Review Article

Management of Malignant Pleural Effusions

Md. Lutfar Rahman[1], Mohammad Arifur Rahman[2], Nizam Uddin Ahmed[3].

Abstract

Malignant pleural effusions (MPE) are a common clinical problem in patients with neoplastic disease. In adults, 95% of neoplastic pleural effusions arise from a metastatic source, with lung and breast carcinoma accounting for 75% of all cases. Median survival following diagnosis ranges from 3 to 12 months and is dependent on the stage and type of the underlying malignancy. Most pleural metastases arise from tumor emboli to the visceral pleural surface, with secondary seeding to the parietal pleura. Other possible mechanisms include direct tumor invasion, hematogenous spread to parietal pleura, and lymphatic involvement. Dyspnoea is the most common presenting symptom and is occasionally accompanied by chest pain and cough. Chest radiographs confirm the size and location of the pleural collection. Thoracocentesis is usually diagnostic and also therapeutic. Exudative and hemorrhagic collections should be considered metastatic until proved otherwise. Various modalities are available in the management of MPE. Careful consideration of the patient's expected survival and quality of life is needed when deciding the optimum treatment modality in such patients.

Introduction

Pleural effusions   containing malignant cells are called malignant Pleural effusion. Malignant pleural effusions are a common clinical problem in patients with neoplastic disease.[1] In adults, 95% of neoplastic pleural effusions arise from a metastatic source, with lung and breast carcinoma accounting for 75% of all cases.[2] Lymphomas, tumours of the genitourinary tract and gastro-intestinal tract as a group account for a further 25%. Pleural effusions from an unknown primary are responsible for 7-15% of all malignant pleural effusions.[3] Most pediatric effusions, on the other hand, are benign. If malignant, lymphomas or leukemias account for half with the remainder a mix of tumors such as neuroblastoma, Wilms tumor, and germ cell neoplasms.[4] Adenocarcinomas whose primary is unknown constitute a distinct entity in patients in whom the source of the pleural malignancy is never found. They are associated with exposure to environmental tobacco smoke.[5] Median survival following diagnosis ranges from 3 to 12 months and is dependent on the stage and type of the underlying malignancy. The shortest survival time is observed in malignant effusions secondary to lung cancer and the longest in ovarian cancer, while malignant effusions due to an unknown primary have an intermediate survival time.[6]

Pathophysiology

Most pleural metastases arise from tumor emboli to the visceral pleural surface, with secondary seeding to the parietal pleura. Other possible mechanisms include direct tumor invasion (in lung cancers, chest wall neoplasm's, and breast carcinoma), hematogenous spread to parietal pleura, and lymphatic involvement. A malignant tumor can cause a pleural

---

1. Professor & HOD of Cardiac surgery, Khwaja Yunus Ali Medical College & Hospital, Enayetpur, Sirajganj, Bangladesh.
2. Assistant Professor, Departmaent of Cardiac surgery, Khwaja Yunus Ali Medical College & Hospital, Enayetpur, Sirajganj, Bangladesh.
3. Consultant, Cardiac surgery, Khwaja Yunus Ali Medical College & Hospital, Enayetpur, Sirajganj, Bangladesh.

Correspondence: Dr. Mohammad Arifur Rahman, Assistant Professor, Departmaent of Cardiac surgery, Khwaja Yunus Ali Medical College & Hospital, Enayetpur, Sirajganj, Bangladesh. Mobile no: 01715028334. e-mail:arifur0207@gmail.com.

effusion both directly and indirectly. Interference with the integrity of the lymphatic system anywhere between the parietal pleura and mediastinal lymph nodes can result in pleural fluid formation . Direct tumor involvement with the pleura may also contribute to the formation of pleural effusions. Local inflammatory changes in response to tumor invasion may cause increased capillary permeability, with resultant effusions.[7,8] Haemorrhagic malignant effusions usually result from invasion of blood vessels directly and/or tumour induced angiogenesis. Vascular endothelial growth factor (VEGF), a cytokine possessing potent angiogenic activity and promoting endothelial permeability, may play a significant role in the formation of malignant effusions and local tumour growth.[9] The term "paramalignant effusions" is reserved for those effusions that are not the direct result of neoplastic involvement of the pleura but are still related to the primary tumor. Important examples include post obstructive pneumonia, with a subsequent parapneumonic effusion; obstruction of the thoracic duct, with the development of a chylothorax; pulmonary embolism; and transudative effusions secondary to post obstruction atelectasis and /or low plasma oncotic pressures secondary to cachexia. Treatment of the primary tumor can also result in pleural effusions. Important causes in this category include radiation therapy and such drugs as methotrexate, procarbazine, cyclophosphamide, and bleomycin. Finally, concurrent nonmalignant disease, such as congestive heart failure, may account for an effusion seen in a patient with cancer.[10]

Clinical Presentation

Patients with malignant pleural effusions are typically symptomatic and complain of dyspnea, cough, or chest pain. Dyspnoea is the most common presenting symptom and is occasionally accompanied by chest pain and cough. Dyspnoea is due to a combination of reduced compliance of the chest wall, depression of the ipsilateral diaphragm, mediastinal shift, and reduction in lung volume stimulating neurogenic reflexes. Chest pain, commonly seen in mesothelioma, is typically localized to the side of the effusion and is described as dull and aching rather than pleuritic, is usually related to involvement of the parietal pleura, ribs, and other intercostal structures. A history of hemoptysis in the presence of a pleural effusion is highly suggestive of bronchogenic carcinoma. A prior history of malignancy is obviously important, as are any relevant occupational exposures, especially to asbestos or other carcinogens. Constitutional symptoms including weight loss, malaise, and anorexia also generally accompany respiratory symptoms. Physical findings indicating pleural effusion are decreased tactile fremitus and dullness to percussion on examination of the posterior chest, accompanied by decreased breath sounds. As the effusion increases in size, there may be hyper resonance on percussion immediately above the fluid level because of compression and overdistention of the lung. Bronchial breath sounds may be prominent. As effusions become massive, tracheal devia tions from mediastinal shifts

are detectable. Malignant pleural effusions rarely cause hemodynamic compromise from tension hydrothorax.[11]

Imaging Techniques

Most patients presenting with malignant pleural effusions have some degree of dyspnea on exertion and their chest radiographs show moderate to large pleural effusions ranging from approximately 500 to 2,000 ml in volume.[12] While only 10% of patients have massive pleural effusions on presentation, malignancy is the most common cause of massive pleural effusion.[13] Massive pleural effusions are defined as those effusions occupying the entire hemithorax. About 15% of patients, however, will have pleural effusions 500 ml in volume and will be relatively asymptomatic. An absence of contralateral mediastinal shift in these large effusions implies fixation of the mediastinum, mainstem bronchus occlusion by tumor (usually squamous cell lung cancer), or extensive pleural involvement (as seen with malignant mesothelioma).
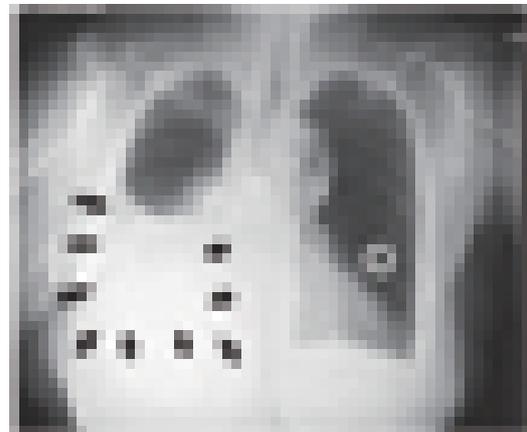

Figure 2: Chest roentgenogram showing large right pleural effusion (outlined by arrows).
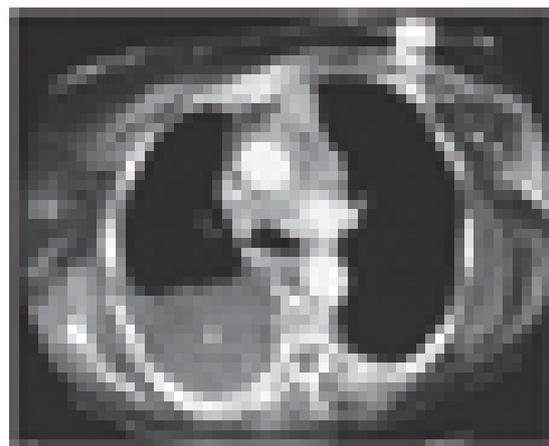

Figure 3: CT images of a malignant pleural effusion

Computerized tomography (CT) scans may identify underlying parenchymal disease, mediastinal lymph node involvement and previously unrecognized small effusions, as well as in demonstrating pleural, pulmonary, or distant metastases[14]; identification of pleural plaques suggests asbestos exposure. Ultrasonography may aid in identifying pleural lesions ,helpful in directing thoracentesis in patients with small effusions and avoiding thoracentesis complications.[15] The role of magnetic resonance imaging (MRI) in malignant effusions is limited, but may be helpful in evaluating the extent of chest wall involvement by tumor. Fluorodeoxyglucose positron emission tomography (PET scanning) is helpful in evaluating the extent of disease in malignant mesothelioma.[16]

Diagnostic Thoracentesis

Thoracentesis confirm the diagnosis of pleural effusion. It is usually preferable to attempt drainage of as much pleural fluid as possible. Physical examination can guide a pleural tap. Ultrasound or other imaging can optimize needle or chest tube placement for effusion drainage in more complex situations . This is particularly useful for a small effusion or pleural disease of long duration complicated by lung consolidation or pleural loculation. Although marking of the area of "deepest" fluid is useful, it is important to perform the thoracentesis with the patient in the same position as during the imaging. There are no absolute contraindications. Relative contraindications include a minimal effusion (1 cm in thickness form the fluid level to the chest wall on a lateral decubitus view), bleeding diathesis, anticoagulation, and mechanical ventilation. There is no increased bleeding in patients with mild to moderate coagulopathy or thrombocytopenia (a prothrombin time or partial thromboplastin time up to twice the midpoint normal range and a platelet count of 50,000 /ml) However, patients with serum creatinine levels of 6.0 mg/ dl are at a considerable risk of bleeding. Important complications of thoracentesis include pneumothorax, bleeding, infection, and spleen or liver laceration.[17]
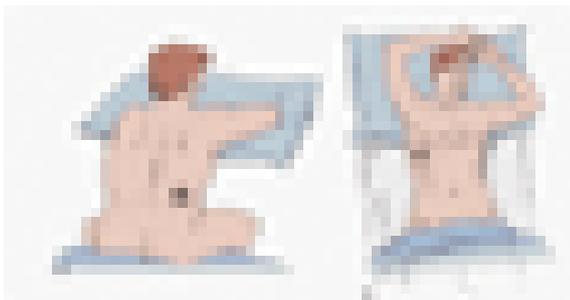

Figure 4: A, Common patient position for insertion of a thoracentesis needle or catheter. Posterior approach allows access to the most dependent (posterior pleural) sulcus to allow maximal drainage of nonloculated fluid. B, Lateral patient positioning for thoracentesis or chest tube placement is also useful for effusions with large lateral collections of fluid. The patient's arm is abducted and flexed over his head to facilitate access to the lateral chest.

Standard Chemistry and Cell Counts

Practically all malignant pleural effusions are exudates. Criteria used to classify effusions as exudative was described by Light: pleural fluid/serum total protein ratio greater than 0.5, pleural fluid/serum lactate dehydrogenase (LDH) ratio greater than 0.6, and pleural fluid LDH greater than 200 U/liter (greater than two thirds of the laboratories' upper limit of normal for serum).[18] Low glucose (<60 mg/dL) and low pH (<7.20) levels are common in malignant pleural effusions.[19] This is attributed to glucose usage and acid production by the malignant cells, leukocytes within the pleural fluid, and also increased pleural membrane metabolism. Pleural fluid amylase is elevated in approximately 10% patients with malignant pleural effusions, even without pancreas gland disease. In fact, an amylase-rich pleural effusion is the most common cause of neoplasm.[20,21] The cell count can also indicate malignancy.Bloody fluid is the strongest positive predictor of malignant effusion. Fluid viscosity has also been studied as a diagnostic test.[22]

Immunocytochemistry and Special Chemistry

Staining patterns of cells obtained from pleural fluid may be helpful to confirm malignancy and can correctly classify its origin. Unfortunately, markers are not yet sufficiently sensitive and specific, but they generally show twice the positivity of cytology alone 80% versus 40%. These tests usually are used after standard cytologic screening and in combination with cytogenetic and other miscellaneous tests to establish a diagnosis. Some of these markers, such as p53, predict a worse prognosis for malignant effusions that are p53-negative.[23]

Cytogenetics

DNA testing by chromosome analysis or flow cytometry predicts the likelihood of malignancy. The evidence of a marker chromosome, aneuploidy, or a hyperdiploid state suggests malignancy. Aneuploid samples (by flow cytometry) yield predictive values as high as 96%. No aneuploidy was found in benign reactive effusions in one series. Telomerase activity occurs in 92% of malignant effusions and in only 6% of benign effusions (with a specificity of 94.2%).[24]

Pleural Cytology and Biopsy

Cytologic evaluations with standard staining (Papanicolaou smears) may confirm malignant pleural effusions. The results are falsely positive in very unusual cases 0.5%. Lung adenocarcinoma is the most frequent diagnosis. Breast cancer effusion specimens have a higher cytology diagnostic yield approximately 78% than lung or other

tissue primaries. The sensitivity is greater than undirected pleural biopsy. Pleural needle biopsy occasionally provides some additional useful diagnostic information (48% in one series) when standard pleural effusion cytology is non diagnostic. However, whether pleural biopsy adds much over fluid cytologic evaluation in cases of suspected malignancy is controversial. In another series, only 7% of the cases had a diagnosis made by use of pleural biopsy when the cytology result was negative. This can be enhanced by the use of ultrasound to perform a directed biopsy. Contraindications are bleeding diathesis, anticoagulation, chest wall infection, and lack of patient co-operation. Important complications include pneumothorax, hemothorax, and vasovagal reactions.[25]

Medical Thoracoscopy

It is primarily a diagnostic procedure. Indicators are the evaluation of exudative effusions of unknown cause, treatment of malignant or other recurrent effusions with talc pleurodesis, staging of malignant mesothelioma or lung cancer, and biopsy of the lung, mediastinum, diaphragm or pericardium . Thoracic surgery backup should be available. It can be performed under local anesthesia or conscious sedation, in an endoscopy suite, using non disposable rigid instruments. Thus, it is considerably less invasive and less expensive than VATS. It can be performed either under direct visual control through the optical shaft of the thoracoscope or indirectly by video transmission.[26,27]

Bronchoscopy

The diagnostic value of bronchoscopy is low in patients with undiagnosed pleural effusions. It should not be undertaken routinely. However, it is indicated when endobronchial lesions are suspected because of hemoptysis, atelectasis, or large effusions without contralateral mediastinal shift, to exclude endobronchial obstruction before attempting pleurodesis when there is absence of lung expansion after therapeutic thoracentesis.[28]

Surgical Biopsy

Video-assisted thoracic surgery (VATS) procedures usually require general anesthesia and single lung ventilation. The surgeon may undertake a more extensive procedure than medical thoracoscopy, using several ports, and often combining diagnosis with treatment. VATS is contraindicated and open biopsy is preferred when the patient cannot tolerate single lung ventilation (e.g., patient undergoing mechanical ventilation, prior contralateral pneumonectomy, or abnormal airway anatomy precluding placement of double-lumen endotracheal tube), if the pleural space contains adhesions that would prevent the safe insertion of the examining thoracoscope, and if there is insufficient expertise to deal with the complications of the procedure.[29]

Management Options

Several factors determine treatment options: symptoms and performance status of the patient, the primary tumour and its response to systemic therapy, and lung re-expansion following pleural fluid evacuation. Treatment of the primary tumour, tumours sensitive to systemic chemotherapy eg. Breast cancer, small cell lung cancers, lymphoma or ovarian carcinomas may be effective in eliminating the effusion and avoiding further intervention.

Observation

If the patient is asymptomatic or there is no recurrence of symptoms after initial thoracentesis. Advice should be sought from the thoracic malignancy multi disciplinary team for symptomatic or recurrent malignant effusions.

Therapeutic pleural aspiration

For patients with limited survival expectancy and poor performance status, repeated therapeutic pleural aspiration provides transient relief of symptoms and avoids hospitalisation .It can be done in patients who have had a previous failed intercostal tube and pleurodesis. The amount of fluid evacuated will be guided by patient symptoms (cough, chest discomfort) and should be limited to 1-1.5 l. Pleural aspiration alone and intercostal tube drainage without instillation of a sclerosant are associated with a high recurrence rate, at 1 month is close to 100% and a small risk of iatrogenic pneumothorax and empyema.[30,31]

Intercostal tube drainage and intrapleural instillation of sclerosant

Pleurodesis requires a diffuse inflammatory reaction and local activation of the coagulation system with fibrin deposition. Antony and colleagues have demonstrated increased growth factor-like activity in mesothelial cells exposed to tetracycline leading to fibroblast proliferation. This activity gradually decays once the tetracycline is removed.

Table1: Chemical pleurodesis[32]

1. Insert small bore intercostals tube(10-14).
2.Controlled evacuation of pleural fluid.
3.Confirm full lung re-expansion and position of intercostal tube with chest radiograph.
4.Administer premedication prior to pleurodesis.
5.Instill Lignocaine solution(3 mg/kg;maximum 250mg) into pleural space followed by sclerosant of choice.
6.Clamp tube for 1hour and consider patient rotation for sclerosant.
7.Remove intercostals tube within 12-72hours if lung remains fully re-expanded and there is satisfactory evacuation of pleural

Size of intercostal tube

Conventional large bore intercostal tubes (24-32 F) have been employed in most studies involving sclerosing agents, because they are thought to be less prone to obstruction by clots, but there is little published evidence to confirm this. It is associated with significant discomfort. Studies using small

bore (10-14 F) intercostal tubes with commonly used sclerosants have reported similar success rates to large bore tubes. The small bore tubes in these studies were inserted either at the patient's bedside by a physician or under radiological guidance. Small bore tubes have been used for ambulatory or outpatient pleurodesis.[33]

Lung re-expansion, fluid drainage, and suction

For successful pleurodesis, the most important requirement is satisfactory apposition of the parietal and visceral pleura, confirmed radiolog ically. Most studies indicate that the lack of a response following instillation of a sclerosant is predominantly due to incomplete lung expansion ,may be due to pleural loculations, a thick visceral peel ("trapped lung"),proximal large airway obstruction, or a persistent air leak. Where complete lung re-expansion or pleural apposition is not achieved and the patient is unsuitable for surgical intervention, pleurodesis should still be attempted. After pleurodesis chest X-ray commonly shows multiloculated fluid collections suggestive of empyema due to rapid pleural adhesion formation with intervening accumulations of inflammatory fluid, generally resolves by 1 to 3 weeks. Some physicians wait for effusion drainage rates to decrease before instilling pleurodesis agents to avoid this phenomenon. For successful pleurodesis, the amount of pleural fluid (<150 ml/day) drained per day is less relevant than radiographic confirmation of fluid evacuation and lung re-expansion. In a randomised study, a shorter period of intercostal tube drainage and hospital stay was seen in the group in whom sclerotherapy was under taken as soon as complete lung re-expansion was documented (majority <24 hours) than in the group in whom pleurodesis was attempted only when the fluid drainage was < 150 ml/ day. The success rate in both groups approached 80%. Large pleural effusions should be drained in a controlled fashion avoiding evacuation of more than 1-1.5 l at one time or slowed to about 500 ml/hour. Aspiration shouid be discontinued if the patient develops chest discomfort, persistent cough, or vasovagal symptoms. Following rapid expansion of a collapsed lung through evacuation of large amounts of pleural fluid at a single time and the use of early and excessive pleural suction, re-expansion pulmonary oedema (RPO) is a well described but rare complication. Putative pathophysiological mechanisms include reperfusion injury of the underlying hypoxic lung, increased capillary permeability, and local production of neutrophil chemotactic factors such as interleukin (IL)-8. For incomplete lung expansion and a persistent air leak suction may be required.Use of high volume, low pressure suction systems is recommended with a gradual increment in pressure to about -20 cm H_2O.[34,35]

Analgesia and premedication

Lignocaine (3 m g/kg; maximum 250 mg) should be administered intrapleurally just prior to sclerosant administration. To alleviate anxiety and pain associated with pleurodesis premedication should be considered.[36]

Selecting a sclerosing agent

Most effective sclerosant available for pleurodesis is talc . Following talc administration a small number of patients (<1%) may develop acute respiratory failure. Tetracycline is modestly effective, preferred sclerosant to minimise adverse event rates and has few severe side effects. Bleomycin is an alternative sclerosant with a modest efficacy rate but is expensive. Most common side effects are pleuritic chest pain and fever.[37]

Sclerosing agent	Recommended Dose		Average Success rate	Common Side effect	Serious complications
Tetracycline	1-1.5g	65%	Chest pain, Fever,cough		None
Sterile talc(Slurry/ Poudrage)	2-5g	90%	Chest pain, Fever		Respiratory failure/ARDS
Bleomycin	60units	61%	Chest pain, Fever,nausea		None
Doxycycline	500mg	76%	Chest pain, Fever		None

Rotation following pleurodesis

After intrapleural instillation of tetracycline class agents patient rotation to achieve adequate distribution of the agent over the pleura is not necessary.[37]

Clamping of intercostal tube

After sclerosant administration the intercostal tube should be clamped for 1 hour. The intercostal tube should be removed within 12-72 hours of sclerosant administration in the absence of excessive fluid drainage (>250 ml/day).[37]

Malignant seeding at intercostal tube or port site

site Following diagnostic and therapeutic pleural aspiration, pleural biopsy, intercostal tube insertion, and thoracoscopy, local tumour recurrence or seeding is uncommon in nonmesothelioma malignant effusions. 40% of patients may develop malignant seeding at the site of diagnostic pleural procedures in mesothelioma. Patients with proven or suspected mesothelioma should receive prophylactic radiotherapy to the site of biopsy or chest drain insertion.[38]

Intrapleural fibrinolytics

For the relief of distressing dyspnoea due to multiloculated malignant effusion resistant to simple drainage intrapleural instillation of fibrinolytic drugs is recommended. A more recent study found that intrapleural streptokinase increased pleural fluid drainage and led to radiographic improvement and amelioration of symptoms in 10 patients with multiloculated or septated malignant effusions. This was well tolerated and no allergic or haemorrhagic complications were reported.[39]

Thoracoscopy in malignant pleural effusion

For the diagnosis of suspected but unproven malignant pleural effusion and for the control of recurrent malignant pleural

procedure with low complication rates.[40]

Long term indwelling pleural catheter drainage

An alternative method for controlling recurrent and symptomatic malignant effusions including patients with trapped lung is insertion of a long term tunnelled pleural catheter. A specific catheter has been developed for this purpose. The length of hospitalisation for the indwelling catheter group was significantly shor ter (1 day) than that of the doxycycline pleurodesis group (6 days). In the indwelling catheter group spontaneous pleurodesis was achieved in 42 of the 91 patients. A late failure rate (defined as re accumulation of pleural fluid after initial successful control) of 13% was reported compared with 21% for the doxycycline pleurodesis group.[41,42]

Pleurectomy

It is an effective but invasive method for those who have failed to respond to other forms of treatment for treating malignant pleural effusions. Complications may include haemorrhage, empyema, and cardiorespiratory failure (operative mortality rates of 10-13%). The advent of video assisted thoracic surgery (VATS) has enabled parietal pleurectomy to be performed without a formal thoracotomy.[43]

Figure 6: PleurX catheter. A, Patient connects the PleurX catheter to a bottle for self-drainage. B, Close-up of the catheter. Note the one-way valve mechanism (white arrow) and Velcro cuff to provide tissue ingrowth (black arrow).

Figure 7: Video-assisted thoracic surgery (VATS) image parietal pleurectomy. L, Lung; P, parietal pleural peel.

Prognosis

Because of population variations in primary cell types and regional preferences in therapies used to control effusions, the prognoses of patients with malignant effusions vary among clinical settings. After malignant pleural effusion diagnosis is typical,a survival rate of less than 50% at 6 months and 6% at 2 years are observed . Also in these series, patients had a particularly short survival (13.9 weeks) when treated only by serial thoracenteses rather than more aggressive therapies . Alternatively, a longer interval between the initial diagnosis of cancer and the malignant effusion favors survival. A more favorable survival rate are associated with breast cancer effusions , particularly when they are estrogen receptor positive and the cells show a morula clustering pattern on cytology. In other cancers ,the presence of large clusters of malignant cells on smears also has a favorable prognosis. Unfavorable tumor surface receptors adversely affect prognosis.

References

1. Rodriguez-Panadero F, Borderas Naranjo F, Lopez-Mejias J. Pleural metastatic tumours and effusions: frequency and pathogenic mecha nisms in a post-mortem series. Eur Respir J 1989;2:366-369.

2. Fiocco M, Krasna MJ. The management of malignant pleural and pericardial effusions. Hematology /Oncology Clinics 1997;11(2):253-265,.

3. Molengraft van de FJJM, Vooijs GP. Survival of patients with malignancy-associated effusions.Acta Cytol 1989; 33:911-916.

4. Hallman JR, Geisinger KR. Cytology of fluids from pleural, peri-toneal and pericardial cavities in children. A comprehensive survey. Acta Cytol 1994;38(2):209-217,

5. Ang P, Tan EH, Leong SS, Koh L, Eng P, Agasthian T, etal. Primary intrathoracic malignant effusion: a descriptive study. Chest 2001 Jul 1;120(1):50-54..

6. Sears D , Hajdu SI. The cytologic diagnosis of malignant neoplasms in pleural and peritoneal effusions. Acta Cytol 1987; 31:85-97.

7. Miserocchi G. Physiology and pathophysiology of pleural fluid turnover.Eur Respir J 1997; 10:219-225.

8. Meyer PC. Metastatic carcinoma of the pleura.Thorax 1966;21:437-443.

9. Kraft A, Weindel K, Ochs A. Marth C, Zmija J. Schumacher P. Gastl G. Vascular endothelial growth factor in the sera and effusions of patients with malignant and nonmalignant disease. Cancer: Interdisciplinary International Journal of the American Cancer Society.1999; 85(1):178-187.

10. Sahn SA. Pleural diseases related to metastatic malignancies. Eur Respir J 1997;10:1907-1193.

11. Judson MA, Sahn SA. Pulmonary physiologic abnormalities caused by pleural disease. Semin Respir Crit Care Med 1995; 16:346-353.

12. Chernow B, Sahn SA. Carcinomatous involvement of the pleura: an analysis of 96 patients. Am J Med 1977;63:695-702.

13. Maher GG, Berger HW. Massive pleural effusions: malignant and non-malignant causes in 46 patients. Am Rev Respir Dis 1972;105:458-460.

14. O'Donovan PB, Eng P. Pleural changes in malignant pleural effusions:appearance on computed tomography. Cleve Clin J Med 1994;61:127-131.

15. Grogan DR, Irwin RS, Channick R. Complications associated with thoracentesis: a prospective randomized study comparing three different methods. Arch Intern Med 1990;150:873-877.

16. Bittner RC, Felix R. Magnetic resonance (MR) imaging of the chest:state of the art. Eur Respir J 1998;11:1392-1404.

17. Heffner JE, Brown LK, Barbieri CA. Diagnostic value of tests that dis-criminate between exudative and transudative pleural effusions. Chest 1997;111:970-980.

18. Light RW. Pleural diseases. Dis Mon. 1992;38(5):261-331..

19. Rodríguez-Panadero F, López Mejías J. Low glucose and pH levels in malignant pleural effusions. Diagnostic significance and prognostic value in respect to pleurodesis. Am Rev Respir Dis 1989;139(3):663-667.

20. Good Jr JT, Taryle DA, Sahn SA. The pathogenesis of low glucose, low pH malignant effusions. Am Rev Respir Dis. 1985; 131(5):737-741.

21. Villena V, Perez V, Pozo F, Lopez-Encuentra PM. Amylase levels in pleural effusions:a consecutive unselected series of 841 patients. Chest. 2002;121(2):470-474.

22. Chang LC, Hua CC, Liu YC, Chu CM, Chen HJ, Lee N. Pleural fluid viscosity may help identifying malignant pleural effusions. Respirology. 2008;13(3):341-345.

23. Lai CL. Tsai CM, Tsai TT. Kuo BI, Chang KT, Fu HT. Presence of serum anti-p53 antibodies is associated with pleural effusion and poor prognosis in lung cancer patients. Clinical Cancer Research. 1998;4(12):3025-3030.

24. Motherby H, Kube M, Friedrichs N, Nadjari B, Knops K, Donner A, at al Bocking A. Immunocytochemistry and DNA-image cytometry in diagnostic effusion cytology I.Prevalence of markers in tumour cell positive and negative smears. Analytical Celluiar Pathology.1999;19(1):7-20.

25. Irani DR, Underwood RD, Johnson EH, Malignant pleural effusions. A clinical cytopathologic study. Archives of Internal Medicine. 1987; 147(6):1133-1136.

26. Loddenkemper R, Boutin C. Thoracoscopy: diagnostic and therapeutic indications. Eur Respir J 1993;6:1544-1555.

27. Loddenkemper R, Thoracoscopy-state of the art. Eur Respir J 1998;11:213-221.

28. Poe RH, Levy PC, Israel RH, Ortiz CR. Kally MC. Use of fiberoptic bronchoscopy in the diagnosis of bronchogenic carcinoma: a study in patients with idiopathic pleural effusions. Chest 1994;105:1663-1667.

29. McKneally MF, Lewis RJ. Statement of the AATS/STS Joint Commit-tee on thoracoscopic and video-assisted thoracic surgery. Ann Thorac Surg 1992;54:1.

30. Antunes G, Neville E, Duffy J. Ali N. BTS guidelines for the management of malignant pleural effusions, Thorax. 2003; 58(Suppl 2):ii29-ii38.

31. Stretton F, Edmonds P, Marrinan M. Malignant pleural effusions. Eur J Palliative Care 1999; 6:5-9.

32. Antony VB , Rothfuss KJ, Godbey SW, Sparks JA, Hott JW. Mechanism of tetracycline-hydrochloride-induced pleurodesis. Am Rev Respir Dis 1992; 146 :1009-1013.

33. Morrison MC, Mueller PR, Lee MJ. Sclerotherapy of malignant pleural effusion through songraphically placed small-bore catheters. AJR 1992; 158 :41-43.

34. Tarver RD, Broderick LS, Conces DJ. Reexpansion pulmonary edema. Journal of thoracic imaging 1996; 11(3):198-209.

35. Mahfood S, Hix WR, Aaron BL. Reexpansion pulmonary edema.Ann Thorac Surg1988; 45:340-345.

36. Wooten SA, Barbarash RA, Strange C, Sahn SA . Systemic absorption of tetracycline and lidocaine following intrapleural instillation. Chest 1988; 94(5):960-963.

37. Martinez-Moragon E, Aparicio J, Rogado MC, Sanchis J, Sanchis F, Gil-Suay V. Pleurodesis in malignant pleural effusions: a randomized study of tetracycline versus bleomycin. European Respiratory Journal.1997; 10(10):2380-2383.

38. Berger L , Dargan EL, Huang BL. Dissemination of cancer cells by needle biopsy of the lung.J Thorac Cardiovasc Surg 1972; 63:430-432.

39. Davies CWH, Traill ZC, Gleeson FV. Intrapleural streptokinase in the management of malignant multiloculated pleural effusions. Chest 1999; 115 :729-733.

40. Loddenkemper R. Thoracoscopy: state of the art. Eur J Respir 1998; 11:213-221.

41. Warren WH, Faber LP. Clinical experience with Pleurx catheters for malignant pleural effusions. Chest 2000; 118 (Suppl):130S.

42. Lee KA, Harvey JC, Reich H. Management of malignant pleural effusions with pleuroperitoneal shunting. J Am Coll Surg 1994; 178 :586-588.

43. Fry WA, Khandekar JD. Parietal pleurectomy for malignant pleural effusions.Ann Surg Oncol 1995; 2:160-164.