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

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

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

ACKNOWLEDGMENT We thank Ms. Mayo Yamamoto for assistance in preparation of the manuscript. This study was supported by "The Special Coordination Funds for Promoting Science and Technology from the Japanese Ministry of Education, Culture, Sports, Science, and Technology," "Grants-in-Aid for Scientific Research (KAKENHI B 24390335) from the Japan Society for the Promotion of Science (JSPS)," and "UOEH Grant for Advanced Research (H24-1) from University of Occupational and Educational Health, Japan."

APPENDIX

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

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

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

ECOG Eastern Cooperative Oncology Group

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

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

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

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

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

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

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

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

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

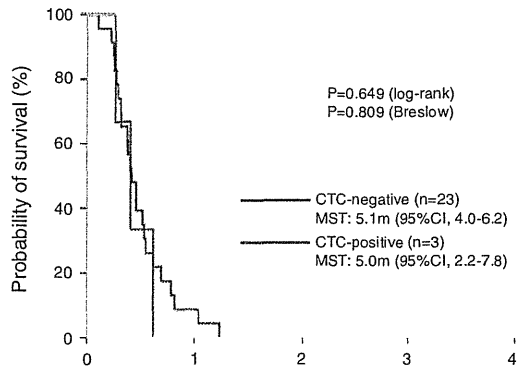

FIG. 5 Survival curves according to CTC count in nonepithelioid-type MPM patients

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

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

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

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

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

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Disclosures: Authors have nothing to disclose with regard to commercial support.

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J Thorac Cardiovasc Surg 2013;145:909-10
0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2013.01.039

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

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

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

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

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

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

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

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

Key Words: TNM classification, NSCLC, visceral pleural invasion

(*J Thorac Oncol.* 2013;8:606-611)

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

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

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Disclosure: The authors declare no conflicts of interest.

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ISSN: 1556-0864/13/0805-0606

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

PATIENTS AND METHODS

Patient Cohort

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

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

Statistical Analysis

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

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

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

RESULTS

Patient Characteristics and Visceral Pleural Invasion

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

Survival Differences

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

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

TABLE 1. Patient Characteristics

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

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

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

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

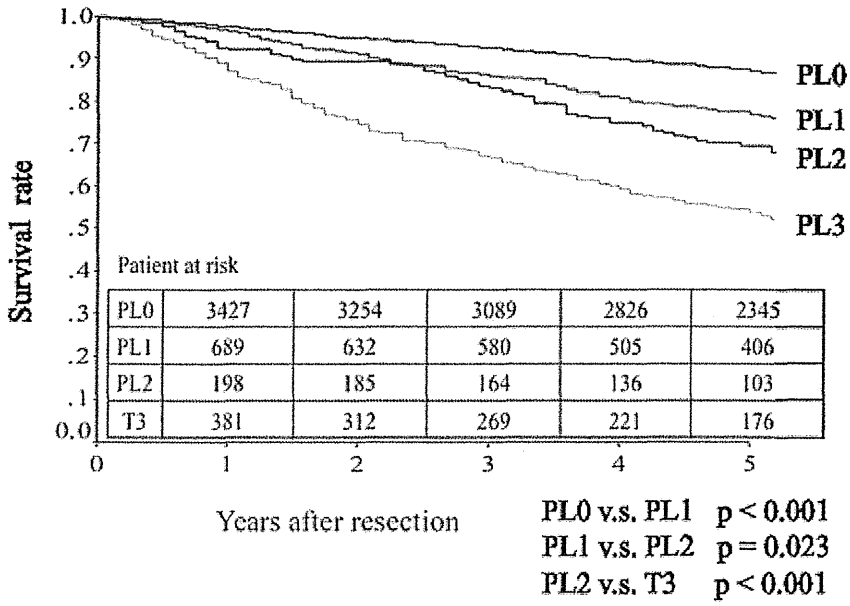

FIGURE 1. Overall survival curves of PL0, PL1, PL2, and T3 patients.

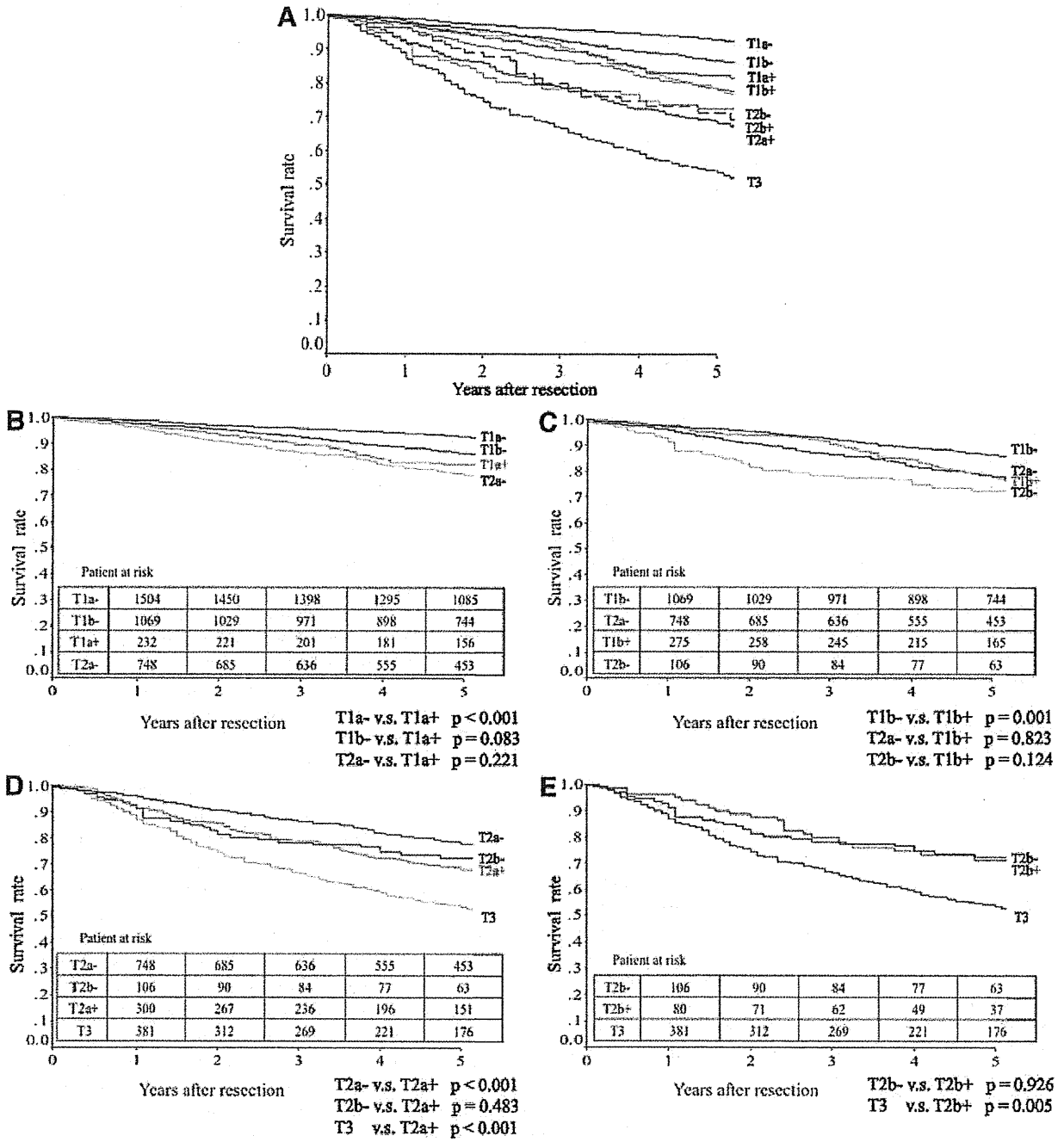

FIGURE 2. (*A*) Survival curves stratified by T stage and VPI status. (*B*) Survival curves of T1a/VPI–, T1b/VPI–, T2a/VPI–, and T1a/VPI+. (*C*) Survival curves of T1b/VPI–, T2a/VPI–, T2b/VPI–, and T1b/VPI+. (*D*) Survival curves of T2a/VPI–, T2b/VPI–, T2b/VPI–, and T2a/VPI+.(*E*) Survival curves of T2b/VPI–, T3, and T2b/VPI+.

tumors with VPI and T2a tumors without VPI ($p = 0.823$) or T2b tumors without VPI ($p = 0.124$).

Figure 2*D* shows the survival impact of VPI on T2a tumors. T2a tumors with VPI had a significantly poorer prognosis than T2a tumors without VPI ($p < 0.001$). There were no significant survival differences between T2a tumors with VPI and T2b tumors without VPI ($p = 0.483$). T2a tumors with VPI had a significantly better prognosis than T3 tumors ($p < 0.001$).

Figure 2*E* shows the survival impact of VPI on T2b tumors. There were no significant survival differences between T2b tumors with VPI and T2b tumors without VPI ($p = 0.926$). T2b tumors with VPI had a significantly better prognosis than T3 tumors ($p = 0.005$).

DISCUSSION

VPI is known to be a poor prognostic factor of NSCLC patients and is defined as a factor to upgrade T1a/T1b tumors to T2a in the 7th Edition of the TNM Classification for Lung and Pleural Tumours.[11,12,14] Travis et al.[13,17,18] recommend the use of elastic stains when invasion beyond the elastic layer is not clear on evaluation of HE sections. Although the Japan Lung Cancer Society also recommends using not only HE staining, but also elastic staining such as Victoria-blue van Gieson staining in VPI evaluation, the JJCLCR did not collect data regarding staining or how extensively VPI was evaluated in each participating institution. This is a major limitation of the present study.

In the present study, PL1 patients had a significantly poorer prognosis than PL0 patients, consistent with many previous reports.[1-10] PL2 patients had a significantly poorer prognosis than PL1 patients. The survival difference between PL1 and PL2 patients remains controversial. Kawase et al.[10] analyzed a cohort of more than 2700 patients, using the current VPI definition and elastic staining in all cases for VPI diagnosis, and reported no survival differences between PL1 and PL2 patients. Moreover, several other researchers have reported similar results.[2,6,9] In contrast, Sakakura et al.[4] reported significant differences in survival between PL1 and PL2 patients, but they did not describe whether or not they used elastic stains in diagnosing VPI status. In the data of the JJCLCR registry, it is not clear in what portion of the accumulated cases elastic staining was employed, and there remains some uncertainty regarding the determination of pleura invasion. Some PL0 patients might have been miscategorized as PL1 without the use of elastic staining, which may have led to the significant survival difference observed between PL1 and PL2 patients. To conclude whether or not a difference between PL1 and PL2 survival is valid, it is necessary to study more patients with VPI diagnoses made with the help of elastic staining.

To analyze the prognostic impact of VPI on T-status classification in the current cohort, we defined VPI to include PL1 and PL2 patients, as defined by the 7th edition of the TNM Classification for Lung and Pleural Tumours. T1a with VPI had a significantly poorer prognosis than T1a without VPI, but there were no significant survival differences between T1a with VPI and T1b without VPI, or between T1a with VPI and T2a without VPI. To summarize, T1a with VPI had prognosis similar to that of T1b/T2a without VPI, which suggests it is credible to upgrade T1a with VPI to T2a.

T1b with VPI had a significantly poorer prognosis than T1b without VPI, but there were no significant survival differences between T1b with VPI and T2a without VPI or between T1b with VPI and T2b without VPI. To summarize, T1b with VPI had a similar prognosis to T2a/T2b without VPI, which suggests it is reasonable to upgrade T1b with VPI to T2a, as described in the 7th edition of the TNM Classification for lung cancer.[11,12]

The most significant information of the present study is the outcome of T2a with VPI. T2a with VPI had a significantly poorer prognosis than T2a without VPI. There were no significant survival differences between T2a with VPI and T2b without VPI. T2a with VPI had a significantly better prognosis than T3. To summarize, T2a with VPI had a similar prognosis to T2b without VPI, which suggests T2a with VPI should be upgraded to T2b.

TABLE 2. T-Classification Comparison

Tumor Diameter, cm	VPI Ctatus	7th Edition T-Classification	Our Proposal
<2	−	T1a	T1a
<2	+	T2a	T2a (or T1b)
2.1–3	−	T1b	T1b
2.1–3	+	T2a	T2a
3.1–5	−	T2a	T2a
3.1–5	+	T2a	T2b
5.1–7	−	T2b	T2b
5.1–7	+	T2b	T2b

VPI− = PL0, VPI+ = PL1 or PL2.
VPI, visceral pleural invasion.

In the current cohort, there were no significant survival differences between T2b with VPI and T2b without VPI. T2b with VPI had a significantly better prognosis than T3. To summarize, T2b with VPI had a prognosis similar to that of T2b without VPI, which suggests there is no need to upgrade T2b with VPI. These suggestions are summarized in Table 2, and they include some differences from the conclusions of previous publications.[2,8,10]

A major limitation of the current study is that we do not know how thoroughly VPI was evaluated including elastic staining, in each participating institution. The differences observed may have been attributable to misdiagnoses of VPI status due to the lack of elastic staining use. However, the recommendation of the 7th edition of the TNM classification, that is, to upgrade T-classification according to VPI status, was determined on the basis of the results of some retrospective studies of small cohorts, in contrast to the large number cohort accumulated by the IASLC Lung Cancer Project. Moreover, the IASLC Lung Cancer Project also lacks detailed information on VPI status evaluation methodology. Therefore, we consider that a worldwide large-scale study that is limited to patients whose VPI status is diagnosed using elastic staining is necessary to determine the true impact on survival of pleural invasion and VPI.

In conclusion, in addition to the current TNM Classification recommendations—to upgrade tumors of 3 cm or less with VPI to T2a—tumors greater than 3 cm and 5 cm or less with VPI should be upgraded to T2b. However, more detailed further research is necessary for the next edition of the TNM classification for lung and pleural tumours, using a large-scale database with VPI status diagnosed using elastic staining.

ACKNOWLEDGMENTS

Supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare, Japan.

The authors thank Roderick J. Turner and Professor J. Patrick Barron, chairman of the Department of International Medical Communications at Tokyo Medical University, for their editorial review of this manuscript. The authors also thank Dr. Kanji Nagai, MD, PhD, of the Division of Thoracic Oncology at the National Cancer Center Hospital East, Kashiwa, Chiba, Japan, for his scientific advice.

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European Journal of Cardio-Thoracic Surgery 43 (2013) 795–799
doi:10.1093/ejcts/ezs419 Advance Access publication 24 July 2012

ORIGINAL ARTICLE

Pulmonary metastasectomy for osteogenic and soft tissue sarcoma: who really benefits from surgical treatment?

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Received 12 April 2012; received in revised form 2 June 2012; accepted 8 June 2012

Abstract

OBJECTIVES: Surgical resection is widely accepted as a beneficial treatment of pulmonary metastases originating from osteogenic and soft tissue sarcomas despite adequate validation. The factors associated with the selection of patients who receive pulmonary metastasectomy (PM) are controversial and not well known. In this study, we aimed to identify the prognostic factors associated with survival after treatment with PM and to disclose the candidates who profit from PM being performed on patients with osteogenic and soft tissue sarcomas.

METHODS: We retrospectively reviewed the variables and survival outcomes in 52 consecutive patients who underwent PM to treat lung metastases originating from osteogenic and soft tissue malignancies from April 1996 to January 2011. Prognostic factors associated with overall survival after the first PM were evaluated using univariate and multivariate analyses.

RESULTS: Fifty-eight PM procedures were performed in 52 patients as the first PM including 6 bilateral diseases. Wedge resection was the most frequently performed PM procedure (84%), and video-assisted thoracic surgery was introduced in 34 (59%). The median follow-up of the patients was 33 months and the 5-year survival rate after the first PM was 50.9%. Forty-eight (92%) patients underwent complete resection during the first PM. Thirty-three patients (62%) experienced relapse after the first PM. Among those patients, 20 received redo surgeries for pulmonary relapse, and the 5-year survival rate in this group was 49.7%. According to univariate analyses, the use of complete resection, the number of metastatic nodules (one or two) and the length of the disease-free interval prior to the first PM were each found to be significant favourable factors. According to a multivariate analysis, the use of complete resection and the number of metastatic nodules were both found to be independent prognostic factors associated with overall survival. Although our cohort included 15 patients with poor prognostic factors (29%), 5 patients who underwent redo surgery survived >22 months.

CONCLUSIONS: The survival of those patients with one or two pulmonary nodules and those who underwent complete resection was favourable following the treatment of osteogenic and soft tissue sarcomas with PM. Redo surgery may also provide some survival benefit in patients with poor prognostic factors.

Keywords: Pulmonary metastases • Pulmonary metastasectomy • Osteosarcoma • Soft tissue sarcoma

INTRODUCTION

The lungs are one of the most common organs targeted by metastatic malignancies. It is widely believed that malignant diseases with pulmonary metastases are so advanced that the prognoses of patients are unfavourable. In cases of orthopaedic sarcoma, especially those originating in the extremities, it has been reported that ~20% relapse in the lungs [1, 2]. Patients with osteogenic and soft tissue sarcomas sometimes develop metastatic nodules in peripheral lung areas, which cannot be sufficiently treated with therapies other than surgical resection. Because of surgical accessibility concerns and drug-resistant characteristics in the selected population, pulmonary metastasectomy (PM) has come to be accepted as a potentially effective treatment.

Although a number of retrospective analyses have reported the outcomes and efficacy of PM, the true benefits of this treatment have not been disclosed due to the heterogeneity of the disease. Others have reported 5-year survival rates of 15–52% and have suggested that the number of nodules, the length of the disease-free interval (DFI) prior to PM, the histology of the primary tumour and the size of the pulmonary nodule are each prognostic factors associated with survival outcomes [3–5]. Controversies still remain among the reports regarding these prognostic factors. In addition, we have acknowledged that ~40% of patients who underwent PM to treat osteogenic and soft tissue sarcomas experienced relapses in the lungs. Treatment with repeated PM has also recently been introduced without an adequate investigation of its efficacy.

We review here our experience with PMs performed for osteogenic and soft tissue sarcomas and aim to investigate the prognostic factors associated with the selection of patients.

PATIENTS AND METHODS

Patients

From April 1996 to January 2011, 52 consecutive patients underwent surgical resection at Nagoya University Hospital to treat pulmonary metastases originating from orthopaedic sarcomas. In all patients, the primary tumours were pathologically diagnosed prior to pulmonary resection. However, preoperative diagnoses of the pulmonary nodules were made based on the radiological findings of chest computed tomography (CT).

Whether or not surgery was deemed to be indicated was determined based on the background, respiratory function, the length of the DFI after treatment of the primary site, number of pulmonary nodules and location of the tumour in the lungs of each patient. In all 52 patients, the primary and distant sites, except for the lungs, were controlled, and PMs were performed with the intention of completing radical resections.

Investigated variables

The data regarding gender, age, histology and sites of the primary tumours were reviewed as variables for the patient characteristics. Furthermore, the following six clinical variables were investigated for each patient: the length of the pre-PM DFI before the first PM (pre-DFI), the laterality of the lung nodules, the type of PM procedure, the number of metastatic pulmonary nodules, the completeness of PM, the frequency of PM, the length of the post-PM DFI after PM (post-DFI) and the prognosis (survival, recurrence). In the univariate analysis of the number of metastatic pulmonary nodules, the patients were classified into two groups: patients with one or two nodules, and patients with three or more nodules.

Statistical analyses

The overall survival rate of each patient was measured from the date of the first PM until either death or the last day of the follow-up. The length of the DFI (pre-DFI) was calculated from the day of treatment of the primary tumour to the day of the first PM. Survival curves were created using the Kaplan–Meier method. Univariate analyses were performed using the log-rank test based on the Kaplan–Meier method to assess the prognostic significance of the individual factors. A multivariate analysis was performed on the significant variables of the univariate analyses using the Cox regression hazard model to access the independent prognostic values of the potential factors. These statistical analyses were completed using the SPSS software for Windows (version 12.0; Chicago, IL, USA). In both univariate and multivariate analyses, $P < 0.05$ was considered to be significant.

RESULTS

The characteristics of the 52 patients are shown in Table 1. The majority of the patients were male (65%). The median age of the patients was 41 years. Forty-two percent of the patients were younger than 40 years of age, and only four patients older than 70 years of age were included. The most dominant histological type of primary tumour observed was osteosarcoma (42%), and the remaining half of the patients suffered from soft tissue sarcomas. Most of the patients (85%) had unilateral diseases, and approximately half of the patients (54%) had solitary lung nodules. The maximum number of metastatic nodules occurring in one patient was 10. During surgery, two unexpected pulmonary nodules were found in two cases, and multiple pleural disseminated nodules were disclosed in three cases. Fifty-eight PM procedures were performed in 52 patients as the first PM including six bilateral diseases of one-staged surgery. Wedge resection was the most frequently performed PM procedure (84%). Video-assisted thoracic surgery was introduced in 34 procedures (59%), and the rest were performed through thoracotomy. Complete resection was accomplished in 92% of the patients. On the other hand, PMs were incomplete in four patients. Three were due to unexpected pleural dissemination, and one was due to a positive surgical margin in the bronchus. Postoperative complications were identified in four patients; pneumonia, prolonged air leakage, wound infection and arrhythmia in one each. Thirty-six (69%) of 52 patients received chemotherapy after the first PM, and 49 (94%) experienced chemotherapy during their overall treatment course. The median length of the DFI before the first PM (pre-DFI) was 13.3 months, including one synchronous case.

Table 1: Patient characteristics

Variables	$n = 52$	%
Gender (male/female)	34/18	
Age (year, median/range)	41/7–74	
Histology		
Osteosarcoma	22	42
MFH	7	14
Liposarcoma	6	12
Synovial sarcoma	4	8
Others	13	24
Primary site		
Extremities	37	72
Trunk	15	28
Unilateral	44	85
Number of nodules (1/2/3/4/5/10)	28/9/8/4/2/1	
First PM procedure		
Wedge resection	49	84
Segmentectomy	5	9
Lobectomy or more	4	7
Complete resection	48	92
Pre-DFI (months; median/range)	13.3/0–130	
Recurrence after the first PM	33	62

Of 48 patients who underwent complete resection of the pulmonary metastases, 15 survived to be free of disease after the first PMs. Each of these patients had unilateral diseases with one or two metastatic nodules, and the median survival time (MST) of this group was 50 months. However, 33 patients experienced relapses of the lung metastases. Among these patients, 20 underwent repeated PM for recurrent lung disease. Despite such aggressive surgical treatment, re-recurrence was observed in 13 patients (65%) with short DFI intervals after the first PMs were performed (post-DFI, median: 6.9 months). Thirteen patients did not meet the criteria for repeated PM, including patients with

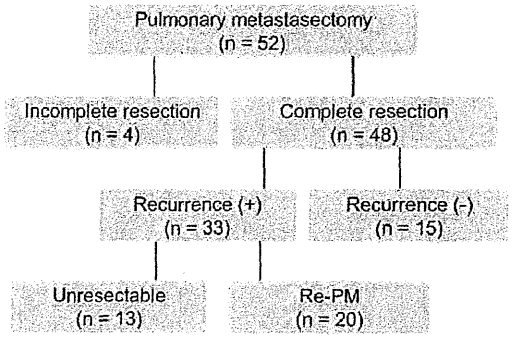

Figure 1: The enrolment and survival outcomes of the patients with pulmonary metastases originating from osteogenic and soft tissue sarcomas.

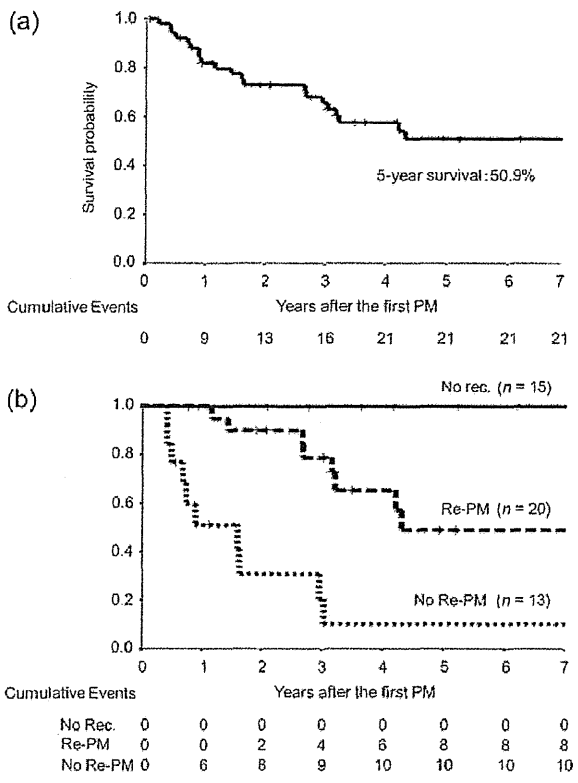

Figure 2: (a) The overall survival of the patients after the first PMs who received surgery to treat lung metastases originating from osteogenic and soft tissue sarcomas. (b) The overall survival curves according to the frequency with which PM was performed. No rec.: no recurrence; Re-PM: repeated PM.

three or more metastatic nodules and shorter pre-DFI (median: 9.7 months) at the first PMs (Fig. 1). Redo PMs were not performed for these patients due to extrathoracic recurrence in four, multiple pulmonary metastases in four, pleural dissemination in two, intrathoracic recurrence involving the subclavian vessels in one, and hilar lymph node metastasis in one. One patient refused redo surgery for her metastatic pulmonary disease.

The MST and 5-year survival rate of all 52 patients was 33.3 months and 50.9%, respectively (Fig. 2a). The MST and 5-year survival rate of the 20 patients who underwent repeated PM was 38.3 months and 49.7%, respectively, while those of the 13 patients who did not undergo repeated PM was 8.7 months and 10.3%, respectively (Fig. 2b).

The univariate analyses demonstrated that the number of metastatic nodules, the length of the pre-DFI and the use of complete resection were each significant prognostic factors associated with the overall survival after the first PMs were performed (Table 2). A multivariate analysis showed that the number of metastatic nodules and the completeness of resection were both independent prognostic factors, while the length of the pre-DFI was not significant (Table 3).

In our present population, we identified 15 patients with unfavourable factors. The MST and 5-year survival rate in this group was 11 months and 15.6%, respectively. Although all of these patients experienced recurrences after the first PMs were performed, five patients (33%) who underwent repeated PM achieved longer survival times. We did not identify any trends in characteristics, including histology, history of chemotherapy, length of pre-DFI or length of post-DFS in these patients (data not shown).

DISCUSSION

It is widely accepted that treatment with PM offers a potential cure for patients with metastatic malignancies, despite a lack of validation with prospective studies. The large cohort study conducted by the International Registry of Lung Metastases reported a 5-year survival rate of 36% in patients who underwent complete resection of pulmonary metastases compared with that of 7% in patients who underwent incomplete resection [6]. Regarding PM performed to treat metastases of sarcomatous histology, limited numbers of retrospective studies report beneficial effects of PM or increased patient survival rates. Although others have reported 5-year survival rates of 15–52% in patients selected to received PM and have also identified several prognostic factors, including the use of complete resection of the pulmonary metastases, the length of the DFI prior to PM (pre-DFI), the number of nodules, tumour diameter and the use of redo surgery, controversies remain among these reports [3–5, 7–12]. A report from Massachusetts General Hospital (MGH), which is one of the most recent retrospective studies and included 97 patients, showed that resectability, laterality, the length of the DFI, the number of metastases and the use of redo surgery were important factors in determining whether patients were selected to receive PM [13]. This report documented a 50.1% overall survival rate in carefully selected patients and also commented on the presence of selection bias.

In the present study, we reported that having a small number of nodules, especially fewer than three, and undergoing complete resection, were found to be favourable prognostic factors associated with overall survival in PM patients. Concerning the number of metastatic nodules, some reports have supported our results [3, 11, 14], while others have demonstrated that fewer than two or five nodules predict favourable outcomes [13, 15]. Our cohort included 15 patients who underwent resection of three or more metastatic nodules and who had 5-year survival rates as low as 15.6%. The majority of these patients had short pre-DFI and post-DFI of <12 months, and all of these patients experienced relapse. After conducting statistical analyses and detailed case investigations, we conclude that whether PM is performed should be carefully decided in patients in whom three or more nodules are diagnosed prior to surgery.

Table 2: Univariate analyses of the factors associated with overall survival after PM

Variables	Survival (month)	3-year survival (%)	5-year survival (%)	*P*-value
Gender				
Male	33.3	63.6	50.3	0.99
Female	22.8	70.7	53.0	
Age				
<40	36.4	70.7	50.0	0.94
≥40	35.5	62.5	51.6	
Histology				
Osteosarcoma	38.0	65.2	50.3	0.62
Non-osteosarcoma	32.0	64.7	49.9	
Primary site				
Extremities	41.9	63.1	52.6	0.84
Trunk	13.9	75.7	28.4	
Laterality				
Unilateral	36.4	70.1	53.2	0.28
Bilateral	19.2	38.1	38.1	
Number of nodules				
<2	38.3	78.6	63.1	<0.001
≥3	10.5	31.2	15.6	
PM procedure				
Limited resection	36.4	69.1	51.7	0.45
Lobectomy or more	32.2	40.0	40.0	
Complete resection				
Yes	27.6	70.0	54.2	<0.001
No	6.2	0.0	0.0	
Pre-DFI				
<12 months	17.2	35.8	30.5	0.003
≥12 months	38.3	85.1	65.1	
Redo PM				
Yes	38.3	77.0	53.8	0.34
No	19.2	59.7	49.6	

DFI: disease-free interval; PM: pulmonary metastasectomy.

Table 3: A multivariate analysis of the factors associated with overall survival rates after the first PM

Variables	Hazard ratio	95% CI	*P*-value
Number of nodules	1.16	1.10–2.503	0.016
Pre-DFI	0.997	0.98–1.015	0.759
Complete resection (yes/no)	0.15	0.035–0.596	0.007

DFI: disease-free interval; CI: confident interval.

The completeness of resection is another independent prognostic factor that has been identified by previous reports. Suzuki *et al.* [12] reported that the 5-year survival rate in patients who underwent incomplete resection was 8.3%, and no patients survived 5 years in the report published by Kim *et al.* [13] from MGH. There were no 3-year survivors in our four cases of incomplete resection. Because resectability is a factor confirmed by surgical or postoperative pathological findings, it may not be useful for surgeons to utilize resectability as a prognostic factor to predict a patient's survival preoperatively. However, since an accurate preoperative diagnosis of resectability is not given in some cases even with current diagnostic modalities, our results promote the use of PM in patients with potentially resectable disease.

Several reports have demonstrated the DFI interval between the treatment of the primary tumour and the first PM to be one of the factors predicting a patient's survival outcome [4, 13]. Kim *et al.* [13] have suggested that a DFI exceeding 12 months is an independent prognostic factor. On the other hand, Smith *et al.* and Garcia *et al.* have reported DFI of >25 months in patients with soft tissue sarcomas and >20 months in patients with bone sarcomas, respectively [4, 16]. In the present study, although the survival of patients with pre-DFI of >12 months, who consisted of half of our population, was favourable, this factor did not reach a level of statistical significance due to a lack of power. A larger series study may prove this factor to be significant. Unfortunately, the cut-off values for the pre-DFI interval used to determine whether or not PM should be performed still remain controversial.

Currently, redo surgery is also considered to be an important treatment for achieving longer survival times for PM patients. Several studies have suggested that re-recurrent patients who undergo redo PM have a survival advantage compared with those who undergo single PM [13, 17, 18]. Furthermore, Blackmon *et al.* [19] have demonstrated that survival rates improve in accordance with the frequency with which PM is performed. According to those reports, it is possible that cases of redo surgery include patients with longer DFI, who might have less-aggressive tumours. Although our analysis did not demonstrate a statistically significant impact of redo surgery on the survival of PM patients, five patients who underwent redo surgery survived >22 months despite having unfavourable factors.

Our data showed that undergoing complete resection and having fewer than three metastatic nodules were both independent favourable predictors of overall survival. Although our study included some limitations of patient selection bias and a small series, our results suggest that whether PM is performed in patients with three or more pulmonary nodules should be carefully considered and strong efforts for complete resection should be made. Even if patients who undergo PM to treat osteogenic and soft tissue sarcomas experience relapse in the lungs, aggressively performing redo PM in selected patients may also improve survival.

Conflict of interest: none declared.

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European Journal of Cardio-Thoracic Surgery 43 (2013) 799–800
doi:10.1093/ejcts/ezs448

EDITORIAL COMMENT

Forty years on: pulmonary metastasectomy for sarcoma

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Keywords: Pulmonary metastases • Pulmonary metastasectomy • Osteosarcoma • Soft-tissue sarcoma

We searched the literature for evidence concerning pulmonary metastasectomy for sarcoma. A systematic review includes data on 1357 patients from 18 surgical follow-up studies [1]. The report from Nagoya University in this issue [2] is characteristic of the genre: a 15-year experience is described of a mixed series of 52 consecutive patients with bone or soft-tissue sarcoma. The majority (28 of 52) had a solitary metastasis, and most of the rest had two or three metastases (17 of 52). Overall survival was 51% five years after the first pulmonary metastasectomy.

From the 1970s, rather than being an occasional individualized decision, as it was for other cancers, pulmonary metastasectomy has become an established practice in the care of

European Journal of Cardio-Thoracic Surgery 43 (2013) e92
doi:10.1093/ejcts/ezs627 Advance Access publication 12 December 2012

Solitary fibrous tumour of the mediastinal pleura: the origin detected with three-dimensional computed tomography angiography

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Received 28 August 2012; received in revised form 15 October 2012; accepted 2 November 2012

Keywords: Solitary fibrous tumour of the mediastinal pleura • 3D-CT angiography

We present an intrathoracic mass suspected of originating in the mediastinum on three-dimensional computed tomography (3D-CT) angiography. Although the origin was not determined on CT (Fig. 1), 3D-CT angiography clearly demonstrated the feeding artery (Fig. 2). The vessel was easily identified during operation, and the tumour was diagnosed as a solitary fibrous tumour.

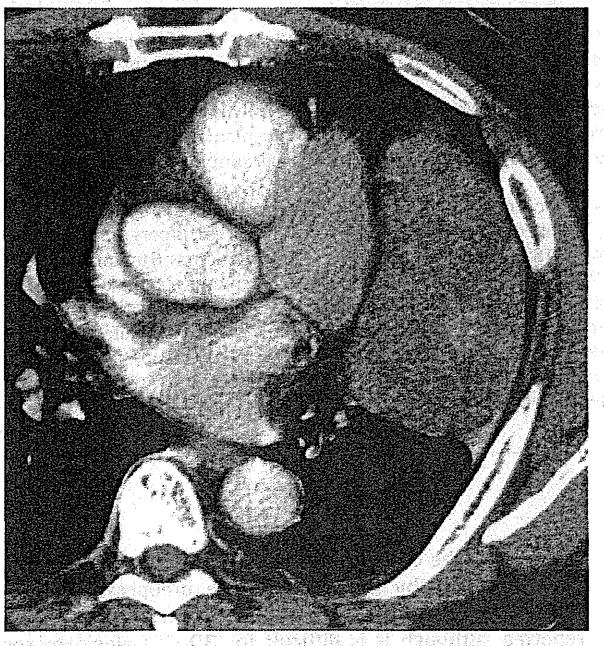

Figure 1: Contrast-enhanced computed tomography demonstrated a well-circumscribed, smooth and inhomogeneous mass in the left thorax.

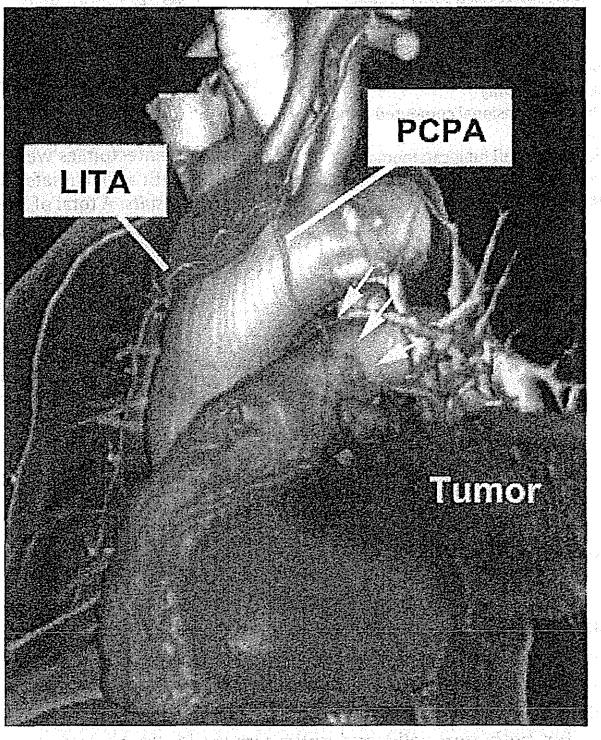

Figure 2: Three-dimensional computed tomography angiography showed that the blood supply to the lesion was continuing from a pericardiacophrenic artery (PCPA), which was a branch of the left internal thoracic artery (LITA), not from the lung or the chest wall.

Lung Cancer 81 (2013) 410–415

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Planning of segmentectomy using three-dimensional computed tomography angiography with a virtual safety margin: Technique and initial experience

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ARTICLE INFO

Article history:
Received 30 December 2012
Received in revised form 12 April 2013
Accepted 3 June 2013

Keywords:
Segmentectomy
Three-dimensional computed tomography (3DCT)
Non-small cell lung carcinoma
Safety margins
Resection planning

ABSTRACT

Objectives: In preoperative segmentectomy simulation for primary lung cancer, it is important to identify the intersegmental pulmonary veins and the relationship between them and the surgical safety margin. We have adopted a method that incorporates a virtual safety margin into three-dimensional computed tomography angiography images in order to plan adequate segmentectomy for lung cancer patients. In this study, we describe the new preoperative planning technique and review cases in which we performed segmentectomy based on its results.
Methods: We reviewed clinical, radiological, and pathological records and selected patients who underwent segmentectomy for a primary lung cancer lesion with a diameter of 2 cm or less. These segmentectomies were planned using preoperative three-dimensional computed tomography angiography with a virtual safety margin.
Results: A total of 17 primary lung cancers in 16 patients (11 male and 5 female, aged 52–82 years) were removed by segmentectomy, planned using the new technique. In 6 of 17 tumors (35%) were non-solid type adenocarcinomas, 3 tumors (18%) were partly solid type adenocarcinomas, 6 tumors (35%) were solid type adenocarcinomas and 2 tumors (12%) were squamous cell carcinomas. Pathological examination revealed no positive surgical margins and no lymph node metastases in any patients.
Conclusions: Three-dimensional computed tomography angiography with a virtual safety margin was able to non-invasively visualize the three-dimensional distances and the relationships between the primary tumor and intersegmental pulmonary veins. It was able to aid in the preoperative planning of a suitable segmentectomy procedure for patients with a primary lung cancer lesion of 2 cm or less in diameter.

1. Introduction

Patients with lung cancer often have cardiopulmonary complications such as chronic obstructive pulmonary disease (COPD), interstitial pneumonia, and ischemic heart disease. Segmentectomy preserves pulmonary function to a greater degree than lobectomy; its use for lung cancer has therefore been increasing for both non-solid and solid tumors [1–3]. In preoperative segmentectomy simulation, it is important to identify the intersegmental pulmonary veins, i.e., those that divide the pulmonary segments [4–6]; the branching patterns of the pulmonary arteries and veins exhibit a great deal of variety from patient to patient [7]. The efficacy of three-dimensional computed tomography angiography (3D-CTA) for the preoperative assessment of both the pulmonary arteries and pulmonary veins has been reported, although it is difficult for 3D-CTA alone to recognize the relationship between the intersegmental veins and the surgical safety margin, currently defined as 2 cm from the primary tumor [4–6,8,9]. We have therefore adopted a method for lung cancer patients that merges a virtual safety margin with 3D-CTA images. We previously reported on 2 patients who underwent segmentectomy, based on this technique, for primary lung cancer [10].

In the present study, we describe the new preoperative planning technique. In addition, we performed a retrospective review of patients who underwent segmentectomy using 3D-CTA with a virtual safety margin to examine the reliability of using this technique to plan for segmentectomy.

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0169-5002/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.lungcan.2013.06.001

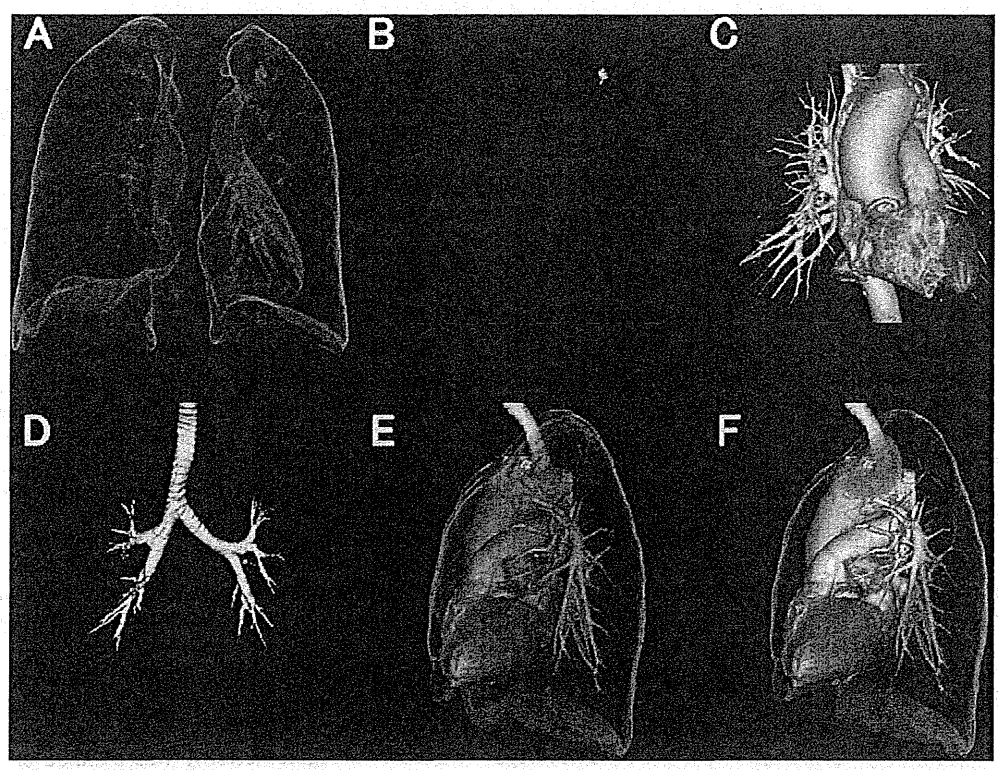

Fig. 1. Construction of three-dimensional computed tomography angiography (3D-CTA) with a virtual safety margin. The lung (A), the primary tumor in the left upper lobe (B), the pulmonary vessels (C), and the trachea and bronchi (D) are separately segmented and color coded by CT value (Hounsfield units). (E) All organs and the primary tumor are merged into the 3D-CTA image. (F) The left upper lobe with the primary tumor is removed from the image to improve visualization of the lobular distribution of bronchi and vessels. Finally, the virtual 3D safety margin (blue sphere) is merged with the 3D-CTA image. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

2. Patients and methods

2.1. Patients

This retrospective study was approved by the institutional review board of our institution with a waiver for informed consent. Since 2011, all preoperative 3D-CTA with a virtual safety margin for segmentectomy at our institution have been determined by a chest radiologist (S.I.) with 18 years of experience reading thoracic CTs. We searched clinical, radiological, and pathological records and selected patients for inclusion who underwent segmentectomy between April 2011 and July 2012 for a primary lung cancer lesion, 2.0 cm or less in diameter. Any lymph node and distant metastases were not detected by preoperative enhanced CT, FDG-PET, and intraoperative lymph node sampling. We reviewed the patients' age, sex, tumor size (maximal diameter), internal opacity on thin-section CT, histological type, and pathological stage based on the Union for International Cancer Control 7 (UICC-7) staging guidelines. Internal opacity was classified into 3 types: solid, partly solid, and non-solid. The solid type was defined as a tumor containing no ground-glass opacity on thin-section CT, the partly solid type was defined as a tumor with a ratio of maximum consolidation diameter to maximum tumor diameter of ≥25%, and the non-solid type was defined as having a ratio of <25% [1].

2.2. Computed tomography

3D-CTA data were obtained using a 64-channel multi-detector row CT (Aquilion 64, Toshiba Medical Systems Corp., Tokyo, Japan). Patients were scanned in the craniocaudal direction with inspiratory apnea. The scanning parameters were set to a voltage of 120 kV with auto-milliamperage (maximum, 450 mA). The gantry rotation time was 0.5 s. The slice thickness and reconstruction interval were 1 mm and 0.8 mm, respectively, using a standard algorithm. Vascular access was obtained using a 20-G needle in the cubital vein. For vessel enhancement, 96 mL of a non-ionic contrast medium (Optiray 320: 320 mg I/mL ioversol, Tyco Healthcare Japan, Inc., Tokyo, Japan; or Iopamiro 370: 370 mg I/mL iopamidol, Bayer HealthCare, Tokyo, Japan) was used at a flow rate of 3.0 mL/s. Ioversol was used in patients with a body weight of ≤60 kg and iopamidol was used in patients with a body weight of >60 kg. The injection of the contrast medium was immediately followed by 24 mL of saline at the same flow rate, using a double-barrel power injector (Dual Shot GX, Nemoto Kyorindo Co., Ltd., Tokyo, Japan). The scan delay was evaluated by an automatic bolus tracking system with a circular region of interest (ROI) localized on the descending aorta at the level of the tracheal bifurcation. Scanning started automatically when the attenuation at the ROI reached 150 Hounsfield units (HUs).

2.3. Three-dimensional computed tomography angiography with a virtual safety margin

The thin-section CT images were transferred to a commercial 3D workstation (Ziostation, Amin, Inc., Tokyo, Japan), where the chest radiologist constructed the thoracic 3D-CTA. The lung, the primary tumor, the pulmonary vessels, and the trachea and bronchi were separately segmented and color coded by CT value, as defined by the tissue's Hounsfield units (Table 1 and Fig. 1). These volume-rendered images were then merged into the 3D-CTA. Next, the lobes containing the primary tumors were removed from the 3D lung images to improve visualization of the lobular distribution of