Is there a role for pre-operative contrast-enhanced magnetic resonance imaging for radical surgery in malignant pleural mesothelioma?

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Abstract

Objective: To assess the use of contrast-enhanced magnetic resonance imaging (CEMRI) in addition to computed tomography in the pre-operative assessment of patients for radical surgery in malignant pleural mesothelioma. Methods: Over a 45-month period, 51 of 76 patients assessed (69 men and seven women), underwent extra-pleural pneumonectomy or radical pleurectomy/decortication. Post-operative pathological stage was correlated with radiological staging, with particular emphasis on tumour resectability. Results: Seventeen (22%) patients were found on CEMRI to have unresectable, but histologically unconfirmed disease, not previously seen on CT. Fifty-one (67%) patients proceeded to radical surgery, but pathological nodal data were incomplete in three, so excluding these patients from further analyses. The median pre-operative interval after CEMRI was 17 days. Two patients were found to have unexpectedly extensive disease at thoracotomy, thus the sensitivity of CEMRI for prediction of resectability was 97%. Using the International Mesothelioma Interest Group system, tumour stage was correctly predicted by CEMRI in 48% of patients, but understaged in 50% of cases, largely due to the underestimation of pericardial involvement, but this did not affect resectability and had no significant effect on prognosis. Nodal stage was correctly identified in 60% of patients. CEMRI was successful in predicting pathological tumour stage T3 or less (sensitivity of 85%; specificity of 100%), but less so in identifying tumour stage T2 or less (sensitivity of 23%; specificity of 96%) or N2 nodal disease (sensitivity 66%; specificity 73%). Conclusions: CEMRI is most useful in the differentiation of T3 and T4 disease and may be unnecessary at earlier stages. Its multiplanar tumour localisation abilities are of value in the assessment of resectability. It is unlikely to contribute significantly to nodal staging, but it remains a valuable adjunct in the selection of patients for radical surgery.

Keywords: Mesothelioma; Staging; Radical surgery; Magnetic resonance imaging

1. Introduction

The incidence of malignant pleural mesothelioma (MPM) is increasing and is expected to account for a quarter of a million deaths throughout Western Europe over the next 35 years [1]. Despite the traditionally nihilistic approach to treatment, there may be a role for radical surgery in early stage disease, in combination with other treatment modalities, and prolonged survival has been seen in selected patient groups [2,3].

Radiological evaluation of the extent of disease is therefore very important. Due to its availability, ease to perform, proficiency of interpretation and relative low cost, the traditional and most widely used method of assessment is computed tomography (CT). Magnetic resonance imaging (MRI) has been proposed as a useful imaging modality in MPM because of its superiority to CT in the assessment of mediastinal and great vessel involvement [4], and also diaphragmatic and chest wall invasion [5,6]. The addition of intravenous contrast enhancement to MRI has been shown to be of convincing diagnostic value aiding the prediction of malignancy in those with asbestos exposure and pleural lesions [6–8].

We report our single centre experience using contrast-enhanced MRI (CEMRI) in patients with mesothelioma under consideration for radical surgery. Using the results of surgical resection and intra-operative staging we have explored the correlation of radiological and pathological staging, with particular reference to its usefulness in the assessment of resectability.
2. Materials and methods

Over a 45-month period, 76 patients with a diagnosis of non-sarcomatoid MPM, made by percutaneous or thoracoscopic pleural biopsy were assessed for radical surgery. Definitive histological evidence of sarcomatoid mesothelioma was a contraindication to further assessment, in accordance with local policy. There were 69 men and seven women, with a median age at diagnosis of 59 years (range 41–75 years).

All patients had previously undergone contrast-enhanced thoracic and upper abdominal CT to exclude those with unresectable disease due to local tumour invasion, contralateral pleural involvement or evidence of more distant metastatic disease. They then proceeded to contrast-enhanced MRI. A 1.5-Tesla Siemens Vision scanner was used, with T1 breath-hold 2D FLASH (fast low angle shot) images obtained in axial, sagittal and coronal planes, before and after intravenous administration of 0.1 mmol/kg gadolinium-diethylene-triamine pentaacetic acid (DTPA) contrast. Areas of interest identified on the CT scans were investigated further with T1 breath-hold gated and T1 2D FLASH cine images. Previous port, drain and biopsy sites were marked with oil capsules. MR images were reviewed independently by one of two specialist thoracic radiologists, and the tumour staged according to the International Mesothelioma Interest Group (IMIG) staging system [9]. Lymph nodes of short-axis diameter greater than 1.0 cm were considered pathologically enlarged, according to standard criteria for lung cancer [10]. In conjunction with radiological evaluation, the fitness of patients for surgery was assessed according to the British Thoracic Society guidelines for pneumonectomy [11].

Resectability was defined by the absence of mediastinal organ or full-thickness pericardiomyocardial involvement, absence of diffuse or multifocal chest wall disease, transdiaphragmatic extension or spread directly into the spine (any stage T4 disease). Contrast enhancement of sites of previous entry to the chest were not, in themselves, seen as any contraindication to radical treatment, as these were widely excised at surgery. Suitable patients then underwent extra-pleural pneumonectomy (EPP) or radical pleurectomy/decortication (PD) according to established techniques [12,13]. Systematic clearance of ipsilateral mediastinal and internal mammary lymph node groups was performed. The pre-operative CEMRI stage was compared to the final pathological stage obtained using the IMIG system mentioned previously.

2.1. Statistical analysis

The sensitivity, specificity, positive predictive value, negative predictive value, false positive rate and false negative rate were calculated to assess the ability of CEMRI to predict tumours of stage T3 or less. This was repeated for tumours of stage T2 or less and nodal disease of stage N2 or less. Time difference between CT and CEMRI, and patient survival, according to stage of pericardial involvement, was assessed using the Kaplan–Meier method [14].

3. Results

With CEMRI, contrast enhancement of tumour was seen in all patients (Fig. 1). CEMRI revealed the presence of 17 (22%) unresectable T4 or M1 tumours, which were not identified by CT. These were due to enhancement indicating mediastinal organ involvement in nine patients (Fig. 2), diffuse chest wall involvement in 2, infra-diaphragmatic spread in a further two and metastatic contralateral pleural disease in four patients. These findings were not confirmed histologically. In total, 51 patients proceeded to EPP or PD, and 25 patients had either no further surgical intervention or a lesser resection. Lesser resections included VATS debulking pleurectomy in five patients (T3 on CEMRI, but medically unsuitable for radical surgery) and chest wall resection for localised biphasic disease in two (T3 on CEMRI). One patient declined surgical intervention despite apparent resectability (T2N0 on CEMRI). The 17 patients with unresectable disease on CEMRI were included in this second group. For all patients, the median time interval...
between CT and CEMRI was 43 days (range 0–609 days). In those who progressed to radical surgery the median time was 44 days (range 0–221 days) and in those with disease taken to be unresectable it was 25 days (range 2–609 days), \( P = 0.82 \).

Of the 51 patients in the radical surgery group, 44 had EPP and seven underwent PD. The median interval from CEMRI to radical surgery was 17 days (range 1–43 days). Two patients, in whom EPP was planned, were found to have more extensive mediastinal disease at thoracotomy than was predicted by CEMRI and so underwent PD. Thus, the sensitivity of the overall prediction of resectability was 97%. There was incomplete nodal staging in three of the patients who underwent PD and therefore they were excluded from all further analyses.

3.1. Pathological staging

Table 1 shows the breakdown of disease stages of the 48 patients with complete pathological information; 73% of patients were found to have stage III disease, and only five patients were within IMIG stages I or II.

3.2. Correlation of radiological and pathological staging

Concordance between MRI and pathological T stage was seen in 23 patients (48%). In 24 of the 48 cases (50%), the tumours were understaged. This was largely due to underestimating of pericardial invasion (22 of 24 cases), but this was not found to compromise resectability. Overstaging of tumour was seen in one patient (2%). This occurred where apparent confluent visceral tumour (T2) seen on CEMRI was shown to be limited to scattered tumour foci on the visceral pleural surface (T1b) at thoracotomy. Considering nodal disease, 29 patients (60%) were correctly staged by CEMRI. This comprised 27 patients of status N0 and two patients with N2 disease. Eighteen patients were found to have more advanced nodal disease than predicted by MRI. Six (13%) of these had N1 disease and the remaining 12 (25%) had N2 disease where N0 status had been predicted. CEMRI overstaged nodal disease in one patient (2%), predicting N2 disease, where N0 was found.

In identifying those patients with stage T3 disease or less, CEMRI was found to have a sensitivity of 85% and a specificity of 100% (positive predictive value 100%; negative predictive value 22%; false positive rate 0%; false negative rate 15%) (Table 2). For T2 disease or less, the sensitivity fell to 23%, with a specificity of 96% (positive predictive value 83%; negative predictive value 59%; false positive rate 4%; false negative rate 77%) (Table 3). Using the same principle, but applying it to the prediction of N2 disease or less, for our series the sensitivity of CEMRI was 66%, and the specificity was 73% (positive predictive value 14%; negative predictive value 97%; false positive rate 26%; false negative rate 33%) (Table 4).

4. Discussion

This retrospective study represents a validation of contrast-enhanced MRI with the pathological results of radical surgery in malignant pleural mesothelioma, which has not previously been reported in detail.

Despite the finding of a number of patients with unresectable disease on CEMRI not previously identified on CT and although this was never confirmed histologically,
it is our observation that this discrepancy is due to the superior ability of CEMRI in the detection and assessment of malignant pleural disease, based on non-homogenous signal intensity or enhancement and certain specific morphological features. These features include circumferential pleural thickening, nodularity and irregularity. There is international agreement in this belief [6–8]. Based on this premise, and despite the successes achieved with limited debulking procedures [15], we felt ethically unable to subject patients to the considerable morbidity associated with, at the very least, exploratory thoracotomy. In some cases this would have required bilateral surgery. Although two patients did undergo thoracoscopic pleurectomy, the remaining patients chose continued treatment under the care of an oncologist. This explains the absence of pathological confirmation of the cases deemed unresectable on MRI.

In conflict with our opinion regarding CEMRI, a study by Heelen et al. comparing contrast-enhanced high-resolution CT reconstructs with unenhanced MRI found, at surgery, insignificant differences between the two techniques, leading the authors to find themselves unable to justify the increased cost of MRI [5]. It is apparent from the text that we have omitted any comparison with CT information in our cohort. The frequent supra-regional nature of patient referral to our centre and the widespread policy of obtaining CT scanning prior to biopsy means that, more often than not, CT imaging is obtained away from our centre leading to a lack of consistency, not only in the scan protocols, but using scanning equipment of different ages and from different manufacturers. For these reasons, a retrospective comparison of CT and CEMRI was considered impossible to justify. It is interesting to note that there was no significant difference in the time between CT and CEMRI in those patients undergoing radical surgery and those taken to be unresectable (radical, 44 days; unresectable, 25 days, \( P = 0.82 \)), which would appear to discount time delay as a cause for unresectability.

It is important to appreciate that the process of the patient undergoing a CEMRI is not an insignificant event and there are contraindications. It has been shown that compared to CT, MRI leads to increased levels of anxiety in patients, due predominantly to the more enclosed environment [16]. To date, we have actually had only one patient who was unable to undergo CEMRI due to symptoms of claustrophobia. Within our local protocol for CEMRI, and relevant to the disease process itself, is the requirement for a 20-s breath-hold whilst obtaining images, which may lead to respiratory distress in those with significant intra-thoracic disease. Finally, those patients with metal implants such as pacemakers, are unable, or at least unsuitable, to undergo MR imaging.

With a sensitivity of 85% and a specificity of 100%, CEMRI was very good at identifying those patients with stage T3 disease or less, therefore excluding unresectable stage T4 disease. However, over half of the cases were understaged due to more advanced pericardial involvement, although this was not found to compromise resectability. It is likely that no currently available imaging modality will prove sufficiently accurate to address the problem of staging pericardial involvement preoperatively (Fig. 3).

The International Mesothelioma Interest Group staging system [9], developed in 1994, was based on the experiences of several pioneering investigators in the field of mesothelioma, and attempted to reconcile previously proposed staging systems using up to date information regarding the influence of T and N status on overall survival. Involvement of the pleura overlying the pericardium stages a tumour as either T1b or T2. With pericardial involvement the stage becomes T3. Should the tumour extend through to the internal surface of the pericardium, the stage advances to T4. All this occurs over the distance of a few millimetres, in close proximity to the constantly moving heart. Clearly, improving image definition will be difficult with currently available technology, despite the use of ECG cardiac gating. However, on examining this series of patients, we postulate that the worsening of prognosis with T4 disease may not apply to pericardial involvement. To illustrate this, the survival of patients found to have T3 and T4 pericardial involvement on pathological examination as either the worst, or equal to the worst area of disease was compared. There was no statistical difference in the median survival of the two cohorts (T3, 417 days; T4, 327 days, \( P = 0.12 \)). Two possible explanations would appear plausible. The first concerns the small numbers in our series making definitive

Table 4

<table>
<thead>
<tr>
<th>Pathological confirmation</th>
<th>N2 disease present</th>
<th>No N2 disease present</th>
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<tbody>
<tr>
<td>Predicted on MRI</td>
<td>N2 disease present</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No N2 disease present</td>
<td>12</td>
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</tbody>
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Fig. 3. T3 pericardium on CEMRI, T4 on pathology. Although a clear fat plane excludes involvement of the myocardium, the differentiation between partial and full-thickness pericardial disease is very difficult.
statistical conclusions difficult and the second maybe that full-thickness pericardial involvement does not alter the prognostic significance and should not be considered as stage T4, unresectable disease. Greater numbers are needed to establish this with certainty. No patients with full-thickness pericardial tumour had evidence of malignant pericardial effusion or myocardial involvement.

CEMRI proved to be less than adequately accurate in assessing nodal disease (sensitivity 66%; specificity 73%; for N2 disease or less). Unfortunately 12 patients were predicted to have no nodal involvement and actually found to have N2 disease. In accounting for this, lymph nodes involved with metastatic tumour being of a size less than 1 cm in short-axis diameter may be implicated. This measurement is used as the radiological cut-off between uninvolved and involved lymph nodes in non-small cell lung cancer [10], but it is being increasingly realised to be a poor predictor of malignant nodal involvement in that disease [17]. There has been no comparable study in malignant pleural mesothelioma, but our data would imply a limited role, if any, for CEMRI in the assessment of nodal disease. Although not the focus of this work, given the data presented, there may, however, be an important role for cervical mediastinoscopy in the evaluation of patients under consideration for radical surgery.

This study was not designed to examine the ability of CEMRI to differentiate benign from malignant pleural disease, as pathological confirmation of MPM had already been obtained in all cases. It is, however, noteworthy that enhancement was seen in all cases. This property of tumour enhancement has previously been shown to be a useful indicator of malignant disease, although the consistently high negative predictive value of CEMRI may be of even greater value [7,8,18,19]. This raises the possibility of using CEMRI as a screening tool in this disease, or as an adjunct in the investigation of patients with pleural abnormalities identified on plain chest radiograph.

Within a regime of multimodality treatment, the idea of neoadjuvant chemotherapy is a concept of increasing interest in MPM. This idea has proven to be feasible in non-small cell lung cancer [20], with several trials active at present, including the LU22 trial in the United Kingdom [21]. The ability of CEMRI to differentiate between active and inactive pleural disease may be of great value in assessing patients treated with neoadjuvant chemotherapy prior to radical surgery for MPM. There are currently no published data on this subject.

The ability of PET scanning to evaluate actively metabolising cells, with extrapolation to the likelihood of malignancy, has led to a huge increase in the use of this technique. It has been shown to have a low false negative rate in the identification of malignant pleural disease [22] and be of value in the evaluation of the presence or absence of regional and distant metastases [23]. Its use is also likely to increase in the follow up of patients after radical surgery [24]. By measuring the intensity of isotope uptake, PET may have a role in prognostication in MPM [25]. Despite these advantages, it is unlikely to better the abilities of CEMRI in the assessment of local disease extent, although the use of fused PET and CT images is proving to be of benefit in patients with thoracic malignancies [26] and is likely to become more widely available in the near future.

It is acknowledged that CEMRI is inaccurate in the assessment of pericardial involvement, but this has made no difference in terms of resectability for our cohort of patients and may be less important in prognostic terms than previously thought. In the assessment of nodal status, CEMRI is unlikely to play a significant role. From a surgical viewpoint, its abilities lie in the differentiation of T3 and T4 disease, although it is perhaps less useful in the early stages of disease when it may confer no extra benefit compared to CT. It is very useful in the assessment of resectability and providing additional information through its multiplanar tumour localisation capabilities. It remains a valuable adjunct in the selection of patients for radical surgery.

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References