Treatment of Malignant Pleural Effusions

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KEYWORDS

• Malignant pleural effusion • Pleurodesis • Indwelling pleural catheter • Nonexpandable lung

KEY POINTS

- Talc slurry, with a chest drain or talc poudrage, via thoracoscopy has equivalent pleurodesis success rates.
- Indwelling pleural catheters (IPCs) enable effective ambulatory home-based control of fluid volumes.
- Combining IPC with talc instillation increases pleurodesis rates above standard IPC use alone.
- Accelerated IPC drainage strategies increase pleurodesis rates above standard IPC use alone.
- Combination IPC and thoracoscopic talc poudrage does not shorten the length of hospitalization when compared to thoracoscopic talc poudrage alone.

INTRODUCTION

Malignant pleural effusion (MPE) describes pleural effusions secondary to cancerous involvement of the pleura from any primary tumor.[1] It is a common cause of morbidity in patient with malignancy, with 15% of people diagnosed with cancer developing pleural effusion during the course of their disease.[2] The majority of patients with MPE is symptomatic, with breathlessness the most common symptom.[3] Given the poor prognosis, the aims of treatment are predominately palliative symptom control and optimizing quality of life (QOL).[4] Some patients will benefit not just from relief of dyspnea but also from a resultant increase in performance status making them suitable for further systematic anti-cancer therapy (SACT).[4] Given this, treatment is typically initiated on the basis of symptoms limiting QOL (and occasionally performance status), rather than purely on the existence of excessive pleural fluid within the thoracic cavity.[1,5]

Over the last 10 years, there has been substantial progress in MPE management pathways, with improved prognostication and greater number of management options, allowing for a more personalized approach. This article with summarize the latest evidence and developments in the treatment of MPE.

Personalizing Malignant Pleural Effusion Management: Individualized Prognostication

The prognosis of MPE is typically poor, with a median survival of 5 to 12 months,[5–7] although this varies significantly by tumor type. Mesothelioma has, on average, the longest median survival and lung cancer the shortest.[6,8,9] Several studies and case series have been published analyzing the utilization of MPE biochemistry and its role in predicting survival. These have identified a correlation between low pleural pH (particularly <7.2),[1,10–14] and low pleural glucose (typically <60 mg/dL)[7,11,12,15] with worse prognosis. Other, small studies have refuted these associations,[7,16] and most importantly, a meta-analysis published in 2000 found both variables to be of insufficient predictive value regarding prognosis to be of clinical use.[17] Size of effusion

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Abbreviations

AEs	adverse events
ARDS	acute respiratory distress syndrome
CI	confidence interval
CXR	chest x-ray
ECOG	European Cooperative Oncology Group
ECOG PS	European Cooperative Oncology Group performance status
ICD	intercostal chest drain
IPCs	indwelling pleural catheters
LAT	local-assisted thoracoscopy
LDH	lactate dehydrogenase
LoS	length of stay
MPE	malignant pleural effusion
NEL	nonexpandable lung
NLR	neutrophil-to-lymphocyte ratio
QOL	quality of life
RCT	randomized-controlled trial
RPO	re-expansion pulmonary edema
SACT	systematic anti-cancer therapy
STI	speckle-tracking imaging
TIMP1	tissue inhibitor of metalloproteinases 1
TP	talc poudrage
TS	talc slurry
VATS	video-assisted thoracoscopy surgery

has also been identified as negatively correlating with prognosis,[6,12,18] with conflicting results regarding the prognostic value of the extent of pleural carcinomatosis.[7,14]

Type of cancer and performance status have repeatedly been associated with survival in MPE,[6,10,11,15,17] in addition to stage of cancer. These latter variables are incorporated in the LENT score, the first published validated prognostic scoring system for all types of MPE.[8] LENT stratifies patients with a confirmed diagnosis of MPE based on their pleural lactate dehydrogenase (LDH) level, European Cooperative Oncology Group (ECOG) performance status, neutrophil-to-lymphocyte ratio, and tumor type into low-risk (median survival 319 days), moderate-risk (median survival 130 days), or high-risk (median survival 44 days) groups (**Table 1**). It was robustly developed using an international patient cohort (UK, Australia and the Netherlands), and it is easy to use, utilizing readily available information. It has its limitations, however; over 60% of studied patients fell into the moderate-risk group, which also had the widest range of survival, potentially limiting clinical applicability.[19] It was also developed before testing for common lung cancer genetic mutations that carry better prognosis.[20,21] This may limit the generalizability of LENT in Asian regions where gene mutations such as epidermal growth factor receptor mutations are more common.

The second validated scoring system for MPE, PROMISE, was published in 2018.[9] PROMISE similarly utilizes ECOG performance status and cancer type in its system, with the remaining variables including previous treatment with chemotherapy or radiotherapy, hemoglobin level, serum white cell count, and C-reactive protein (CRP) in its clinical score, with the addition of tissue inhibitor of metalloproteinases 1 (TIMP1) in its biological score variant (**Table 2**). The resultant score divides patients into groups A to D with the following 3 month mortality risk: A less than 25%, B 25 to less than 50%, C 50% to less than 75%, and D greater than 75%. Like the LENT score, PROMISE benefits from a robust validation data set (notably larger than LENT) and, like LENT, uses largely readily available data (except for TIMP1). It also has very similar limitations of a requirement for a pleural intervention.

Knowledge of likely prognosis is clearly beneficial to both the patient and treating physician, as it allows better discussions on optimal treatment pathways. Importantly, neither LENT nor PROMISE has been shown to improve patient-reported outcomes.

TREATMENT OPTIONS

The current treatment options for MPE are invasive and include therapeutic thoracentesis, chest drain insertion, indwelling pleural catheter (IPC), thoracoscopy, and pleurodesis techniques. There is evidence that certain combination techniques can lead to better outcomes. The following section will describe all treatment options and their relative risks and benefits.

Therapeutic Thoracentesis

Therapeutic thoracentesis is typically the first-line intervention for patients with MPE. The vast majority of patients will experience symptomatic improvement from therapeutic thoracentesis.[4,5,22] It is a simple procedure that can be delivered as an outpatient or day case by a wide range of health professionals.[23,24] This means wait times for thoracentesis can be minimal. It can also be used to establish the extent a patient's symptoms are caused by their MPE, which is essential in guiding the next steps in symptom management.[1,25] This, in combination with repeat imaging postprocedure, is also part of the clinical assessment for nonexpandable lung (NEL),[1] which is a significant consideration in planning next steps in MPE care as will be discussed later.

Thoracentesis, however, can cause complications and a repeat pleural procedure is usually required. Large volume therapeutic aspirations

Table 1
The LENT score calculation[8]

	Variable	Score
L	LDH level in pleural fluid (IU/L)	
	<1500	0
	>1500	1
E	ECOG PS	
	0	0
	1	1
	2	2
	3–4	3
N	NLR	
	<9	0
	>9	1
T	Tumor type	
	Lowest risk tumor types • Mesothelioma • Hematological malignancy	0
	Moderate risk tumor types • Breast cancer • Gynecological cancer • Renal cell carcinoma	1
	Highest risk tumor types • Lung cancer • Other tumor types	2

Risk Categories	Total Score
Low risk	0–1
Moderate risk	2–4
High risk	5–7

Abbreviations: ECOG PS, European Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio.

Table 2
PROMISE score calculation[9]

Biological PROMISE Score	Points
Chemotherapy	
No	0
Yes	3
Radiotherapy	
No	0
Yes	2
Hemoglobin (g/dL)	
>16	0
14–16	1
12–14	2
10–12	3
<10	4
White blood cell count (10^8 cells per L)	
<4	0
4–6.3	2
6.3–10	4
10–15.8	7
>15.8	9
C-reactive protein (IU/L)	
<3	0
3–10	3
10–32	5
32–100	8
>100	10
ECOG performance status	
0–1	0
2–4	7
Cancer type	
Mesothelioma	0
All other types of cancer	5
Lung	6
TIMP1 (ng/mg protein)	
<40	0
40–160	1
>160	2

Abbreviations: ECOG, Eastern Cooperative Oncology Group; TIMP1, tissue inhibitor of metalloproteinases 1.
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raise concerns over re-expansion pulmonary edema (RPO). The significance of RPO lies in its oft-quoted mortality of up to 20%, which ubiquitously references Mahfood and colleagues'[26] review of 53 cases. Given the now broader published data on the subject, and the occurrence of 0 deaths in number of studies totaling 10,525 procedures,[27–29] the reality is likely to be significantly lower. Also reassuring is the article currently in press by Shojaee and colleagues[30] showing no differences in rates of RPO when utilizing wall suction versus gravity-enabled large volume thoracentesis.

Beyond the risk of RPO in pleural aspirations, each procedure carries a risk of symptomatic hypotension/vasovagal (<1%), organ puncture (<1%), intrapleural bleeding (<1%), failed procedure (4%), pneumothorax (<5%), pain (5%),[31–33] and malignant metastatic seeding along the procedure tract (varying risk dependent on cancer type with particular concern around mesothelioma).[31] The results of the awaited PROSPECT study should further elucidate the rates of, risk factors for, and mechanisms behind, these complications.[34] While the risk of each procedure is low, each has the potential to be life-threatening, and the risk to the patient multiplies with each procedure. Most patients with MPE will reaccumulate fluid after an initial pleural aspiration,[23,35] with

around a third needing a further pleural procedure within 2 weeks.[23,36] Relying, therefore, on recurrent aspiration as a primary treatment modality, as compared to a more definitive approach for the second procedure, can therefore expose the patient to a greater total number of procedures and more complications.[23]

There is currently no validated predictive model for the speed of fluid reaccumulation after a first procedure. Two published studies have found an association between a larger volume initial aspiration and fluid recurrence,[35,36] while one has also demonstrated an increased chance of fluid recurrence with larger initial effusion size on chest x-ray (CXR), higher pleural LDH, and positive cytology.[36] In the latter study, however, the positive predictive value of the resultant model incorporating these factors had poor predictive value and lacked external validity.[36] The results of the awaited REaccumulation rate of Pleural Effusion After Therapeutic aspiration (REPEAT) study[37] may provide further insight into this vital area of research.

Overall, the risk and benefit profile of repeated thoracentesis as a primary management technique for MPE supports its use only in those with a very short survival.[38]

Intercostal Chest Drain and Chemical Pleurodesis

When a patient has demonstrated symptomatic relief with drainage of their MPE and there is sufficient fluid in the pleural space, an intercostal chest drain (ICD) can be inserted with the intention of draining the fluid and instilling a chemical sclerotic agent. The efficacy of pleurodesis (defined preferentially as a lack of radiological recurrence in combination with the need for no further pleural interventions, or secondarily on purely radiological groups) via a combination of ICD and chemical agent instillation overall is 65% to 90% in research conditions.[1,2,10,39] Extensive research has been undertaken to identify the optimal chemical pleurodesis agent including studies of talc, tetracycline, bleomycin, silver nitrate, viscum, doxycycline, mepacrine, mitoxantrone, mustine, bacteria (eg, *Corynebacterium parvum*, *Streptococcus pyogenes*, and *Staphylococcus aureus*) and others.[1,2,4,39] A recent Cochrane review,[2] in addition to systematic and narrative reviews from several other teams,[1,2,5,10,40,41] however has concluded that the data do not support recommending any specific agent in terms of pleurodesis efficacy. Less commonly, reviews have been conducted to compare side effect rates between pleurodesis agents with again no significant differences identified in fever,[2,41] pain,[2,41] mortality,[2] or wound infection.[41] Each review in this field has also highlighted the high heterogeneity between studies, in particular differing definitions of pleurodesis, inclusion criteria, and outcome time points, resulting in difficulties combing studies and wide credible intervals and confidence intervals.[1,2,5,10,40] It is possible that if further modern studies with standardized study outcomes were undertaken, a superior agent may be identified.

Talc is now the most commonly used agent, with the greatest number of studies evaluating its efficacy and assessing its side effect profile.[2,5] Doses from 2.5 to 14 g have been used in research[1]; however, there has been no systematic study of the optimal dose in humans. Based on expert opinion, the American Thoracic Society recommends a maximum dose of 5 g to minimize the risk of complications.[1] The size of talc particles has been more adequately established with multiple human and animal studies identifying lower rates of local and systemic inflammation associated with graded (large particle size) versus ungraded (low particle size) talc.[42,43]

Other variables in the ICD and chemical pleurodesis technique have been evaluated to optimize chances of successful pleurodesis. Patient rotation after instillation of the sclerosant has been demonstrated to be largely inconsequential to the distribution of the agent within the pleural space through 2 studies utilizing scintographic tracking of sclerosant movement,[44,45] and in one small randomized-controlled trial (RCT) of rotation versus no rotation, to have no impact on pleurodesis rates or survival.[46] While the studies are limited in number and with small populations, given the patient discomfort and nursing time required in patient rotation, this practice has been mostly abandoned.

Three prospective randomized trials have been published comparing small versus large chest drains in combination with a sclerosant for MPE. Two single-center studies (combined patient number of 83) identified no significant difference in pleurodesis rates, complications, or pain. The TIME1 study,[47] the largest multicenter randomized trial (114 patients eligible for tube size comparison), demonstrated small bore tubes may be inferior to larger chest tubes in terms of pleurodesis success, failing to meet the 15% noninferiority criteria for pleurodesis failure. The study was, however, underpowered for this outcome because of the high number of patients undergoing thoracoscopies. Smaller drains may be less painful, with lower average pains scores statistically. This did not, however, reach a clinically significant level. There was no between group difference in all-cause mortality or adverse events (AEs). No data were presented on a length

of stay (LoS) comparison. A 2018 meta-analysis comparing large versus small drains in combination with a sclerosant (3 studies) or alone (1 study) in a total of 231 patients identified no significant difference in pleurodesis efficacy or "complication proportion" (the definition of which is poorly detailed) in pooled analysis.[48]

The duration of drainage presclerosant and postsclerosant instillation has also been the subject of a handful of studies. Villanueva and colleagues[49] and Ozkul and colleagues[50] both compared usual care (sclerosant instillation once radiological confirmation of lung expansion and drain outputs <150 mL/24 h or <300 mL/24 h, respectively) versus installation on radiological confirmation of lung expansion and effusion resolution regardless of ongoing output. Both identified no significant difference in pleurodesis rates between the 2 groups but with a significant reduction in LoS (a difference of 5 and 6.8 days, respectively) favoring the experimental group (those receiving sclerosant instillation regardless of ongoing drain output). Gupta and colleagues[51] and Goodman and Davies[52] compared postsclerosant instillation drainage duration and identified a shorter duration (12 and 24 hours after talc, respectively) was associated with equal pleurodesis success rates and significantly shorter LoSs versus usual care. Finally, a hybrid "rapid pleurodesis" approach with shorter presclerosant and postsclerosant drainages was trailed by Yildirim and colleagues,[53] again identifying equal pleurodesis rates with significantly shorter LoSs (median of 2.3 days in the rapid group vs 8.3 in the usual case group). All these studies are single-site and largely of sample sizes of 25 to 106 patients. A multicenter study with an adequately powered sample size is needed to optimize the drainage duration for this technique as it would offer significant patient advantages.

Advantages and disadvantages of intercostal chest drain and talc

Like all pleural procedures, ICD placement involves well-established immediate risks like those described earlier. Delayed complications of ICD placement most notably include drain dislodgement (1.3%–9.2%), drain blockage (8.2%), surgical emphysema (<5%), skin and pleural infection (<1%), RPO (<1%), and ultimately death (up to 0.1%).[32] Rates of complications vary broadly based on numerous factors including the experience of the practitioner, placement in an emergency in the emergency department versus elective insertion by a specialist, patient body mass index (particularly above 30) and size of drain, among others.[32,54]

Instillation of talc also carries independent risk. As talc works by inducing inflammation, the most common risks are pain and fever.[2] In a large Cochrane study rates of MPE treatment, rates of fever and pain associated with talc slurry (TS) were 5.6% to 35.7% and 0% to 100%, respectively.[2] Severity of pain associated with talc is hard to identify although TIME1 utilized 0 to 100 mm visual analog scores and reported mean scores of 22.0 to 26.8 mm.[47] Concerns have long existed around talc associated acute respiratory distress syndrome (ARDS)/acute respiratory failure. It is very challenging to properly identify the rates of these outcomes genuinely attributable to TS administration as the MPE patient group is by nature complex and at risk of respiratory deterioration. While early case series reported worrying high levels, large studies and service audits have since identified rates closer to 0% to 4%.[55–58] A large prospective cohort study with the primary outcome of talc safety found no cases of ARDS associated with talc in 558 patients.[59] Similarly, a meta-analysis including 4482 patients who underwent thoracoscopic talc insufflation identified 0 cases of ARDS and 0 cases of respiratory failure.[57]

A final disadvantage of treatment with ICD and a sclerosant is the necessity of a hospital admission. The average LoS in the published studies utilizing talc is 4 to 15.4 days.[60–65] While overall this is a short time period, given the often short prognosis of the MPE cohort, this can represent a significant part of their remaining time spent away from their family in hospital. As described earlier, however, it is possible that LoS could come down with new "rapid pleurodesis" approaches.

The main advantage treatment with ICD and a sclerosant is the high pleurodesis rate as described earlier. In addition, as the ICD and sclerosant pathway has been in practice for a long time, it is underpinned by a large volume of robust evidence to enable patients to be confident of making an informed choice. The rate of significant AEs is also low, as outlined earlier. ICD and sclerosant is, therefore, an option suitable for most patients with the key exceptions of those with a very short prognosis and those with nonexpandable lung (NEL; to be discussed later).

Medical Thoracoscopy and Talc Poudrage

Medical thoracoscopy is largely undertaken utilizing conscious sedation plus an opiate cough suppressant and local anesthetic. It is also referred to as local-assisted thoracoscopy (LAT). Newer anesthetic techniques, such as regional anesthetic blocks (paravertebral,[66] erector spinae,[67] or

serratus anterior plane blocks),[68] for analgesia during LAT are used in some centers. While LAT is undertaken for diagnostic purposes, it offers an excellent opportunity to simultaneously undertake definitive treatment of MPE in the form of talc poudrage (TP), and/or insertion of an IPC.

Advantages and disadvantages

The procedural risks of LATs are like that of ICD insertion as described earlier, namely pain, infection, hemorrhage, damage to surrounding structures (lung, diaphragm, and vasculature) and pneumothorax. On large-scale review of the published data, the BTS quote a rate of minor complications of 7.3% (95% confidence interval [CI] 6.3%–8.4%) and 1.8% (95% CI 1.14%–2.2%) for major complications.[69] Where poudrage is undertaken, the patient is also at risk of talc-related complications as previously described. LoS for LAT is on average 4.6 days.[69]

The key benefit of LAT is the ability to combine visual inspection and biopsy with multiple management techniques, such as TP and division of septations. In addition, the rates of pleurodesis at poudrage are high at around 80%.[55,69,70]

Talc poudrage versus intercostal chest drain and talc slurry

The comparison of TP versus TS has been the subject of numerous studies. A network meta-analysis by the Cochrane group published in 2019 ranked TP first in the management of malignant pleural effusion, above other treatment options including TS.[2] The evidence for this, however, was considerably weakened in sensitivity analysis restricting data to only higher quality studies. In addition, all comparisons in both clinical and statistical outcomes showed high heterogeneity. Subsequently the TAPPS study was published, which definitively demonstrated no significant difference between TS and TP in pleurodesis failure rates, total days in hospital, AEs, or QOL.[71] These results have been mirrored in other studies demonstrating no significant difference in QOL,[65] length of hospital stay,[64,65] pleurodesis rates,[55,56,64] chest pain,[55,70] dyspnea,[65,70] or overall adverse event rates.[55,56,64,70] In a review of the evidence, number of complications per patient was higher in the TP group versus the TS group by the BTS Pleural Guidelines group.[72]

Local-assisted thoracoscopy and indwelling pleural catheters

Another advantage of LAT is the potential for combining the procedure with the insertion of an IPC. Two small nonrandomized prospective observational studies have examined this possibility and identified high pleurodesis rates (both reporting 92%), short hospital LoS (median 1.79–3 days), improvements in postprocedure dyspnea, minimal AEs, and short time from IPC placement to removal (median 6–7.54 days).[73,74] The first RCT in this area is the TACTIC trial, which compared TP at thoracoscopy in combination with same day IPC insertion versus poudrage alone.[75] Results, recently presented at the British Thoracic Society 2024 Winter Conference, demonstrated that while the combined approach did not increase pain scores, or complications, the pleurodesis success rates were lower than the existing TP literature. It did, however, significantly reduce the need for repeat pleural procedures. We look forward to seeing the full results in publication soon.

Indwelling Pleural Catheters

IPC insertion presents another treatment option for symptomatic MPE. This is generally undertaken as a day case procedure. Initially, IPCs were reserved as a second-line measure for those unsuitable for chemical pleurodesis. There have now been several RCTs that have demonstrated equipoise (or in some cases superiority of IPCS over chemical pleurodesis) between IPC insertion and chemical pleurodesis (via drain, LAT, or video-assisted thoracoscopy surgery [VATS]) in terms of dyspnea control, QOL,[60,76–79] and chest pain.[60] The Australasian Malignant Pleural Effusion trial (AMPLE) study,[76] in addition to others,[79] has also identified a reduction in total days spent in hospital in those treated with IPC as opposed to talc pleurodesis. Similarly, the TIME2 study documented a shorter LoS for the initial procedure (median 0 vs 4 days) in favor of IPCs,[60] mirrored in the study by Putnam and colleagues.[77] There have been conflicting findings on the impact of IPC on time to death,[60,76] and on the frequency of AEs.[60,76,79] Finally, patients treated with IPCs were demonstrated in both TIME2[60] and AMPLE (Australasian Malignant Pleural Effusion trial) [76] to require significantly fewer subsequent ipsilateral pleural procedures than those treated with ICD and talc (6% vs 22% and 4.1% vs 22.5%, respectively).

An important detractor in the comparisons of IPC versus talc pleurodesis is the ubiquitously demonstrated lower pleurodesis rates in patients treated with an IPC. Across a broad range of studies, autopleurodesis rates are reported to be around 40%,[77–82] with a few outliers at 11.4%,[80] 23%,[83] and 68.0%.[78] Time from IPC insertion to autopleurodesis ranges from 26.5 to 121 days.[77,79–82] There may also be an under appreciation (by clinicians) on the burden that the IPC, with its frequent home drainages, may pose on a patient.

Enhanced indwelling pleural catheters approaches

A small number of studies have examined combining IPCs with talc pleurodesis. The IPC-Plus trial,[83] a randomized placebo-controlled study of IPC in addition to talc installation at day 10 after insertion, described significantly higher rates of pleurodesis in the talc group (43 vs 23% at day 35, 51% vs 27% at day 70). In addition, the talc group had significantly higher QOL scores and no significant difference in number of patients experiencing a complication. Dyspnea scores favored the talc group but only reached significance at one time point. The Early Pleurodesis via IPC with Talc for Malignant Effusion (EPIToME) study (only published in abstract) trailed same day IPC insertion and talc instillation for those with adequate lung expansion resulting in a 74% pleurodesis rate.[84] Only 46.1% of the 102 patients, however, had sufficient lung expansion after IPC insertion to follow the talc pathway. The recently published OPTIMUM study, an RCT trial of IPC $\pm$ talc versus talc via ICD, identified no significant difference between the 2 groups in global health status, dyspnea, or chest pain scores.[85]

A further area of study to optimize IPC use is the frequency of IPC drainage. The ASAP study,[81] in addition to AMPLE (Australasian Malignant Pleural Effusion trial) 2,[80] identified significantly higher rates of autopleurodesis in daily drainage versus alternate day or symptom-guided drainage strategies, respectively, in addition to shorter time to pleurodesis. While AMPLE (Australasian Malignant Pleural Effusion trial) 2 also reported greater QOL in the daily drainage group,[80] this was not supported by the ASAP data.[81] Neither study found a significant difference in AE rate.[80,81] Finally, AMPLE (Australasian Malignant Pleural Effusion trial) 2 found no significant difference between the 2 drainage strategies regarding number of admissions, duration of admissions, duration of pleural effusion-related admissions, or time to death.[80]

Another approach being studied to increase pleurodesis rates is the use of a silver nitrate-coated IPC in the SWIFT study.[86] This was based on the hypothesis that the silver nitrate would gradually elute within the pleural space and lead to more gradual pleurodesis without the acute inflammatory complications associated with talc. The study identified that the silver nitrate-coated IPC failed to meet the superiority criteria over the standard IPC for its primary outcome of pleurodesis rates. There was also no significant difference in time to pleurodesis, thoracic pain, dyspnea, or QOL (as defined by the EuroQual 5-dimension 5-level (EQ-5D-5 L) questionnaire). The study, however, suffered from several procedural challenges in conducting the study, and a baseline imbalance in patient characteristics, making the results difficult to interpret.

Finally, one study has evaluated factors that predict the removal of IPCs in patients with MPE. A multivariate analysis conducted by Warren and colleagues[87] identified type of cancer (breast and gynecological), the identification of malignant cells in pleural fluid cytology, and the absence of NEL all as positive predictors of IPC removal, while those with lung cancer and "other" cancers were less likely to have their IPCs removed. The article did not, however, include an analysis controlling for the length of survival, and so the reader is unable to determine if the variables remain predictive of IPC removal when adjusted for mortality. In particular, given the longer survival in patients with MPE associated with breast or gynecological cancer versus those with lung cancer in this study, and in several other publications,[8,9,88] it is quite possible the documented association between cancer type and IPC removal is simply a demonstration of a longer possible window for IPC removal in those with breast or gynecology malignancies.

Research is just starting in evaluating alternative digital drainages for IPCs. One small case series has been published so far (in summary form) examining the Passio catheter and drainage system from BEARPAC Medical,[89] while the AESOP trial (ISRCTN 16390322) of PleurX versus Passio is currently recruiting.

Advantages and disadvantages

As already partly described, the advantages of IPC use lie in the ability to conduct the procedure on an outpatient basis, in addition to the consistent improvements in QOL and breathlessness. Given the often-short prognosis of patients with MPE, these are significant advantages. Patients, where able, are also able to be more involved in their own treatment by draining their IPCs based on their symptoms whenever they wish to.[5]

The psychosocial impact of IPCs on patients already suffering from a significant change in sense of self and autonomy is, however, noteworthy,[4,90] and significantly under researched. While in theory patients can self-manage IPCs, many are unable to do this (eg, due to frailty). We await the results of National Institute for Health and Care Research (NIHR)-funded study lead by the University of East Anglia aiming to codevelop an intervention to support self-management of IPCs in MPE with interest.[91]

A prime concern around IPC use is pleural infection. Rates of IPC-related pleural infection vary

from 0% to 12%,[60,76,82,92,93] with in a review of 1021 patients identifying a rate of 4.8%.[94] Most pleural infections can be managed with antibiotics without the need to remove the IPC and mortality rates are low (6% in the above-mentioned large review).[94] Published rates of IPC-related cellulitis are similar at 1.6% to 5.5%.[76,80,82,93]

Other potential complications of IPC and their published frequencies are as follows: symptomatic loculation (1.4%–13.5%),[76,79,82,92] tube dislodgement (1%),[81] tube blockage (4.1%–8.1%),[76,80,81] and pain (highly variable rates). Tube fractures on removal are also known to occur but little data are published on the frequency, although the limited available data suggest retention of IPC tubing causes no harm to the patient.[95] Metastatic seeding along IPC lines, similar to that post-LAT, has also been documented. Studies are limited so exact rates are difficult to define, with current frequencies reported as 0.4% to 10%.[81,82,84,96] This, however, varies significantly with tumor histology and is significantly more common in mesothelioma than other tumor types.[92,96] Finally, concerns have been raised regarding the loss of protein from the body in often already cachexic patients by repeatedly removing typically exudative effusions. While this is more of a concern with chylothorax, this is a sufficiently large area such that it is outside the scope of this review to consider. One study has presented data comparing protein and albumin levels in IPC versus talc pleurodesis via ICD/LAT/VATS and found no significant difference between the groups.[79]

Surgical Approaches

RCTs of surgical treatment versus another standard of care in the treatment of MPE are near nonexistent, with the BTS 2023 pleural guidelines authors unable to identify any such studies.[4] As such, surgical treatment in this area has been guided by heavily selected case-series and observational studies. Surgical approaches beyond TP are not recommended by United Kingdom or American guidelines for MPE (with the possible exception of within NEL—see later).[1,4] The currently recruiting AMPLE (Australasian Malignant Pleural Effusion trial) 3 trial,[97] a multicenter RCT of VATS versus IPC ± talc, is a forerunner in the area with keenly awaited results. While focused on mesothelioma rather than MPE, first of the Mesothelioma And Radical Surgery (MARS1) (87) (extrapleural pneumonectomy vs no surgery),[98] MARS2 (extended pleurectomy and decortication with chemotherapy vs chemotherapy alone),[99] and MesoVATS (VATS partial pleurectomy vs ICD with talc or LAT with talc),[100] all identified either no benefit of surgery or actively favored the comparison in terms of survival,[98,99] QOL,[98] AEs/complications,[98,100] length of hospital stays,[100] and cost analysis.[99,100] MARS1 (first of the Mesothelioma And Radical Surgery) also highlighted a significant concern in surgical approaches for pleural malignancy, the small size of the patient population who are fit enough for this treatment and have disease at a stage where surgery could be beneficial; in this study only 20% of those screened were eligible for randomization after initial chemotherapy.[98]

Nonexpandable Lung

There is no widely accepted definition of NEL. It is generally, however, agreed to refer to a significant lack of visceral pleura to parietal pleura apposition, with the BTS 2023 pleural guidelines using greater than 25% of the lung not apposed to the chest wall on CXR as its criteria.[4] NEL encapsulates both visceral thickening with secondary lack of lung expansion, in addition to endobronchial tumors with resultant chronic lobar/lung collapse.[4]

The diagnosis of NEL poses significant challenges. Most research studies utilize a diagnosis based on CXR, often in combination with response during and after therapeutic aspiration. Clinicians typically use a similar definition, in combination with UltraSound Scan (USS) or Computed Tomography (CT) appearance of pleural thickening and position/appearance of pleural effusion.[25] This, however, is problematic as significant interobserver variability in CXR interpretation has been demonstrated, making a single CXR reading unreliable.[25,101,102] The degree of absent lung apposition used to define NEL in trials also varies between 10% and 50% making it challenging to identify the prevalence of NEL within studies,[55,60,64,70,80,103] to assess the response of these patients to a given trial treatment and to meta-analyze and generalize trial outcomes.

Pleural manometry has shown positive results in small studies in predicting NEL during therapeutic thoracentesis with a pleural elastance of greater than 19 cm H_2O demonstrating 40% to 79% sensitivity and 94% to 100% specificity.[104,105] The pre-EDIT feasibility study shows comparable values with a pleural elastance of 14.5 cm H_2O or greater (sensitivity 100%, specificity 67%), a value deliberately chosen to be lower to avoid missing patients with NEL in the trial.[106] Mean pleural pressure was also shown to be significantly lower in NEL than in all other etiologies in one study.[107]

Salamonsen and colleagues[104] demonstrated the utility of pleural ultrasound to predict NEL prior to aspiration. The study used M-mode and speckle-tracking imaging (STI) to analyze the motion and strain respectively of the atelectatic ipsilateral lower lobe showing reasonable sensitivity and specificity of both mechanisms, particularly STI, and suggesting cutoff values of 6% STI, 1 mm M-mode, and 19 cm H_2O pleural elastance as clinically useful parameters. The use of M-mode assessment of lung movement in predicting NEL has been further demonstrated by other teams.[108] Finally, post-LAT airflow has also shown to be significantly lower in patients with NEL.[109]

No RCTs focused solely on patients with NEL have been published and many studies actively exclude patients with NEL, as such evidence in this area is largely taken from the small number of patients with NEL in larger trials. MesoTRAP (RCT of VATS with partial pleurectomy and decortication vs IPC for NEL in mesothelioma)[110] is however actively recruiting and we await the results. Within these limited data field, IPC insertion has repeatedly been found to be beneficial for symptom control in NEL[10] and is currently the mainstay of practice.[4,38]

Loculated Malignant Effusions

Data are scarce on the prevalence of symptomatic loculated pleural effusions in patients with MPE, with one review identifying a rate of 5% to 14% of patients with MPE treated with an IPC.[92] There have been no RCTs of surgery specifically focusing on this question. This may be, in part, due to the association of a moderate-to-high degree of loculations with shorter prognosis[111] and so potentially the perception of a lack of suitability for such invasive treatment options in this population. Fibrinolytics for this group have been explored in 3 RCTs (study sizes of 44–71 patients)[61,112,113] and one controlled study measuring against a historical control group,[114] all of which assessed fibrinolysis versus control in inpatients with an ICD in situ. One retrospective observational review analyzed the use of fibrinolysis in patients treated with an IPC.[115] Choice of agent, frequency of administration, and dose of agent vary widely across clinical practice and within research.[61,112–115]

This small data group has identified that fibrinolytics in this patient cohort improves size of pleural effusion on radiology[61,112,114] and improves the degree of loculation on CT (Computed Tomography).[114] Conflicting results have been seen with regard to whether fibrinolytics do increase the volume of fluid drainage[112,113] or not.[61] Similarly, the TIME3 study identified no significant difference in dyspnea scores associated with fibrinolytic use,[61] while patients in the fibrinolytic group were found to have significantly better dyspnea control in a small study by Saydam and colleagues.[113] TIME3 also found no significant difference in time to pleurodesis failure, nor in QOL between the groups.[61] The study did, however, identify a significant difference in favor of the fibrinolytic group in regard to length of hospital stay and median survival. Finally, Thomas and colleagues[115] identified in those who had responded to fibrinolytic therapy, symptomatic loculations recurred in 40.9% in a median of 13 days.

While the results of TIME3 have been significant for the community treating this challenging patient group, it should be noted that 34 of the 71 patients in the study died within the first 28 days, which was the key period over which data for the primary outcomes were collected.[61] As the authors highlight, ongoing studies would be better to focus on the use of fibrinolytics via IPCs given the high mortality of this patient population.

Systemic Anticancer Therapies and Malignant Pleural Effusion

Patients with MPE are a markedly heterogenous population. This factor, in combination with rapid advances in cancer treatment, makes generalizing summaries around the role of systematic anti-cancer therapy (SACT) in MPE impossible. No RCTs have been conducting in patients with MPE as a combined population directly comparing SACT versus no SACT in the management of MPE and discussion of SACTs for all cancer types goes beyond the scope of this review. Interest is growing, however, on the use of monoclonal antibiotics, immunotherapies, and chemotherapies in turning off the tap of MPE production.[116–118] The use of anti-Vascular Endothelial Growth Factor (VEGF) agents (eg, bevacizumab), in particular, has been examined in a number of studies in non-small cell lung cancer with some positive results in regarded to fluid accumulation control[119] and prognosis.[118,120]

SUMMARY

There is now a broad range of published data describing management approaches for MPE including thoracentesis, talc via ICD, LAT or IPC, and IPC. Research has identified mechanisms through which these treatments can be optimized when used alone, and demonstrated benefits of using these methods in combination. Surgical approaches for MPE lack the same body of RCT evidence, but still have an important

role in selected cases. The results of several ongoing studies, particularly those exploring the speed of fluid reaccumulation and AEs associated with MPE treatment approaches, are keenly awaited. Considerable research is still required in the management of MPE in the context of NEL.

CLINICS CARE POINTS

- Patient prognosis is highly important in considering appropriate treatment pathways. While the PROMISE and LENT scores have been validated, their impact on guiding clinical care and on patient outcomes has yet to be evaluated.
- The patient's priorities in managing their MPE is a crucial driving factor in choosing the most appropriate treatment pathway and should be discussed early in their care.
- Where rapid IPC removal is considered feasible and a priority to the patient, aggressive drainage strategies should be used.
- IPCs should be the first-line option for patients with NEL; however, research focusing primarily on this challenging group is lacking.

DISCLOSURE

None.

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