2.657	0.0079	0.580–0.921
Stage (I + II)	3.438	0.0006	0.561–0.854
NLR	2.359	0.0183	1.005–1.059

TABLE 4. Multivariate Analyses of Factors in Relation to Recurrence free Survival, Using the Cox Proportional Hazards Model

Prognostic Variables	Hazard Ratio	*P*	95% CI
AFP	5.376	<0.0001	1.000–1.000
Albumin	3.517	0.0004	0.551–0.844
ICGR15	2.509	0.0121	1.003–1.021
NLR	2.096	0.0361	1.002–1.060
Portal vein thrombus	2.337	0.0194	0.487–1.032
Multiple	2.211	0.0728	0.512–0.960
Stage (I + II)	2.603	0.2673	0.659–1.123
Sex	1.096	0.368	0.892–1.345
Tumor size	1.008	0.8641	0.965–1.044
Age	1.003	0.9082	0.991–1.010

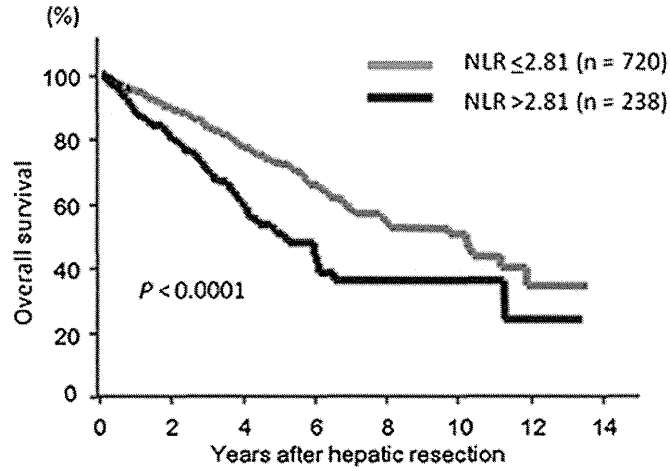

FIGURE 1. Comparison of overall survival rates in the low (<2.81) and high (≥2.81) blood NLR groups. The overall 1-, 3-, and 5-year survival rates were 95.5%, 83.9%, and 72.9% in the low (< 2.81) NLR group and 87.1%, 68.9%, and 51.5% in the high (≥2.81) NLR group, which was a significant difference ($P < 0.0001$).

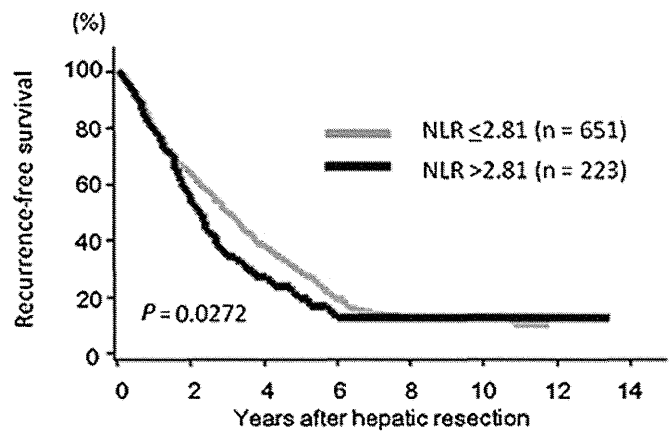

FIGURE 2. Comparison of recurrence-free survival rates in the low (<2.81) and high (≥2.81) NLR groups. The recurrence-free survival rate was significantly higher in the low NLR group than in the high NLR group ($P = 0.0272$).

TABLE 5. Comparison of Recurrence Patterns Between the Low and High NLR Groups

NLR	Nodular	Multiple	Extrahepatic	*P*
<2.81 (n = 351)	243 (69.2%)	86 (24.5%)	22 (6.3%)	0.0002
≥2.81 (n = 115)	55 (47.8%)	48 (41.7%)	12 (10.4%)	—

Nodular indicates fewer than 3 recurrent intrahepatic tumors; multiple, 3 or more recurrent intrahepatic tumors.

multiple tumors in the liver were significantly more frequent in the high NLR group than in the low NLR group ($P = 0.0002$).

Immunohistochemical Examination

We performed immunohistochemical staining for CD163 in 150 consecutive cases at Kyushu University Hospital. Figure 3A

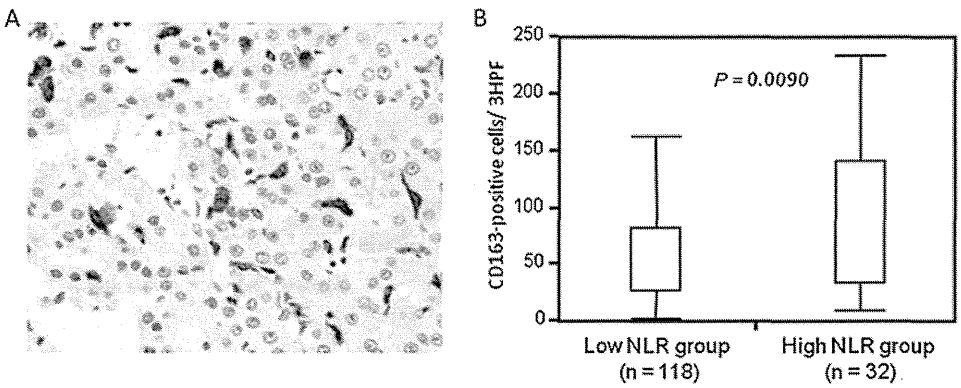

FIGURE 3. A, Immunohistochemical CD163 staining of a hepatocellular carcinoma specimen (×200). B, CD163-positive cell counts in the low and high NLR groups ($P = 0.0090$). HPF indicates high-power field.

shows CD163 staining of TAMs. We compared tumor infiltration by CD163-positive cells between the high and low NLR groups. CD163-positive cell counts were significantly higher in tumors in the high NLR group than in the low NLR group (91.0 ± 82.5 vs 61.2 ± 47.4, $P = 0.0090$; Fig. 3B).

DISCUSSION

Indicators of poor liver function, such as low serum albumin level and high ICGR15, and tumor invasion factors, such as large tumor size, presence of portal vein thrombosis, multiple HCC, and high serum AFP level, have previously been reported to be predictors of poor prognosis in patients with HCC.[31,32] The results of this study clearly show that the high preoperative NLR was an independent predictor of poor survival after hepatectomy in patients with HCC.

Although a high NLR is thought be associated with systemic inflammation, the cause of this inflammation remains unclear. Hashimoto et al[22] reported that a high CRP level was an independent prognostic factor in patients who underwent hepatectomy for HCC. Fever and high CRP level are suspected to be caused by humoral factors, especially inflammatory cytokines such as interleukin (IL)-6, IL-8, and tumor necrosis factor-α. However, fever is extremely rare in patients with HCC, and this mechanism cannot be applied to all patients with a high NLR.

Some reports have indicated that macrophage infiltration into HCC is related to the aggressiveness of the tumor.[10,11] Macrophages can assume a range of different phenotypes based on environmental stimuli. The extremes of this range in vitro are the M1 phenotype, associated with active microbial killing, and the M2 phenotype, associated with tissue remodeling and angiogenesis.[10,11,32] When monocytes in the tumor are exposed to tumor-derived anti-inflammatory molecules such as IL-4, IL-10, transforming growth factor-β1, and prostaglandin E2, they polarize into M2 macrophages.[11] The M2 phenotype macrophage seems to be the dominant type in tumors, with TAMs characterized by high expression of M2 macrophage antigens such as CD163 and high constitutive expression of IL-6 and IL-10.[33,34] Our immunohistochemical analysis showed that high infiltration of TAMs was associated with a high NLR. TAMs express some cytokines, such as IL-6 and IL-8, within the lesion, and these cytokines may promote systemic neutrophilia.[35–37] Ubukata et al[38] demonstrated that a high NLR is significantly correlated with high numbers of Th2 cells in patients with gastric cancer. Th2 cells express IL-4 and IL-10, which polarize macrophages to TAMs. A high NLR is associated with a high infiltration of TAMs and high inflammatory cytokine production in the tumor. On the contrary, our histological examination revealed that local accumulation of neutrophils into HCC might not play an important role in NLR elevation (date not shown). This phenomenon may be explained by complex expression of several cytokines. Kuang et al[39] demonstrated that intratumoral neutrophils did not have a critical role in tumor progression but peritumoral neutrophils did, and proinfilammatory IL-17 secreted by lymphocytes recruits neutrophils to peritumoral stroma. IL-17 is one of the proinflammatory cytokines. Peritumoral IL-17 may enhance systematic neutrophils in our study. Close relationship between TAMs and IL-17–producing cells was reported previously.[34,40] Thus, similar mechanism may be one of the cause of NLR elevation in HCC patients. From this point of view, a high infiltration of TAM is a first and important step of NLR elevation. Further examination is necessary to determine this clear mechanism.

There are a many reports regarding the promotion of distant metastasis of cancer cells by TAMs. Rolny et al[41] demonstrated that inhibition of TAM infiltration into tumors, by neutralizing antibodies to monocyte chemoattractants, reduces metastasis. Recent studies have provided evidence that TAMs and cytokines, such as IL-1, tumor necrosis factor, IL-6, and IL-8, increase metastasis. IL-6 levels are much higher in HCC patients than in healthy adults.[42] Harimoto et al[43] reported an HCC patient with a high IL-8 level, high CRP level, and pyrexia who had an extremely poor outcome after hepatectomy. Liu et al[44] demonstrated that IL-6 induced antiapoptotic activity via the STAT3 signaling pathway in human HCC cell lines. These phenomena may be related to TAMs, which can produce IL-6 and IL-8. Anti-inflammatory treatment may be beneficial in the treatment of HCC, and further study is necessary to investigate this.

CONCLUSIONS

Neutrophil-to-lymphocyte ratio is an easily measurable inflammatory biomarker. Our results show that NLR is an independent predictor of survival after hepatectomy in patients with HCC and that accumulation of TAMs in the tumor may be one of the causes of NLR elevation.

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Solid tumors versus mixed tumors with a ground-glass opacity component in patients with clinical stage IA lung adenocarcinoma: Prognostic comparison using high-resolution computed tomography findings

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Objective: This study aimed to compare malignant behavior and prognosis between solid tumors and mixed tumors with a ground-glass opacity component on high-resolution computed tomography.

Methods: We examined 436 of 502 consecutive patients with clinical stage IA adenocarcinoma who had undergone preoperative high-resolution computed tomography and F-18-fluorodeoxyglucose positron emission tomography/computed tomography; 66 patients with tumors with pure ground-glass opacity components were excluded. Tumor type (solid, n = 137; mixed, n = 299) and surgical results were analyzed for all patients and their matched pairs.

Results: In all patients, solid tumors showed a significantly greater association ($P < .001$) with lymphatic, vascular, and pleural invasion and lymph node metastasis compared with mixed tumors. The disease-free survival was also worse in patients with solid tumors ($P = .0006$). Analysis of 97 pairs matched for solid component size confirmed that solid tumors were significantly associated with lymphatic, vascular, and pleural invasion ($P = .008$, $P = .029$, $P = .003$, respectively) and poor prognosis. When maximum standardized uptake value and solid component size were matched (n = 79), the differences in pathologic prognostic parameters and disease-free survivals between patients with solid and mixed tumors disappeared.

Conclusions: Solid tumors exhibit more malignant behavior and have a poorer prognosis compared with mixed tumors, even when the solid component size is the same in both tumor types. However, differences in malignant behavior can be identified using maximum standardized uptake values determined by F-18-fluorodeoxyglucose positron emission tomography/computed tomography. (J Thorac Cardiovasc Surg 2013;146:17-23)

The recent development of high-resolution computed tomography (HRCT) and low-dose computed tomography (CT) screening has improved the detection of small lung cancers, especially lung adenocarcinomas.[1-3] These often contain a nonsolid component that presents as a ground-glass opacity (GGO) on HRCT and is closely associated with bronchioloalveolar carcinoma.[4,5] We have previously reported the benefits of comparing solid component size (the maximum dimension of the solid component excluding GGO) on HRCT with whole tumor size for predicting the pathologic invasiveness of tumors or the prognosis of clinical stage IA lung adenocarcinomas.[6] It remains unclear whether GGO-containing tumors have the same malignant behavior and prognosis as pure solid tumors after matching for solid component size.

Whether or not differences exist in malignant behavior between pure solid tumors and mixed tumors with a GGO component on HRCT remains controversial. Therefore, we used HRCT to compare malignant behavior, including lymphatic, vascular, and pleural invasion, and prognosis between solid tumors and mixed tumors having a GGO component in patients with clinical stage IA lung adenocarcinoma.

PATIENTS AND METHODS

Between August 1, 2005, and December 31, 2009, we enrolled 502 patients with clinical T1N0M0 stage IA lung adenocarcinoma who were admitted to 1 of the following 4 institutions: Hiroshima University, Kanagawa Cancer Center, Cancer Institute Hospital, and Hyogo Cancer Center. HRCT and F-18-fluorodeoxyglucose positron emission tomography/CT

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GTS

Abbreviations and Acronyms

CT	= computed tomography
DFS	= disease-free survival
FDG-PET	= F-18-fluorodeoxyglucose positron emission tomography
FOV	= field of view
GGO	= ground-glass opacity
HRCT	= high-resolution computed tomography
SUV	= standardized uptake value
SUVmax	= maximum standardized uptake value

(FDG-PET/CT) followed by curative R0 resection were performed in all patients, who were staged according to the seventh edition of the TNM classification of malignant tumors.[7] Mediastinoscopy and endobronchial ultrasonography were not routinely performed because HRCT revealed no swelling of mediastinal or hilar lymph nodes and FDG-PET showed no accumulation in these lymph nodes in all patients. Sublobar resections (segmentectomy or wedge resection) were performed if the tumor mainly comprised a GGO component or had no lymph node metastasis on intraoperative assessment. Tumors with pure GGO were excluded from the analyses because they are noninvasive and have an extremely good prognosis.[8,9] 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 because this was a retrospective review of medical records from a prospective database.

High-Resolution Computed Tomography

Chest images were obtained using 16-row multidetector CT independently of subsequent FDG-PET/CT examinations. High-resolution images of the tumors were acquired using the following parameters: 120 kVp; 200 mA; section thickness, 1 to 2 mm; pixel resolution, 512 × 512; scanning time, 0.5 to 1 seconds; a high spatial reconstruction algorithm with a 20-cm field of view (FOV); and mediastinal (level, 40 HU; width, 400 HU) and lung (level, −600 HU; width, 1600 HU) window settings. GGO was defined as a misty increase in lung attenuation that did not obscure underlying vascular markings. We defined solid component size as the maximum dimension of the solid component in the lung windows after excluding the GGO component.[6] Solid tumors were defined as pure solid tumors without a GGO component, whereas mixed tumors were defined as tumors with a GGO component regardless of the GGO proportion.

F-18-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

Patients were instructed to fast for more than 4 hours before intravenous injection of 74 to 370 MBq of FDG. After injection, they were instructed to relax for at least 1 hour before FDG-PET/CT scanning. Blood glucose was calculated before tracer injection to confirm a level of less than 150 mg/dL.[10] Patients with blood glucose values 150 mg/dL or greater were excluded from PET/CT image acquisition. Images were obtained using Discovery ST (GE Healthcare, Little Chalfont, UK), Aquiduo (Toshiba Medical Systems Corporation, Tochigi, Japan), or Biograph Sensation16 (Siemens Healthcare, Erlangen, Germany) integrated PET/CT scanners. Low-dose, unenhanced CT images of 2- to 4-mm section thickness for attenuation correction and localization of lesions identified by PET were obtained from the head to the pelvic floor of each patient using a standard protocol. Immediately after CT, PET covered the identical axial FOV for 2 to 4 minutes per table position depending on the condition of the patient and scanner performance. All PET images with a 50-cm FOV were reconstructed using an iterative algorithm with CT-derived attenuation correction. Variations in standardized uptake values (SUVs) among institutions were minimized using an anthropomorphic body phantom. A calibration factor was obtained by dividing the actual SUV by the gauged mean SUV in the phantom background to decrease interinstitutional SUV inconsistencies; the final SUV used is referred to as the revised maximum SUV (SUVmax).[11,12] Adjustment of interinstitutional variability in SUV narrowed the range from 0.89 to 1.24 to 0.97 to 1.18 when the SUVmax ratio was expressed as the SUVmax reported by each institute relative to the SUVmax reported by the control institute.

Follow-up Evaluation

All patients who underwent lung resection were followed up from the day of surgery. Postoperative follow-up procedures, including physical examination and chest roentgenography every 3 months and chest and abdominal CT examinations every 6 months, were performed for the first 2 years. Thereafter, physical examination and chest roentgenography were performed every 6 months, whereas chest CT examination was performed every year. Recurrence was determined by radiographic features or histologic evidence.

Statistical Analysis

Data are presented as numbers (%) or mean ± standard deviation unless otherwise stated. Frequencies were compared using the chi-square test for categoric variables, and the Fisher exact test was applied to small samples in all cohort patients. McNemar tests were used for analyses of matched-pair patients. Mann–Whitney U tests and t tests were used to compare continuous variables in all cohort patients. Wilcoxon tests were used for analyses of matched-pair patients. Disease-free survival (DFS) was defined as the time from the date of surgery until the first event (relapse or death from any cause) or last follow-up. The duration of DFS was analyzed using the Kaplan–Meier method. Differences in DFS were assessed using the log-rank test. We applied matching to balance the assignment of the included patients and correct for tumor type (solid or mixed), which confounded survival. The variables were solid component size or SUVmax. Solid and mixed tumor pairs with an equivalent solid component size or SUVmax were selected by a 1-to-1 match. All 436 patients were pooled and sorted in ascending order according to their solid component size or SUVmax. The selection process began from the first 2 cases with the lowest solid component size or SUVmax. If 1 case exhibited a solid tumor and the other case exhibited a mixed tumor, both were selected as a matched pair. If this was not the case, then 4 cases were included. In the same way, solid and mixed tumors were matched by their solid component size or SUVmax in 1:1, 2:2, 3:3, or 4:4 blocks. A patient who did not have a suitable match within the acceptable rank range was excluded from further analysis, and the matching process moved down the sort list until all possible matched pairs were included. The selected patients formed well-matched 1:1 pairs in both groups. Data were analyzed using the Statistical Package for the Social Sciences (v 10.5; SPSS Inc, Chicago, Ill).

RESULTS

Of the 502 patients, 66 who had tumors with pure GGO components were excluded; the remaining 436 patients were included in this analysis. Of the 436 study patients, 137 had solid tumors and 299 had mixed tumors. The mean follow-up period after surgery was 20.2 ± 12.5 months, during which the disease recurred in 29 patients (6.7%). The mean follow-up period was similar for solid and mixed tumors (21.4 ± 12.8 months and 19.7 ± 12.4 months, respectively, $P = .235$). Of the 29 cases of recurrence, 9 (2.1%) were local (including mediastinal lymph node metastasis), 3 (0.7%) were local and distant, and 17

(3.9%) were distant. Age, sex, and whole tumor size on HRCT were not significantly different between patients with solid and mixed tumors. Solid tumors were significantly correlated with a large solid component size, a high SUVmax, and the presence of lymphatic, vascular, and pleural invasion and lymph node metastasis ($P < .001$, $P < .001$, $P < .001$, $P < .001$, $P < .001$, $P = .001$, respectively; Table 1).

Local recurrence occurred in 5 patients (3.6%) with solid tumors (1 involving the bronchial stump and 4 involving the mediastinal lymph nodes) and 4 patients (1.3%) with mixed tumors (1 involving the residual lung after segmentectomy and 3 involving the mediastinal lymph nodes). A significant difference in DFS was identified between patients with solid tumors (n = 137; 2-year DFS, 83.1%) and those with mixed tumors (n = 299; 2-year DFS, 94.2%; $P = .0006$; Figure 1, *A*).

After matching for solid component size, there were 97 well-matched solid and mixed tumor pairs. Significant differences were identified in whole tumor size, SUVmax, and lymphatic, vascular, and pleural invasion between the 2 tumor types ($P < .001$, $P < .001$, $P = .008$, $P = .029$, $P = .003$, respectively, Table 2). Solid tumors were significantly correlated with a small whole tumor size, a high SUVmax, and the presence of pathologic invasiveness.

Furthermore, a difference in DFS was identified between patients with solid tumors (n = 97; 2-year DFS, 83.5%) and those with mixed tumors (n = 97; 2-year DFS, 91.8%; Figure 1, *B*) after matching for solid component size.

After matching for SUVmax, there were 96 well-matched solid and mixed tumor pairs. No significant differences in clinical characteristics, except for solid component size, were found between the 2 tumor types (Table 3).

A difference in DFS was identified between patients with solid tumors (n = 96; 2-year DFS, 87.1%) and those with mixed tumors (n = 96; 2-year DFS, 90.4%; Figure 1, *C*) after matching for SUVmax.

After matching for solid component size and SUVmax, there were 79 well-matched solid and mixed tumor pairs. No significant differences in clinical characteristics, except for whole tumor size, were found between the 2 tumor types (Table 4).

Furthermore, there was no difference in DFS between patients with solid tumors (n = 79; 2-year DFS, 87.0%) and patients with mixed tumors (n = 79; 2-year DFS, 83.9%; Figure 1, *D*) after matching for solid component size and SUVmax.

Figure 2 shows examples of solid and mixed tumors with the same solid component size (1.0 cm). Regardless of tumor type, tumors with low SUVmax were not associated with lymphatic invasion, whereas those with high SUVmax were.

TABLE 1. Comparison of solid and mixed tumor characteristics in all cohort patients

	Solid tumors (n = 137)	Mixed tumors (n = 299)	*P*
Age (y)	65.5 ± 10.5	65.7 ± 8.8	.85
Sex			.12
Male	71 (51.8%)	130 (43.5%)	
Female	66 (48.2%)	169 (56.5%)	
Whole tumor size (cm)	2.1 ± 0.6	2.0 ± 0.6	.69
Solid component size (cm)	2.1 ± 0.6	1.1 ± 0.7	<.001
SUVmax	4.9 ± 3.3	2.6 ± 2.9	<.001
Lymphatic invasion			<.001
Negative	89 (65.0%)	270 (90.3%)	
Positive	48 (35.0%)	29 (9.7%)	
Vascular invasion			<.001
Negative	79 (57.7%)	264 (88.3%)	
Positive	58 (42.3%)	35 (11.7%)	
Pleural invasion			<.001
Negative	100 (73.0%)	278 (93.0%)	
Positive	37 (27.0%)	21 (7.0%)	
Lymph node metastasis			<.001
Negative	114 (83.2%)	284 (95.0%)	
Positive	23 (16.8%)	15 (5.0%)	
Procedure			.001
Lobectomy	111 (81.0%)	190 (63.5%)	
Segmentectomy	9 (6.6%)	48 (16.1%)	
Wedge resection	17 (12.4%)	61 (20.4%)	

SUVmax, Maximum standardized uptake value.

DISCUSSION

The present study demonstrated, as expected, that solid tumors were associated with highly malignant variables, such as large solid component size, high SUVmax, and lymphatic, vascular, and pleural invasion and lymph node metastasis in all cohort patients. In addition, patients with solid tumors had worse DFS than those with mixed tumors. A retrospective study has previously shown that pure solid tumors have malignant potential with nodal or pleural involvement and worse DFS compared with predominantly solid tumors with a GGO component.[13] Other studies have also revealed that tumors with a predominant GGO component are less invasive and have a more favorable prognosis in patients with clinical stage IA lung adenocarcinomas.[4,8,14] Our study is consistent with these findings.

With regard to the tumor size on HRCT, solid component size is more useful than whole tumor size for predicting pathologic invasiveness and prognosis. In our previous study, solid component size was found to have a higher predictive value for lymphatic, vascular, and pleural invasion compared with whole tumor size; furthermore, solid component size was an independent prognostic factor for DFS.[6] It was not clear whether mixed tumors and solid tumors have similar malignant behaviors and prognoses when both have the same solid component size on HRCT. Therefore, we conducted a matched analysis to compare solid and mixed tumors after matching for solid component size in both tumor types. Even after matching for solid component

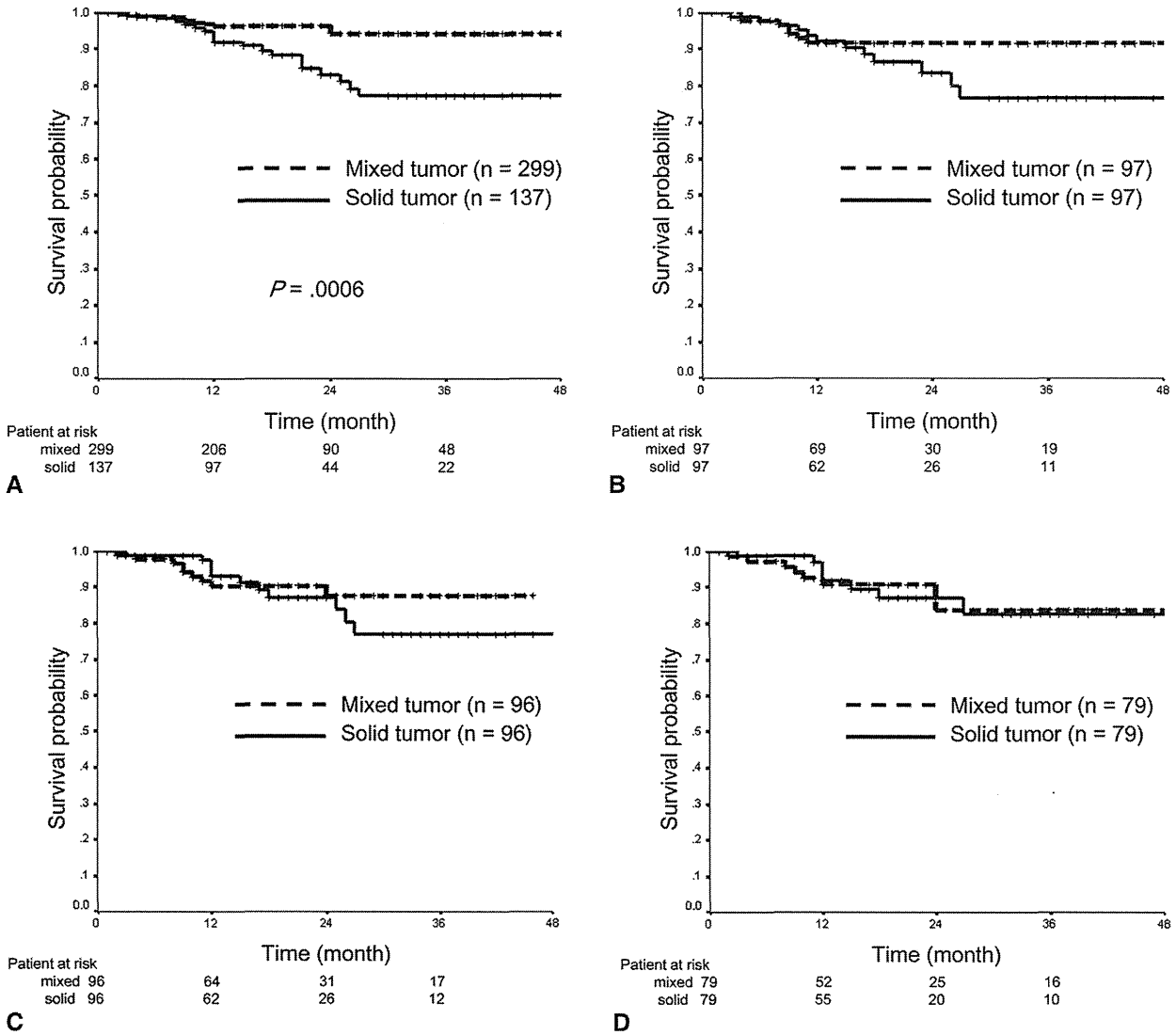

FIGURE 1. DFS curves of patients according to tumor type on HRCT. A, In all cohort patients, 2-year DFS of 94.2% (mean DFS of 47 months; 95% confidence interval [CI], 46-48 months) and 83.1% (mean DFS of 42 months; 95% CI, 39-45 months) were identified for mixed and solid tumors, respectively ($P = .0006$). B, In patients matched for solid component size, 2-year DFS of 91.8% (mean DFS of 46 months; 95% CI, 43-48 months) and 83.5% (mean DFS of 42 months; 95% CI, 38-45 months) were identified for mixed and solid tumors, respectively. C, In patients matched for SUVmax, 2-year DFS of 90.4% (mean DFS of 42 months; 95% CI, 39-44 months) and 87.1% (mean DFS of 42 months; 95% CI, 38-46 months) were detected for mixed and solid tumors, respectively. D, In patients matched for solid component size and SUVmax, 2-year DFS of 83.9% (mean DFS of 43 months; 95% CI, 40-47 months) and 87.0% (mean DFS of 43 months; 95% CI, 40-47 months) were detected for mixed and solid tumors, respectively.

size in both tumor types on HRCT, solid tumors were more frequently correlated with high SUVmax and malignant behavior compared with mixed tumors. In addition, the DFS of patients with solid tumors was worse than that of patients with mixed tumors. This means that solid tumors have more malignant potential than mixed tumors even if both tumor types have the same solid component size on HRCT. This is a new finding. SUVmax on PET/CT is reported to be a predictor of malignant behavior and prognosis in cases of lung adenocarcinomas.[6,11,12,15-17] SUVmax on PET/CT is a preoperative factor, whereas lymphatic, vascular, and pleural invasion are postoperative factors. We have previously reported that SUVmax is a significant predictor of malignant behavior.[6,11,12,16,17]

We experimentally performed a matched analysis to compare solid and mixed tumors after matching for SUVmax. In this matched model, solid tumors and mixed tumors had similar clinical characteristics except solid component size, but there seemed to be a difference in DFS. Although both tumor types have the same SUVmax, solid tumors seem to have a worse potential than mixed tumors.

TABLE 2. Comparison of solid and mixed tumor characteristics in patients matched for solid component size

	Solid tumors (n = 97)	Mixed tumors (n = 97)	*P*
Age (y)	64.9 ± 10.4	66.1 ± 10.0	.63
Sex			.054
Male	50 (51.5%)	36 (37.1%)	
Female	47 (48.5%)	61 (62.9%)	
Whole tumor size (cm)	1.8 ± 0.5	2.3 ± 0.5	<.001
Solid component size (cm)	1.8 ± 0.5	1.8 ± 0.5	N/A
SUVmax	4.8 ± 3.4	3.0 ± 2.5	<.001
Lymphatic invasion			.008
Negative	63 (64.9%)	81 (83.5%)	
Positive	34 (35.1%)	16 (16.5%)	
Vascular invasion			.029
Negative	62 (63.9%)	76 (78.4%)	
Positive	35 (36.1%)	21 (21.6%)	
Pleural invasion			.003
Negative	71 (73.2%)	88 (90.1%)	
Positive	26 (26.8%)	9 (9.9%)	
Lymph node metastasis			.13
Negative	82 (84.5%)	90 (92.8%)	
Positive	15 (15.5%)	7 (7.2%)	
Procedure			.38
Lobectomy	74 (76.3%)	83 (85.6%)	
Segmentectomy	7 (7.2%)	8 (8.2%)	
Wedge resection	16 (16.5%)	6 (6.2%)	

SUVmax, Maximum standardized uptake value; *N/A*, not applicable.

TABLE 3. Comparison of solid and mixed tumor characteristics in patients matched for maximum standardized uptake value

	Solid tumor (n = 96)	Mixed tumor (n = 96)	*P*
Age (y)	65.4 ± 10.4	65.5 ± 9.3	.94
Sex			.26
Male	49	40	
Female	47	56	
Whole tumor size (cm)	2.0 ± 0.6	2.1 ± 0.6	.24
Solid tumor size (cm)	2.0 ± 0.6	1.5 ± 0.7	<.001
SUVmax	4.0 ± 2.6	4.0 ± 2.6	N/A
Lymphatic invasion			.12
Negative	65	74	
Positive	31	22	
Vascular invasion			.47
Negative	62	67	
Positive	34	29	
Pleural invasion			.071
Negative	70	81	
Positive	26	15	
Lymph node metastasis			.54
Negative	80	84	
Positive	16	12	
Procedure			.50
Lobar resection	77	73	
Segmentectomy	6	15	
Wedge resection	13	8	

SUVmax, Maximum standardized uptake value; *N/A*, not applicable.

TABLE 4. Comparison between solid and mixed tumor characteristics in patients matched for solid component size and maximum standardized uptake value

	Solid tumor (n = 79)	Mixed tumor (n = 79)	*P*
Age (y)	64.4 ± 10.7	66.0 ± 8.9	.27
Sex			.62
Male	37 (46.8%)	41 (51.9%)	
Female	42 (53.2%)	38 (48.1%)	
Whole tumor size (cm)	1.8 ± 0.5	2.2 ± 0.5	<.001
Solid component size (cm)	1.8 ± 0.5	1.8 ± 0.5	N/A
SUVmax	3.7 ± 2.4	3.7 ± 2.6	N/A
Lymphatic invasion			.31
Negative	53 (67.1%)	60 (75.9%)	
Positive	26 (32.9%)	19 (24.1%)	
Vascular invasion			1.0
Negative	56 (70.9%)	56 (70.9%)	
Positive	23 (29.1%)	23 (29.1%)	
Pleural invasion			.71
Negative	62 (78.5%)	65 (82.3%)	
Positive	17 (21.5%)	14 (17.7%)	
Lymph node metastasis			.80
Negative	67 (84.8%)	69 (87.3%)	
Positive	12 (15.2%)	10 (12.7%)	
Procedure			.15
Lobar resection	61 (77.2%)	66 (83.5%)	
Segmentectomy	5 (6.3%)	8 (10.1%)	
Wedge resection	13 (16.5%)	5 (6.3%)	

SUVmax, Maximum standardized uptake value; *N/A*, not applicable.

In a next step, we evaluated whether mixed tumors exhibited malignant behavior and prognosis similar to those of solid tumors after matching for solid component size and SUVmax. In this matched model, solid tumors and mixed tumors had similar clinical characteristics and DFS. As shown in Figure 2, tumors with equivalent solid component size and SUVmax had the same malignant behavior (eg, lymphatic invasion), regardless of type. The DFS of patients with solid and mixed tumors was also comparable after matching for solid component size and SUVmax. These findings indicate that solid tumors and mixed tumors show similar biological behavior and prognosis when both have the same solid component size on HRCT and the same SUVmax value on PET/CT. In other words, solid component size on HRCT and SUVmax on PET/CT are important factors for evaluating malignant behavior of clinical stage IA lung adenocarcinomas before surgery, and this is regardless of the GGO proportion. Solid and mixed lung adenocarcinoma tumors with low SUVmax reflect pathologic noninvasiveness and may be good candidates for sublobar resection. We have previously reported, in the same population who were evaluated in the current study, that tumors with SUVmax less than 1.5 were not associated with lymph node metastasis or recurrence,[12,18] and we recommend that individuals with clinical stage IA lung adenocarcinomas with

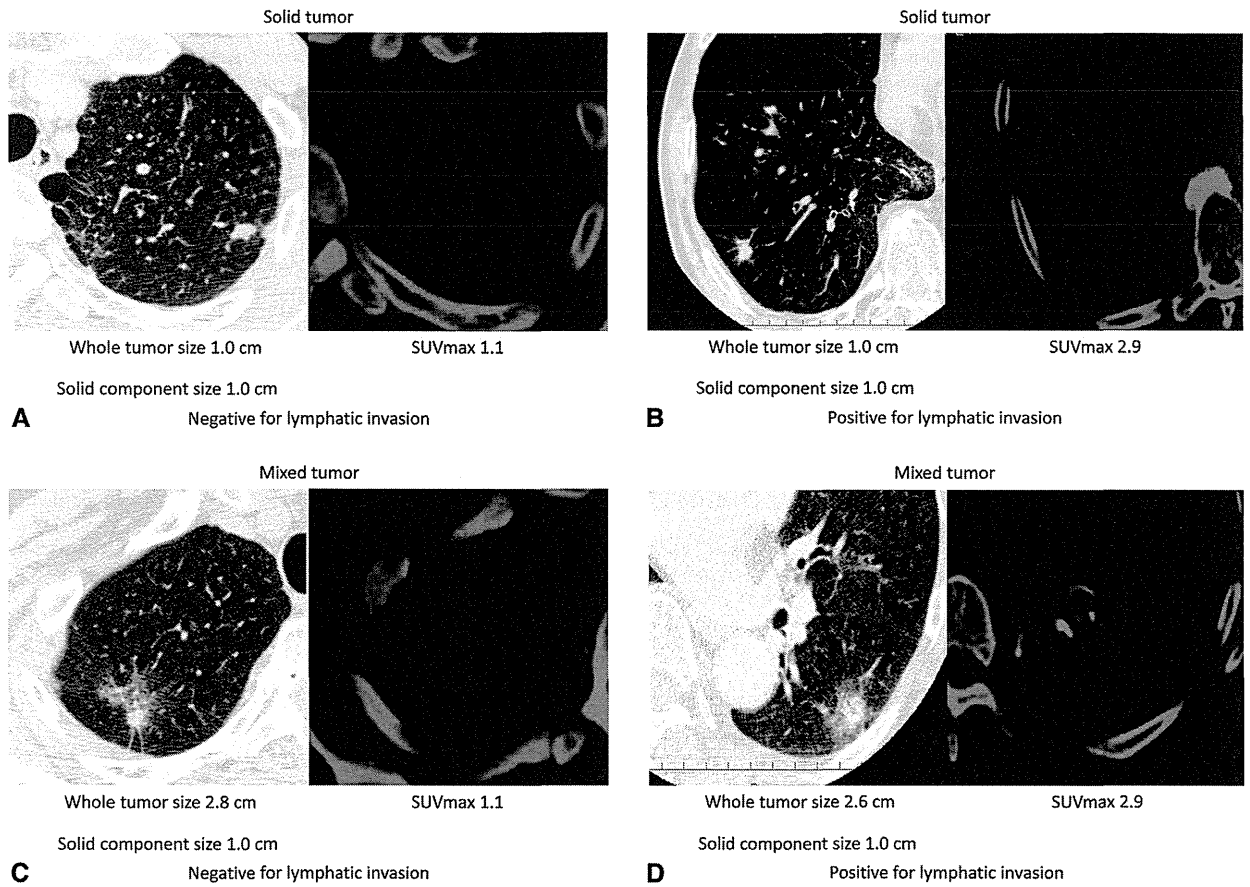

FIGURE 2. Examples of solid and mixed tumors on HRCT. A, Whole tumor size = solid component size: 1.0 cm, SUVmax: 1.1. This solid tumor was negative for lymphatic invasion. B, Whole tumor size = solid component size: 1.0 cm, SUVmax: 2.9. This solid tumor was positive for lymphatic invasion. C, Whole tumor size: 2.8 cm, solid component size: 1.0 cm, SUVmax: 1.1. This mixed tumor was negative for lymphatic invasion. D, Whole tumor size: 2.6 cm, solid component size: 1.0 cm, SUVmax: 2.9. This mixed tumor was positive for lymphatic invasion. *SUVmax,* Maximum standardized uptake value.

SUVmax less than 1.5 should undergo sublobar resection with adequate surgical margins.[18]

One of the strengths of this study is the use of PET/CT in all patients. PET/CT, which is the diagnostic tool of choice for patients with non–small cell lung cancer, improves the sensitivity of preoperative staging and reduces the frequency of futile thoracotomies.[19] In addition, SUVmax on PET/CT is a known prognostic factor for non–small cell lung cancer, especially for adenocarcinoma.[6,11,12,16,17] For patients with clinical stage IA lung adenocarcinoma who do not undergo PET/CT, tumor type (solid or mixed) is an important factor for predicting malignant behavior and prognosis. Because the follow-up period was short in this study, long-term follow-up is needed to confirm the DFS results.

CONCLUSIONS

In cases of clinical stage IA lung adenocarcinoma, solid tumors are more malignant than mixed tumors even after matching for solid component size in both tumor types. However, solid tumors have the same malignant potential and prognosis as mixed tumors when both tumor types are matched for solid component size on HRCT and SUVmax on PET/CT.

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Clinical Trial Note

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A Feasibility Study of Induction Pemetrexed Plus Cisplatin Followed by Pleurectomy/Decortication Aimed at Macroscopic Complete Resection for Malignant Pleural Mesothelioma

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A prospective multi-institutional study has been initiated in Japan to evaluate the feasibility of induction chemotherapy using pemetrexed plus cisplatin, followed by pleurectomy/decortication aimed at macroscopic complete resection in patients with resectable malignant pleural mesothelioma. The study was initiated on September 2012, for which 24 patients will be recruited over a period of 2 years. The primary endpoint is the macroscopic complete resection rate, regardless of the surgical technique employed (i.e. pleurectomy/decortication or extrapleural pneumonectomy). The secondary endpoints are the pleurectomy/decortication rate, macroscopic complete resection rate by pleurectomy/decortication, pulmonary function at 3 months after surgery, adverse events, treatment-related mortality, response rate to chemotherapy and 3-year overall survival rate.

Key words: extrapleural pneumonectomy – induction chemotherapy – malignant pleural mesothelioma – macroscopic complete resection

INTRODUCTION

Malignant pleural mesothelioma (MPM) is an extremely poor-prognosis malignant tumor caused by asbestos exposure. The number of cases of this tumor in Japan is expected to rise in the future (1–3). MPM is very difficult to cure. While extrapleural pneumonectomy (EPP) is performed with radical intent, the outcome is not very good in patients treated with surgery alone (4). The current standard for possible cures for this disease has shifted to a multidisciplinary approach combining induction chemotherapy with cisplatin and pemetrexed followed by EPP and radiation therapy (trimodality therapy).

In recent years, another operative method, known as pleurectomy/decortication (P/D), has come into the spotlight. EPP is a very invasive surgery and shows cardiorespiratory depression and high rates of mortality and complications. P/D is less invasive than EPP. As of yet, it is not apparent which risk-benefit ratio of P/D and EPP is better as a part of multimodality therapy. It has been reported that the survival rate of P/D is higher than or equal to that of EPP (5–8). The possible reasons for this are as follows:

(1) The perioperative mortality rate of P/D is lower than that of EPP.
(2) Patients who had P/D receive better treatment than those who received EPP at the time of recurrence.

Postoperative quality of life is maintained to a larger extent in those patients who have undergone P/D rather than EPP (9). The results of major clinical trials for trimodality therapy, including EPP, have been reported by cancer study groups in North America, the University of Toronto and Europe (10–12). In all clinical trials, only around 50% of patients completed trimodality therapy, thus suggesting that trimodality therapy, including EPP, poses major difficulties even at some of the world's most experienced and top-ranking facilities. In addition, both a high complication rate and a number of treatment-related deaths were reported in a Japanese multi-institutional clinical trial for trimodality therapy conducted in 2008. Considering this, the survival benefits of this therapy reported from clinical trials in Europe and the USA are not high. Therefore, the risk-benefit ratio of this treatment is not satisfiable.

There is no good evidence of multimodality therapy involving P/D. However, the benefit of adding induction chemotherapy to P/D may be speculated in the light of that for EPP (13–15). The study protocol is a clinical trial to evaluate induction chemotherapy with pemetrexed plus cisplatin followed by P/D aimed at macroscopic complete resection (MCR) for resectable MPM (16). The study protocol was approved by the protocol review committee and activated on 12 October 2012. The study has been registered at the UMIN Clinical Trials Registry as UMIN000009092 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGEST OF THE STUDY

Purpose

The aim of this study is to evaluate the feasibility of multimodality therapy for resectable MPM, comprised induction chemotherapy using pemetrexed plus cisplatine (PC) followed by P/D aimed at MCR.

Study Setting

This is a multi-institutional, single-arm study.

Study Method

Figure 1 shows a flow chart of the study.

Endpoints

The primary endpoint is MCR rate regardless of the surgical technique employed (i.e. P/D or extrapleural pneumonectomy). MCR is defined as the surgical removal of all gross tumor tissue (16,17). Secondary endpoints are as follows: (i) P/D rate, (ii) MCR rate by P/D, (iii) pulmonary function

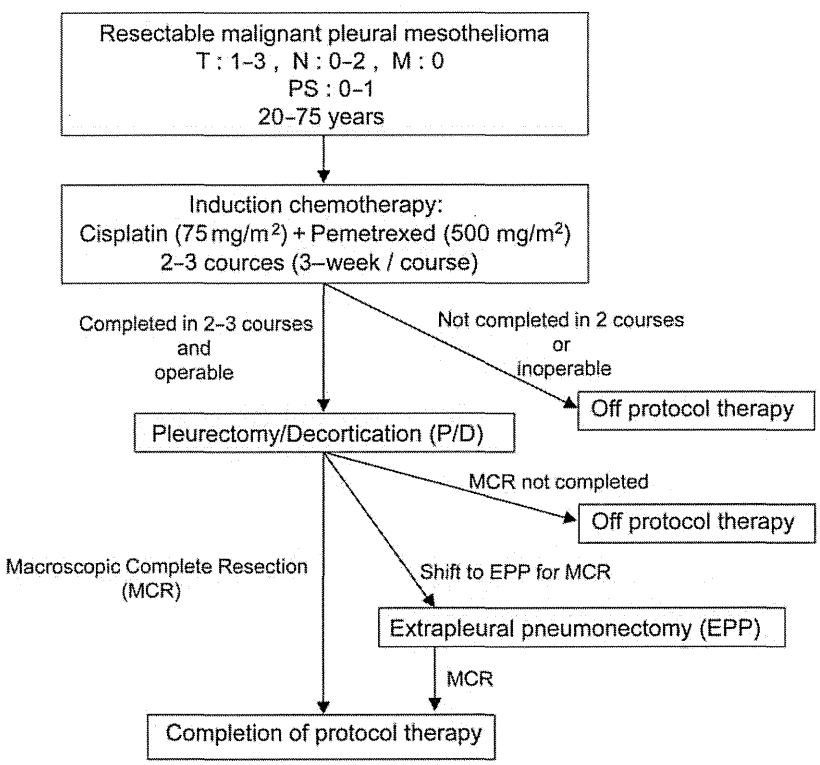

Figure 1. Flow chart of the study.

at 3 months after surgery, (iv) incidence of treatment-related adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 guidelines (18), (v) treatment-related mortality, (vi) response rate for induction chemotherapy evaluated by a modified version of the Response Evaluation Criteria in Solid Tumors [modified RECIST (19)], (vii) 3-year overall survival rate in all eligible patients with MCR.

Eligibility/Inclusion Criteria

Patients are eligible for the trial if they have a histologically confirmed diagnosis of MPM, including all subtypes and clinical T1–3, N0–2, M0 disease considered to be resectable. Other requirements are as follows: no prior treatment with chemotherapy, surgery or radiation therapy (RT) for the disease; age between 20 and 75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; a predicted postoperative forced expiratory volume of >1000 ml in 1 s; adequate bone marrow, hepatic, renal, cardiac and respiratory functions; a life expectancy of >12 weeks; and written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria: serious systemic complications including poorly controlled diabetes or hypertension, active infectious diseases, interstitial pneumonia or lung fibrosis; simultaneous or metachronous (within 5 years) double cancers; serious drug allergy or hypersensitivity to any drugs; pregnancy or breast-feeding; Grade 2 or greater peripheral neuropathy at registration; or considered as clinically inappropriate for registration.

TREATMENT METHODS

Induction Chemotherapy

Induction chemotherapy consists of three cycles of pemetrexed at 500 mg/m^2 followed by cisplatin 75 mg/m^2 on Day 1, given every 21 days. Folic acid (0.5 mg per daily oral administration) and vitamin B12 (1 mg intramuscularly every 9 weeks) are administered a week before the first dose of chemotherapy and continue to be administered throughout the induction chemotherapy. Dose adjustments of chemotherapy are required for renal and nonhematologic toxicity as well as hematologic effects. Dose delays of up to 42 days are permitted for recovery from drug toxicity. Tumor response is assessed through computed tomography (CT) following the completion of induction chemotherapy using unidimensional measurement of the pleural thickness perpendicular to the chest wall or mediastinum and modified RECIST criteria.

Pleurectomy/Decortication and Extrapleural Pneumonectomy

All patients undergo P/D or EPP within 42 days of the last dose of induction chemotherapy unless there is deterioration of organ functions that would make the surgery intolerable. P/D complies with the definition of the International Association for the Study of Lung Cancer (IASLC) staging committee and the International Mesothelioma Interest Group (IMIG). The above report does not prescribe whether P/D mandates the removal of a part of the pleura without macroscopic disease. Therefore, in this study, it is stipulated that P/D requires mandatory removal of all the parietal pleura and removal of all the area of the visceral pleura with macroscopic disease. If it is necessary to achieve MCR, P/D permits resecting either of the diaphragm, pericardium, chest wall and lung parenchyma. EPP is defined as an en-bloc resection of the entire pleura, lung, ipsilateral diaphragm and pericardium (20). Also, while it is impossible to achieve MCR through P/D, EPP is performed in cases where operators deem that MCR can be achieved through EPP. If lymph node metastasis is confirmed by pathological examination, excision of this is also a prerequisite for MCR. Mediastinal nodal dissection is recommended in all patients having either P/D or EPP.

Study Design and Statistical Methods

The primary analysis of this study was to estimate the MCR rate and 95% confidence interval (CI). If the lower limit of the 95% CI exceeds 0.5, the protocol treatment will be considered feasible. Thus, 24 patients were planned to be enrolled onto this study, with planned accrual of 2 years and follow-up of 3 years after the accrual completion. This sample size was considered sufficient to estimate 95% confidence intervals for the true MCR rate within a width of ± 0.2, when the true MCR rate is expected to be 70%.

Study Monitoring

The Data and Safety Monitoring Committee (DSMC) will make independent recommendations to investigators regarding the continuation, termination or modification of the trial. Protocol compliance, safety and study progress will also be monitored by the DSMC.

Participating Institutions

A total of 24 institutions in Japan with certified specialists in oncology and surgery will participate in this trial.

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Conflict of interest statement

None declared.

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