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NARRATIVE REVIEW

# Update on the clinical management of malignant pleural effusion: a narrative review.

**Tannia Rivera Rivera[1]*, Erika Serrano Bueno[2]**

1. Intensive Care Unit, National Oncology Institute “Dr. Juan Tanca Marengo,” Society for the Fight Against Cancer (Solca), Guayaquil-Ecuador.
2. Postgraduate Department, School of Medicine, University of Espiritu Santo Specialties, Guayaquil, Ecuador.

***Correspondence:**

mdtrivera@yahoo.com

Avda. Pedro Menéndez Gilbert, next to Cdla. The Atarazana. Intensive Care Service, National Oncology Institute “Dr. Juan Tanca Marengo. Guayaquil, Ecuador. Telephone [593] 04-3 718 300.

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## Abstract

Introduction: Approximately 50% of pleural effusions (PE) are neoplastic. The clinical behaviorof neoplastic PE is highly symptomatic due to its large volume and early recurrence.

Purpose of review: This review aims to outline the role of the different diagnostic and therapeutic methods of malignant PE. We look for updated reports that include the best survival results for the other current treatments.

Recent findings: Light's criteria are the standard to differentiate a malignant exudate. Ultrasound-guided thoracentesis should be used as a diagnostic/therapeutic method. In patients with malignant PE, permanent drainage is recommended with the placement of a chest tube and a hydraulic seal with closed drainage. Pleurodesis with the installation of talc is recom- mended in patients with malignant PE to reduce volume, PE recurrences, and hospitalizationtime.

Conclusions: For the correct management of malignant PE, several aspects must be consid- ered, such as identifying the presence of malignant cells by cytological study and ruling out infection. Pleural ultrasound allows for defining the volume of the PE. It will enable deciding on drainage at that time, with the possibility of inserting an intrapleural catheter, to evaluate the likelihood of sclerosing the pleurae through pleurodesis. However, to reach this decision, it is necessary to analyze each of the details that could play an essential role in good manage- ment and definitive resolution or, on the contrary, decide on palliative management, constantly investigating each case to provide symptom improvement. In addition, improving the patient's quality of life.

Keywords:

MESH: Pleural effusion; Pleural cavity; Pleural diseases; Pleural effusion, Malignant; Thora- coscopy; Talc; Exudates and transudates; Thoracentesis; Pleurodesis.

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## Introduction

The pleural cavity contains fluid necessary to prevent pleural friction. The alteration of the oncotic and hydrostatic pressure causes an increase in the volume of the liquid, called pleural effusion. Approximately 50% of pleural effusions are neoplastic. The purpose of this review was to define, through an algorithm, the diagnostic and therapeutic methodology, the role of interventionism and ultrasound to reduce symptoms and hospitalizations, as well as to deter- mine which interventions are beneficial for the management of pleural effusion in cancer pa-tients with poor prognosis and quality of life.

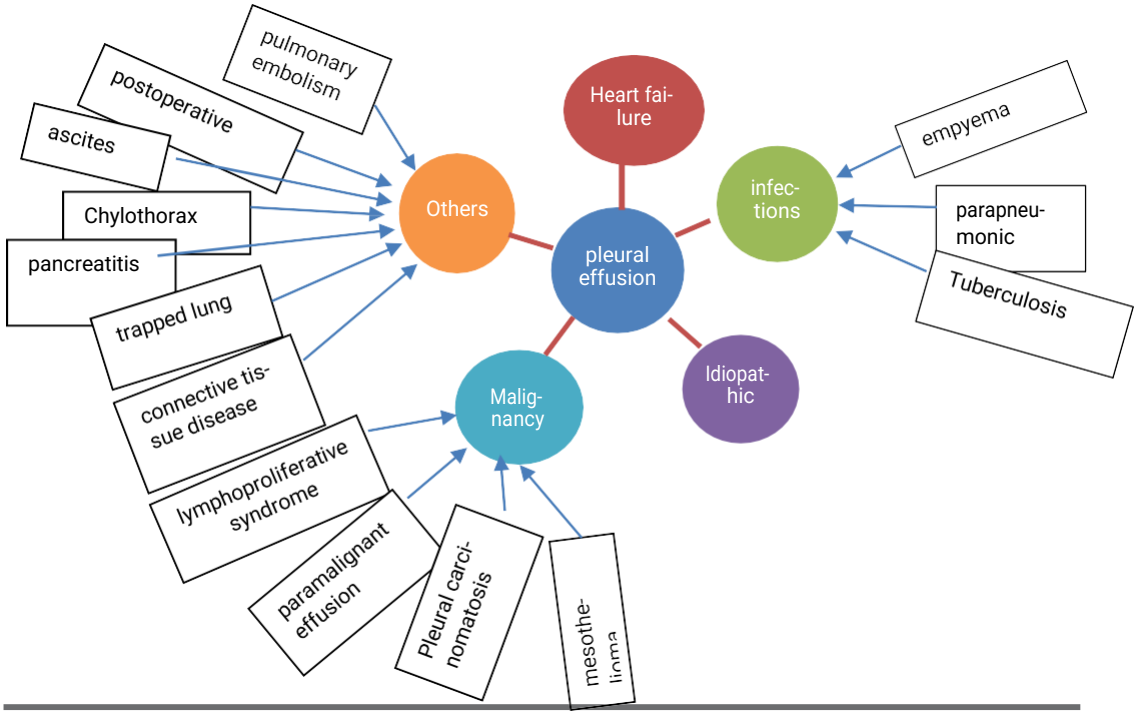
The objective of this narrative review was to make a state of the art of ton subject on themost relevant and updated literature.

## Etiology and pathogenesis

Under normal conditions, the pleural cavity is considered a virtual cavity; between its visceral layer attached to the lung and the parietal layer attached to the chest wall, it contains 20 ml of pleural fluid, corresponding to 0.3 ml/kg [1]. The increase in its production is directly related to the etiology [2]. The functions of the pleural space are 1) to decrease friction between the parietal and visceral pleurae, which allows lung movement during inspiration and exhalation;

2) to maintain negative pressure to prevent lung collapse [3]; and 3) to regulate the production of pleural fluid by maintaining homeostasis of hydrostatic and oncotic pressures between the systemic circulation, the pulmonary circulation, and the pleura [4]. The fluid that accumulates due to loss of homeostasis is called pleural effusion (PE). In pleural inflammatory conditions, it has characteristics of a transudate; in states of infection or malignancy, it has features of an exudate. Another mechanism of fluid entry into the pleural cavity is the passage of ascitic fluid from the abdomen through the diaphragmatic wall due to increased abdominal pressure [5]. Among the most common causes of PE are heart failure, associated infections, and neo- plasms. Approximately 50% are associated with oncological reasons [6]. See figure 1.

Figure 1. Most common causes of pleural effusion




## Clinical picture

The primary characteristic clinical manifestation is pleuritic pain originating from the inflamed parietal pleura with nociceptive properties. Occasionally, patients report oppressive-type chest pain. The most frequent symptom is dyspnea preceded by a cough that can be progressive according to the size and increase of the PE; this dyspnea is related to pleural occupation and collapse of a lung segment with the consequent decrease in lung volume [4]. However, the symptoms could be variable depending on the etiology of PE; dyspnea could be accompanied by desaturation, as an alteration in the oxygenation and ventilation-perfusion mechanism, and another sign found is weight loss, which would be related to chronic infection or malignancy. PE may not cause symptoms in some instances and may be an incidental radiological finding[2].

From the physical examination to the auscultation of the lung field, there is the absence of respiratory sound and dullness in the thoracic percussion depending on the volume of the PE [2]. It is essential to determine whether the effusion is unilateral or bilateral because it plays a vital role in the diagnosis. The investigation questions include past histories of recent infec- tions and associated symptoms such as fever, malaise, or weight loss. It is essential to estab- lish the duration of these symptoms, a history of relevant chronic cardiovascular diseases, which could be the cause of bilateral PE, such as kidney or liver failure, and ask about the regular consumption of medication or other drugs and any exposure to asbestos, which could lead to death. Alteration of pleural pressure increases its production [4]. Unilateral PE always requires a thoracocentesis for the biochemical study, cytology, and culture of the pleural fluid[2].

## Pleural fluid studies

For the study of PE, taking a sample through thoracocentesis is essential to differentiate be- tween transudate and exudate, with Light's criteria: proteins, lactate dehydrogenase (LDH), and glucose; the determination proposed in 1972 by Dr. Richard Light includes a simultaneous comparison of these parameters at the blood level (Table 1). These criteria predict an exudate with a sensitivity of 94.7% and a low specificity [7]. The visual macroscopic analysis of the pleural fluid can guide the diagnosis: the milky appearance corresponds to a chylothorax, the purulent or empyema appearance to an infectious origin, and the bloody appearance to ma- lignancy or trauma [4, 5, 7]. Other points to consider in the biochemical determination are the search for amylase in suspected esophageal perforation or pancreatitis and the resolution of lipids or triglycerides confirming the presence of a chylothorax that may accompany sponta- neous or mediastinal tumoral thoracic duct rupture [2, 7].

**Table 1.** Light criteria

| | transudate | exudate |
|---|---|---|
| biochemical definition | Proteins < 30 g/l | Proteins > 30 g/l |
| Causes | left ventricular failure<br>Renal failure<br>liver failure<br>Dysproteinemia | Infection (empyema, parapneumonic, TB)<br>Malignancy (Primary and secondary)<br>Inflammatory (Vasculitis, Autoimmune Di- sease)<br>Pulmonary embolism (with infarction)<br>esophageal perforation<br>hypothyroidism<br>Chylothorax Pseudo-Pseudochylothorax<br>Post cardiovascular surgery<br>drugs |
| **Light criteria** | | |
| Exudate is diagnosed when one or more of these criteria are met.<br>LP Protein/Serum Protein >0.5<br>LDH LP/serum LDH >0.6<br>LDH LP is above 2/3 of serum LDH<br>If the protein in the pleural fluid is 25-35 g/l or the level is abnormal, Light's criteria apply.<br>LDH: lactate dehydrogenase. PF: pleural fluid. TB: Tuberculosis | | |

## Biomarkers

### Tuberculosis

In identifying tuberculosis in the pleural fluid, nucleic acid (DNA) amplification is used with the Xpert® and GenExpert® commercial tests. They have a sensitivity of 72%, with the benefit of obtaining results in 2.5 hours; however, these tests have low diagnostic performance because the types other than tuberculous mycobacteria are not identified. They have a high cost [8]. Another molecular test is the QuantiFERON-γ, performed using the ELISA technique. It has a sensitivity of 72% and a specificity of 78% [9, 10]. A third test is the measurement of adenosine deaminase (ADA) in the pleural fluid. The measurement cutoff to define positivity is between 40 and 50 IU/L, with a sensitivity and specificity of 95% for this diagnosis. Its usefulness is high in countries with high prevalence, and its positivity would often dispense with a pleural biopsy [11]. False-negative results have been reported in ancient ages; False-positive results in infectious processes (parapneumonic effusion, empyema) and neoplasms such as lympho- mas, adenocarcinomas, and mesotheliomas [9].

### Tumor markers

Among the requested tumor markers and their cutoff points in the pleural fluid is Carcinoembryonic Antigen (CEA) >45 ng/ml, Alpha Feto Protein (AFP) >30 ng/ml, CA125 >35 ng/ml,

CA15-3 >77 IU/ml and CA19-9 >37 ng/ml, which are determined by electrochemical luminescence with their corresponding reagents [10, 12].

Cytology

In cancer patients, 40% of cytological studies of pleural fluid have very low sensitivity and specificity. The performance of the test depends on several factors, such as the type of tumor, the optimal amount of sample for study (between 20 and 40 ml), and the fundamental role of the experience of the cytologist who examines the model [12]. The optimal amount of pleural fluid for a cytological study is 20-40 ml; the technique used for this study is Papanicolau and May-Grünwald-Giemsa staining.

Chest X-ray

The radiological evaluation confirms the suspicion of PE and establishes the diagnostic and therapeutic behavior in the initial phase of PE. Standard chest radiography identifies PD >200 m; in lateral projection, up to 50 ml or more accumulated volume could be detected, usually at the costophrenic angle [13, 14]. Radiographs are also indicated for the therapeutic follow-up of PE in evaluating pleural thickening, pulmonary collapse, pulmonary masses, and pneumo-thorax [13].

Ultrasound

Ultrasound is an evaluation that can be performed at the patient's bedside as an adjunct to conventional chest imaging [15]. It is widely used in patients who cannot adopt the standing position, so it is used daily in medium and highly complex units such as the intensive care unit (ICU). Ultrasound-guided thoracentesis is considered a mandatory method to avoid complica- tions. Additionally, ultrasound is a method with high sensitivity when identifying pleural me- tastases and pleural thickening [6, 13, 14]. The four main characteristics of the pleural fluid are

1) anechoic pleural fluid, 2) complex pleural fluid without septation, 3) the presence of septa- tion in the PE, and 4) homogeneous echoic PE. The transudate appears sonographically as a PE with free, anechoic, and nonseptate fluid; the exudate appears as a septate, echoic, com- plex-looking PE [15].

Computed tomography

Computed tomography (CAT) allows direct identification of nodules, primary neoplasms in the lung parenchyma or in the pleura that are not easily visible on a chest X-ray and allows for distinguishing a pleural effusion from lesions caused by pneumonia, an embolism, or cancer, with a better specificity if the study is contrasted; however, despite its high sensitivity, it is not possible to distinguish between a metastatic pleura and mesothelioma [4]. The pleural analy- sis requires a multislice CT with multiplanar reconstruction, with 3D reconstruction, whose margins must be analyzed through the mediastinal window, taking into account the density of the tissue measured in Hounsfield units (HU). The soft tissue density is 40-400 HU, and that of the pulmonary window is between 500/and 1500 HU. Multislice CT has a sensitivity of 88% and a specificity of 94% for the diagnosis of neoplasms [6, 13].

The usefulness of positron emission computed tomography (PET-CT) allows the visuali- zation of metabolically active tissue to the contrast medium 18 deoxy fluoro glucose (FDG), which is intensely captured by tissues with malignant cells [13]. This study is used to stage tumor pathologies for pleural pathologies with suspicion of malignancy, define the biopsy puncture site, and rule out mesothelioma or pleural asbestosis [6].

## Who should perform drainage by thoracentesis?

The vast majority of the time, thoracentesis is indicated not only to obtain samples for studies but also to relieve symptoms and improve the quality of ventilation. It is necessary for differential diagnosis in patients with neoplastic and infectious processes. In patients with a previous diagnosis of congestive heart failure, nephrotic syndrome, and ascites, where the PE is bilateral, drainage will occasionally not be necessary. Treating the underlying pathology to avoid excessive production could solve this problem [4, 14]. PE is an emergent treatment when it is accompanied by hemodynamic and respiratory compromise. If an emergent puncture is needed, it should be done with the complete technique and in an area that meets the condi- tions of asepsis during the emergency (procedure room, for example; in contrast, if the punc- ture or drainage can be scheduled, the ideal is to perform it in an aseptic area and under ultra- sound guidance.

The puncture technique in thoracocentesis is as follows: after asepsis and antisepsis, the space to be punctured is located, analgesia and local anesthesia are administered, and a cath- eter #14 or 16 is stuck with a 20 or 50 cc syringe. Then, we aspirated and collected the liquid for the study. The juice obtained was divided into 20-40 ml aliquots in sterile containers for cytochemical, bacteriological, and cytological examination [5, 14].

## Malignant pleural effusion

Cytologically confirmed PEs for malignancy represent 50% of cases. It is the initial presenta- tion of an oncological disease as a manifestation of a primary or metastatic lung or pleural tumor in many cases. The cancers most common because of malignant PE are lung, breast, hematological, gastrointestinal, and gynecological tumors [1]. Malignant PE is relapsing and highly symptomatic, so it isn't easy to manage. According to the British Thoracic Society guidelines, the most reasonable options are indwelling catheters, minimal thoracotomy with a chest tube, and chemical pleurodesis with sclerosing substances that cause inflammation and pleural scarring to avoid its accelerated production [16]. For those patients who are in the end-of-life phase with a persistent malignant PE or who have a "trapped lung," with an esti- mated maximum survival time of 3 months, the indwelling chest tube with hydraulic seal and vacuum drainage reduces the time prolonged hospital stays, decreases, and controls the pa- tient's symptoms [16].

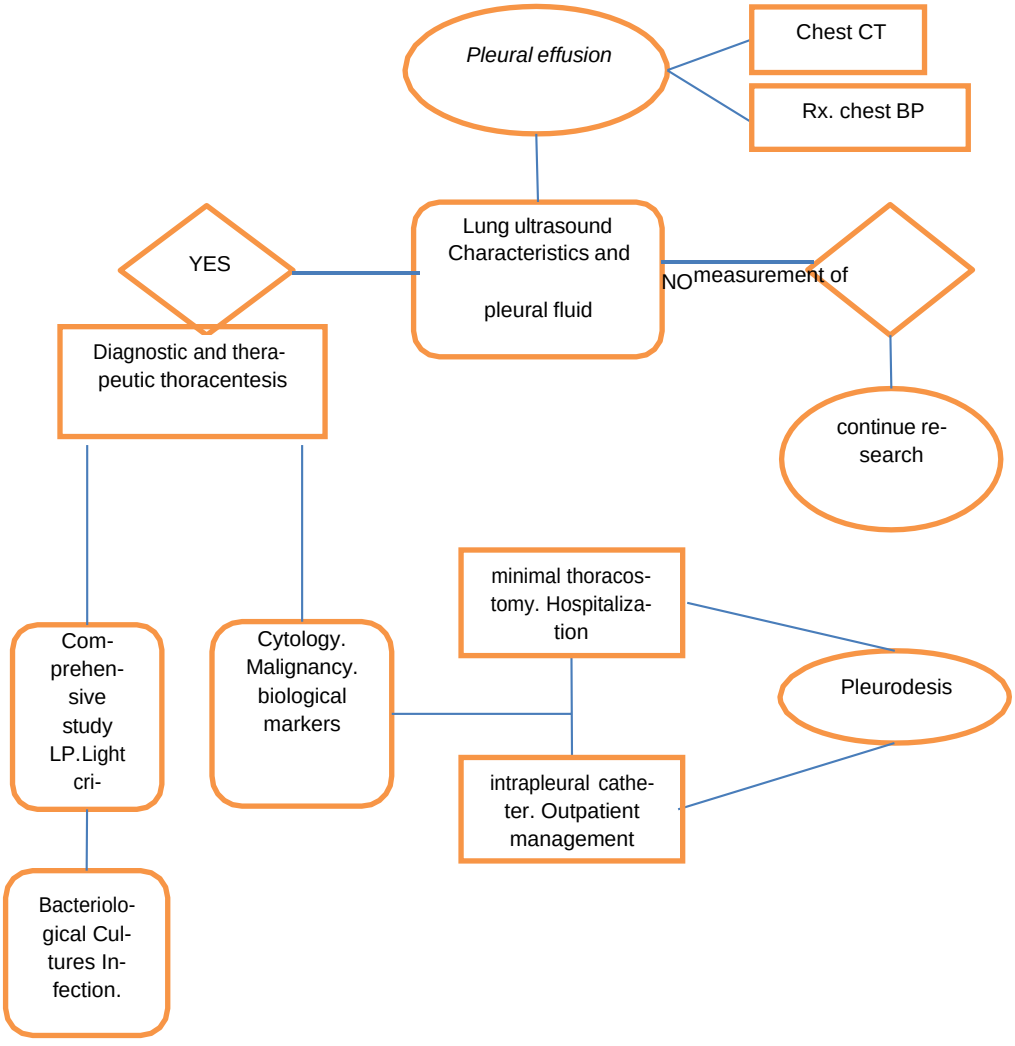
## Pleurodesis

The objective of performing pleurodesis is to provide definitive treatment for the hyperproduction of DP and the relief of symptoms. It is a palliative treatment that is expected to last [17]. According to Wong et al., in a study carried out in Hong Kong, only the placement of the per- manent drainage catheter and the time of permanence were described, and a high rate of autopleurodesia was obtained before the use of any sclerosing substance. One of the recom- mendations of the British Thoracic Society is to instill sclerosing substances into the pleura through the drainage tube as a definitive treatment: talc (magnesium silicate), povidone-io- dine, bleomycin, 5-fluorouracil, tetracyclines, Corynebacterium parvum and mitomycin. Of all

these sclerosing agents, talc has the best results. Installation is often painful due to chemical pleurisy; other complications include fever, acute pneumonitis, acute respiratory failure, and empyema [14, 18, 19], requiring hospitalization for observation. Ideally, no operation is per- formed for patients with thickened pleurae with low fluid production or those that trap the lung [19]. The video thoracotomy technique with tube placement allows a better view of the pleural surface, allowing direct biopsy of the pleural layer and, in turn, dusting with talc or the chosen chemical substance to sclerosis the pleura [18, 19]. It is not yet known whether the method of sprinkling the sclerosing substance has better results than installation through the chest tube.

## Algorithm for the management of malignant pleural effusion

Figure 2. Algorithm for the management of malignant pleural effusion



## Conclusions

For the correct management of malignant PE, malignant cells must be identified by the cyto- logical study and ruled out. Pleural ultrasound allows for defining the volume of the PE. It will enable deciding on drainage at that time, with the possibility of inserting an intrapleural cath- eter, to evaluate the likelihood of sclerosing the pleurae through pleurodesis. However, to reach this decision, it is necessary to analyze each of the details that could play an essential role in good management and definitive resolution or, on the contrary, decide on palliative management, constantly analyzing each case to provide improvement of symptoms and im-prove the quality of life of the patient.


## Abbreviations

PE: Pleural effusion. CT: computerized axial tomography. LDH: Lactic dehydrogenase.

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### Author contributions

Tannia Rivera Rivera: conceptualization, methodology, resources, writing (review and editing), supervision, project management.

Erika Serrano Bueno: conceptualization, methodology, research, resources, writing (original draft), writing (review and editing), project management.

All authors read and approved the final version of the manuscript.


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Does not apply to narrative reviews.

### Consent to publication

This does not apply to studies that do not publish explicit images such as CT scans, MRIs, and physical exam images.

### Conflicts of interest

The authors declare that they have no conflict of interest or competence.

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