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Dynamic contrast-enhanced CT for the assessment of tumour response in malignant pleural mesothelioma: a pilot study

Eyjolfur Gudmundsson[1] · Zacariah Labby[1,3] · Christopher M. Straus[1] · William F. Sensakovic[1,4] · Feng Li[1] · Buerkley Rose[2] · Alexandra Cunliffe[1,5] · Hedy L. Kindler[2] · Samuel G. Armato III[1]

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Abstract

Objectives The aim of this pilot study was to investigate the utility of haemodynamic parameters derived from dynamic contrast-enhanced computed tomography (DCE-CT) scans in the assessment of tumour response to treatment in malignant pleural mesothelioma (MPM) patients.

Methods The patient cohort included nine patients undergoing chemotherapy and five patients on observation. Each patient underwent two DCE-CT scans separated by approximately 2 months. The DCE-CT parameters of tissue blood flow (BF) and tissue blood volume (BV) were obtained within the dynamically imaged tumour. Mean relative changes in tumour DCE-CT parameters between scans were compared between the on-treatment and on-observation cohorts. DCE-CT parameter changes were correlated with relative change in tumour bulk evaluated according to the modified RECIST protocol.

Results Differing trends in relative change in BF and BV between scans were found between the two patient groups ($p = 0.19$ and $p = 0.06$ for BF and BV, respectively). No significant rank correlations were found when comparing relative changes in DCE-CT parameters with relative change in tumour bulk.

Conclusions Differing trends in the relative change of BF and BV between patients on treatment and on observation indicate the potential of DCE-CT for the assessment of pharmacodynamic endpoints with respect to treatment in MPM. A future study with a larger patient cohort and unified treatment regimens should be undertaken to confirm the results of this pilot study.

Key Points

- *CT-derived haemodynamic parameters show differing trends between malignant pleural mesothelioma patients on treatment and patients off treatment*
- *Changes in haemodynamic parameters do not correlate with changes in tumour bulk as measured according to the modified RECIST protocol*
- *Differing trends across the two patient groups indicate the potential sensitivity of DCE-CT to assess pharmacodynamic endpoints in the treatment of MPM*

Keywords Mesothelioma · Multidetector computed tomography · Response Evaluation Criteria in Solid Tumours · Haemodynamics · Perfusion imaging

✉ Eyjolfur Gudmundsson
egudmundsson@uchicago.edu

[1] Department of Radiology, The University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637, USA

[2] Department of Medicine, The University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637, USA

[3] Present address: University of Wisconsin School of Medicine and Public Health, Madison, WI 53792, USA

[4] Present address: Imaging Administration, Florida Hospital, Orlando, FL 32803, USA

[5] 3M, St. Paul, MN 55144, USA

Abbreviations

BF	Tissue blood flow
BV	Tissue blood volume
CI	Confidence interval
DCE-CT	Dynamic contrast-enhanced computed tomography
MPM	Malignant pleural mesothelioma
RECIST	Response Evaluation Criteria in Solid Tumours

Introduction

Malignant pleural mesothelioma (MPM) is a rare malignancy that affects the pleura, a membrane that surrounds the lungs and lines the inner wall of the thoracic cavity. The primary cause of MPM is exposure to asbestos, with the disease on average appearing 40 years following initial exposure to the material. Prognosis is poor, with a median survival of approximately 1 year [1, 2]. Computed tomography (CT) is the primary imaging modality used for the diagnosis and evaluation of MPM. Presentation of the disease on CT scans can present challenges, since the tumour has a similar appearance to the surrounding soft tissue and pleural effusion [3].

The standard clinical method to assess MPM tumour response to treatment is based on the modified Response Evaluation Criteria in Solid Tumours (RECIST) guidelines and involves image-based linear thickness measurements made at up to six locations in the chest [4]. Patients are subsequently classified on the basis of changes in these summed thickness measurements as partial response, progressive disease and stable disease according to the original RECIST criteria for solid tumours [5]. MPM tumour is typically aspherical, casting doubt on the applicability of the RECIST criteria to the classification of MPM tumour response [6]. Imaging-based measurement of MPM tumour volume has received some attention by researchers recently as a potential marker for patient response to treatment [7–9].

Novel molecularly targeted therapies are under active development for use in the treatment of MPM [10]. Vascular endothelial growth factor signalling has been found to play a key role in MPM biology, which has led researchers to investigate antiangiogenic therapies for use in the treatment of MPM [11, 12]. Both immunotherapeutic and antiangiogenic agents used in the treatment of cancer have been found to produce radiologic tumour response incompatible with the RECIST protocol, giving rise to other proposed response criteria for these types of therapy [13–15]. Studies have shown that haemodynamic parameters derived using DCE-CT may be sensitive to the decrease in tumour vascularisation induced by both cytotoxic and targeted cancer therapies in various types of cancer [16].

Dynamic contrast-enhanced CT (DCE-CT) is an imaging technique that involves the repeated acquisition of images during and following the intravenous injection of contrast media [17, 18]. DCE-CT adds a temporal component to a CT scan that allows for the tracking of blood flow to different tissues over the duration of an imaging procedure. In this way, information can be obtained on the haemodynamic properties of the tissues of interest. DCE-CT has been proposed as an alternative to standard imaging-based methods of response assessment based on changes in tumour morphology and has recently been applied to the assessment of tumour response in a variety of cancers, including non-small cell lung cancer and hepatocellular carcinoma [16, 19, 20].

In recent years, imaging techniques that provide direct information on tumour function have been researched widely as ways to providing earlier indicators of treatment efficacy. Chemotherapeutic treatments are known to alter the haemodynamic characteristics of a variety of cancers and earlier indicators of tumour therapeutic response would prove valuable in the treatment of MPM. The aim of this pilot study was to investigate the ability of haemodynamic information derived from DCE-CT scans to assess tumour response in MPM patients.

Materials and methods

Patient cohort

Patients were considered eligible for this study if they had been diagnosed with MPM with pathological confirmation, and if they were scheduled to receive a clinically indicated standard contrast-enhanced chest CT scan. Patients were also required to have had tumour with a thickness of at least 1 cm located axially between the superior-most point of the diaphragm and the superior-most point of the aortic arch on a previous chest CT examination. This requirement ensured that patients would have a sufficient volume of disease to allow for quantitative analysis. Furthermore, patients were only included if they were not considered potential candidates for surgical intervention and had not undergone talc pleurodesis in the 3 months prior to the first DCE-CT scan.

The final patient cohort included 14 patients, of which nine were on chemotherapeutic treatment and five on observation not receiving therapy. Patient accrual occurred from mid-2010 to late 2013, and the study was approved by the institutional review board at the University of Chicago. All patients provided written consent for their participation. As of June 1, 2016, 13 out of 14 patients had died (median survival from diagnosis 1225 days, range 281–2717 days). The final patient cohort is summarised in Table 1.

DCE-CT protocol

A Philips Brilliance iCT 256-slice scanner was used for all scans used in this study. All DCE-CT acquisitions were integrated with the standard imaging protocol for clinically indicated chest CT scans for MPM patients. The image-acquisition protocol included two dynamic contrast-enhanced phases, one prior to and one following a standard CT scan of the full chest. First, a scout scan was performed to localise the anatomic region to be dynamically imaged, which was set to the scanner's maximum axial width of 55 mm for acquisitions not requiring table movement. The dynamic section of each patient was chosen such that it included clearly visible tumour located as superior as possible to minimise the effects of respiratory motion. Furthermore, all dynamic sections were positioned between the top of the aortic arch and the top of the diaphragm. Iohexol contrast media (brand name Omnipaque, 350 mg/ml iodine concentration; Amersham

Table 1 Patient characteristics (n = 14)

Characteristic	N (%)
Sex	
Male	11 (79%)
Female	3 (21%)
Age at diagnosis (years)	
Median	76
Range	52–84
Histology	
Biphasic	2 (14%)
Desmoplastic	1 (7%)
Epithelioid	10 (71%)
Sarcomatoid	1 (7%)
Treatment regimen	
No treatment	5 (36%)
ARQ 197	1 (7%)
Carboplatin, pemetrexed	1 (7%)
CBP501, cisplatin, pemetrexed	1 (7%)
Cisplatin, pemetrexed	2 (14%)
GDC-0980	1 (7%)
Pemetrexed	1 (7%)
Vorinostat	2 (14%)

Health, Princeton, NJ) was used in the standard volume (90 ml) for a full chest CT scan followed by 30 ml of saline chaser. The injection rate was 6 ml/s.

The dynamic acquisition protocol consisted of an early phase of 20 scans with a 3-s temporal sampling and a later phase of 5 scans with a 5-s temporal sampling following the full chest CT scan. Image acquisition of the first dynamic phase began concurrently with the injection of contrast. Patients were instructed to use shallow breathing during the two dynamic phases. The start time of the second dynamic phase varied slightly across patients; the median start time of the second dynamic phase was 114 s after injection (range 108–213 s). The imaging parameters of the dynamic phases were set to 120 kVp with 100 mAs (0.33 s rotation time) for the initial 10 patients accrued for this study. The kVp setting was changed to 100 kVp for both scans of the last four patients included in the study, following an optimisation study of exposure parameters with respect to image quality and patient dose. This change was expected to lead to a slight increase in image noise; however, the scans remained easily visually interpretable after the change in kVp. Reconstructions for the DCE-CT acquisitions were set for 3-mm slices using filtered back projection and the standard kernel without edge enhancement and a median pixel size of 0.66 mm (range 0.56–0.69 mm).

Phantom studies indicated that the dynamic component of the imaging protocol would contribute approximately 1.5 times the dose of the standard chest CT scan, a finding based on the approximate linear scaling relationship between patient effective dose in CT and the reported dose–length product when the same body region is imaged [21, 22]. Each patient underwent two DCE-CT scans at 60-day intervals on average (median 50 days, range 41–126 days) in conjunction with standard clinically indicated scans.

Image post-processing and quantitative analysis

DCE-CT data were analysed using in-house software. Data acquired during the second dynamic phase were not used in the analysis because of the start-time variability across patients. Images were corrected for motion across dynamic time points through deformable registration of all axial sections at each individual time point of the dynamic phase to the 20th dynamic time point using the Advanced Neuroimaging Tools software package, which utilises a diffeomorphic symmetric normalisation transform for deformable registration [23]. Volumetric regions were manually constructed by an imaging scientist trained in thoracic anatomy around all visible MPM tumour on the dynamic sections of each patient. Temporal

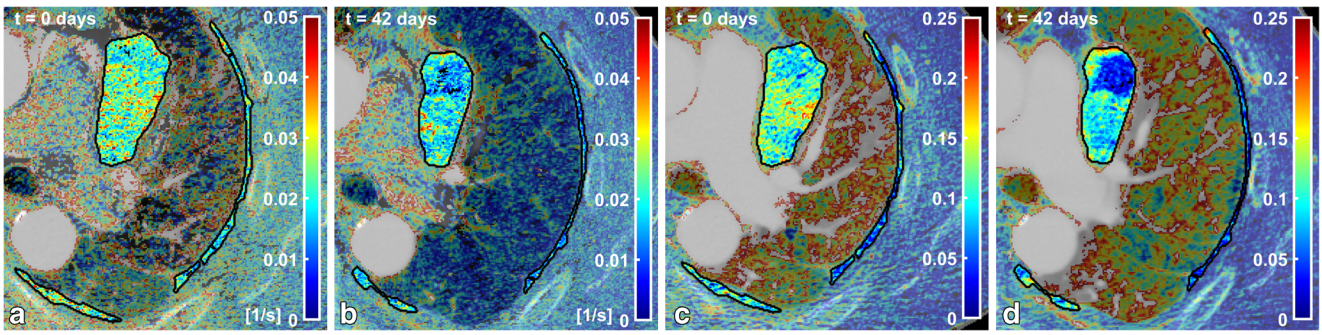

Fig. 1 Example DCE-CT parameter maps of a patient on vorinostat treatment in this study: BF parameter map, **a** scan 1, **b** scan 2; BV parameter map, **c** scan 1, **d** scan 2. MPM tumour regions shown with black solid lines. The parameter map outside tumour regions is partially transparent and overlaid on the corresponding greyscale CT section. This patient showed a 22% decrease in BF, an 8% decrease in BV and a 10% decrease in modified RECIST tumour thickness measurements between scans. BF tissue blood flow, BV tissue blood volume, DCE-CT dynamic contrast-enhanced computed tomography, RECIST Response Evaluation Criteria in Solid Tumours

Table 2 Median change in tumour DCE-CT parameters between scans for the two patient groups

DCE-CT parameter	Patient group	Median change (range)	*p* value	HL estimate (95% CI)
BF	Treatment	− 16.1% (− 22.2% to 8.4%)	0.19	− 11.7% (− 19.6%, 4.3%)
	Observation	− 1.9% (− 6.7% to 0.1%)		
BV	Treatment	− 9.4% (− 18.6% to 11.4%)	0.06	− 14.5% (− 23.3%, 3.5%)
	Observation	5.8% (− 1.5% to 14.5%)		

BF tissue blood flow, *BV* tissue blood volume, *CI* confidence interval, *DCE-CT* dynamic contrast-enhanced computed tomography, *HL* Hodges–Lehmann estimate of the median difference in relative change between the treatment and observation groups

p values were calculated using a two-sided Wilcoxon rank-sum test

minimum- and maximum-intensity projection image sets were used to exclude visible calcifications, blood vessels, collapsed lung and pleural effusion from tumour regions. Fissural tumour, tumour within the hilar region, and tumour invading the chest wall were excluded by following expected pleural margins, using the ribs as reference. A volumetric region was constructed within the ascending aorta close to the level of bifurcation of the pulmonary artery to measure the arterial input function required for the calculation of DCE-CT parameters. All regions were reviewed and validated by an experienced thoracic radiologist at our institution.

DCE-CT parameter maps of tissue blood flow (BF) and tissue blood volume (BV) were obtained using the maximum slope method. Figure 1 shows example BF and BV parameter maps from a patient on treatment in this study. BF was calculated as the ratio of the maximum initial slope in the tissue and the maximum arterial enhancement over baseline, and was expressed in units of seconds^{-1} [17, 18]. BV was calculated as the unitless ratio of the maximum tissue enhancement over baseline and the maximum arterial enhancement over baseline [24, 25]. Tumour DCE-CT parameter values were calculated as the mean value of the respective parameter map across all pixels within the volumetric tumour regions.

Change in tumour bulk was assessed using summed linear thickness measurements acquired by a research radiologist on the full chest CT scan according to the modified RECIST protocol [4].

Statistical analysis

Statistical comparisons were made using Revolution R Enterprise 6.1.0 (Revolution Analytics, Mountain View, CA) running R 2.14.2. The Shapiro–Wilk test revealed that relative changes in DCE-CT parameter values between scans did not follow a normal distribution. Therefore, the two-sided Wilcoxon rank-sum test was used to test the null hypothesis that the distributions of relative changes in BF and BV were identical between patients on treatment and patients on observation. Point estimates of the median differences in relative change in BF and BV between scans when comparing a patient on treatment with a patient on observation were obtained using the Hodges–Lehmann estimator, and nonparametric 95% confidence intervals

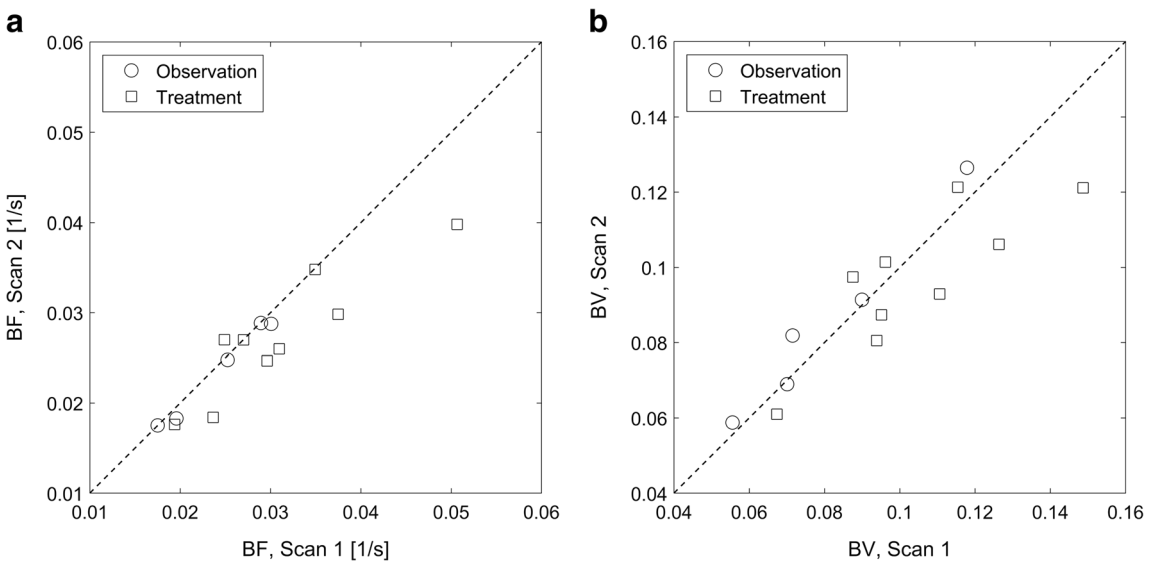

Fig. 2 Mean DCE-CT parameter values (**a** BF and **b** BV) in patients on observation and patients on treatment. The dashed line shows the line of equality. BF tissue blood flow, BV tissue blood volume, DCE-CT dynamic contrast-enhanced computed tomography

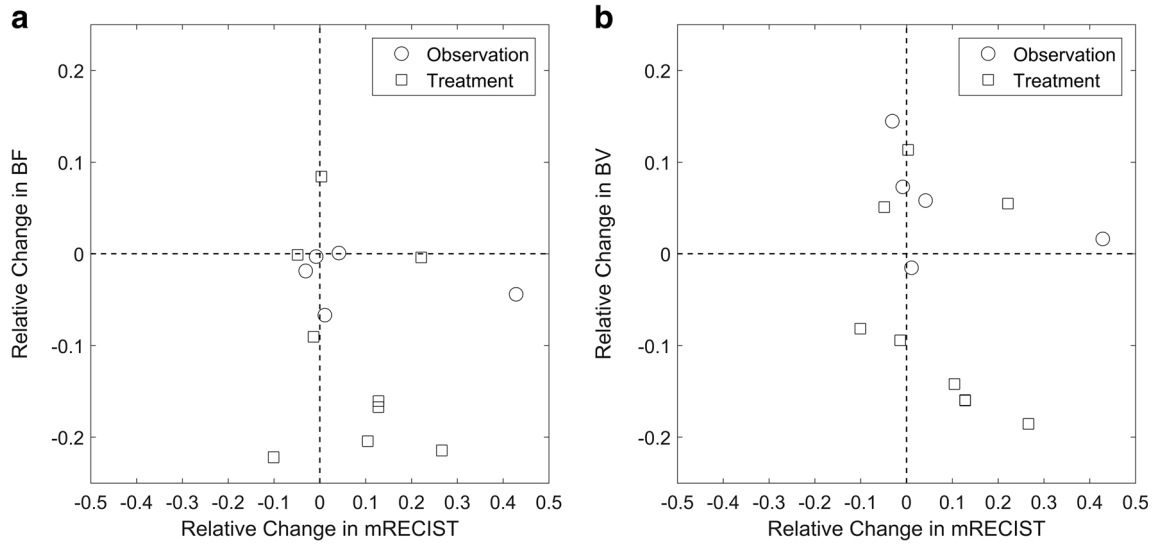

Fig. 3 Relative change in mean DCE-CT parameter values (a BF and b BV) in patients on observation and patients on treatment as a function of relative change in tumour bulk as measured by modified RECIST. The dashed lines represent no change between scans. Note that the scale of the x-axis differs by a factor of 2 from that of the y-axis. BF tissue blood flow, BV tissue blood volume, DCE-CT dynamic contrast-enhanced computed tomography, RECIST Response Evaluation Criteria in Solid Tumours

(CI) for this difference were obtained using the method described by Bauer [26, 27].

Spearman's rank correlation coefficient ρ was calculated to assess the correlation between relative change in DCE-CT parameter values and relative change in tumour bulk between scans.

The Bonferroni correction was applied to the significance level of all statistical tests to account for the number of comparisons made. Since eight statistical tests were made, the significance level of individual comparisons was adjusted to $\alpha = 0.05/8 = 0.0063$, according to the Bonferroni correction [28].

Results

Tumour volume

The median volume of MPM tumour used for DCE-CT parameter calculation across all scans was 41.6 cm^3 (range 8.6–149.9 cm^3). This corresponded to a median fraction of 9% of the total volume of MPM tumour within each patient's thorax, as estimated using an in-house semi-automated tumour segmentation method (range 4–75%) [9].

DCE-CT parameters

Table 2 shows the median relative change in BF and BV between the two scans for patients on treatment and for patients on observation. The distributions of relative change in BF and BV between scans in the two patient groups were not found to be significantly different ($p = 0.19$ and 0.06 for BF and BV, respectively). The Hodges–Lehmann estimates (95% CI) of the median difference in relative change in BF and BV when comparing patients on treatment with patients on observation were − 11.7% (− 19.6%, 4.3%) and − 14.5% (− 23.3%, 3.5%), respectively. Figure 2 shows the mean BF and BV for scan 2 as a function of scan 1 for both patient cohorts. The line of equality is shown as a dotted line.

Figure 3 shows relative changes in BF and BV as a function of relative change in tumour bulk as measured by modified RECIST, with dashed lines showing the lines of no change between scans. Table 3 presents rank correlation statistics comparing mean relative change in BF and BV between scans to relative change in tumour thickness between scans as measured using modified RECIST. The p values are based on a null hypothesis of $\rho = 0$. No significant correlation was found between change in either BF or BV and change in tumour bulk.

Table 3 Spearman rank correlation coefficients ρ and the corresponding p values for correlation between relative changes in DCE-CT parameters and relative change in tumour bulk as measured using modified RECIST

DCE-CT parameter	$\rho_{\text{All patients}}$	$\rho_{\text{Treatment}}$	$\rho_{\text{Observation}}$
BF	− 0.165	− 0.05	0.1
	($p = 0.57$)	($p = 0.91$)	($p = 0.95$)
BV	− 0.437	− 0.433	− 0.5
	($p = 0.12$)	($p = 0.25$)	($p = 0.45$)

BF tissue blood flow, *BV* tissue blood volume, *CI* confidence interval, *DCE-CT* dynamic contrast-enhanced computed tomography, *RECIST* Response Evaluation Criteria in Solid Tumours

p values were calculated for a null hypothesis of $\rho = 0$

Discussion

Compared with patients on observation, patients on treatment in the current study showed an overall decrease in BF and BV between scans. Although these differences did not reach statistical significance, the observed trends suggest the potential utility of DCE-CT parameter analysis in the assessment of pharmacokinetic endpoints for MPM patients. The decrease in both BF and BV between scans for patients on treatment is consistent with the expectation that chemotherapeutic agents disturb tumour function. No significant rank correlation was found between relative change in DCE-CT parameters between the two scans of each patient and relative change in tumour bulk between the two scans as measured according to the modified RECIST protocol. This result could be due to the greater sensitivity of DCE-CT parameters to the altering effects of chemotherapeutic agents on tumour function than that of traditional response measures, which rely solely on disease morphology; additional studies will be required to further evaluate this effect.

Application of DCE-CT to the assessment of MPM tumour response has been limited. Meijerink et al. [29] included two MPM patients within their cohort of 16 patients; BF was found to have decreased substantially for both patients following antiangiogenic treatment. The patient cohort of the current study included two patients on antiangiogenic treatment (ARQ 197 and GDC-0980); the relative change in BF between scans for these two patients was found to be − 0.4% and − 21.4%.

The unique morphology and growth pattern of MPM affects the analysis of DCE-CT data sets. The axial and lateral extent of MPM tumour can differ greatly from other cancers of the thorax to which DCE-CT analysis has previously been applied (e.g. non-small cell lung cancer). This study used in-house software specifically designed for analysis of such regions.

This pilot study had several limitations. The patient cohort for the study was small, and the heterogeneity of the treatment cohort in terms of treatment regimens further limited the conclusions that can be drawn. Correlation of haemodynamic change with patient survival to evaluate treatment efficacy was not pursued because of the aforementioned non-uniformity of treatments within the treatment group and the inability to control for treatments and interventions outside the approximate 2-month window for which the patients were monitored in our study. A future DCE-CT study of MPM patients could be designed to include only patients undergoing the same treatment, which would allow for correlation of haemodynamic change with patient survival. The second dynamic imaging phase of the DCE-CT protocol for this study was deemed unusable for DCE-CT parameter comparison between patients because of variability in the starting time of this phase between scans; this variability did not impact the calculation of the first-pass DCE-CT parameters used in this study. The mean transit time, as a measure of tumour contrast washout, requires imaging at the latter end of the DCE-CT protocol; the imaging protocol for future studies should be modified to standardise the start time of the second dynamic phase and to ensure that sufficient washout has occurred.

In this study, the standard CT imaging protocol for MPM patients was modified to include DCE-CT imaging of two patient groups, one on chemotherapeutic treatment and one on observation. Each patient underwent two DCE-CT scans. Relative change in the DCE-CT parameters BF and BV showed differing trends across the two patient groups, thus indicating the potential sensitivity of DCE-CT to assess pharmacodynamic endpoints in the treatment of MPM. No significant correlations were found between relative changes in DCE-CT parameters and changes in tumour bulk as measured according to the modified RECIST protocol. Evaluation of the relationship between DCE-CT parameter change and tumour response to treatment or patient survival will require a larger and more consistent group of patients on unified treatment regimens.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Samuel G. Armato III, Ph.D., at the University of Chicago.

Conflict of interest The authors of this manuscript declare relationships with the following companies: SGA receives royalties and licensing fees for computer-aided diagnostic technology through the University of Chicago. SGA is a consultant for Aduro Biotech, Inc.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional review board approval was obtained.

Methodology
- prospective
- diagnostic or prognostic study
- performed at one institution

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