Review Article

Advances in mesothelioma imaging and implications for surgical management

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Abstract: In malignant pleural mesothelioma (MPM), surgery may be offered for diagnostic or palliative purposes, or in selected patients as part of a multi-modality radical treatment strategy. Imaging results are routinely used to select patients for surgery in these settings. However, the initially subtle morphology and subsequent rind-like growth pattern of the primary tumour combined with complex pleural space geometry and unfamiliar nodal drainage to present major challenges in this regard. In this article, we summarize recent imaging developments that allow clinicians to make better diagnostic, staging and perioperative decisions in MPM. We also discuss the challenges involved in selecting patients for palliative MPM surgery, particularly those with non-expansile (or trapped) lung.

Keywords: Mesothelioma; imaging; surgery; staging; diagnosis

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Introduction

Malignant pleural mesothelioma (MPM) is a locally invasive, asbestos-related cancer (1,2) that arises from the pleural surfaces, which encapsulate the lung and thoracic cavity. Surgery is most frequently performed in MPM during diagnostic work-up, but may also be offered in selected patients as part of a radical multi-modality treatment strategy, by extended pleurectomy/decortication (EP/D), or in historical series by extra-pleural pneumonectomy (EPP). Occasionally, palliative surgery may be offered in patients with symptomatic pleural effusion and/or associated trapped lung. The evidence associated with surgery in these settings has been reviewed elsewhere in this issue. This article will focus on the many recent developments in MPM imaging, which have the potential to enhance pre-, intra- and post-operative decision making. We have structured this article around the key clinical scenarios in which MPM surgery may be offered but have not included any data regarding use of the Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST criteria in MPM, since these are not routinely used to assess surgical response. However, MPM surgery is likely to remain one component of multi-modality regimens and an understanding of this topic is essential. Readers are therefore directed to relevant publications on this topic (3-5).

Imaging for diagnostic surgery

MPM presents in an undifferentiated fashion, most frequently with breathlessness +/- pain, associated with a unilateral pleural effusion +/- mass. The low sensitivity of fluid cytology, which is frequently the first invasive test performed, for MPM (effectively zero in many non-
specialist cytology centres (6,7) places great importance on the perceived performance of the imaging conducted at first presentation. These results will often be used to justify surveillance vs. immediate histological sampling, ideally by video-assisted thoracoscopic surgery (VATS) or local anaesthetic thoracoscopy (LAT), which both offer >90% MPM sensitivity (8).

**Chest radiograph (CXR)**

The CXR will typically reveal a pleural effusion +/- loss of hemi-thoracic volume, nodular pleural thickening, fissural thickening or a pleural mass, but these are insensitive and non-specific features (9,10). Right-sided abnormalities are more common and bilateral disease is exceptionally rare (11). Calcified (or non-calcified) pleural plaques are consistent with prior asbestos exposure, but are not specific markers for MPM (12,13).

**Thoracic ultrasound (TUS)**

TUS assessment should be part of the standard work-up for all patients with suspected pleural malignancy, including MPM. Advantages including speed, ease of use and mobility. Use of a convex, low-frequency transducer probe (e.g., 3.5 MHz) allows visualization and estimation of pleural effusion volume, identification of tumour nodules (14,15) and selection of a safe site for fluid aspiration (16). A higher frequency, linear probe (5 or 7.5 MHz) allows more detailed assessment of the chest wall and parietal pleura. Sonographic evidence of nodular pleural thickening, pleural thickening >1 cm +/- diaphragmatic nodules are highly specific (95–100%) markers of pleural malignancy in general, but offer poor sensitivity (40%) (17). Therefore, a bland TUS should not preclude further investigation. TUS findings can also be helpful in determining the most appropriate biopsy strategy, particularly in selecting patients for VATS, in preference to LAT. While LAT is suitable for most patients and can frequently be performed locally without onward referral, a highly loculated pleural space may be better managed using VATS. Recent advances in ultrasound application include use of M-mode and Speckle Tracking analyses to non-invasively predict non-expansile lung (NEL) (18). Given the evolving importance of NEL in MPM (see ‘Imaging prior to Palliative Surgery’ section), these may be worth integrated into clinical practice, if validated in larger studies.

**Computed tomography (CT)**

**Technical considerations**

Multi-slice CT facilitates detailed examination of any body part and isotropic multi-planar image reformatting. Optimal CT assessment requires volume imaging, 60–90 seconds after iodinated contrast injection (19). CT pulmonary angiography is insensitive to MPM (27% in a recent study) (20) and is of very limited value. The imaged volume must include the thorax and abdomen, including the inferior costophrenic sulci.

**Typical morphological CT features**

Pleural effusion and pleural thickening are common but non-specific CT features. Pleural plaques are visible on CT in 20% (21) to 43% (22) of patients with MPM, but have been more frequently reported in cohorts of benign pleural disease (23). No CT feature reliably differentiates MPM from metastatic pleural malignancy, which in clinical practice is often the primary question, although circumferential and mediastinal pleural thickening are more common in MPM (24).

**Real-life diagnostic performance**

Previous small studies suggested that CT was very accurate for detection of pleural malignancies, including MPM, with morphological abnormalities (e.g., pleural enhancement, nodular or mediastinal pleural thickening) being associated with high sensitivity (96%) and specificity (80%) (23). However, cross-sectional imaging is uniquely challenging in MPM. The disease is distributed heterogeneously over a large surface area and adopts a sessile (flat) configuration in early stage disease. In our experience, early stage MPM is frequently CT-occult but easily visualized at LAT, see Figure 1 for an example. This is corroborated by two recent studies regarding the real-life performance of CT in this setting. Hallifax et al. reported only 68% sensitivity [negative predictive value (NPV 65%)] (25) in 370 patients referred for LAT, while Tsim et al. reported a 58% sensitivity (NPV 54%) in 315 patients (20) recruited to the DIAPHRAGM study (ISRCTN 10079972), at first presentation of MPM (26). This relative insensitivity of CT may well be an important factor in the frequent diagnostic delays experienced by MPM patients (27). An efficient diagnostic pathway therefore requires recognition that the only CT (20,25) [or TUS (17)] abnormality in MPM may be a new, bland pleural effusion. CT may help selection of the most
appropriate biopsy procedure, e.g., tumour nodules may be most amenable to image-guided biopsy, but fluid loculation is poorly visualized on CT and selection of LAT vs. VATS should incorporate other data.

**Perfusion CT**
Perfusion CT involves sequential high-resolution image acquisition after injection of iodinated contrast. This allows estimation of the tumour micro-vasculature, based on blood flow, volume and capillary permeability (28), which has potentially significant clinical application given the emerging importance of anti-angiogenic therapies, including bevacizumab (29) and nintedanib (30). A recently reported prospective pilot study described a potential treatment-specific fall in tumour blood volume and perfusion in 8 MPM patients receiving various therapies (31,32), but these data require further validation. CT perfusion is limited in this regard, since it involves high radiation exposure. Evolving, low-dose CT techniques, incorporating iterative reconstruction (33), projection view sharing (34) and reductions in tube current-time product and voltage may abrogate some of these concerns but at present, they limit applications of the technique.

**Positron emission tomography (PET) and PET-CT**

**Technical considerations**
PET exploits increased uptake of radioactive metabolic tracers [e.g., 18fluoro-deoxy-glucose (FDG)] by cancer cells to generate relatively selective imaging. Integrated PET-CT combines metabolic PET data with CT, overcoming the low spatial resolution of PET. Patients are typically fasted for 4–6

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*Figure 1* Comparison of CT and thoracoscopic appearances in early stage malignant pleural mesothelioma (MPM). (A,B) Axial computed tomography images of a patient diagnosed with early stage MPM in our unit. These demonstrate a large pleural effusion (PE), but no obvious areas of pleural thickening. (C,D) Local anaesthetic thoracoscopy (LAT) images recorded in the same patient demonstrating widespread parietal pleural tumour (some highlighted by white arrows) after complete evacuation of the large pleural effusion. Note the descending thoracic aorta (Ao) also covered by tumour, the deflated left lower lobe (LLL) and the left hemi-diaphragm (LHD).
hours before injection of 3.5–5.2 MBq/kg of $^{18}$FDG, 60–120 minutes before scanning. Maximal tracer uptake can then be recorded within user-defined regions of interest, generating end-points including peak standardized uptake value (SUV\text{max}) and total glycolytic volume (TGV), which integrates SUV and estimated pleural tumour volume. SUV values are influenced by patient characteristics, e.g., blood glucose and technical factors, e.g., scanner and parameters chosen.

**Diagnostic performance**

SUV\text{max} is typically higher in MPM [reported mean SUV\text{max} 6.5 (3.4)] than in benign pleural disease [reported mean SUV\text{max} 0.8 (0.60) (35)], but PET-CT has a limited role in primary diagnostics. This reflects limited availability, but also contradictory meta-analyses [sensitivity 95\%, specificity 82\% (36) vs. 81\% sensitivity, 74\% specificity (37)], which highlight that false negatives may occur in early stage MPM, because, similar to small (<8 mm) bronchial neoplasms (38), sensitivity is reduced in small volume pleural tumours. Additionally, false positives may result from inflammatory/infectious pleurites, such as rheumatoid pleuritis, tuberculosis, and prior talc pleurodesis (35-37).

**Biopsy planning**

Theoretically, PET-CT can be used to select the best site for biopsy and is used in some centres for this purpose. The multi-centre, randomised TARGET trial (ISRCTN 14024829) is currently recruiting in the UK, to determine whether this improves diagnostic accuracy, relative to operator-selected biopsy using standard CT images.

**Magnetic resonance imaging (MRI)**

**Technical considerations**

MRI utilizes electromagnets to generate a magnetic field, which can be harnessed to polarize (or excite) tissue protons and to detect energy released during their subsequent relaxation. Modern systems generate field strengths up to 7-Tesla (T), but most clinical systems operate at 1.5–3-T. MRI is ideally suited to MPM, because of high spatial resolution and the high natural contrast provided by adjacent, proton (water)-rich, pleural effusion. Pleural fluid demonstrates low (dark) signal on T1-weighted images due to the slower T1 relaxation of free water relative to adjacent tissues (e.g., fat). On T2-weighted imaging, free water within a pleural effusion is high (bright) in signal, optimizing detection of septa. This is particularly helpful in the selection of cases for VATS over LAT. Paramagnetic gadolinium-based contrast agents can be used to enhance contrast between tissues, and are limited only by a significant renal impairment (39). In many centres, MRI remains an ancillary diagnostic or staging tool due to increased scan times and lower availability, relative to CT.

**Typical morphological features**

The morphological features of MPM on MRI are similar to those on CT. However, previous studies demonstrate superior sensitivity (91–100\%) and specificity (73–80\%) (23,40) for MRI relative to CT. However, the real-life analyses of CT performance recently reported (20,23) have not been possible for MRI, reflecting its less frequent clinical use.

**Diffusion-weighted MRI (DWI-MRI)**

In 2010, Gill et al. first described DWI-MRI in MPM, reporting that the apparent diffusion coefficient (ADC), a measure of the relative diffusion of water molecules within tissues, was reduced in the pleura of patients with MPM, relative to those with benign disease (41). In addition, epithelioid MPM was associated with higher ADC values than sarcomatoid MPM (41). Coolen et al. subsequently confirmed this and reported 71\% sensitivity and 100\% specificity, based on an ADC threshold of 1.52×10^{-3} mm²/s (42). The same authors subsequently reported a subjective correlate termed ‘pleural pointillism’, which describes inhomogeneous pleural hyperintensity on high b-values DW images (1,000 s/mm²). In a larger study (n=109, 57 of whom had MPM), this was associated with 93\% sensitivity and 79\% specificity for pleural malignancy (43). Pointillism, named after the post-impressionistic painting technique it resembles when present, has the advantage of simplicity of reporting over computation of ADC values, but the disadvantage of greater subjectivity. Coolen et al. reported a $\kappa$ of only 0.53, which was lower than subjective morphology in the same study (e.g., mediastinal thickening $\kappa$ 0.71) (43). Moreover, the ‘added value’ of DWI-MRI, needs further clarification, given the additional time required for acquisition and reporting. MPM staging was not reported by Coolen et al, but 67\% patients had ‘shrinking lung’ (43), which is generally a feature of late stage disease where morphology alone performs well. Nevertheless, pointillism is quick to report and DW-MRI may prove valuable, subject to validation in other centres.

**Perfusion MRI**

Unlike perfusion CT, perfusion MRI is not limited by high
radiation exposure, and more promising applications exist. These include dynamic contrast enhanced MRI (DCE-MRI) and early contrast enhancement MRI (ECE-MRI).

**DCE-MRI**

DCE-MRI is a direct correlate of CT perfusion and allows computation of various pharmacokinetic parameters. Giesel et al. reported kinetic values that correlated with tumour vascularity and vascular permeability and were predictive of response to anti-angiogenic therapy in 19 patients (44,45). Coolen et al. subsequently found that use of DCE-MRI in cases with indeterminate DWI-MRI increased sensitivity (71% to 93%) at the cost of slightly reduced specificity (100% to 94%) (42). However, a major drawback of DCE-MRI is that it requires a visible tumour mass for deployment, limiting its genuine ‘added value’ over standard diagnostic morphology.

**ECE-MRI**

ECE-MRI is a recently reported technique that, unlike DCE-MRI can be applied in patients with minimal pleural thickening (32). In a recent pilot study, Tsim et al. acquired coronal 3D spoiled gradient echo sequences during breath holding before and repeatedly after gadolinium contrast. Peak signal intensity was measured in up to 15 user-defined regions of interest; including areas of bland pleural thickening if no tumour was visible (see Figure 2 for examples). Peak enhancement occurred at or before 4.5 minutes (labelled by the authors as ECE), and correlated with tumour micro-vessel density (MVD) (32) and adverse survival. Although labelled ECE, this time-point is later than peak enhancement after iodinated contrast [60-90 seconds (19)] but is concordant with a study recently reported by Armato et al., in which MRI peak enhancement occurred after 280 seconds (32). This delayed enhancement interval may reflect factors other than the microvasculature, including delayed clearance of gadolinium (an extra-cellular agent) from peri-tumoral stroma, which is particularly prevalent in MPM (46). In contrast to pleural pointillism, inter-observer agreement for MRI-ECE ($\kappa$ 0.784) exceeded...
that for subjective CT ($\kappa$ 0.65) and MRI morphology ($\kappa$ 0.593), possibly reflecting the semi-objective definition of ECE. If validated in larger studies, MRI-ECE might genuinely add ‘disease detection’ value over traditional morphology, which could increase the proportion of patients eligible for potentially radical surgery.

**Imaging prior to radical surgery for MPM**

*The mesothelioma multi-disciplinary team (MDT)*

Radiological assessment prior to radical surgery should be undertaken by a dedicated Mesothelioma MDT. MDT working improves diagnostic performance and is associated with recruitment to trials (47). The value of the MDT in concentrating expertise cannot be over-stated, given the low incidence of MPM and the challenges involved in MPM diagnostics and staging (48–51). Successful assessment prior to radical surgery requires an understanding of (I) the anatomy and the definitions of potential resectability; (II) the strengths and weaknesses of each imaging modality; and (III) the likely impact on the patient of under- or over-staging. An integrated approach to imaging prior to radical surgery is summarized in Figure 3.

**Managing uncertainty**

The aim of potentially radical surgery in MPM is macroscopic complete resection (MCR) and failure to achieve this adversely affects prognosis (52,53). The extent of apparent pre-operative involvement should therefore always be weighted, realistically, against the surgical expectation to achieve MCR. In our opinion, multiple or large areas of doubt regarding resectability should contraindicate surgery in most cases. A commonly encountered area of uncertainty is the definition of what is anatomically ‘resectable’. While there is broad consensus that T4 or N2 or M1 disease should be considered unresectable, several factors may influence the decision.

Figure 3 Summary of pre-operative imaging investigations prior to consideration of radical surgery for malignant pleural mesothelioma.
to offer surgery in borderline cases (e.g., T3 possibly T4, possible mediastinal N1 disease) and these are discussed in detail below. These should balance the risks of pre-operative over-staging and exclusion from potentially beneficial surgery vs. under-staging and overly aggressive, futile surgery. However, previous studies frequently report up-staging of patients at surgery. In 2012, Rusch et al. reported upstaging in up to 80% of 1,056 MPM patients treated surgically for pre-operatively (or clinically) staged stage I or II disease, and 23% of patients with pre-operative stage III disease (54).

Identification of technically unresectable T4 disease

Since T3 is defined as locally advanced, potentially resectable tumour and T4 as technically unresectable tumour, differentiation between these requires previous experience. Consequently, centre- and volume-dependent factors become important in making high quality pre-surgical staging decisions. CT allows a reasonable assessment of lung involvement (i.e., T1 vs. T2 disease), a greater extent of which may be acceptable in cases of intended lung removal (EPP). However, MRI is superior to CT in detecting invasion of the chest wall, diaphragm and bony structures, which will constitute at least T3 disease (55,56). Stewart et al. performed contrast-enhanced 1.5-T MRI on 69 patients with apparently resectable MPM following contrast-enhanced CT scanning, and found CT-occult, unresectable (T4) disease in 17/76 (22%) patients (57). PET-CT is relatively insensitive to extra-pleural invasion, as shown by a previous report of 67% sensitivity for T4 disease (58). Therefore, in cases where diagnostic CT imaging demonstrates T3 (and therefore potential T4) disease (e.g., a single focus of chest wall invasion) or the patient has symptoms suggestive of multi-focal chest wall invasion (e.g., severe chest pain) regardless of CT T-stage, it is our practice to perform contrast-enhanced MRI if radical surgery is being considered.

Tumour volumetry

In lung cancer, recent data have demonstrated the powerful prognostic impact of small increases in primary tumour size, resulting in adoption of 1 cm increments in T-stage descriptors in the updated staging system (59). In MPM, the technical challenges involved measurements of this precision are greater due to the tumour’s rind-like growth pattern and the complex shape of the pleural cavity. Nevertheless, Nowak et al. recently reported that unidimensional measures of maximum pleural tumour thickness were consistently associated with decreasing survival, node positivity and overall stage in the updated MPM staging database (48). However, unidimensional measurements are limited by inter-observer variability, with Armato et al. reporting up to 30% variance between reporters (60). Computer-aided analysis can improve consistency but this remains high in minimally-measurable (<7.5 mm) lesions (61,62) and cannot overcome obvious concerns regarding poor representation of the overall disease. Volumetry is the logical solution to this but is complicated by further technical challenges, which are gradually being addressed. Either CT, MRI or Integrated PET/CT can be used, but the higher contrast resolution afforded by MRI relative to CT (55,63-65), particularly in resolving tumour from adjacent effusion, renders it a potentially more powerful, but less studied volumetric tool. Using CT, Pass (66) and Gill (67) both reported that above-median MPM tumour volumes (>100 cm³ in 48 patients, >500 cm³ in 88 patients) were associated with adverse survival in single centre analyses. Kircheva et al. also reported that resected tumour volume, measured by water displacement, was a better predictor of survival than T stage, based on current clinical descriptors (68). Plathow et al. reported the only published analysis of MRI volumetry in MPM but did not relate volumetric results to survival. However, MRI volumetry did out-perform CT in determining therapy response according to modified RECIST criteria (69). The larger, multi-centre volumetric CT study (n=164, 129 of whom were analysed) was recently able to define 3 prognostic groups based on cut-points of 91.2, 245.3 and 511.3 cm³, with associated median survival times of 37, 18 and 8 months, respectively (70). However, this study also identified significant inter-observer variability (71). More evolved computational techniques, e.g., the random walk-based method recently reported by Chen et al. (72), are required to address this, and to reduce the time required to report volumetric studies. Deployment of these techniques in larger cohorts, using agreed software is required for validation of volume-based T descriptors that might augment or replace the current descriptive definitions. Use of MRI might also reduce inter-observer variation in comparison to CT (73), but issues related to availability and reporter familiarity need to be overcome. Addition of volumetric metabolic data may also help to select patients for radical surgery, given the powerful prognostic impact of volumetric PET-CT, recently reported by Nowak et al. (74).
Intra-operative identification of residual disease

It has long been acknowledged that it may be difficult to identify small volumes of residual tumour intra-operatively (75) and thus achieve MCR. Keating et al. recently reported results of a small pilot study design to augment this assessment, using intra-operative detection of indocyanine green (ICG), a near-infrared (NIR) optical contrast agent that localizes to areas of tumour via enhanced permeability and retention. ICG (5 mg/kg) was injected intravenously in 8 patients 24 hours prior to surgery. After what was thought to be MCR, the wound bed was imaged intra-operatively using a NIR device, revealing NIR fluorescent residual disease in all 8 patients, from whom 1 to 4 additional areas of tumour were resected (mean 1.8), and confirmed histologically (32) (see Figure 4). This potentially important data has yet to be published in full, but warrants further study.

Identification of nodal involvement

Methodological and practical issues

The sub-classification of hilar (N1) and mediastinal (N2) lymph nodes used in lung cancer is not valid in MPM, in which setting malignant lymph may drain directly into the mediastinum (76,77). This is reflected in the 8th edition for TNM staging manual for MPM (49), in which mediastinal nodes have been re-classified as N1. No randomised data exist to inform decisions regarding the appropriateness of EP/D in patients with mediastinal node involvement, which may frequently be technically resectable, albeit extra-pleural and associated with considerable survival disadvantage (49). The nodal staging literature is also complicated in MPM by a tendency to compare one imaging modality with another, with less frequent use of gold-standard histological confirmation than is the case with T-staging, and considerable variation in the extent of nodal dissection during surgery, depending on operator, institution and procedure (49). The latter results in considerable variation in the reported incidence of nodal metastases and contributes to the limited histological reference standards for imaging studies. In addition, the location and distribution of abnormal nodes in MPM [e.g., peri-diaphragmatic (PD), peri-cardiac (PC), see Figure 5 for an example] may preclude comprehensive staging using minimally-invasive endoscopic techniques, such as endobronchial ultrasound (EBUS).

Imaging of nodal metastases

CT is of limited value in assessment of the mediastinum in MPM. Pathological nodes are frequently missed or over-called (previous studies report AUC values of <0.5) (56) and nodal size on CT and pathological status have shown no correlation in previous studies (56). Isolated PET should

Figure 4 Resected malignant pleural mesothelioma (MPM) tumor specimens imaged in white light (left panel) and near infrared (NIR) light (right panel). The NIR image demonstrates NIR fluorescence in residual areas of tumour not visualized intra-operatively, reflecting pre-operative injection of indocyanine green (ICG).
also not be used since it offers low sensitivity (11%) (78). In a previous comparative study, integrated PET-CT delivered the highest accuracy for nodal metastases (see Figure 5 for examples), relative to isolated PET, CT and MRI (79). In this study, Plathow et al. reported 100% sensitivity and 100% specificity for N1 nodal metastases using PET-CT in

**Figure 5** Pre-operative computed tomography (CT) and integrated positron emission tomography (PET)-CT images acquired in a male patient with clinical stage T2N1M0 Epithelioid malignant pleural mesothelioma (MPM). (A) and (B) are coronal and axial images, respectively, demonstrating tumour extension into the posterior costophrenic recess, but without clear trans-diaphragmatic invasion, which would constitute T4 disease. (C) Demonstrates an abnormal pericardial lymph node (yellow arrow), which exhibits a standardised uptake value (SUV) intermediate between the mediastinal blood pool and liver. (D) On preceding contrast-enhanced CT this appears to be a cluster of at least 2 lymph nodes (yellow arrow). This site would not be sampleable by any minimally invasive technique, but would be resectable.
54 patients, 52 of whom had surgical verification of stage. However, neither the nature of the surgery nor the extent of the nodal dissection performed was reported (79). These perfect results have not been replicated by other groups. Sørensen et al. reported 50% sensitivity, 75% specificity, 50% positive predictive value (PPV) and 50% NPV for integrated PET-CT prior to EPP in 24 patients. Erasmus et al. reported 38% sensitivity, 78% specificity, 60% PPV and 58% NPV using the same technique in a similar cohort. The case for investigation beyond CT is well made by Sørensen et al., who reported that PET-CT prevented futile surgery in 12/42 (29%) patients, due to distant metastases or T4 disease (80). Although integrated PET-CT is the most accurate test (79), it should not be relied upon in isolation (58,80). Suspicious sites should be sampled where possible although the extent to which these results should influence surgical decision making is an area of debate.

Current practice
Several centres have recently reported their outcomes following radical surgery (EPP or EP/D), including many patients with mediastinal node involvement. In 2012, Nakas et al. reported that only positive ‘accessible’ [to cervical mediastinoscopy (CM)] mediastinal nodes, in stations 3a, 4 and 7, were associated with a survival disadvantage in 212 patients who underwent EPP or EP/D in the UK. Patients with positive, ipsilateral extra-mediastinal or ‘inaccessible’ (to CM) nodes [internal mammary (IM), PC, PD, stations 5 and 6] had a similar survival to patients with N0 disease and prognostic data from EBUS staging of lower mediastinal stations was non-contributory (81). This non-comparative data has led some to offer radical surgery to patients with radiologically abnormal IM, PC, PD or station 5/6 nodes as long as these are technically resectable (Nakas 2012), but ideally after a staging CM to identify superior mediastinal (N1) disease (82,83). In a contradictory US series, mediastinal node involvement had no impact on subsequent survival (68). In the currently recruiting MARS-2 trial an intermediate approach has been adopted. No specific nodal staging beyond CT is mandatory and patients can be allocated to EP/D so long as their disease is technically resectable and confined to one hemi-thorax. Mediastinal (N1) disease is not therefore an absolute exclusion criterion to EP/D in this important trial.

Identification of metastatic disease
Metastatic disease may be more common in MPM than has been traditionally been taught. In a recent, large post-mortem series (n=318) extra-pleural disease was evident in 87.7% of patients and extra-thoracic disease in 55.4% (84). Case reports of unusual metastatic sites (muscle, skin and colon) have also recently been published (85–87). Given its widespread availability and low-cost contrast-enhanced CT should initially be used for metastatic staging. However integrated PET-CT is more sensitive (58,78) and should be considered after CT if radical surgery is contemplated. For equivocal extra-thoracic abnormalities MRI may occasionally be useful, e.g., regarding potential bone lesions.

Imaging prior to palliative surgery
Partial P/D (PP/D) may be helpful in palliating selected patients, particularly those with a gross visceral pleural cortex or a malignant empyema (88). In this setting, pre-operative cross-sectional imaging (by CT +/- MRI) allows some estimation of the relative risks and benefits of the procedure, with large tumour volumes and wider total trapped lung surface decreasing the chances of good technical and symptomatic success. However, the evidence base for palliative surgery is currently limited. In the MesoVATS trial, PP/D demonstrated no survival advantage over simple talc pleurodesis, and was associated with increased complications and increased cost (89). However, patients with NEL were largely excluded and might have the most to gain from this procedure. The Meso-TRAP trial has therefore been initiated to determine the value of PP/D in patients with trapped lung (or NEL) relative to placement of an IPC, which is the standard of care in this setting (90). The study is currently recruiting patients to a randomised feasibility phase, including the following inclusion criterion for: ‘clinically significant trapped lung’. Accurate and consistent radiological detection of this is therefore of fundamental importance, but poses considerable and often underestimated problems.

Radiological definition of ‘trapped’ or NEL
NEL can be simply defined as failure of full lung re-expansion after drainage of pleural fluid, and may result from malignant or reactive visceral pleural thickening, proximal endobronchial obstruction or reduced parenchymal compliance. A thick visceral cortex may be obvious on CT prior to first pleural intervention, but in the absence of this, NEL can be difficult to predict using...
baseline radiology (CXR, CT or MRI). This is reflected in a significant proportion of patients admitted for an attempt at fluid drainage and talc pleurodesis not receiving talc because of unexpected NEL, including up to 25% of patients recruited recent pleurodesis phase III trials. Emerging ultrasound end-points might enhance NEL prediction prior to fluid drainage, including M-mode and speckle tracking imaging analyses (18) (see TUS section), but NEL can also be challenging to detect after fluid is removed. Serial CXRs may reveal a classic (ex vacuo) pneumothorax, but Martin et al. recently reported considerable disagreement between two reporters regarding the presence of post-drainage NEL. The subjective method currently advocated by the BTS (based on less than 50% re-apposition of the pleural surfaces), was associated with a $\kappa$ of only 0.68 and 81% sensitivity/87% specificity. During surgical thoracoscopy, NEL can be directly and accurately visualized based on the extent of lung re-inflation during positive pressure ventilation, allowing a judgement to be made regarding IPC vs. talc pleurodesis (91). However, visual assessment performs poorly during LAT, with only 12.5% cases of NEL correctly identified in a recent survey, although this study was small, retrospective and judgements were based on 30 second video-clips only (92). Given the emerging potential importance of NEL in selecting MPM patients for PP/D, better radiographic correlates of this phenomenon are urgently required.

**Conclusions**

The peculiar biology and unique growth pattern of MPM pose particular imaging challenges. Nevertheless, there have been significant recent developments in diagnostic imaging and radiological staging that may facilitate better surgical decision-making in MPM patients and ultimately better outcomes. However, many require further prospective evaluation in large, multi-national collaborative studies.

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**Footnote**

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**References**


systemic fibrosis: suspected causative role of gadodiamide
used for contrast-enhanced magnetic resonance imaging. J
40. Falaschi F, Battolla L, Zampa V, et al. Comparison of
computerized tomography and magnetic resonance in
the assessment of benign and malignant pleural diseases.
MRI of malignant pleural mesothelioma: preliminary
assessment of apparent diffusion coefficient in histologic
disease: diagnosis by using diffusion-weighted and dynamic
contrast-enhanced MR imaging--initial experience.
pleural mesothelioma: visual assessment by using pleural
pointillism at diffusion-weighted MR imaging. Radiology
2015;274:576-84.
44. Giesel FL, Bischoff H, von Tengg-Kobligk H, et
al. Dynamic contrast-enhanced MRI of malignant
pleural mesothelioma: a feasibility study of noninvasive
assessment, therapeutic follow-up, and possible predictor
45. Giesel FL, Choyke PL, Mehndiratta A, et al.
Pharmacokinetic analysis of malignant pleural
mesothelioma-initial results of tumor microcirculation
and its correlation to microvessel density (CD-34). Acad
46. O’Byrne K, Rusch V. Malignant Pleural Mesothelioma.
47. Tsim S, Dick C, Roberts F, et al. 76 Early experience of
a regional mesothelioma MDT in the West of Scotland.
48. Nowak AK, Chansky K, Rice DC, et al. The IASLC
Mesothelioma Staging Project: Proposals for Revisions of
the T Descriptors in the Forthcoming Eighth Edition of
the TNM Classification for Pleural Mesothelioma. J
49. Rusch VW, Giroux D. Do we need a revised staging system
for malignant pleural mesothelioma? Analysis of the IASLC
pleurectomy and chemoradiation for malignant pleural
mesothelioma: the outcome of incomplete resections.
cytoreduction in the treatment of malignant pleural
mesothelioma: meeting summary of the International
Mesothelioma Interest Group Congress, September
52. Heelan RT, Rusch VW, Begg CB, et al. Staging of
malignant pleural mesothelioma: comparison of CT and
53. Stewart DJ, Martin-Ucar A, Pilling JE, et al. The effect of
extent of local resection on patterns of disease progression
2004;78:245-52.
54. Erasmus JJ, Truong MT, Smythe WR, et al. Integrated
computed tomography-positron emission tomography
in patients with potentially resectable malignant pleural
mesothelioma: Staging implications. J Thorac Cardiovasc
55. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC
Lung Cancer Staging Project: Proposals for the Revisions of
the T Descriptors in the Forthcoming Eighth Edition of
the TNM Classification for Lung Cancer. J Thorac Oncol
56. Armato SG, Oxnard GR, MacMahon H, et al.
Measurement of mesothelioma on thoracic CT scans: a
comparison of manual and computer-assisted techniques.


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