# Video-assisted thoracoscopic surgery in the management of malignant pleural disease

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**Abstract:** Surgical treatment of malignant pleural diseases is usually indicated in advanced disease with a limited prognosis. associated with significant morbidity. Minimally invasive approaches must be offered as first line treatment since they reduce chest wall trauma, preserve respiratory muscle function and therefore expedite recovery. Most of the evidence for therapeutic video-assisted thoracoscopic surgery (VATS) pleural surgery is for primary malignant pleural mesothelioma (MPM) whilst in the treatment of metastatic non-small cell lung cancer (NSCLC) therapeutic VATS is concerned mainly in the prevention of pleural effusion or the treatment of malignant empyema. An increasing amount of management decisions using VATS in malignant pleural disease is evidence-based. There have been and continue to be well constructed clinical trials of the various potential therapeutic applications of VATS in this context. VATS allow for therapeutic manipulation of the pleural environment including dissection techniques aimed at symptom control by direct tumour debulking. We will consider the role of VATS in the management of malignant pleural disease in the context of a lung that will expand; when the lung is entrapped and when the lung is entrapped by a malignant empyema. In the first scenario the therapeutic choice is between simple VATS administration of chemical pleurodesis or the more controversial subtotal parietal pleurectomy. When the lung is entrapped but the cavity still cleans the choice is between the insertion of an indwelling pleural catheter (IPC) or the highly disputed VATS visceral pleurectomy to re-expand the lung. When a malignant effusion becomes infected the entrapped lung may form a malignant pleural empyema and the debate is between just debridement or the more technically challenging decortication. We will attempt to evaluate all of these procedures and formulate a management algorithm.

**Keywords:** Video-assisted thoracoscopic surgery (VATS); mesothelioma; lung cancer; pleurectomy; decortication; indwelling pleural catheter (IPC)

## Introduction

Malignant pleural disease includes the following conditions either the pleura may represent the site of the primary tumour [malignant pleural mesothelioma (MPM)] or a metastatic site from proximal or distant organs. The disease can be categorized by whether the lung will expand or whether it is entrapped. It may present as diffuse or nodular pleural thickening, with or without a malignant pleural effusion (MPE).

The approximate annual incidence of MPEs in the United States is 200,000 (1) with an overall incidence of both malignant and paramalignant effusion up to 50% in patients with thoracic or extra-thoracic malignancies (2).

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**Table 1** Summary of VATS procedures in malignant pleural disease

| VATS procedure | Indication | Description | Intended outcome |
|---|---|---|---|
| Parietal pleurectomy | Limited role in MPM in low-risk patients with lung expansion (MesoVATS trial conclusion) | Subtotal removal of parietal pleura—usually diaphragm and pericardium spared | Effusion control maintenance of QoL |
| Visceral pleurectomy | TL (in MesoTRAP trial in UK) | Near total removal of visceral pleura to free all the lobes | lung expansion improvement in QoL no need for permanent drain |
| Talc pleurodesis | Malignant effusion but lung re-expands. Preferred in high-risk patients with MPM (MesoVATS trial) | Chemical pleurodesis with talc | Symptom control |
| IPC | TL (in MesoTRAP trial in UK) as adjunct to talc pleurodesis if lung expands | VATS insertion ± combined with talc insufflation | Symptom control |
| Debridement/ decortication | Empyema—stage II or III | Evacuation of loculations and removal of inflammatory cortex | Sepsis control-enable adjuvant chemotherapy lung re-expansion/ improved respiratory function |

VATS, video-assisted thoracoscopic surgery; MPM, malignant pleural mesothelioma; QoL, quality of life; IPC, indwelling pleural catheter; TL, trapped lung.

In Europe, the frequency of MPE is estimated at nearly 400,000 patients per year and ca 50,000 new MPE are diagnosed in the UK every year.

MPE is traditionally attributed to a defect in the pleural fluid drainage but the lymphatic block cannot explain the co-existent immune-response. Recent evidence in fact highlights the pivotal role of an interaction of the host immune-system with the cancer cells which triggers the extravasation and may be modulated by especially vascular endothelial growth factor-A (VEGF-A). Immune-cells appear self-sustaining thus increasing the vascular permeability, cancer cell transmigration, and angiogenesis. These factors offer potential inhibitory targets for the pleural effusion mechanism (3,4).

Patients with non-small cell lung cancer (NSCLC) with pleural seeding and MPE (M1a) have poor outcomes, with a median survival time (MST) of 11.5 months (5). Thus, when pleural involvement is an accidental intraoperative finding even if localized the current consensus favours open-close surgery followed by chemotherapy or targeted therapy for stage IV disease. There is no evidence to date that the resection of the primary tumour has a favourable impact on the prognosis (6).

## The role of video-assisted thoracoscopic surgery (VATS) in malignant pleural disease

Surgical treatment of malignant pleural diseases is considered palliative (7) as the indication is usually advanced disease associated with significant morbidity. Minimally invasive approaches must be offered as first line treatment since they have the important advantages of causing less surgical trauma, reduced post-operative pain.

The accuracy of VATS for diagnostic purposes is undebatable with a 95% sensitivity rate for malignancy and its effectiveness in preventing effusion recurrence by facilitating chemical pleurodesis has been widely recognized (8). Most of the evidence for therapeutic VATS pleural surgery is for primary MPM. In the treatment of metastatic NSCLC therapeutic VATS is concerned mainly in the treatment of infected malignant effusion.

We will consider the role of VATS in the management of malignant pleural disease in the following processes (*Table 1*): (I) chemical pleurodesis or parietal pleurectomy if the lung expands; (II) indwelling pleural catheter (IPC) insertion or visceral pleurectomy in the entrapped lung; (III) debridement/decortication for the malignant pleural empyema.

*Lung seen to expand at VATS*

### VATS talc pleurodesis

VATS represent an invaluable diagnostic tool particularly in pleural Mesothelioma where the low diagnostic rate of pleural fluid cytology alone (20–32%), especially in the sarcomatoid type, makes of it an unreliable technique that needs to be supported with supplementary techniques as immunohistochemistry (9,10). Video-assisted thoracoscopy for the diagnosis of malignant mesothelioma has been also recommended as the technique of choice, allowing extensive inspection of the pleura and the taking of multiple and large biopsies that include subpleural tissue for the histological assessment of invasion (11). If the lung will expand, in order to achieve pleural symphysis talc poudrage is usually performed using 4–8 grams of sterile talc powder insufflated into the pleural space. Talc has been shown to have better efficacy than other sclerosants to prevent recurrence with a success rate of 81% to 100%. A recent study investigated the success rate and complications of low dose (5 gr) compared to high dose talc (10 gr) in patients with MPE, showed how the recurrence of pleural effusion (at 6 weeks) or immediate morbidity (48 hours) were statistically not significant between the two groups (P>0.05). Adult respiratory distress syndrome (ARDS) was not seen in either group (12).

### VATS parietal pleurectomy

As the parietal pleura seems to be most important in the physiologic mechanism of fluid production and absorption because of its proximity to lymphatic openings to the pleural cavity by and micro-vessels (13) the procedure of parietal pleurectomy can achieve successful recurrence free rates >90% at 12 months (14) with relatively lower risk then open surgery (15).

VATS parietal pleurectomy aims to produce fusion of the pleural cavity by using a similar technique to that used in pneumothorax surgery. Under general anaesthesia with single-lung ventilation, the first step is to evacuate the pleural effusion under vision and to assess whether the lung will re-expand with ventilation or whether it is entrapped which would contraindicate a parietal pleurectomy. The parietal pleurectomy is started from the anterior thoracoscopic access port and continued posteriorly down to the mediastinum and the costophrenic angle by blunt dissection of the extrapleural plane. The pleura over the pericardium and the diaphragm is usually spared but the remainder of all the visible foci of carcinomatosis are removed. Nevertheless, the adhesiolysis and debridement of pockets of effusions will eventually release the lung parenchima. At the end of the procedure the lung re-expansion is assessed. One or two chest drains are placed in the apex of the lung and at the base respectively and suction is applied.

Previous early reports had shown the feasibility and a better survival rate following a VATS debulking pleurectomy-decortication in advanced disease when compared to a thoracoscopic biopsy alone. In a retrospective study on 64 patients with MPM investigating the operative outcome of pleurectomy as a palliative treatment in patient unsuitable for extrapleural pneumonectomy the results showed that patients undergoing debulking of the tumour, drainage of the effusion, decortication, re-expansion of the lung, and pleurodesis had an overall median survival of 21.7 months (with a range of 1.4–52.7 months) when of epithelial histology versus 5.8 months for the sarcomatoid or mixed type (P=0.0001) (16). An UK cohort study comparing the actuarial survival of 79 patients with advanced MPM undergoing VATS pleural biopsy or VATS pleurectomy decortication showed feasibility and a significant improvement in survival in the debulking arm (127 *vs.* 416 d) (17).

The prognostic significance of video-assisted thoracoscopic partial pleurectomy (VAT-PP) compared to the standard approach with VATS talc pleurodesis offered to control the pleural effusion secondary to MPM has been assessed in the controlled randomised trial, the MesoVATS trial (18). The results showed that overall survival (OS) rates were not significantly different between the treatment groups and the VAT-PP approach was associated with increased side-effects related to the surgical procedure i.e., air leak and extended hospital stay and was therefore found to be economically disadvantageous. OS at 6 months was in fact estimated to be 78% in the VAT-PP group and 80% in the talc pleurodesis group, and at 1 year was estimated to be 52% and 57% respectively. Since the OS was the main outcome analyzed for the two groups in the study the benefits of the improved quality of life (QoL) were not sufficiently outlined (19). However, subgroup analysis showed that for patients with a favourable European Organization for Research and Treatment of Cancer (EORTC) prognostic score not only was OS at 6 months 88% but that there was significant effusion control and QoL improvement for up to 12 months. The overall impression created by the publication of the MesoVATS

trial was that there is no role for VATS-PP as there was no survival benefit over talc pleurodesis. At 1 year, OS was 37% in high-risk patients in the VAT-PP group and 53% in high-risk patients in the talc pleurodesis group, and 63% and 61% in the low-risk group for VAT-PP and talc pleurodesis, respectively. There remain, however, doubts surrounding the heterogeneity in surgical method (variable degree debulking in the experimental arm, medical and surgical thoracoscopy) and the patient population (different subtypes and stages of disease) which mean that the procedure may still have a role in selected patients. QoL of patients with malignant effusions should be evaluated with regard to those symptoms that are related to the effusion itself. Relief of dyspnea remains the primary objective for most patients. Ideally, therapy should minimize discomfort, as well as limit hospitalization time, in these patients with an often-limited life span. However, an important aspect in any treatment is prevention of reoccurrence of the symptomatic effusion (20).

While VATS-PP may be justified in the better prognostic group in the context of metastatic pleural involvement from cancers of non-pleural origin, these cytoreductive strategies are not routinely offered due to the usual concomitant detrimental effect of systemic therapies on patient's condition and the poorer life expectancy (21).

### Entrapped lung seen at VATS

### VATS placement of an IPC

An IPC is a silicone tube that is placed into the pleural cavity, tunnelled subcutaneously with a small (pro-fibrotic) cuff, with the other end exiting the patient with a one-way valve. Once tunnelled beneath the skin into the pleural cavity it can remain in place indefinitely, allowing easy drainage at home or in an ambulatory setting, by patients and their caregivers with minimal training. Management of symptoms as an outpatient allows patients to maintain control over their lives and minimizes the time the spent in the hospital (22).

There is increasing evidence that IPC are safe and effective in managing patient symptoms and improving the QoL median hospital length of stay for VATS pleurodesis is estimated as of 4 to 5 days, whereas an IPC is often inserted as a day-case surgical procedure. In addition, chemical pleurodesis requires sufficient body inflammatory response to fuse the visceral and parietal pleura in a short period of time. The tunnelled pleural catheter (TPC) procedure instead does not require this limitation and can be used in a wider set of patients (23).

In the TIME2 trial, an unblinded randomized controlled trial comparing IPC to talc pleurodesis, the IPC was inserted on an outpatient basis outpatient draining immediately a large amount of fluid, drainage was advised for 3 times weekly or as required for relief of dyspnoea. It showed how the dyspnoea improved in both groups, with no significant difference in the first 42 days (24). The improvement in dyspnoea and QoL in patients treated with IPC is comparable to talc pleurodesis up to 6 months, after which IPC may be superior in relieving dyspnoea and with the potential of autopleurodesis (25). Autopleurodesis is considered completely achieved when a decline in the amount of pleural fluid is observed (less than or equal to 50 mL on three consecutive attempts of drainage), absent or very minimal pleural effusion on the chest X-ray (CXR) (blunting <25% of the chest), and absence of symptoms. Spontaneous pleurodesis can develop in 40–70% of patients with IPC *in situ*, which permits catheter removal.

A rapid pleurodesis procedure, using the combination of thoracoscopy guided talc delivery for pleurodesis with TPC insertion at the same procedure takes advantages of both management strategies and minimizes some disadvantages. This method has previously been shown in two series to decrease hospital length of stay (mean 1.8–2 days), and duration of TPC use (mean 8–10 days) measured by time to pleurodesis while significantly improving dyspnoea and QoL in patients with MPE. It is to be considered an optimal management should the costs not be considered. The OPTIMUM trial is designed to determine whether full outpatient management of MPE with an IPC and pleurodesis improves QoL compared with traditional inpatient care with a chest drain and talc pleurodesis (26).

Nevertheless, catheter related complications can occur and include wound site infection, empyema, blocked or dislodged IPC, leakage around the catheter, pain or severe discomfort. Catheter tract metastases (CTM) although not uniformly defined in the different studies are new, solid chest wall lesions over the IPC insertion site and/or the tunneled subcutaneous tract. The reported incidence of procedure-tract metastases ranges in available literature from <1% to 10% and MPM seems the most predisposing cancer accounting for the majority of cases of IPC-related CTM (27).

Moreover, the presumed catheter and/or cancer induced fibrin deposition within the pleural cavity, along with the pleural symphysis resulting from the continuous drainage, can unfavorably induce septations and loculations, thus limiting effective IPC drainage. Hence, breathlessness in absence of pleural infection can be explained by the residual

effusion. IPC-related symptomatic loculations are reportedly present in 6–14% of IPC-treated patients (28), and typically occurs at about 2 months after IPC insertion (27).

Guidelines have advocated the use of IPCs in those patients with MPE that have failed pleurodesis or in those with trapped lung (TL) (unsuitable for pleurodesis). 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 wouldn't be fit for a major operation. In a case review from 6 UK Centres aiming at estimating the survival in cases of pleural infection treated with IPC for MPE the rate of pleural infection was calculated as being the 3.6%. Surprisingly the study showed that patients with mesothelioma or lung cancer associated with pleural infection outlived the cohort without a pleural infection with an almost doubled MST (753 *vs.* 339 d for mesothelioma, 138 *vs.* 74 d for lung cancer) hypothesizing a trigger role for the pleural infection in stimulating an immune response (29).

One advantage of VATS over percutaneous image-guided insertion of IPC is that the surgical operator is able to proceed to other thoracic surgical options, if appropriate, at the time of the thoracoscopy. In particular, on the basis of the intra-operative assessment of the extension of the pleural tumour involvement and the entity of the lung potential of expansion the IPC can be inserted at the end of the procedure. In a study on 116 patients with proven MPE a VATS technique, under general anaesthesia for fit patients (41/116), was preferred in those whose history or radiology wasn't obviously suggestive of TL.

**VATS visceral pleurectomy**
In advanced malignant pleural disease, the lung may become entrapped by a thickened visceral pleural rind of tumour which prevents its expansion causing underlying collapse and respiratory compromise. Therefore, the symptoms of dyspnoea are usually compounded by ventilation-perfusion mismatch within the entrapped lobe or lobes. This progressive disease process results in dyspnoea in most cases which can affect significantly the patients' QoL. The lung re-expansion achieved as result of a successful decortication can successfully impact on the hypoxia and ventilation perfusion mismatch. The visceral pleurectomy will be carried out one anatomical layer lower than in a decortication for empyema with an incision of the visceral pleura with endoscopic shears which allows to suspend an edge with artery forceps and starting the blunt dissection from the underlying parenchyma with a blunt dissector.

Intermittent continuous positive airway pressure can be applied to the operative lung to facilitate the dissection. The goal is to free all the lobes allowing adequate lung expansion and apposition of the parenchyma against the chest wall.

The ideal treatment of MPE should include adequate and enduring relief from symptoms (in particular dyspnoea), minimize hospitalization, and reduce adverse effects. Any planned treatment should balance the therapeutic benefit provided against the required period of convalescence for a disease with a limited life expectancy. 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 tumour progression and prolonging survival (30). In presence of recurrent pleural effusion and thickened cortex the benefits of VATS visceral pleurectomy in relieving the TL in metastatic adenocarcinoma and MPM have been shown since early reports (31).

In a prospective cohort study enrolling 51 patients presenting with malignant meosthelioma (MM) undergoing palliative surgical debulking relief of chest wall pain was observed too. And the authors suggest that intercostal nerve compression could be the explanation. The author reports 78.4 % of symptom control at 6 weeks (P value =0.01) and 70.6% and 41.2% at 3 and 6 months respectively. Patients with epithelial cell type and no weight loss were significantly more likely to retain symptomatic control than those with neither of these features (P<0.01) (32).

The recent randomized AMPLE trial failed to show any significant improvement in terms of breathlessness relief in the IPC arm over talc pleurodesis. The question of whether VATS visceral pleurectomy is more effective than a continuous drainage of the pleural effusion with an IPC is being addressed in the MesoTRAP trial (25).

This multicentre pilot clinical trial has been designed to be a preliminary study to a full Phase III study where the most effective management of a "TL" will be determined. It aims at randomizing 38 patients with TL and pleural effusion due to MPM who will be allocated in a 1:1 ratio to either video-assisted thoracoscopic partial visceral pleurectomy/decortication (VAT-PD) or IPC. The main inclusion criteria for the eligibility in the trial are: confirmed MPM, a "clinically significant TL requiring intervention in the opinion of the clinical team", presence of pleural effusion (following re-accumulation), and fitness to undergo VAT-PD.

The primary outcome measure is the improvement of breathlessness confirming; the main purpose of non-radical

treatments as symptomatic relief. The secondary outcomes include changes in 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.

### VATS debridement/decortication

A loculated malignant effusion may become secondarily infected, especially if multiple percutaneous drainage interventions or an IPC device have been attempted. VATS debridement is sufficient if the underlying lung will expand but VATS decortication of the inflammatory cortex may be successful even if the lung is entrapped (see above). The resolution of ongoing pleural infection is important if the patient is to be considered for cytotoxic chemotherapy.

In a recent single-centre review of 561 patients with initial diagnosis of empyema, negative pre-operative cytology, absence of radiological or clinical features, 35 patients (6.2%) had a post-operative histological diagnosis of malignancy. Two third of the patients were treated by VATS approach (33). The role of VATS has been widely described in benign simple or complicated empyema (34). A recent meta-analysis seems showing that video-assisted thoracic decortication (VATD) might be comparable or even better than open thoracic decortication in terms of operative time, postoperative hospital stays, chest tube duration, prolonged air leak rate, morbidity and mortality (35). But the literature lacks studies on the application of video-assisted thoracic surgery in malignant empyema. Empyema post VATS lung resection for lung cancer are rarely reported though. Only 1 (0.1%) case of empyema over 139 cases of pulmonary complications following VATS lobectomy for lung cancer was reported in a recent retrospective study where no mention of the treatment was made (36).

### Conclusions

VATS is designed to reduce chest wall trauma, preserve respiratory muscle function and therefore expedite recovery. Nowhere is this more important than in those patients with a limited prognosis with advanced malignant pleural disease. VATS also allow for therapeutic manipulation of the pleural environment including dissection techniques aimed at symptom control by direct tumour debulking.

### Acknowledgments

### Footnote

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