Malignant pleural effusions and trapped lung

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Abstract: Malignant pleural effusions (MPEs) are of great importance for the prognosis of patients with oncological diseases. The current review focuses on the problem of the management of patients with MPEs complicated with trapped lung, which is still a subject of discussion. "Trapped lung" describes the situation in advanced malignant pleural disease in which the lung is unable to fully expand to fill the hemithorax, rendering the parietal and visceral pleura either partly or completely unopposed, with the presence of a residual cavity. A variety of diagnostic approach for the condition of a trapped lung (imaging or invasive) are analyzed. Nowadays the optimal approach to MPE with a trapped lung is still a subject of discussion. In general, the management is a challenge for the thoracic surgeon and medical oncologists and focuses on palliative relieving of the symptoms and reduction of the hospitalization rates rather than on cure, because of the end-stage of the neoplastic disease Different strategies for palliative treatment are debated, including placement of indwelling pleural catheters, surgical decortications (open thoracotomy or closed VATS), pleuroperitoneal shunts and intra-pleural fibrinolytic therapy. The last two are not routinely applicable. Any planned treatment should balance the therapeutic benefit provided against the required period of convalescence for a disease with a limited life expectancy. Randomized controlled multicenter clinical trials in patients with comparable diseases and comorbidity are needed to clarify which is the most appropriate treatment modality. To the present date, VATS decortication seems to be an excellent therapeutic method offering as large as possible macroscopic reduction of the tumor and re-expansion of the lung in surgically fit patients. VATS has a significantly less operative risk than radical invasive surgical interventions, minimizes the surgical trauma and pain, shortens the postoperative in-hospital stay, resulting respectively in susceptible Quality of Life improvement.

Keywords: Malignant pleural effusions (MPEs); trapped lung; management; indwelling pleural catheters; video-assisted thoracic surgery (VATS) decortication

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Introduction

Malignant pleural effusions (MPEs) are of great importance for the prognosis of patients with oncological diseases. The median survival time from the diagnosis of a MPE usually does not exceed more than six months, and in most cases, it varies between 1–12 months (1,2). So a change in the management pattern, i.e., shifting the focus from treatment to a palliative care plan focused particularly on MPE and the control of the symptoms associated with it, is required (3,4). An inappropriate treatment modality may worsen the symptoms and consequently shorten the patient's life (3). The estimated annual incidence of MPEs in the USA exceeds 150 000 cases, and this number ranges from

Table 1 The incidence rate of the neoplastic diseases causing trapped lung (23)

Malignant tumor	Number of patients	%
Breast	20	38.5
Mesothelioma	17	32.7
Ovary	7	13.5
Lung	3	5.8
Colon	1	1.9
Lymphoma	1	1.9
Esophagus	1	1.9
Adenocarcinoma (unknown origin)	2	3.8

375,000 to 400,000 in Europe (4,5). In some of the patients diagnosed with MPE, a complication such as trapped lung may be observed in approximately 5–20% of the cases (6). The management of MPE in the presence of trapped lung is hugely challenging because these patients generally have a poor long-term prognosis with a median survival time of 7 months for mesothelioma up to ~30 months for metastatic breast carcinoma (7,8).

Pathophysiology of the trapped lung in MPEs

Normally the pleural space is a tiny capillary space between the visceral and parietal pleural layers that usually contains a small amount of pleural fluid: 10–20 mL (9). The parietal pleura is more critical for the pleural fluid exchange in the pleural cavity because it is adjacent to the microvessels and lymphatic openings. Malignant pleural diseases (MPD) may include either primary tumors of the pleura (malignant pleural mesothelioma, MPM) or secondary involvement from neoplasms of intra- or extrathoracic organs. They can be manifested as diffuse or nodular pleural thickening with or without a concomitant MPE (10). The presence of malignant cells in the pleural fluid indicates the obliteration of the pleural defence mechanisms—dislocation of cells from the primary tumor due to loss of adhesion, adherence and penetration of the blood vessel wall, migration to the pleura, production of growth factors and blocking the lymphatic evacuation tracts (11,12). The development of MPE is connected with many vasoactive mediators—vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF), chemokinine ligand 2, osteopontin and possible protective molecules like endostatin, which allow the occurrence of vasoactive events. Some myeloid cells like macrophages, neutrophils, eosinophils, lymphocyte subtypes (Th1 and Th17), interferon-gamma (IFN-γ) and many interleukins also play a role. IFN-γ inhibits the Th17-cell differentiation and promotes the MPE formation, whereas the IL-17A inhibition of the Th1-cell subpopulation differentiation prevents the formation of MPE (12,13). The final result from the interactions between tumor cells and host vascular and immune system is a disturbance between the formation and absorption of the pleural fluid which leads to accumulation of the same in the cavity and causes symptoms in the patient depending on the amount of the liquid, the speed of its increasing and the presence of any respiratory and cardiac comorbidity.

"Trapped lung" describes the situation in advanced MPD in which the lung is unable to fully expand to fill the hemithorax, rendering the parietal and visceral pleura either partly or entirely unopposed, with the presence of a residual cavity (14,15). Trapped lung can occur as a result of (I) pleural thickening (may be due to direct infiltration with malignant tissue or development of fibrotic tissue), particularly of the visceral pleura, causing encasement of the lung; (II) multiple metastatic nodules on the visceral pleura, restricting the expansion—pleural carcinomatosis (14,16,17); (III) proximal endobronchial obstruction, causing distal lung collapse or chronic atelectatis with a concomitant malignant or paramalignant (most often transudative) pleural effusion, and (IV) radiation-induced fibrotic transformation of the visceral pleura (14,18). Some authors differentiate between "lung entrapment", in which an active pleural process such as malignancy causes a visceral pleural peel to form, thus preventing lung re-expansion, and "trapped lung", in which the fibrous peel has arisen as a consequence of remote inflammation in the pleural space that is no longer active (14,19,20). The name "trapped lung" covers both clinical entities, but there are no randomized controlled trials explicitly investigating trapped lung. Consequently, the evidence must be interpreted in the context of selection bias, including patients in the studies, indication for treatment and interventional procedures (15). Metastatic pleural effusions are characterized by high fibrogenic potential and increased the production of transforming growth factor by the tumor cells (17). The growth factor activates fibroblast proliferation and collagen matrix synthesis (21,22). These processes observed in pleural metastases lead to fibrotic reorganization of the visceral pleura. The trapped lung is a progressive disease that affects the quality of life (QoL) of the patient with the

leading symptom of dyspnoea significantly as a result of ventilation-perfusion mismatch within the entrapped lobe or lobes (10). Qureshi *et al.* (23) tried to determine the incidence rate of the trapped lung considering the primary tumor location in 52 patients treated with insertion of a pleural catheter (*Table 1*).

Diagnosis of the trapped lung

Whether trapped lung can be predicted is still a question with current importance. Pleural manometry, transthoracic ultrasonography and patient's symptoms during aspiration of the MPE are methods, proposed for predicting of the trapped lung condition (24-27). None of them till now have been proven prospectively in randomized controlled trials, and further evidence is needed before their routine application in clinical practice (15). The removal of the MPE relieves the overall symptoms, so the volume of fluid drained should be strictly guided according to symptoms. If a cough or chest discomfort is observed due to severe dull or sharp pain because of stretching of the visceral pleura against the intrathoracic vacuum space, thoracentesis must be stopped immediately. In such cases, an underlying trapped lung could be suspected. Radiographically, this may be identified as a pneumothorax ex vacuo (i.e., caused by an inability of the lung to expand to fill the thoracic cavity after pleural fluid has been drained) and is not a procedure complication (28-30).

Thoracic ultrasound (TUS) is useful to confirm the presence of pleural fluid and to differentiate between pleural fluid, pleural thickening and consolidation. It can also suspect a malignant etiology with certain features highly suggestive of malignancy, such as (I) presence of pleural thickening >1 cm; (II) diaphragmatic nodularity or thickening >7 mm; (III) visceral pleural thickening and pleural nodularity/irregularity (31). TUS has a sensitivity (Se) of 73% and specificity (Sp) of 100% in identifying malignancy and is comparable with computed tomography (CT) scans in demonstrating visceral pleural disease and diaphragmatic nodularity (32). TUS can also be used in the management of MPEs with reduction of the rate of pneumothorax with 16% and haemorrhage with 39% after thoracentesis (33). It is a safe, cost-effective and accurate imaging method for visualization of pleural lesions with or without the presence of pleural effusions and successfully assists minimally invasive diagnostic procedures such as transthoracic true-cut needle biopsies. TUS-guided true-cut biopsies demonstrate accurate histological verification for accessible with the method lesions in 96%, with Se of 93% and Sp of 100% for MPD (34).

In the past the contrast-enhanced CT of the thorax was considered as the gold standard of imaging in pleural malignancy, especially when specific criteria were met: (I) a circumferential pleural thickening (Sp 100%, Se 41%); (II) nodular pleural thickening (Sp 94%, Se 51%); (III) parietal pleural thickening >1 cm (Sp 94%, Se 36%), and (IV) mediastinal pleural involvement (Sp 88%, Se 56%). Nevertheless, CT cannot reliably differentiate MPM from pleural metastases (35). Magnetic resonance imaging (MRI) provides better imaging of soft tissue than CT, can detect invasion into the chest wall and diaphragm and also small effusions, can assess better pleural thickening and extra-pleural fat, but it is not as effective as CT for imaging lung parenchyma (36). Neither CT-scan nor MRI suggests reliable criteria for diagnosing of a trapped lung.

Elastance of the pleural space seems to be the best predictor for trapped lung and outcome of pleurodesis according to a cohort study in 65 patients with symptomatic MPEs (24). The elastance is defined as the decline in the pleural fluid pressure in H_2O cm after removal of 500 mL effusion due to thoracentesis (change in pressure/change in volume). Under normal conditions, if the fluid is added to a closed system (the thorax), the pressure will rise; and as the fluid is removed, the pressure will drop until an equilibrium pressure is reached. In the chest, the pleural pressure at functional residual capacity (FRC) usually is slightly negative (–3 to –5 cm H_2O) because the chest tends to expand, and the lung's elastic recoil results in a tendency for the lung to collapse. In the setting of a trapped lung, despite the presence of a pleural effusion, the pleural pressure is low, and it drops significantly with the removal of fluid (6,37). The upper limit of the normal range of pleural space elastance has been estimated as 14.5 cm H_2O/L, with any value >15.5 cm H_2O/L not being compatible with overall respiratory system mechanics. An elastance, which is higher than 14.5 cm H_2O/L, is highly likely to represent a local mechanical abnormality in the pleural space as Huggins *et al.* (38) report in their study with 11 patients having trapped lung. Patients with elastance of 19 cm H_2O or more have a high incidence of trapped lung, and none of them achieved successful chemical pleurodesis. So the measurement of elastance of the pleural space was proposed as a simple and effective method for the diagnosis of the trapped lung (24).

The accuracy of video-assisted thoracic surgery (VATS) for diagnostic purposes is undebatable (39). One advantage

of VATS is that the surgeon can proceed to other thoracic surgical options, if appropriate, at the time of the procedure based on the intra-operative assessment of the extension of the pleural tumour involvement and the entity of the lung potential of expansion (10). However, because of the invasive nature of VATS and the need for general anesthesia it is unsuitable for many patients who have comorbidities (40).

Management of the trapped lung

In the past two retrospective studies have looked at the consequences and outcome of trapped lung and suggest that in itself, it may be well tolerated by some patients (41,42). The focus in these patients should be on the extent to which breathlessness is a limiting symptom, and if it can be reliably relieved. In the case of the trapped lung, there may be arguments for accepting the situation. Unavailing surgical interventions impose a further burden on the patient with a substantial additional risk of introducing infection (43).

Nowadays, the optimal approach to MPE with a trapped lung is still a subject of discussion. In general, the management is a challenge for the thoracic surgeon and medical oncologists and focuses on palliative relieving of the symptoms and reduction of the hospitalization rates rather than on cure, because of the end-stage of the neoplastic disease (30).

Different strategies to managing malignant trapped lung include (I) indwelling pleural catheters (IPCs) placement; (II) surgical pleurectomy/decortication (P/D); (III) pleuroperitoneal shunting; (IV) intra-pleural fibrinolytic therapy.

Indwelling pleural catheters

The IPC consists of a 66 cm long and 15.5 F wide silicone tube, which has fenestrations along the distal 24 cm. The surgeon places this distal end into the pleural cavity, tunnelled subcutaneously with a small (pro-fibrotic) cuff, with the other end exiting the patient. On the exiting surface of the catheter, a one-way valve is installed that allows fluids and air to go out from the pleural cavity but not in. The catheter can be inserted and tunnelled with the patient under local anesthesia and conscious sedation as a same-day outpatient procedure or after a VATS-procedure with hospital stay (44). Once tunnelled beneath the skin into the pleural cavity, it can remain in place indefinitely, allowing patients and their caregivers an easy drainage procedure at home or in ambulatory settings, requiring minimal training. Management of symptoms as an outpatient allows patients to maintain control over their lives and minimizes the time spent in the hospital (2,45). IPCs offer long-term access to the pleural cavity, they represent ideal portals for local drug delivery with the potential of being an acceptable compromise in patients who would not be fit for a major operation (23). The published data known so far report that chemotherapy did not increase the rate of IPC-related infections and that radiotherapy was well tolerated and carried out safely without catheter removal (46,47). Catheter tract metastases, a complication consisting in new, solid chest wall lesions over the IPC insertion site and/or the tunneled subcutaneous tract, have a reported incidence in the available literature from <1% to 10% and MPM seems to be the most predisposing cancer accounting for the majority of cases of IPC-related catheter tract metastases (48).

IPCs are suitable for palliative treatment of patients with pathologically proven diagnosis of MPE, primarily symptomatic one; with short to intermediate life expectancy (>30 days); failed pleurodesis with recurrent MPE after the procedure or a trapped lung, including also trapped lung confirmed by VATS (30,49-51). An IPC is contraindicated in patients with uncontrolled coagulopathy; extensive malignant involvement of the skin; infection over the site of the insertion and in some cases of multiloculated or septated pleural effusions that would not be adequately drained even after an IPC placement (52).

Placement of an IPC can be a reasonable treatment of choice for a trapped lung since chemical pleurodesis is not feasible without the potential of parietal and visceral pleural apposition and repetitive needle thoracentesis is not without inherent risks and morbidity. In a retrospective study of IPC placement for palliative symptom control, catheter relieved symptoms, improved quality of life, and contributed to a substantial increase in mobility (2,28,30). It is thought, that the symptomatic improvement after an IPC insertion is a result of the reduced distension of the affected thoracic cavity with reversal of mediastinal shift and decompression of the unaffected lung, which occurs after the drainage of large unilateral pleural effusions. Physiological improvements may not be the only factor involved, the psychological effects of draining large volumes of effusion should also not be ignored. Patients confirm relief in their condition after placement of IPC in several studies suggesting that symptomatic benefit is gained from the use of these devices in 48–94% of the patients with MPE and trapped lung (51,53,54). Qureshi *et al.* (23) report that despite the trapped lung, IPC induced spontaneous

pleurodesis in 48% of patients after a mean of 94 days. Even in the presence of a trapped lung, the IPC drainage could lead to autopleurodesis, although less frequently (55-57).

A single systematic review focusing on the problem concluded that IPCs are indicated in the trapped lung (15,58). The conclusion was based on two studies out of 14 included in the review. The study, performed by Pien *et al.* (53), was a retrospective review of 11 patients with trapped lung who underwent IPC insertion and home drainage. All but one patient described the symptomatic benefit, and 12 out of 13 catheters placed remained *in situ* until the patient died. Serious adverse events and complications, i.e., empyema, wound site infection, IPC blockage or dislodgement, catheter fracture, leakage around the catheter, pain or severe discomfort, can occur as possible catheter-related complications, but most of them can be treated successfully (10,53). IPC-related symptomatic loculations are reportedly present in 6–14% of IPC-treated patients and typically occur at about two months after IPC insertion (14,48). Qureshi *et al.* (23) report that complications occurred in 15.4% from the patients, treated with IPC for MPE with trapped lung. Data for 8 patients were published, describing chest pain in 6 patients on their initial drainage, generally well controlled with analgesic medications; catheter occlusion in 2 patients, requiring replacement; cellulitis, treated with antibiotics in 2 patients; air leak and surgical emphysema in 2 patients and development of loculations with catheter removal also in 2 patients. Tumor seeding of the catheter tract was not found (23). Demmy *et al.* (59) randomized 57 patients with MPE to IPC placement with daily drainage *versus* beside talc pleurodesis, with a composite primary outcome of "success" based on reliable drainage, pleurodesis and 30-day survival. IPCs were significantly more successful for the primary outcome (62% versus 46%, P=0.064) and the secondary outcome (82% versus 52%, P=0.024). The subgroup of 9 patients with trapped lung had higher effusion control rates at 30 days in the IPC arm, compared with the talc pleurodesis arm, and better dyspnoea-free exercise scores (7.8 versus 4.5, P=0.02).

Several observational studies are reporting the value of IPC in MPE with trapped lung. Some of them give data for the number of patients who experienced symptomatic relief; others subjectively graded the size of the response in individuals. IPCs appear to be effective in the trapped lung, with symptomatic improvement in >94% of patients in 5 studies totalling 133 patients although a single study of 48 patients reported lower symptom relief rates (only 48%) (28,60-63). Three of these studies included patients who had undergone VATS and been diagnosed with trapped lung intra-operatively, and so received an IPC at the end of the procedure (28,61,63). In these studies, it is impossible to determine which procedure was responsible for which outcomes, both in terms of symptomatic benefit and adverse events, which were numerous. Length of hospital stay was consistently shorter for trapped lung patients treated with IPCs than for comparator groups (usually comprising patients with non-trapped lung undergoing VATS talc-poudrage) (23,64).

Open window thoracostomy (OWT), initially introduced by Eloesser (65) and subsequently modified by others (66,67), is an infrequently used but valid alternative measure the surgeon may undertake when facing the failure of intrapleural catheter drainage and trapped lung (68). Catheter infection and or cancer-induced fibrin deposition within the pleural cavity, along with the pleural symphysis resulting from the continuous drainage, can unfavourably induce septations and loculations, thus limiting adequate IPC drainage. A similar condition is reported in 6–14% of IPC-treated patients, and typically occurs at about two months after IPC insertion (48,69). OWT controls the infection. It creates a draining fistula, converting in an excellent alternative approach in selected patients with secondarily infected MPE wherein IPC-drainage and the antibiotics have not succeeded to clear the infection, or if there is a desire to maintain drainage of the pleural space without the presence of a foreign body.

Surgical pleurectomy/decortication

In advanced MPD, the lung may become entrapped by a thickened visceral pleural rind of tumor which prevents its expansion causing underlying collapse and respiratory compromise which can affect the patients' QoL significantly (10). The removal of the parietal tumor cortex and allowing the lung parenchyma re-expansion and its apposition against the chest wall may relieve a restrictive ventilatory deficit, have a positive impact on hypoxia and ventilation-perfusion mismatch, reduce chest wall pain and discomfort, prevent recurrent pleural effusions, resulting respectively in susceptible QoL improvement (10,70). Improvement in dyspnoea is due not only to drainage of the effusion but also to the expansion of the underlying lung, which pleurodesis alone could not achieve. There is evidence from surgery for empyema that decortication of an entrapped lung increases vital capacity, forced expiratory volume and lung perfusion (71,72). The reasons for the relief of chest wall pain observed are

unclear, but this may be due to relief of intercostal nerve compression (73).

The decortication (visceral pleurectomy) should be carried out one anatomical layer lower than in a decortication for empyema (10). The goal of this procedure is not to achieve complete macroscopic clearance of the tumor, but to obtain satisfactory lung expansion and apposition of the parenchyma against the chest wall (73). As per any other debulking techniques, the visceral pleurectomy aims for achieving therapeutic and palliative effects thanks to its potential to offer cytoreduction with the presumptive benefit of delaying tumor progression and prolonging survival (74).

There were no randomised trials reporting on the effectiveness of P/D for MPEs. Tan *et al.* (75) analysed five case series covering 260 patients (76,77), including a series of mesothelioma (70,77) and other malignant disease patients in which tumor debulking and decortication were part of the procedure. In others, decortication was performed when the lung was seen to be 'trapped' by tumor and accumulation of fibrin on the visceral pleura (76,77). Perioperative mortality of up to 12.5% was reported (76), and there appears to be a high incidence of prolonged air leak postoperatively, 10–20%.

The visceral pleurectomy may be performed by either open thoracotomy (70,73) or closed VATS (78-80).

In an early study, it was recommended that posterolateral thoracotomy and P/D could be tried for pleurodesis even in MPM patients with advanced stages if the patient is a surgical candidate (70). Martin-Ucar *et al.* (73) advised that careful consideration has to be given before performing decortication via thoracotomy, due to the increased risk of prolonged air-leakage (15%) and empyema development (6%) if the lung fails to re-expand. However, they felt that no other method has proven superior in achieving lung expansion and symptom control in the trapped-lung syndrome.

In Martin-Ucar *et al.* (73) retrospective study visceral decortication was performed in 34 not indicated for radical surgery MPM patients either via VATS (n=3) or *via* a limited lateral thoracotomy (n=31). The overall significant symptomatic benefit was obtained up to 3 months after surgery, but subsequently increasing mortality offset these benefits. The improvements in dyspnoea and pain scores were both consistent with other studies (70). Epithelial cell type and absence of weight loss before surgery were found to predict significantly longer survival and successful symptom control. Failure of symptom relief occurs due to local recurrence, rather than re-accumulation of effusion (73).

Surgical treatment of MPEs is palliative, as the indication is usually advanced disease associated with significant comorbidity, and the minimally invasive approach is the first choice (2). VATS is designed to reduce the chest wall trauma, preserve respiratory muscle function and therefore expedite recovery. Nowhere is this more important than in MPE patients with a limited prognosis with advanced MPD. VATS also allows for therapeutic manipulation of the pleural environment, including dissection techniques aimed at symptom control by direct tumor debulking (10).

In a prospective cohort study, Nakas *et al.* (81) found that VATS P/D is the only method to effectively palliate the subgroup of patients with MPM and trapped lung which are not indicated for radical surgery without the complications of thoracotomy (73). This procedure appears to prolong survival, as well (80). Following draining the effusion and completion of parietal pleurectomy, positive airway pressure is applied, and the visceral pleura is decorticated. When lung apposition to the chest wall is achieved, 10 mL of aerosolized fibrin-based glue is sprayed to the surface of the lung (81). The combined parietal pleurectomy and visceral decortication should have superior results compared to pleurectomy and talc pleurodesis since it aims to release the trapped lung and control the pleural effusion by eliminating the space. It can alleviate symptoms and appears to prolong survival, but further research is needed to assess its role in the management of MPM.

There are a small series of retrospective studies which provide low-grade evidence for safely provided effective treatment (79), "good outcomes" (78), achieving 90% effusion control at 12 months (77) in patients with trapped lung who underwent VATS decorticatons. The successful lung mobilisation, combined with pleurectomy to lower the burden of the disease, can obliterate the pleural space effectively (82).

The question of whether VATS visceral pleurectomy is more effective than continuous drainage of the pleural effusion with an IPC is being addressed in the multicentre pilot clinical MesoTRAP trial (83). It aimed at randomizing 38 patients with trapped lung and pleural effusion due to MPM who were allocated in a 1:1 ratio to either VATS partial visceral P/D or IPC. The initial results confirmed the improvement of breathlessness which is also the primary purpose of the non-radical treatment as symptomatic relief. The secondary outcomes included changes in the chest pain, the assessment of post-procedure QoL according to two different questionnaires (EQ-5D-5L and EORTC

QLQC30) and survival at 30 days and 12 months post-randomization.

According to the Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of MPM P/D should not be proposed in a curative intent but could be considered in patients to obtain symptom control, primarily symptomatic patients with entrapped lung syndrome who cannot benefit from chemical pleurodesis (grade 2C, very weak recommendation according the ACCP-system grading). The VATS approach is preferred in such cases (grade 1C, strong recommendation) (84).

A loculated MPE may become secondarily infected, especially following multiple thoracenteses or an IPC placement. VATS decortication of the inflammatory cortex may be successful even if the lung is entrapped. It is especially crucial if the patient is considered for cytotoxic chemotherapy.

The literature lacks studies on the application of VATS in malignant empyema (10). In a single-centre review of 561 patients with an initial diagnosis of benign empyema, 35 patients (6.2%) had a postoperative histological verification of malignancy. Two-third of the patients were treated by the VATS approach (85). A recent meta-analysis seems to show that VATS-D might be comparable or even better than open decortication in terms of operative time, postoperative hospital stays, chest tube duration, prolonged air leakage rate, morbidity and mortality (86). VATS-D was proved to be of potential benefit, even in selected patients outside stage I empyema (87).

Pleuroperitoneal shunting

Pleuroperitoneal shunting has been previously described as effective in patients with extensive involvement of the visceral pleura with tumor. Although it risks translocation of tumor cells into the peritoneal cavity, the risk is acceptable because of the improvement in respiratory function—better ventilation of the diseased lung, some protection from mucous retention, atelectasis and pneumonia. A complication that limits the use of this method is a possible failure of the shunt (88). Schulze *et al.* (89) report for a placement of 14 pleuroperitoneal shunts as an alternative to talc pleurodesis after VATS when the complete expansion of the lung could not be achieved due to tumor implants on the visceral pleura (visceral carcinomatosis). In 119 VATS procedures, 105 talc pleurodesis and 14 pleuroperitoneal shunt procedures were performed in this trial. Clinical relief of dyspnoea was obtained in 73% (n=8 of 14) of the patients with 30-day mortality in the group of 21% (n=3), and 14.3% (n=2) developed procedure-related complications. The mean length of the hospital stay after implantation of the shunt was 8.1 days (±1.9 days), and the mean survival for the patients was 4.3 months (±1.9 months) (89). Genc *et al.* (90) determined early and late complications for 14.8% from the patient (n=21 out of 160) who underwent a pleuroperitoneal shunt placement. Complications described include shunt occlusion (in 12–25%, requiring replacement of the shunt), infections, sepsis and tumor seeding or implantation into the peritoneal cavity (88,91). However, the supporting evidence is of poor quality for this invasive procedure, complications rates are high, and pleuroperitoneal shunts are not currently used in routine clinical practice (88-90).

Intra-pleural fibrinolytic therapy

Hsu *et al.* (92) investigated the use of 100,000 IU urokinase *via* IPCs in surgically inoperable patients with trapped lung or loculated effusions. Three out of 12 patients with trapped lung demonstrated "excellent" radiographic improvement following treatment, which persisted until death in 2 out of the 3. No adverse events were reported. However, the relevance of radiographic resolution, specifically its inconsistent relationship with symptoms, makes this finding difficult to interpret in a clinical context. Also, a single case report was published by Tauchi *et al.* (93) for the use of intrapleural urokinase for the treatment of poor expansion lung with MPE due to breast cancer with trapped lung. In the reported case, an immediate resolving of the multilocular pleural effusion after the administration of the agent with complete pulmonary re-expansion was achieved. However, more extensive studies are needed for this kind of therapy to be correctly assessed and consequently recommended for the routine clinical practice.

Conclusions

Whether a trapped lung could be predicted is still a question with current importance, and various invasive and non-invasive methods are trying to find out the best diagnostic approach and optimal solution. It highly depends on the patient, the comorbidity and the primary goals that are needed to be achieved, so the optimal approach to MPE with a trapped lung is a subject of present and future discussions. The management nowadays is focused on the palliation of the patients, the control over their

symptoms, shortening of the hospital stay, minimizing the adverse events due to the invasive treatment procedures and respectively prolonging the life expectancy. Further prospective trials need to be performed in order to solve the challenges of the diagnostic and therapeutic process and to determine the best treatment methods.

There is a lack of good-quality published evidence, but IPC appears to be an effective option in the management of MPE and especially with trapped lung (15). The adverse effects offered by the IPCs can successfully be either conservatively or surgically treated. Dedicated prospective trials are needed to evaluate the utility of IPCs in trapped lung fully, and also to evaluate surgical interventions and the role of fibrinolytic therapy. At the present moment, IPCs present an acceptable treatment strategy with benefits on the patient's symptoms, hospital stay, reduced morbidity and mortality rates. Pleuroperitoneal shunting could also be used in some patients with extensive neoplastic involvement of the visceral pleura, providing improvement in the respiratory function, but with the risk of translocation of tumor cells in the peritoneal cavity. Due to the many complications reported, it is not routinely applicable. A similar statement can be addressed to the intra-pleural fibrinolytic therapy, because of the highly selected type of patients, namely those with loculated MPE and trapped lung, undergoing the procedure.

In patients with MPE and trapped lung who can be assessed as indicated for invasive surgical procedures, VATS P/D seems to be an excellent therapeutic method offering as large as possible macroscopic reduction of the tumor and re-expansion of the lung. VATS has a significantly less operative risk than radical invasive surgical interventions, minimizes the surgical trauma and pain, shortens the postoperative in-hospital stay, resulting respectively in susceptible QoL improvement. At the present moment, VATS could be suggested as a first choice method for MPE patients who can be surgically treated.

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