Video assisted thoracoscopic and open chest surgery in diagnosis and treatment of malignant pleural diseases

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Abstract: Parenchymal cancers of lung, breast, gastrointestinal tract and ovaries as well as lymphomas and mesotheliomas are among the most common cancer types causing malignant effusions, though almost all tumour types have been reported to cause a malignant effusion. The prognosis heavily depends on patients' response to systemic therapy however, regardless of the causing pathology and histopathologic form, malignant pleural disease is normally associated with a poor prognosis. To date, there are not sufficient data to allow accurate predictions of survival that would facilitate decision making for managing patients with malignant pleural diseases. Interventions are directed towards drainage of the effusion and, when appropriate, concurrent or subsequent pleurodesis or establishing long-term drainage to prevent re-accumulation. The rate of re-accumulation of the pleural effusion, the patient's prognosis, and the severity of the patient's symptoms should guide the subsequent choice of therapy. In contemporary medicine, not many cancers have managed to generate as intense debates concerning treatment, as malignant pleural mesothelioma. The relative advantages of surgery, radiation, chemotherapy and any combination of the three are continuously reassessed and reconsidered, even though not always based on scientific evidence. The aim of surgery in mesothelioma may be prolongation of life, in addition to palliation of symptoms. Longer recovery periods from more extensive surgical procedures could be justified, in carefully selected patients. Surgical options include: Video assisted thoracoscopic (VATS) pleurodesis, VATS partial pleurectomy (VATS PP)—both parietal and visceral; open pleurectomy decortication (PD)—with an extended option (EPD) and extrapleural pneumonectomy (EPP). Current evidence implies that EPD can be performed reliably in specialised centres with good results, both in terms of mortality and survival; however, no operation has yet been shown to be beneficial in a prospective randomized controlled clinical trial.

Keywords: Thoracic surgery; thoracotomy; video assisted thoracoscopic (VATS); pleural diseases; malignant; breast cancer; lymphoma; mesothelioma; asbestos; mesothelioma and radical surgery (MARS)

Introduction

There are three different mechanisms by which the pleura can be involved by malignancy: primary tumour, extension from adjacent tumour or pleural metastases (via haematogenous or lymphatic spread). The disease can manifest either with a solid or fluid component, or a combination of the two. Regardless of the causing pathology and histopathologic form, malignant pleural disease is normally associated with poor prognosis (1,2).

Patients with intrathoracic or extrathoracic malignancies complicated by malignant pleural effusions have a median survival of 4 months (2). Parenchymal cancers of lung, breast, gastrointestinal tract and ovaries as well as lymphomas and mesotheliomas are among the most

Table 1 Causes of paramalignant pleural effusions (9)

Local effects of tumor
Lymphatic obstruction
Bronchial obstruction
Trapped lung
Chylothorax
Superior vena cava syndrome
Systemic effects of tumour
Pulmonary embolism
Hypoalbuminemia
Complications of therapy
Radiation therapy
Chemotherapy

common cancer types causing malignant effusions, however near all tumour types have been described to cause a malignant effusion (3-8).

The incidence of malignant and paramalignant effusions in patients with metastatic malignancies can be as high as up to 50% (2). Paramalignant pleural effusions result from mechanical effects caused by the tumours to the pleural space (airway obstruction, mediastinal lymph node involvement, superior vena cava syndrome) while pleural fluid cytology and biopsies may remain non-diagnostic (*Table 1*). Histopathology results from fluid cytology or pleural biopsies are positive for cancer when a malignant effusion is present (9). It has been suggested from studies contacted post-mortem, that pleural metastases can occur due to tumour emboli on the visceral pleura which may result to parietal pleural seeding (10,11). Direct spread via neighbouring tumours as well as indirect spread via blood or lymphatic streams may also occur. When a topical inflammatory process develops due to tumour invasion, it could potentially lead to increased capillary permeability and development of effusions (12).

The prognosis heavily depends on patients' response to systemic therapy. To date, there are not sufficient data to allow accurate predictions of survival that would facilitate decision making for managing patients with malignant pleural diseases. Management in most cases remains palliative; it should be stressed however that the appropriate management approach should be based on available treatment options and medical expertise as well as the patient's clinical status. Malignant pleural effusions can severely impair patients' quality of life. Multiple palliative approaches are available to drain the effusion, and

to prevent it from accumulating, thus providing adequate symptomatic relief. Asymptomatic patients with malignant pleural effusions do not normally require treatment. Enrolment of patients in clinical trials, when these are available, is imperative for standardisation of different approaches, as well as utilisation of multi-modality and multi-level treatments that would provide the best possible outcome. Time is one of the few privileges we can provide to these patients; and we should aim to make every second count, taking good care not to sacrifice the quality of their remaining life in exchange.

Diagnosis

Dyspnoea remains the commonest presenting symptom in patients with malignant effusions. Patients may also present with non-specific symptoms, such as loss of appetite, loss of weight and fatigue, depending on the stage of their disease. More specific symptoms, including localised chest pain, cough and haemoptysis, are normally associated with distinct pathologies such as mesothelioma or bronchogenic carcinoma (13). Patients with a malignant effusion due to sarcoma have been reported to present with a pneumothorax (14).

Pleural effusions holding at least 50 mL of fluid can be visualised on lateral chest films thus initiating more detailed investigations (15). Other radiographic signs include crowded ribs, elevated hemidiaphragm, pleural thickening, lung atelectasis and ipsilateral mediastinal shift (16).

Thoracic ultrasound can be also used to confirm fluid collections, assess their characteristics and guide intervention (17,18). When morphological criteria similar to contrast-enhanced CT are applied, thoracic ultrasound can differentiate malignant and benign effusions with an estimated sensitivity of 79% and specificity of 100% (19).

Computed tomography with contrast enhancement provides the most useful information for the evaluation of patients with suspected malignant effusions, while also allowing for the detection of associated intra or extrathoracic disease (lymphadenopathy, parenchymal/bone lesions). CT thorax can differentiate benign from malignant disease by identifying specific characteristics, such as pleural thickening (20,21). In the case of pleural mesothelioma differentiation from metastatic pleural malignancy can be more challenging, as the two conditions share many CT features. Characteristics indicative of mesothelioma include involvement of the interlobar fissures, pleural thickening >1 cm and presence of calcified pleural plaques (22).

Table 2 Management of malignant and paramalignant pleural effusions (27)

Management plan	Result
Observation	Advised for asymptomatic effusions; however, most will progress and require therapy
Therapeutic thoracentesis	Provides prompt relief of dyspnoea; most effusions will recur if the underlying cause is not treated
Chest catheter drainage only	Most effusions tend to recur following catheter removal
Chest catheter drainage with chemical pleurodesis	Variable response rate with 60% to 90% of patients responding to talc pleurodesis
Thoracoscopy with talc insufflation	Control of effusion with similar frequency as chest catheter drainage with talc pleurodesis
Long-term IPC	Control of effusion and improvement of symptoms in most patients. Some patients may experience spontaneous pleurodesis, allowing for the catheter to be removed
Pleural abrasion or pleurectomy	Requires thoracoscopy or thoracotomy. Effectively controls effusions in nearly all patients
Pleuroperitoneal shunt	When other options have failed, or are not indicated; may be useful for chylothorax
Chemotherapy	May be effective in some tumour types, such as breast cancer, lymphoma, and small cell lung cancer
Radiotherapy	Mediastinal radiation therapy may be effective in lymphoma and lymphomatous chylothorax

IPC, indwelling pleural catheter.

Magnetic resonance imaging is not routinely used in the investigation of pleural effusions. It can however prove useful in occasions when use of contrast agents is contraindicated as well as for the assessment of diaphragmatic and chest wall involvement, where it has been confirmed to have superior accuracy when compared to computed tomography (23).

Positron emission tomography for malignant pleural disease has a reported sensitivity of 93% to 100% and specificity of 67% to 89% (24). False-positive results can occur in patients with accompanying inflammatory pleural conditions or following interventions, such as talc pleurodesis (25). Fused images can be used to guide diagnostic biopsies and differentiate between activity due to talc pleurodesis, by detecting pleural thickening with increased CT attenuation (26).

Principles of management of malignant effusions of the pleura

As prognosis remains poor, management of malignant pleural effusions is primarily palliative and aims to provide effusion control, allowing for symptomatic relief (*Table 2*). Early interventions are strongly advocated by some centres, in order to reduce future complications by preventing development of pleural loculations and infected cavities.

Interventions are directed towards drainage of the effusion and, when appropriate, concurrent or subsequent pleurodesis is performed to prevent fluid re-accumulation. Alternatively, permanent or semi-permanent drainage may be established for long-term management of recurrences. An initial thoracentesis does not decrease the effectiveness of subsequent procedures to produce pleurodesis. The appropriate management plan is devised based on individual patient characteristics such as the rate of re-accumulation, disease prognosis, and severity of symptoms.

Chemical pleurodesis has been widely adopted for means of palliation in patients troubled by symptomatic and recurrent effusions; a great selection of chemicals can be used, employed via different techniques, in an attempt to produce pleurodesis (*Table 3*). To this date, it remains somewhat uncertain if one agent is superior to another (28) however talc pleurodesis remains the preferred choice in many centres (29).

Management of malignant pleural effusions in specific diseases

Metastatic carcinoma

Lung
Lung cancer is the primary cause of malignant pleural effusions. During the course of the disease, the probability of such effusions to manifest can reach 35% (30). Even though effusions can occur with any histologic type,

Table 3 Success rates of commonly used pleurodesis agents (27)

Agent	Success rate reported (%)	Dose required
Talc	70–100	2.5–10 g
Doxycycline	60–81	500–1,000 mg
Iodopovidone	64–96	washout
Bleomycin	64–84	60 units

adenocarcinoma is the most frequent type observed (13,31). Presence of pleural effusion usually indicates an advanced stage of the disease (32), however further investigations should be carried out to confirm or exclude pleural involvement, as the effusion could be due to mechanical obstruction or imbalance of regional lymphatics and not associated with direct pleural disease (33). When non-invasive diagnostic techniques are unable to yield diagnosis, video assisted thoracoscopic surgery (VATS) is indicated. Not only it allows direct visualisation of the entire thoracic cavity and facilitates obtaining pleural biopsies from multiple locations, but also offers the option of providing concomitant treatment by achieving lung re-expansion and performing pleurodesis procedures, in a more efficient manner (34).

In metastatic pleural disease, unfavourable prognosis means that longer recovery periods from majorly invasive procedures are not justified. Surgery should be offered for diagnosis and palliation only, thus a minimally invasive technique such as VATS instead of open thoracotomy should be the only surgical approach to be considered (35).

Breast

Breast carcinoma ranks as the second most frequent cause of malignant pleural effusion. During the course of the disease, the probability of such effusions to manifest can be as high as 23% (30). Breast cancer patients can have different degrees of invasion (36) and can present with unilateral, ipsilateral or bilateral effusions (37,38). Further investigations for exclusion of non-malignant effusions should always be considered in patients who underwent postoperative chemotherapy (39). These effusions respond well to conservative management, whereas surgical management should be directed towards symptomatic relief and prevention of recurrence. Median survival will depend on response to systematic therapy (40), therefore it is vital that these patients can commence their treatment at earliest possible, without having to go through long recovery periods from their operations. Staged VATS procedures

may be required for management of bilateral malignant effusions.

Hematopoietic or lymphoid malignancies

Lymphoma

Lymphomas are the cause of 10% of malignant pleural effusions (41). In Hodgkin's lymphoma pleural effusion develops in the later stages of the disease, while in non-Hodgkin's lymphoma effusion can be seen as early as the time of diagnosis (42). The effusion may be unilateral or bilateral. The enlarged mediastinal lymph nodes are responsible for the obstruction of lymphatic flow in Hodgkin's disease, while in non-Hodgkin's lymphoma this is caused by direct infiltration of the parietal and/or visceral pleurae by tumour (43). Chylothorax most commonly manifests in non-Hodgkin's lymphomas (44).

Systematic chemotherapy is the treatment of choice while mediastinal radiotherapy is also given in cases of mediastinal involvement (44). If chylothorax occurs, conservative management is usually recommended as first line management, which consists of tube thoracostomy drainage, combined with low fat, medium-chain triglyceride supplemented regimens, or total parenteral nutrition in an attempt to reduce recurrence (45,46).

Surgical thoracoscopy is reserved for refractory chylothorax, which permits adequate drainage of the thoracic cavity and allows for concurrent pleurodesis to be performed, while it also facilitates ligation of the thoracic duct when indicated (47-50). Pleuroperitoneal shunt may also be considered when other measures fail to control reaccumulation of chyle (51). Although effective palliation has been reported in approximately 70–100% of patients, the incidence of shunt occlusion is as high as 25% at a median time of 2.5 months (29). Furthermore, the shunts can apply further burden on the patients, as they have to be frequently pumped during the course of a day.

Myeloma and leukaemia

Pleural effusions develop in about 6% of patients with multiple myeloma, of which less than 1% are classified as malignant (52). They reflects poor prognosis, with mean survival of less than 4 months (53). Suspected mechanisms include extension of plasmacytomas of the chest wall, invasion from adjacent skeletal lesions, direct pleural involvement by myeloma or following lymphatic obstruction secondary to lymph node infiltration (54).

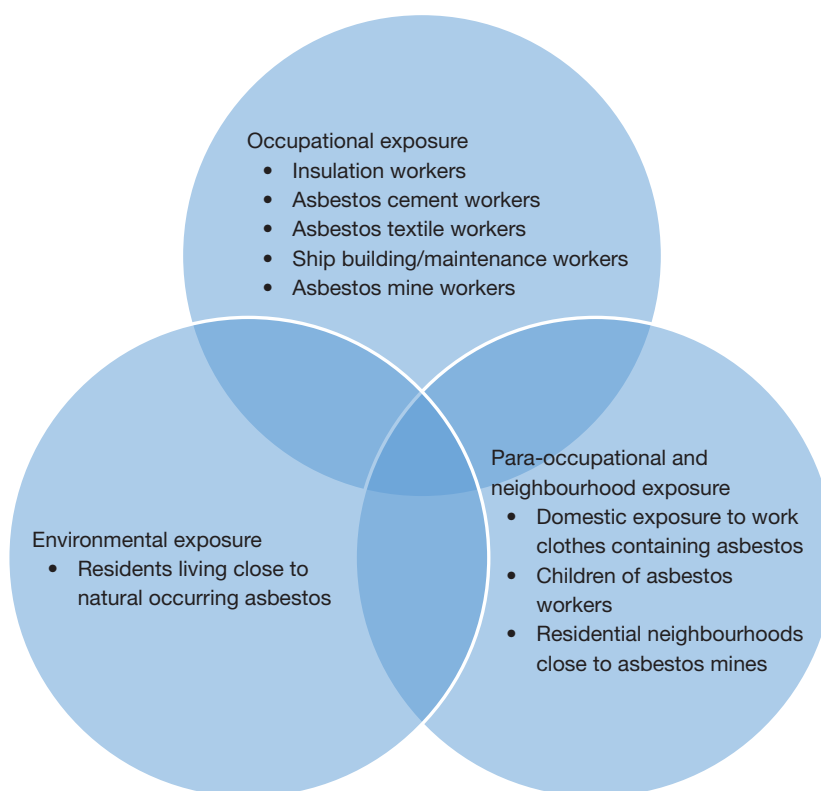In patients with chronic myeloid leukaemia pleural

Figure 1 Common asbestos exposure types associated with malignant mesothelioma (57).

effusion is rare, and hasn't been thoroughly examined (55). The possible mechanisms of exudative pleural effusion include leukemic infiltration into the pleura, extramedullary haemopoiesis, possible obstruction of pleural capillaries or infiltration of interstitial tissue by leukemic cells, increased capillary permeability, non-malignant causes (infection, hypoproteinemia) and drugs (56).

Systemic treatment is indicated; surgical management is restricted to diagnostic and pleurodesis procedures.

Malignant pleural mesothelioma

Less than 1% of all new cancer cases in the UK are diagnosed with mesothelioma. In 2014 alone 2,700 new cases were diagnosed with the disease, which equals more than 7 new cases every day. The disease predominantly affects males and half of the newly diagnosed cases are individuals aged 75 and over. One in every hundred men born in 1940s are estimated to die because of it. Mesothelioma incidence rates in Great Britain have increased almost six-fold since the late 1970s and by around a tenth over the last decade, with a larger increase

in females than males. Incidence rates for mesothelioma in the UK are projected to fall by 53% between 2014 and 2035, to 3 cases per 100,000 people by 2035. Approximately 2,100 people had survived the disease in the UK at the end of 2006, ten years after they were diagnosed with mesothelioma. Asbestos has been linked with approximately 94% of mesothelioma cases in the UK and remains the main potentially avoidable risk, while other risk factors may be related however they haven't been as extensively studied (Cancer Research UK: https://www.cancerresearchuk.org/) (*Figure 1*).

The global incidence of mesothelioma is not easy to estimate, mainly because it is a relatively rare cancer and not reported by many developing countries. Based on a combination of mortality data and asbestos use, an average of 14,200 mesothelioma cases are diagnosed worldwide each year. The highest number of cases in the world in encountered in the United States and the UK. In most European countries, the increase in incidence slowed down or remained static between the late 1980s and mid 1990s however, production and use of asbestos continues in many parts of the world, with Russia and China being

the main exporters (Cancer Research UK: https://www.cancerresearchuk.org/).

In contemporary medicine, not many cancers have managed to generate as intense debates regarding treatment as does malignant pleural mesothelioma. The relative advantages of surgery, radiation, chemotherapy and any combination of the three, are continuously reassessed and reconsidered, even though not always based on scientific evidence. The average life expectancy for mesothelioma patients ranges from 12 to 21 months; about 40% of mesothelioma patients survive the first year following diagnosis, and 20% live more than 2 years. There's great variation between individual reports which is unsurprising, considering the long incubation period and the often-late diagnosis of the disease. Today patients live longer than ever before, some survive 3, 5, even 10 years (American Cancer Society: https://www.cancer.org) (Asbestos.com: www.asbestos.com).

The aim of surgery in mesothelioma may be prolongation of life, in addition to palliation of symptoms. Longer recovery periods from more extensive surgical procedures could be justified, in carefully selected patients. Surgical options include: VATS pleurodesis, VATS partial pleurectomy (VATS PP)—both parietal and visceral; open pleurectomy decortication (PD)—with an extended option (EPD) and extrapleural pneumonectomy (EPP).

Diagnostic and palliative surgical procedures

Most patients during the time of their presentation will be found to be in an advanced stage of the disease, and there are currently not enough data to support that a radical surgical approach would be of benefit, given the risks of the operation and the long recovery period. In these end-stage scenarios surgery might be performed with a palliative intent, aiming to reduce the amount of fluid in the pleural cavity and allow lung re-expansion. Palliative surgical procedures should be primarily minimally invasive, to reduce the potential harmful effects of a thoracotomy (58).

Thoracoscopy for biopsy and pleurodesis

"Medical thoracoscopy" can be performed with a rigid bronchoscope under local or regional anaesthesia. The procedure can be performed for diagnosis or treatment, when it involves talc pleurodesis. A study by Valsecchi *et al.*, that included 2,752 patients who received medical thoracoscopy between 1984 and 2013, found that the overall likelihood that medical thoracoscopy would provide the information needed to accurately diagnose lung diseases such as mesothelioma increased from 57% to nearly 80%

over the course of the study period. Mesothelioma patients who presented with a pleural effusion, had a greater diagnostic yield than patients without an effusion (59).

VATS biopsy and pleurodesis is generally performed under general anaesthesia with double lumen intubation. It can also be accomplished with single lumen intubation or sedation and local anaesthesia (60). The patient is placed on the operating table in lateral decubitus position and the chest is prepped and draped as it would for a thoracotomy. Following lung isolation, the camera and the instruments are inserted in the thoracic cavity, preferably via a single, limited incision below the tip of the scapula, in the line of a future thoracotomy incision [thus limiting the possibility of disease dissemination via the wound (61)]. A small open incision may be performed in the case of a "dry" presentation of the disease when a complete obliteration of the pleural space precludes thoracoscopy. Detailed exploration of the thoracic cavity is performed after drainage of the effusion and biopsies are obtained from the anterior, posterior and diaphragmatic pleura. Deep and large biopsies, preferably including fat and/or muscle should be taken to enable assessment of possible tumour invasion. The anaesthetist is asked to re-inflate the lung, and its ability to fully re-expand and approximate the chest wall is evaluated. When the lung is seen to fully re-expand, asbestos-free talc is insufflated in the chest taking caution to distribute the powder to cover the entire cavity. After talc has been administered, a chest tube is positioned and remains *in situ* on mild suction, for a period of at least 48 hours, to allow the inflammatory process to take place and the lung to attach to the chest wall. The pleural space will then become sealed with scar tissue and fluid won't be able to re-accumulate. Talc pleurodesis has been found to achieve control of symptoms and low rate of recurrence (62,63). It has also been reported that a complete and persistent lung expansion after the procedure leads to a better prognosis (64). Povidone iodine can also be used in substitute of talc (65), especially if there's a suspicion for an infection complicating the effusion.

Chemical pleurodesis may be effective only when pleural apposition can be achieved, which depends on the ability of the underlying lung to fully re-inflate. Visceral pleura involvement by the tumour will normally result to an entrapped lung. In these cases, insertion of a permanent drainage catheter (66) or the risks and benefits of more extensive surgery, will need to be considered (67).

Both medical thoracoscopy and VATS are safely acceptable, with low mortality rates reported in the

literature (68). VATS positive predictive value has been reported to be as high as 99.7% (69). Compared to medical thoracoscopy, VATS allows for a more efficient drainage of loculated effusions trapped in dense fibrous bands. Medical thoracoscopy can be a cost-effective procedure in patients with poor tolerance for general anaesthesia, in an outpatient setting. Ideally, every case should be discussed between surgeons and interventional pulmonologists in a multidisciplinary setting. The TAPPS trial is currently underway to aid with decision making.

(I) TAPPS trial

An open-label controlled trial, designed to randomise 330 patients, with a confirmed malignant pleural effusion requiring intervention, to undergo either small bore (<14/Fr) Seldinger chest drain insertion followed by instillation of sterile talc (4/g), or to undergo medical thoracoscopy and simultaneous poudrage (4/g). The primary outcome measure will be the rates of pleurodesis failure (defined as the need for further pleural intervention for fluid management on the side of the trial intervention, at 3 months) (70).

Indwelling pleural catheter (IPC) insertion is an alternative to pleurodesis for definitive management of recurrent pleural effusions (71,72). These are soft, small-bore silicone catheters that can be tunnelled under the skin to avid risks of wound-site infections. The distal end of the catheter contains a one-way valve, which can be connected to a specially designed bottle allowing pleural drainage at home performed by the patient or a healthcare assistant, as per needed. The frequency of drainage is mostly guided by patients' symptoms, after the early period when it's performed daily, or on alternate days. IPCs can be used in patients in whom pleurodesis has failed or is contra-indicated, or as an alternative first-line treatment instead of pleurodesis. Spontaneous pleurodesis because of frequent, complete drainage may develop in up to 70% of patients without a trapped lung after an average of 52 days, and the catheter can then be safely removed. Catheter related complications include malfunction, blockage and site related pain (73). The reported incidence of procedure-tract metastases ranges in available literature from <1% to 10% (74,75).

There are currently not enough data to support whether chemical pleurodesis or the placement of a permanent pleural catheter for intermittent pleural drainage produces superior palliation, shorter hospital stay, and less morbidity. A study by Freeman *et al.* showed that pleural catheters provided palliation of patients' malignant pleural effusions and freedom from re-intervention equal to that of talc pleurodesis after thoracoscopy. The placement of catheters also resulted to reduced hospital stay, shorter interval to the initiation of systemic therapy and lower rates of operative morbidity (76). The TIME2 and AMPLE trials have been designed with a purpose of providing conclusive information.

(II) The second therapeutic intervention in malignant effusion (TIME2) trial

An unblinded randomized controlled trial comparing IPC to talc. Preliminary analysis demonstrated lower initial hospital stay in the IPC group, while dyspnoea improved from baseline and chest pain decreased from baseline in both arms (77,78).

(III) The Australasian malignant pleural effusion (AMPLE) trial

A multicentre, randomised study designed to compare IPC versus talc pleurodesis. Its primary end point will be the duration of hospital stay for any number of admissions, initiating at the moment of treatment until death or end of study. Secondary end points will include hospital days specific to pleural effusion management, adverse events, self-reported symptom and quality-of-life scores.

Thoracoscopic debulking: partial pleurectomy/ decortication

More advanced stages of the disease can result to an entrapped lung and parietal pleurectomy debulking may be considered as an addition to talc pleurodesis (79). It may be carried out effectively by VATS, achieving 90% effusion control at 12 months (80). The pleural space can be effectively obliterated by successful lung mobilisation combined with pleurectomy to lower the burden of the disease (81).

VATS PP can be performed via one or more ports. Parietal pleurectomy is performed by developing the extrapleural plane using thoracoscopic or traditional instruments, working down to the diaphragm and over the apex. The dissection plane is extended to the upper mediastinum, if possible. It is not normally possible to extend the dissection of the parietal pleura off the pericardium and the central portion of the diaphragm. Lung re-expansion is assessed and if it has not been achieved following fluid drainage, the anaesthetist is asked to apply positive pressure ventilation and then sharp and blunt dissection of the visceral pleura is undertaken in order to release the trapped lung. After securing haemostasis, apical and basal intercostal drains are routinely inserted and initially managed with mild suction. Their stay is guided by air leak. Systematic lymph node dissection is not routinely undertaken as the results of it are not expected to alter

further management, which will involve systematic therapy.

A best evidence topic by Srivastava *et al.* reviewed five prospective cohort studies to examine whether VATS decortication improved prognosis in patients with advanced malignant mesothelioma. The study concluded that VATS provides a diagnostic tool, while drainage of effusion and pleurectomy/decortication improves the quality of life and may also increase survival. However, definitive conclusion could not be drawn, thus a trial was designed in an attempt to give an answer to the question.

(I) MesoVATS trial

An open-label, parallel-group, controlled trial randomised patients to undergo either video assisted thoracoscopic partial pleurectomy (VAT-PP) or talc pleurodesis. Overall survival (OS) at 1 year was 52% in the VAT-PP group and 57% in the talc pleurodesis group. Surgical complications were significantly more common after VAT-PP and median hospital stay of VAT-PP patients was longer compared to the talc pleurodesis group. As a result of this trial VAT-PP was not recommended, and talc pleurodesis was considered more preferable. Significant quality of life improvement was observed for the VAT-PP patients at 6 and 12 months which would suggest a role for this treatment in patients who are expected to survive longer than 6 months (82).

As simple pleurodesis is considered ineffective in patients with an entrapped lung (66), palliation of dyspnoea may be achieved by decortication of the visceral surface. Whether this is more effective than continuing drainage of the effusion with an in dwelling pleural catheter will be addressed in the proposed MesoTRAP trial.

(II) MesoTRAP trial

MesoTRAP trial is a multicentre, randomised, feasibility study of IPC versus VAT pleurectomy decortication (VAT-PD) for trapped lung in mesothelioma. The study will provide information as to whether a full randomised controlled trial is achievable in a reasonable time frame and the number of patients required while a full trial will determine best management of trapped lung in malignant pleural mesothelioma (83).

Potential benefits of the association of fibrinolytics and talc is another area of interest. The Third Therapeutic Intervention in Malignant Effusion Trial (TIME3) was designed to provide more insight.

(III) TIME3 trial

TIME3 trial is a randomised controlled trial designed to assess dyspnoea relief and pleurodesis success following intrapleural urokinase in patients with non-draining malignant pleural effusion. Pleurodesis failure was not found to be significantly different between the urokinase and placebo groups while intrapleural urokinase was not found to improve dyspnoea. It was concluded that in this group of patients with high mortality and significant residual dyspnoea, alternative palliative measures should be considered.

Radical surgical procedures

Cancer-directed surgery has been independently associated with better survival (84), however substantial controversy remains as to what should be the recommended treatment strategy for malignant pleural mesothelioma.

Several studies contacted over the years have shown that patients with favourable disease characteristics may benefit from surgery with curative intent, in the context of multimodality therapy (85). Non-epithelioid histology, poor performance status (PS), low haemoglobin, male gender, high platelet count, high lactate dehydrogenase and high white blood cell count have been identified as poor prognostic indicators in mesothelioma (86). In a study by J. Francart *et al.*, the same variables, except for gender, were found to be significant for progression free survival (87). At multivariate analysis of the SEER study, independent significant predictors of survival were female gender, disease stage (distant versus local disease) and age. Survival was improved in the most recent calendar year of diagnosis, for patients diagnosed in 2005–2009 versus patients diagnosed in 1973–1989. Epithelial histology was associated with best survival in comparison to the other histologic types (84).

A widely acceptable staging system for malignant pleural mesothelioma had been practically non-existent for more than 40 years. A TNM staging system based on outcomes of retrospective surgical series and limited clinical trials was proposed by the International Mesothelioma Interest Group (iMig) in collaboration with the International Association for the Study of Lung Cancer (IASLC) in 1994 and was accepted by the American Joint Commission on Cancer and the Union for International Cancer Control. Since then it's considered the international staging standard (*Tables 4,5*).

More recently, the IASLC Staging Committee, developed an international database for the first evidence-based revision of the TNM staging system, and the eighth edition of the TNM classification for pleural mesothelioma is currently underway. According to revisions of TNM descriptors, both clinical and pathological T1a and T1b are expected to collapse to a single T1 classification (89), both clinical and pN1 and pN2 categories should fall into a single N category comprising ipsilateral, intrathoracic nodal metastases (N1) and nodes previously categorized

Table 4 The 1995 International Staging System for Mesothelioma (88)

TNM	Description
T (tumour)	
T1a	Tumour limited to the ipsilateral pleura including mediastinal and diaphragmatic pleura
	No involvement of the visceral pleura
T1b	Tumour involving the ipsilateral pleura including mediastinal and diaphragmatic pleura
	Scattered foci of tumour also involving the visceral pleura
T2	Tumour involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:
	Involvement of diaphragmatic muscle
	Confluent visceral pleural tumor (including the fissures), or extension of tumour from visceral pleura into the underlying pulmonary parenchyma
T3	Describes locally advanced but potentially resectable tumour; tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleural) with at least one of the following features:
	Involvement of the endothoracic fascia
	Extension into the mediastinal fat
	Solitary, completely resectable focus of tumour extending into the soft tissues of the chest wall
	Non-transmural involvement of the pericardium
T4	Describes locally advanced technically unresectable tumour; tumour involving all the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with at least one of the following features:
	Diffuse extension or multifocal masses of tumour in the chest wall, with or without associated rib destruction
	Direct transdiaphragmatic extension of tumour to the peritoneum
	Direct extension of tumour to the contralateral pleura
	Direct extension of tumour to one or more mediastinal organs
	Direct extension of tumour into the spine
	Tumour extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumour involving the myocardium
N (lymph nodes)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal thoracic nodes
N3	Metastases in the contralateral mediastinal, contralateral internal thoracic, ipsilateral, or contralateral supraclavicular lymph nodes
M (metastases)	
Mx	Presence of distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Table 5 The 1995 International Staging System for Mesothelioma (88)

Stage	TNM
IA	T1a N0 M0
IB	T1b N0 M0
II	T2 N0 M0
III	Any T3M0
	Any N1M0
	Any N2M0
IV	Any T4
	Any N3
	Any M1

Table 6 Eighth edition of the IASLC Staging System for Mesothelioma (89-91)

Stage	T	N	M
IA	T1	N0	M0
IB	T2 T3	N0	M0
II	T1 T2	N1	M0
IIIA	T3	N1	M0
IIIB	T1 T2 T3	N2	M0
	T4	Any N	M0
IV	Any T	Any N	M1

as N3 should be reclassified as N2 (90). No changes were proposed for M descriptors (91) (*Table 6*).

EPP

EPP is a highly complex intervention during which the parietal and visceral pleurae are resected en bloc with ipsilateral lung, hemidiaphragm and pericardium and has been associated with significant postoperative morbidity and mortality (92). Because locoregional recurrence comprises a major barrier to long-term survival, adjuvant radiotherapy has been advocated for local disease control; the removal of the lung in EPP allows for high-dose radiation without the risk of causing radiation pneumonitis. However, the routine use of hemithoracic radiotherapy was not shown to provide significant survival benefit according to the results of a recent randomised, international, multicentre phase 2 trial (93). Nonetheless, EPP has been combined with a range of other neoadjuvant and adjuvant strategies,

including systematic and intrapleural chemotherapy and photodynamic therapy, aiming to improve OS (67,94).

(I) Mesothelioma and radical surgery (MARS) feasibility study

The study was designed to assess feasibility and subsequently proceed to a larger study that would compare extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma. It was terminated because EPP was found to be associated with high morbidity, concluding that radical surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients.

The results were heavily criticised, as the trial had failed to recruit a significant number of patients and concluded based on only 30 deaths. This was a feasibility study, designed to assess the possibility of completing a larger trial to clarify the role of EPP and not to test the benefit (or absence) of EPP for patient outcome. Moreover, the histological types of patients who underwent operation were not reported, and the regimens applied to those receiving chemotherapy had been critiqued as being uncontrolled. Thus, its results could not had been directly compared to previous prospective multimodality studies in which survival was reported by intention to treat from the commencement of therapy (95).

The role of surgical cytoreduction in the treatment of malignant pleural mesothelioma was thoroughly discussed 1 year following the results of MARS trial during the 2012 iMig Congress. A team of surgeons, medical oncologists, radiation oncologists, epidemiologists, and basic scientists, agreed that surgical macroscopic complete resection and control of micrometastatic disease play a vital role in the multimodality therapy of MPM, thus surgical cytoreduction is indicated when macroscopic complete resection can be achieved. Patients diagnosed with malignant pleural mesothelioma should be initially assessed in multidisciplinary meetings while the decision for the type of surgery should be made based on clinical factors as well as on judgment and expertise of individual surgeons. The histologic subtype should be identified and clinical staging should also take place, before commencement of treatment (96).

EPP may still have a role when tumour invasion precludes sparing of the lung, as it is important to perform surgery with aim to obtain macroscopic clearance, or could be considered in young, fit patients with early stage epithelioid disease (97). Cervical mediastinoscopy should always precede EPP to exclude mediastinal involvement to a

possible extend (98-100). It should be highlighted however that the survival benefit which has been reported in the subgroup of the early stage, nodal free, fit patients could potentially be attributed to rigorous staging performed before an EPP and a "Will Rogers phenomenon" of stage migration. EPD patients who do not undergo lobar lymph node sampling at the time of their operation may be incorrectly understaged as N0.

Procedure technique

An epidural catheter is placed before the operation for postoperative pain control. The patient is then placed in lateral decubitus position and following double lumen intubation and single lung ventilation, an extended s-shaped posterolateral thoracotomy incision is performed, including when possible any previous incisions performed for diagnostic and pleurodesis purposes. Incisions that cannot be included in the thoracotomy incision should be excised separately at the end of the procedure unless the patient is expected to receive radiotherapy post-op. The thoracotomy incision can be extended further, towards the costal margin, providing exposure for diaphragmatic resection and reconstruction when necessary. The sixth rib is divided posteriorly to allow better access into the thoracic cavity. A median sternotomy approach has also been reported in selected cases with no chest wall involvement and low burden of disease as an alternative approach that would result in better pain control and speedier post-operative recovery (101).

An extrapleural plane is created by using blunt dissection, with sweeping motion of fingers, to separate the tumour from the endothoracic fascia. The dissection continues up to the apex, then down to the diaphragm, anteriorly to the pericardium, and posteriorly to the spine. Special care should be applied when dissecting near the azygous vein on the right and the aorta on the left, as dissection may lead to avulsion of the azygous vein or intercostal branches off the aorta. On the left side, attention is taken to identify the plane between the tumour and the adventitia of the aorta and the oesophagus. A nasogastric tube is positioned prior to dissection in order to aid in identifying the oesophagus; the tube can be kept *in situ* for gastric decompression, to minimize the risk of aspiration in the early postoperative period. Alternatively an oesophageal bougie can also be positioned, as its rigid shape makes it easier to identify. Caution should also be applied when dissecting apically to avoid injury to the subclavian vessels, as well as when dissecting near the superior vena cava on the right. Anteriorly, the plane is continued until the border of the

thymic fat and the pericardium. The anterior pericardium is incised and the inner surface is inspected for evidence of invasion, particularly in cases of substantial pleural effusion. The pericardium is resected en bloc with the anterior mediastinal pleura.

Inferiorly the diaphragmatic tumour is resected, taking care to identify the phrenic veins draining from the diaphragm directly into the inferior vena cava on the right. On the left a rim of diaphragmatic crus is preserved, to minimize risk of gastric herniation. The plane between tumour and normal diaphragmatic muscle or peritoneum at the level of the costophrenic sulcus can be developed to free the tumour from the diaphragm, however when involvement of the diaphragm is suspected it should be removed entirely to ensure macroscopic clearance margins.

The sequence in which the hilar structures are divided is decided by their exposure. The superior and inferior veins are divided intrapericardially. Although the right pulmonary artery is usually divided intrapericardially, the left is generally divided extrapericardially, due to its short intrapericardial length. The mainstem bronchus is dissected free from lymph nodes, divided and closed, and the bronchial stamp is tested for air leak. An intercostal muscle flap or similar strategies can be applied at the end of the procedure, to minimise risk of a bronchopleural fistula. The specimen consisting of pleura, lung and diaphragm, with or without pericardium, is removed en-bloc. Systematic lymph node dissection is undertaken for staging purposes.

The diaphragm is reconstructed with a Gore-tex® patch. An absorbable mesh is used for pericardial reconstruction, to prevent cardiac herniation and facilitate postoperative radiotherapy. The pericardial patch must be loose with adequate fenestrations to minimize risk of tamponade, but secure enough to prevent herniation. The inferior border of the pericardial patch must be secured to the diaphragmatic patch in addition to the pericardial rim, to prevent herniation of abdominal contents medially.

A large-bore chest tube, usually 32 Fr, is positioned near the diaphragmatic patch to allow for monitoring of bleeding and/or stump breakdown. The thoracotomy incision is closed and the intercostal muscles are re-approximated, to prevent fluid draining through the wound from the pleural space.

Interestingly, a case of video-assisted thoracoscopic EPP has also been reported (102).

Complications

Patients after their operation should be transferred to a highly monitored environment, such as an intensive care

or high dependency unit. The first days of the operation are crucial to the recovery period, as immediate post-op complications should be recognised and addressed promptly. The extensive dissection could result in injuries to endothoracic structures, causing bleeding, vocal cord paralysis, hypotension, arrhythmias, increased risk of aspiration, chylothorax, herniation, thromboembolic events, fistulae, sepsis and death (103).

EPD

Even before the publication of the MARS trial results, a transition from EPP to EPD was already underway due to the shift in demographics of mesothelioma patients, the strict selection criteria applied for EPP, the reported risks and unverified benefits associated with the procedure (104). The transition from EPP to EPD, primarily enabled surgeons to operate on patients that would be denied a pneumonectomy because of age or frailty, without significantly affecting hospital resources and OS (105).

Current evidence suggests that EPD should be preferred when technically feasible, as it is associated with a 2 ½-fold lower short-term mortality than EPP (106). Even though it should be emphasized that patient selection and treatment strategies are different between EPP and EPD, a meta-analysis found that when EPD was performed in a selected group of patients, it resulted to lower perioperative morbidity and mortality with comparable, if not superior, long-term survival compared to EPP, in the context of multi-modality therapy (107).

(I) MARS 2 trial

A feasibility study comparing EPD versus no PD in patients with malignant pleural mesothelioma, randomised to undergo chemotherapy only or chemotherapy and lung-sparing surgery. Mr Eric Lim, the principal investigator of the study recently reported that MARS2 has indeed been proven feasible and will now proceed to the full trial that seeks to randomise 326 patients to determine the impact of EPD, the currently most commonly performed operation, on OS (108).

Pleurectomy and decortication should be intended to provide macroscopic complete resection leaving only microscopic disease (R1 resection). An EPD with resection of pericardium and/or diaphragm may be required to achieve macroscopic clearance. This contrasts with VATS PP which leaves an R2 resection with visible residual disease. MesoVATS suggested benefit in EORTC low risk patients (Epithelioid histopathology, good PS) for VATS PP however even in these better prognosis "good actors" with epithelioid, node negative disease, EPD still holds a survival benefit over VATS PP.

(II) VATS PP vs. open PD

The MesoVATS trial showed that video-assisted partial pleurectomy decortication (VATS-PP) conferred no survival benefit over talc pleurodesis, but did improve pleural effusion control and quality of life in low risk patients based on the EORTC prognostic score. A study contacted at Glenfield hospital in Leicester by Sharkey et al., compared clinico-pathological data for 279 consecutive surgical patients from a prospective single centre database where 65 patients underwent VATS-PP and 214 had EPD. Patients were split into (MesoVATS) high-risk and low-risk groups based on three or more of: non-epithelioid histology, white blood cell count >8.2, ECOG PS >0 and male gender. Results showed that 38 (58.5%) VATS-PP patients, and 146 (68.2%) EPD patients fell into the low-risk group. There was a significant survival difference between the high and low-risk groups overall [8.72 vs. 15.1 months (P=0.005)]. Female gender and non-epithelioid histology were poor prognostic factors in both high and low risk groups. In the low risk group, there was a significant survival advantage for those patients with epithelioid histology and with a PS of 0 undergoing EPD versus VATS-PP [17.4 vs. 10 months (P=0.017)]. The study concluded that whilst VATS-PP may give better effusion control and improved quality of life over talc pleurodesis in low-risk patients, patients with epithelioid histology and PS 0 should preferentially be considered for more radical surgery (109).

The conclusion was based on the results from a previous study by the same group, which was conducted to determine whether extended pleurectomy decortication (EPD) conveys any survival benefit over VATS PD. According to the results from that study, 30- and 90-day mortality was similar between the two groups of patients as was OS. From the EPD group a smaller subgroup of node negative patients showed better survival compared to VATS. Marginally better survival was also noted again after EPD, in patients with epithelioid disease. The extent of surgery had no effect on survival in patients with biphasic cell type. It was only the smaller subgroup of epithelioid, node negative, EPD patients that demonstrated significantly better survival compared to the epithelioid VATS PD subgroup (110).

Procedure technique and complications

The procedure follows similar steps with an extrapleural pleurectomy. The lung is preserved with only non-anatomical resections being performed when necessary, if parenchymal involvement through the visceral pleura is evidenced or suspected intraoperatively. After the parietal

pleura has been fully mobilized, it is incised to create a plane into the pleural space. The underlying lung is stripped away from parietal pleura, also removing all areas of visceral pleural tumour. Talc pleurodesis which normally proceeds open radical surgery will have caused a thick fibrotic reaction, fusing pleurae together, and that can provide substantial aid during visceral decortication. In patients with extensive visceral pleural disease, this part of the dissection may require a considerable amount of time and is expected to result to an extensively or completely denuded lung. The difficulty is depending on the frequency of septae which interrupt the smooth parenchyma of the lung surface, creating lobules that make visceral pleurectomy technically challenging. Intriguingly, removal of the tumour from the pulmonary fissures can be completed swiftly as the number of septae present in the fissure is almost always minimal.

As per the definition of the procedure (111), diaphragmatic and/or pericardial resection might be required to secure macroscopic clearance of the disease. During diaphragmatic reconstruction, caution should be taken to ensure that the prosthesis will be positioned at the same level as the native diaphragm and will have enough tension to overcome the abdominal pressure, allowing the lung to re-expand to a satisfactory degree. Dehiscence of the diaphragmatic patch can be avoided by placing a nasogastric tube during the time of the operation, which will remain during the first post-operative days relieving any gas that builds in the stomach. Patients can be either slowly re-introduced to oral feeding or parenteral feeding can be given for a short period of days, as per individual surgeon's preferences.

After complete excision of the tumour from the lung parenchyma, the chest is vigorously irrigated to remove remaining cells. Two or three large-bore chest tubes, usually 32Fr, are positioned at the end of the procedure to ensure adequate air and fluid drainage, allowing for lung re-expansion. Fluid output is normally high during the first post-operative days and prolonged air leak is to be expected. Drains should remain *in situ* until oral feeding is commenced, to identify a potential complication of thoracic duct leakage and chylothorax. Patients can be safely discharged home with a drain once they have recovered to a satisfactory level, with air leak being the only reason requiring medical attention. They can be regularly reviewed as outpatients and their drains can be removed once air leak ceases.

Conclusions

Malignant metastatic disease is associated with a poor prognosis and even though multiple well-tolerated techniques exist, management is intended for control of effusion and palliation.

Malignant pleural mesothelioma is a heterogeneous disease with prognosis determined by cell sub-type and by nodal stage. The selection of the optimal surgical procedure should balance its morbidity with the benefits to the patient. Those with node positive, non-epithelioid disease (bad actors) should receive minimally invasive VATS with the aim of effusion control. Those of better PS with node negative, epithelioid disease should be considered for open surgery but with the specific aim of macroscopic complete resection. Only in the minority with stage I, epithelioid MPM below the median age with PS 0 should be considered, unless proven otherwise.

In all above scenarios, the role of surgery within multimodality therapy should be remembered, as any benefit to surgery in mesothelioma relies heavily on the addition of effective adjuvant therapies. Ongoing research adds to our knowledge; a better genetic and molecular understanding of the disease characteristics may lead to development of modern treatment options, allowing for a successful multimodality therapy in the foreseeable future.

Current evidence implies that (Extended) pleurectomy decortication can be performed reliably in specialised centres with good results, both in terms of mortality and survival; however, no operation has been shown to be beneficial in a prospective randomized controlled clinical trial.

Lastly, when selecting any treatment modality, we need to always remember to weigh into our decisions the patient's preferences and the effect our actions will impose to the quality of life of the patients themselves, and the family that supports them.

Footnote

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