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Early Contrast Enhancement: A novel magnetic resonance imaging biomarker of pleural malignancy

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ABSTRACT

Introduction: Pleural Malignancy (PM) is often occult on subjective radiological assessment. We sought to define a novel, semi-objective Magnetic Resonance Imaging (MRI) biomarker of PM, targeted to increased tumour microvessel density (MVD) and applicable to minimal pleural thickening.

Materials and methods: 60 consecutive patients with suspected PM underwent contrast-enhanced 3-T MRI then pleural biopsy. In 58/60, parietal pleura signal intensity (SI) was measured in multiple regions of interest (ROI) at multiple time-points, generating ROI SI/time curves and Mean SI gradient (MSIG: SI increment/time). The diagnostic performance of Early Contrast Enhancement (ECE; which was defined as a SI peak in at least one ROI at or before 4.5 min) was compared with subjective MRI and Computed Tomography (CT) morphology results. MSIG was correlated against tumour MVD (based on Factor VIII immunostain) in 31 patients with Mesothelioma.

Results: 71% (41/58) patients had PM. Pleural thickening was < 10 mm in 49/58 (84%). ECE sensitivity was 83% (95% CI 61–94%), specificity 83% (95% CI 68–91%), positive predictive value 68% (95% CI 47–84%), negative predictive value 92% (78–97%). ECE performance was similar or superior to subjective CT and MRI. MSIG correlated with MVD (r = 0.4258, p = .02).

Discussion: ECE is a semi-objective, perfusion-based biomarker of PM, measurable in minimal pleural thickening. Further studies are warranted.

1. Introduction

Radiological detection of pleural malignancy (PM) is frequently difficult because overt pleural tumour may be occult and pleural effusion may be the dominant, or only, feature [1]. This is particularly true in early stage Malignant Pleural Mesothelioma (MPM), where extra-pleural malignant features are frequently absent. Recent studies reflect these challenges, reporting low sensitivity and considerable inter-observer variation, using Computed Tomography (CT) in a routine clinical setting [2,3].

Dynamic contrast-enhanced CT (DCE-CT) or perfusion CT allows assessment of tumour microcirculation, including blood flow and capillary permeability [4]. Previous studies have demonstrated potential utility in assessment of pulmonary nodules and MPM [5–7]. A major advantage of perfusion CT is its widespread availability, however, the multiplicity of protocols using different mathematical models [8] and high radiation burden have limited its widespread use in routine clinical practice to date [9,10].

Positron Emission Tomography (PET)-CT is a useful modality in staging of thoracic malignancy, particularly when evaluating nodal and distant metastatic disease, however its role in the differentiation of benign and malignant pleural effusions is less well-established. Recent

Abbreviations: ECE, Early Contrast Enhancement; ROISIG, Region of Interest Signal Intensity Gradient; MSIG, Mean Signal Intensity Gradient

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meta-analyses have demonstrated a pooled sensitivity of 81% and specificity 74% for detecting PM, with considerable variation between studies [11]. Tumours with low metabolic activity, such as early stage epithelioid MPM are more likely to have a false negative PET-CT and false positives in patients with inflammatory pleuritis, TB pleuritis and previous pleurodesis are well recognised [12–14].

Efficient diagnosis is further complicated by the variable performance of pleural cytology, which has a mean sensitivity of 60% (depending on tumour type) but extremely low negative predictive value (NPV) in MPM, for which histological confirmation remains mandatory in most centres. Thoracoscopy offers excellent sensitivity, but is associated with additional healthcare costs, increased procedure-related risk and limited availability. Diagnostic delays are therefore common in patients with PM.

A reliable, non-invasive imaging marker would be a major clinical advance, allowing pathway rationalization and early direction of patients to thoracoscopy, including those with probable early-stage MPM. Ideally, this should be objective, to improve reporting consistency, and applicable to patients with minimal pleural thickening, since it would offer limited additional value in cases with overt nodular disease. Magnetic Resonance Imaging (MRI) is an attractive modality for this purpose, facilitating both high contrast-resolution anatomical and perfusion studies. Dynamic-Contrast-Enhanced MRI (DCE-MRI) exploits the pathognomonic increase in blood vessel density typical of cancers and related to neoangiogenesis [15–18]. DCE-MRI has previously been used to reliably differentiate malignant from benign breast and prostate lesions [18,19] and to generate prognostic [15–18] and predictive (regarding response to anti-angiogenic chemotherapy) [20] data in advanced MPM. However, DCE-MRI requires bulky pleural tumour for application, making it unsuitable for early diagnostics. Neoangiogenesis is an early biological event in tumourigenesis [21] and is therefore likely to be present in patients with smaller pleural tumour volumes. We hypothesised that novel MRI methodology targeted to increased micro-vessel density (MVD) could accurately identify patients with PM, including those with minimal pleural thickening.

2. Materials and methods

2.1. Study design

A prospective cohort study was performed, incorporating patients recruited to an MRI pilot study and the DIAPHRAGM study (ISRCTN registration 10079972), which contained an MRI sub-study. [22] Table 1 summarises the objectives and *a priori* outcome measures. Consecutive patients presenting to the Glasgow Pleural Disease Unit were invited to participate (January 2013 − October 2016), based on the following eligibility criteria.

- Inclusion criteria: 1) suspected PM requiring histological sampling (by thoracoscopy or image-guided pleural biopsy); this was defined by the presence of a unilateral pleural effusion, pleural thickening or pleural mass lesion and non-diagnostic pleural fluid analysis (including negative fluid cytology); 2) sufficient fitness for pleural biopsy 3) informed written consent.
- Exclusion criteria: 1) pregnancy; 2) gadolinium allergy; 3) renal impairment (eGFR < 30 ml/min); 4) known MRI contraindication (e.g. cardiac pacemaker)

All patients underwent routine clinical work-up, [23] including contrast-enhanced CT and pleural biopsy by local anaesthetic thoracoscopy (LAT), where technically possible. Video-assisted thoracoscopic surgery (VATS) or image-guided pleural biopsy were permitted alternatives. Study procedures were limited to contrast-enhanced MRI prior to pleural biopsy and measurement of tissue MVD using surplus formalin-fixed, paraffin-embedded (FFPE) tissue, where available. The study protocol was approved by the West of Scotland Research Ethics Service (12/WS/0219, 13/WS/0240).

2.2. Sample size and assumptions

An *a priori* sample size calculation was not possible given the novel nature of the primary contrast-enhanced MRI outcome measure. A target sample size of 60 was deemed to be large enough for these methods to be developed and tested. Assuming a 50% incidence of MPM in the study cohort (based on our unit's MPM incidence at LAT), 30 MPM patients would also allow a moderate correlation (r = 0.5) between the relevant secondary outcome measures to be detected with 80% power at a 5% two-sided level of statistical significance.

2.3. MRI acquisition

66 patients underwent 3-Telsa MRI (Siemens Magnetom Verio or Prisma® (Erlangen, Germany)). Imaging protocols were developed in the first 6 patients, who did not receive contrast and are not included in

Table 1
Study objectives and outcome measures.

Study objective	Outcome measures
Primary	
To determine whether perfusion-based, ce-MRI can differentiate pleural malignancy from benign pleural disease with comparable or superior sensitivity and specificity to subjective CT or MRI morphology assessment	Diagnostic classification based on • MRI contrast enhancement pattern • CT morphology assessment • MRI morphology assessment Diagnostic assessment including pleural biopsy results
Secondary	
To determine whether there is a correlation between contrast enhancement pattern at MRI and tumour vascularity To determine the reproducibility of ECE, CT and MRI morphology	• Mean Signal Intensity Gradient at ce-MRI • Tumour MVD based on Factor VIII immunostaining in FFPE pleural biopsies • Inter-observer agreement (Cohen's Kappa) • Intra-observer agreement for ECE only (Cohen's Kappa)
Exploratory	
To determine whether there is an association between: 1. ce-MRI parameters and Survival 2. Tumour vascularity and Survival	• MSIG at ce-MRI • Overall Survival (months) • Tumour MVD (Factor VIII immunostaining in FFPE pleural biopsies) • Overall Survival (months)

ce-MRI; Contrast-enhanced Magnetic Resonance Imaging, CT; Computed Tomography, ECE; Early Contrast Enhancement, FFPE; Formalin-Fixed Paraffin-Embedded; MVD; Micro-vessel Density.