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# Early Response to Chemotherapy in Malignant Pleural Mesothelioma Evaluated Using Diffusion-Weighted Magnetic Resonance Imaging: Initial Observations

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## ABSTRACT

**Introduction:** We compared the magnetic resonance imaging total tumor volume (TTV) and median apparent diffusion coefficient (ADC) of malignant pleural mesothelioma (MPM) before and at 4 weeks after chemotherapy, to evaluate whether these are potential early markers of treatment response.

**Methods:** Diffusion-weighted magnetic resonance imaging was performed in 23 patients with MPM before and after 4 weeks of chemotherapy. The TTV was measured by semi-automatic segmentation (GrowCut) and transferred onto ADC maps to record the median ADC. Test-retest repeatability of TTV and ADC was evaluated in eight patients. TTV and median ADC changes were compared between responders and non-responders, defined using modified Response Evaluation Criteria In Solid Tumors on computed tomography (CT) at 12 weeks after treatment. TTV and median ADC were also correlated with CT size measurement and disease survival.

**Results:** The test-retest 95% limits of agreement for TTV were −13.9% to 16.2% and for median ADC −1.2% to 3.3%. A significant increase in median ADC in responders was observed at 4 weeks after treatment ($p = 0.02$). Correlation was found between CT tumor size change at 12 weeks and median ADC changes at 4 weeks post-treatment ($r = -0.560$, $p = 0.006$). An increase in median ADC greater than 5.1% at 4 weeks has 100% sensitivity and 90% specificity for responders (area under the curve = 0.933, $p < 0.001$). There was also moderate correlation between median tumor ADC at baseline and overall survival ($r = 0.45$, $p = 0.03$).

**Conclusions:** Diffusion-weighted magnetic resonance imaging measurements of TTV and median ADC in MPM have good measurement repeatability. Increase in ADC at 4 weeks post-treatment has the potential to be an early response biomarker.

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## Introduction

Malignant pleural mesothelioma (MPM) is an aggressive disease, accounting for more than 38,000 deaths per year worldwide.[1] Most patients are unsuitable for curative resection owing to disease stage or fitness. Chemotherapy currently plays a central role in disease management, either as definitive treatment or for neoadjuvant/adjuvant treatment. The overall disease prognosis remains poor, with a median life expectancy of 9.5 months from diagnosis and only 10% survival at 5 years.[2,3]

Given the encouraging efficacy observed from immune checkpoint inhibitors, accurate assessment of disease response provides a potential opportunity for earlier and more aggressive intervention in nonresponders, and conversely abandoning futile systemic therapy. Current treatment response assessment of MPM is reliant on using the modified Response Evaluation Criteria In Solid Tumors version 1.1 (mRECIST v.1.1).[4] Although version 1.1 has clarified several issues unclear from version 1.0 to allow more homogenous tumor measurement, the nonspherical growth pattern of mesothelioma poses substantial challenges for using unidimensional size-based measurements to evaluate tumor burden and the changes with treatment. Furthermore, assessment using computed tomography (CT) is typically made at 12 weeks after systemic therapy commencing and cannot reliably provide early assessment of treatment effects. This is increasingly important as early signals of drug efficacy in mesothelioma tend to be made on objective response rates, or progression-free survival (PFS) rates at 12 weeks, both of which may also be unreliably estimated by mRECIST criteria.

Diffusion-weighted magnetic resonance imaging (DWI) is a functional magnetic resonance imaging (MRI) technique that can quantify disease burden and inform on tissue cellularity to provide better treatment response assessment.[5] DWI is sensitive to the microscopic mobility of water, which reflects underlying tissue cellularity. Water mobility is impeded in cellular tumor tissue, which reveals high signal intensity on DWI and can be segmented to measure the total tumor volume (TTV). At the same time, the extent of water mobility in the disease volume can be quantified by the apparent diffusion coefficient (ADC), which is inversely correlated with tumor cellularity. In responders to treatment, the TTV is hypothesized to decrease, whereas the ADC measurement increases reflecting a reduction in tumor cellularity.[6] Nevertheless, to our knowledge, no previous study has investigated whether changes in TTV and the median ADC of MPM have any relationship with response by size measurement assessed by CT-mRECIST criteria or with disease survival in patients treated with chemotherapy (i.e., standard carboplatin/cisplatin and pemetrexed treatment).

The main aim of our study was to compare the TTV and median ADC in patients with MPM before and at 4 weeks after chemotherapy treatment. The TTV and median ADC changes were compared between responding and nonresponding patients defined using CT mRECIST at 12 weeks after treatment. We evaluated correlations between changes in the TTV and median ADC with changes in CT-based tumor size measurement. We also evaluated whether there was any relationship between the TTV/median ADC values with disease survival.

## Materials and Methods

### Study Design

We conducted a prospective, single-center, non-randomized imaging study at the Royal Marsden Hospital, London, United Kingdom, in a 30-month period (2015–2017). This study was approved by the Institutional Research and Ethics Committee. Patients with histologically proven malignant mesothelioma who were being treated with chemotherapy (carboplatin/cisplatin and pemetrexed) underwent DWI scans before treatment and at 4 weeks post-treatment. CT scans as per standard of care were performed before treatment and at 12 weeks post-treatment. Treatment response in this study was defined using mRECIST v.1.1 criteria at 12 weeks after treatment, and the DWI parameters (TTV and median ADC) were compared between responders/nonresponders and with disease survival. The first eight patients in the study also underwent two baseline DWI studies within 7 days to evaluate the measurement repeatability of the TTV and median ADC.

### Patient Population

Patients with treatment naive, histopathologically confirmed MPM and measurable disease on CT who had no contraindications for MRI were enrolled in the study. Written informed consent was obtained before patient enrollment in the study, and patient information was anonymized before analysis. All patients received standard of care cisplatin or carboplatin with pemetrexed chemotherapy according to institutional standards.

### Imaging Studies

**CT Studies.** CT scans were performed according to institutional standard, after three cycles of cisplatin/carboplatin-pemetrexed chemotherapy, at 12 plus or minus 2 weeks after starting therapy. Baseline CTs were performed at locally referring hospitals; alternatively, an in-house CT was performed if baseline CT was not within 6 weeks of cycle one chemotherapy. Scans were performed on a LightSpeed 16 CT scanner (GE Medical Systems) in the axial plane. Anatomical coverage was

typically from the thoracic inlet to the level of the iliac crest. The image size was 512 by 512 pixels, with slice thickness of 1.25 mm, partitioned for viewing at 3 mm or 5 mm. Pixel size was between 0.68 times 0.68 mm$^2$ and 0.88 times 0.88 mm$^2$ for all patients.

**MRI Studies.** All MRI scans were performed within 2 weeks before commencing therapy and at 4 weeks after starting cycle one of chemotherapy. Imaging was performed on a 1.5 T MR scanner (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany) using surface body array coils. All patients were imaged in the head-first supine position. Morphologic MR imaging included the following: (1) axial T1-weighted three-dimensional (3D) FLASH breath-hold volume interpolated technique with fat-selective prepulse (VIBE) (breath-hold; TR/TE 2.39/0.78 msec; slice thickness 5.0 mm; number of signals averaged 2; FoV read 380 mm; pixel size, 1.5 × 1.5 mm; number of slices: 52); (2) 3D coronal T2-weighted SPACE acquisitions (free breathing with navigator; TR/TE 3500/100; slice thickness, 3.0 mm; number of signals averaged, 1.4; FoV read, 360 mm; pixel size, 1.8 × 1.9 mm; number of slices: 60/64); and (3) coronal dynamic T2-weighted TruFISP sequence (TR/TE 3.02/1.51 msec; pixel size: 0.7 × 0.7 mm; number of slices: 1).

In addition, axial DWI using three b-values (100, 500, 800 s/mm$^2$) were acquired with chemical fat suppression using a free-breathing single-shot spin-echo planar imaging sequence with the autocalibrating parallel imaging technique (GRAPPA). Multiple signal averages (N = 4) were used to average the signal over physiological motion to reduce breathing artifacts and increase the image signal-to-noise. Owing to spatial nonlinearities in the diffusion-encoding gradients,[7] the extent of the imaging volume along the scanner (z-axis) was limited to 25 cm to reduce bias in ADC estimates.[8] Nevertheless, to ensure full thoracic coverage, two imaging stations (30 slices per station, with each covering a range of 15 cm) were acquired. The total time for DWI acquisition was 11 minutes. The DWI sequence was optimized for image quality and acceptable acquisition time using parameters found in Table 1.

For the first eight patients, repeatability test-retest assessment was made by patients undergoing a repeat baseline DWI study at one to seven days after the initial study. The same radiographic team was used to position the patient in the scanner, and imaging was performed using the same imaging protocol as described previously.

## Image and Data Analysis

**CT-mRECIST Analysis.** A radiologist with 5-year experience (SP) in CT performed mRECIST v.1.1 measurements[4] before treatment and at 12 weeks after treatment. In each patient, six measurements of the solid pleural disease were acquired in total, two at each level and across three different levels of the thorax at least 1 cm apart from each other as per criteria. The measurements were taken at levels avoiding regions with adjacent lung collapse or consolidation. These measurements were summed to derive the total tumor size. These measurements were acquired at similar levels and positions in each patient at baseline and at 12-week post-treatment CT studies.

We calculated the percentage change in the total tumor size by comparing the baseline (B) and post-treatment (P) CT measurements as follows:

% change = [(P − B) / B] × 100

Tumor response was defined as per the mRECIST v.1.1 criteria[4]: Complete response was recorded when lesions were no longer visible on CT, with no evidence of tumor elsewhere. Partial response (PR) was defined as minimum 30% decrease in the total tumor size at the 12-week post-treatment. Progressive disease (PD) was defined as an increase of at least 20% in the total tumor size at the 12-week post-treatment scan, with a minimum absolute growth of 5 mm as per mRECIST v.1.1.[4] Stable disease was defined as an increase in tumor size that does not qualify for PD or a decrease that does not qualify as PR.

## DWI Analysis

The TTV was segmented using a 3D semiautomatic tool, GrowCut,[9,10] coded within the Osirix Medical viewing software[11] with background and foreground seeds drawn on the normal tissue and disease, respectively, on the mean b = 100 s/mm$^2$ images. On these images, both solid tumor and cystic disease/effusions have high signal intensities while maintaining good image signal-to-noise. The segmented regions of interest (ROIs) were reviewed by a radiologist with more than 10 years of experience in body DWI (DMK), who adjusted the segmentations to ensure that the drawn regions represented the full disease extent but excluding adjacent lung consolidation or atelectasis. The ROIs were then transferred to the ADC maps. We applied a threshold to classify solid disease, by removing voxels with ADC values more than 2000 × 10$^{-3}$ mm$^2$/s representing cystic or likely nonviable disease.[12] From this, the adjusted TTV and the associated median ADC of the solid disease volume were recorded for each patient (Fig. 1).

The TTV and median ADC of the solid disease in each patient were calculated at baseline and at 4 weeks post-treatment.

## Statistical Analysis

The ADC of MPM averaged over different histologic subtypes is 1.10 × 10$^{-3}$ mm$^2$/s with SD of 0.1 × 10$^{-3}$

**Table 1.** Parameters of the DWI Sequence

| Parameters | Values | Parameters | Values |
|---|---|---|---|
| Sequence | Single-shot EPI | Coil | Body array coil |
| Breathing | Free breathing | Fat-suppression technique | SPAIR |
| Slice orientation | Axial | Phase-encode direction | Anteroposterior |
| Diffusion gradient Scheme | Single spin echo | Diffusion-encoding scheme | Orthogonal |
| b-value (s/mm$^2$) | 100/500/800 | Parallel imaging | GRAPPA $= 2$ |
| Ref. line | 30 | Repetition time (msec) | 8100 |
| Echo time (msec) | 82 | NSAs | 4 (separated) |
| Slice thickness (mm) | 5 | Slice gap (mm) | 0 |
| Number of slices per volume | 30 | Acquired pixel size (mm $\times$ mm) | $3 \times 3$ |
| Field of view | $380 \times 273$ | Acquired matrix | $128 \times 92$ |
| Readout bandwidth (Hz/pixel) | 1860 | Echo-train length | 1 |
| Partial Fourier factor | 6/8 | | |

DWI, diffusion-weighted magnetic resonance imaging; EPI, echo-planar imaging; NSA, number of signal average; Ref., reference.

mm$^2$/s.[13] Therefore, a sample size of 21 patients would allow us to detect the 10% increase in the median ADC values in responders to treatment with 80% power (using Mann-Whitney $U$ test; one-sided $\alpha = 0.05$).

Statistical analysis was performed using MedCalc software (MedCalc Software Ltd., Ostend, Belgium, version 19.6.1). For the eight patients who underwent two baseline DWI repeatability studies, we performed Bland-Altman analysis to determine the 95% limits of agreement (coefficient of repeatability) of the TTV and median ADC in percentage difference.

We compared the TTV and median ADC values measured at 4 weeks between responders and non-responders, defined by mRECIST CT classification at 12 weeks after therapy, using the Wilcoxon signed rank test. In addition, Pearson correlation statistics was used to compare the relationship of the following: (1) percentage CT tumor size change at 12 weeks with percentage change in TTV at 4 weeks, (2) percentage CT tumor size change at 12 weeks with percentage change in median ADC at 4 weeks, and (3) percentage change in TTV with percentage change in volume at 4 weeks. For significant correlations, we performed receiver operating curve (ROC) analysis to determine the Youden index for identifying responders to treatment. For all analyses, a $p$ value of less than 0.05 was deemed statistically significant.

## Results

### Patient Characteristics

A total of 24 patients with histopathologically proven MPM (17 epithelioid, six biphasic, one sarcomatoid) were enrolled in the clinical trial. In total, 23 patients had assessable disease on MRI and underwent baseline scan and at 4-week post–pemetrexed-based chemotherapy treatment. One patient was excluded because of image artifacts confounding disease measurements.
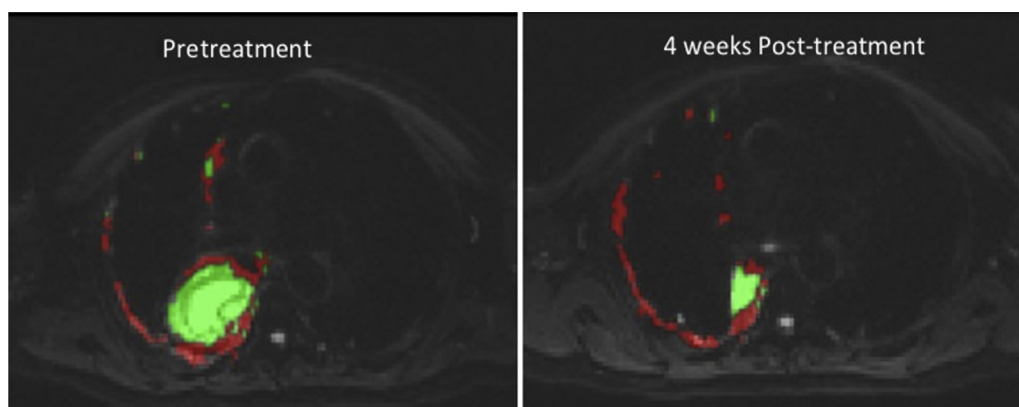


**Figure 1.** DWI images (b $= 100$ mm$^2$/s) of a 75-year-old male patient with MPM at pretreatment and at 4 weeks post-treatment. The red regions overlay on the b100 images represent the classified solid tumor, whereas the green regions reveal predominant cystic disease. DWI, diffusion-weighted magnetic resonance imaging; MPM, malignant pleural mesothelioma.

The median interval between baseline and 4-week post-treatment MRI scans was 4.3 weeks (range: 2.9–6.1 wk). There were 20 males, 3 females, with a median age of 70 years (range 57–78 y). The disease was located in the right hemithorax in 19 patients and in the left hemithorax in four patients. All patients had Eastern Cooperative Oncology Group performance score of 0 to 1 and received cisplatin-carboplatin-pemetrexed chemotherapy. Of 24 patients, 19 (79%) received carboplatin-pemetrexed and five (21%) received cisplatin-pemetrexed, and all received six cycles of chemotherapy.

## Measurement Repeatability

By Bland-Altman analysis, the 95% limits of agreement for the TTV of solid tumor were found to be −13.9% to 16.2%. The 95% limits of agreement for the median ADC value of solid tumor were −1.2% to 3.3%.

## CT Evaluation of Treatment Response

By CT-mRECIST, the response to chemotherapy was as follows: 0 of 23 (0%) had complete response, 3 of 23 (13.0%) had PR, 15 of 23 (65.2%) had stable disease, and 5 of 23 (21.7%) had PD, resulting in an objective response rate of 13%. Patients with stable disease and PD were deemed nonresponders in our analyses, whereas patients having PR were considered responders.
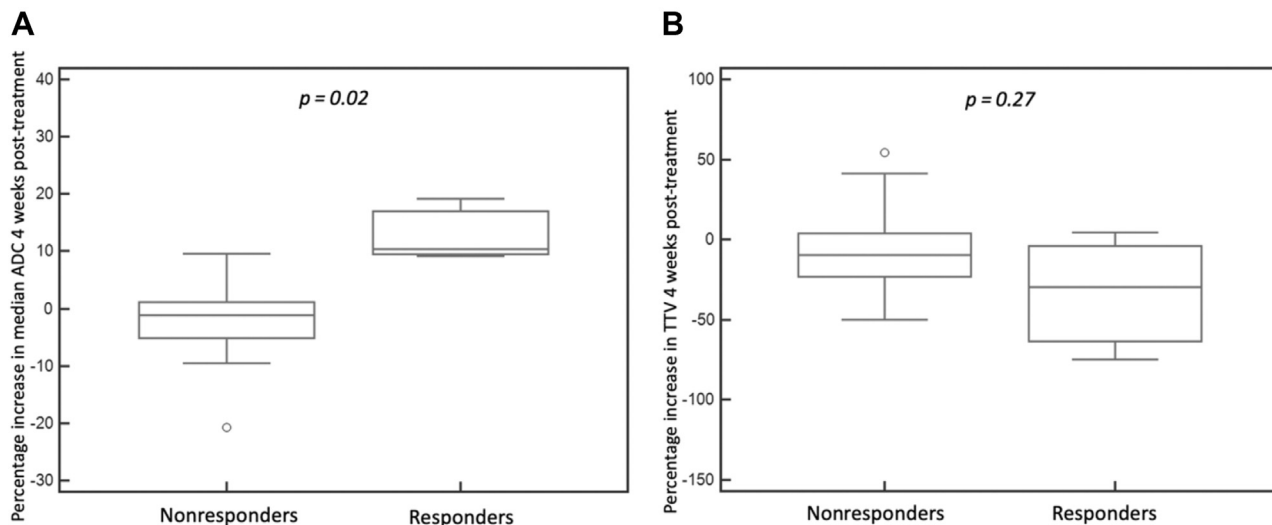
## DWI Assessment of Responders Versus Nonresponders at 4 Weeks

When evaluating the DWI response to treatment at 4 weeks, we found that the responders (n = 3) had a significantly larger percentage increase in the median ADC of the solid tumor than the nonresponders (n = 20) (10.4% versus −1.12%, $p = 0.02$) Fig. 2A. The solid tumor volume did not reveal a significant decrease between responders and nonresponders (−29.6% versus −9.7%, $p = 0.27$) Fig. 2B.

## Correlations Between mRECIST and DWI (TTV, ADC)

**Percentage TTV Change at 4 Weeks and Percentage Size Change by mRECIST at 12 Weeks.** There was no significant correlation between the percentage DWI TTV change at 4 weeks post-treatment and percentage CT tumor size change by mRECIST at 12 weeks ($r = 0.33$, $p = 0.13$) (Fig. 3A).

**Percentage Median ADC Change at 4 Weeks and Percentage Size Change by mRECIST at 12 Weeks.** There was moderate negative correlation between the percentage change in median ADC at 4 weeks



**Figure 2.** Box and whisker plots revealing (*A*) percentage change in median ADC value at 4 weeks post-treatment and (*B*) percentage change in TTV at 4 weeks post-treatment and for responders versus nonresponders defined by modified RECIST criteria on CT imaging at 12 weeks post-treatment. The horizontal lines are the medians; the ends of the boxes reveal the lower and upper quartiles (25th and 75th percentiles). The whiskers reveal the fifth and 95th centiles. The circles indicate outliers. Mann-Whitney *U* test was performed to compare between groups, and the *p* values are found on the plots. Responders had a significantly higher percentage increase in median ADC after treatment compared with nonresponders. (*p* < 0.05). ADC, apparent diffusion coefficient; CT, computed tomography; RECIST, Response Evaluation Criteria In Solid Tumors; TTV, total tumor volume.

**A**



**B**
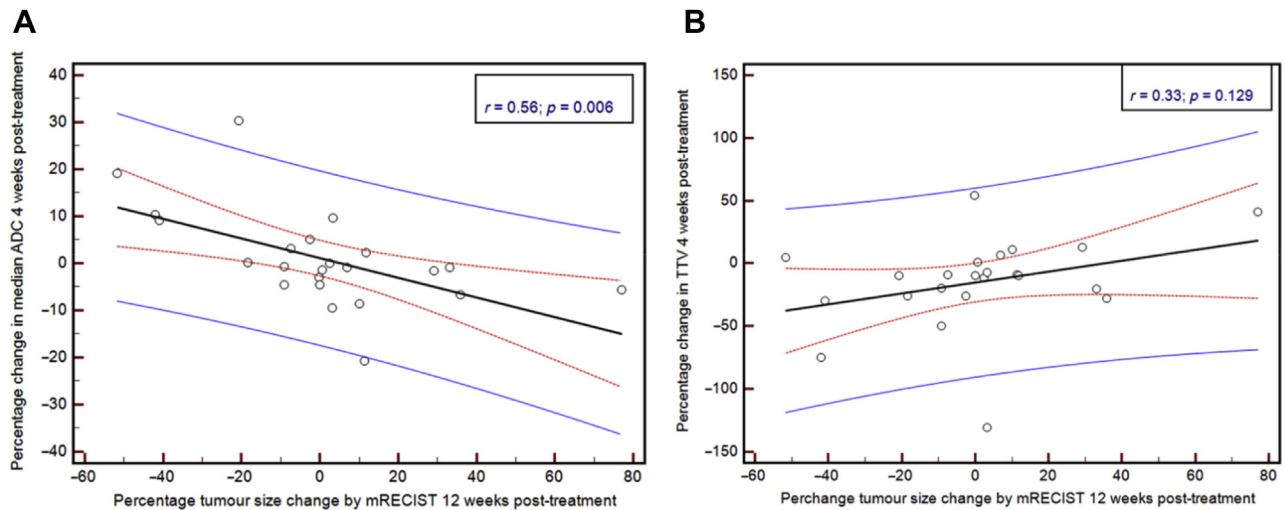
Figure 3. Correlation plots of (A) percentage change in median ADC at 4 weeks with percentage tumor size change by mRECIST on CT at 12 weeks and (B) percentage change in TTV at 4 weeks with percentage tumor size change by mRECIST on CT at 12 weeks. The 95% confidence and prediction intervals of the regression line are found as red-dotted and blue-dotted lines, respectively. There was a moderate correlation between percentage median ADC increase at 4 weeks and percentage tumor size reduction at 12 weeks. ADC, apparent diffusion coefficient; CT, computed tomography; mRECIST, modified Response Evaluation Criteria In Solid Tumors; TTV, total tumor volume.

and percentage CT tumor size change by mRECIST at 12 weeks ($r = -0.56$, $p = 0.005$) (Fig. 3B).

### ROC Analysis

By ROC analysis, we found that an increase of the median ADC by 5.1% after treatment had a high sensitivity of 100% (95% confidence interval [CI]: 29%–100%) and specificity of 90% (95% CI: 68%–99%) for detecting responders at 4 weeks after treatment (Az = 0.93, $p < 0.001$) (Fig. 4).

### Relationship Between Pretreatment DWI Measurements and Disease Survival

Of the 23 patients, there were 21 observed deaths in a 2-year follow-up period. The median overall survival (OS) from starting the treatment was 11 months (range: 1.8–53.4 mo). No correlation was found between the pretreatment solid tumor volume ($r = -0.04$, $p = 0.85$), percentage change in median ADC at 4 weeks post-treatment ($r = -0.21$, $p = 0.34$), or percentage change in TTV at 4 weeks post-treatment ($r = 0.19$, $p = 0.37$) with OS. Nevertheless, there was a moderate correlation between the pretreatment median ADC of solid tumor and the patient OS ($r = 0.45$, $p = 0.031$) (Fig. 5).

## Discussion

To best of our knowledge, this is the first study to date to estimate the total solid tumor burden and its associated water diffusivity measurement (median ADC) to evaluate the treatment effectiveness of patients with MPM after chemotherapy.

DWI derives its signal from the motion (diffusion) of water molecules within the tissue microstructure. Hypercellular tissues (e.g., tumors) with intact cell membranes impede water diffusion and have lower ADC values compared with healthy tissue.[14,15] DWI produces images with high lesion-to-background contrast owing to the low diffusion rates and high T2 relaxation time of water in tumor tissues. This makes it suitable to use DWI images for semiautomatic disease segmentation to provide estimates of the TTVs and the associated global tumor median ADC.[16,17]

When responding to treatment, the cellularity of the tumor decreases leading to an increase in ADC. Documenting the ADC values pretreatment and post-treatment enables the assessment of treatment response; a significant increase in ADC is associated with treatment success.[18–23] In our study, we found that the tumor ADC measured at 4 weeks after therapy could identify responders earlier than conventional CT on the basis of tumor size measurement (RECIST).[24] Studies in different tumor types have revealed that increase in ADC can occur within days of starting treatment and correlate with pathologic response and OS.[19,25–28]

To apply ADC measurements meaningfully for disease assessment, it is important to understand its measurement repeatability, which can result from variations in acquisition parameters across scanners and sites, analysis methods, patient factors, and intraoperator and interoperator variabilities.[29,30] Authors have reported test-retest ADC variability ranging from 3.2% to 8.3% in breast cancer,[30–33] 10% in prostate cancer,[34] and 25% to 30% in the abdomen and liver.[35,36] Nevertheless, the
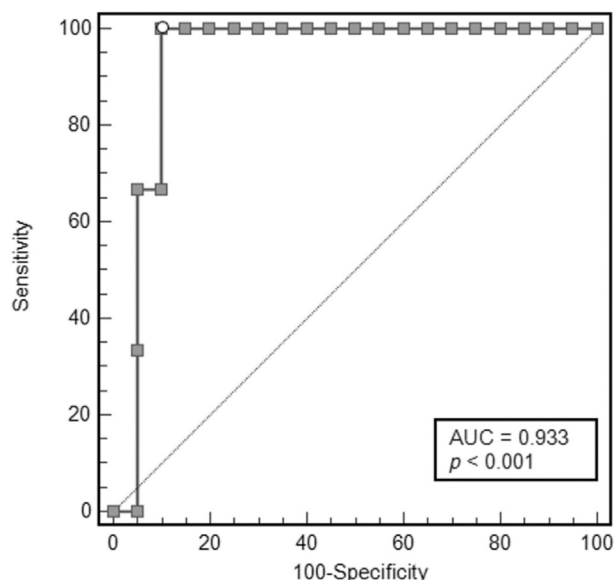
**Figure 4.** Receiver operating curve characteristics of the percentage change in median ADC at 4 weeks post-treatment for identifying responders versus nonresponders to treatment defined by mRECIST on CT imaging at 12 weeks post-treatment. ADC, apparent diffusion coefficient; CT, computed tomography; mRECIST, modified Response Evaluation Criteria In Solid Tumors.

ADC measurement repeatability of mesothelioma in an entire disease volume has not been previously reported. In our study, we found that even using a free-breathing DWI technique, there was excellent ADC measurement repeatability of $-1.2\%$ to 3.3% for the median ADC value of solid tumor. The measurement repeatability of the
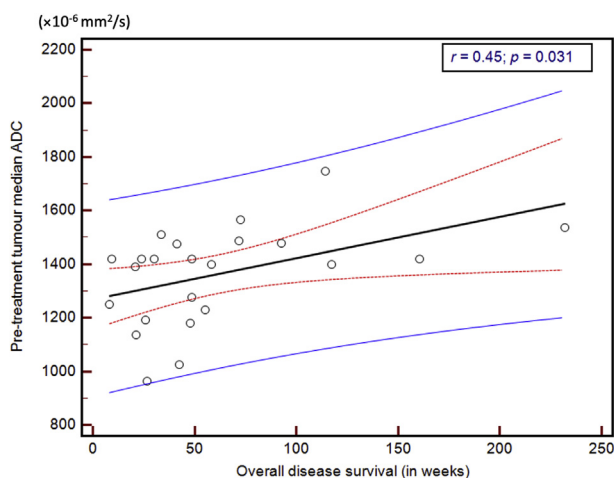


**Figure 5.** Correlation plot of the pretreatment tumor median ADC with overall disease survival. The 95% confidence and prediction intervals of the regression line are found as red-dotted and blue-dotted lines, respectively. There was a moderate correlation between the pretreatment median ADC value with overall disease survival. ADC, apparent diffusion coefficient.

TTV for the solid tumor was also good with the 95% limits of agreement on the mean of $-13.9\%$ to 16.2%. Both the TTV and global ADC were found to be useful for evaluating the response of metastatic bone disease in patients with prostate cancer[16,18] and thus have the potential to also be valuable imaging biomarkers for response assessment in patients with mesothelioma. DWI is a technique that is available on all modern MRI scanners, and the software to process the data to derive TTV and global ADC is progressively being developed on vendor systems.

Although RECIST is widely used in clinical trials, there are challenges in implementing mRECIST for MPM owing to the nonspherical growth pattern of the disease. The rather laborious measurement process and the complex measurement site selection might lead to poorer measurement repeatability (30%) and higher interobserver variability (27%).[37] In addition, mRECIST is not useful for detecting early disease response to treatment. This is particularly problematic in developing new drugs for MPM when overall response rates can be unreliable, mandate measurable disease for the patient population, and defining progression can be problematic leading to variability in defining PFS. Hence, the reliability of single-arm trials for drug development in MPM has proven problematic with many encouraging drugs failing in subsequent larger randomized trials.

In our study, the median ADC of the solid tumor in mesothelioma evaluated by DWI at 4 weeks was found to have a moderate correlation with mRECIST measurements derived from CT at 12 weeks after treatment, suggesting the ADC provides earlier insights into disease response, before standard CT measurements. Moreover, at 4 weeks after treatment, the responders revealed a significantly larger percentage increase in the median ADC (10.4%) value of the solid tumor than the non-responders ($-1.15\%$), which is consistent with literature published on esophageal, rectal, pancreatic, and prostate cancers and myeloma.[19,38-40] Such an early indicator of response would clearly be helpful for optimizing treatment management of MPM as patients who are unlikely to respond could be offered other emerging treatments at an earlier time point. Nevertheless, there was no significant change in the TTV in either the responders or nonresponders at 4 weeks after treatment, nor was there a significant correlation between the percentage TTV change at 4 weeks with CT mRECIST tumor measurements at 12 weeks post-treatment. This suggests that the ADC value is likely to be a more sensitive early response biomarker than the TTV.

By ROC analysis, we found that a median ADC increase of more than 5.1% at 4 weeks post-treatment had a high diagnostic sensitivity of 100% and specificity of 90% for detecting responders to treatment. A 5.1%

increase in ADC is within the limits of repeatability for our technique to confidently detect. Even though the diagnostic sensitivity is associated with a wide CI, the diagnostic specificity seems high with 95% confidence limits of 68% to 99%. Thus, future studies should aim to evaluate ADC as an independent early response biomarker in a larger prospective trial.

Interestingly, we have revealed that the pretreatment ADC values of the solid tumor in MPM could have prognostic value; a positive correlation was identified between the pretreatment tumor median ADC and the patient OS ($r = 0.47$). Nevertheless, change in ADC did not predict OS in our data set. This was perhaps due to an underpowered data set for OS, as the study was powered for response assessment. Other authors have also reported a correlation between baseline ADC values and OS in glioblastoma, cervical cancer, and nasopharyngeal carcinoma.[41–43] Several papers have revealed that low ADC values are correlated with more aggressive histological subtypes, higher cellularity, poor differentiation, nodal involvement, and higher tumor burden.[41,44–46] Kim et al.[47] reported on a cohort of 258 women with invasive breast cancer and found that higher ADC difference between the minimum and maximum ADC pixel values at baseline is associated with poorer distant metastasis-free survival. This suggests that the ADC differences may reflect both tumor cellularity and heterogeneity. Heterogeneous tumors can harbor aggressive subclonal populations that are susceptible to metastasize.

Therapeutics for MPM are now changing for the first time in more than 10 years with the first positive randomized phase 3 trial, CheckMate 743, revealing nivolumab-ipilimumab combination improved OS over cis-/carbo-platin-pemetrexed chemotherapy.[48] This immunotherapy combination will undoubtedly become a standard of care in the near future especially for sarcomatoid disease, and other trials of combination chemotherapy-immunotherapy will also shortly report, potentially also adding to future treatment options in a disease wherein treatment has been unaltered since 2003.[49] Nevertheless, although immune checkpoint inhibitors may be active in MPM, it is unclear which patients derive benefit because CheckMate 743 indicated a group of patients with markedly inferior PFS over chemotherapy before 7 months of follow-up, compared with thereafter, with a marked improvement in PFS for nivolumab-ipilimumab, translating to an overall significant OS benefit in the intention-to-treat trial population. Moreover, atypical response patterns such as pseudoprogression are well characterized with immune-checkpoint inhibitors in MPM, rendering RECIST criteria difficult to implement in routine care for immunotherapy. Additional trials of novel immune strategies for MPM such as cell-based and viral therapies are recruiting for mesothelioma with encouraging preliminary data, and hence developing an early imaging signal of benefit from drug therapy in the immunotherapy era will be critical to optimal drug selection for later phase development. We therefore suggest building on our pilot data with additional larger studies of patients treated with immune-checkpoint, inhibitor-based therapeutics to evaluate and validate our findings that ADC changes at 4 weeks after chemotherapy predict response and further establish DWI as a potential imaging tool for patient and drug selection in MPM.

There are important limitations to our study. First, this clinical study had a small patient cohort. Nonetheless, this statistically powered feasibility study established a suitable imaging technique, quantified the measurement repeatability of TTV and ADC, while providing valuable initial insights toward the potential value of ADC as an early response and prognostic biomarker. Second, although measurement repeatability was established in our study, the intraobserver and interobserver variances were not evaluated as part of this study. Nevertheless, on the basis of TTV and ADC measurements in metastatic prostate cancer, the TTV and ADC were found to have good interobserver and intraobserver agreement.[50] Finally, considering the limitations of response assessment on the basis of CT mRECIST, correlating DWI with additional end points such as time to next treatment, quality of life, and OS could have provided more evidence on the value of MRI as a surrogate for clinical benefit, but further work will help establish this.

In conclusion, in this feasibility study, we found that volume-based analysis of DWI provided good insight into the early functional response of mesothelioma to chemotherapy. Both the TTV and ADC have good measurement repeatability and the ADC changes at 4 weeks after treatment seem to have significant potential as early response and prognostic biomarkers for malignant mesothelioma treatment evaluation.

## CRediT Authorship Contribution Statement

**Sebastian Curcean:** Writing - original draft, Writing - review & editing, Visualization.

**Lin Cheng, Sanjay Popat, Mary O'Brien, Anna Minchom:** Investigation, Writing - review & editing.

**Simona Picchia:** Methodology, Writing - review & editing.

**Nina Tunariu:** Methodology, Investigation, Writing - review & editing.

**David Collins:** Methodology, Software, Validation, Writing - review & editing.

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