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Review article

Malignant Pleural Effusion Pathophysiology, Causes, Epidemiology, and Therapies: Updates Review

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Abstract

Background*. Pleural effusion (PE) is frequently seen in ordinary medical practice, often resulting from various underlying pathological conditions. Lung cancer is the primary etiology of malignant PE, with breast cancer ranking second in prevalence. PE is mostly attributed to many prevalent etiologies, including congestive heart failure, parapneumonia, paramalignant, empyema, and pulmonary embolism. Pleural fluid aspiration facilitates the distinction between various forms of PEs. In addition to addressing the primary pathology, malignant PE management encompasses a spectrum of interventions, including antibiotics, pleurodesis, video-assisted thoracoscopy, early thoracic surgeon consultation, thoracoscopy, and the insertion of a long-term indwelling pleural catheter.* ***Methods****. The evaluation presented below is predicated upon relevant literature published between Jan 2020 and Sept 2023, obtained by a meticulous PubMed, Google, and Google Scholar search for updates about malignant PEs. We used different keywords and expressions concerning malignant PE. We aim to review the pathophysiology, epidemiology, and therapy updates of malignant PEs. The appropriate management of malignant PE requires a thorough exclusion of other differential diagnoses. The available therapy choices have been expanded significantly. These therapeutic choices are affected by the underlying pathology. Despite the great changes in malignant PE treatment, the anticipated future diagnostic tests for the causation of the effusion, enhanced pleurodesis agents, advancements in interventional procedures, and the genetic makeup of the afflicted individuals are expected to expand, dynamically altering the diagnostic and therapeutic choices.*

Keywords: *Malignant Pleural Effusion, Pleural Aspiration, Thoracoscopy, Thoracentesis Pleurodesis, Tunneled Pleural Catheter.*

Introduction

Malignant pleural effusion (PE) is an abnormal fluid buildup inside the pleural space with cancer cells. Although the exact prevalence of malignant PE is unknown, it is not a non-prevalent medical condition. The PE causes significant vary, including benign conditions such as heart failure, pancreatitis, and more consequential occurrences linked to malignancy. Malignant PE presence has prognostic implications. The management of malignant PE and the available therapeutic interventions mostly depend on the underlying etiology, necessitating accurate determination of the cause in every instance.

Malignant PE is a common complication associated with metastatic cancer, impacting over 150,000. American individuals with lung, lymphoma, breast, and metastatic cancers. Approximately 126,825 admissions were linked to this condition in 2012 [1,2]. Malignant PE is a profound disabling condition impacting patients' life quality [3,4]. Most patients experience symptoms, with dyspnea being the most predominant presentation. Other symptoms include cough, chest pain, malaise, weight loss, anorexia, and other constitutional symptoms

that may also be because of the primary cancer [5]. Pleural metastasis most commonly originates from the breast and lung, followed by gastrointestinal tract tumors and lymphomas [1].

The therapies for malignant PE aim at recurrence prevention, symptom improvement, and enhancing quality of life with reduced hospitalization rate and stay. The available therapies can be organized to be utilized together or chronologically (for example, pleurodesis and thoracocentesis). The best therapeutic approach is individualized and must be resolute by considering different factors, including underlying diseases, clinical background, general condition, performance status, sensible access to medical support and devices, and medical and family support.

In this review article, we searched the PubMed, Google, and Google Scholar engines for the recently published articles from Jan 2020 to Sept 2023 about malignant PE pathogenesis, epidemiology, and therapy options updates. To achieve the target of the review, Malignant PE, the pathogenesis of malignant effusion, mechanisms of malignant PE, types of malignant PE, advances in malignant PE treatment, the outcome of malignant PE, and surgical treatment of malignant PE.

Mechanisms of Malignant Pleural Effusion

Each pleural cavity contains around 0.26 mL of fluid per kilogram of body weight, roughly 18 mL in an adult weighing 70 kg [6]. The pleural fluid production is attributed to the parietal pleura, whereas its reabsorption occurs via parietal pleural lymphatic channels. Maintaining normal pleural fluid volume in the pleural space relies on the equilibrium of hydrostatic and oncotic pressures within the systemic and pulmonary circulation and inside the pleural space [7]. Disruptions to the homeostatic balance often serve as the underlying cause for transudative PEs, and it is conventionally believed that exudative PEs arise due to heightened permeability of the pleural membranes and microvasculature [8]. It was noted that the parietal pleural lymphatic channels can enhance their flow rate and reabsorption by a significant factor of 20 times [7]. PE may be conceptualized as a condition characterized by an excessive production that surpasses the typical resorption processes, an interference with the customary resorption mechanisms, or a combination of both [9].

The pleural space is a genuine cavity 10 to 20 μm wide and located between the mesothelium layers of the parietal and visceral pleura [10]. Only the parietal pleura contains stomata, 2-to-12 μm wide apertures between mesothelial cells [11]. The stomata are the typical exit points for pleural fluid, protein, and cells that leave the pleural space [11,12]. These stomata connect directly with lymphatic lacunae roofs, which contain collagen bundles. The lymphatic lacunae converge to form accumulating lymphatics, which drain into lymphatic channels along the ribcage and descend into the mediastinal lymph nodes. The microvessels of the parietal pleura are located closer to the pleural surface (approximately 10-12 μm) than those of the visceral pleura [13], controlling the rate of production and reabsorption of the pleural fluid.

Malignant PE may happen because of initial pleural cancers, mostly mesothelioma, or extrapleural cancers that spread to the pleura. Direct pleura invasion from nearby breasts, lungs, or chest wall cancers is another way that cancer can spread to the pleura and cause PEs. Roughly 10% of people with malignant PE at presentation their tumor site not diagnosed [14,15]. Malignant PE is the third underlying etiology for PE in developed countries, following para-pneumonic and heart failure PEs [14,15]. The existence of malignant PE means that cancer has spread, negatively affecting life expectancy (usually only 3-12 months) [14] and quality of life.

Epidemiology of Malignant Pleural Effusion

The estimated PE prevalence in industrialized nations was 320 cases/million. However, the malignant PE prevalence corresponds to the underlying malignant disease prevalence [16]. Nonetheless, it is anticipated that at least 1.5 million cases occur annually in the US [16]. The global incidence of malignant PE is unidentified; however, it was noted that the incidence of malignant PE in some nations, such as the USA, was predicted to be > 200000 cases/year. Malignant PE is one of the principal etiologies of exudative PEs, ranging between 42%-77% as exudative PEs [17].

A PE appearance is the first indication of malignancy in 13% of patients. Although certain etiologies have a gender preference, it is generally accepted that the incidence of PE is the same for both sexes. Nearly two-thirds of malignant PEs are found in females linked to breast and gynecologic cancers. In the USA, PE in malignant mesothelioma is commoner in

men, likely due to their greater occupational asbestos exposure. In a Chinese study of the in-patient in 2018, PE prevalence was estimated at 0.47%. One of the common causes was malignancy (23.7%), which occurred notably in 60 - 79 years inpatients (13.0%), and in those > 80 years was 5.5% [18]. Racial differences in malignancy and malignant PE may reflect the racial variation in the incidence of the underlying disorder.

Malignancy is globally the second most frequent cause of exudative effusions [19]. The most common causes of malignant EFs include solid organ cancers like lung breast cancer and hematologic diseases like lymphoma. About lung cancer specifically, 15% of patients have PEs at the time of initial diagnosis, and approximately 50% of patients encounter a malignant PE at some point throughout their therapy [19]. More than 125 thousand hospitalizations and > 5 billion US Dollars in healthcare expenses are attributed each year to diagnosing and treating malignant PE [19]. While the presence of the malignant PE typically indicates a poor prognosis with a life expectancy of less than 12 months from diagnosis (as short as 2-3 months in lung/GI cancers or as long as 12 months in hematologic or ovarian malignancies), recent management advances have aided patients and their families in pursuing comfort-based end-of-life care, providing not only relief from breathlessness caused by PEs but also shorter stays in the hospital [20,21]. The goal of therapy is to relieve the difficulty of breathing brought on by this condition since controlling effusions does not change how the disease develops and progresses. These methods have depended on symptom-driven thoracenteses, pleurodesis agents, and indwelling pleural catheters up until now [22].

Etiology

Malignant PE is frequently caused by lung cancer or nearby structures cancer when the cancer cells reach the pleura via direct extension or through the bloodstream. The causes and percentage of the reported percentage of malignant PE are listed in Table 1.

Table 1.

Common causes of malignant PE	**Less Common causes of malignant PE**
Lung cancers (40-50%)	Synovial sarcoma
Lymphomas (20-30%)	Osteosarcoma
Breast cancer (25%)	Low-grade sarcoma
Ovarian cancer (5%)	Liposarcoma
Stomach cancer (5%)	Angiosarcoma
Renal cell carcinoma 1-2%	Epithelioid hemangioendothelioma
Metastases of other cancers	Myxoid chondrosarcoma
Malignant mesothelioma	Ovarian cancer
	Pleural primary cancers
	Malignant fibrous histiocytoma
	Primary malignant melanoma
	Ewing sarcoma
	Thymoma
	Myeloma
	Leukemia

Malignant Pleural Effusion Types

The malignant PE fluid is mostly hemorrhagic; however, serous and serohemorrhagic occur in malignant PE. Hemorrhagic PE is the commonest, most exudative type, with abundant red blood cells and malignant cells.

Another type of PE that occurs in cancer patients is called paramalignant effusion. The paramalignant PE has no cancer cells but happens in people with known cancer. The paramalignant PE happens because of the tumor's indirect effects, chronic obstruction, post-obstructive pneumonia, lymphatic blockage, low albumin levels, vena cava superior syndrome, thromboembolism, and some types of cancer treatment [14,23].

Gross hemorrhagic PEs signify direct participation in the pleura, while serous effusions happen because lymphatics cannot keep up with the fluid and usually leak out. Malignant PEs may have protein levels ranging from 1.5 to 8 g/dl.

Diagnostic Approach of Malignant Pleural Effusion

Most patients presenting with malignant pleural effusion are symptomatic, but up to 25% are asymptomatic with an incidental finding of effusion on physical exam or chest radiography [24]. Breathlessness, the most common presenting symptom, reflects reduced chest wall compliance, ipsilateral diaphragm depression, mediastinal shift, and decreased lung volume [25]. It is important to note that chest pain is a far less common symptom and is mostly caused by malignant affection of the parietal pleura, ribs, and other intercostal structures. Constitutional symptoms, such as weight loss, malaise, and anorexia, typically accompany respiratory symptoms.

A massive PE is characterized by complete or near-complete opacification of one lung on a chest X-ray. It typically presents with symptoms and is often linked to malignancy [26]. Malignant PE diagnosis depends mainly on pleural fluid analysis, cytology, and biopsy to detect the type of tumor, particularly if primary pleural cancer is suspected.

Malignant Pleural Effusion Management

The therapies for malignant PE aim to prevent recurrence, improve symptoms, and enhance quality of life with reduced hospitalization rate and stay [27]. The available therapies can be organized to be utilized together or chronologically (for example, pleurodesis and thoracocentesis). The best therapeutic approach is individualized and must be resolute by considering different factors, including underlying diseases, clinical background, general condition, performance status, sensible access to medical support and devices, and medical and family support.

Managing pleural fluid is a complex process that requires a multidisciplinary approach and careful consideration to prevent complications. Rapid and abundant intrapleural fluid removal can lead to re-expansion lung edema, which might be lethal. To avoid this, experts recommend aspirating < 1500 ml/session of fluid. In cases where thoracentesis does not improve dyspnea, other potential causes should be evaluated, such as underlying lung disease, endobronchial obstruction, pulmonary embolism, and lymphangitis carcinomatosis. To achieve optimal results, it is to ensure that dyspnea is relieved and lung expansion is achieved before fluid re-accumulates and symptoms return. This is typically done using a chest tube and a sclerosing agent. By following these guidelines, patients can receive the best possible care and minimize the risk of complications [14,15]. The local pleural therapeutic options available are listed in Table 2.

Table 2. Local pleural therapeutic measure of malignant pleural effusion.

Method	Description
Thoracentesis	Aspiration of pleural fluid by needle or cannula under local anesthesia
Tube thoracostomy	Tube insertion at mid-axillary line to drain fluid in the pleural or air
Pleural catheter with tunnel	Indwelling catheters inserted intrapleural for frequent pleural fluid draining
Pleuroperitoneal shunt	A shunt between the pleural and peritoneum to drain fluid from pleural to peritoneum, which absorbs fluid to circulation
Drainage and pleurodesis	Complete pleural fluid drainage followed by pleural plyers adhesions induced by chemicals (e.g Talc, bleomycin)
Pleurectomy	Complete or partial surgical removal of the pleura, as I mesothelioma effusion or tumor
Extrapleural pneumonectomy	Excision of the impacted lung, portions of the diaphragm, pericardium, and pleura

Medical Procedures for Malignant Pleura Effusion

Malignant PE management has been facilitated using videoscopic techniques. The techniques vary from the relatively simple act of draining fluid without or with elimination of the pleural space by sclerosing agents' injection into the pleural space. There is no conclusive evidence that surgery offers a definitive advantage over medical pleurodesis. Nevertheless, the comfort level experienced during videoscopic procedures is inferior to straightforward intrapleural tube insertion. Even with Talc, there is potential for an unfavorable response, and additional complications may arise, including pain, pneumonia, infection,

thrombosis, induction of respiratory distress syndrome, and exacerbation of pre-existing cardiovascular conditions, increasing death risk. The interventional therapies are not required in small asymptomatic malignant PE. Therapy of the underlying malignancies by chemo/radiotherapy can produce good PE control, especially in lymphoma, breast cancer, and small lung cell carcinoma. All pleural interventional procedures have undesirable effects on patients; therefore, offering a conservative approach when possible is commonly advisable [28].

Pleural Fluid Drainage (Thoracocentesis)

Thoracentesis consists of pleural cavity drainage using a 14–18 G chest tube. Although thoracentesis may only provide temporary relief due to a high recurrence, it can still be the optimal choice for very frail patients (with an Eastern Cooperative Oncology Group score (ECOG) score of 3-4) who have a poor life expectancy or are not suitable candidates for pleurodesis or insertion of indwelling pleural catheter (IPC) [5,29].

The main advantages of thoracocentesis include the capacity to drain the fluid in the space effectively, the ability to be conducted in outpatient settings, and its methodical simplicity. No specific limit for the fluid size can be drained; however, caution must be applied when draining volumes exceeding 1.5 L. In a study of 185 individuals with thoracentesis-drained malignant PE, they developed pulmonary edema due to lung re-expansion (0.5%), which had no linkage to the size of the fluid drained [30]. Careful monitoring and assessment of symptoms are essential to drain the maximum fluid volume. However, it is equally important to rely on the expertise of healthcare providers to determine the optimal time to halt the fluid drainage process.

Symptoms such as cough, dyspnea, and pain are critical indicators that guide the decision [28]. As such, thoroughly understanding and analyzing these symptoms is essential to ensure the effective and safe implementation of gravitational drainage [28]. Healthcare providers must approach this technique with confidence and a deep understanding of the patient's needs to achieve the best possible outcomes. Thoracentesis is a highly effective procedure when performed correctly, but following the guidelines' recommendations is imperative to minimize potential risks and ensure the best possible outcome [14,15].

Pleurodesis

Pleurodesis is an effective medical procedure that can help patients suffering from symptomatic effusion and improve their quality of life. By creating adhesion between the pleura, this procedure can bring relief to patients with reasonable life expectancy. However, it is important to note that in some cases, such as when there is excessive drainage from the chest tube or the patient has a trapped lung, pleurodesis may not be successful. In such instances, alternative treatment options can be explored to ensure the best possible outcome for the patient [31]. Although various methods of creating pleurodesis have been used, there has yet to be a consensus on the ideal approach. Despite the challenges posed by surgical pleurodesis and the temporary solution of chemical instillation, we remain committed to finding new and innovative ways to heal the pleura without causing further injury, providing better patient outcomes.

In most cases, fluid draining from the pleural cavity is necessary to treat a malignant PE. This is done by inserting a chest tube. After complete fluid drainage, a sclerosing agent is introduced between the pleural layers, inducing an inflammatory reaction to merge the pleural layers. After the drainage diminishes, the chest tube can be detached. Usually, this therapy method requires a hospital stay of 7 days.

Several agents, including silver nitrate, tetracycline, bleomycin, hydrogen peroxide, mepacrine, iodopovidone, mitoxantrone, hypertonic saline, and corynebacterium parvum, were studied for pleurodesis. However, talc is considered effective and commonly used for pleurodesis [32–35]. Clinical studies have noted that using talc poudrage via thoracoscopic or chest tube slurry delivery method resulted in similar successful outcomes [31] compared to the usual blind chest tube Talc injection with saline.

Talc-induced pleurodesis is a medical procedure that involves talc instillation via a chest tube, IPC, or video-assisted thoracic surgery (VATs). This procedure is performed after lung expansion, confirmed by radiologic study. The lung expansion usually occurs 24-36 hours after the tube placement. The pleurodesis, used to treat malignant PEs, can be completed using small or large-bore tubes (12-14 and 20-32F). However, the size of the chest drain does not seem to affect pleurodesis efficacy and success, although a smaller tube introduction causes less pain [36]. Lidocaine is the most used local anesthetic, administered before

the pleurodesis at a maximum dose (3 mg/kg) [5]. Typically, 3-6 g of sterile talc is mixed in 100 ml of normal saline, and the tube is clamped for 1-2 hours [5,37]. Although the tube removal is based on the drained fluid volume, the tube removal time does not impact the pleurodesis result significantly. Although most malignant PE pleurodesis requires hospital admission, some people have talc-induced pleurodesis by small-bore tubes safely managed in an outpatient clinic with regular outpatient follow-up [38]. Intrapleural talc poudrage delivery is also achieved by VATs. An atomizer device spreads 3-6 grams of talc between the pleural two layers [5]. One of the main benefits of this procedure is that it can help with diagnosis. However, it is an invasive procedure unsuitable for patients with low-performance status or significant comorbidity. Pain and fever are common after pleurodesis, and talc pleurodesis-associated complications include acute pneumonitis, hypoxia, acute respiratory distress syndrome, respiratory failure, and death [31,39]. Talc pleurodesis fails in 30 to 50%, but further pleurodesis can be performed with the same or other mentioned different agents [14].

There is still much debate in the medical community regarding the most effective pleurodesis technique. In a randomized controlled trial (RCT) involving 501 patients, no significant difference was found between the success rate of the two pleurodesis techniques after 30 days [37]. However, the subgroup of patients with breast and lung malignancy achieved better pleurodesis with VATs talc [37]. In a meta-analysis by Clive et al., talc poudrage was more effective [40]. Similarly, based on their meta-analysis, another study found talc poudrage more effective [41]. Therefore, based on the literature review, both techniques are considered safe and effective. However, it is vital to consider the patient's background, performance status, and the need for pleural biopsy before deciding the most suitable technique.

IPCs, or indwelling pleural catheters, are medical devices that allow patients to drain PEs at home by themselves using vacuumed bottles with the help of family members or caregivers. However, the catheter must be placed in a hospital setting, either in inpatient or outpatient care. The insertion involves using ultrasound guidance, the Seldinger technique, and tunneling.

Intercostal pleural catheterization has effectively controlled the symptoms of malignant PE and improved life quality scores in different studies [3,42]. In some studies, IPC has been compared with pleurodesis and found to be similarly effective. An RCT comparing the two techniques regarding hospitalization durations found a nonsignificant statistical difference, favoring IPC [42]. A bigger randomized trial compared IPC with talc's pleurodesis regarding dyspnea improvement found a non-significant difference [43]. Overall, IPC is an excellent tool that might be utilized in patients with collapsed lungs who require frequent thoracocentesis. Furthermore, it can be an alternative technique for pleurodesis.

Surgical Therapy of Malignant Pleural Effusion

Pleurectomy

A parietal pleurectomy (PPE) or lung decortication is a very efficient surgical technique for effectively managing the reoccurrence of an effusion. The procedure is conducted using either thoracoscopy or thoracotomy. Optimal outcomes are attained when the main abnormality is a breast carcinoma or a malignant mesothelioma. Nevertheless, its efficacy is restricted for lung cancer-associated malignant PE. Although PE treatment is complemented by common consequences such as empyema, heart failure, or hemorrhage at rates as high as 34%, it remains a dependable choice. Despite notable mortality rates (9%) in inpatients and 17% within three months for all causes, this procedure is only conducted on very suitable individuals who lack response to chemical pleurodesis, have a life expectancy exceeding six months, and have excellent general health [15]. When the decortication is performed as a supplementary pleurectomy treatment, complications rise to 70% and a 20% mortality rate following surgical pleurectomy [15]. Hence, it is crucial to conduct a comprehensive evaluation to choose suitable individuals for this procedure.

A study was undertaken on 19 patients diagnosed with malignant PE who resisted standard treatment modalities [31]. The patients underwent thoracoscopic pleurectomy using a single port. All patients had a successful pleurectomy surgery without any problems, morbidity, or death. The total success rate of thoracoscopic pleurectomy by uniport catheter was 91.4%, surpassing the thoracoscopic talc powder success rate. Consequently, according to their research results, the authors highly advocate for pleurectomy with uniportal VATs as an effective pleurodesis technique for malignant PE.

Approximately half of lung cancers are accompanied by malignant PE, which is linked with a worse prognosis compared to individuals without malignant PE [14,15]. A study of 771

patients with non-small-cell lung carcinoma and malignant PE revealed that these patients had a mean survival of 10 months, and only 2% had a five-year survival rate. Consequently, malignant PEs were reclassified as M1a or Stage IV in the 7th edition of the Tumor, Node, Metastasis (TNM) staging system [44]. Patients diagnosed with distant metastases (M1b) and malignant PE have a median survival of approximately three months. Conversely, patients with M1b without malignant PE have a higher median survival of five months [45]. Trapped lung is common in lung malignancies where pleurodesis is not recommended, where the ideal therapy is IPC.

An important factor contributing to both paramalignant conditions and malignancy-related pulmonary embolisms is the obstruction of lymphatic fluid flow from the pleural space. This blockage can occur in various places, such as the parietal pleura stoma, mediastinal lymph nodes, and mammary draining lymph nodes. The infiltration of pleural tumors into the lymphatic system causes an inflammatory reaction, increasing micro-capillary permeability [15]. Surgical, radiological, and chemotherapy as a signal therapy option or combination are suitable to minimize the risk of malignant PE due to these obstructions.

It is important to note that individuals with reduced EGFR who have anaplastic lymphoma kinase fusion are more susceptible to malignancy-related pulmonary embolism. Patients with EGFR or ALK abnormalities must be treated with tyrosine kinase inhibitors, such as gefitinib or erlotinib, as they respond more favorably to these drugs. Erlotinib is highly effective in penetrating the pleural space, making it essential to conduct tests on malignant PE fluid to detect these mutations, which can guide treatment protocols. Based on the available evidence, we strongly recommend using IPC in cases with confined lungs and conducting tests for EGFR and ALK mutations in patients diagnosed with adenocarcinoma. These measures have the potential to alter the approach to therapy significantly and are critical for successful treatment.

Indwelling pleural catheter (IPC)

Home IPC is a highly effective treatment approach for malignant PEs, allowing for rapid symptom relief, improved life quality, and significantly reduced hospitalization time. This technique suits stable patients who must drain the recurrent PE at home.

IPCs offer a novel approach to managing symptoms in malignant PE. These catheters, made of silicone and ranging from 15.5 to 16F in size, feature a fenestrated proximal end implanted into the pleural space and a one-way valve at the other end. By enabling intermittent pleural drainage, IPCs are an attractive choice for individuals with trapped lungs or failed pleurodesis. Evidence shows that IPCs are a preferred first-line therapy for malignant PE, surpassing pleurodesis. Notably, IPCs are used in ambulatory patients, making them an excellent option for outpatient care [14,43].

Spontaneous pleurodesis develops in up to 70% of patients with IPCs previously having full lung expansion, following which the IPC can be removed [14,46]. Complications after using IPCs are rare (about 12%) and mostly minor (e.g., cellulitis, IPC-related pleural infection, and catheter blockage). Catheter tract metastases occur around 10%, particularly in mesothelioma, but can be managed with radiotherapy [39,47].

Shunting

A pleuroperitoneal shunt (PPS) can be a life-changing device for patients struggling with a trapped lung or failed pleurodesis. PPS consists of two catheters introduced into the pleural and peritoneal spaces; A one-way valve connects the pump chamber. The pump is compressible; it transferences fluid from the pleural to the peritoneal cavity, providing much-needed relief. Studies showed that PPS is an effective alternative to pleurodesis, providing symptom relief in 95% of patients. While there is a risk of complications, such as occlusion, which can occur in up to 25% of cases, shunt revision, removal, and/or replacement can resolve these issues. However, with the advent of IPCs, the use of PPSs has significantly decreased. While IPCs are a promising alternative, PPS remains a viable option for patients who have exhausted other options. If a patient with malignant PE struggles with a trapped lung or failed pleurodesis, the PPS technique might be an option [14].

Therapy of Malignant PE Effusion of Specific Diseases

Lung and Pleura Cancer

Lung cancer with malignant PE has a worse prognosis [14]. In a study of 771 non-small-cell lung carcinoma patients with malignant PE, they lived an average of 10 months, and only 2% lived a five-year. As stated earlier, the International Association for the Study of Lung

Cancer (IASLC) Lung Cancer Staging Project reclassified malignant PEs predicting life expectancy [48]. Lung cancer-trapped lung treatment is IPCs, as pleurodesis is not the best option [14].

The most common pleural cancer is adenocarcinoma, that causes malignant PE. Lung cancer with malignant PE autopsy examination showed visceral and parietal pleural metastases, although it is very rare. Visceral pleural metastatic foci in lung cancer may spread through vascular embolization or due to the migration of tumor cells from the visceral to the parietal pleura layers because of direct adhesions.

Patients with epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) fusion are at an increased risk for malignant PE [45,48]. Tyrosine kinase inhibitors (gefitinib or erlotinib) are more successful in treating ALK or EGFR mutations, and erlotinib penetrates the pleural cavity well. Since these mutations are easy to detect and advise on, malignant PE patients should have them assessed [14,49]. These data support IPC for patients with restricted lungs and EGFR and ALK mutation testing in cancer patients, which may change therapeutic strategies.

Gefitinib and erlotinib are an EGFR inhibitor. They act via interrupting signaling mediated by the epidermal growth factor receptor (EGFR) in target cells. Hence, they are only effective in cancers with mutated and overactive EGFR. Unfortunately, gefitinib resistances might occur when other mutations are present.

PE occurs in almost 90% of mesothelioma individuals upon first admission. To alleviate dyspnea and chest pain, palliative treatment is necessary, and a parietal pleura biopsy is usually required for diagnosis. While pleurodesis results cannot be precisely predicted in mesothelioma patients, it is unlikely to be successful. It is common for mesothelioma patients to have a trapped lung, but IPCs provide a favorable alternative. Also, pleurectomy/decortication and EPP are viable treatment options [14].

Pleural sarcomas certainly develop in the pleural. Despite the challenge in identifying these tumors, immunohistochemistry and molecular testing can accurately help to diagnose most spindle cell tumors of the intrapleural cavity. An accurate diagnosis is essential for these neoplasms as they require unique treatments and have different prognoses. While treatment is difficult, the principle is complete excision with 2-3 cm safe margins resection. Additionally, adjuvant radiotherapy and chemotherapy are commended for incomplete resection and insufficient margins [14].

Thymomas Associated Malignant Pleural Effusion Therapy

Thymomas do not commonly spread; however, if they do, they often metastasize into the pleura. Fortunately, the outcomes of thymoma pleural metastases are better than those of other primary tumor metastases. Pleural implants may appear several years after removing both encapsulated localized and invasive thymomas, yet pleural recurrences are uncommon, accounting for < 10% of thymomas resected. Pleural involvement may occur after thymoma removal or due to the spread of tumor cells during surgery, principally if the mediastinal pleura was opened. Proper care and monitoring can minimize the risk of recurrence, and the patient can have a good prognosis [50].

A study evaluated 20 thymoma individuals who underwent thymectomy and were re-operated for metastases of pleura [50]. The partial pleurectomy was conducted for the pleural implant. A pleural catheter was introduced in wide pleural involvement, and intrapleural heated chemotherapy was applied. After the pleural metastases resection, the results revealed a 5 and 10-year survival rate of 43.1% and 25.8%, respectively. Diaphragmatic involvement represents a more advanced disease, making the outcome worse. Others reported that following extrapleural pneumonectomies and total or partial pleurectomy, Five-year survival after resection ranges between 71-92%. The surgical intervention in these cases usually depends upon the tumor extent. Neoadjuvant or adjuvant chemotherapy is recommended. Moreover, radiotherapy is also suggested if there is a residual disease or the surgical margin is positive for thymoma cells [51].

The Thymic Working Group of the European Association of Thoracic Surgeons (ESTS) thoroughly investigated the effectiveness of surgical pleural metastases of thymic epithelial tumor resection in 152 patients across 12 centers between 1977 and 2014. The study revealed that 70.4% of the patients had pleural involvement, and about 29.6% had pleural metastases in the first intervention. Pleural metastases were primarily caused by thymoma (88.8%) and, to a lesser extent, by thymic carcinoma (11.2%). The surgical procedures performed were extrapleural pneumonectomy in 40 patients, total pleurectomy in 23, and partial pleurectomy in 88 individuals. The survival rate was remarkably improved (96.4%,

91.0%, 87.2%, and 62.7%) for 1, 3, 5, and 10 years, respectively. It was noted that relapse-free and total survival for patients who underwent extrapleural pneumonectomy, total, or partial pleurectomy were not statistically significant. However, thymic carcinomas had a greater impact on overall and relapse-free survival, especially with incomplete resection [52].

It was noted that surgical therapy for recurrent pleural metastases had considerably better overall survival rates when compared with pleural metastases at the first operation. The observed difference was due to the tumor being more aggressive and involving the pleura in the initial stages [52]. It is crucial to note that complete resection remains the ideal therapy for thymic epithelial tumors presented by pleural involvement, regardless of the surgical method chosen. Previous studies have noted that patients who undergo complete resections have a better chance of survival, even in recurrent resections [53]. Therefore, it is imperative to prioritize complete resection when possible. Additionally, some authors suggest using hyperthermic intrapleural chemotherapy with pleura surgical resection to decrease recurrences of PE in thymomas [50].

Breast Cancer Associated Malignant Pleural Effusion Therapy

Breast cancers have a 25% probability of developing malignant PE, which can be unilateral or bilateral. It is crucial to note that the median survival of patients depends on the response to systematic treatment, and the average survival after PE development due to breast cancer pleural metastases is approximately 15 months. Therefore, instant action must be applied. Palliative techniques like recurrent thoracentesis, talc pleurodesis, or permanent pleural catheter are commonly practiced in poor outcomes patients. These palliative procedures do provide symptomatic relief from breathlessness via unceasing fluid drainage. However, pleurectomies are the most effective in improving breast cancer survival with malignant PE [54]. Thus, pleurectomy is always promptly recommended in breast cancer-associated malignant PE [14,55].

Renal cell carcinoma Associated Pleural Effusion Therapy

Renal cell carcinomas (RCC) are an uncommon cause of PEs, accounting for only 1% - 2% of malignancy-related PE. However, the PE is more due to lung hematological metastasis than the direct tumor metastasis to the pleural. Furthermore, isolated pleural metastases without concurrent lung metastasis are rare. One explanation is that the hematogenous RCC cells enter the bloodstream via the Batson venous plexus. Batson venous plexus is a veins network without valves surrounding the vertebral column and spinal cord. This plexus is communicated with other veins (azygos, bronchial, hemiazygos, and intercostal veins). It is worth noting that RCCs leading to malignant PEs are more common in clear cell and papillary RRC tumor types, which tend to be high-grade. In some cases, tumor invasion of the intercostal blood supply and drain vessels can lead to spontaneous hemothorax in patients with RCC metastasis [56]. Surgery is unequivocally the preferred treatment for localized metastases because RCCs, apart from interferon therapy, are usually unresponsive to chemotherapy [56].

Lymphoproliferative Diseases Associated Malignant Pleural Effusion Therapy

Pes are prevalent lymphoma complications. PE in lymphoma might be due to pleural lymphoma (only 0.3–1%), infection, hypoproteinemia, and/or lymphatic return obstruction. It indicates a poor prognosis despite its rarity as the initial and primary manifestation of lymphoma [57–60].

Around 20% to 30% of lymphoma patients develop PE. In contrast, multiple myeloma and leukemia rarely cause PE [36]. Hodgkin's disease leads to malignant PE via lymphatic obstruction. In contrast, malignant PE in non-Hodgkin lymphoma is likely because of direct pleural invasion and/or lymphatic obstruction. Primary PE in lymphoma, which is uncommon, consists of two primary types: primary PE and pyothorax-associated lymphoma [61]. Chylothoraxes account for < 10% of PEs in lymphoma.

PE is reported as a prognostic factor in lymphoma, negatively impacting outcome. The recommended therapy course is systematic chemotherapy, with mediastinal radiotherapy if mediastinal lymph nodes are affected. Even though lymphomas are successfully responsive to chemotherapy, pleurodesis and tunneled pleural catheters are/are necessary for approximately 37.5% [27].

For cancer-associated chylothorax, conservative interventions are typically employed, such as low-fat, medium-chain triglyceride-dietary regimens or a tube thoracostomy with total

parenteral nutrition to minimize the recurrence likelihood. In comparison, chemotherapy may effectively resolve chylous PEs secondary to lymphoma, IPC, or pleurodesis, which can be considered if chemotherapy fails. The VATS procedure is conducted for the unresponsive chylothorax to therapy, allowing for satisfactory fluid drainage from the intrapleural cavity, and at the same sitting, pleurodesis can be conducted [14].

Ovarian Cancer Associated Pleural Effusion Therapy

Ovarian cancer affects 1 in 70 women. It can spread to other body parts, including the pleura. To treat advanced-stage ovarian cancer, adjuvant therapy, and cytoreductive surgery are used effectively. Over 30% of Stage IV ovarian cancer females have PEs [27]. In treating ovarian cancer-related malignant PE, computed tomography scans are often used to assess the extent and the size of thoracic disease, which would prevent surgical cytoreduction of abdominal lesions if large. However, the radiographic scanning alone to evaluate intrathoracic lesions and the extent of diaphragmatic pleural involvement still needs further evaluation.

The existence of the macroscopically detected intrathoracic disease manipulates the patient's therapy strategies, especially if unresected tumor deposits > 1 to 2 cm, which could result in unsatisfactory disease clearance following intra-abdominal cytoreduction. VATS can detect the burden of pleural tumors, enable intrathoracic cytoreduction, and evenly reveal gross tumor remnants in the pleural surfaces and cavity, making complicated abdominal surgery unnecessary [14,61–64].

The efficacy of the thoracoscopy strategy for advanced epithelial ovarian cancer therapy was investigated. A study confidently demonstrated the potential benefits of performing VATS simultaneously with primary cytoreduction in 30 patients to detect intrathoracic disease and assess the possibility of cytoreduction [62]. The study unequivocally demonstrated that patients with progressed cancer who underwent thoracoscopy had significantly longer survival rates than the ones who did not have the procedure. Thoracoscopy is an effective tool for accurately assessing intrathoracic disease severity and performing full cytoreduction in rare cases. The size of the residuals during cytoreductive surgery is a crucial determinant of survival. Survival rates may be reduced in cases with hidden intrathoracic disease larger than the largest recognized abdominal tumor. The study also found that the morbidity risk associated with thoracoscopy was remarkably low [62].

In summary, detecting pleural metastatic lesions is required when treating ovarian cancers. Most cases are diagnosed late and usually advanced, despite the pleura being a common site for metastasis. Therefore, it is usually advisable that every patient should undergo VATS. This procedure is highly recommended as it allows for early pleural metastatic lesion detection, helping to plan more effective treatment strategies [27].

In short, every patient deserves a treatment approach that caters to their unique situation. In the case of malignant PEs with pleural metastases, the therapeutic approach depends on several factors. These factors include tumor type, patient's overall performance, and expected survival. Knowing that options are available even in the most challenging cases is reassuring. Pleurectomy VATs or thoracotomy may be an option in pleural breast and ovarian cancer deposits. Furthermore, extrapleural pneumonectomy is advised for thymoma pleural metastases. Recurrent thoracentesis is also viable for patients with survival times < 45 days. It is possible to overcome this disease with the right approach and emerge victorious.

Malignant Pleural Effusion Outcome

Several variables associated with worse outcomes of malignant PE were reported, including pleural fluid with acidotic PH, hypoalbuminemia, low glucose levels, hypoxia, and leukocytosis [64]. Clive et al. assessed the prognostic factors in 789 patients, including the ECOG performance and LENT scores [65]. A LENT score of 0-1 signifies a reduced risk, 2-4 signifies a moderate risk and 5-7 implies an elevated risk [15].

The duration of survival after diagnosis varies between 3 and 12 months. It is influenced by factors such as the specific type of malignancy, tumor features, the degree of the illness, the presence of other medical conditions, and the composition of the PE [5,65]. Notwithstanding the restricted prognosis, forecasting an individual's lifespan is arduous, intensifying the challenges of pursuing palliative care and enhancing the quality of life. A study revealed a significant association between mortality, PE, and poor performance status [66].

Specifically, lower Karnofsky scores were shown to be indicative of shorter survival times. The median survival time was 1.1 months for those with a Karnofsky score below 30, while

those with a score over 70 had a median survival time of 13.2 months [66]. In a recent investigation, researchers utilized performance status, specifically the ECOG, along with the LENT score. The study revealed that the LENT score exhibited superior prognostic capabilities in predicting survival outcomes compared to using performance status (ECOG) [65]. LENT is a validated score that predicts survival more accurately than ECOG PS alone, aiding clinical decisions for diverse patients [65,67].

Conclusion

Confidently managing malignant PE requires careful attention to the patient's symptoms, underlying cancer, primary tumor site, and general status. Most of the available therapies for PE are symptomatic; however, primary disease surgical removal, chemotherapy, and radiotherapy in certain malignancies effectively control the primary disease and PE treatment and recurrence prevention. The availability of IPCs, day-care clinics, and home support is crucial in determining the most effective treatment approach.

The survival rate is affected by malignant PE. Hence, early detection and therapy improve outcomes and patient's life quality. Although the LENT score for Malignant PE scoring is important, further new scoring systems must be validated.

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