Review Article

Primary lung cancer and pleural effusion—diagnostic and therapeutic approach

Georgia Hardavella[1], Ioannis Karampinis[2]

[1]9th Department of Respiratory Medicine, Athens' Chest Diseases Hospital 'Sotiria', Athens, Greece; [2]Department of Thoracic Surgery, 'Sismanogleio' General Hospital, Athens, Greece

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Georgia Hardavella. 9th Department of Respiratory Medicine, Athens' Chest Diseases Hospital 'Sotiria', Athens, Greece. Email: georgiahardavella@hotmail.com.

Abstract: Suspected and confirmed malignant pleural effusions (MPEs) due to lung cancer constitute a common yet serious clinical problem encountered in acute health care settings and are related to poor quality of life and prolonged hospital stay. This article attempts to provide a concise overview of current management and treatment approaches for confirmed and/or suspected MPEs secondary to lung cancer.

Keywords: Malignant pleural effusion (MPE); lung cancer; diagnosis; management

Received: 28 February 2020; Accepted: 23 March 2020; Published: 25 September 2020.

doi: 10.21037/amj.2020.03.13

View this article at: http://dx.doi.org/10.21037/amj.2020.03.13

Introduction

The presence of a malignant pleural effusion (MPE) automatically classifies patients to advanced cancer stage and it is associated with significant mortality and morbidity (1). MPEs' incidence is 660 per million population worldwide (2) accounting for more than 200,000 people diagnosed each year in the US (3) and over 100,000 people/year across Europe (2,3). Health Care Systems sustain a large burden due to hospital admissions for MPE. A retrospective analysis based on the Healthcare Cost and Utilization Project National Inpatient Sample database reported 126,825 hospital admissions for MPEs in 2012 and interestingly 72,240 included one or more pleural procedures which in the end were not expected to reduce the recurrence rate of MPEs (1). Lung and breast cancer are the most common causes of MPEs and hospitalizations related to them are more likely to include pleural procedures compared to hospitalizations for MPEs due to other types of cancer (1).

In this review, we examine diagnostic and therapeutic approaches in patients with primary lung cancer and pleural effusion and address clinical questions derived from practicing in pragmatic clinical health care settings.

Diagnostic approach

Imaging techniques

Imaging plays an integral role in the diagnostic work up of pleural effusions especially on the background of suspected or confirmed lung cancer. Although chest X-rays have been historically used for the initial diagnosis of pleural effusions, thoracic ultrasound and enhanced chest CT scan have evolved the diagnostic work up. The traceable amount of pleural fluid varies depending on the imaging modality. Thoracic ultrasound is considerably more sensitive than Chest X-rays in detecting smaller volume of pleural fluid and it is independent of view/body posture while chest X-rays' detection of pleural fluid is affected by the projected X-ray view and body posture (e.g., lateral decubitus) (4-8). Although there is published data on how to calculate the amount of pleural effusion identified in a chest CT scan (9,10), to the best of our knowledge there is no published data regarding minimum fluid volume quantity detected by chest CT scan (3-8). *Table 1* summarizes the minimum amount of detectable fluid by each imaging modality (4-8).

All current guidelines for the diagnosis and management

Table 1 Minimum amount of detectable pleural fluid for different imaging techniques

Imaging technique	Minimum amount of fluid detected	Dependent on views
Chest X-ray	10–25 mL	Yes, lateral decubitus position
	50 mL	Yes, blunting of costophrenic recess on lateral upright chest view
	200 mL	Yes, blunting of costophrenic angle on posterior-anterior view
	500 mL	Yes, obliteration of the hemidiaphragm on posterior-anterior view
Thoracic ultrasound	5 mL (physiologic amount of pleural fluid); 20 mL (minimal amount of pleural effusion detected)	No
Contrast enhanced chest CT scan	Not specified in literature	No

of MPEs suggest that pleural ultrasound guidance significantly increases the likelihood of successful pleural fluid aspiration and reduces the risk of complications such as pneumothorax or organ puncture (11-13). In the diagnostic pathway for MPEs secondary to lung cancer, contrast enhanced chest CT scans are the golden standard (11-13). They can provide valuable information on the lung tumor size and stage and the pleural cavity per se; they can distinguish benign and malignant effusions, identify pleural thickening, evaluate major and minor fissures and highlight findings which are suggestive of malignancy such as pleural rind, mediastinal pleural involvement, pleural nodularity, and pleural thickening greater than 1 cm (14,15).

Magnetic resonance imaging (MRI) is costlier than chest CT or thoracic ultrasound, it is not available in all centers and it is compromised by poor spatial resolutions and motion artefacts which make it less satisfactory in the diagnostic work-up of MPEs (14). It is also contraindicated for patients with metallic grafts. Recent evidence suggests that diffusion-weighted magnetic resonance imaging (DWI) can evaluate pleural diseases morphologically and qualitatively, and can identify pleural malignancy (16). However, this is a single institution experience and is based on a limited number of patients, which introduced selection bias and there is discrepancy in the literature concerning optimal DWI techniques and image analysis procedures (17,18). As outlined above, CT imaging with pleural phase contrast is the gold standard to assess MPEs. However, if contrast is contra-indicated (e.g., severe renal failure), MRI can be used to identify chest wall invasion or septation within pleural fluid. In the absence of contrast, T2-weighted images will demonstrate pleural nodularity, as both fluid and extrapleural fat will present high signal in comparison with the low signal pleura (19).

PET CT imaging is commonly used for staging of lung cancer, however its value in predicting benign *vs.* MPE is limited due to high false positive rates in patients with inflammation/infection (11,20). In a diagnostic pathway for suspected MPE secondary to lung cancer, PET CT may be helpful in identifying certain anatomical areas of the pleura to biopsy (21).

Table 2 presents sensitivity and specificity of thoracic ultrasound, CT chest and PET CT for MPEs (22-25).

Thoracentesis, cytology and pathology acquisition

A common clinical scenario is suspected MPE in an asymptomatic patient. One of the questions arising in a pragmatic clinical setting is whether a pleural aspiration or a pleural drainage should be the next step in the diagnostic pathway. In this case, ATS/STS/STR Guidelines (12) recommend that pleural drainage should not be performed in asymptomatic patients however this is conditional recommendation supported by low evidence (26-28). Pleural aspiration is the recommended approach preferably with ultrasound guidance (11-13) unless the patient is symptomatic (dyspnea) where a pleural drainage is required to relieve breathlessness. Draining asymptomatic effusions would only subject the patient to the risks of the procedure without significant clinical benefit. Mean sensitivity of pleural fluid cytology is 60% and this depends on the cytologist's experience, samples' preparation and underlying malignancy (11,29). A second specimen can increase the diagnostic yield by 27%, but more samples (i.e., >2) do not seem to influence the result, instead they increase related diagnostic costs (29,30).

Table 2 Sensitivity and specificity of thoracic ultrasound, CT chest and PET CT in the diagnosis of MPEs

Imaging modality	Sensitivity, %	Specificity, %
Thoracic ultrasound (22)	73	100
Contrast enhanced CT chest (23)	68	78
PET CT (24,25)	93–100	67–89

MPE, malignant pleural effusion.

Table 3 Comparison of performance between medical and surgical thoracoscopy in the diagnosis of suspected MPE

Performance	Medical thoracoscopy	Surgical thoracoscopy
Diagnostic yield (37)	93.6%	96%
Major complications	2.6%	4%
Minor Complications	17.9%	16.2%
Median length of stay (days)	0	3
Patient controlled intravenous anesthesia	0	100%

MPE, malignant pleural effusion.

The evolution of targeted therapies for lung cancer has necessitated pleural tissue acquisition to be used in the diagnosis and genotyping. Blind biopsy of the pleura is not considered to be an option due to its low diagnostic yield and low sensitivity (33%) (31,32). Medical thoracoscopy is a reliable modality for pleural tissue acquisition (33,34); a meta-analysis of 17 individual trials studying this approach in 755 patients calculated an aggregate sensitivity of 91%, specificity of 100% and major complications rate of 1.5% (35). Rahman *et al.* (36) reported a mortality rate of 0.3% for medical thoracoscopy which is most likely linked with therapeutic interventions (talc pleurodesis) rather than the diagnostic process per se. Choosing between surgical and medical thoracoscopy for the diagnosis of a suspicious MPE has been a matter of debate. While surgical thoracoscopy is considered the gold standard, medical thoracoscopy is less invasive, cost-effective, it has a shorter hospital stay and it does not compromise the diagnostic yield. McDonald *et al.* (37) recently published a study comparing medical versus surgical thoracoscopy in the diagnosis of suspect MPE and *Table 3* summarizes the comparison characteristics between the two.

Physician based ultrasound guided pleural biopsy is a safe alternative that can be used in patients that are not eligible for thoracoscopic approach (e.g., frail, with performance status >2, contraindications for general/conscious sedation/collapsed lung) and it presents a reliable diagnostic yield (94%) (38).

Abrams pleural biopsy has only 57% sensitivity for malignancy (11) therefore it is contraindicated as a procedure of choice in the diagnosis of suspected MPEs however it seems that its sensitivity is increased when the procedure is performed with ultrasound guidance and it can be comparable with the sensitivity of CT guided pleural biopsy. Sivakumar *et al.* (39) addressed the above and compared the diagnostic sensitivity and specificity of ultrasound guided Abrams pleural biopsy versus CT guided Tru-Cut pleural biopsy in the undiagnosed pleural effusions with a high suspicion of malignancy. Ultrasound guided Abrams biopsy presented comparable sensitivity with CT guided Tru-Cut biopsy (71.43% *vs.* 75% respectively) while specificity was 100 % in both groups (39).

Routine diagnostic bronchoscopy should not be used routinely in the diagnosis of suspected MPEs and should only be considered when endobronchial lesion is suspected based on chest CT imaging (11).

Molecular markers in lung cancer related MPEs

Current guidelines do not support the routine use of molecular markers in the diagnosis guidance of targeted treatment of suspected lung cancer related MPEs due to the lack of solid supporting evidence (11-13). However, the detection of molecular markers in lung cancer related MPEs has been associated with prognosis and treatment response. Epidermal growth factor (EGFR) mutation status in cell blocks of lung adenocarcinoma MPEs confirmed

by pathology is highly predictive of EGFR tyrosine kinase inhibitors (TKI) efficacy (40). Patients with EGFR mutation in their lung adenocarcinoma related MPE had a better progression free survival (7.33 months) than patients with wild-type EGFR (2.07 months, P=0.032) (40).

Anaplastic lymphoma kinase (ALK) rearrangement detection in lung adenocarcinoma related MPEs can be used as a complementary method for EML4 (echinoderm microtubule-associated protein-like 4)-ALK detection and can predict tumor responsiveness to crizotinib (41).

Dresler *et al.* (42) compared programmed death ligand 1 (PD-L1) expression in MPEs of lung adenocarcinoma with pleural biopsies and the positive expression in MPE was correlated with survival time after systemic anti-tumor treatment. Mean survival time with positive PD-L1 expression in MPE was shorter than that with the negative expression (17.370±1.827 *vs.* 29.944±2.671 months) (χ^2=4.507, P=0.034).

Overall, the clinical implication of molecular markers is limited due to the inadequacy of the validation of the results by subsequent studies.

Treatment approach

Therapeutic drainage and pleurodesis

Patients with large pleural effusion which is confirmed/suspected MPE secondary to lung cancer require therapeutic drainage (large volume thoracentesis) that will relieve the symptom of breathlessness and it will also provide information about the expansion of the underlying lung (12). Trapped lung (i.e., not expandable lung) occurs in 30% MPEs and it can be a contraindication for pleurodesis (11,42-44) and at this point clinicians should consider the option of indwelling pleural catheters (IPCs) that will be commented below (12,13). Patients with symptomatic MPE, expandable lung, and no prior definitive therapy, would benefit from chemical pleurodesis as first-line definitive pleural intervention for management of breathlessness (12,13).

Pleurodesis is a parietal-to-visceral pleural fusion with concomitant obliteration of the pleural space. Complete drainage of the MPE allows parietal-to-visceral pleural apposition and at this point pleurodesis can be accomplished with chemical or mechanical means (30). A profound inflammatory response between the two pleural layers, follows the instillation of the chemical sclerosing agent and this progresses in fibrin accumulation and pleural fibrosis that prevents re-accumulation of fluid in the pleural space (30).

The choice of the sclerosing agent has been historically a matter of discussion in the literature. Various chemicals (talc, iodopovidone, bleomycin, tetracycline etc.) and bacterial products (derived from Streptococcus pyogenes, Staphylococcus aureus and others) have been mentioned in the literature and studies in clinical trials (30). Talc is an asbestos free trilayered magnesium silicate sheet which appears to have been used in pleurodesis since 1935 (45) and appears to be the most effective and least expensive sclerosing agent (46,47). In a Cochrane meta-analysis of 1,499 subjects, talc did not increase mortality post pleurodesis and was found to be the most efficacious agent (48). Dresler *et al.* reported the success rate of talc pleurodesis is approximately 75% at 1 month, but it is progressively reduced to approximately 50% at 6 months (42). The same study reported that talc poudrage is not superior to talc slurry with the exception of lung and breast cancer. However, there are no reliable data, regarding the optimal method for talc delivery, leading to variations in practice and recommendations (11-13). Bhatnagar *et al.* addressed this and performed a randomized controlled trial across 17 UK hospitals where they tested the hypothesis that administration of talc poudrage during thoracoscopy with local anesthesia is more effective than talc slurry delivered via chest tube in inducing a successful pleurodesis (49,50). There was no difference in the rate of pleurodesis failure at 90 days in patients with MPE between thoracoscopic talc poudrage and talc slurry delivered via chest tube.

IPCs

An IPC is a silicone tube giving long term access to the pleural cavity and it is tunneled subcutaneously. There is a one-way valve to the proximal end of the exposed tube which is used to connect to drainage bottles. Fluid drainage is patient driven and it is guided by patients' symptoms offering a sense of intervention control to most patients. IPCs are suitable for patients with recurrent MPEs with both expandable and nonexpandable lungs, patients who failed pleurodesis in the past and have a short life expectancy. They are now considered an acceptable alternative option to pleurodesis in patients with expandable lung, no prior definitive therapy, and symptoms attributable to the effusion. They relieve breathlessness and improve quality of life while they give the opportunity of ambulatory management instead of prolonged hospital admissions (12,51). Symptomatic improvement occurs in 95.6%

patients and 45.6% achieve spontaneous pleurodesis after a median of 52 days (52). The control of breathlessness and quality of life achieved is comparable to talc pleurodesis but with significantly shortened hospital stay (53,54) and importantly patients with IPC require fewer subsequent pleural interventions in comparison with the ones that underwent talc slurry pleurodesis via a chest drain (54). Improved quality of life in the community rather than in the hospital is of essence in this group of patients with limited survival. IPC use is safe with reported risk of death from pleural infection below 0.3% (55).

Clinical scores have been developed to improve our understanding of survival for patients with MPE and guide the selection of appropriate management strategies (56,57). LENT score (56) predicts survival in patients with MPEs and PROMISE score (57) combines biological and clinical parameters to accurately estimate 3-month mortality. Both are clinically relevant prognostic scores that can be applied immediately, and inform treatment decision making therefore avoiding invasive interventions and prolonged hospital stay in patients with limited survival that would prefer and benefit from spending their end of life in the community. Both scores can guide decision making process as to whether talc pleurodesis or IPC would be the intervention of choice tailored to patients' needs.

Pleurectomy

It is an invasive surgical approach where part of the pleura is surgically removed. It can be safely performed and controls the symptoms of MPE secondary to malignant pleural mesothelioma (58). There is no indication for pleurectomy in MPEs secondary to confirmed lung cancer and as such it will not be further discussed in the current review.

Conclusions

MPE due to lung cancer is commonly encountered in pragmatic health care settings. Quality of life, symptom control and palliation are the paramount goal in its management. Diagnostic and therapeutic options and clinical prediction scores continue to expand with ongoing trials and clinical validation to further refine our management approaches. Formerly bed-ridden patients with MPE due to lung cancer are now treated in ambulatory care, have an improved quality of life in the community and spend less time in hospitals. Taking into account the amount of produced scientific evidence for MPEs, we need to re-evaluate our practice on a regular basis to ensure optimal outcomes are achieved.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Dragan Subotic) for the series "Malignant Pleural Effusion" published in *AME Medical Journal*. The article was sent for external peer review organized by the Guest Editor and the editorial office.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2020.03.13). The series "Malignant Pleural Effusion" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Fortin M, Taghizadeh N, Tremblay A. Procedures performed during hospitalizations for malignant pleural effusions: data from the 2012 National Inpatient Sample. Respiration 2018;95:228-34.
2. Fitzgerald DB, Koegelenberg CFN, Yasufuku K, et al. Expert review of respiratory medicine surgical and non-surgical management of malignant pleural effusions. Expert Rev Respir Med 2018;12:15-26.
3. Feller-Kopman D, Light R. Pleural disease. N Engl J Med

2018;378:1754.
4. Qureshi NR, Gleeson FV. Imaging of pleural disease. Clin Chest Med 2006;27:193-213.
5. Evans AL, Gleeson FV. Radiology in pleural disease: state of the art. Respirology 2004;9:300-12.
6. Eibenberger KL, Dock WI, Ammann ME, et al. Quantification of pleural effusions: sonography versus radiography. Radiology 1994;191:681-4.
7. Koh DM, Burke S, Davies N, et al. Transthoracic US of the chest: clinical uses and applications. Radiographics 2002;22:e1.
8. Kuhlman JE, Singha NK. Complex disease of the pleural space: radiographic and CT evaluation. Radiographics 1997;17:63-79.
9. Moy MP, Levsky JM, Berko NS, et al. A new, simple method for estimating pleural effusion size on CT scans. Chest 2013;143:1054-9.
10. Chiao D, Hanley M, Olazagasti JM. CT volumetric analysis of pleural effusions: a comparison with thoracentesis volumes. Acad Radiol 2015;22:1122-7.
11. Roberts ME, Neville E, Berrisford RG, et al. Management of a malignant pleural effusion: British Thoracic Society pleural disease guideline 2010. Thorax 2010;65:ii32-40.
12. Feller-Kopman DJ, Reddy CB, DeCamp MM, et al. Management of malignant pleural effusions. An Official ATS/STS/STR Clinical Practice Guideline. Am J Respir Crit Care Med 2018;198:839-49
13. Bibby AC, Dorn P, Psallidas I, et al. ERS/EACTS statement on the management of malignant pleural effusions. Eur Respir J 2018. doi: 10.1183/13993003.00349-2018.
14. Light RW. Pleural diseases. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2013.
15. Light RW. Pleural effusions. Med Clin North Am 2011;95:1055-70.
16. Usuda K, Iwai S, Funasaki A, et al. Diffusion-weighted imaging can differentiate between malignant and benign pleural diseases. Cancers (Basel) 2019. doi: 10.3390/cancers11060811.
17. Usuda K, Sagawa M, Motono N, et al. Diagnostic performance of diffusion weighted imaging of malignant and benign pulmonary nodules and masses: Comparison with positron emission tomography. Asian Pac J Cancer Prev 2014;15:4629-35.
18. Nasu K, Kuroki Y, Minami M. Diffusion-weighted imaging findings of mucinous carcinoma arising in the ano-rectal region. Comparison of apparent diffusion coefficient with that of tubular adenocarcinoma. Jpn J Radiol 2012;30:120-7.
19. Hallifax RJ, Talwar A, Wrightson JM, et al. State-of-the-art: Radiological investigation of pleural disease. Respiratory Medicine 2017;124:88-99.
20. Porcel JM, Hernández P, Martínez-Alonso M, et al. Accuracy of fluorodeoxyglucose-PET imaging for differentiating benign from malignant pleural effusions: a meta-analysis. Chest 2015;147:502-12.
21. Wang ZJ, Reddy GP, Gotway MB, et al. Malignant pleural mesothelioma: evaluation with CT, MR imaging, and PET. Radiographics 2004;24:105-19.
22. Qureshi NR, Rahman NM, Gleeson FV. Thoracic ultrasound in the diagnosis of malignant pleural effusion. Thorax 2009;64:139-43.
23. Hallifax RJ, Haris M, Corcoran JP, et al. Role of CT in assessing pleural malignancy prior to thoracoscopy. Thorax 2015;70:192-3.
24. Nakajima R, Abe K, Sakai S. Diagnostic ability of FDG-PET/CT in the detection of malignant pleural effusion. Medicine (Baltimore) 2015;94:e1010.
25. Sun Y, Yu H, Ma J, et al. The role of 18F-FDG PET/CT integrated imaging in distinguishing malignant from benign pleural effusion. PLoS One 2016;11:e0161764.
26. Porcel JM, Gasol A, Bielsa S, et al. Clinical features and survival of lung cancer patients with pleural effusions. Respirology 2015;20:654-9.
27. Tremblay A, Robbins S, Berthiaume L, et al. Natural history of asymptomatic pleural effusions in lung cancer patients. J Bronchology 2007;14:98-100.
28. Ryu JS, Ryu HJ, Lee SN, et al. Prognostic impact of minimal pleural effusion in non-small-cell lung cancer. J Clin Oncol 2014;32:960-7.
29. Sahn SA. State of the art. The pleura. Am Rev Respir Dis 1988;138:184-234.
30. Desai NR, Lee HJ. Diagnosis and management of malignant pleural effusions: state of the art in 2017. J Thorac Dis 2017;9:S1111-22.
31. Maskell NA, Gleeson FV, Davies RJO. Standard pleural biopsy versus CT-guided cutting-needle biopsy for diagnosis of malignant disease in pleural effusions: a randomised controlled trial. Lancet 2003;361:1326-30.
32. Pereyra MF, San-José E, Ferreiro L et al. Role of blind closed pleural biopsy in the management of pleural exudates. Can Respir J 2013;20:362-6.
33. Menzies R, Charbonneau M. Thoracoscopy for the diagnosis of pleural disease. Ann Intern Med 1991;114:271-6.
34. Hardavella G, Zachilas D, Doga G, et al. Medical thoracoscopy in the diagnosis and treatment of lung/pleural disease: sharing an experience of 1125 cases. ERJ

2013;42:P3090.
35. Agarwal R, Aggarwal AN, Gupta D. Diagnostic accuracy and safety of semirigid thoracoscopy in exudative pleural effusions: a meta-analysis. Chest 2013;144:1857-67.
36. Rahman NM, Ali NJ, Brown G, et al. Local anaesthetic thoracoscopy: British Thoracic Society Pleural Disease Guideline 2010. Thorax 2010;65 Suppl 2:ii54-60.
37. McDonald CM, Pierre C, de Perrot M et al. Efficacy and cost of awake thoracoscopy and video-assisted thoracoscopic surgery in the undiagnosed pleural effusion. Ann Thorac Surg 2018;106:361-7.
38. Hallifax RJ, Corcoran JP, Ahmed A, et al. Physician-based ultrasound-guided biopsy for diagnosing pleural disease. Chest 2014;146:1001-6.
39. Sivakumar P, Jayaram D, Rao D, et al. Ultrasound-guided Abrams pleural biopsy vs CT-guided Tru-Cut pleural biopsy in malignant pleural disease, a 3-year follow-up study. Lung 2016;194:911-6.
40. Yang J, Lee OJ, Son SM, et al. EGFR mutation status in lung adenocarcinoma-associated malignant pleural effusion and efficacy of EGFR tyrosine kinase inhibitors. Cancer Res Treat 2018;50:908-16.
41. Wang Z, Wu X, Han X, et al. ALK gene expression status in pleural effusion predicts tumor responsiveness to crizotinib in Chinese patients with lung adenocarcinoma. Chin J Cancer Res 2016;28:606-16.
42. Dresler CM, Olak J, Herndon JE 2nd, et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. Chest 2005;127:909-15.
43. Feller-Kopman D. Therapeutic thoracentesis: the role of ultrasound and pleural manometry. Curr Opin Pulm Med 2007;13:312-8.
44. Bhatnagar R, Corcoran JP, Maldonado F, et al. Advanced medical interventions in pleural disease. Eur Respir Rev 2016;25:199-213.
45. Bethune N. Pleural poudrage: new technique for the deliberate production of pleural adhesion as preliminary to lobectomy. J Thorac Surg 1935;4:251-61.
46. Ong KC, Indumathi V, Raghuram J, et al. A comparative study of pleurodesis using talc slurry and bleomycin in the management of malignant pleural effusions. Respirology 2000;5:99-103.
47. Kuzdzał J, Sladek K, Wasowski D, et al. Talc powder vs doxycycline in the control of malignant pleural effusion: a prospective, randomized trial. Med Sci Monit 2003;9:PI54-9.
48. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database Syst Rev 2004;(1):CD002916.
49. Bhatnagar R, Laskawiec-Szkonter M, Piotrowska HE, et al. Evaluating the efficacy of thoracoscopy and talc poudrage versus pleurodesis using talc slurry (TAPPS trial): protocol of an open-label randomised controlled trial. BMJ Open 2014;4:e007045.
50. Bhatnagar R, Piotrowska HEG, Laskawiec-Szkonter M, et al. Effect of thoracoscopic talc poudrage vs talc slurry via chest tube on pleurodesis failure rate among patients with malignant pleural effusions: a randomized clinical trial. JAMA 2019. [Epub ahead of print].
51. Bhatnagar R, Maskell NA. Indwelling pleural catheters. Respiration 2014;88:74-85.
52. Van Meter ME, McKee KY, Kohlwes RJ. Efficacy and safety of tunneled pleural catheters in adults with malignant pleural effusions: a systematic review. J Gen Intern Med 2011;26:70-6.
53. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA 2012;307:2383-9.
54. Thomas R, Fysh EH, Smith NA, et al. Effect of an indwelling pleural catheter vs talc pleurodesis on hospitalization days in patients with malignant pleural effusion: the AMPLE randomized clinical trial. JAMA 2017;318:1903-12.
55. Fysh ET, Tremblay A, Feller-Kopman D, et al. Clinical outcomes of indwelling pleural catheter-related pleural infections: an international multicenter study. Chest 2013;144:1597-602.
56. Clive AO, Kahan BC, Hooper CE, et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. Thorax 2014;69:1098-104.
57. Psallidas I, Kanellakis NI, Gerry S, et al. Development and validation of response markers to predict survival and pleurodesis success in patients with malignant pleural effusion (PROMISE): a multicohort analysis. Lancet Oncol 2018;19:930-9.
58. Waller DA, Tenconi S. Surgery as part of radical treatment for malignant pleural mesothelioma. Curr Opin Pulm Med 2017;23:334-8.

doi: 10.21037/amj.2020.03.13
Cite this article as: Hardavella G, Karampinis I. Primary lung cancer and pleural effusion—diagnostic and therapeutic approach. AME Med J 2020;5:30.