Acta Biomed 2017; Vol. 88, N. 2: 134-142 DOI: 10.23750/abm.v88i2.5558

Review

Diagnostic imaging and workup of malignant pleural mesothelioma

Luciano Cardinale[1], Francesco Ardissone[2], Dario Gned[1], Nicola Sverzellati[3], Edoardo Piacibello[1], Andrea Veltri[1]

[1] Department of Radiology, S. Luigi Hospital, University of Turin, Turin, Italy; [2] Department of Oncology, Unit of Thoracic Surgery, S. Luigi Hospital, University of Turin, Turin, Italy; [3] Department of Clinical Sciences, Section of Radiology, University of Parma, Parma, Italy

Summary. Malignant pleural mesothelioma is the most frequent primary neoplasm of the pleura and its incidence is still increasing. This tumor has a strong association with exposure to occupational or environmental asbestos, often after a long latent period of 30-40 years. Plain chest radiography (CXR) is usually the first-line radiologic examination, but the radiographic findings are nonspecific due to its limited contrast resolution and they need to be complemented by other imaging modalities such as computed tomography (CT), magnetic resonance Imaging (MRI), Positron emission tomography–computed tomography (PET-CT) and ultrasound (US). The aim of this paper is to describe the imaging features of this malignancy, underlining the peculiarity of CXR, CT, MRI, PET-CT and US and also focusing on diagnostic workup, based on the literature evidence and according to our experience. (www.actabiomedica.it)

Key words: malignant pleural mesothelioma, computed tomography, video assisted thoracic surgery, magnetic resonance imaging, thoracic ultrasound, positron-emission tomography

Introduction

Malignant pleural mesothelioma (MPM) is the most frequent primary neoplasm of the pleura. Although asbestos use has been banned in many developed countries, the incidence has been significantly increasing because of widespread occupational exposure over the last decades. Since the latency between first asbestos exposure and tumor development is around 40 years, the peak age incidence ranges from the sixth to the eighth decades and, since most asbestos exposure is work-related, the incidence is markedly higher in men than in women, the annual rates being 15 cases per million and 3 cases per million, respectively, in the United States (1,2).

Most commonly, MPM originates within the parietal pleura located in the lower hemithorax and the costophrenic angle (3,4). It spreads locally to the ipsilateral visceral pleura and relentlessly invades adjacent structures, such as the lung, chest wall, diaphragm, pericardium, and mediastinum. Disease may invade the contralateral pleural space and the peritoneum (4). Lymphatic and hematogenous metastases tend to occur late in natural history but are present at autopsy in approximately 50% of patients with MPM (5).

The clinical manifestations are nonspecific and many patients present with advanced-stage disease and comorbidities. The patient prognosis is poor, with a median survival after diagnosis of approximately 12 months.

The diagnosis of this neoplasm is often made at a late stage and the prognosis is still very poor with a median survival from diagnosis of under a year with supportive care alone. Achieving early diagnosis and helping to select the most appropriate treatment option in MPM patients is mandatory.

In this pictorial essay, the spectrum of imaging features of MPM at Chest Radiography (CXR), Computed Tomography (CT), Magnetic Resonance (MR), Positron Emission Tomography (PET), integrated PET/CT, and Ultrasonography (US) are discussed, and a diagnostic pathway in patients with undiagnosed pleural effusion is proposed, also with a brief reference to cancer staging.

Imaging

CRX is usually the first-line radiologic examination, but the radiographic findings are often nonspecific and others imaging modalities such as CT, PET-CT, MR and US are indicated.

CT is the mainstay imaging technique for primary assessment of pleural disease and affords improved sensitivity and specificity for identification of malignant pleural process. PET/CT, MR and US are complementary techniques for the assessment of pleural disease that can provide additional important diagnostic, staging and prognostic information.

Plain chest radiography (CXR)

CXR, due to its ready availability, is usually the first imaging modality used to detect abnormalities suggesting MPM. The radiographic appearance of MPM is variable and depends on the stage of disease at diagnosis.

A unilateral pleural effusion is the typical finding at presentation and is seen in 30%-80% of patients.

A pleural-based mass, in the absence of pleural effusion, is shown in less than 25% of patients (6) (Figure 1a). Diffuse pleural thickening or extensive lobular pleural-based masses are seen in about half of cases (6).

Tumor growth leads to nodular thickening of interlobar fissures and lung encasement with a rind-like appearance, ipsilateral volume loss and mediastinal shift. Larger pleural-based masses often coexist with multiloculated effusions which tend to obscure the underlying neoplasm (7).

Pleura plaques are thickened areas of parietal pleura composed of connective tissue which can undergo calcification, and are probably the commonest

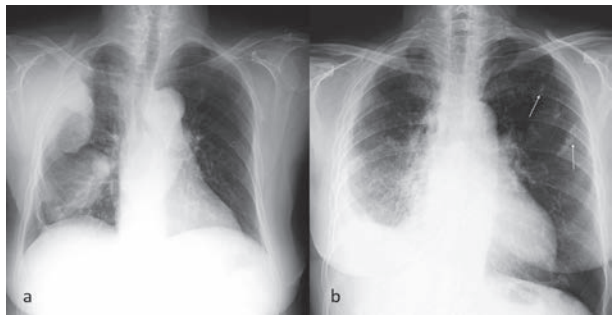

Figure 1. Malignant pleural mesothelioma. Standard posteroanterior chest X-ray (a) demonstrates a large lobulated pleural mass invading the chest wall (note rib destruction). No pleural effusion is seen. Standard posteroanterior chest X-ray (b) showing right pleural effusion and calcified pleural plaques (white arrows) secondary to long-standing asbestos exposure

radiographic manifestation of long-standing asbestos exposure, seen in approximately 20% of cases (Figure 1b). They are more prominent on the domes of the diaphragm and in the lower half of the thorax. Combined pleural and parenchymal changes can cause the "shaggy" heart sign, a partial obscuration of the heart border (1, 7). Although the presence of pleural plaques alone does not *per se* require additional diagnostic workup, a statistically significant association was observed in a 7-year follow-up study of formerly asbestos-exposed workers between pleural plaques, detected on CT, and the risk of MPM (8).

Computed tomography (CT)

Computed tomography (CT) continues to be the mainstay imaging technique for the initial assessment of MPM and plays a primary role in structuring the subsequent diagnostic and staging evaluation as well as therapeutic decision-making process. Technical CT factors are very important for reaching the correct diagnosis. The last generation CT technology (>32 detector rows) allows thin-section volumetric acquisitions providing an isotropic data set, which can be reconstructed in any plane. As a result, these multiplanar reformations allow to easily evaluating the presence of very limited pleural thickening. Employment of a contrast medium is mandatory (1), the CT scanning delay should be also set at 60-80 seconds to optimize the maximum pleural tumor uptake (3) (Figure 2) and the

field-of-view (FOV) due to the tumor growth through the diaphragmatic pillars had to cover a wide area from the lung apex to the to L3. CT features highly suggestive of the disease include nodular or lobular pleural thickening, interlobar fissure thickening, mediastinal pleural thickening, parietal pleural thickening >1 cm, and circumferential pleural thickening. The most common CT finding is pleural thickening and is seen in 90%-92% of patients (9). It greatly varies in extent, thickness, and nodularity. Circumferential pleural thickening with rind-like encasement of the lung and ipsilateral volume loss is seen in advanced-stage disease. Focal pleural masses of >3 cm in diameter are identified in 8%-38% of cases. The next most frequent CT finding is interlobar fissure involvement and is identified, as thickening and/or nodularity, in 73%-86% of patients. Additional CT findings include pleural effusions and plaques and are seen in approximately 75% and 20% of cases, respectively (9). MPM has a propensity for early invasion into adjacent structures. Mediastinal pleura, vascular structures and organs involvement may result in obliteration of fat planes and encasement of great vessels, esophagus and trachea. Involvement of the pericardium can be seen as pericardial thickening and/or effusion. Extension of the tumor into the chest wall may result in obliteration of extrapleural fat planes, invasion of intercostal muscles, and rib displacement or destruction. Thickening of the hemidiaphragm is a common finding. However, CT has shown poor/limited accuracy in identifying transdiaphragmatic tumor extension. Features suggesting transdiaphragmatic invasion include a soft tissue mass that encases the hemidiaphragm and absence of a fat plane between the inferior surface of the muscle and adjacent abdominal organs. Finally, CT can sometimes be useful for the evaluation of intrathoracic lymphadenopathy.

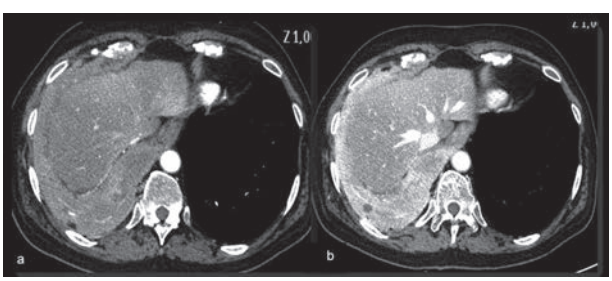

Figure 2. Malignant pleural mesothelioma. Axial contrast-enhanced CT images in arterial (a) and portal phases (b). This example shows that the pleural ticknening is less evident in a more arterial phase than with a 70-80 seconds scan delay. The enhancement of pleural thickening is maximum in the portal phase

Over the last decades, a number of staging systems have been proposed to predict outcome and guide appropriate treatment planning in MPM patients. The International Mesothelioma Interest Group (10) developed a new staging system based on primary tumor local extent (T), lymph node involvement (N), and metastatic disease (M).

Accurate staging based on imaging is pivotal for identifying potential candidates to aggressive surgical procedures and multimodality treatment. However, CT has repeatedly shown limited accuracy in distinguishing between potentially resectable (T3) and technically unresectable (T4) disease as well as in identifying intrathoracic lymph node involvement (11, 12).

Finally, several authors have shown the value of CT in differentiating benign from malignant pleural disease (13-15). Helpful discriminating features of malignant disease on CT scanning include nodular pleural thickening, mediastinal pleural thickening, parietal pleural thickening >1 cm, and circumferential pleural thickening. However, data from a recent study (16) suggest that although the sensitivity of these findings is higher than previously reported (68%), the specificity is significantly lower (78%). Of note, with a negative predictive value of 65%, the absence of these findings does not exclude malignant pleural disease. Besides, these findings have shown a limited importance for differentiation of MPM from metastatic pleural disease (14, 15).

Figure 3 (a,b,c,d,) illustrates some of the findings typically visible on CT imaging in MPM.

Magnetic resonance (MR)

Because of cost reasons, limited availability, and long imaging time, MR is not commonly used in the diagnostic and staging evaluation of MPM patients. However, owing to excellent contrast resolution on unenhanced scans and higher enhancement achieved post-contrast, it has been found useful in equivocal cases as well as in potential candidates to multimodali-

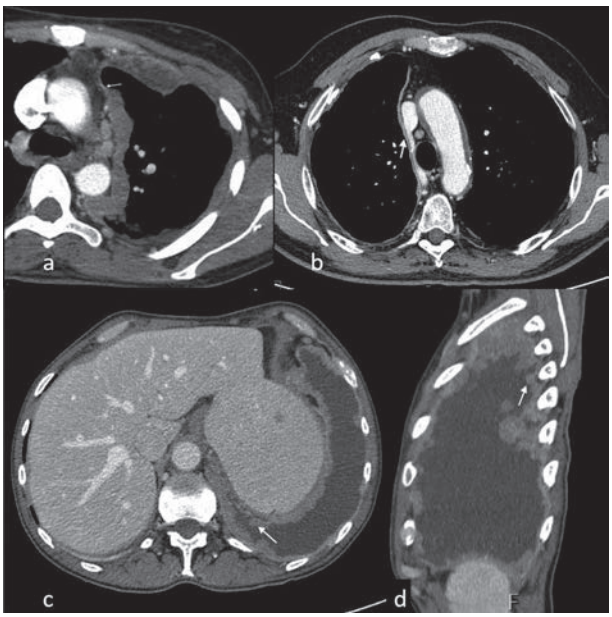

Figure 3. Malignant pleural mesothelioma. Axial contrast-enhanced CT image (a) demonstrates circumferential irregular pleural thickening (white arrow) and mediastinal lymphadenopathy. Axial contrast-enhanced CT image (b) demonstrates right subtle circumferential pleural thickening (white arrow) and ipsilateral volume loss. Axial (c) and sagittal reformatted (d) contrast-enhanced CT images showing extensive nodular pleural thickening (white arrows) and a large-sized pleural effusion

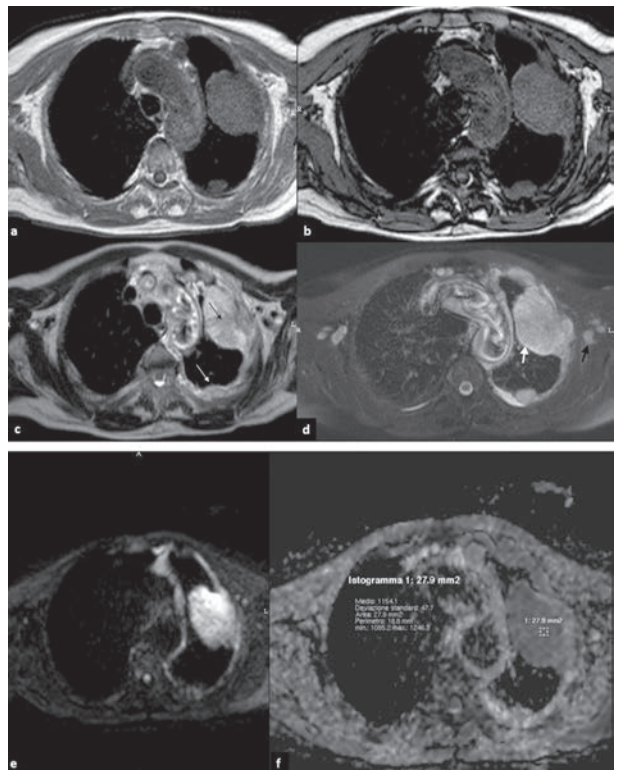

Figure 4. Malignant pleural mesothelioma. Axial T1-weighted MR images showing a iso/hypointense (in phase,a) a large pleural mass involving the chest wall without signal loss (out phase, b), demonstrating absence of fat tissue. Axial T2-weighted (HASTE) MR image (c) shows a pleural mass (black arrow) with irregular hyperintense signal because of presence of fibrous tissue inside tumor lesion. A small posterior pleural nodule is also seen (white arrow). Axial T2-Weighted Fat Saturated MR image (d) shows a hyperintense lesion (white arrowhead) without signal drop because of absence of fat tissue inside. Note also bilateral axillary linphoadenopathy (black arrowhead) and pleural thickening. Axial diffusion-weighted MR image (b value = 750 s/mm2) showing pleural tumor (e) and thickened left pleura with higher signal intensity than adjacent skeletal muscle, with restricted diffusion with low ADC values, more frequent in neoplastic disease (f) (1-1.5)

ty therapy including surgery (17-19). Indeed, the combination of morphological data and information on signal intensity may provide more precise assessment of local disease extent (19). Pleural mesothelioma is characterized by intermediate or slightly hyperintense signal on T1-weighted sequences (Figure 4 a and b) and by more intense signal on T2-weighted sequences, compared with adjacent chest wall healthy tissue (Figure 4c) (20). The signal of pleural mesothelioma may be further enhanced by using gadolinium-based paramagnetic contrast material. Contrast-enhanced T2-weighted fat suppressed sequences (Figure 4d) are the most sensitive sequences for detecting invasion of interlobar fissures and of adjacent structures (17). Furthermore, diffusion-weighted MR (Figure 4e and f) can reveal tissue characteristics based on the diffusivity of water molecules within tissues. With this technique, signal loss can be quantitatively assessed with the apparent diffusion coefficient (ADC), which depends on restriction of water molecules diffusion by cell membranes and macromolecules, indirectly providing information about tissue cellularity (18). As for the assessment of local disease extent, Patz and colleagues (11) compared MR with CT in 34 MPM patients undergoing thoracotomy. Review of imaging findings focused on local invasion of the diaphragm, chest wall, and mediastinum. MR showed slightly higher sensitivity than CT for predicting resectability at the diaphragm and chest wall (100% vs 93%-94%, respectively), most likely because MR provided additional coronal and sagittal images. Heelan and col-

leagues (17) compared the accuracy of MR with that of CT in the preoperative staging of 65 MPM patients. MR and CT imaging showed nearly equivalent diagnostic accuracy in staging, but MR was more accurate for detecting solitary foci of chest wall invasion and endothoracic fascia involvement and for assessing diaphragmatic invasion. However, these findings did not change the surgical approach. Furthermore, the higher resolution and the ability for multiplanar reformations afforded by multidetector CT (MDCT) may provide more accurate assessment of the local extent of MPM.

Positron-emission tomography (PET-CT)

Owing to the ability of providing both metabolic and anatomic information about a lesion, PET and PET/CT have emerged as important complementary techniques for the assessment of pleural disease.

The elevated metabolic activity of tumor cells results in significantly higher ^{18}F-Fluorodeoxyglucose standardized uptake value (SUV) of MPM compared with benign pleural diseases. Several authors (21-25) showed that a SUV cutoff value of 2.0-2.2 differentiated malignant from benign pleural disease with sensitivities of 91%-100% and specificities of 78%-100% (Figure 5a). In addition, PET has been found useful to identify the most appropriate biopsy site for achieving definite diagnosis (Figure 5b). However, PET accuracy in distinguishing benign and malignant pleural disease is limited by false-negative (low-grade variant of MPM) and false-positive (26) (concomitant asbestos-related disease, parapneumonic effusion, uraemic pleural disease, and talc pleurodesis) results while PET has demonstrated suboptimal sensitivity and specificity in staging MPM patients (27-29).

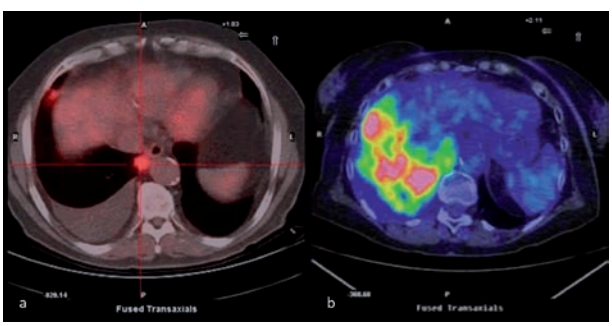

Figure 5. Malignant pleural mesothelioma. Axial fused well-collimated PET/CT image (a) shows two small FDG- avid nodules in the inferior right hemithorax. Axial fused well-collimated PET/CT image (b) shows extensive FDG-avid pleural thickening in the inferior right hemithorax

Due to superior anatomic spatial resolution, integrated PET/CT has been increasingly used for diagnostic and staging evaluation as well as treatment planning of MPM. PET/CT has demonstrated better accuracy in overall staging of MPM patients and in identifying potential candidates to multimodality therapy including aggressive surgical procedures. Indeed, two reviews evaluated the staging information of PET/TC and showed a wide range of accuracy for T, N, and M descriptors (30, 31). Recently, Frauenfelder and colleagues (12) evaluated the accuracy of CT and PET/CT for MPM staging in 28 patients undergoing induction chemotherapy. CT and PET/CT underestimated T stage in up to 30% of patients. PET/CT showed higher accuracy for tumor extent compared with CT (92% vs 84%, respectively) while CT showed higher accuracy for N staging compared with PET/CT (87% vs 78%, respectively). Regarding the International Mesothelioma Interest Group staging system (10), the accuracy of PET/CT in preoperative staging was higher compared with CT (91% vs 82%, respectively). Furthermore, the interobserver agreement for local tumor extent and N staging was lower for CT compared with PET/CT.

PET/CT may also have a role for monitoring treatment response, detecting recurrent disease, and providing prognostic information in MPM patients (29, 31).

Ultrasonography (US)

In the initial evaluation of pleural effusions, US has shown high sensitivity in pleural fluid detection and quantification (32, 33). It plays a pivotal role in image-guided techniques (thoracocentesis, needle biopsy, drain placement) and identifies complex, septated patterns of pleural effusion with higher sensitivity than CT (Figure 6).

Pleural thickening most often appears hypoechoic, but increased echogenicity with focal acustic shadowing is seen in presence of calcification and fibrosis (pleural plaques) (34-38). Mesotheliomas have very ir-

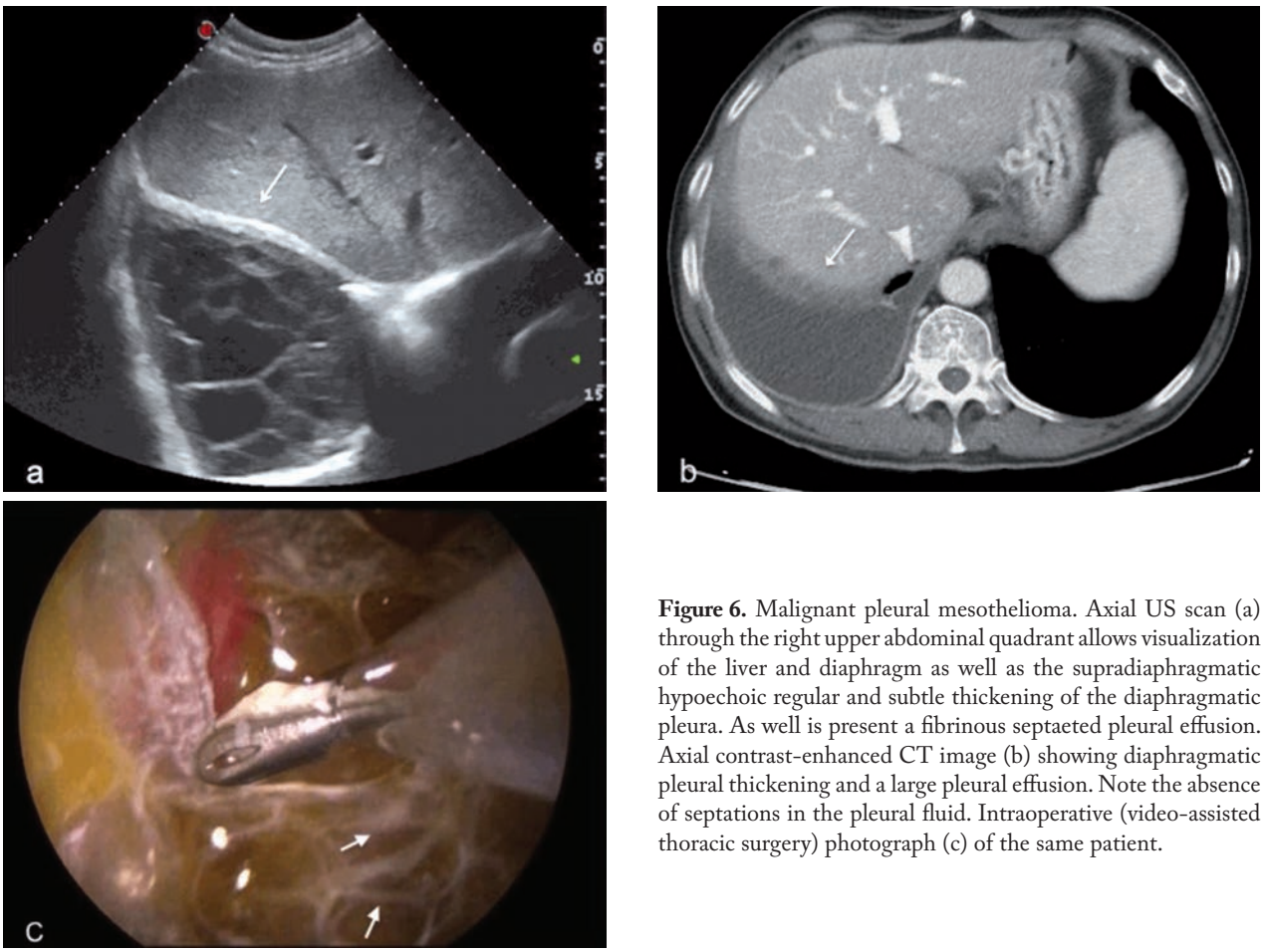

Figure 6. Malignant pleural mesothelioma. Axial US scan (a) through the right upper abdominal quadrant allows visualization of the liver and diaphragm as well as the supradiaphragmatic hypoechoic regular and subtle thickening of the diaphragmatic pleura. As well is present a fibrinous septaeted pleural effusion. Axial contrast-enhanced CT image (b) showing diaphragmatic pleural thickening and a large pleural effusion. Note the absence of septations in the pleural fluid. Intraoperative (video-assisted thoracic surgery) photograph (c) of the same patient.

regular, partly angular, unclear borders. In addition to tumorlike formations, mesotheliomas can also present as extensive, tapestry- like growths with nodules. Using high-frequency transducers, invasions of the chest wall and the diaphragm are visualized as striped, hypoechoic ramifications at the time of diagnosis. (39)

By using similar morphologic criteria as those used in CT (pleural thickening >1 cm, pleural and diaphragmatic thickening >7 mm), Qureshi and colleagues (40) demonstrated that US is able to differentiate malignant from benign effusions with an overall sensitivity of 79% and specificity of 100%, with specificity comparing favourably with CT. The authors' conclusions were that US, being a quick, relatively inexpensive and harmless procedure, may represent a valuable adjunct in the diagnostic pathway of suspected malignant pleural effusion.

Diagnostic pathway: our experience

We participated and contributed to the 2nd Italian Consensus Conference on Malignant Pleural Mesothelioma (41) held in Turin (Italy) on November 24-25, 2011. In the light of this starting point and of several recent international guidelines (42-46), we adopted a tailored diagnostic pathway (Figure 7), based on our experience and hospital facilities, as much as rational and cost-effective as possible in a high-risk area (41,45).

The chest X-ray (CXR) remains the first imaging modality for the approach to patients with suspected MPM. The CXR finding of pleural plaques does not require additional investigations (42), whereas recurrent unilateral pleural effusion (43) not related to any known etiology such as infection or congestive heart

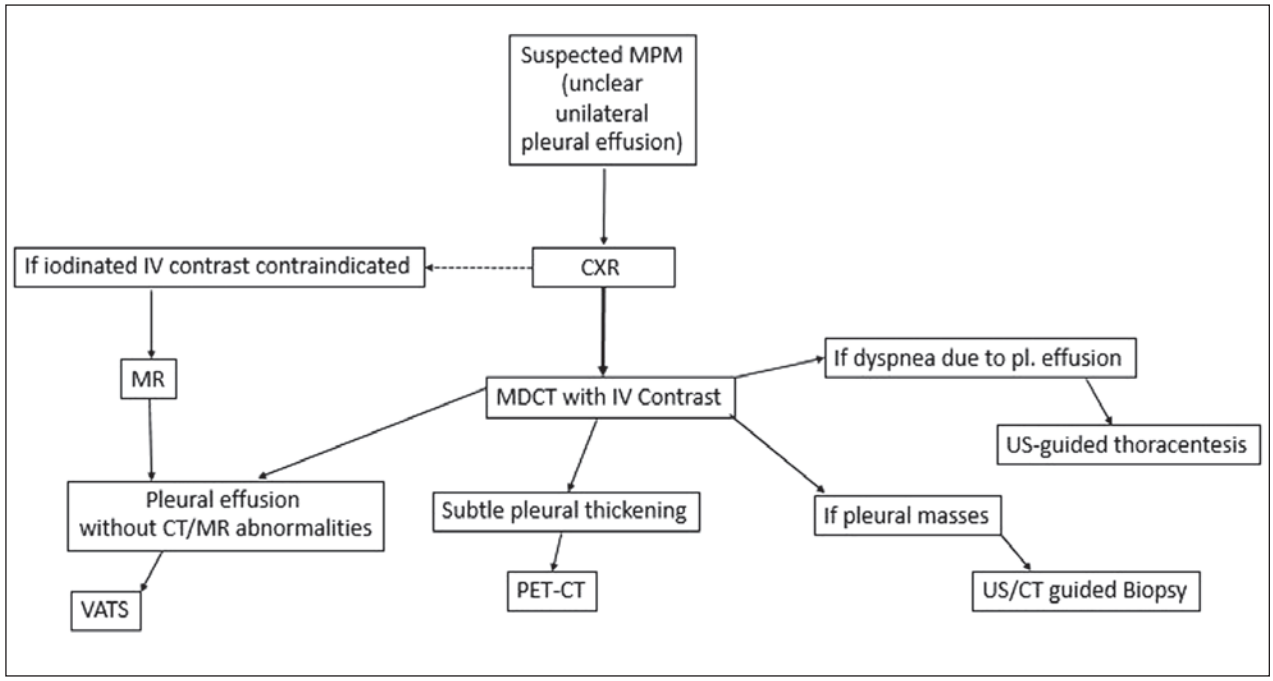

Figure 7. Malignant pleural mesothelioma diagnostic flowchart

failure should be further investigated by CT with contrast medium.

According to the MDCT findings, our targeted diagnostic workup may be summarized as follows:

- 1. In patients presenting with dyspnea due to a pleural effusion, if the clinician has any suspicion for a malignancy, a US guided thoracentesis should be performed.
- 2. Presence of gross irregular pleural masses (with or without pleural effusion) should be further investigated by US or CT guided-biopsy.
- 3. A limited irregular pleural thickening (with or without pleural effusion) may be evaluated by PET-CT scanning.
- 4. Recurrent pleural effusion without any visible abnormality at CT scan should be directly investigated by video assisted thoracoscopy (VATS), a minimally invasive technique with a high diagnostic yield which allows exploration of entire pleural surface and enables targeted biopsies, providing material samples for both histological examination and immunohistochemical analysis.
- 5. MR is used when there are contraindications to iodinated contrast medium and to provide more accurate assessment of chest wall or diaphragmatic invasion in patients deemed potential candidates to aggressive multimodality therapeutic regimens.

Conclusion

Imaging of MPM is a challenge for the radiologist for diagnosis and follow up.

Early diagnosis is still demanding because of subtle pleural lesions, hardly imaging detected.

Each imaging modality has its strenghts and limitations, but their rational and cost-effective combined use is crucial in determining the most appropriate treatment options for patients with MPM.

References

1. Nickell LT Jr, Lichtenberger JP 3rd, Khorashadi L, Abbott GF, Carter BW. Multimodality imaging for characterization, classification, and staging of malignant pleural mesothelio-

ma. Radiographics 2014 Oct; 34(6): 1692-706. doi: 10.1148/rg.346130089.
2. Rusch VW. Diffuse malignant mesothelioma. In: Shields TW, LoCicero J III, Reed CE, Feins RH (eds) General thoracic surgery. Wolters Kluwer/Lippincott Williams & Wilkins, Philadelphia. 2009; 847-59
3. Raj V, Kirke R, Bankart MJ, Entwisle JJ. Multidetector CT imaging of pleura: comparison of two contrast infusion protocols. The British Journal of Radiology 2011; 84(1005): 796-9. doi:10.1259/bjr/55980445.
4. Boutin C, Rey F. Thoracoscopy in pleural malignant mesothelioma: a prospective study of 188 consecutive patients. Part 1: diagnosis. Cancer 1993; 72(2): 389-93.
5. Flores RM, et al. The impact of lymph node station on survival in 348 patients with surgically resected malignant pleural mesothelioma: implications for revision of the American Joint Committee on Cancer staging system. J Thorac Cardiovasc Surg 2008; 136(3): 605-10.
6. Cardinale L, et al. Diffuse neoplasms of the pleural serosa. Radiol Med 2013; 118(3): 366-78.
7. Peacock C, Copley SJ, Hansell DM. Asbestos-related benign pleural disease. Clin Radiol Jun 2000; 55(6): 422-32.
8. Pairon J-C, Laurent F, Paris C. Pleural plaques and the risk of pleural mesothelioma. JNCI J Natl Cancer Inst 2013; 105(4): 293-301.
9. Tamer Dogan O, Salk I, Tas F, Epozturk K, Gumus C, Akkurt I, et al. Thoracic Computed Tomography Findings in Malignant Mesothelioma. Iran J Radiol 2012; 9 (4): 209-11. DOI: 10.5812/iranjradiol.8764
10. Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma: from the International Mesothelioma Interest Group. Chest 1995; 108(4): 1122-8.
11. Patz EF Jr, et al. Malignant pleural mesothelioma: value of CT and MR imaging in predicting resectability. AJR Am J Roentgenol. 1992; 159(5): 961-6.
12. Frauenfelder T, Kestenholz P, Veit-Haibach P, Husmann L, Stahel R, Opitz I, et al. Use of computed tomography and positron emission tomography/computed tomography for staging of local extent in patients with malignant pleural mesothelioma. J Comput Assist Tomogr 2014 Oct 28.
13. Maffessanti M, Tommasi M, Pellegrini P. Computed tomography of free pleural effusions. Eur J Radiol 1987; 7(2): 87-90.
14. Leung AN, Muller NL, Miller RR. CT in differential diagnosis of diffuse pleural disease. Am J Roentgenol 1990; 154(3): 487-92.
15. Metintas M, et al. Computed tomography features in malignant pleural mesothelioma and other commonly seen pleural diseases. Eur J Radiol 2012; 41(1): 1-9.
16. Hallifax RJ, Haris M, Corcoran JP, Leyakathalikhan S, Brown E. Role of CT in assessing pleural malignancy prior to thoracoscopy. Thorax 2014; 0: 1-2. doi: 10.1136/thoraxjnl-2014-206054
17. Heelan RT, et al. Staging of malignant pleural mesothelioma: comparison of CT and MR imaging. AJR Am J Roentgenol 1999; 172(4): 1039-47.
18. Knuuttila A, et al. Evaluation of pleural disease using MR and CT. With special reference to malignant pleural mesothelioma. Acta Radiol 2001; 42(5): 502-7.
19. Gill RR, Umeoka S. Diffusion-weighted MRI of malignant pleural mesothelioma preliminary assessment of apparent diffusion coefficient in histologic subtypes. AJR Am J Roentgenol 2010; 195(2): W125-30. doi: 10.2214/AJR.09.3519
20. Zucali PA, Giaccone G. Biology and management of malignant pleural mesothelioma. Eur J Cancer 2006; 42(16): 2706-14.
21. Yildirim H, Metintas M, Entok E. Clinical value of fluorodeoxyglucose-positron emission tomography/computed tomography in differentiation of malignant mesothelioma from asbestosrelated benign pleural disease: an observational pilot study. J Thorac Oncol 2009; 4: 1480-4.
22. Bénard F, Sterman D, Smith RJ, Kaiser LR, Albelda SM, Alavi A. Metabolic imaging of malignant pleural mesothelioma with fluorodeoxyglucose positron emission tomography. Chest 1998; 114: 713-22.
23. Duysinx B, Nguyen D, Louis R. Evaluation of pleural disease with 18-fluorodeoxyglucose positron emission tomography imaging. Chest 2004; 125(2): 489-93.
24. Kramer H, Pieterman MR. PET for the evaluation of pleural thickening observed on CT. J Nucl Med 2004; 45: 995-8.
25. Orki A, Akin O, Tasci AE. The role of positron emission tomography/computed tomography in the diagnosis of pleural diseases. Thorac Cardiovasc Surg 2009; 57: 217-21.
26. Treglia G, Sadeghi R. Diagnostic accuracy of 18F-FDG-PET and PET/CT in the differential diagnosis between malignant and benign pleural lesions: a systematic review and meta-analysis. Academic Radiology 2014 Jan; 21(1): 11-20. doi: 10.1016/j.acra.2013.09.015.
27. Schneider DB, Clary-Macy C, Challa S, et al. Positron emission tomography with F18-fluorodeoxyglucose in the staging and preoperative evaluation of malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2000; 120(1): 128-33.
28. Wang ZJ, et al. Malignant pleural mesothelioma: evaluation with CT, MR imaging, and PET. Radiographics 2004; 24(1): 105-19.
29. Flores RM, et al. Positron emission tomography defines metastatic disease but not locoregional disease in patients with malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2003; 126(1): 11-6.
30. Basu S, Saboury B, Torigian DA, et al, Current evidence base of FDG-PET/CT imaging in the clinical management of malignant pleural mesothelioma: emerging significance of image segmentation and global disease assessment (2011). Mol Imaging Biol 2011; 13 (5):801-11. doi: 10.1007/s11307-010-0426-6. Review.
31. Sharif S, Zahid I, Routledge T, Scarci M. Does positron emission tomography offer prognostic information in malignant pleural mesothelioma? Interact Cardiovasc Thorac Surg 2011; 12(5): 806-811.
32. Rahman N, Davies RJO, Gleeson FV. Investigating suspected malignant pleural effusion. BMJ 2007; 334: 206.

33. McLoud T, Flower C. Imaging the pleura: sonography, CT and MR imaging. AJR Am J Roentgenol 1991; 156: 1145-53.
34. Mathis G. Introduction-emergency ultrasonography. Ultraschall Med 2008; 29(4): 11-22.
35. Gorg C. Colour Doppler ultrasound mapping of chest wall lesions. Br J Radiol 2005; 78(928): 303-7.
36. Saito T, Kobayashi H, Kitamura S. Ultrasonographic approach to diagnosing chest wall tumors. Chest 1988; 94(6): 1271-5.
37. Bandi V, et al. Ultrasound vs. CT in detecting chest wall invasion by tumor: a prospective study. Chest 2008; 133(4): 881-6.
38. Popic Ramac J, et al. The possibilities and limitations of direct digital radiography, ultrasound and computed tomography in diagnosing pleural mesotelioma. Coll Antropol 2010; 34(4): 1263-71.
39. Reuss J. The Pleura In Gebhard Mathis (Ed.) Chest Sonography, SBN 978-3-540-72427-8 Springer Berlin Heidelberg New York: 36-37.
40. Qureshi NR, Rahman NR, Gleeson FV. Thoracic ultrasound in the diagnosis of malignant pleural effusion. Thorax 2009; 64: 139-43.
41. Pinto C, Betta PG, Fava C, Papotti M, Pastorino U, Scagliotti G, et al. Second Italian consensus conference on malignant pleural mesothelioma: state of the art and recommendations. Cancer Treat Rev 2013 Jun; 39(4): 328-39. doi: 10.1016/j.ctrv.2012.11.004. Epub 2012 Dec 12.
42. Armato SG, Labby ZE, Coolen J, Feigen M, Persigehl T, Gill RR. Imaging in pleural mesothelioma: a review of the 11th International Conference of the International Mesothelioma Interest Group. Lung Cancer 2013 Nov; 82(2): 190-6. doi: 10.1016/j.lungcan.2013.08.005. Epub 2013 Aug 15.
43. Hooper C, Lee YC, Maskell N; BTS Pleural Guideline Group. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline. Thorax. 2010 Aug; 65 Suppl 2: ii4-17. doi: 10.1136/thx.2010.136978.
44. Stahel RA, Weder W, Lievens Y, Felip E. Malignant pleural mesothelioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21(Suppl5): v126-v128.
45. Van Zandwijk N, Clarke C, Henderson D, et al. Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. Journal of Thoracic Disease 2013; 5(6): E254-E307. doi:10.3978/j.issn.2072-1439.2013.11.28.
46. Novello S, et al. The Third Italian Consensus Conference for Malignant Pleural Mesothelioma: State of the art and recommendations. Crit Rev Oncol/Hematol 2016

Received: 26 June 2016
Accepted: 2 August 2016
Correspondence:
Dr. Edoardo Piacibello
Corso Trapani 15 - 10139 Turin (Italy)
E-mail: edopiaci@gmail.com , edoardo.piacibello@hotmail.it