Imaging, Diagnosis, Prognosis

Clinical Cancer Research

A Novel Prognostic Model for Malignant Mesothelioma Incorporating Quantitative FDG-PET Imaging with Clinical Parameters

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Abstract

Purpose: Existing prognostic systems for malignant pleural mesothelioma do not incorporate imaging information. We aimed to identify the contribution of quantitative fluorodeoxyglucose positron emission tomography (FDG-PET) analysis to other prognostic variables in this disease.

Experimental Design: Patients with malignant pleural mesothelioma underwent helical thoracoabdominal computed tomography and FDG-PET scans at baseline. Patients were treated as clinically indicated and followed for survival. FDG-PET variables derived included total glycolytic volume, a composite of tumor volume and glycolytic activity.

Results: Ninety-three patients were accrued from 2003 to 2006. Of 89 eligible assessable patients, 28 had undergone pleurodesis before enrolment. Seventeen patients remained alive at analysis; median survival is 15.4 months. On univariate analysis, significant prognostic factors were: total glycolytic volume on FDG-PET ($P = 0.003$), sarcomatoid histology ($P < 0.0005$), weight loss ($P = 0.031$), computed tomography stage ($P = 0.015$), and European Organization for Research and Treatment of Cancer good prognostic score ($P = 0.049$). In patients with epithelioid or biphasic histology, baseline total glycolytic volume remained predictive of survival in patients with ($P = 0.01$) or without ($P = 0.018$) previous pleurodesis. In multivariate analysis, no variable other than histology contributed to the model in patients with sarcomatoid histology; total glycolytic volume and weight loss contributed to the models in patients with nonsarcomatoid histology. computed tomography–assessed tumor-node-metastasis stage did not contribute to the model. A nomogram, which incorporates quantitative PET parameters and pleurodesis into prognostic information, is presented.

Conclusions: Sarcomatoid histology remains the strongest prognostic factor. In patients with non sarcomatoid disease, volumetric FDG-PET parameters are more predictive of survival than tumor-node-metastasis staging, suggesting that tumor volume and glycolytic activity may be more important determinants of prognosis in malignant pleural mesothelioma than anatomic extent of disease. *Clin Cancer Res; 16(8); 2409–17. ©2010 AACR.*

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Malignant pleural mesothelioma has a poor prognosis, with almost all patients dying from their disease. The prognosis for individual patients is variable, with a median survival without treatment of around 9 months from diagnosis and occasional patients surviving from 2 to 5 years (1, 2). Combination chemotherapy has led to modest survival improvements (3, 4).

Prognostic information is important to individual patients and their families and to stratify patients in clinical trials. In mesothelioma, the most widely used staging system, developed by the International Mesothelioma Interest Group, uses surgical definitions of T stage and uses N stages that are arguably more relevant to the lymphatic drainage of non–small cell lung cancer than pleural malignancy, which commonly bypasses the ipsilateral hilar lymph

Translational Relevance

Malignant pleural mesothelioma has a variable prognosis. As with any cancer, prognostic information is important for selection and stratification in clinical trials and is critical to patients, their families, and their doctors. In addition, in malignant pleural mesothelioma, the issue of responsibility for occupational or environmental exposure to asbestos often arises and frequently leads to litigation with the treating physician as an expert required to provide an estimate of the patient's life expectancy. There are currently no accepted molecular markers of prognosis in this disease; hence, other indicators of prognosis are needed. Here, we show in a prospective study that volumetric and intensity parameters obtained from FDG–positron emission tomography imaging at baseline are prognostic in this disease. This information is incorporated into a prognostic nomogram with clinical parameters. After further validation, this nomogram could be translated as a useful instrument for patient selection and prognostic stratification in clinical trials of novel therapies. Furthermore, it has potential for future clinical and medicolegal use.

nodes and involves mediastinal nodes(5–7). The prognostic value of tumor-node-metastasis (TNM) staging in malignant pleural mesothelioma has not been validated in large series, and staging is not commonly used to stratify patients in clinical trials. TNM staging may not accurately reflect the burden of disease in mesothelioma, and local disease bulk may be as important in determining the course of disease as the presence or absence of distant metastases.

The most well-validated prognostic scoring systems in malignant pleural mesothelioma are the eponymous Cancer and Leukemia Group B (CALGB) and European Organization for Research and Treatment of Cancer (EORTC) systems, both reported in 1998 (2, 8, 9). These use clinical variables to assign prognostic groups. However, since these analyses were applied, more robust statistical methods have been developed. In particular, a well-accepted method has emerged that has controlled the optimistic bias produced by models developed from single data sets by the application of bootstrapping. Furthermore, a measure of concordance (Harrell's C) that is an analogue of the area under a receiver operating characteristics (ROC) curve has been developed. Finally, robust methods for the construction of nomograms are now available (10–12). These have been applied recently for the construction of a prognostic nomogram in mesothelioma using clinical and staging variables (13).

There have also been significant advances in imaging and molecular diagnostics that could potentially be incorporated into a prognostic model. Molecular and pathologic characterization of malignant pleural mesothelioma has resulted in reports of several potential prognostic factors; however, most are either unavailable in clinical practice or have not been validated adequately in conjunction with clinical factors (14–17). Over the past 10 years, fluorodeoxyglucose positron emission tomography (FDG-PET) scanning has become commonly used. Its role in malignant pleural mesothelioma is still under investigation; however, malignant pleural mesothelioma is clearly FDG avid, and PET may provide staging and prognostic information and be useful in assessing response to chemotherapy (18–22). In addition, PET scanning is suited to semiautomated volumetric analysis of tumor bulk.

The aim of this study was to determine how quantitative FDG-PET imaging adds prognostic information to conventional clinical variables at diagnosis and to construct a prognostic nomogram.

Materials and Methods

Patients. Participants were newly referred patients over 18 y old with histologically or cytologically confirmed malignant pleural mesothelioma at a single tertiary referral centre. Patients who had previously received any specific antitumor treatment (surgery, chemotherapy, or radiotherapy) were ineligible, as were patients in whom an FDG-PET scan was contraindicated due to claustrophobia or uncontrolled diabetes mellitus. Patients who had undergone talc pleurodesis were originally enrolled on the study, which started before publication of a report that previous pleurodesis altered PET imaging characteristics in pleural mesothelioma (23). Following this publication, the protocol was amended to discontinue recruitment of patients with previous pleurodesis, and analyses were done according to pleurodesis status. Patients with any Eastern Cooperative Oncology Group (ECOG) performance status were eligible. Histology was reviewed centrally (A. Segal) and was grouped as sarcomatoid, epithelioid, or biphasic. There were no cases with other rare histologic categories. Patients were prospectively accrued from October 2003 to September 2006. The study was approved by the institutional Human Research Ethics Committee and Radiation Safety Office, and all participants gave written informed consent.

Clinical assessment and management. All patients had a full clinical assessment at baseline, including history of asbestos exposure and smoking, clinical examination, and determination of ECOG performance status. Laboratory investigations included full blood count, liver function tests, urea, and electrolytes. Lactate dehydrogenase was not included. Patients underwent a helical computed tomography scan of the thorax and abdomen and a whole body FDG-PET scan within 28 d following consent and registration and before any therapy. Computed tomography and PET scans were done within 14 d of each other. Any suspicious lesion found on one modality only was investigated further to confirm its nature. Patients were

deemed unable to be assessed if these time constraints were exceeded.

Patients were treated as clinically indicated. Results of PET scans done specifically for the study did not influence the management plan. Combination chemotherapy initially consisted of cisplatin and gemcitabine(24) and, subsequently, cisplatin and pemetrexed because pemetrexed became available for mesothelioma at the study site. Trimodality treatment with extrapleural pneumonectomy, combination chemotherapy, and hemithoracic radiation was used in selected patients. Palliative radiotherapy was used when indicated. Patients were followed up for survival, which was calculated from the date of study enrolment.

Imaging. Helical thoracic computed tomography scan was done with contrast using 5 mm slices (Phillips Brilliance 64 Slice or General Electric Lightspeed VCT). Computed tomography staging was done by a radiologist who was blinded to FDG-PET results.

Whole body FDG-PET imaging was done on a GSO Phillips Allegro PET scanner. Patients fasted for 6 h and scanning commenced 90 min following 215 MBq/m^2 FDG administration. Emission scans were done on multiple bed positions, with 4 min per bed position and 50% overlap per field of view. Transmission imaging was done with ^{137}Cs for attenuation correction, with a transmission imaging time of ~10 min. The data were corrected for randoms, and scatter correction was implemented in PET reconstruction, which was done using a 2D RAMLA algorithm.

All FDG-PET scans were staged by two experienced PET physicians, using Unio Internationale Contra Cancrum (UICC) TNM staging criteria (2002), with consensus reporting used to attain agreement. The PET physicians were blinded to patient outcome and to computed tomography stage as determined by the radiologist but were permitted to use the computed tomography scan for anatomic correlation.

In addition to visual staging, semiquantitative analysis of PET scans was done using a previously described three-dimensional iterative region growing algorithm to define tumor volumes of interest and derive a total glycolytic volume and maximum standardised uptake

Table 1. Patient characteristics

Characteristic	No pleurodesis (*n* = 61), *n* (%)	Pleurodesis (*n* = 28), *n* (%)	All patients (*n* = 89), *n* (%)
Gender			
Male	54 (88.5)	24 (85.7)	78 (87.6)
Histology			
Epithelioid	49 (80.3)	20 (71.4)	69 (77.5)
Biphasic	8 (13.1)	5 (17.9)	13 (14.6)
Sarcomatoid	4 (6.6)	3 (10.7)	7 (7.9)
Smoking status			
Exsmoker	28 (47.6)	19 (73.1)	47 (54.7)
Current	4 (6.7)	2 (7.7)	6 (7.0)
Never smoked	28 (47.6)	5 (19.2)	33 (38.4)
Asbestos exposure			
Yes	58 (96.7)	25 (92.6)	83 (95.4)
Chest pain			
Yes	29 (52.7)	20 (80.0)	49 (61.3)
Dyspnea			
Yes	45 (81.8)	23 (92.0)	68 (85.0)
ECOG PS			
0	25 (41.7)	8 (29.6)	33 (37.9)
1	31 (51.7)	16 (59.3)	47 (54.0)
2	4 (6.7)	3 (11.1)	7 (8.1)
Pleurectomy			
Yes	3 (4.9)	2 (7.1)	5 (5.6)
Weight loss			
Yes	37 (60.7)	11 (39.3)	48 (53.9)
CT stage (*n* = 84)			
I	11 (18.3)	1 (4.2)	12 (14.3)
II	7 (11.7)	1 (4.2)	8 (9.5)
III	24 (40.0)	7 (29.1)	31 (36.9)
IV	18 (30.0)	15 (62.5)	33 (39.3)

Abbreviations: CT, computed tomography; PS, performance status.

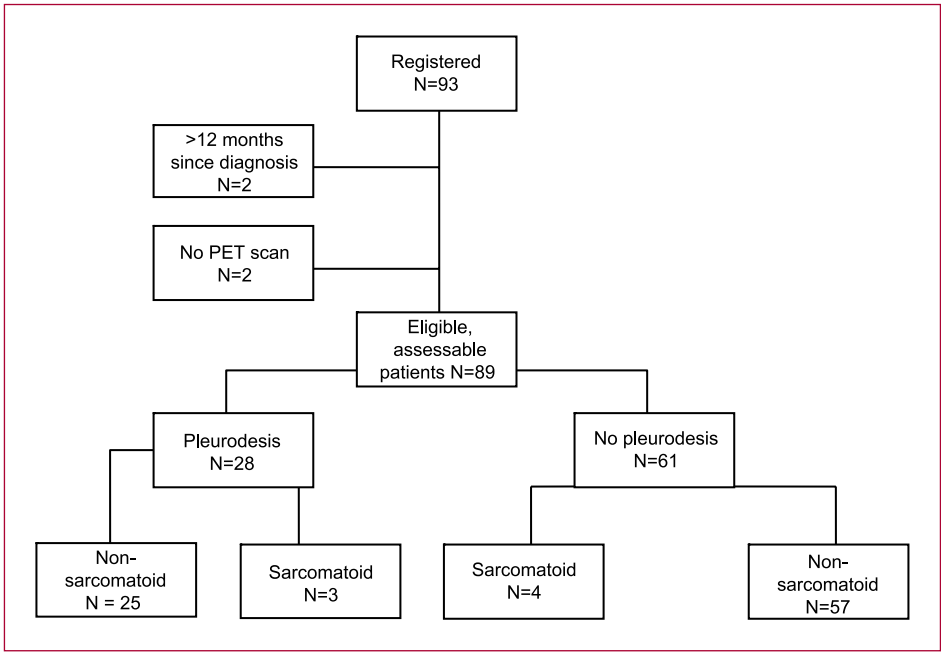

Fig. 1. Trial profile with the disposition and characteristics of 93 patients registered on the study.

value (SUVmax; refs. 21, 25). All SUV measurements were calculated using body weight. The region growing software was implemented in Interactive Data Language (version 6.1) on a Windows platform. It has been previously validated in phantom studies and in a clinical trial of response assessment in mesothelioma (21, 25). The growing function of the algorithm uses an adaptive threshold to delineate three-dimensional tumor boundaries. The threshold, which is reapplied at each iteration, is determined by the current mean, the activity in neighboring pixels, and the maximum normal background activity in liver (21, 25). Contiguous three-dimensional volumes of interest (VOI) are generated, and the operator is required to reseed on noncontiguous tumor elements. Total glycolytic volume (TGV) and SUVmax were then determined from the tumor VOI, with TGV being a measure of metabolic activity and volume of the whole tumor mass, whereas SUVmax represents the maximum SUV value in the tumor VOI. The interobserver variability of this method for obtaining TGV is ~5% in the clinical setting (26). Published phantom studies confirm a strong correlation between TGV and actual lesion activity ($r = 0.982$; $P < 0.0005$) and an SD for repeated measurements of 5% for TGV values > 100 (24). The quantitative PET analysis was done by two research physicians experienced in PET, who were blinded to computed tomography stage and patient outcome. Analysis was batched over the duration of the study but no statistical analysis was done until study completion.

Statistical analysis. Survival was assessed from the date of study registration. Cox proportional hazards model was used to assess variables in univariate analysis. Variables that were significant at $P \leq 0.2$ were incorporated into multivariate models, and SEs were assessed using bootstrapped estimation with 500 replications. A number of continuous prognostic variables, particularly those produced by the PET imaging, show a log-normal distribution. These variables were transformed using a natural log transformation, which produced a symmetrical distribution and a linear relationship to the hazard ratio. The transformed variables were used in subsequent statistical analysis. Patients with epithelioid or biphasic disease were considered nonsarcomatoid for the purposes of analysis. Separate models were fitted for sarcomatoid and nonsarcomatoid cases. The distorting influence of pleurodesis on PET scanning using FDG (23) was accommodated by fitting a pleurodesis and a nonpleurodesis model for those with nonsarcomatoid histology. The predictive accuracy of the models was assessed using Harrell's C, a measure of concordance for survival models. A value of 50% is equivalent to chance alone, values >65% are clinically relevant, and values >80% indicate high predictive accuracy (27). A nomogram was produced using the R (Design) package, which incorporates software designed by Harrell (http://biostat.mc.vanderbilt.edu/wiki/Main/Design). Confirmation of the prognostic model used a Classification and Regression Tree (CART) model (28). For all analyses, $P < 0.05$ was considered statistically significant.

Results

Patient characteristics. Ninety-three patients were accrued to the study (Table 1; Fig. 1); median time from diagnosis was 0.7 months (interquartile range, 0.2-2.2 months). Two patients were ineligible because of a prolonged length of

time since diagnosis, and two were unable to be assessed because they did not have PET scans done. All 89 eligible patients had a confirmed diagnosis of mesothelioma, with epithelioid histology predominating (78%). Most patients were male (88%) and had a history of asbestos exposure (95%) in keeping with the known epidemiology of the disease. Most patients were symptomatic at presentation, with chest pain, dyspnea, weight loss, or a combination of symptoms. Most patients had an ECOG performance status of 0 or 1 at presentation (92%). Twenty-eight of 89 patients had undergone pleurodesis.

Eighty-four of 89 patients had computed tomography imaging that was assessable for determination of tumor stage. Of the remaining five patients, one did not undergo a baseline computed tomography and four had computed tomography imaging unavailable for assessment, incomplete, or from which tumor stage could not be determined. These patients had complete PET imaging and clinical investigation data and were included in the evaluation. Most patients had stage III or IV disease by computed tomography staging (76%), including almost all of the group who had undergone pleurodesis (92%; Table 1). Fifty-four patients (61%) subsequently had chemotherapy during their disease course. Three patients underwent trimodality therapy with extrapleural pneumonectomy, combination chemotherapy, and hemithoracic irradiation. One patient underwent extrapleural pneumonectomy and died of postoperative complications. At analysis, 72 deaths had been reported from this cohort, and the median survival for all patients was 15.4 months.

Univariate analysis. The following factors were significantly associated with survival in univariate analysis before imaging variables were included in the model: sarcomatoid histology ($P < 0.0005$), weight loss ($P = 0.031$), and EORTC good prognosis category ($P = 0.049$; Fig. 2A). Sarcomatoid mesothelioma is a small proportion of total diagnoses (<10%), and the prognosis for this group of patients was exceedingly poor (Fig. 2B). When imaging variables were examined by Cox regression, TGV was a significant predictor of survival ($P = 0.003$), as was computed tomography stage ($P = 0.013$) and PET volume ($P = 0.008$). SUVmax trended toward significance only ($P = 0.055$). Kaplan-Meier curves for overall survival are shown for all patients (Fig. 2C) and the nonsarcomatoid group ($P = 0.0008$; Fig. 2D) using a data-determined split point for total glycolytic volume by CART analysis. Total glycolytic volume was analyzed separately in patients with nonsarcomatoid histology. Total glycolytic volume was a significant predictor for both groups despite the reduced power (nonpleurodesis, $P = 0.018$; pleurodesis, $P = 0.010$; Fig. 3).

Multivariate analysis. Multivariate Cox regression analysis including all patients found some univariate predictors to be redundant and the most parsimonious multivariable models for the groups defined by sarcomatoid histology (Table 2) showed that, in patients with sarcomatoid histology, the addition of other prognostic factors was not contributory (Harrell's C = 0.62). In patients with nonsarcomatoid histology and no pleurodesis, TGV and weight loss remained in the model, with total glycolytic volume as the strongest predictor (hazard ratio,

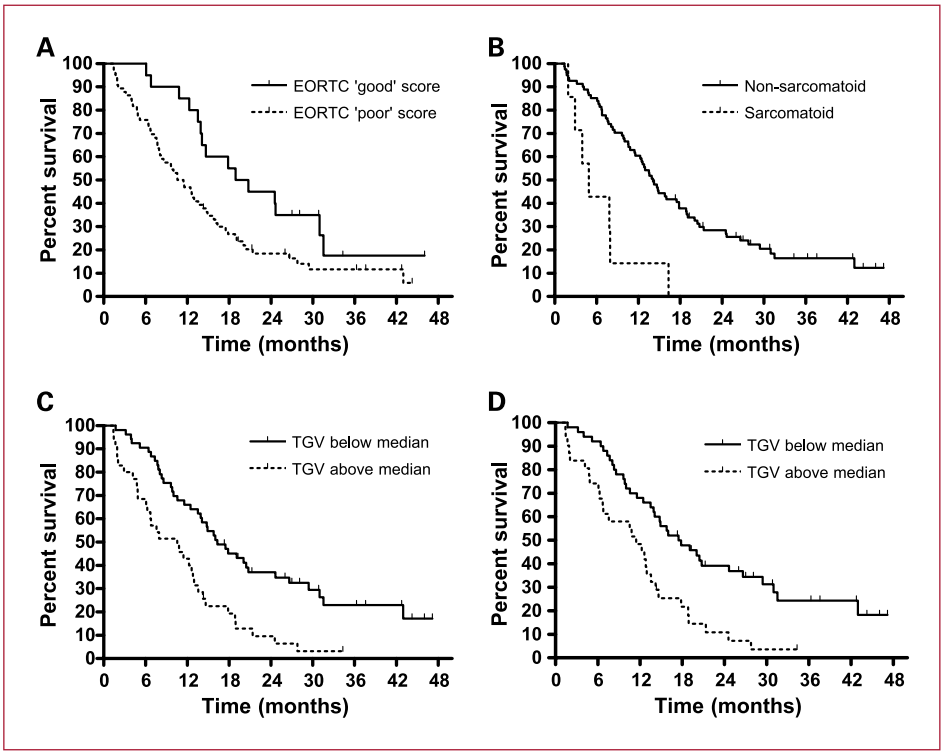

Fig. 2. Kaplan-Meier curves for survival are shown for all patients by European Organization for Research and Treatment of Cancer prognostic group (A; $P = 0.049$), all patients by histology (B; $P = 0.0005$), all patients by total glycolytic volume (C; above and below data determined split for total glycolytic volume for all patients; $P = 0.0005$), and patients with nonsarcomatoid histology only by total glycolytic volume (D; above and below data determined split for total glycolytic volume for all patients; $P = 0.0008$). EORTC, European Organization for Research and Treatment of Cancer; TGV, total glycolytic volume.

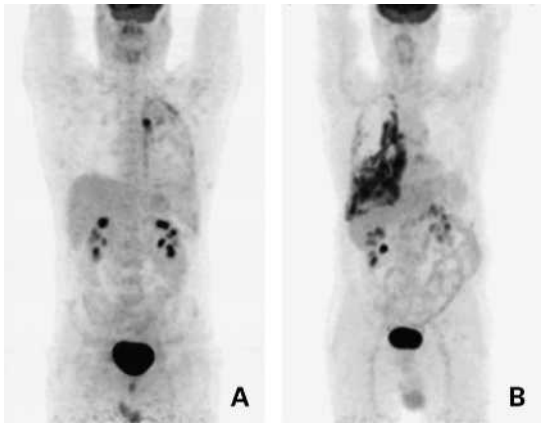

Fig. 3. FDG-PET images of two different patients with mesothelioma, with similar SUVmax values but a 10-fold difference in total glycolytic volume values. A, patient with a left-sided mesothelioma with an SUVmax value of 9.6 and total glycolytic volume value of 240. B, patient with a right-sided mesothelioma, with SUVmax of 9.4 and total glycolytic volume of 2,523. This illustrates the concept of determining tumor burden by using total glycolytic volume as opposed to using SUVmax value alone.

1.22; $P = 0.009$) and Harrell's C = 0.67. In those with previous pleurodesis, TGV and weight loss again contributed to the model (Harrell's C = 0.71; total glycolytic volume hazard ratio, 1.77; $P = 0.05$). Computed tomography determined TNM stage was not a significant contributor in models that included TGV.

A prognostic nomogram was developed for patients with nonsarcomatoid disease (Fig. 4). Weight loss is defined as ≥10 kg unintentional weight loss in the previous 6 months. The inclusion of a variable for pleurodesis allows for a correction factor to adjust for the contribution of inflammatory uptake due to pleurodesis to the total glycolytic volume; pleurodesis did not contribute to model for survival. The nomogram is used as follows: use a ruler to assess the points assigned to each variable on the upper scale, then sum the points. Having identified the total points score, use the ruler to extrapolate from the lower points scale to a projected median survival in months. For example, a patient with TGV of 12,000, no weight loss, and previous pleurodesis gains 67 points from TGV, with none for weight loss or pleurodesis; projected survival time is 11 to 12 months. A patient with TGV of 2,500, no weight loss, and no pleurodesis gains 17 points from TGV, with none for weight loss and 17 for pleurodesis status, giving a total of 34 points and a projected survival time ~14 to 15 months.

Discussion

Imaging findings have previously been incorporated into useful prognostic models in other cancers (29); however, this is the first report showing that a composite variable of volume and glycolytic activity has value at the time of tertiary referral in patients with malignant pleural mesothelioma. This finding is in keeping with the known growth pattern of mesothelioma as a local disease and was valid in patients with or without previous pleurodesis and in all histologic variants on univariate analysis. Previous reports have shown that increasing tumor volume is associated with decreased survival in surgically managed mesothelioma patients (30); however, it is unclear whether these findings also apply to patients with more advanced disease who are not undergoing surgical resection.

Sarcomatoid histology is known to be an indicator of poor prognosis in patients with malignant pleural mesothelioma (2, 8, 9, 31, 32), and the findings of this study reinforce this observation from numerous series, with no patient with sarcomatoid disease surviving beyond 18 months. Among all patients, TGV was a significant univariate predictor of survival; however, when the groups were split by histology, no other factor was prognostic in those with sarcomatoid disease. This suggests that sarcomatoid histology alone is such an important adverse feature that patients with sarcomatoid mesothelioma can be considered in a different group and that randomized clinical trials in malignant pleural mesothelioma should stratify patients at for histology. However, most mesothelioma patients do not have pure sarcomatoid histology, and within patients with nonsarcomatoid histology, prognosis is variable. Hence, it becomes relevant to generate prognostic models to distinguish between those with good and poor prognoses. Other factors thus become important prognostic variables, including weight loss, gender, and TGV. Pleurodesis induces an intense inflammatory response in the pleura, which may result in false positive uptake on FDG-PET imaging. Despite this, the TGV value obtained from the FDG-PET scans was a strong predictor of survival in the pleurodesis and nonpleurodesis patient groups. Statistical analysis showed that pleurodesis does however influence the patient group by introducing a bias in TGV because of the inflammatory component. This has been corrected in the nomogram by adding points to patients who have not had pleurodesis rather than subtracting points in the pleurodesis group. Assigning a correction factor to account for the TGV difference in the pleurodesis and nonpleurodesis groups allows the nomogram to be applicable to pleurodesis and nonpleurodesis patients.

Although PET imaging is becoming increasingly available, its role in mesothelioma has not been clearly established, and the accessibility of mesothelioma patients to PET imaging is often limited because of restrictions on reimbursement. Several studies have shown the value of FDG-PET in M staging in patients with mesothelioma in whom extrapleural pneumonectomy is being considered; however, PET has been shown to have limited sensitivity in T and N staging (19, 33). In a later paper, Flores et al. (18) incorporated SUVmax into a prognostic model with histology and stage in a series of 137 patients with untreated proven malignant pleural mesothelioma, showing that

SUVmax > 10 was associated with poor prognosis (hazard ratio, 1.05; $P = 0.02$), with each unit increase in SUVmax increasing the risk for death by 5%. However, in that study, the SUVmax cut point was chosen to minimize the P using the maximal χ^2 method. In our patient group, SUVmax did not significantly predict survival in univariate analysis; however, in the present study, a volumetric parameter has been added, showing the utility of PET to quantify active tumor burden rather than intensity of glycolytic uptake alone. The use of mean SUV from a region of interest has also been proposed for response assessment (34). This would be difficult to apply in mesothelioma because of the anatomic pattern of spread of this disease and the difficulty in selecting a reproducible representative lesion from the pleura.

An important strength of the use of PET imaging is the ability to measure intensity of metabolic activity in addition to volume, although volume alone was also a significant prognostic variable in this study. Furthermore, because of the volumetric nature of PET acquisitions and the differential intensity levels of tumor and background semiautomated computer programming for measurement of volume on PET scanning can be undertaken. The software used in this analysis has previously been made available to other centers, which have been able to successfully do similar analyses, and will be made available on request. Three-dimensional volumetric analysis by computed tomography scans is possible with sophisticated software; however, this often requires volumes to be manually defined or generated on a slice by slice basis. Correlation of PET-defined metabolically active tumor volumes with computed tomography–defined anatomic tumor volumes would be of interest but was beyond the scope of this study.

The region-growing algorithm has been successfully applied to images obtained on a variety of different PET cameras, including PET/computed tomography. The methodology is unchanged; however, the absolute TGV and SUV values will differ slightly on different PET/PET–computed tomography camera systems primarily because of the differences in reconstruction of the PET component of the scan. This study was done using an older generation scanner, Phillips Allegro, which does not incorporate the comprehensive scatter correction that is routinely used with the new generation PET–computed tomography scanners. A validation study to confirm the utility of the TGV values on the prognostic nomogram using a PET–computed tomography camera system is currently being undertaken and will be of value in confirming the transferability of the nomogram to other PET imaging systems. It is well recognized that many factors, including uptake phase, fasting time, blood sugar level, imaging, and reconstruction protocols, may influence semiquantitative PET measurements such as SUVmax (35). TGV values may also therefore be influenced by these known variables, and if semiquantitative measures are to be used in a prognostic staging or nomogram system, standardizing imaging protocols is important to ensure the SUVmax or TGV values obtained can be compared across different patient groups.

Having shown that TGV is a powerful prognostic indicator, this study explored different strategies to translate this to clinically useful information. This is particularly difficult

Table 2. Prognostic models for all patients and subgroups with robust estimation using bootstrapping

Variable	HR	95% CI		*P*	Harrell's C	*n*
		LCL	UCL			
All patients						
TGV (ln)	1.29	1.13	1.47	<0.001	0.652	88
Weight loss	2.05	1.23	3.43	0.006		
Patients with nonsarcomatoid histology						
TGV (ln)	1.27	1.11	1.46	<0.001	0.650	81
Weight loss	2.02	1.23	3.30	0.005		
Patients with sarcomatoid histology						
TGV (ln)	1.64	*	*	0.969	0.619	7
Weight loss	1.31	*	*	0.993		
Patients with non sarcomatoid histology and no pleurodesis						
TGV (ln)	1.22	1.05	1.43	0.009	0.674	56
Weight loss	1.83	0.96	3.48	0.066		
Patients with non sarcomatoid histology and pleurodesis						
TGV (ln)	1.77	1.00	3.13	0.051	0.706	25
Weight loss	2.42	0.07	80.0	0.621		

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; TGV, total glycolytic volume; LCL, lower confidence limit; UCL, upper confidence limit; ln, natural log transformation.

*The confidence interval is very wide because of the small sample size and robust method of estimation.

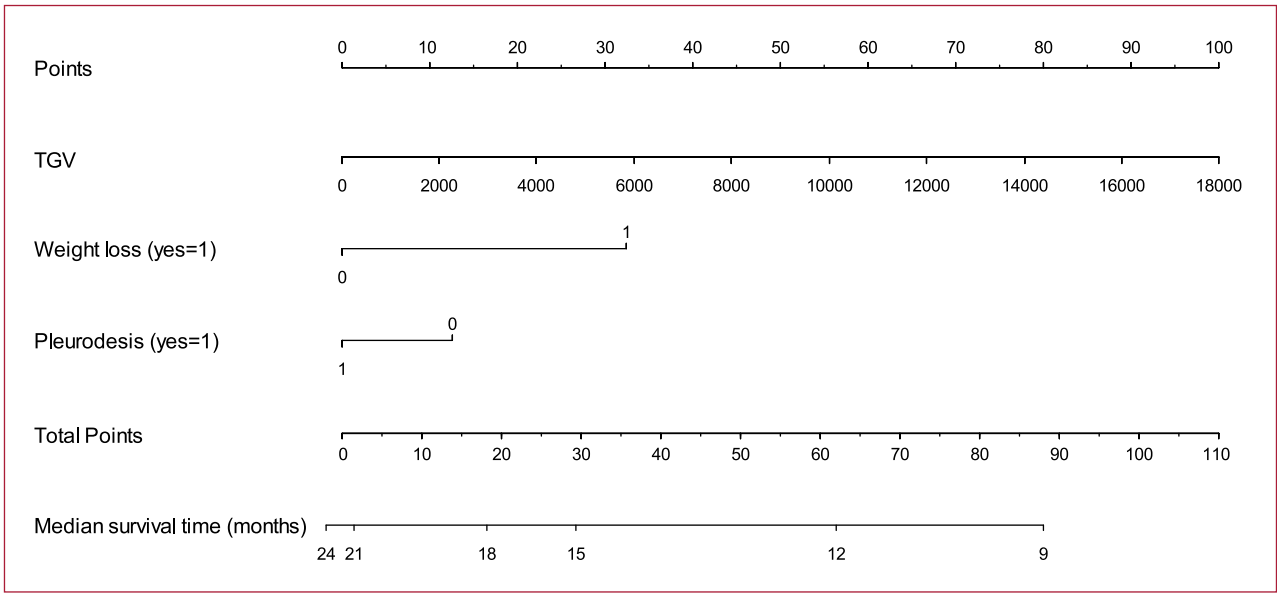

Fig. 4. Prognostic nomogram for predicting survival in months for patients with malignant pleural mesothelioma presenting to a tertiary referral center. The nomogram includes values for total glycolytic volume on FDG-PET scan in SUV milliliters, presence or absence of >10 kg weight loss in the previous 6 mo, and presence or absence of pleurodesis in the previous 6 mo.

because the relationship between total glycolytic volume and risk for death is nonlinear. The inclusion of a prognostic nomogram that incorporates a quantitative imaging parameter is novel and potentially clinically useful; however, we acknowledge that this model was derived from relatively small patient numbers. Nevertheless, survival outcomes are available for almost all patients. Although internally cross-validated by bootstrapping, they should be refined using additional data from other centers to increase subject numbers and reliability and show broader applicability outside of our site. This should be followed by validation using an independent data set. Although it would be clinically useful to include an estimate of confidence intervals surrounding prognostic estimates, these are currently broad because of the sample size limitations.

This patient group included patients presenting to a tertiary referral centre for either diagnosis or a management opinion. Most of the patients had a good performance status, and this may reflect a high awareness of symptoms of mesothelioma in Western Australia with consequent early referral or selection bias in those patients who were referred to this tertiary referral centre. Furthermore, participants were those who were well enough to consent to participate in a study, which entailed additional investigations. Hence, the results of this study may not be applicable to those with poor performance status at presentation. Nevertheless, the patients in this study are similar to those likely to be offered therapeutic clinical trials. The patient group was not treated with a uniform management protocol, and this may be a potential limitation of the applicability of the nomogram.

Despite these caveats, this is one of the largest reported PET imaging series in mesothelioma published to date. This study confirms the poor prognosis of patients with sarcomatoid mesothelioma and suggests, together with numerous previous studies, that histology alone is an important prognostic factor that should be considered in clinical trial stratification. We have also for the first time shown that a parameter incorporating volumetric and metabolic information (TGV), in addition to clinical parameters, can have prognostic importance in this patient population and that quantitative information derived from PET scanning can be incorporated into a simple nomogram. Although requiring further development and validation, this strategy may allow clinicians to incorporate PET imaging information into information provided to patients on prognosis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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