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REVIEW

Interventional management of recurrent malignant pleural effusion: state of the art in 2021

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ABSTRACT

OBJECTIVE: This narrative review aims to describe and compare different interventional methods for the management of recurrent malignant pleural effusion and offers perspectives for the future era.

BACKGROUND: Dyspnea as a result of the recurrent malignant pleural effusion is one of the main factors decreasing the quality of life in patients with oncologic diseases. To date, there is no strict guideline for the management of malignant pleural effusions.

RESULTS: Several different techniques are available to prevent production of the effusion or to provide intermittent drainage, however, the principle of these methods remains palliative. The choice of treatment in any patient depends mainly on the preferences of the patient, speed of the fluid production, expandability of the lung, and predicted survival of the patients. The interventional methods of managing malignant pleural effusions are described in detail, including thoracocentesis, chemical pleurodesis, talc poudrage pleurodesis, slurry pleurodesis, thoracoscopic procedures, indwelling pleural catheters, implantable pleural ports, and pleuroperitoneal shunting.

CONCLUSION: Pleurodesis and fully implantable devices such as pleural ports may become the most useful techniques in the future, mainly because of better comfort for the patients and no need for repeated pleural punctures *(Ref. 55)*. Text in PDF *www.elis.sk*

KEY WORDS: malignant pleural effusion, pleurodesis, thoracoscopy, pleural catheters, ports.

Introduction

Malignant pleural effusion (MPE) is defined as a pleural effusion containing malignant cells or as a pleural effusion in case of the neoplastic involvement of the pleura even without positive fluid cytology. Postmortem studies suggest that the majority of pleural metastases are caused by tumor emboli to visceral pleura with a potential involvement of the parietal pleura (1), followed by other mechanisms such as direct invasion of the tumor, hematogenous spread to parietal pleura, and involvement of the lymphatic nodes. Paramalignant pleural effusion is defined as a pleural effusion that occurs in oncologic patients due to various causes (secondary to pulmonary embolism, post-obstructive pneumonia, lymphatic obstruction, etc.) but without direct neoplastic involvement of the pleura.

The incidence of the MPEs is over 100,000 people in Europe and over 150,000 in the United States (2, 3) each year, which puts a major financial burden on the health systems. According to one postmortem series, MPEs were found in 15 % of the patients who died with malignancies (1). It is most common in patients with lung and breast cancer (50–65 % of MPEs) (4–6), followed by lymphoma, gynecological malignancies, mesothelioma, etc. (5). In 5 to 10 % of MPEs, no primary tumor is identified (7). With the increasing incidence of malignant diseases and increase in survival of patients in recent years, not surprisingly, a trend towards an increasing incidence of malignant pleural effusions has been observed.

MPE is a sign of advanced-stage disease and is associated with an unfavorable prognosis with the median survival from 1 month to 12 months, depending on the type of cancer (8, 9). The worst survival rates are reported in patients with lung cancer and the longest in patients with mesothelioma and hematological malignancies (9). Survival rates in patients with non-small-cell lung carcinoma (NSCLC) have significantly improved over the last few years due to the arrival of targeted therapies (10).

A vast majority of the MPEs are exudates according to Light's criteria (11), but in a retrospective study by Ryu et al around 3 % (12) of the patients have transudative MPE, which can consequently lead to prolonged diagnosis time because of the missing cytology.

The expandability of the lung is an essential condition for the success of pleurodesis. It can be easily examined by pleural manometry (standardized by Doelken and colleagues (13)) or by measuring diaphragmatic excursions and velocity of diaphragm

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contraction using M-mode ultrasound during thoracocentesis (14). According to the official ATS/STS/STR

Clinical Practice Guideline, non-expandable lung (NEL) occurs in one-third of MPE patients (15). There are two types of NEL, namely lung entrapment and trapped lung. A trapped lung is caused by the formation of a fibrous peel on the visceral pleura (in the absence of both malignancy or active inflammation of the pleura) that mechanically prevents the expansion of the lung. Lung entrapment is caused by active pleural or lung inflammation, infection, or malignancy. The underlying malignant or inflammatory disease is the primary clinical issue in these conditions (16).

Contrary to earlier ideas, it has been proven that NEL is not an irreversible state. The lung can expand with a latency of few days after drainage or after a longer time interval as a result of cancer therapy. In the Australasian Malignant Pleural Effusion 2 trial (AMPLE-2), patients with NEL could even develop autopleurodesis especially if the drainage is performed on daily basis through an indwelling pleural catheter (IPC) (17, 18).

Symptomatic patients with MPE display progressive dyspnea, cough, chest pain, but up to a third are asymptomatic (7). Many patients also suffer from weight loss, anorexia, and malaise because of the advanced phase of their primary illness.

Since 2013, physicians can calculate the predicted survival of their patients using the LENT score (9) and choose the best option for the management of the MPE, considering also its cost-effectiveness. The score is based on the evaluation of LDH levels in pleural effusion, ECOG-PS values, neutrophil-to-lymphocyte ratio and tumor type. The clinician is then able to split patients into 3 groups, namely those at low, medium, or high risk with an average survival of 319, 130, and 44 days, respectively. This distribution then helps to consider individual palliative-therapeutic modalities.

Materials and methods

An extensive literature search using Pubmed and Scopus databases was performed by the authors. The search period was from 1970 to date and the searched terms were "malignant pleural effusion", "recurrent pleural effusion", "interventional management" AND "pleural effusion". The abstracts were extracted first, checked for relevance, and subsequently, the full texts of the selected manuscripts were retrieved using the hospital and university library sources. All authors participated in the literature search and final selection of the articles used for the purpose of this narrative review. A total number of 55 articles were used as references.

Therapeutic options

Thoracocentesis

Thoracocestesis, first described in 1852, is a relatively simple and safe procedure that can be performed in an outpatient setting with minimal training. This procedure has no absolute contraindications. Relative contraindications include small effusions (separation between the chest wall and lung less than 1 cm), coagulopathy, anticoagulation therapy, and mechanical ventilation. Pleural fluid is drained (recommended up to max. 1500 mL owing to the risk of the re-expansion pulmonary edema) through a needle or plastic cannula attached to an extension thin tube after local anesthesia. The recommended method of puncture uses ultrasound guidance (19). The most common complications after thoracocentesis are pneumothorax (less than 2 % (1, 4)), infections (empyema, infection of the skin), bleeding, hemothorax, re-expansion pulmonary edema, and spleen or liver laceration. The risk of complication rises with the number of thoracocenteses. This method may serve as the primary therapeutic modality and is further preferred in patients who have slow fluid accumulation, predicted short survival or poor performance status that excludes more invasive methods. The disadvantage of this method is that the patient is dependent on the hospital care and the future accumulation of the fluid is not prevented. Although its effect on patient dyspnea is generally positive, the improvement in oxygen saturation after the procedure is not statistically significant (20).

Chemical pleurodesis

Chemical pleurodesis is performed to obliterate the pleural space and thus prevent the production of the effusion. Talc pleurodesis is the most effective form of chemical pleurodesis in MPE (21, 22). Other commonly used sclerosing agents are tetracycline, doxycycline, and bleomycin.

The most common adverse events are chest pain and fever. Fever typically occurs 4 to 12 hours after the procedure and may last for 72 hours. Acute respiratory distress syndrome (ARDS) is the most severe adverse event. It was proven that talc preparations with predominantly small (< 25 μm) particles can cause substantial inflammation of the lung and hypoxemia. Therefore, it is recommended to use only preparations with calibrated large-sized particles for clinical use (23). Patients undergoing talc pleurodesis should be in a good nutritious state, without active inflammatory disease, not receiving corticosteroids or the chronic dose of the corticosteroids should be reduced as they may prevent the desired inflammatory response (24). Only patients without evidence of bronchial obstruction or trapped lung, with the evidence of a complete re-expansion of the lung, are indicated for pleurodesis. There are three options for administering talc into the pleural cavity, namely pleuroscopic talc poudrage, slurry pleurodesis, and VATS with pleurodesis.

Talc poudrage pleurodesis during pleuroscopy

Talc poudrage pleurodesis was first reported in 1935 (25). It can be performed with local anesthesia under conscious sedation. The trocar is inserted into the pleural cavity and subsequently, both parietal and visceral pleurae can be examined and MPE may be aspirated by a semi-flexible or rigid videopleuroscope/pleuroscope. After a thorough aspiration, approximately an amount of 4 g of sterile talc is administered. The drainage system is usually connected to an active suction after the procedure with the intent to quickly remove residual periprocedural pneumothorax and enable apposition of the parietal and visceral pleurae to obtain maximum pleurodesis effect. The success rate of this procedure is about 68–78 % (26, 27). Failures of pleurodesis in these studies were usually due to incomplete pleural drainage, trapped lung, dislocation of the chest tube, or early death. Often, this group of patients also

has a low willingness to undergo, albeit minimally invasive procedures, which is understandable due to the nature of their condition.

Slurry pleurodesis

Chest-tube (slurry) pleurodesis is a less invasive method of chemical pleurodesis. First, a chest tube is installed into the pleural cavity with the intent to evacuate pleural fluid. Subsequently, the talc is administered through the chest tube. There is no substantial evidence of the inferiority of slurry pleurodesis to pleuroscopic poudrage pleurodesis. According to a retrospective study by Fortin et al which studied hospitalizations for MPE during 2012 based on data from the Canadian national register, slurry pleurodesis was performed more frequently than pleuroscopic talc poudrage (57 vs 43 %, $p < 0.001$), and it was associated with a longer hospital stay (4.9 vs 5.9 days, $p < 0.001$). However, the cost-effectiveness was the same (28). A recent multicenter randomized clinical trial compared the efficacy of thoracoscopic talc poudrage and talc slurry application through the chest drain on the development of pleurodesis in 330 patients (29). Both methods were found to be equally effective with a failure rate of 22 % and 24 %, respectively.

VATS with pleurodesis

The most invasive but safe method of pleurodesis with low morbidity (30, 31) is similar to pleuroscopic poudrage pleurodesis. It uses larger trocars under general anesthesia. An advantage of this method is a more complete view into the pleural cavity with the possibility of performing more complicated biopsies of the lung and selected hilar lymph nodes. In patients with trapped lung due to adhesions, the lysis of the adhesions is feasible using the graspers with either surgical pleurodesis or pleurectomy/lung decortication in selected cases. Duration of chest-tube drainage after VATS pleurodesis in comparison with slurry pleurodesis was shorter according to a study by Luh et al (32). The success rate of VATS talc pleurodesis is reported to be 93 % according to a retrospective study (33). Patients with poor performance status or those who could not tolerate one-lung ventilation are contraindicated. The most common postoperative complications (reported in 3–25 %) are chest pain (25 %), fever (15 %), prolonged air leak (4 %) and empyema (1.5–4.5 %) (31).

Indwelling pleural catheter (IPC)

The indwelling pleural catheter is a relatively new intervention for managing patients with MPE. The most widely used 15,5Fr PleurX catheter was first approved by the FDA in 1997. Initially taken as a second-line treatment for patients with MPE after failed pleurodesis or patients with NEL, not only did it expand its role to both first-line treatment and chemical pleurodesis with no significant difference in the quality of life (26), it also received an approval for use in all recurrent pleural effusions. Absolute contraindications include an active pleural or cutaneous infection, coagulopathy, and malignant masses over the proposed insertion site. IPCs can be inserted on an outpatient basis, followed by the education of the patients and their families, and subsequent home drainage. A patient with IPC is no longer bound to the hospital care and has self-control over respiratory symptoms. The optimal frequency of drainage is not clear, but the ASAP trial (Impact of Aggressive versus Standard Drainage Regimen Using a Long-Term Indwelling Pleural Catheter) suggests daily drainage superiority over every other day in terms of autopleurodesis rate and time to pleurodesis (34). AMPLE-2 trial found a higher incidence of spontaneous pleurodesis in 60 days and better quality of life in daily drainage when compared with the symptom-guided drainage, while dyspnea scores and mortality were similar (35). Spontaneous pleurodesis as an additional effect of IPC placement was reported in 46 % in the meta-analysis by Van Meter et al (36), and the average time to pleurodesis was 52 days. As mentioned in the introduction, autopleurodesis was even seen in patients with NEL, although less frequently (37). IPC-related complications are minor and easily treatable, including pleural infection (< 5 %) (38), displacement, blockage, fluid loculation, and catheter tract metastases (39, 40). In cases with pleural infection, antibiotic therapy without IPC removal is recommended in the first place (41). According to the TIME2 randomized controlled trial, IPCs had several advantages in comparison with slurry pleurodesis. There was a significant decrease in dyspnea in the IPC group 6 months after the procedure, while the difference in length of hospital stay was –3.5 days, adverse events occurred in 40 % in the talc group vs in 13 % in the IPC group, and further pleural procedures were needed in 22 % vs 6 % in the IPC group. However, several studies suggest that despite lower initial costs for IPC treatment the overall costs might be higher because of the potential of increased community care costs (26, 42, 43).

Combined approaches

In patients with short life expectancy, the clinicians are trying to combine the advantages of an IPC insertion and talc pleurodesis in an effort to minimize both duration of the hospital stay and risk of adverse events. The first method is outpatient slurry pleurodesis via IPC, as shown in the IPC-PLUS trial (44), the second option is the insertion of IPC instead of a conventional chest drain after thoracoscopic pleurodesis. Both methods are reported to have a success rate of pleurodesis about 90 % (45). In the IPC-PLUS trial, 10 days after the outpatient insertion of an indwelling pleural catheter patients with no evidence of substantial lung entrapment were randomly divided into two groups. The first group received 4 g of talc slurry, while placebo was administered in the second group. Successful pleurodesis at day 35 after the procedure, as the primary outcome, was observed in 43 % of the patients in the talc group as compared with 23 % in the placebo group. No significant excess of blockages of the IPC was noted in the talc group.

Considering cost-effectiveness, according to Shafiq and colleagues (46), the daily drainage of IPC and talc suspension administered through an IPC were more effective but also cost more than drainage of IPC only when symptomatic. In comparison, the daily drainage was more costly and less effective than IPC+talc, and that was why this approach was considered "dominant" for the cost-effectiveness analysis. An analysis of sensitivity indicated that the IPC+talc approach was more cost-effective in 54 % of the cases, while symptom-guided drainage was cost-effective in the remaining 46 %. Drainage guided by the symptoms was also more cost-effective in patients with a life expectancy shorter than 4 months.

Subcutaneous implantable pleural port (SIPP)

The subcutaneous implantable pleural port is the latest form of drainage management in patients with MPE. First use of modified peritoneal port-a-caths for a drainage of MPE was reported in 1986 in a patient with adenocarcinoma of the lung (47). It can be placed under local anesthesia and sedation, usually during short-term hospitalization, but it is also possible to manage it in an outpatient setting. Pleural fluid is removed by a Huber needle connected to a tube by trained family members or by a nurse at the patient home. In a prospective study by Kriegel et al spontaneous pleurodesis was observed in 36.8 % of the patients within 2 months (48). Out of 168 SIPPs used in 137 patients, 3 infectious complications and 3 mechanical complications occurred. As well as in the IPC, ATB therapy is considered the first-line treatment when an infection occurs. According to Daniel et al (49), besides infectious complications, two types of mechanical complications were observed in their group of 29 patients: the expulsion of the port and disconnection of the port. Monsky et al studied the changes in the quality of life in palliative care patients with implanted pleural and peritoneal port systems (50). Port implantation improved the patient comfort, quality of life, as well as clinical symptoms. A special, fully implanted system with a multi-perforated cuffed catheter (Celsite Drainaport, B.Braun AG, Melsungen, Germany) is commercially available for long-term drainage of the MPE, and has been used in our institution since 2018. There is currently no comparative study comparing the benefits of SIPP vs. other methods of MPE management.

Pleuroperitoneal shunting

This interventional method is based on the derivation of the pleural fluid from the pleural cavity intraperitoneally using a manual pump (Denver shunt) or via passive movement related to the posture (LeVeen shunt) (51). Despite the decreasing incidence of this method, pleuroperitoneal shunting may be useful in refractory MPE, trapped lung syndrome, and ineffective chemical pleurodesis. Another indication is chylothorax, where this approach allows effective chyle recirculation (52). The overall efficacy is 80–95 % if the patients are adequately selected. The complication rate however may be as high as 15 % in oncological patients (53).

Future directions

Several methods of managing the recurrent malignant pleural effusion are available. According to current consensus and guidelines, no method is strictly preferred. The choice of the treatment depends on the aim of palliative care. If early pleurodesis is expected, the methods of talcage should be preferred. If not, the subcutaneous implantable pleural port should be a method of choice in a patient with good performance status, mainly owing to to increasing quality of life, lower need for hospital admissions, and potentially lower risk of infectious complications. According to recent literature (46) in patients with malignant pleural effusion and expandable lungs, IPC + talc may be cost-effective as compared to symptomatic drainage of IPC, although there is considerable uncertainty surrounding this estimate. IPC daily drainage is under no circumstances a cost-effective strategy although we know it can form spontaneous pleurodesis more often.

Furthermore, the development of new oncological markers (54) and complex strategies for early diagnosis of lung cancer (55) may decrease the incidence of recurrent malignant effusion in the population.

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