OPEN

# Supplementary Prognostic Variables for Pleural Mesothelioma

## *A Report from the IASLC Staging Committee*

*Harvey I. Pass, MD,* Dorothy Giroux, MS,† Catherine Kennedy, RM, RA,‡ Enrico Ruffini, MD,§ Ayten K. Cangir,‖ David Rice,¶ Hisao Asamura,# David Waller,** John Edwards,†† Walter Weder,‡‡ Hans Hoffmann,§§ Jan P. van Meerbeeck,‖‖ and Valerie W. Rusch,¶¶ on behalf of the IASLC Staging Committee and Participating Institutions*

**Introduction:** The staging system for malignant pleural mesothelioma is controversial. To revise this system, the International Association for the Study of Lung Cancer Staging Committee developed an international database. This report analyzes prognostic variables in a surgical population, which are supplementary to previously published CORE variables (stage, histology, sex, age, and type of procedure).

**Methods:** Supplementary prognostic variables were studied in three scenarios: (1) all data available, that is, patient pathologically staged and other CORE variables available (2) only clinical staging available along with CORE variables, and (3) only age, sex, histology, and laboratory parameters are known. Survival was analyzed by Kaplan–Meier, prognostic factors by log rank and stepwise Cox regression modeling after elimination of nonsignificant variables. *p* value less than 0.05 was significant.

**Results:** A total of 2141 patients with best tumor, node, metastasis (TNM) stages (pathologic with/without clinical staging) had nonmissing age, sex, histology, and type of surgical procedure. Three prognostic models were defined. *Scenario A (all parameters)*: best pathologic stage, histology, sex, age, type of surgery, adjuvant treatment, white blood cell count (WBC) (≥15.5 or not), and platelets (≥400 k or not) (n = 550). *Scenario B (no surgical staging)*: clinical stage, histology, sex, age, type of surgery, adjuvant treatment, WBC, hemoglobin (<14.6 or not), and platelets (n = 627). *Scenario C (limited data)*: histology, sex, age, WBC, hemoglobin, and platelets (n = 906).

**Conclusion:** Refinement of these models could define not only the appropriate patient preoperatively for best outcomes after cytoreductive surgery but also stratify surgically treated patients after clinical and pathologic staging who do or do not receive adjuvant therapy.

**Key Words:** Mesothelioma, Surgery, Prognosis, Registry, Staging.

(*J Thorac Oncol*. 2014;9: 856–864)

The role of surgery in patients with malignant pleural mesothelioma (MPM) would be less controversial if there was an accurate and minimally invasive method that could forecast outcomes for individuals who are surgical candidates. MPM patients tend to be older individuals who are frequently functionally impaired and may have difficulty with aggressive therapy; however, there is a cadre of MPM patients who, with favorable biology and a multimodal approach, benefit from intense therapy. Factors that predict to a poor overall survival or rapid time to progression could potentially help medical oncologists and surgeons select only those patients who should undergo potentially harmful cytoreductions with the present 4% operative mortality.[1] The best-known clinical prognostic scoring systems for MPM have originated from the European Organisation for Research and Treatment of Cancer (EORTC) and the Cancer and Leukemia Group B,[2,3] and use a combination of biological and clinical factors. Poor performance status (PS), nonepithelioid histology, male sex, low hemoglobin, high platelet count, high white blood cell count, and high lactate dehydrogenase were found to be poor prognostic indicators in mesothelioma, and subsequently validated. Such detailed analyses with sufficient numbers of patients for meaningful assessment have been lacking in the surgically treated population.

In collaboration with the International Mesothelioma Interest Group, the International Staging and Prognostic Factors Committee of the International Association for the Study of Lung Cancer (IASLC) formed a Mesothelioma Domain to improve the current staging system resulting in the

*Department of Cardiothoracic Surgery, NYU Langone Medical Center, New York, New York; †Statistics Department, Cancer Research and Biostatistics, Seattle, Washington; ‡Department of Cardiothoracic Surgery, University of Sydney, Strathfield Private Hospital Campus, Sydney, Australia; §Department of Thoracic Surgery, University of Torino, Ospedale San Giovanni Battista, Torino, Italy; ‖Department of Thoracic Surgery, Ankara University Faculty of Medicine, Ankara, Turkey; ¶Department of Thoracic and Cardiovascular Surgery, M. D. Anderson Cancer Center, Houston, Texas; #Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan; **Department of Thoracic Surgery, Glenfield Hospital, Leicester, United Kingdom; ††Department of Cardiothoracic Surgery, Northern General Hospital, Sheffield, United Kingdom; ‡‡Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland; §§Department of Thoracic Surgery, Thoraxklinik, University of Heidelberg, Heidelberg, Germany; ‖‖Thoracic Oncology, University Hospital, Ghent, Belgium; and ¶¶Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Harvey I. Pass, MD, Department of Cardiothoracic Surgery, NYU Langone Medical Center, 530 First Avenue, 9V, New York, NY 10016. Email: harvey.pass@med.nyu.edu



ISSN: 1556-0864/14/0906-0856

first large, international MPM database, which includes more than 2000 staged patients with MPM diagnosed from 1995 to 2008 (see Supplementary Appendices, Supplementary Digital Content, http://links.lww.com/JTO/A583). As described by Rusch et al.,[4] a set of covariates were identified as predictive of survival in a "CORE" model for this analysis, which included best staging information, age, sex, histology (epithelioid or not), and type of surgical procedure (palliative versus extrapleural pneumonectomy or pleurectomy decortication. This report summarizes an analysis of additional tumor or patient characteristics for their prognostic ability as mandated by the Prognostic Factors Subcommittee of the Mesothelioma Domain. Armed with the CORE model described above, the aim of this study was to analyze potential clinical and laboratory prognostic variables from a surgical and nonsurgical perspective by studying cohorts of patients from the registry with or without known pathologic staging (i.e., relying on clinical tumor, node, metastasis [TNM]) to develop prognostic models.

## MATERIALS AND METHODS

### Population

From January 4, 1995, to August 18, 2009, a total of 3101 patients met the screening criteria for having been diagnosed with MPM after 1995 and were available for follow-up. Of these 3101 patients, 2316 were staged either by pathological findings (pTNM, n = 1976) or by clinical findings (cTNM, n = 1265). Of these 2316 cases with the best possible TNM staging, 2141 had complete data on age, sex histology, and type of surgical procedure, and are cases that form the "CORE" model of predictive factors.

### Definitions for Supplementary Prognostic Variables

The CORE variable demographics for the 2141 subjects are detailed in Table 1. Additional potential prognostic clinical variables for MPM that were available in the database included the use of chemotherapy or radiotherapy at any time (adjuvant therapy), smoking history, history of asbestos exposure, history of weight loss (defined as greater than 5% versus lesser than 5% in the previous 6 months), Eastern Cooperative Oncology Group (ECOG) PS, chest pain, and dyspnea. Smokers included current and former smokers, and ECOG PS ranged from 0 to 3 in the full database but was limited to 0 to 1 in the 2141 patients included in the analysis. For this surgical cohort of patients, 72.2% of patients having either a potentially curative (extrapleural pneumonectomy, pleurectomy decortication, or other) or a palliative surgical procedure (surgical exploration, pleurectomy, or pleurodesis) received adjuvant therapy. Laboratory parameters that were also analyzed included, hemoglobin, white blood cell count, and platelet count. Table 2 documents the number of subjects with clinical and laboratory data for these variables. Missing data for the 2141 patients ranged from 9.7% (use of adjuvant therapy) to 84.4% (history of weight loss).

### Statistical Analysis

Survival was measured from date of pathologic diagnosis to the date of last contact (at which time they were censored) or death attributable to any cause. Median survival was estimated using the Kaplan–Meier regression method. Prognostic groups were assessed by Cox regression analysis of survival, using the SAS system for Windows version 9.2 (SAS Institute Inc., Cary, NC) PHREG method. Significance values from pair-wise comparisons reflect the Wald test; those from joint model effects (e.g., comparing the full model to the null model) reflect the likelihood ratio test. All covariates in regression analyses were modeled categorically using indicator variables, and the threshold for statistical significance was set at a $p$ value of 0.05. Age was classified into three categories, with cutpoints at 50 and 65 years. Covariates that met the criteria for statistical significance by univariate analysis were further evaluated for inclusion in multivariable regression models, using a stepwise algorithm with backward selection.

**TABLE 1.** CORE Variable Demographics (n = 2141)

| | Number | Percentage |
|---|---|---|
| Stage | | |
| I | 242 | 11.3 |
| II | 452 | 21.1 |
| III | 1057 | 49.4 |
| IV | 390 | 18.2 |
| Age | | |
| <50 | 324 | 15.1 |
| 50 to <65 | 1064 | 49.7 |
| 65 or older | 753 | 35.2 |
| Sex | | |
| Female | 419 | 19.6 |
| Male | 1722 | 80.4 |
| Histology | | |
| Epithelioid | 1544 | 72.1 |
| Nonepithelioid | 597 | 27.9 |
| Surgical procedure | | |
| Palliative | 671 | 31.3 |
| EPP | 1173 | 54.8 |
| PD | 297 | 13.9 |

EPP, extrapleural pneumonectomy; PD, pleurectomy/decortication.

## RESULTS

### CORE Model for Survival

Table 3 shows the hazard ratios and $p$ values for comparisons based on a Cox regression model of the CORE survival model as of March 2013 for all 2141 patients without missing data. All comparisons shown in the table are significant, except stage II versus stage I and the oldest versus the middle age groups (not shown). This model can be further consolidated into two categories for age (≥50 years versus younger).

### Cox Regression Models: Pathological Staging Included

Table 4 shows the results of the Cox regression models including each proposed covariate in a univariate model and each proposed covariate in addition to the covariates of best

 

**TABLE 2.** Supplementary Variables Used for Modeling Survival

| | Number | |
|---|---|---|
| Clinical parameters | 2141 | 100.0% |
| Adjuvant therapy | | |
| Surgery alone | 388 | 18.1% |
| Surgery ± chemo or RT | 1546 | 72.2% |
| No data | 207 | 9.7% |
| Smoking history | | |
| Nonsmoker | 350 | 16.3% |
| Smoker | 452 | 21.1% |
| No data | 1339 | 62.5% |
| History of asbestos exposure | | |
| No | 463 | 21.6% |
| Yes/probable exposure | 1259 | 58.8% |
| No data | 419 | 19.6% |
| History of weight loss | | |
| No | 254 | 11.9% |
| Weight loss | 79 | 3.7% |
| No data | 1808 | 84.4% |
| ECOG PS | | |
| PS 0 | 283 | 13.2% |
| PS 1 | 441 | 20.6% |
| No data | 1417 | 66.2% |
| Chest pain | | |
| No | 593 | 27.7% |
| Chest pain | 490 | 22.9% |
| No data | 1058 | 49.4% |
| Dyspnea | | |
| No | 469 | 21.9% |
| Dyspnea | 751 | 35.1% |
| No data | 921 | 43.0% |
| Laboratory parameters | | |
| Hemoglobin, g/dl | | |
| Total | 2141 | 100.0% |
| No data | 953 | 44.5% |
| Hemoglobin <14.6 (low) | 954 | 44.6% |
| Hemoglobin ≤14.6 (high) | 234 | 10.9% |
| White blood cell count, $\times 10^3/\mu l$ | | |
| Total | 2141 | 100.0% |
| No data | 1081 | 50.5% |
| WBC ≥15.5 (high) | 30 | 1.4% |
| WBC <15.5 (low) | 1030 | 48.1% |
| Platelet count, $\times 10^3/\mu l$ | | |
| Total | 2141 | 100.0% |
| No data | 676 | 31.6% |
| PLT ≤400 (high) | 364 | 17.0% |
| PLT <400 (low) | 1101 | 51.4% |

RT, radiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; WBC, white blood cell count; PLT, platelet count.

stage (pathological), histology, sex, age, and type of surgery (palliative versus EPP/pleurectomy/decortication). Only the covariates that were independently statistically significant in addition to the CORE model parameters were included in the stepwise Cox regression algorithm. These covariates included adjuvant therapy, asbestos exposure, weight loss, chest pain, hemoglobin, platelets, and white blood cell count (WBC) (Figures 1 and 2). Lack of adjuvant therapy, along with the presence of asbestos exposure, weight loss, and chest pain, as well as low hemoglobin, high platelet count, and high white blood count, was found to be associated with a worse prognosis independent of the CORE variables.

**TABLE 3.** Analysis of Maximum Likelihood Estimates (n = 2141)

| | Hazard Ratio | *p* Value |
|---|---|---|
| Stage | | |
| II vs. I | 1.17 | 0.0953 |
| III vs. I | 1.48 | <0.0001 |
| IV vs. I | 1.86 | <0.0001 |
| Histology | | |
| Other histology vs. epithelial | 1.67 | <0.0001 |
| Sex | | |
| Male vs. female | 1.27 | 0.0002 |
| Age | | |
| Age 50–64 vs. <50 | 1.26 | 0.0022 |
| Age 65+ vs. <50 | 1.34 | 0.0002 |
| Treatment | | |
| Palliative vs. curative intent | 1.70 | <0.0001 |

Stepwise Cox Regression modeling with backwards selection was performed on a number of models, all of which included combining the CORE model with combinations of the supplementary variables with and without laboratory data. In

**TABLE 4.** Initial Cox Regression Modeling of Supplementary Factors

| | | Univariate Model | | Added to CORE Model | |
|---|---|---|---|---|---|
| **Covariate** | **N** | **HR** | ***p* Value** | **HR** | ***p* Value** |
| No adjuvant Trt (no vs. yes) | 1934 | 1.712 | <0.0001 | 1.551 | <0.0001 |
| Smoking history (yes vs. no) | 802 | 1.173 | 0.0546 | 1.147 | 0.113 |
| Asbestos exposure (yes/prob vs. no) | 1722 | 1.211 | 0.002 | 1.151 | 0.0344 |
| Weight loss (yes vs. no) | 333 | 1.69 | 0.0002 | 1.581 | 0.0016 |
| ECOG PS (1+ vs. 0) | 724 | 1.288 | 0.0046 | 0.935 | 0.2731 |
| Chest pain (yes vs. no) | 1083 | 1.314 | <0.0001 | 1.306 | 0.0001 |
| Dyspnea (yes vs. no) | 1220 | 0.981 | 0.7737 | 0.96 | 0.5445 |
| Serum LDH (continuous) | 474 | 1 | 0.5376 | 1 | 0.3532 |
| Hemoglobin (<14.6 vs. not) | 1188 | 1.297 | 0.0022 | 1.37 | 0.0003 |
| Platelets (≥400 vs. not) | 1465 | 1.602 | <0.0001 | 1.767 | <0.0001 |
| WBC (≥15.5 vs. not) | 1060 | 1.71 | 0.0062 | 1.869 | 0.0016 |

Trt, treatment; Prob, probably; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; HR, hazard ratio; WBC, white blood cell count.

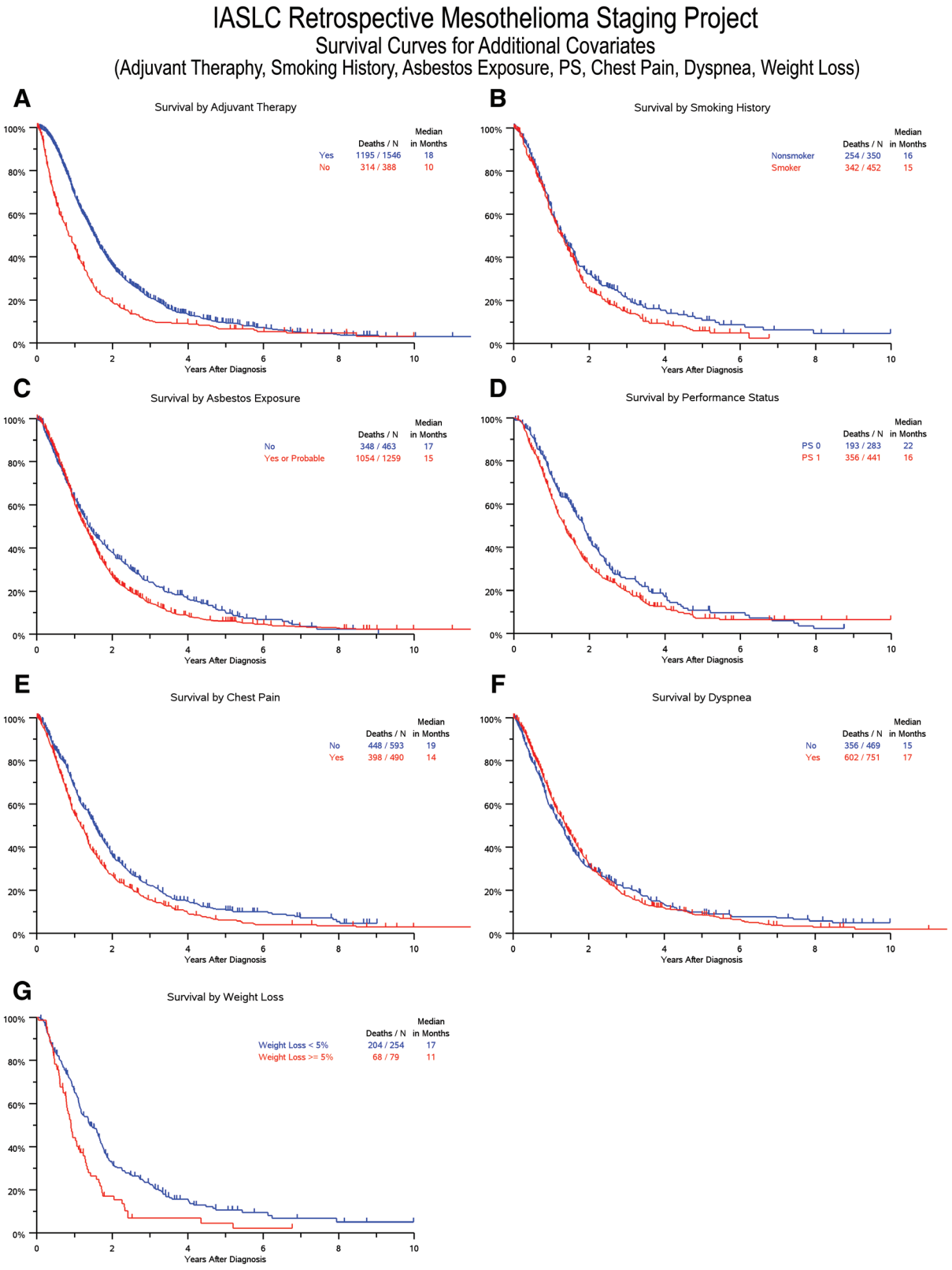


**FIGURE 1.** Kaplan–Meyer survival curves for clinical parameters detailed in Table 4. IASLC, International Association for the Study of Lung Cancer; PS, performance status.

 

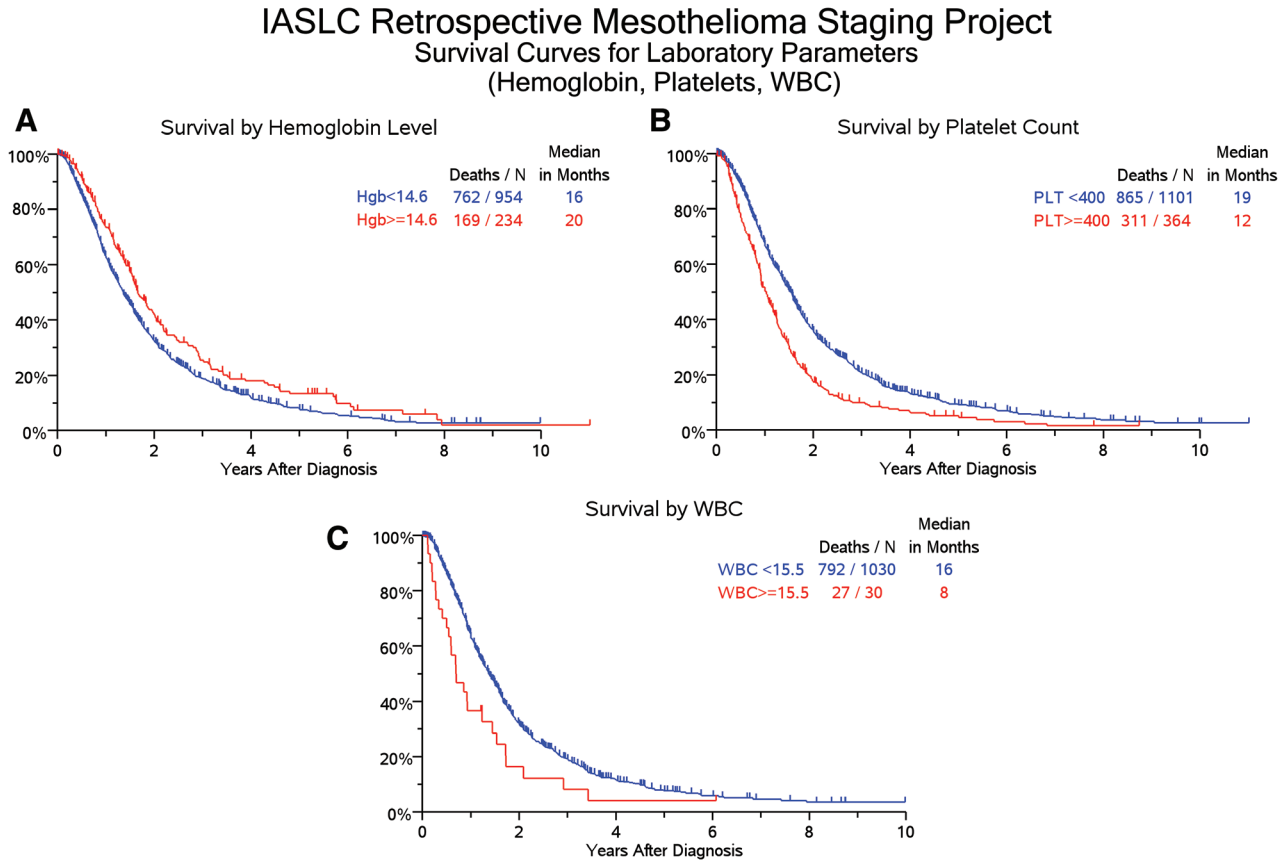


**FIGURE 2.** Kaplan–Meyer survival curves for laboratory parameters detailed in Table 4. IASLC, International Association for the Study of Lung Cancer; WBC, WBC, white blood cell count; Hgb, hemoglobin; PLT, platelet count.

the initial model, all of the parameters were included, and, after this model fit, the covariate with the least significance for predicting outcomes was removed, and this was continued until all the remaining covariates in the model were significant at the 0.05 level. As seen in Table 5, a number of starting models were included, which varied in patient numbers from 268 to 1027.

Because the starting model must have all of the covariates, including the CORE variables, only 268 of the 2141 patients could be evaluated in this way (set 1 plus labs/set 4: only two North American data sets included weight loss). Table 6 reveals that the final model included best stage, histology, sex, type of surgery, adjuvant treatment, weight loss, and WBC.

The most robust model (but compromised because of the exclusion of cases with missing weight loss or asbestos exposure data) for 550 patients was set 5 (set 3 plus labs), which included an evaluation of best stage, histology, sex, age, type of surgery, adjuvant treatment, chest pain, WBC, hemoglobin, and platelets (Table 7).

## Cox Regression Models: Clinical Staging

When *clinical* stage (available in 1265 patients) was substituted in the CORE variables instead of pathologic staging as the "best stage," a final model of 627 patients was similar to that with pathologic staging with the exception that hemoglobin level was also an independent prognostic variable (Table 8).

## Cox Modeling in the Absence of Staging: Presentation Model

To simulate the situation of a potential surgical patient presenting only with a diagnosis of mesothelioma before any staging procedure to evaluate the patient for surgery, the CORE model was adjusted to include only age, histology, and sex. In this case, the impact of adjuvant therapy, type of operation, or staging would be unknown. Of the 2749 individuals with CORE variables of histology, sex, and age, 906 individuals also had laboratory data. The univariate model (presentation model) added to the modified CORE model reveals that weight loss, chest pain, and the laboratory parameters were significant variables (Table 9).

The final model after stepwise backward regression (Table 10) reveals that histologic subtype of MPM, sex, age, platelet count, and white blood cell count was predictive of outcome.

# DISCUSSION

The IASLC Mesothelioma Domain was the first international effort to improve on the staging of this orphan disease by establishing an international retrospective registry

**TABLE 5.** Number of Cases with Addition Prognostic Factors Available by Source

| | | | Set 1 | Set 2 | Set 3 | Set 4 | Set 5 |
|---|---|---|---|---|---|---|---|
| | Labs, WBC, Hemoglobin, Platelets | CORE Variables Only | adj trt, Asbestos Exposure, Weight Loss, Chest Pain | adj trt, Asbestos Exposure, Chest Pain | adj trt, Chest Pain | Set 1 + Labs | Set 3 + Labs |
| NCI/WSU/NYU (USA) | 141 | 184 | 156 | 179 | 183 | 137 | 140 |
| MDACC (USA) | 170 | 173 | 134 | 134 | 167 | 131 | 164 |
| EORTC | 42 | 42 | 0 | 37 | 42 | 0 | 42 |
| JLHWO (JPN) | 0 | 129 | 0 | 124 | 129 | 0 | 0 |
| Ankara (TUR) | 0 | 221 | 0 | 0 | 0 | 0 | 0 |
| Padova (ITA) | 57 | 85 | 0 | 56 | 85 | 0 | 57 |
| IEO (ITA) | 134 | 135 | 0 | 35 | 46 | 0 | 46 |
| Leicester (GBR) | 157 | 177 | 0 | 0 | 0 | 0 | 0 |
| Zurich (CHE) | 106 | 128 | 0 | 128 | 128 | 0 | 106 |
| Toronto (CAN) | 23 | 82 | 0 | 0 | 0 | 0 | 0 |
| Heidelberg (DEU) | 0 | 97 | 0 | 0 | 0 | 0 | 0 |
| MSKCC (USA) | 0 | 514 | 0 | 125 | 142 | 0 | 0 |
| MesoNat (FRA) | 0 | 10 | 0 | 9 | 9 | 0 | 0 |
| Sydney (AUS) | 0 | 67 | 0 | 0 | 0 | 0 | 0 |
| Torino (ITA) | 0 | 97 | 0 | 95 | 96 | 0 | 0 |
| Total | 830 | 2141 | 290 | 922 | 1027 | 268 | 550 |

NCI, National Cancer Institute; WSU, Wayne State University; NYU, New York University; MDACC, M. D. Anderson Cancer Center; EORTC, European Organisation for Research and Treatment of Cancer; JLHWO, Japan Labour, Health, and Welfare Organization Hospitals; IEO, Istituto Europeo di Oncologia; MSKCC, Memorial Sloan Kettering Cancer Center; adj, adjuvant; trt, treatment; WBC, white blood cell count.

examining CORE variables associated with survival after either palliative or after potentially curative surgery. CORE variables that were associated in multivariate analyses to be prognostically important included best stage, age, sex, histology (epithelioid or not), and the type of surgical procedure (palliative versus EPP/progressive disease). The 2141 patients in the present registry represent the largest such collection of surgically treated patients with mesothelioma, in whom all of these CORE variables were recorded.[4]

When the registry was first developed, the registry designers were influenced by the Cancer and Leukemia Group B and the EORTC prognostic indices that were the first to attempt to define additional factors, which included PS, symptoms, and selected laboratory parameters. The EORTC analysis eventually included not only overall survival but also progression-free survival.[5] The clinical factors chosen for the IASLC Mesothelioma Registry supplementary prognostic analyses included the use of chemotherapy at any time (adjuvant therapy), smoking history, history of asbestos exposure, history of weight loss, defined as greater than 5% versus less than 5% in the previous 6 months, ECOG PS, chest pain, and dyspnea. Laboratory parameters included hemoglobin level, platelet count, white blood cell count, and lactate dehydrogenase level before the attempted surgical procedures. The chemotherapy data were standardized neither for the regimen used nor for the timing of the therapy, that is, neoadjuvant

**TABLE 6.** Stepwise Regression Modeling for 268 Patients with All Variables

| | Variable | Hazard Ratio | *p* Value |
|---|---|---|---|
| Stage | II vs. I | 1.52 | 0.2389 |
| | III vs. I | 2.61 | 0.0031 |
| | IV vs. I | 3.60 | 0.0004 |
| Histology | Other histology vs. epithelial | 1.74 | 0.0001 |
| Sex | Male vs. female | 2.30 | <0.0001 |
| Treatment | Palliative vs. curative intent | 2.66 | 0.0002 |
| Adjuvants | Adjuvant treatment: no vs. yes | 1.71 | 0.0008 |
| Weight loss | Yes vs. no | 1.48 | 0.0155 |
| WBC | ≥15.5 vs. <15.5 | 3.77 | 0.0004 |

WBC, white blood cell count.

**TABLE 7.** Final Model of Clinical, Pathologic, and Laboratory Variables (n = 550)

| | Variable | Hazard Ratio | *p* Value |
|---|---|---|---|
| Stage | Pathologic stage II vs. I | 1.48 | 0.0802 |
| | Pathologic stage III vs. I | 2.2 | 0.0002 |
| | Pathologic stage IV vs. I | 2.49 | 0.0001 |
| Histology | Other histology vs. epithelial | 1.8 | <0.0001 |
| Sex | Male vs. female | 1.7 | 0.0006 |
| Age | Age ≥50 vs. younger | 1.61 | 0.012 |
| Treatment | Palliative vs. curative intent | 1.67 | 0.0008 |
| Adjuvant treatment | No vs. yes | 1.7 | 0.0002 |
| Platelets | ≥400 vs. <400 | 1.5 | 0.0004 |
| WBC | ≥15.5 vs. <15.5 | 2.39 | 0.0007 |

WBC, white blood cell count.

 

**TABLE 8.** Final Model, Clinical Staging Only (n = 627)

| | | Hazard Ratio | *p* Value |
|---|---|---|---|
| Clinical stage | Clinical stage II vs. I | 1.43 | 0.0098 |
| | Clinical stage III vs. I | 1.35 | 0.0358 |
| | Clinical stage IV vs. I | 1.57 | 0.0506 |
| Histology | Other histology vs. epithelial | 1.80 | <0.0001 |
| Sex | Male vs. female | 1.72 | 0.0002 |
| Age | Age ≥50 vs. younger | 1.51 | 0.0198 |
| Treatment | Palliative vs. curative intent | 1.36 | 0.0286 |
| Adjuvant treatment | No vs. yes | 1.65 | <0.0001 |
| Hemoglobin | <14.6 vs. ≥14.6 | 1.41 | 0.0051 |
| Platelets | ≥400 vs. <400 | 1.48 | 0.0003 |
| WBC | ≥15.5 vs. <15.5 | 1.69 | 0.0373 |

WBC, white blood cell count.

**TABLE 10.** Final Presentation Model without Staging (n = 906)

| | Variable | Hazard Ratio | *p* Value |
|---|---|---|---|
| Histology | Other histology vs. epithelial | 1.798 | <0.0001 |
| Sex | Male vs. female | 1.535 | 0.0003 |
| Age | <50 vs. older | 1.568 | 0.0011 |
| Platelets | <400 vs. ≥400 | 1.707 | <0.0001 |
| WBC | <15 vs. ≥15 | 1.763 | 0.0059 |

WBC, white blood cell count.

or postoperative. In fact, whether the patients received preoperative or postoperative chemotherapy (or both) could not be ascertained from the data because it was collected, and this can be construed as a weakness of this registry. Moreover, 193 patients had radiation along with surgery without chemotherapy, 608 had chemotherapy along with surgery but no radiation, and 579 surgery patients had both chemotherapy and radiotherapy, and any subanalysis of these cohorts for supplemental prognostic factors did not have enough common elements to make insightful conclusions. The extent of missing data in this first registry is unfortunate but it is hoped that this problem will be minimized in the ongoing prospective registry. For the final analysis, only 252 of the 2141 (12%) individuals, representing data from four North American Institutions had information on all of these supplementary variables in addition to the CORE variables, and stepwise regression modeling revealed that adjuvant therapy use, smoking history, WBC level, and weight loss were prognostically relevant. Indeed, the parameters that were most problematic included smoking history, weight loss, and ECOG PS. Because this was a surgical series of patients, it can be safely assumed that the majority of patients were ECOG 0 or 1, and that PS may not stratify in the models because of its relative homogeneity. Other factors such as the important symptom of chest wall pain, as well as all of the laboratory parameters, were recorded in approximately 50% of the patients with CORE variables. As such, further analyses using as many patients as possible with the remainder of the supplementary variables and laboratory values (n = 550) revealed that adjuvant therapy, WBC count, and platelets were prognostic indicators. Obviously one must consider that such analyses are compromised by the missing data; however, the number of patients in these internationally based, but compromised, analyses compares favorably with all of the studies to date attempting to prognosticate MPM using clinical and laboratory data.

The goal of registries such as this one is to be able to find those prognostic factors that have high fidelity and require minimal cost/invasion of the patient, and that in some combinatorial model would potentially change the treatment algorithm for a mesothelioma patient. Because this is a surgical based registry, there are obvious advantages in developing such models, including the presence of complete pathologic data from the time of the cytoreduction. In real life, however, the decision to operate on a patient with mesothelioma relies on factors apart or potentially complementary to pathologic stage, which is a major portion of the CORE variables in this study. An analysis of the cohort of 906 patients, who had parameters that could be

**TABLE 9.** Cox Regression Modeling: Presentation Model

| | | Univariate Model | | Added to Modified CORE Model[a] | |
|---|---|---|---|---|---|
| **Covariate** | **N** | **HR** | ***p* Value** | **HR** | ***p* Value** |
| Smoking history (yes vs. no) | 881 | 1.173 | 0.0439 | 1.142 | 0.0997 |
| Asbestos exposure (yes/prob vs. no) | 1995 | 1.223 | 0.0006 | 1.104 | 0.1088 |
| Weight loss (yes vs. no) | 378 | 1.840 | <0.0001 | 1.790 | <0.0001 |
| ECOG PS (1+ vs. 0) | 1015 | 0.961 | 0.5651 | 0.891 | 0.1005 |
| Chest pain (yes vs. no) | 1254 | 1.263 | 0.0003 | 1.295 | <0.0001 |
| Dyspnea (yes vs. no) | 1436 | 0.991 | 0.8874 | 0.954 | 0.4470 |
| Serum LDH (continuous) | 547 | 1.000 | 0.4987 | 1.000 | 0.5824 |
| Hemoglobin (<14.6 vs. not) | 1299 | 1.279 | 0.0022 | 1.300 | 0.0012 |
| Platelets (≥400 vs. not) | 1585 | 1.600 | <0.0001 | 1.699 | <0.0001 |
| WBC (≥15.5 vs. not) | 1142 | 1.755 | 0.0029 | 1.755 | 0.0029 |

[a]Age, histology, and sex.
LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; WBC, white blood cell count.

**TABLE 11.** Clinicopathologic Prognostic Studies of MPM

| Year | Author | N | Univariate Predictors | Multivariate Predictors |
|---|---|---|---|---|
| 2013 | Baud | 170 | Asbestos exposure, age, ASA class III vs. ASA classes I and II, nonepithelioid histology, CRP >3 mg/liter, and white cell count >12,000/mm$^3$ | Nonepithelioid histology, age, CRP, WBC >12,000/mm$^3$ |
| 2011 | Nojiri | 314 | Demographic and laboratory parameters | Age >70, nonepithelial, low PS, high WBC, High CRP |
| 2010 | Tanrikulu | 363 | Glucose <40,CRP >50 ↓ survival | KPS, serum LDH, presence of pleural effusion, pleural thickening >1 cm, and PLT >420 k |
| 2010 | Richards | 354 | Stratification of T and N status, epithelial only | N2b vs. N2a nodal status with different hazard ratio |
| 2009 | Francart | 523 | PS >0, stage IV, nonepithelial ↓ PFS | Age, histotype, stage, PS, hgb, WBC |
| 2009 | Yan | 456 | Young age, pleural effusion, epithelial, EPP, PET scan, adjuvant therapy ↑ survival | Epithelial and EPP: ↑ survival |
| 2007 | Flores | 945 | Histology, sex, smoking, asbestos exposure, laterality, surgical resection by extrapleural pneumonectomy or pleurectomy/ decortication, American Joint Committee on Cancer stage, and symptoms | Surgical resection, nonsmokers, female, no pain, epithelial, left side: ↑ survival |
| 2005 | Steele | 145 | EORTC prognostic index: PS, nonepithelial, male, low hgb, high platelet count, high WBC, high LDH ↓ survival | PS, WBC, hgb, uncertain diagnosis, sarcomatoid: ↓ survival |
| 2004 | Neumann | 155 | Epithelial, young age, female sex ↑ survival | Epithelial, young age, female sex: ↑survival |
| 2000 | Edwards | 142 | Male sex, older age, weight loss, chest pain, poor PS, low hgb, leukocytosis, thrombocytosis, and nonepithelial cell type ↓ survival | Cell type, hgb, white cell count, PS, and sex |
| 1998 | Herndon | 337 | CALGB prognostic index: PS, chest pain, dyspnea, PLT >400,000/μl, weight loss, LDH level >500 IU/liter, pleural involvement, low hgb level, high WBC count, and increasing age older than 75 years | Pleural involvement, LDH >500 IU/liter, poor PS, chest pain, PLT >400,000, nonepithelial histology, and increasing age older than 75 years |

PET, positron emission tomography; PS, performance status; PFS, progression-free survival; LDH, lactate dehydrogenase; hgb, hemoglobin; PLT, platelet count; WBC, white blood cell count; CRP, C reactive protein; CALGB, Cancer and Leukemia Group B; MPM, malignant pleural mesothelioma; EORTC, European Organisation for Research and Treatment of Cancer; KPS, Karnovsky performance status; EPP, extrapleural neumonectomy; ASA, American Society of Anesthesiologists.
Table was modified from the study by Pass.[25]

assessed noninvasively on presentation, validated the findings of many of the previous studies listed in Table 11. The phenotype for a poor prognosis was defined as males older than 50 years old who presented with nonepithelial histotype and elevated platelet and WBC counts.[2,3,5–13]

The future and use of the MPM registry will depend on prospective accumulation of international cases along with uniform standardization of important demographic variables. For the CORE variables, further subdivision of the type and extent of surgical cytoreduction will be accomplished by the incorporation of recently published guidelines for their definition.[14] Supplementary prognostic fields must be expanded to include more precise quantification of radiographic parameters, such as tumor volume and standardization of positron emission tomography-computed tomography interpretation[15–19] (Table 12). Numerous studies have documented a relationship between post-treatment/postsurgical MPM survival and elevated standard uptake values (SUV); however, validation of a specific threshold standardized uptake value or standardization of SUV quantitation is lacking.

**TABLE 12.** Radiographic Prognostic Studies

| Marker | Year | Author | N | Univariate Predictors | Multivariate Predictors |
|---|---|---|---|---|---|
| PET-CT | 2013 | Abakay | 177 | Male sex, nonepithelial, KPS <60, stage III to IV, hgb <12.3 g/dl, serum ALP >79 U/liter, presence of pleural thickening >1 cm, BSC treatment regimen, SUVmax >5 | Male sex, KPS <60, BSC, stage III to IV, SUVmax >5 |
| CT volume | 2012 | Gill | 88 | Tumor volume predicts survival after EPP | Tumor volume, hgb, adjuvant therapy |
| PET-CT | 2011 | Sharif | 1108 | SUV >10 associated with decreased survival in best-evidence review of 15 articles | NA |
| PET-CT volume | 2010 | Lee | 13 | High metabolic tumor volume decreased survival | Metabolic tumor volume |
| Quantitative FDG | 2010 | Nowak | 89 | High total glycolytic volume decreased survival, histology, weight loss, CT stage, EORTC prognostic score | Total glycolytic volume and weight loss for sarcomatoid histology |

PET, positron emission tomograpy; CT, computerized tomography; SUV, standardized uptake value; hgb, hemoglobin; KPS, Karnovsky performance status; BSC, best supportive care; ALP, alkaline phosphatase; EORTC, European Organisation for Research and Treatment of Cancer; FDG, fluoroxy-deoxyglucose; EPP, extrapleural pneumonectomy; NA, not available.
Table was modified from the study by Pass.[25]

 

Finally, a number of tissue-based and blood-based genomic, epigenetic, and proteomic markers have been published either as single entities or as part of a profile for the prognostication of MPM.[20–24] The majority of these have not been validated either in independent cohorts or in blinded analyses. The challenge for the registry is whether such markers can be added as fields. At the least, however, if the prospective registry is maintained, and participating institutions have ongoing tissue and blood procurement protocols for archiving of samples, the registry will represent a valuable coordinating entity for such validations.

## ACKNOWLEDGMENTS

*The Mesothelioma Applied Research Foundation and the International Association for the Study of Lung Cancer provided funding to support the International Mesothelioma Staging Project. The sponsors had no input in the committee's analysis of the data or in the committee's suggestions for revisions to the staging system.*

## REFERENCES

1. Rusch V, Baldini EH, Bueno R, et al. 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. *J Thorac Cardiovasc Surg* 2013;145:909–1010.
2. Fennell DA, Parmar A, Shamash J, et al. Statistical validation of the EORTC prognostic model for malignant pleural mesothelioma based on three consecutive phase II trials. *J Clin Oncol* 2005;23:184–189.
3. Edwards JG, Abrams KR, Leverment JN, Spyt TJ, Waller DA, O'Byrne KJ. Prognostic factors for malignant mesothelioma in 142 patients: validation of CALGB and EORTC prognostic scoring systems. *Thorax* 2000;55:731–735.
4. Rusch VW, Giroux D, Kennedy C, et al; IASLC Staging Committee. Initial analysis of the International Association for the Study of Lung Cancer mesothelioma database. *J Thorac Oncol* 2012;7:1631–1639.
5. Francart J, Vaes E, Henrard S, et al. A prognostic index for progression-free survival in malignant mesothelioma with application to the design of phase II trials: a combined analysis of 10 EORTC trials. *Eur J Cancer* 2009;45:2304–2311.
6. Baud M, Strano S, Dechartres A, et al. Outcome and prognostic factors of pleural mesothelioma after surgical diagnosis and/or pleurodesis. *J Thorac Cardiovasc Surg* 2013;145:1305–1311.
7. Nojiri S, Gemba K, Aoe K, et al. Survival and prognostic factors in malignant pleural mesothelioma: a retrospective study of 314 patients in the west part of Japan. *Jpn J Clin Oncol* 2011;41:32–39.
8. Tanrikulu AC, Abakay A, Kaplan MA, et al. A clinical, radiographic and laboratory evaluation of prognostic factors in 363 patients with malignant pleural mesothelioma. *Respiration* 2010;80:480–487.
9. Richards WG, Godleski JJ, Yeap BY, et al. Proposed adjustments to pathologic staging of epithelial malignant pleural mesothelioma based on analysis of 354 cases. *Cancer* 2010;116:1510–1517.
10. Yan TD, Boyer M, Tin MM, et al. Prognostic features of long-term survivors after surgical management of malignant pleural mesothelioma. *Ann Thorac Surg* 2009;87:1552–1556.
11. Flores RM, Zakowski M, Venkatraman E, et al. Prognostic factors in the treatment of malignant pleural mesothelioma at a large tertiary referral center. *J Thorac Oncol* 2007;2:957–965.
12. Neumann V, Rütten A, Scharmach M, Müller KM, Fischer M. Factors influencing long-term survival in mesothelioma patients—results of the German mesothelioma register. *Int Arch Occup Environ Health* 2004;77:191–199.
13. Herndon JE, Green MR, Chahinian AP, Corson JM, Suzuki Y, Vogelzang NJ. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. *Chest* 1998;113:723–731.
14. Rice D, Rusch V, Pass H, et al; International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group. 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;6:1304–1312.
15. Abakay A, Komek H, Abakay O, et al. Relationship between 18 FDG PET-CT findings and the survival of 177 patients with malignant pleural mesothelioma. *Eur Rev Med Pharmacol Sci* 2013;17:1233–1241.
16. Gill RR, Richards WG, Yeap BY, et al. Epithelial malignant pleural mesothelioma after extrapleural pneumonectomy: stratification of survival with CT-derived tumor volume. *AJR Am J Roentgenol* 2012;198:359–363.
17. Sharif S, Zahid I, Routledge T, Scarci M. Does positron emission tomography offer prognostic information in malignant pleural mesothelioma? *Interact Cardiovasc Thorac Surg* 2011;12:806–811.
18. Lee HY, Hyun SH, Lee KS, et al. Volume-based parameter of $^{18}$F-FDG PET/CT in malignant pleural mesothelioma: prediction of therapeutic response and prognostic implications. *Ann Surg Oncol* 2010;17:2787–2794.
19. Nowak AK, Francis RJ, Phillips MJ, et al. A novel prognostic model for malignant mesothelioma incorporating quantitative FDG-PET imaging with clinical parameters. *Clin Cancer Res* 2010;16:2409–2417.
20. Gordon GJ, Dong L, Yeap BY, et al. Four-gene expression ratio test for survival in patients undergoing surgery for mesothelioma. *J Natl Cancer Inst* 2009;101:678–686.
21. Pass HI, Goparaju C, Ivanov S, et al. hsa-miR-29c* is linked to the prognosis of malignant pleural mesothelioma. *Cancer Res* 2010;70:1916–1924.
22. Kao SC, Vardy J, Chatfield M, et al. Validation of prognostic factors in malignant pleural mesothelioma: a retrospective analysis of data from patients seeking compensation from the New South Wales Dust Diseases Board. *Clin Lung Cancer* 2013;14:70–77.
23. Kao SC, Klebe S, Henderson DW, et al. Low calretinin expression and high neutrophil-to-lymphocyte ratio are poor prognostic factors in patients with malignant mesothelioma undergoing extrapleural pneumonectomy. *J Thorac Oncol* 2011;6:1923–1929.
24. Kao SC, Pavlakis N, Harvie R, et al. High blood neutrophil-to-lymphocyte ratio is an indicator of poor prognosis in malignant mesothelioma patients undergoing systemic therapy. *Clin Cancer Res* 2010;16:5805–5813.
25. Pass HI. Biomarkers and prognostic factors for mesothelioma. *Ann Cardiothorac Surg* 2012;1:449–456.