Title: A comparison between MRI and CT in the assessment of primary tumour volume in mesothelioma

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Abstract

INTRODUCTION

Primary tumour staging in Malignant Pleural Mesothelioma (MPM) using Computed Tomography (CT) imaging is confounded by perception errors reflecting low spatial resolution between tumour and adjacent structures. Augmentation using perfusion CT is constrained by radiation dosage. In this study, we evaluated an alternative tumour staging method using perfusion-tuned Magnetic Resonance Imaging (MRI).

METHODS

Consecutive patients with suspected MPM were recruited to a prospective observational study. All had MRI (T1-weighted, isotropic, contrast-enhanced 3-Tesla perfusion imaging) and CT (contrast-enhanced) pre-biopsy. Patients diagnosed with MPM underwent MRI and CT volumetry, with readers blinded to clinical data. MRI volumetry was semi-automated, using signal intensity limits from perfusion studies to grow tumour regions within a pleural volume. A similar CT method was not possible, therefore all visible tumour was manually segmented. MRI and CT volumes were compared (agreement, correlation, analysis time, reproducibility) and associations with survival examined using Cox regression.

RESULTS

58 patients were recruited and had MRI before biopsy. 31/58 were diagnosed with MPM and these scans were used for volumetry. Mean (SD) MRI and CT volumes were 370cm^3 and 302cm^3, respectively. MRI volumes were larger (average bias 61.9 (SD 116), 95% limits (-165.5 - 289), moderately correlated with CT (r=0.56, p=0.002) and independently associated with survival (HR 4.03 (95% CI 1.5 – 11.55), p=0.006). CT volume was not associated with

survival, took longer than MRI (mean (SD) 151 (19) v 14 (2) minutes, p=<0.0001) and was less reproducible (inter-observer ICC 0.72 for CT, 0.96 for MRI).

CONCLUSIONS

MRI and CT generate different tumour volumes in MPM. MRI volumes were larger and independently associated with survival. MRI volumetry was quicker and more reproducible than CT.

TRIAL REGISTRATION

ISRCTN10079972

Key Words: Magnetic Resonance Imaging; Computed Tomography; Malignant Pleural Mesothelioma; Staging; Volume; Response Assessment

INTRODUCTION

Primary tumour volume (T-volume) is a critical determinant of survival and a key component of Tumor, Node, Metastases (TNM) staging in most cancers. Simple surrogates of tumour volume, such as unidimensional measurements perform well in other cancers (e.g. Lung Cancer). (1) However, Malignant Pleural Mesothelioma (MPM) forms a complex, rind-like primary tumor that is difficult to accurately measure. As a result, current T-staging describes extent of invasion into adjacent tissues and do not account for tumour size, demonstrating poor concordance with subsequent pathological staging (2) and prognostic accuracy in 'real world' populations. (3) A more representative measure of primary tumour size would likely enhance current TNM staging and could also facilitate improvements in tumour response assessment.

Multiple studies have reported a relationship between CT T-volume and OS. (4-7) However, CT volumetry has not translated to practice because of the laborious nature of the necessary manual segmentation. While this could be offset by evolving semi-automated methods, (8) CT is also fundamentally limited by low soft tissue contrast between areas of tumour and adjacent structures, resulting in high inter-observer variation between readers. (9, 10)

Magnetic Resonance Imaging (MRI) offers higher soft tissue contrast than CT, resulting in increased sensitivity to chest wall and diaphragm invasion, (11-13) higher contrast with adjacent effusion (11) and higher inter-observer agreement in multiple studies. (14, 15) Thus, MRI is potentially a more suitable tool for volumetric T-staging, particularly since it can be augmented by perfusion imaging, which delivers enhanced sensitivity in the

detection of pleural malignancy, even in patients with minimal pleural thickening. (14) While perfusion CT has similar potential to optimize MPM imaging, (16) clinical utilisation of this technique is currently constrained by concerns regarding radiation dosage. (17, 18)

In the current study, we developed and evaluated a novel MRI volumetry protocol in a prospective observational study, making use of perfusion data acquired in the same patients. MRI and CT volumetry techniques were compared, as was their relationship with subsequent OS.

MATERIALS AND METHODS

Study objectives and outcome measures are summarised in Table 1.

1.1 Patient Selection, Recruitment and Design

Patients were recruited prospectively to an initial pilot study and subsequently to an MRI sub-study embedded in the DIAPHRAGM study (ISRCTN10079972) (19) between January 2013 and October 2016. Ethical approval was granted by the West of Scotland Research and Ethics Service (12/WS/0219, 13/WS/0240). Inclusion criteria were: suspected MPM (defined by a pleural effusion or pleural mass lesion) requiring thoracoscopy or image-guided biopsy, sufficient fitness for biopsy, informed written consent. Exclusion criteria were: pregnancy, allergy to gadolinium-based contrast agents, renal impairment (eGFR <30ml/min), known MRI contraindication.

MRI and CT imaging were acquired prior to pleural biopsy and volumetric analyses were only performed in cases diagnosed with MPM. All volumetric studies were performed using

dedicated segmentation software (Myrian®, Intrasense, France). Volumetric readers were respiratory physicians (ST and AK) and a radiologist (GWC) with 8, 4 and 12 years of training and experience in both pleural disease and thoracic imaging respectively. Only the primary reader's analyses (ST for MRI and AK for CT) were used for survival analyses. The secondary reader's analyses (GWC for MRI and ST for CT) were used to assess inter-observer agreement. All readers were blinded to other data and each other's results.

1.2 MRI

1.2.1 MRI Acquisition and MRI volume phantom

MRI scans were acquired using a 3-T Siemens Magnetom scanner (Verio®: January 2013-August 2015, Prisma®: August 2015-October 2016 (Siemens, Erlangen, Germany)). The acquisition methodology has been reported in detail. (14) Briefly, T1-weighted, fat-saturated, 3D-spoiled gradient echo sequences were acquired pre-contrast and at multiple time points up to 13.5 minutes after intravenous gadobutrol (Gadavist (0.1 mmol/kg), Bayer Healthcare, Germany). Median slice thickness was 1.8mm, with no inter-slice gap, and mean number of slices was 121 (SD 8). Images were acquired in the coronal plane during a short breath-hold (16 – 18 seconds) at end-inspiration. Image were acquired isotropically allowing multi-planar reformatting and analysis.

A phantom composed of a perspex outer casing and solid central cylinder with a shallow rim of fluid was created to broadly mimic the human pleural space and provide a reference standard for volumetric measurements.

1.2.2 MRI Volumetric Analyses

Selection of the optimum post-contrast time-point for volumetric analyses

Mean signal intensity (SI) values from MRI perfusion studies were plotted against time, generating SI/time curves for all patients. The time point that demonstrated the maximum pleural SI, and/or the maximum SI differential between pleura and adjacent tissues in the majority of patients was selected for all volumetric studies.

Creation of a Contour Mask

A 'contour mask' outlining the visible pleura was first defined by the operator, serving to anatomically constrain subsequent region-growing. This required free-hand manual delineation of the pleura every 8 – 10 slices, followed by automated propagation of the mask throughout the image series. Axial images were used for manual delineation, but the mask was reviewed in the coronal and sagittal planes to confirm accurate coverage and adjusted as required.

Tumour Region Growing: Perfusion-tuned Segmentation

Tumour regions were then grown within the contour mask using four different semi-automated methods, all of which used data from MRI perfusion studies performed in the same cases. Methods 1-3 required the user to place up to 3 seed points within the contour mask on areas of representative pleural tumour. The segmentation software (Myrian® Intrasense, France) was then directed to segment all tissue within the mask exhibiting SI values that fell within 3 different pre-specified ranges, derived from the preceding perfusion

data. Method 4 did not require placement of a seed point ROI, instead the software was directed to segment all tissue within the contour mask that fell within a pre-specified SI threshold range. The details of each set of SI limits is described below:

1. Method 1 utilised **summarised** perfusion data acquired in 28 of the 31 previously reported patients in whom at least one ROI demonstrated a pathological (malignant) MR perfusion curve, defined as 'MRI-early contrast enhancement (MRI-ECE)'. (14) The 3/31 patients with false negative MR perfusion studies ('ECE-negative') were excluded from this tuning process on the basis that the ROI sampled in these patients may represent false negative sampling of benign pleura interspersed between pleural tumour. only ROIs (n=273 of the total 492 ROI) demonstrating a malignant perfusion curve shape (ECE) (see online supplementary appendix Figure 1(b)) were used to set the segmentation limit. This intentionally excluded ECE-negative ROIs which we hypothesised may reflect image sampling from areas of adjacent peri-tumoral stroma or benign disease. The final segmentation limits were derived by recording the SI range (minimum to maximum) in the selected ROIs, summarising these data by a median SI value. This was then divided in 2 allowing region growing either side of seed-points placed within the contour mask. This resulted in SI limits for region growing = Seed point SI +/- 81AU.

2. Method 2 utilised **summarised** perfusion data from the same 28/31 cases with evidence of MRI-ECE. However, all ROIs (n=492) were used to set segmentation limits, regardless of whether ECE was present within each ROI, therefore including data from adjacent tissues. The final segmentation limits were derived by recording the SI range (minimum to maximum) in the selected ROIs, summarising these data

by a median SI value. This was then divided in 2 allowing region growing either side of seed-points placed within the contour mask. This resulted in SI limits for region growing = Seed point SI +/- 99AU

3. Method 3 utilised the **individual** perfusion data from each patient to set the SI limits for later segmentation of their tumour volume. By this method, limits were based on the minimum and maximum SI for all of the ROIs in that patient. The perfusion data were used regardless of the performance of MRI-ECE in that subject.

4. Method 4 also utilised the **individual** perfusion data from each patient to set the SI limits, based on the mean SI measured in that patient +/- 2 standard deviations. Like method 3, the perfusion data were used regardless of the performance of MRI-ECE in that subject.

The performance of each method was pseudo-objectified using a scoring matrix (see online supplementary appendix table 1) to determine the optimum segmentation approach for use throughout the study. This matrix allocated scores (from 4 to 1) for best to worst performance across 4 domains: accuracy (relative to an MRI phantom containing a known volume of water, and subjective assessment (by ST) regarding the coverage of areas of visible tumour), intra-observer agreement (by intra-class correlation co-efficient) and analysis time (in minutes). For brevity, only the volumes generated using the optimum method are reported in the Results section herein, but all data are available in the online supplement.

1.3 CT

1.3.1 CT Acquisition

CT examinations were performed within routine care, using a variety of scanners (GE Medical Systems BrightSpeed, LightSpeed or Optima 660 or Toshiba Aquilion). In all patients, multi-slice helical CT axial images were reconstructed with a maximum contiguous slice thickness of 2mm, mean number of slices was 225 (31). Images were acquired following intravenous pump injection of 75 – 95ml of iodinated contrast material (Omnipaque 300, GE Healthcare, USA). Image acquisition was bolus-tracked to trigger in the portal venous phase (65 seconds post contrast administration). Patients with non-contrast, non-contiguous or pulmonary arterial phase scans were excluded from volumetric analyses.

1.3.2 CT Volumetric Analyses

An attempt was made to deploy a similar semi-automated segmentation method on CT images, utilising differential Hounsfield Units (HU) between pleural tumour and adjacent structures. A contour mask was drawn by a single operator (AK) using the same methodology as was applied to the MR images, and was propagated throughout the volume as before, using (Myrian® Intrasense, France). We then sought to identify a suitable set of radiodensity threshold limits for subsequent region growing within the contour mask. However, since CT perfusion data had not been acquired, we could not use an identical method to that used for MRI. Using the single set of post-contrast images available, 15 ROI were placed on areas of representative pleural disease, using identical methods those using for MRI. Radiodensity (HU) was recorded within each of these individual ROIs, in addition to

single ROIs placed on adjacent structures (intercostal muscle, diaphragm, pleural fluid and lung). All ROIs were placed using a track-ball mouse and cursor by AK. The median (range) radiodensity in areas of pleural tumour, intercostal muscle, diaphragm, pleural fluid and lung was 49 (15 – 127) HU, 21 (4 – 55) HU, 38 (7 – 65) HU, 10.8 (1 – 35) HU and -837 (-1003 – 17) HU, respectively. As summarised in Figure 3, there was significant overlap between the radiodensity of the pleura and adjacent structures, making it impossible to define pleura-specific segmentation limits. Nevertheless, semi-automated segmentation was attempted in the hope that the contour mask would adequately constrain region-growing to the target tissues, without the requirement for a fully manual segmentation process. For this attempt, segmentation limits were used based on the radiodensity range (minimum to maximum) measured in the pleural ROIs in all 23 patients were this data was available (ROI *n*=154). The ranges for the cohort were then summarised as a median value and divided by two, allowing region growing either side of seed-points placed within the contour mask.

The segmentation limits derived by this step = seed point +/- 11 HU. However, using 1 or 2 seed points placed on pleural tumour resulted in under-segmentation of pleural tumour (see online supplementary appendix Figure 2(A) and use of 3 seed points on pleural tumour resulted in over-segmentation, with erroneous inclusion of adjacent structures such as pleural fluid and structures outside the contour mask (see online supplementary appendix Figure 2(B)). A remedy for this significant over-segmentation was not found after discussion with the Myrian® software developers. This led us to conclude that a semi-automated region-growing step for tumour segmentation was not feasible using CT. All volumetric studies were therefore performed using a fully manual segmentation method, involving free-hand manual definition of visible pleural tumour on every axial slice.

1.4 Statistical Analyses

The primary objective was assessed using descriptive statistics and intra-class correlation co-efficient (ICC). For the latter, 15/31 MRI cases were randomly selected and re-analysed for assessment of intra- and inter-observer agreement. The relationship between T-volume derived by MRI and by CT, and clinically derived T-stage (based on TNM version 7) was examined using Spearman's rho test and Jonckheere's trend test.

Survival analyses were performed using Kaplan-Meier univariate methods, followed by multivariate Cox proportional hazards regression modelling (backwards stepwise, including only variables associated with a p-value <0.2 in univariate analyses). Candidate predictor variables for the univariate analyses included T-volume derived from MRI and CT, and factors previously associated with survival in MPM, such as age, performance status, disease stage, histological sub-type, blood results including haemoglobin (Hb), albumin and inflammatory biomarkers. For the univariate analyses, MRI and CT T-volumes were dichotomised around increasing intervals of 100cm^3 to determine the cut-point that resulted in the widest separation of the survival curves.

MRI and CT volumes were compared using Bland-Altman analyses and a paired T-test. 14/28 randomly selected CT examinations re-analysed for inter-observer agreement, using ICC. All statistical analyses were performed using GraphPad Prism v7 (San Diego, USA) and SPSS Statistics v22.0 (IBM, New York, USA). A p value $\leqslant 0.05$ was considered statistically significant

RESULTS

2.1 Patient Population

58 patients were recruited and had 3T contrast-enhanced MRI and contrast-enhanced CT prior to any significant pleural intervention or treatment. 31/58 (53%) had a final diagnosis of MPM and were eligible for volumetric analyses. 31/31 (100%) underwent MRI volumetry. 28/31 (90%) underwent CT volumetry; 3/31 (10%) were excluded having had CTPA performed at emergency first presentation. The median time between CT and MRI was 19 (IQR 10.5 - 31) days. Examples of MRI and CT imaging acquired in the same patients are presented in Figure 1.

28/31 (90%) patients were male, mean (SD) age was 76 (7) years and 27/31 (87%) were asbestos-exposed. Histological MPM subtypes were: epithelioid (21/31 (68%)), biphasic (4/31 (13%)), sarcomatoid (5/31 (16%)) and mesothelioma *NOS* (1/31 (3%)). Clinical staging was performed according to TNM 8 at a specialist MPM MDT. 20/31 (65%) had stage IA disease, 6/31 (19%) stage IB disease, 1/31 (3%) stage II disease, 2/31 (7%) stage IIIA disease, 1/31 (3%) stage IIIB disease and 1/31 (3%) stage IV disease. 5/31 (16%) had nodal and/or distant metastatic disease. 6/31 (19%) patients subsequently completed four cycles of platinum/pemetrexed chemotherapy.

2.2 Primary Objective: Optimum MRI Segmentation Method

In the majority of patients (25/31 (81%)) the maximum pleural SI, and/or the maximum SI differential between pleura and adjacent tissues occurred at 4.5 minutes post-contrast (see Figure 2(A)). Images acquired at this time-point were therefore used for all volumetric analyses. Method 2 (seed point SI +/- 99AU) proved to be the optimum method for MRI

segmentation based on the pre-defined scoring matrix incorporating accuracy (relative to MRI phantom), subjective visual assessment of tumour coverage, intra-observer agreement and analysis time. The volumetric data for each patient by each method and their associated performance characteristics are presented in the online supplement (online supplementary Tables 1 and 2, respectively). Using the optimum method (method 2) the mean (SD) analysis time was 14 (2) minutes (12-14 minutes to produce the contour mask and 1 minute for semi-automated segmentation) and reproducibility was high (intra- and inter-observer agreement by ICC 0.875 (0.665-0.953) and 0.962 (95% CI 0.893-0.987), respectively). The median difference in T-volume between MRI readers was 47 (IQR 18 – 75) cm^3).

2.3 Secondary Objectives

2.3.1 Comparison between MRI and CT tumour volumes

The mean T-volume by MRI (n=31) was 370 (SD 137) cm^3. By CT (n=28) mean T-volume was 302 (SD 102) cm^3 (mean difference 69cm^3, p=0.009). MRI T-volumes were consistently larger than CT-volumes (average bias 61.9 (SD 116), 95% limits (-165.5-289), and the data were moderately correlated (Pearson's r 0.56, p=0.002), see Figure 4.

2.3.2 Relationship between MRI and CT tumour volumes and clinically defined Tumour Stage

Mean MRI and CT T-volumes for each clinical T stage is summarised in Table 2. There was no correlation between MRI T-volume and clinical T-stage (Spearman's rho = 0.02, p=0.897, Jonckheere's trend test p=0.935) or CT T-volume and clinical T-stage (Spearman's rho = 0.29, p=0.13, Jonckheere's trend test p=0.11).

2.3.3 Relationship between MRI tumour volumes and Survival

The median OS for all patients (n=31) was 14 months, and was significantly lower in patients with higher tumour volume, dichotomised around 300cm^3, see Figure 2. The difference in median OS observed in all 31 cases increased when this analysis was confined to patients with epithelioid MPM (21/31) and further increased when this was constrained to epithelioid cases without nodal or distant metastatic involvement (18/31). Figure 2 also demonstrates that in all patients (n=31), increasing tumour volume, by tertile ($\leqslant$250cm^3, 250-400cm^3, $\geqslant$400cm^3), was associated with decreasing median OS.

In univariate analyses, summarised in Table 3, MRI T-volume was superior to clinical T-stage, overall disease stage and CT T-volume as a predictor of OS. In subsequent multivariable Cox regression, Haemoglobin and MRI T-volume were the only independent prognostic factors identified (HR 3.75 (IQR 1.60 – 8.76), p=0.002 and HR 4.03 (95% CI 1.5 – 11.55), p=0.006), respectively.

2.3.4 Relationship between CT tumour volumes and Survival

There was no significant relationship between CT T-volume and OS when CT T-volume was dichotomised around 300cm^3 (see Figure 3). However, a difference in median OS was observed when CT T-volume was dichotomised around 200cm^3 and 400cm^3. These observed differences were not enhanced by limiting these analyses to epithelioid cases nor those without nodal or distant metastatic disease. In univariate survival analyses, summarised in Table 3, CT T-volume was not associated with OS and was not included in subsequent multivariable cox regression models.

2.3.5 Reproducibility and Time Taken

MRI reproducibility and the time taken to perform this were earlier, under the Primary Objective. Mean CT T-volume analysis per patient was 151 (SD 19) minutes, significantly longer than MRI volume analysis time (14 (2) minutes, p <0.0001). Inter-observer agreement for CT readers was moderate (ICC 0.72 (IQR 0.18 – 0.9). The median difference in T-volume between the two readers was 75.5 (IQR 52 – 146) cm^3. This was not significantly different to the median difference between readers using MRI (p=0.15).

DISCUSSION

In this study, we report the evaluation of a novel MRI method for the semi-automated segmentation of primary tumour (T-) volume in MPM and compare its performance to that of the current reference standard, CT volumetry. The region-growing step used for MRI was tuned to the specific contrast enhancement characteristics of the target tumour, using data acquired at MR perfusion. CT segmentation could not be tuned in this manner due to poor spatial resolution between tumour and adjacent structures. Higher T-volumes were associated with adverse survival, whether measured by MRI or CT, but MRI volumes were consistently larger and were independently associated with survival (HR 2.11 (95% CI 1.05 – 4.27, p=0.037). The observation of larger volumes using MRI than CT appears most likely to reflect superior contrast between pleural tumour and adjacent structures (see Figure 1 for examples), allowing inclusion of these areas of disease on MRI but not CT. CT volumes were not independently associated with survival, although CT volume approached statistical significance in univariate analyses, in which the smaller number of CT cases (28 v 31 MRI) may have contributed. Nevertheless, CT volumes, took longer to compute (mean (SD) 151

minutes (19) v. 14 (2) minutes, respectively (p=<0.0001)) and were less reproducible (inter-observer 0.72 v. 0.96, respectively) than MRI volumes.

MRI volumetry was associated with high levels of accuracy relative to an MRI phantom, and in the absence of a direct comparison with actual tumour volume (e.g. via surgical resection) relationships between measured tumour volume and subsequent survival has been used here a surrogate for the accuracy of the volumetry technique. The fidelity of the relationship between OS and MRI T-volume is supported by increasing prognostic significance in cases where competing determinants of survival other than primary tumour volume were removed. (20) Our results regarding the impact of high T-volumes on OS are concordant with previous studies that utilised CT. (4-7) However, to our knowledge, this is the first study that has observed such an effect with MRI, and certainly the first to demonstrate superiority of MRI over CT volumetry.

The observed superiority of MRI is potentially due to the subjective nature of manual tumour segmentation, which is necessary using CT, compounded by perception difficulties when differentiating pleural tumour from adjacent tissues and effusion. Earlier studies have shown that MRI offers superior definition of pleural tumour, relative to adjacent tissues and pleural effusion. (21, 22) MRI is thus superior to CT in the clinical staging MPM when assessing potential chest wall or diaphragmatic tumour invasion. (12, 23-26) Consequently, current UK guidelines recommend staging MRI in case where detection of advanced T-stage (T4) will alter clinical management. (27)

In this study, MRI T-volume also out-performed clinically defined T-stage in multivariate survival models. Current T-stage descriptors only describe the pleural surfaces affected and

the extent of invasion into adjacent tissues. (28) Therefore the lack of any relationship between clinical T-stage and T-volume by either CT or MRI is not surprising, and it is notable that the lowest measured volumes were recorded in the T4 sub-group. Moreover, this is concordant with Armato *et al*, who reported no difference in CT-derived tumour volume by T-stage in a similarly sized cohort of MPM patients, (29) but are discordant with Rush *et al* who reported increasing CT-derived T-volume with increasing T-stage in a larger study. (7) This suggests a relationship probably exists between these factors, but that unlike most cancers, current T-staging is not principally driven by tumour size, which in this study, when measured by MRI, was a more powerful determinant of survival.

3.1 MRI Segmentation Methodology

The MRI segmentation method reported here utilised perfusion data measured in the same cohort in which volumetry was performed. The SI limits used in the region-growing step were set at +/- 99 AU, relative to up to 3 seed points placed on areas of visible pleural tumour, based on pseudo-objective scoring of 4 different segmentation methods. Region-growing (tumour segmentation) was then further constrained by the anatomical limits of the pleural contour mask. This two-part tuning of the segmentation volume delivered good performance, with considerably less user interaction and time required than previous CT methods, (4-7) The average time taken (14 (2) minutes) is more practical than previous techniques, but assumes that the SI limits used in the region growing step ('Method 2' as described in Section 1.2.2) can be generalised to all patients with MPM. If not, the preceding perfusion analyses may need to be repeated for each case, which would add time. Since previous data do not exist to support or dispute this SI range, external validation studies are required. However, Patel *et al* reported that optimal MRI contrast enhancement occurred

2.5 to 5 minutes after injection of Gadolinium in patients with MPM, (30) supporting our use of the 4.5 minutes post-contrast scan for volumetric measurements.

3.2 Comparison with CT Volumetry

In the current study, inter-observer agreement regarding CT T-volumes was poorer than that for MRI T-volumes (ICC 0.72 versus ICC 0.96). In a multi-centre study of CT volumetry, Rusch *et al* reported good correlation (Spearman's rho = 0.822) between readers (agreement was not reported) and an absolute difference in CT volume of $\leqslant 200cm^3$ in 80% of cases. (7) In the current study, absolute differences in MRI T- volume between reporters were small (median $47cm^3$) and inter-observer agreement was excellent (ICC 0.964). A root cause analysis of discrepancies between CT volumetric readers in the earlier study concluded that limited resolution between tumour and adjacent tissues was responsible for 50% of the errors reported in that series. (9) This same limitation of CT was evident in the current study, in which we were unable to deploy semi-automated segmentation because of overlapping radiodensity values between pleural tumour and adjacent tissues (see Figure 3 and online supplementary appendix Figure 2). The superior contrast resolution afforded by MRI is also shown in Figure 1, where pleura and pleural masses are clearly more easily identified on MRI in comparison to CT. A further potential advantage of the MRI volumetry method described herein is the ability to exploit differences in perfusion characteristics between pleural tumour, pleural plaque and adjacent structures. Perfusion CT could theoretically be used to overcome the limitations of standard CT in this regard. (31, 32) However high radiation burden limits its use in practice, (17, 18) due to the requirement for multiple high volume acquisitions over multiple time-points. These advantages may be

offset in some patients and some centres by disadvantages to MRI, including reduced availability, the longer time needed for image acquisition, MRI contra-indications (e.g. claustrophobia) and increased cost compared with CT.

3.3 Potential Clinical Implications

If these results are reproduced in larger, multi-centre studies, MRI T-volume could be useful as an adjunct, or alternative, to current clinical T-staging in MPM. These studies are actively being pursued by our group and others and will require international collaboration given the low prevalence of MPM in any individual centre. MRI volumetry may also be a better method of response assessment than modified RECIST (Response Evaluation Criteria in Solid Tumours), (33, 34) which has low reproducibility. (8, 35) A semi- or fully-automated 'volumetric RECIST', such as that described by Chen *et al* (8) could also utilise the methods here. Additional technological advances, including further automation using artificial intelligence (AI), are likely to further reduce analysis time.

3.4 Study Limitations

The principal limitation of this study is the small sample size, mandating that this method be externally validated. In addition, the CT and MRI scans were not done on the same day (median time between scans 19 days). However, both scans were done prior to pleurodesis and before commencement of systemic therapy in all cases. Of the 6 patients who received chemotherapy, only one patient was in the good prognosis, low MRI T-volume group. We are therefore confident that this factor does not explain the better survival observed. Finally, CT scans were acquired as part of routine clinical practice and were therefore not

protocolised. However, only high quality, bolus tracked, portal venous phase contrast CT scans were included in the final analyses.

CONCLUSION

The novel perfusion-tuned MRI volumetry method reported here appears accurate, reproducible and reasonably practical in patients with MPM. MRI T-volume segmentation is quicker and more reproducible than CT T-volume segmentation, probably reflecting the semi-automated methodology, which cannot be deployed using CT because of inferior spatial resolution and lack of feasible CT perfusion protocols. MRI T-volume was an independent predictor of survival and out-performed CT-derived T-volume, clinical T-stage and overall disease stage in this regard. Further external validation studies are warranted.

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Table 1. Study objectives and outcome measures

Research Objectives	Outcome Measures
Primary	

To determine optimum methods for primary T-volume assessment by MRI based on accuracy, reproducibility and time taken	Outcome of a scoring matrix for different segmentation methods comprised of:
	• Accuracy:
	  ○ % measurement error relative to a MRI phantom containing a known volume of water
	  ○ appropriate coverage of pleural tumour in patients; based on subjective visual assessment
	• Intra-observer agreement by ICC
	• Time taken

Secondary	
1. To determine any relationship, and the level of agreement between T-volumes defined by MRI and CT	• Bland Altman Limits of Agreement and Bias between MRI T-volume and CT T-volume • Pearson/Spearman Correlation Coefficient** between MRI T-volume and CT T-volume
2. To determine any relationship between T-volume defined by MRI and CT, and T-stage	• MRI T-volume • CT T-volume • Clinically-defined T-stage (TNM version 8)
3. To determine any relationship between T-volume defined by MRI and CT, and survival	• MRI T-volume • CT T-volume • Median overall survival
4. To determine the level of reproducibility between CT and MRI volumetry readers, and the time taken to perform each analysis	• Inter- and intra-observer ICC comparing MRI T-volume and CT T-volume • Time taken (minutes)

T-volume; tumour volume, MRI; Magnetic Resonance Imaging, CT; Computed Tomography, ICC; intraclass correlation co-efficient

** Pearson correlation coefficient will be used if data are normally distributed and Spearman correlation coefficient will be used if data are not normally distributed

Table 2. Primary tumour volume (T-volume) measurements based on contrast-enhanced MRI and CT according to clinical T-stage in patients with Malignant Pleural Mesothelioma. 31 patients underwent MRI volumetry, 28 patients underwent CT volumetry.

T-stage	**Median MRI T-volume** (n=31)	**Median CT T-volume** (n=28)
T1	342.5 cm^3 (20/31)	263 cm^3 (18/31)
T2	349 cm^3 (1/31)	409 cm^3 (1/31)
T3	363 cm^3 (9/31)	360.5 cm^3 (8/31)
T4	259 cm^3 (1/31)	109 cm^3 (1/31)

MRI; Magnetic Resonance Imaging; CT; Computed Tomography

Table 3. Prognostic factors for 31 patients with Malignant Pleural Mesothelioma (MPM) analysed in a univariate Cox proportional hazards model

Variable	*n*	*Hazard ratio*	*95% Confidence Intervals*	*p value*
Sex				
Female	3			
Male	28	4.044	0.952 - 17.188	0.058
Age	31	1.006	0.950 - 1.065	0.829
ECOG Performance Status				
0/1	24			
2/3	7	1.943	0.966 - 3.911	0.063
Haemoglobin				
⩾14g/dl	17			
<14g/dl	14	2.035	1.154 - 3.589	**0.014**
White Cell Count				
<8.2 x10 9/l	15			
⩾8.2 x 10 9/l	16	0.668	0.380 - 1.174	0.161
Serum albumin				
⩾35g/l	17			
<35g/l	14	1.678	0.946 - 2.975	0.077
Histological Subtype				
Epithelioid	21			
Non-epithelioid	10	2.074	0.912 – 4.716	0.082
Clinical Primary Tumour Stage				
cT1	20			
cT2	1	1.213	0.157 - 9.361	0.853
cT3	9	1.699	0.103 - 28.030	0.711
Clinical Overall Stage				
I/II	26			
III/IV	5	1.595	0.592 – 4.295	0.356
MRI Tumour Volume				
<300cm^3	11			
⩾300cm^3	20	2.273	1.162 - 4.446	**0.016**
CT Tumour Volume				
<200cm^3	4			
⩾200cm^3	24	7.217	0.951 – 54.753	0.056

ECOG; Eastern Cooperative Oncology Group, MRI; Magnetic Resonance Imaging, CT; Computed Tomography