Assessment of Therapy Responses and Prediction of Survival in Malignant Pleural Mesothelioma Through Computer-Aided Volumetric Measurement on Computed Tomography Scans

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Purpose: The purposes of this study were (1) to calculate the tumor volume in patients with malignant pleural mesothelioma using computed tomography (CT) scan images and a computer-aided measurement technique and (2) to investigate whether the baseline volume, or volume change after chemotherapy, predicts patient survival.

Methods: We compiled the clinical characteristics and outcome from 30 patients enrolled in two clinical trials at our cancer center in which the patients were treated with induction chemotherapy followed by surgery and radiation. CT scans of 30 patients were obtained at baseline and after two cycles of chemotherapy. Tumor volumes were calculated using a semiautomated computer algorithm. Overall survival was measured using a landmark time at 3 months post-treatment start date such that all patients had already received two cycles of chemotherapy and a follow-up scan. Association of volume changes with overall survival were determined by a Cox Proportional Hazards Model or log-rank test. The relationship between both pre and postoperative clinical stage and baseline tumor volume was analyzed using the rank sum test.

Results: The median baseline tumor volume was 473 cm^3 (range, 61 cm^3–2108 cm^3). Patients with high preoperative stages (III and IV) had larger baseline tumor volume than those with low preoperative stages (I and II) ($p = 0.05$). Patients with baseline volumes smaller than 619 cm^3 tended to survive longer than those with baseline volumes larger than or equal to 619 cm^3 ($p = 0.07$). Percentage change of tumor volume from baseline to first follow-up CT after two cycles of chemotherapy was significantly associated with overall survival (hazard ratio: 1.94 [95% confidence interval, 1.05–3.60], $p = 0.04$). Whereas the relative change in modified RECIST measurements was not significantly associated with overall survival (hazard ratio: 1.06 [95% confidence interval, 0.96–1.16], $p = 0.25$). By classifying changes of tumor volumes between two scans into two groups, i.e., "increase" and "decrease," a significant difference in survival was found between those who increased and decreased after two cycles of chemotherapy ($p = 0.03$).

Conclusions: Changes in tumor volume after two cycles of chemotherapy predicted overall survival in patients with malignant pleural mesothelioma. Tumor volume at baseline was shown to be associated with preoperative clinical stage and survival. Computer-aided volumetric measurements may enable more reliable therapeutic response assessment and could provide additional prognostic information.

Key Words: Malignant pleural mesothelioma, Therapy response assessment, Chest CT, Tumor volume, Image segmentation.

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Malignant pleural mesothelioma (MPM) is an aggressive primary tumor with a well-established link to asbestos exposure.[1] It was predicted that number of deaths of MPM would be 72,000 in the next 40 years in the United States, and the mortality rate is increasing worldwide.[2] Most patients present with disease involving the entire ipsilateral pleura, however, there is no universally accepted standard therapy for patients with locally advanced disease. The results from multiple studies using a multimodality approach to MPM, including surgery, chemotherapy, and radiation, have been encouraging.[3,4] They have sparked enthusiasm to investigate new drugs to improve patients' survival. Finding the optimal therapy and methodology for accurately gauging response to these therapies is therefore key and of great clinical importance.

Computed tomography (CT) has been the primary imaging modality for diagnosis, staging, and response assessment of MPM because of its ability to provide anatomic details of both normal and abnormal structures, its wide

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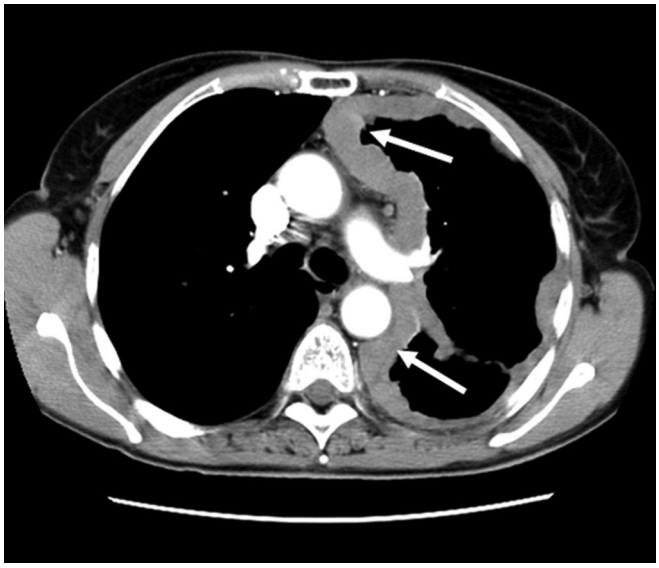

FIGURE 1. Circumferential and irregular shape of malignant pleural mesothelioma showed limitations of 2D measurement (arrows).

availability, and relatively low cost.[5–8] For therapeutic response assessment, the bidimensional World Health Organization criteria[9] and the simplified unidimensional RECIST criteria[10] are considered the gold standard in clinical practice and clinical trials. However, MPM typically spreads as a rind around the pleura, which prevents standard linear tumor measurements (Figure 1). This particularly complicates the ability to measure the extent of disease and the response to therapy—an issue in both standard clinical practice and when conducting clinical trials. Studies have shown the inadequacy of the standard RECIST criteria in the assessment of therapeutic response in MPM.[11–13] The recently modified RECIST criteria, which recommend measuring tumor thickness at a location perpendicular to chest wall or mediastinum, have been published and are being used in clinical trials, aiming at improving response assessment in MPM.[14] Nonetheless, the linear measurement is not able to faithfully capture the change in tumor burden and lacking in reproducibility because of the circumferential and axial growing patterns of MPM.[15]

Preliminary data by Pass et al. demonstrate that preoperative tumor volume is predictive of overall and progression-free survival. Similarly, post resection residual tumor burden predicts outcome.[16,17] The tumor volumes in the study by Pass et al., however, were obtained by manually delineating tumor contours—an extremely time consuming procedure. Ceresoli et al.[12] highlight the importance of computer-assisted CT techniques for response assessment. To date, automated/semiautomated tools for the identification and quantification of tumor volumes have not been validated for therapeutic assessment and clinical and prognostic use.

In this study, we applied a semiautomatic three dimensional computer method[18] to assist in the measurement of tumor volumes on serial CT scans retrieved from two clinical trials. The purposes of our study were to investigate whether the MPM volumes on baseline study or volume changes after chemotherapy would associate with patient survival, and whether the volumetric technique would have any advantage over the modified RECIST measurement.

PATIENTS AND METHODS

Patients

Imaging and clinical data from 30 patients were retrospectively collected from two Institutional Review Board approved, HIPPA compliant phase II clinical trials that were performed at our referral-based cancer center.[4,19] In both of these studies, patients received up to four cycles of induction chemotherapy (gemcitabine/cisplatin or pemetrexed/cisplatin). Those patients without disease progression were then referred for resection by extrapleural pneumonectomy followed by postoperative hemithoracic radiation. CT scanning was performed to assess response to chemotherapy after every two treatment cycles. All patients in the two protocols received the same therapy, regardless of their MPM volumes.

CT images were acquired from a LightSpeed QX/I, LightSpeed16, and a HiSpeed CT/I (GE Medical Systems, Milwaukee, WI), using the standard contrast-enhanced diagnostic imaging technique (current: 180 mA–440 mA, Pitch: 0.938–1.5, Tube rotation speed: 0.5 seconds rotation, reconstruction: Lung algorithm, 120 kvp). Slice thicknesses were 5 mm ($n = 32$), 7 mm ($n = 1$) or 7.5 mm ($n = 24$) without overlapping.

Computer-Aided Tumor Volume Quantification

A semiautomatic computer method was used to assist in the identification and segmentation of tumor volumes that were associated with MPM.[18] The method used a sequential segmentation strategy to "dissect" MPM from surrounding normal organs/tissues such as chest wall, liver, and spleen, by combining different image processing techniques including a chest-rib interpolation and the gradient vector flow snake.[18,20] The MPM was then segmented from the heart, stomach and lung parenchyma using a multiple thresholding technique. To ensure correctness and consistency of MPM volumes, computer-generated tumor contours on baseline and follow-up scans were side-by-side displayed and carefully reviewed by a thoracic radiologist with 25 years of experience in chest CT interpretation. Suboptimal computer results were corrected by the radiologist with the help of an imaging viewer system developed in our research group (Figure 2). To study inter-radiologists' measurement variation, a second radiologist (a radiology fellow in body imaging with 5 years experience) independently edited the computer results, also in a side-by-side way.

Statistical Methods

Overall survival was measured from day 1 of the treatment until death or the last follow-up. The survival curves were computed using the Kaplan-Meier method.[21] Overall survival from the baseline and the follow-up measurements were analyzed separately. In the baseline analysis, to determine the optimal cut point for tumor volume in predicting patient survival, a minimum p value approach was

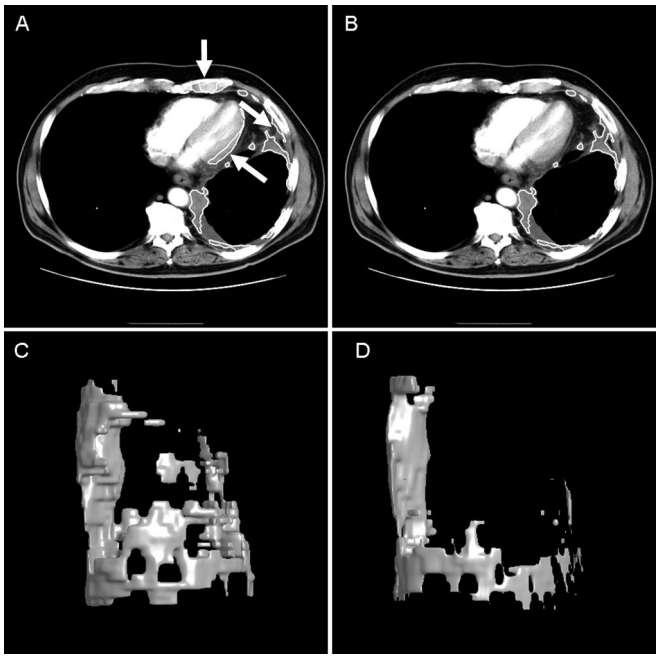

FIGURE 2. Computer segmentation of tumor corrected by radiologist. *A,* computer result on original image with suboptimal segmentation and inclusion of other tissues (arrows). *B,* manual correction on computer result. *C* and *D,* 3D rendering of the baseline alignant pleural mesothelioma (MPM) volume (596 cc) and the first follow-up MPM volume (208 cc).

used.[22] In the analysis using measurements from follow-up scans, a landmark analysis was performed at 3 months, as this was the time point by when the first follow-up scans should have been performed. Changes in volumes and modified RECIST measurements between the baseline and follow-up scans were computed using the percent relative change. The association between the relative changes in these measurements and overall survival were determined using Cox Proportional Hazards Regression.[23] Their predictive accuracies were quantified using the C-Index,[24] and indices were compared. A C-index is interpreted in the same way as an area under the curve, where 0.5 indicates the method is as efficient as flipping a coin, and values of 1.0 indicate perfect prediction. To determine whether there was any relationship between preoperative and postoperative clinical stages (using the International Mesothelioma Interest Group criteria[25]) and baseline CT volume, we collapsed stage into high (stages III and IV) and low (stages I and II) based on tumor, node, metastasis (TNM) staging criteria. The distribution of variables by stage was evaluated using the rank sum test.[26] Interobserver variability was assessed using the Concordance Correlation Coefficient (CCC).[27] Perfect agreement between radiologists is signified by a CCC equal to one and no agreement between radiologists is signified by a CCC equal to zero. Values of the CCC close to one imply very good agreement. Statistical significance was identified at the 5% level. All analyses were conducted using SAS 9.2 for Windows (SAS, Cary, NC) or the Hmisc package in R.

RESULTS

Overall Survivals

Thirty MPM patients were included in this analysis, 23 males and seven females. The age of the patients ranged from 34 to 76 with an average of 60 years old. MPM were pathologically proven. Most patients ($n = 23$) had surgery after chemotherapy. Among these patients, 27 had one follow-up scan performed after two cycles of treatment (2–6 weeks, median 5 weeks).

The median overall survival was 16 months. There were 26 deaths with median survival of 13.2 months (range, 3.3–47.4), while the four survivors have a median follow-up of 36.1 months (range, 17.4–49.5). The overall survival curve was shown in Figure 3.

Baseline Analysis

On baseline scans, the mean MPM volume was 596 ± 520 cm^3 (range, 61 cm^3–2108 cm^3; median, 473 cm^3). A threshold, 618.49 cm^3 in our study determined by the minimum p value approach, was applied to separate patients into two categories: the group with larger tumor volumes ($n = 10$), and the group with smaller tumor volumes ($n = 20$, four censored). The median survival months of the large and the small volume groups were 10.2 and 21.5, respectively. Patients in the small volume group had a slight tendency to survive longer ($p = 0.07$) (Figure 4*A*). Categorizing patients into two groups above and below the median volume showed no significant survival differences ($p = 0.36$).

Thirteen patients with low radiologic TNM stage (stage I, $n = 3$; stage II, $n = 10$) had median volume of 290 cm^3 (range, 61 cm^3–1447 cm^3); whereas seventeen patients with high radiologic TNM stage (stage III, $n = 12$; stage IV, $n = 5$) had median volume of 596 cm^3 (range, 84 cm^3–2108 cm^3). Patients with high stage had significantly larger tumor volume than those with low stage ($p = 0.05$). Twenty-three patients had postoperative staging. There was no significant volumetric difference between the low stage group ($n = 8$) and the high stage group ($n = 15$, $p = 0.59$).

Early Follow-up Analysis

Among the 27 patients who had at least one follow-up CT scan performed after two cycles of chemotherapy, the changes of MPM volumes were computed. Change of tumor volume was significantly associated with overall survival (hazard ratio: 1.94 [95% confidence interval, 1.05–3.60], $p = 0.04$). The more tumor growth occurred, the less likely was a patient to survive and vice versa. Twenty-five patients had modified RECIST measurements obtained from the clinical trials. The relative change between baseline and follow-up showed no significant association with overall survival (hazard ratio: 1.06 [95% confidence interval, 0.96–1.16], $p = 0.25$). The predictive ability of the volumetric measurement (C-index = 0.74) is significantly higher than that of the modified RECIST measurement (C-index = 0.5, $p = 0.05$).

A significant difference in survival was found between the group of patients who had an increase in tumor

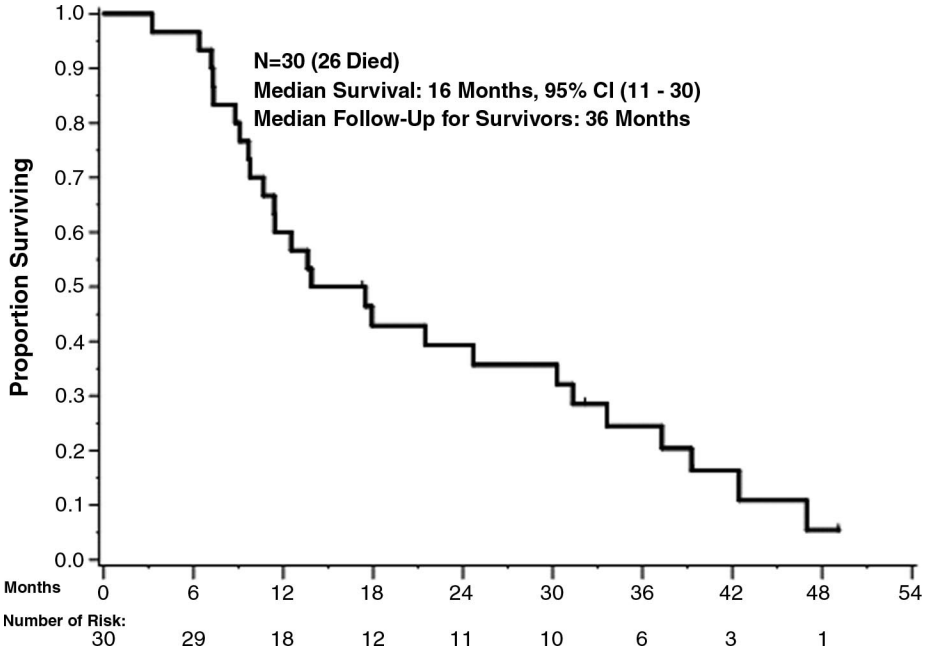

FIGURE 3. Overall survival curve.

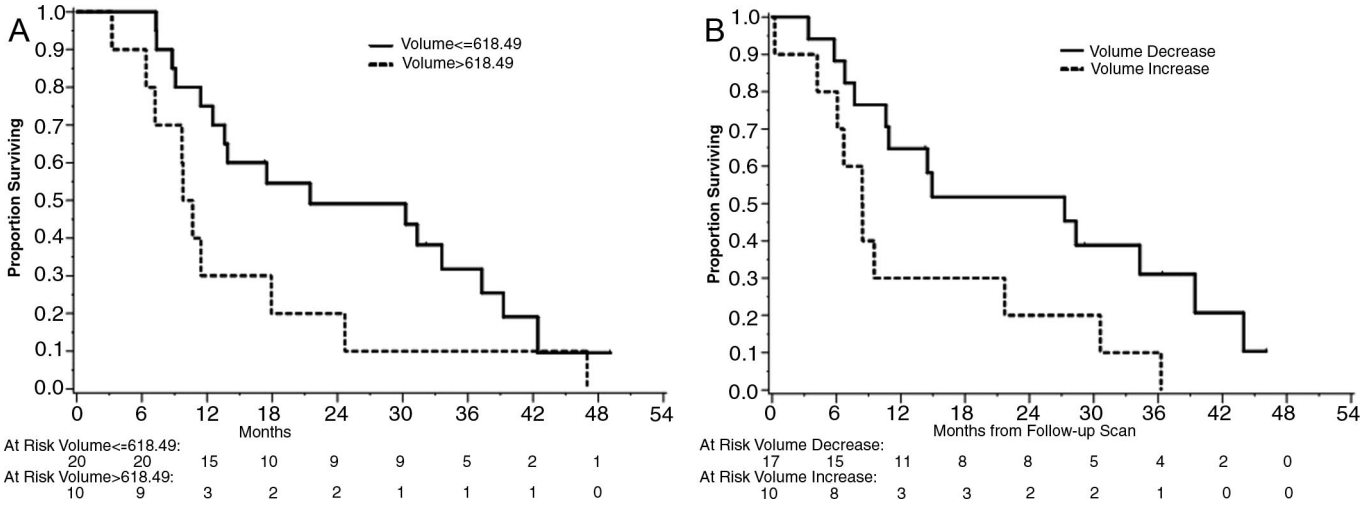

FIGURE 4. Survival analysis of baseline and early follow-up. *A,* patients with small MPM volume in baseline tends to survival longer ($p = 0.07$). *B,* patients whose MPM volume decreased in early follow-up and longer survival ($p = 0.03$).

volume after chemotherapy ($n = 10$) and the group who had a decrease in tumor volume ($n = 17$, $p = 0.03$) (Figure 4*B*). The median survival of the former was 11.5 months, whereas the median survival of the latter was 18.1 months.

Interobserver Variation

Both baseline and follow-up measurements had good reproducibility between the two radiologists, whereas there was a slight decline in reproducibility for the percent change from baseline to follow-up, as shown in Table 1:

TABLE 1. Concordance Correlation Coefficient (CCC) Between Two Radiologists

	CCC (95% CI)
Baseline volume	0.993 (0.988–0.998)
Follow-up volume	0.991 (0.984–0.997)
Change from baseline to follow-up	0.872 (0.821–0.922)

DISCUSSION

Many patients with MPM present with disease confined to the ipsilateral pleural. As such, resection by pleurectomy or extrapleural pneumonectomy is often considered when a patient is adequately fit to tolerate surgery and chest wall invasion by tumor is not apparent. Combined modality therapy, incorporating chemotherapy, and radiotherapy along with the surgery have also been studied now by several

groups. This aggressive approach remains controversial, however, because recurrence develops quickly and survival remains poor.

Because of its irregular shape and circumferential-axial growth pattern, MPM size cannot be appropriately assessed for response to therapy using the conventional RECIST and World Health Organization criteria.[11–13,15,28] Furthermore, the measurement sites are hard to locate reproducibly on serial CT scans, causing considerable variations in the measurements.[29,30] Although criteria based on the unidimensional and bidimensional methods are proposed and applied to clinical trials,[31–33] and the modified RECIST showed improved response assessment in larger patient number,[14] these intrinsic limitations still remain.

In this study, we attempted to investigate whether the tumor volume, or change in tumor volume of MPM calculated on serial CT scans could be useful in the assessment of tumor response to chemotherapy and the prediction of patient survival. If tumor volume can be reliably estimated from CT images, volume change would more accurately reflect true tumor size change and would likely better indicate tumor response to therapy.

We found that changes in tumor volumes between baseline and follow-up performed at two cycles after chemotherapy were significantly associated with survival, whereas changes in modified RECIST measurements at the same time interval did not show such a correlation. In addition, patients with reduced tumor volume at the first follow-up were shown to have longer survival than those patients with increased tumor volume. This corresponds to the overall results from the multicenter induction chemotherapy study.[4] In that trial, radiologic response to chemotherapy was the best predictor of survival, even compared with other well established prognostic factors such as histologic subtype, gender, stage, and lymph node involvement.

Calculating MPM volume is impractical without the aid of a computer due to time constraints, interobserver variability, and large number of slices. In this study, our semiautomatic computer method assisted the radiologist in the tumor volume measurement. We were able to separate MPM from its surrounding anatomic structures including (but not limited to) chest wall, mediastinum, and liver, using a sequential organ dissection strategy, that has previously been described with the gradient vector flow snake for the liver extraction[20] and the chest-rib interpolation technique for the chest wall extraction.[18] One advantage of this algorithm was to use the specific model/knowledge of the organ to identify the edge between the organ and tumor, which was otherwise difficult to be delineated due to similar densities of the two.

In clinical practice, as in our study, we expect the computer method to be integrated into a user-friendly system that allows operator to run the software and radiologist to review computer results (i.e., tumor contours) and correct any result if it is not satisfactory. The edited result will be served as the "final result" to calculate the tumor volumes and volume changes for assessing tumor response to therapy and predicting patient survival.

Our prognostic baseline volume-survival result was different from the previously reported data by Pass et al.[17] In our study, the threshold for categorizing large-volume and small-volume disease was 618 cm^3, rather than the 100 cm^3 as reported in the experiments of Pass et al. One possible reason for the discrepancy between our threshold and Pass et al. is that the criteria for patient registration differed in the two studies. We did not set a prerequisite for tumor thickness or tumor volume when selecting patients, but Pass et al. included only patients who had a maximum tumor thickness of 5 mm after debulking. As it was, the difference in survival between the two groups approached statistical significance, suggesting the possibility of a relationship between preoperative MPM volume and patient survival.

We used a different classification system ("increase" or "decrease") than the RECIST and modified-RECIST criteria, both of which use a threshold of 30% to define a therapeutic response. The outcome of the two groups in our experiments showed significant difference, suggesting that soon after chemotherapy the volume might begin to change in different directions (increase or decrease) and predict patient survival. However, this needs to be further investigated by a large dataset of patients and accounting for measurement variables such as repeatability, interobserver variation, and partial volume artifact.

Positron emission tomography (PET) with the radiopharmaceutical agent ^{18}F-fluorodeoxyglucose (FDG) has been increasingly applied in MPM to assess therapy response and shown promise.[8,34–38] Maximum standard uptake value (SUV_{max}) on ^{18}F-FDG PET is the most commonly used measurement to evaluate treatment response in mesothelioma.[8] Studies have shown that baseline SUV_{max}, a combination of SUV_{max} and histology, and change of SUV_{max} in early follow-up scan correlate well with patient survival.[34,35,37] Total lesion glycolysis (the total metabolic activity inside the tumor volume)[39] and total glycolytic volume (a measure of the composite of volume and total metabolic activity) are found superior to SUV_{max} and modified RECIST in assessing tumor response and/or predicting patient's survival.[36] However, preliminary data from gastrointestinal stromal tumor study showed that by lowering the RECIST cut-off scale and combining tumor density change, CT performed equally well to FDG PET as a biomarker for response assessment.[40] In addition, the confounding factor of talc pleurodesis also results in an increased and persistent uptake of FDG. PET imaging is more expensive, less accessible and has lower spatial resolution compared with the widely used CT. It would benefit the patients and reduce cost if MPM volumes and their changes after treatment on CT scans could be proven useful in the prediction of patient survival and accurately and practically measured.

Our study had some limitations. First, only tumor volume and volume change were considered to predict survival. Other clinical factors such as histology, pathologic stage, gender, asbestos exposure, smoking, symptoms, and laterality can also affect patient survival.[41] About half of the patients in this study had talc pleurodesis, and it is difficult to determine the effect this would have on the results. Nonethe-

less, in the majority of cases, the pleural rind was readily apparent on CT imaging, and the effects of talc pleurodesis would not impact the measurements in a significant way. Our results might have been affected by observer bias and heterogeneous thick slice thicknesses. Finally, the study population was relatively small making it difficult to achieve appropriate statistical significance for several results as indicated earlier. Our findings need to be validated in future MPM clinical trials with a large patient population.

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