Int J Clin Exp Med 2015;8(10):18367-18374
www.ijcem.com /ISSN:1940-5901/IJCEM0014061

Original Article

Massive localized malignant pleural mesothelioma (LMPM): manifestations on computed tomography in 6 cases

Weigen Yao, Hanqing Yang, Guolai Huang, Yang Yan, Honglin Wang, Dongfang Sun

Department of Radiology, The People's Hospital of Yuyao, Yuyao 315400, P. R. China

Received August 6, 2015; Accepted October 13, 2015; Epub October 15, 2015; Published October 30, 2015

Abstract: Objective: Our study analyzed the clinical symptoms and computed tomography (CT) manifestations of massive localized malignant pleural mesothelioma (LMPM) patients to improve the knowledge and diagnosis of this disease. Methods: Our study collected 6 massive LMPM patients pathologically confirmed by CT in the department of Radiology of the People's Hospital of Yuyao, Zhejiang Province, from January, 2007 to June, 2013; data of patients were also collected. The clinical symptoms, clinicopathological characteristics, CT manifestations, treatments and prognosis of enrolled patients were analyzed. Results: Our study enrolled 6 LMPM patients (2 males; 4 females) classified to epitheliated type (n = 4) and sarcomatous type (n = 2) with mean age of 62.7 ± 7.4, and 5 of them had a history of asbestos exposure. CT manifestations revealed that large soft-tissue mass close to pleura, which was smooth and lobulated, was discovered in all patients with maximum diameter of 10~15 cm and mean diameter of 13.67 ± 1.15 cm; The mean value of CT was 36.29 ± 2.62 HU; after enhancement, the mean value was increased to 76.36 ± 7.73 HU; patients showed zones of small patchy necrosis and large patchy necrosis. The following presentations were founded: enlargement of tumor vessel which showed arborization (2 patients), mass wrap around the descending aorta in left lower chest (1 patient), strips of fat density in mediastinum superior (1 patient), pleural tail sign (3 patients). Among 6 patients, pleural effusion (n = 4), mediastinal lymph node enlargement (n = 3), invasion and destruction of local ribs (n = 2). Median survival time of patients were 20 months (2 cases conducted operation), 24 (2 cases chose combined radiotherapy and chemotherapy) and less than 6 months (2 cases underwent chemotherapy). Conclusion: To sum up, CT showed important diagnostic values on massive LMPM patients; patients with a history of asbestos exposure, large soft-tissue mass of pleura with an abundant blood supply and wrap around large vessels might increase the risk of massive LMPM.

Keywords: Localized malignant pleural mesothelioma, mass-type, computed tomography, asbestos exposure, malignant pleural mesothelioma, biomarker levels, diagnosis, prognosis, median survival time

Introduction

Mesothelioma has been traditionally characterized as a massive, diffuse tumor that leads to excruciating chest pain [1]. Malignant pleural mesothelioma (MPM) is a highly aggressive malignancy arising from pleura cavity with a median survival of often less than 12-month as well as 5-year survival rate of less than 5% with best supportive care [2-4]. The incidence of MPM increases over the last decades with deaths of approximately 43,000 annually worldwide, furthermore, continued decreases are not expected before 2020 [5]. MPMs mostly occurred among men between 50 and 70 years with a latency period of 20-50 years [6]. About 69-90% of all cases with malignant MPM are related with environmental and occupational exposure to asbestos [7, 8]. In the early stages, MPM has a wide range of morphological manifestations that makes it hard to discriminate MPM and other malignancies; nowadays, the diagnosis of MPM is likely in patients with a history of exposure to asbestos as well as clinical symptoms of dyspnoea, pleural effusion and chest pain [9]. Localized MPM (LMPM), originating from mesothelial cells, has immunohistochemical, histological and ultrastructural features of diffuse MPM (DMPM) but shows better prognosis [10]. Owing to rare occurrence,

only a few cases about LMPM have been reported in the literature [11]. In this regard, many details about LMPN still remain unexplored, and there is a real need to estimate clinical symptoms of LMPN patients by available diagnostic tools for improving diagnostic accuracy.

Currently computed tomography (CT) is the first and most common option for initial evaluation, staging, and response assessment of MPM; if the subtypes could be predicted using CT, patients could be better selected preoperatively [12]. CT is documented to be superior to radiography in the diagnosis and staging of MPM; evidence revealed that pleural fluid cytology and fine needle pleural biopsy provides 25-33% and 21-77% sensitivity, respectively; while a combination of chest CT and positron emission tomography shows a specificity of 93% and 88% sensitivity with an overall accuracy of 93% [4, 13]. CT also has ability to provide anatomic details of both normal and abnormal structures; moreover, it was applied commonly due to its wide availability as well as comparatively low cost [14]. In this study, we analyzed the clinical symptoms, clinicopathological characteristics, CT manifestations, treatments and prognosis of massive LMPM patients to improve the knowledge as well as diagnostic ability of this disease.

Materials and methods

Ethics statement

The current study was approved by the Ethical Committee of the People's Hospital of Yuyao, Zhejiang Province. All study participants signed a document of informed consent which was. In accordance with the Declaration of Helsinki [15].

Subjects

Our study collected 6 massive LMPM patients pathologically confirmed by CT in the department of Radiology of the People's Hospital of Yuyao, Zhejiang Province, from January, 2007 to June, 2013; and data of patients were also obtained. Among 6 patients aged from 56 to 76 (mean age: 62.7 ± 7.4), 2 of them were males and other 4 were females. Two male and one female (50.0%) had a history of smoking. The median time from attack to diagnosis was 3.26 months (range from 0.6 to 10 months). Five of six had a history of asbestos hand-spinning ranged from 1 to 10 years; one of them have not touched asbestos, but lived in area of asbestos production. All patients had uncomfortable symptoms. Major clinical symptoms of 5 patients were chest pains, cough and expectoration; symptoms of other one were chest stuffiness, shortness of breath and breathing difficulty. Four patients had various amounts of chest fluid; 1 had a fever; 2 lost about 3-6 kg in weight; 2 patients had superficial lymphadenopathy.

Diagnostic criteria

Diagnostic criteria for CT were based on Yilmaz U et al. [16]: the pleural surface was smooth in regular pleura thickening, and thickness was less than 3 cm; the nodular pleura thickening showed various degrees of irregular pleura thickening, and thickness was equal or larger than 3 cm; annular pleura thickening involved the entire side of the lung including mediastinal reflection. Localized pleura thickening only involved a range of lobi pulmonis. Fissura interlobaris pleural related to irregular pleura thickening, nodules, lump or fissura interlobaris hydrops. Mediastinal pleura involved mediastinal pleura thickening. Few amount of pleural effusion was defined as effusion less than 1/3 of one pleural; moderate amount of pleural effusion was effusion ranged from 1/3 to 2/3 of one pleural; large amount of pleural effusion was effusion more than 2/3 of one pleural. Minor axis of intrathoracic lymph nodes larger than 10 mm was determined as abnormal.

Included criteria were as follows: (1) enrolled patients were localized pleural thickening and MPM with large soft tissue mass; (2) patients had one or more symptoms such as chest pains, cough, chest stuffiness and shortness of breath; (3) pleura thickening and pleural effusion were estimated using ultrasonography of thorax or CT; (4) histodiagnosis was accordant to *Guidelines for pathologic diagnosis of malignant mesothelioma* in 2012 [17]; and (5) patients had routine chest CT scan and enhancement scanning. Exclusive criteria: (1) patients had incomplete clinical data; (2) except MPM, patients also had other primary tumors or a history of other primary tumors.

Detection approaches

General electric (GE) Lightspeed 16-row spiral CT-scanner (Milwakee, WI, USA) was applied.

Table 1. Immunohistochemistry (IHC) for estimating expressions of molecular markers

markers	Epitheliated type (n = 4)		Sarcomatous type (n = 2)	
	Expression	Rate (%)	Expression	Rate (%)
CK	+	83.3 (5/6)	+	100 (6/6)
MC	+	83.3 (5/6)	+	100 (6/6)
CR	+	100 (6/6)	+	100 (6/6)
Vim	+	100 (6/6)	+	100 (6/6)
HBME-1	+	100 (6/6)	+	100 (6/6)
CEA	-	100 (6/6)	-	100 (6/6)
TTF-1	-	100 (6/6)	-	100 (6/6)

Note: CK, cytokeratin; MC, mesothelioma cells; CR, calretinin; Vim, vimentin; HBME-1, human bone marrow endothelial cells-1; CEA, carcinoembryonic antigen; TTF-1, thyroid transcription factor-1.

Routine chest computed tomography (CT) scan and enhancement scanning were conducted in all patients; scanning range was from apex of lung to the bottom of diaphragm; slice thickness and slice gap of scanning were 5 mm. The non-ionic contrast medium iohexol (1.5 ml/kg, containing iodine 300 mg/ml) was used in enhancement scanning; a high pressure injector was also applied through antecubital vein for a bolus injection at 3 ml/s; scan delay was 30 s in arterial phase and 70 s in venous phase. Original data after scanning was reestablished with 1.25 mm, and conducted with multiplanar reconstruction (MPR) in work station. The CT value of lesions was determined using the average value of three solid areas of different region of interest (ROI). Enhancement degree of lump was also estimated before and after enhancement.

Observation of tumor and pathology cytology markers

History, clinical manifestation and imaging results of patients were recorded. Tumor markers in peripheral blood serum of 6 patients were detected including cancer antigen 125 (CA125), cancer antigen 199 (CA199), squamous cell carcinoma antigen (SCCA), carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP); at the same time, tumor tissues of patients were also collected; expressions of molecular markers (including cytokeratin (CK), mesothelioma cells (MC), calretinin (CR), vimentin (Vim), human bone marrow endothelial cells-1 (HBME-1), carcinoembryonic antigen (CEA) and thyroid transcription factor-1 (TTF-1) were estimated with immunohistochemistry (IHC). All recorded data was also analyzed.

Follow-up

Follow-up was carried out through clinical recheck, letter or phone call end up to 31, December, 2014 with rate of 100% (6/6). Median follow up was 13.0 (range 0.3-158) months with average follow-up time of 24.4 months. The survival time was from date of diagnosis to death time.

Results

Tumor markers

The tumor markers were detected in 6 patients including CA125, CA153, SCC, CEA and AFP. CA125 (293 u/ml) in 1 patient was higher than normal people; CA153 (177 u/ml) in 1 of 6 was higher as compared with normal controls; and the tumor markers in other 4 patients were in normal range. Blood platelets of 2 patients were increased and 1 was decreased. Examination of hydrothorax was conducted in 5 patients. One of 5 had bloody pleural fluid, and pleural effusion was frequently yellow (citrine or turbid) in other 4 patients. Biochemical indices results showed 3 patients had effusion. Histopathology was conducted in exfoliated cells; the results demonstrated no existence of cancer cells.

Histopathology results

Histopathology types of 6 LMPM patients were epitheliated type (n = 4) and sarcomatous type (n = 2). Two patients were determined by exairesis and biopsy pathologic diagnosis; other 4 patients were estimated by aspiration biopsy through chest wall mass and exairesis at pleural nodule. One patient was wrongly diagnosed as having tuberculosis (TB) in initial diagnosis. The results of molecular markers expressions revealed that CK and MC positive expressions (both 5/6) were lower than CR, Vim, HBME-1, CEA and TTF-1 positive expressions as well as negative expressions (all 6/6) (**Table 1**).

CT results

Large soft-tissue mass strongly associated with pleura founded in all patients, among which 5 were located in chest (4 in left and 1 in right) and 1 placed in anterior superior mediastinum. The maximum diameter of the mass was 10~15 cm with mean diameter of 13.67 ± 1.15 cm. The soft-tissue mass was smooth and lobu-

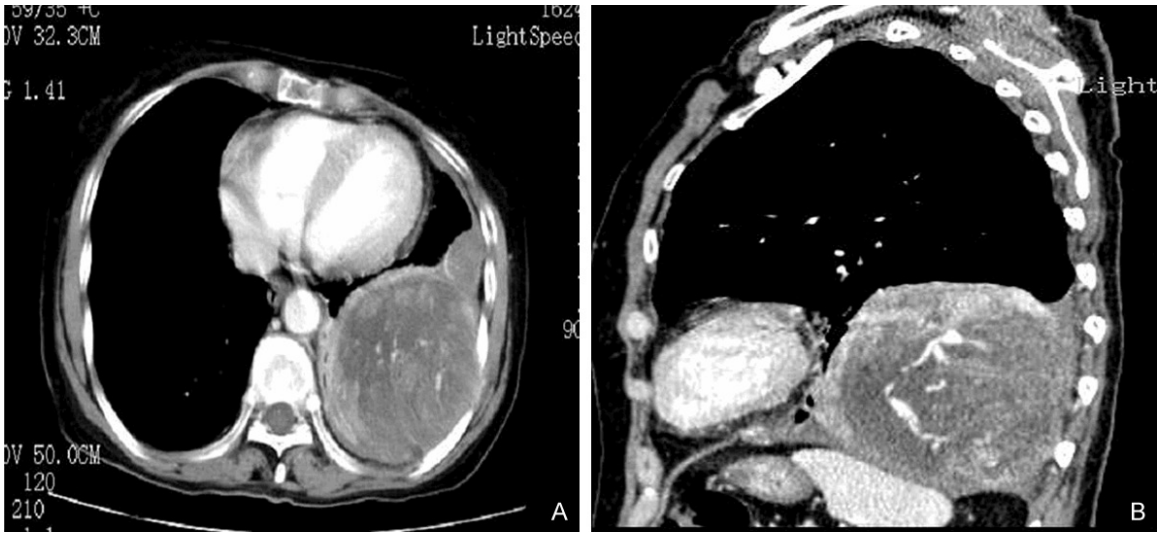

Figure 1. Large mass in Left chest wall; after enhancement, the outcomes showed vast necrotic area and enlargement of tumor vessel which showed arborization. (A: Computed tomography (CT) enhancement; B: Coronal recombination).

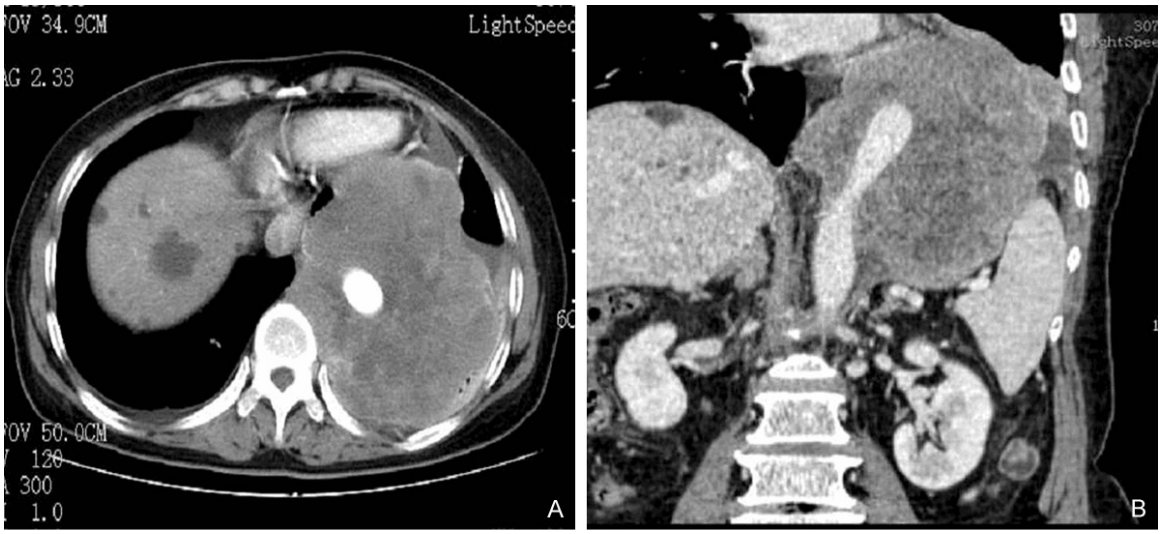

Figure 2. Large soft-tissue mass in left lower chest; after enhancement, patchy necrotic area wrap around aorta descendens and indistinct development were discovered. (A: Computed tomography (CT) enhancement; B: Coronal recombination).

lated. The mean value of CT was 36.29 ± 2.62 HU; after enhancement, the mean value was increased to 76.36 ± 7.73 HU. Four patients showed small patchy necrotic area, and 2 patients demonstrated large patchy necrotic area. One patient revealed several daughter foci adjacent to a large mass; the diameter of the maximum was about 3 cm. Two of 6 demonstrated large and enhanced soft-tissue mass, as well as enlargement of tumor vessel which showed arborization (**Figure 1A** and **1B**). One patient was founded with different density inside the lesion in left lower chest, and without obviously enhanced vascular while encircling the descending aorta (**Figure 2A** and **2B**). Strips of fat density were founded in mediastinum superior, after enhancement, the imaging revealed inferior border of mass was grown around the great vessels (as **Figure 3A** and **3B**). Six pleura adjacent to lesions were thickened

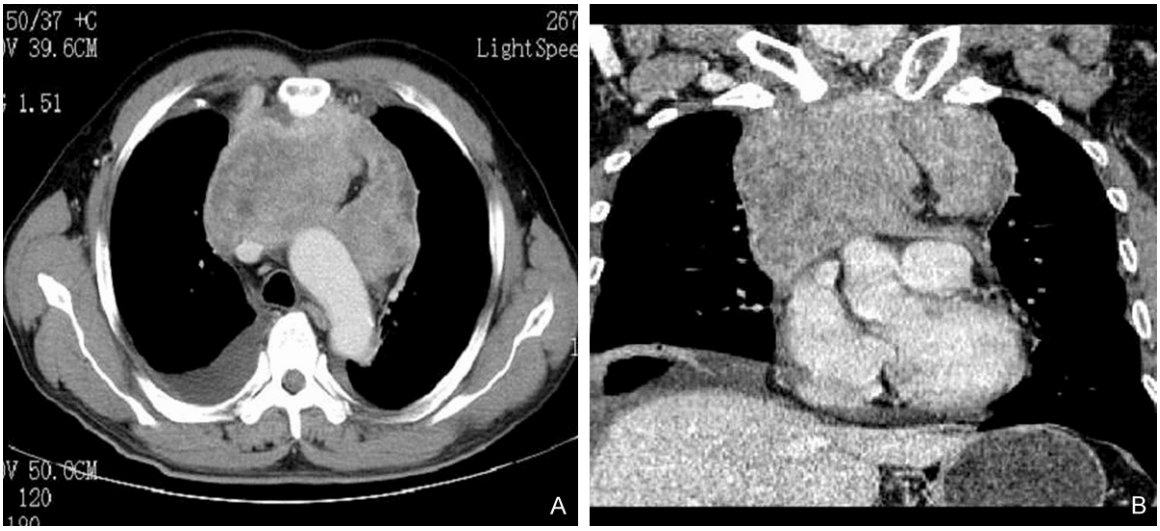

Figure 3. Large soft-tissue mass in anterior superior mediastinum; after enhancement, irregularly shape and strips of fat density were founded. (A: Computed tomography (CT) enhancement; B: Coronal recombination).

apparently; local nodositas was founded. Pleural effusion was discovered in 4 patients (medium pleural effusion: 1; slight pleural effusion: 3), among which 2 have founded in one side, and other 2 were founded in both pleural (**Figures 1A**, **1B**, **2A** and **2B**). Lymph node enlargement in mediastinum of 3 patients was occurred (**Figure 3A** and **3B**) with maximal diameter of 2 cm. Local ribs of 2 patients were invaded and destroyed (as shown in **Figures 1A**, **1B**, **2A** and **2B**).

Follow-up

Among 6 MPM, 2 patients had 1 year follow-up before operation, and showed reduplicated pleural effusion diagnosed as bloody pleural fluid. The pre-operative enlargement for tumor was 3 months. Two patients were conducted with operation; among them 1 patient treated with radical surgery, and another 1 received palliative operation. However, the existence of palindromia and metastasis was founded 1 year after operation, and appeared as local chest wall mass, mediastinal lymph nodes and pleural metastasis, and rib destruction, with median survival time of 20 months. Two patients received thoracic radiotherapy plus chemotherapy. Three months after treatment, diameter of the mass was decreased about 1/3 with median survival time of 24 months. Two patients who received only chemotherapy (pemetrexed + cis-platinum complexes) revealed poor effects. Diameter of the mass was increased about 1/4 after 3 months; and both of 2 patients were died in 6 months.

Discussion

Owing to the low incidence of massive LMPN, many details about this disease still remain unexplored. In this regard, we explored the clinical symptoms, clinicopathological characteristics, CT manifestations, treatments and prognosis of this disease. In 1931, Klemperer and Rabin classified mesothelioma as diffused tumor and localized tumor which was a solitary circumscribed nodular tumor derived from submesothelial layer [18]. In study of Tamer Dogan O et al., the most common CT findings consists pleural thickening which could be classified as diffuse (maximum), nodular and mass-type (minimum) [19]. Previous research have documented that the initial clinical symptoms includes be dyspnea, commonly related with developing pleural effusion, pleural pain; furthermore, notable hemithorax retraction is often founded and pain becomes especially intense and persistent in the advanced stages [20, 21]. The results in the current study showed that massive LMPN patients revealed symptoms including pleural thickening, pleural effussion, peripheral tissue and organ involvement or rib damage suggesting that these presentations might be the diagnostic basis of massive LMPN.

Although the chest X-ray (CXR) remains the first approach in diagnosis of MPM, and provides

information on the presentation of diffuse pleural thickening, effusion and masses, CT is also essential for the proper estimation and determining diagnostic procedures [19, 22]. However, CT showed poor sensitivity in estimating mediastinal lymph nodes, contralateral mediastinal shift as well as peritoneal involvement [23-25]. Magnetic resonance imaging (MRI) showed greater contrast as compared to CT for determining chest wall invasion, while it could not detect metastatic disease [26]. Combined positron-emission tomography and CT (PET-CT) is especially effective for pre-surgery MPM staging, estimating treatment response as well as detecting possible relapse; while it revealed poor sensitivity and specificity for determining N2 disease in MPM [27-29]. In the present study, CT provides favorable diagnosis effect on massive LMPM, revealing that CT might be a reliable diagnostic method for massive LMPM patients. However, the further study considering above diagnostic approaches such as CXR, MRI and PET-CT should be conducted.

About 80% of MPM was closely related with workplace exposure to asbestos, particularly white asbestos (cristolite) and blue asbestos (crocidolite) [30]. The latency period between asbestos exposure and presentation of the MPM is long-generally approximately 40 years, but outlying values vary greatly, indicating that the incidence of this disease might still rise [31]. The incidence of MPM in Europe might be expected to peak in 2020 on the basis of asbestos exposure figures [5]. Hence, a history of asbestos exposure might increase the risk of LMPM. In this research, the results demonstrated that a history of asbestos exposure, large soft-tissue mass of pleura with an abundant blood supply and wrap around large vessels of patients might have the potential of massive LMPM.

Well-conducted in vitro studies demonstrated that although good performance status, epithelioid histology, earlier stage and younger age predict survival and are applied currently to select patients treated with radical multimodality, the clinical outcomes are variable and could range between few months and more than 2 years [32, 33]. We chose three treatments including opration, combined chemotherapy and radiotherapy, and chemotherapy. Our results indicated that patients received combined chemotherapy and radiotherapy treatment showed the best prognosis, and patients only treated with chemotherapy had a worse survival. These outcomes revealed that combined chemotherapy and radiotherapy might be the most effective treatment for massive LMPM patients.

Some limitations in our research should be paid attention. We examined the expressions of molecular markers by using IHC, and differences were founded between epitheliated type and sarcomatous type LMPM. However, owing to the small number of cases, these results should be determined in further research. Furthermore, the study comparing diagnostic approaches such as CXR, MRI and PET-CT should also be conducted. In short, CT showed important diagnostic values on massive LMPM patients; patients with a history of asbestos exposure, large soft-tissue mass of pleura with an abundant blood supply and wrap around large vessels might have the potential risk of this disease.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Weigen Yao, Department of Radiology, The People's Hospital of Yuyao, No. 800 Chengdong Road, Yuyao 315400, P. R. China. Tel: +86-0574-62619191; E-mail: yaoweigen_ywg@126.com

References

[1] Kent M, Rice D, Flores R. Diagnosis, staging, and surgical treatment of malignant pleural mesothelioma. Curr Treat Options Oncol 2008; 9: 158-170.

[2] Davidson B. Prognostic factors in malignant pleural mesothelioma. Hum Pathol 2015; 46: 789-804.

[3] Lang-Lazdunski L. Surgery for malignant pleural mesothelioma: why, when and what? Lung Cancer 2014; 84: 103-109.

[4] van Meerbeeck JP, Scherpereel A, Surmont VF, Baas P. Malignant pleural mesothelioma: the standard of care and challenges for future management. Crit Rev Oncol Hematol 2011; 78: 92-111.

[5] Buikhuisen WA, Hiddinga BI, Baas P, van Meerbeeck JP. Second line therapy in malignant pleural mesothelioma: A systematic review. Lung Cancer 2015; 89: 223-31.

[6] Carbone M, Ly BH, Dodson RF, Pagano I, Morris PT, Dogan UA, Gazdar AF, Pass HI, Yang H.

Malignant mesothelioma: facts, myths, and hypotheses. J Cell Physiol 2012; 227: 44-58.
[7] Goldberg S, Rey G, Luce D, Gilg Soit Ilg A, Rolland P, Brochard P, Imbernon E, Goldberg M. Possible effect of environmental exposure to asbestos on geographical variation in mesothelioma rates. Occup Environ Med 2010; 67: 417-421.
[8] Aguilar-Madrid G, Robles-Perez E, Juarez-Perez CA, Alvarado-Cabrero I, Rico-Mendez FG, Javier KG. Case-control study of pleural mesothelioma in workers with social security in Mexico. Am J Ind Med 2010; 53: 241-251.
[9] Stigt JA, Boers JE, Groen HJ. Analysis of ''dry'' mesothelioma with ultrasound guided biopsies. Lung Cancer 2012; 78: 229-233.
[10] Maeda R, Isowa N, Onuma H, Miura H, Tokuyasu H, Kawasaki Y. Minute localized malignant pleural mesothelioma coexisting with multiple adenocarcinomas. Gen Thorac Cardiovasc Surg 2010; 58: 91-94.
[11] Liu H, Cheng YJ, Chen HP, Hwang JC, Chang PC. Multiple bowel intussusceptions from metastatic localized malignant pleural mesothelioma: a case report. World J Gastroenterol 2010; 16: 3984-3986.
[12] Seely JM, Nguyen ET, Churg AM, Muller NL. Malignant pleural mesothelioma: computed tomography and correlation with histology. Eur J Radiol 2009; 70: 485-491.
[13] Zhou H, Tamura T, Kusaka Y, Suganuma N, Subhannachart P, Vijitsanguan C, Noisiri W, Hering KG, Akira M, Itoh H, Arakawa H, Ishikawa Y, Kumagai S, Kurumatani N. Development of a guideline on reading CT images of malignant pleural mesothelioma and selection of the reference CT films. Eur J Radiol 2012; 81: 4203-4210.
[14] Armato SG 3rd, Entwisle J, Truong MT, Nowak AK, Ceresoli GL, Zhao B, Misri R, Kindler HL. Current state and future directions of pleural mesothelioma imaging. Lung Cancer 2008; 59: 411-420.
[15] Goggs R, Savage JS, Mellor H, Poole AW. The small GTPase Rif is dispensable for platelet filopodia generation in mice. PLoS One 2013; 8: e54663.
[16] Yilmaz U, Polat G, Sahin N, Soy O, Gulay U. CT in differential diagnosis of benign and malignant pleural disease. Monaldi Arch Chest Dis 2005; 63: 17-22.
[17] Husain AN, Colby T, Ordonez N, Krausz T, Attanoos R, Beasley MB, Borczuk AC, Butnor K, Cagle PT, Chirieac LR, Churg A, Dacic S, Fraire A, Galateau-Salle F, Gibbs A, Gown A, Hammar S, Litzky L, Marchevsky AM, Nicholson AG, Roggli V, Travis WD, Wick M; International Mesothelioma Interest Group. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 2013; 137: 647-667.
[18] Nakas A, Martin-Ucar AE, Edwards JG, Waller DA. Localised malignant pleural mesothelioma: a separate clinical entity requiring aggressive local surgery. Eur J Cardiothorac Surg 2008; 33: 303-306.
[19] Tamer Dogan O, Salk I, Tas F, Epozturk K, Gumus C, Akkurt I, Levent Ozsahin S. Thoracic computed tomography findings in malignant mesothelioma. Iran J Radiol 2012; 9: 209-211.
[20] Stahel RA, Weder W, Lievens Y, Felip E; ESMO Guidelines Working Group. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 Suppl 5: v126-128.
[21] Teh E, Fiorentino F, Tan C, Treasure T. A systematic review of lung-sparing extirpative surgery for pleural mesothelioma. J R Soc Med 2011; 104: 69-80.
[22] Cardinale L, Ardissone F, Asteggiano F, Laugelli EM, Penna D, Fava C. Diffuse neoplasms of the pleural serosa. Radiol Med 2013; 118: 366-378.
[23] Tan C, Barrington S, Rankin S, Landau D, Pilling J, Spicer J, Cane P, Lang-Lazdunski L. Role of integrated 18-fluorodeoxyglucose position emission tomography-computed tomography in patients surveillance after multimodality therapy of malignant pleural mesothelioma. J Thorac Oncol 2010; 5: 385-388.
[24] Salahudeen HM, Hoey ET, Robertson RJ, Darby MJ. CT appearances of pleural tumours. Clin Radiol 2009; 64: 918-930.
[25] Saraya T, Yokoyama T, Ishii H, Tanaka Y, Tsujimoto N, Ogawa Y, Sohara E, Nakajima A, Inui T, Sayuki H, Fujiwara M, Oka T, Kawachi R, Goya T, Takizawa H, Goto H. A case of malignant peritoneal mesothelioma revealed with limitation of PET-CT in the diagnosis of thoracic metastasis. J Thorac Dis 2013; 5: E11-16.
[26] Plathow C, Staab A, Schmaehl A, Aschoff P, Zuna I, Pfannenberg C, Peter SH, Eschmann S, Klopp M. Computed tomography, positron emission tomography, positron emission tomography/computed tomography, and magnetic resonance imaging for staging of limited pleural mesothelioma: initial results. Invest Radiol 2008; 43: 737-744.
[27] Basu S, Saboury B, Torigian DA, Alavi A. 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. Mol Imaging Biol 2011; 13: 801-811.
[28] Zahid I, Sharif S, Routledge T, Scarci M. What is the best way to diagnose and stage malig-

nant pleural mesothelioma? Interact Cardiovasc Thorac Surg 2011; 12: 254-259.
[29] Shinohara T, Shiota N, Kume M, Hamada N, Naruse K, Ogushi F. Asymptomatic primary tuberculous pleurisy with intense 18-fluorodeoxyglucose uptake mimicking malignant mesothelioma. BMC Infect Dis 2013; 13: 12.
[30] Shukla A, Barrett TF, MacPherson MB, Hillegass JM, Fukagawa NK, Swain WA, O'Byrne KJ, Testa JR, Pass HI, Faux SP, Mossman BT. An extracellular signal-regulated kinase 2 survival pathway mediates resistance of human mesothelioma cells to asbestos-induced injury. Am J Respir Cell Mol Biol 2011; 45: 906-914.
[31] Bianchi C, Bianchi T, Bucconi S. Malignant mesothelioma of the pleura in nonagenarian patients. Tumori 2011; 97: 156-159.
[32] Cao C, Tian D, Manganas C, Matthews P, Yan TD. Systematic review of trimodality therapy for patients with malignant pleural mesothelioma. Ann Cardiothorac Surg 2012; 1: 428-437.
[33] Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwisle J, Snee M, O'Brien M, Thomas G, Senan S, O'Byrne K, Kilburn LS, Spicer J, Landau D, Edwards J, Coombes G, Darlison L, Peto J, trialists M. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol 2011; 12: 763-772.