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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

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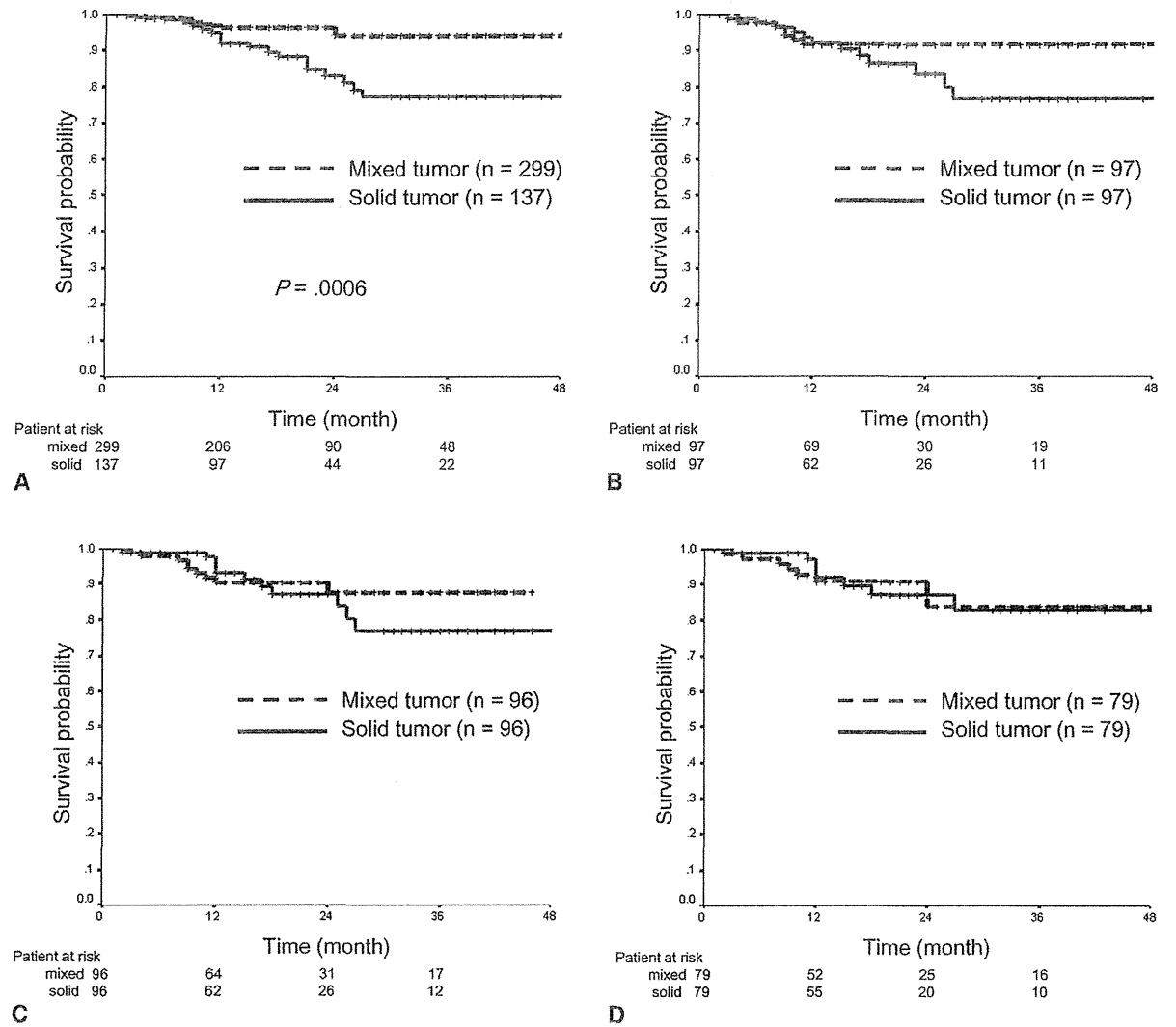

FIGURE 1. DFS curves of patients according to tumor type on HRCT. A, In all cohort patients, 2-year DFS of 94.2% (mean DFS of 47 months; 95% confidence interval [CI], 46-48 months) and 83.1% (mean DFS of 42 months; 95% CI, 39-45 months) were identified for mixed and solid tumors, respectively ($P = .0006$). 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

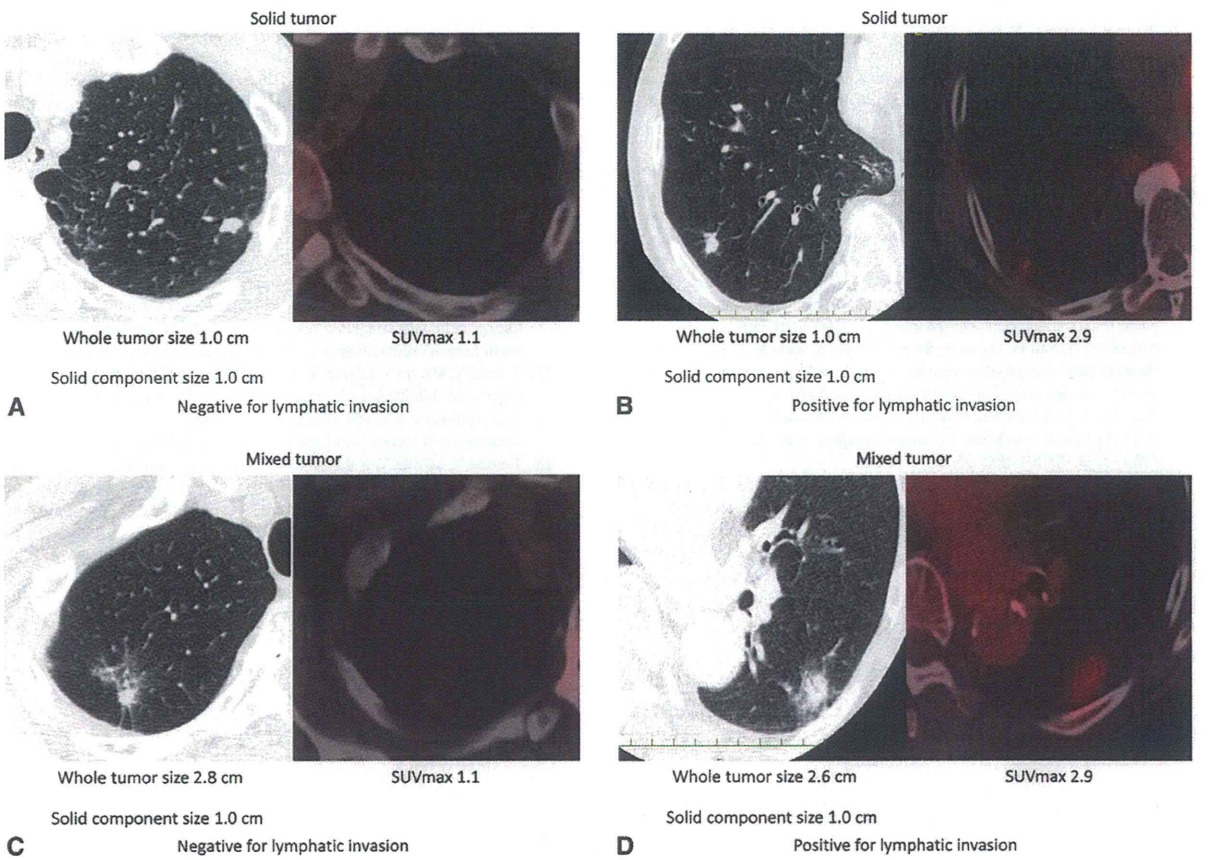

FIGURE 2. Examples of solid and mixed tumors on HRCT. A, Whole tumor size = solid component size: 1.0 cm, SUVmax: 1.1. This solid tumor was negative for lymphatic invasion. B, Whole tumor size = solid component size: 1.0 cm, SUVmax: 2.9. This solid tumor was positive for lymphatic invasion. C, Whole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

References

1. Okada M, Koike T, Higashiyama M, Yamato Y, Kodama K, Tsubota N. Radical sublobar resection for small-sized non-small cell lung cancer: a multicenter study. *J Thorac Cardiovasc Surg.* 2006;132:769-75.
2. Nakayama H, Yamada K, Saito H, Oshita F, Ito H, Kameda Y, et al. Sublobar resection for patients with peripheral small adenocarcinomas of the lung: surgical outcome is associated with features on computed tomographic imaging. *Ann Thorac Surg.* 2007;84:1675-9.
3. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med.* 2011;365:395-409.
4. Nakata M, Saeki H, Takata I, Segawa Y, Mogami H, Mandai K, et al. Focal ground-glass opacity detected by low-dose helical CT. *Chest.* 2002;121:1464-7.
5. Jang HJ, Lee KS, Kwon OJ, Rhee CH, Shim YM, Han J. Bronchioloalveolar carcinoma: focal area of ground-glass attenuation at thin-section CT as an early sign. *Radiology.* 1996;199:485-8.

6. Tsutani Y, Miyata Y, Nakayama H, Okumura S, Adachi S, Yoshimura M, et al. Prognostic significance of using solid versus whole tumor size on high-resolution computed tomography for predicting the pathological malignant grade of tumors in clinical stage IA lung adenocarcinoma: a multicenter study. *J Thorac Cardiovasc Surg*. 2012;143:607-12.
7. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. International Association for the Study of Lung Cancer International Staging Committee; Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of Malignant Tumours. *J Thorac Oncol*. 2007;2:706-14.
8. Suzuki K, Asamura H, Kusumoto M, Kondo H, Tsuchiya R. "Early" peripheral lung cancer: prognostic significance of ground glass opacity on thin-section computed tomographic scan. *Ann Thorac Surg*. 2002;74:1635-9.
9. Nakamura H, Saji H, Ogata A, Saijo T, Okada S, Kato H. Lung cancer patients showing pure ground-glass opacity on computed tomography are good candidates for wedge resection. *Lung Cancer*. 2004;44:61-8.
10. Delbeke D, Coleman RE, Guiberteau MJ, Brown ML, Royal HD, Siegel BA, et al. Procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0. *J Nucl Med*. 2006;47:885-95.
11. Nakayama H, Okumura S, Daisaki H, Kato Y, Uehara H, Adachi S, et al. Value of integrated positron emission tomography revised using a phantom study to evaluate malignancy grade of lung adenocarcinoma. *Cancer*. 2010;116:3170-7.
12. Okada M, Nakayama H, Okumura S, Daisaki H, Adachi S, Yoshimura M, et al. Multicenter analysis of high-resolution computed tomography and positron emission tomography/computed tomography findings to choose therapeutic strategies for clinical stage IA lung adenocarcinoma. *J Thorac Cardiovasc Surg*. 2011;141:1384-91.
13. Inoue M, Minami M, Sawabata N, Utsumi T, Kadota Y, Shigemura N, et al. Clinical outcome of resected solid-type small-sized c-stage IA non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2010;37:1445-9.
14. Suzuki K, Kusumoto M, Watanabe S, Tsuchiya R, Asamura H. Radiologic classification of small adenocarcinoma of the lung: radiologic-pathologic correlation and its prognostic impact. *Ann Thorac Surg*. 2006;81:413-9.
15. Cerfolio RJ, Bryant AS, Ohja B, Bartolucci AA. The maximum standardized uptake values on positron emission tomography of a non-small cell lung cancer predict stage, recurrence, and survival. *J Thorac Cardiovasc Surg*. 2005;130:151-9.
16. Okada M, Tauchi S, Iwanaga K, Mimura T, Kitamura Y, Watanabe H, et al. Associations among bronchioloalveolar carcinoma components, positron emission tomographic and computed tomographic findings, and malignant behavior in small lung adenocarcinomas. *J Thorac Cardiovasc Surg*. 2007;133:1448-54.
17. Tsutani Y, Miyata Y, Misumi K, Ikeda T, Mimura T, Hihara J, et al. Difference in prognostic significance of maximum standardized uptake value on [18F]-fluoro-2-deoxyglucose positron emission tomography between adenocarcinoma and squamous cell carcinoma of the lung. *Jpn J Clin Oncol*. 2011;41:890-6.
18. Tsutani Y, Miyata Y, Nakayama H, Okumura S, Adachi S, Yoshimura M, et al. Prediction of pathological node-negative clinical stage IA lung adenocarcinoma for optimal candidates undergoing sublobar resection. *J Thorac Cardiovasc Surg*. 2012;144:1365-71.
19. Fischer B, Lassen U, Mortensen J, Larsen S, Loft A, Bertelsen A, et al. Preoperative staging of lung cancer with combined PET-CT. *N Engl J Med*. 2009;361:32-9.

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Clinical Trial Note

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

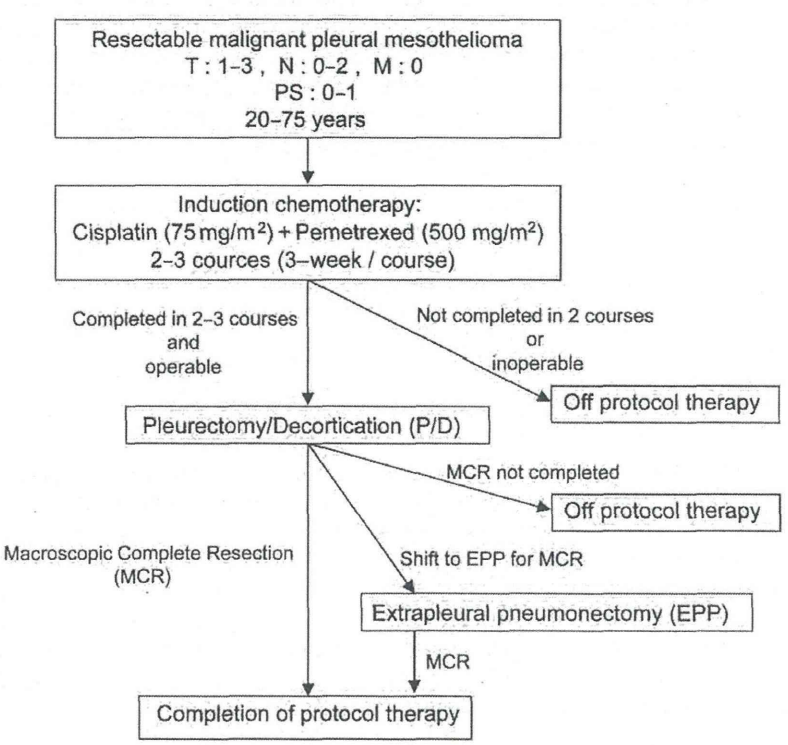

Figure 1. Flow chart of the study.

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.

References

1. Nakano T. Current therapies for malignant pleural mesothelioma. *Environ Health Prev Med* 2008;13:75–83.
2. Murayama T, Takahashi K, Natori Y, Kurumatani N. Estimation of future mortality from pleural malignant mesothelioma in Japan based on an age-cohort model. *Am J Ind Med* 2006;49:1–7.
3. Hasegawa S, Tanaka F. Malignant mesothelioma: current status and perspective in Japan and the world. *Gen Thorac Cardiovasc Surg* 2008;56:317–23.
4. Campbell NP, Kindler HL. Update on malignant pleural mesothelioma. *Semin Respir Crit Care Med* 2011;32:102–10.
5. Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. *J Thorac Cardiovasc Surg* 2008;135:620–26, 626 e621–623.
6. Okada M, Mimura T, Ohbayashi C, Sakuma T, Soejima T, Tsubota N. Radical surgery for malignant pleural mesothelioma: results and prognosis. *Interact Cardiovasc Thorac Surg* 2008;7:102–6.
7. Luckraz H, Rahman M, Patel N, Szafranek A, Gibbs AR, Butchart EG. Three decades of experience in the surgical multi-modality management of pleural mesothelioma. *Eur J Cardiothorac Surg* 2010;37:552–6.
8. Lang-Lazdunski L, Bille A, Lal R, et al. Pleurectomy/decortication is superior to extrapleural pneumonectomy in the multimodality management of patients with malignant pleural mesothelioma. *J Thorac Oncol* 2012;7:737–43.
9. Rena O, Casadio C. Extrapleural pneumonectomy for early stage malignant pleural mesothelioma: An harmful procedure. *Lung cancer* 2012;77:151–5.
10. Krug LM, Pass HI, Rusch VW, et al. Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. *J Clin Oncol* 2009;27:3007–13.
11. de Perrot M, Feld R, Cho BC, et al. Trimodality therapy with induction chemotherapy followed by extrapleural pneumonectomy and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. *J Clin Oncol* 2009;27:1413–8.
12. Van Schil PE, Baas P, Gaafar R, et al. Trimodality therapy for malignant pleural mesothelioma: results from an EORTC phase II multicentre trial. *Eur Respir J* 2010;36:1362–9.
13. Weder W, Kestenholz P, Taverna C, et al. Neoadjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma. *J Clin Oncol* 2004;22:3451–7.
14. Flores RM, Krug LM, Rosenzweig KE, et al. Induction chemotherapy, extrapleural pneumonectomy, and postoperative high-dose radiotherapy for locally advanced malignant pleural mesothelioma: a phase II trial. *J Thorac Oncol* 2006;1:289–95.
15. Tsutani Y, Takuwa T, Miyata Y, et al. Prognostic significance of metabolic response by positron emission tomography after neoadjuvant chemotherapy for resectable malignant pleural mesothelioma. *Ann Oncol* 2012;0:1–6.
16. Sugarbaker DJ. Macroscopic complete resection: the goal of primary surgery in multimodality therapy for pleural mesothelioma. *J Thorac Oncol* 2006;1:175–6.
17. Rice D, Rusch VW, Pass H, et al. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma. A consensus report of the international association for the study of lung cancer international staging committee and the international mesothelioma interest group. *J thorac oncol* 2011;6:1304–12.
18. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. http://evs.nci.nih.gov/ftp1/CTCAE/About.html
19. Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Ann Oncol* 2004; 15:257–60.
20. Sugarbaker DJ, Mentzer SJ, Strauss G. Extrapleural pneumonectomy in the treatment of malignant pleural mesothelioma. *Ann Thorac Surg* 1992;54:941–6.