Indwelling pleural Catheters for the treatment of Malignant Pleural Effusions.

Expert Review of Respiratory Medicine

Abstract

Introduction
The presence of a Malignant Pleural Effusion (MPE) is a marker of advanced disease and associated with a poor prognosis. Patients are in a palliative stage of their disease and often suffer distressing symptoms including breathlessness and pain. Indwelling Pleural Catheters (IPCs) are effective in managing pleural effusions and allow ambulatory drainage of the pleural space, reducing symptoms associated with effusions and lowering overall hospital stay. The role of IPCs as a first line option in managing MPEs is expanding with a multitude of recent studies into the optimal application of IPCs, necessitating a review of the current literature.

Areas covered
This article will provide an overview of IPCs in MPE; how they're inserted, their indications, continuing management, complications and possible future applications.

Expert Opinion
IPCs should be considered first-line management of MPEs, alongside standard talc pleurodesis. Recognition of the advantages and disadvantages of each approach allows a more informed patient choice. It is recognized that the use of IPCs can provoke pleurodesis, leading to removal of the catheter. For patients in whom prompt removal of the catheter is a priority, then a more aggressive drainage regime or instillation of talc via the IPC is a reasonable option.

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Key words: Malignant pleural effusion, Indwelling pleural catheter, Talc Pleurodesis

1.0 Introduction

Malignant Pleural Effusions (MPEs) are a common cause of significant cancer related morbidity, with an estimated incidence of 500,000 new cases in the USA and Europe combined [1]. Patients are typically symptomatic, often suffering from breathlessness, a non-productive cough, chest pain, indigestion and early satiety [2]. The presence of MPE is a poor prognostic marker, with a median prognosis between 3 and 12 months [2, 3]. Accordingly, the treatment aims should focus on palliating distressing symptoms, minimizing invasive procedures, whilst decreasing hospital stay and complications. The standard first line treatment is a therapeutic needle aspiration, where pleural fluid is withdrawn via a needle or cannula. It is recognized that not all patients experience improvement in symptoms following fluid removal, and the initial aspiration helps determines the extent of therapeutic benefit (if any) to the individual patient, It will also help to diagnose trapped (non-re-expandable) lung, which is important to identify as influences further management. The majority of malignant effusions will recur and are often refractory to oncological therapies,

with the patient usually requiring further definitive procedures. Historically, patients with recurrent MPEs were offered complete drainage of their effusion, via an intercostal drainage (ICD) as an inpatient, with subsequent instillation of a pleurodesis agent, such as medical grade talc, to induce pleural inflammation and subsequent symphysis of the parietal and visceral pleural. The aim of this procedure is to obliterate the pleural space and prevent re-accumulation of pleural fluid. This has an approximate success rate of 70% [2, 4, 5, 6], with talc recognized as the most effective agent [7]. However, it necessitates a prolonged inpatient stay and the patients can experience pain from the resultant pleural inflammation. Additionally, it is not useful in patients with significant trapped lung, where the visceral and parietal space do not oppose, due to incomplete re-expansion of the lung.

1.1
An IPC is a tunneled silicone tube which is inserted aseptically, allowing long-term access to the pleural space. This facilitates recurrent ambulatory drainage of the effusion in the community, providing symptomatic relief. This approach was originally seen as a second-line option, after conventional talc pleurodesis had failed. However, there is now robust evidence that IPCs are as effective in managing symptoms as chemical pleurodesis, allowing a personalized approach to patient care. The primary aim of IPCs is to improve symptoms of dyspnea by controlling effusion re-accumulation with repeated drainages and were initially intended to stay in-situ for the patient's disease course. However, it has been found that up to 43% of patients with IPCs achieved spontaneous pleurodesis (auto-pleurodese) enabling the IPC to be removed with an average IPC duration of 52 days [8]. Several recent studies have investigated protocols aimed at 'rapid pleurodesis' using IPCs, with the aggressive drainages regimes or the introduction of an intrapleural agent [9]. This raises the concept that IPCs are not just a 'destination' treatment, but can be used as a 'means to an end' to achieve pleurodesis [10].

2.0
IPC insertion

IPCs can be inserted as an outpatient procedure, with patients discharged the same day. Anticoagulation and antiplatelets should be stopped prior to the procedure, except for low-dose aspirin. Patients should be consented and made aware of possible complications, including bleeding, infection, failure of procedure and pneumothorax. Absolute contraindications include uncorrected coagulopathy; pleural infection with evidence of ongoing sepsis, and either evidence of skin infection or significant cutaneous malignant disease over the identified insertion site. The insertion should be performed in a sterile fashion in a procedure room or day theatre with oxygen saturation monitoring. An example of an IPC system is shown in figure 1a. The patient is typically placed in the lateral decubitus position, with the patient lying on the side contralateral to the effusion, although they can be inserted in other patient positions. Bedside thoracic ultrasound should be used to assess the effusion size, and to facilitate marking of an insertion point. A sterile technique should then be used from then on. After local anesthetic infiltration, two small incision are made, one at the pleural insertion point and one 7-10 cm anterior to this, which will form the proximal end to the tunneled track. The IPC catheter is tunneled along this track, with the pro-fibrotic cuff which promotes tissue growth and keeps the drain in-situ, situated approximately a third along the track (Figure 1b). The distal end of the catheter is then inserted into the pleural cavity, using the Seldinger technique. The incisions are then sutured closed, although the catheter itself is not sutured in place. A one-way valve on the external end is then attached to a drainage bag or vacuum bottle system (Figure 1c). Subsequent drainages, where 500 to 1000millleters are drained over approximately 15 minutes, can be

performed in the community by a district nurse, relative or the patient. When not draining the external end is covered with a dressing (Figure 1d).

3.0 Complications

3.1 Immediate complications

The immediate risks on insertion are uncommon and usually minor and include bleeding, pain and local skin infection. It is not uncommon for the post-procedure chest radiograph to demonstrate air within the pleural space. Often, this will be indicative of a trapped lung, a phenomenon recognized in 20-30% of patients with a malignant effusion [5, 11]. Sometimes, a small amount of air is introduced during the insertion of the catheter, which will often resolve with serial drainages of the IPCs. If there is evidence of an enlarging hydropneumothorax, with increasing symptoms of breathlessness or pain, then the possibility of a bronchopleural fistula should be considered.

3.2.1 Long-term complications

There were initial concerns surrounding the risk of long-term infection with the pleural catheter. However, data from observational and randomized studies have demonstrated a reassuring low incidence of associated infection with one large multicenter multinational retrospective study of over a thousand patients, demonstrating a 4.8% IPC-related pleural infection rate [12]. The common causative pathogens of Staphylococcus aureus, Pseudomonas Aeruginosa and Enterobacteriaceae differ from those that typically cause pleural infection secondary to pneumonia, suggesting they are two distinct disease processes [12]. Typically the infection occurs at least 6 weeks post insertion, indicating they are not secondary to the insertion but due to later spread of pathogens from the patient's skin or lung parenchyma [13]. Therefore, careful management and care of the catheter in the community should help minimize this risk. Reassuringly, the mortality rate from IPC-related infection is low (0.29%) and the majority of patients can be managed as an outpatient with oral antibiotics without requiring IPC removal [12]. If this approach is unsuccessful, then patient may require hospital admission for intravenous antibiotics and placing the catheter on continuous free-drainage to facilitate resolution of the infection. In loculated pleural infection, the IPC provides a port for introduction of tissue plasminogen activator and DNase therapy if required [13]. The possibility of IPC related pleural infection has been a concern in patients who are receiving chemotherapy, but multiple studies have shown no significant increase in infection rates in this cohort [14, 15].

3.2.2

Catheter tract metastases (CTM) occur when malignancy is seeded along the IPC tract, causing painful subcutaneous nodules. The true incidence of this phenomena is unclear, and studies have reported between 1.9 and 10% [16, 17]. This wide variation likely reflects the higher frequency of CTM in mesothelioma patients. Catheter tract metastases are usually treated with analgesia and external beam radiotherapy and does not necessarily require removal of the IPC. Although early trials on the use of prophylactic radiotherapy post large bore pleural procedure provided conflicting results [18, 19, 20], the recent SMART trial, robustly found no difference in CTM incidence in the immediate and deferred radiotherapy groups [21].

3.2.3

Catheter blockage from fibrinous exudates preventing continuing drainage, is another complication of IPCs, with an incidence of less than 5% [22]. Flushing with saline initially or with fibrinolytics has shown high success rates of resumed drainage in 83-100% [23, 24]. Re-occlusion was seen in 32% of patients in one study with a success rate of 72% after a second dose of fibrinolytic, with low risk of hemothorax and infection (2% and 3% respectively) [24]. Patients can become symptomatic with loculations forming in the pleural cavity where there is residual pleural fluid which cannot be drained in the absence of pleural infection. An incidence of 5-14% is reported and is thought to be secondary to fibrin deposition secondary either to the IPC itself or the malignant process, causing septations and fluid loculation [25]. Observational data suggests that intrapleural fibrinolytic use can improve pleural fluid drainage and symptoms in selected patients with an IPC and symptomatic loculation, with a small associated risk of bleeding [25].

3.2.4

IPC removal may be complicated by the formation of fibrotic tissue around the cuff leading to difficulty in removal and possible IPC fracturing or iatrogenic severing of the IPC, with a retained internal catheter. This has been reported in 10% of cases and long term follow up shows that retained fragments are safe with no evidence of complications so aggressive removal should be avoided [26].

4.0

Current practice

The current British Thoracic Society (BTS) pleural guidelines recommend talc pleurodesis as the first line option in patient with malignant pleural effusions. IPCs were recommend in patients with a prognosis of over 1 month in whom either talc-pleurodesis was unsuccessful or in patients with evidence of significant trapped lung [2]. Early trials demonstrated effectiveness of IPCs comparable to doxycycline pleurodesis with shorter hospitalization time [27]. More contemporary, robust clinical trials, however, provide strong support for the use of IPCs as a first line option in any patient with a MPE, enabling patients the choice between IPC and conventional talc pleurodesis [28]. Demmy et al. supported daily drainages via IPC as superior for palliation compared to talc pleurodesis with better dyspnea scores and survival with effusion control at 30 days. [29] Whilst the first large randomized trial to compare the efficacy of IPC with conventional talc pleurodesis via chest drain in palliating symptoms, the TIME 2 trial, found that both approaches improved breathlessness, with no significant difference between visual analogue score (VAS) for breathlessness between the cohorts for the first 42 days (24.7mm and 24.4mm in the IPC and talc pleurodesis group respectively) [16]. At 6 months the results favored IPCs (mean difference of -14.0 mm, 95% CI =-25.2 to -2.8; P = 0.01) [16]. The study also found that the IPC cohort was associated with shorter length of hospital stay (median 0 versus 4), but with higher rates of complications (OR, 4.70; 95% CI, 1.75-12.60; P=.002), results which have been replicated in subsequent studies [16]. The AMPLE study randomized patients between IPCs and talc pleurodesis, with a primary end-point of days spent in hospital from procedure to death or to 12-month follow-up visit. IPCs were associated with a shorter hospital inpatient stay (10 versus 12 days p 0.03), with most reduction due to fewer effusion-related hospitalization days [6]. Though statistically significant, the clinical significance to a patient of a reduction of 2 days total admission length is unclear. IPCs, importantly, were associated with fewer overall invasive pleural procedures (3 vs 16 p 0.001), with only 4% IPC–treated patients required further pleural drainages, compared to 23% of talc-pleurodesis patients. There were no significant between-group differences in improvements in breathlessness or quality

of life, with both groups obtaining symptomatic benefit [6]. These findings of fewer days in hospital and re-intervention with equivocal impact on breathlessness have been reproduced in further randomized controlled trials [30]. The outcomes from these studies has been incorporated in the recent guidance published by the American Thoracic Society (ATS) Management of Malignant Pleural Effusions Clinical Practice Guideline (2018), which concludes that either IPCs or chemical pleurodesis be used as first-line definitive intervention for management of dyspnea (conditional recommendation, low confidence in estimate of effects) [31].

5.0
Rapid pleurodesis regimes.

It is recognized that a proportion of patients with an IPC achieve spontaneous pleurodesis. Recent studies have explored how to expediate this process, either by a more aggressive drainage regime, or by instilling an intrapleural sclerosant agent via the IPC. Currently, there is no standard optimal drainage frequency through an IPC. The TIME 2 trial advised IPC drainages at 3 times weekly or as required for relief of dyspnea, whilst the AMPLE trial drainages advised a symptom guided approach. The ASAP study was designed to determine if a more aggressive regime would provoke pleurodesis, randomizing patients with IPCs between daily drainages or alternate day drainages, with the primary outcome of incidence of auto-pleurodesis. It determined the rate of auto-pleurodesis, defined as complete or partial response based on symptomatic and radiographic changes, was greater in the aggressive drainage arm than the standard drainage arm (47% vs. 24%, respectively; P = 0.003). The aggressive drainage arm was associated with shorter median time to auto-pleurodesis (54 versus 90 days) with no difference in patient satisfaction, adverse events or quality of life scores [32]. However, a large proportion of the patients died or withdrew from the study during follow up. The AMPLE 2 trial also investigated whether aggressive (daily) regimes or a symptom-guided drainage approach was more effective in alleviating breathlessness[33]. They found no difference in breathlessness between the two groups, although it did support the ASAP results that patients were more likely to pleurodese with aggressive drainages (44% vs 16·9% P=0·004 at 6 months). Daily drainages were also associated with improved quality of life, as assessed by EQ-5D-5L, compared to the symptoms guided approach, despite no clear benefits in reported breathlessness or pain scores.

Cancer patients are at risk of malnutrition due to physical and metabolic effects of the cancer, as well as the effects of anticancer therapies, and poor nutritional status is associated with a poorer prognosis [34]. There has been little work on the effect of regular IPC drainages of protein- rich pleural fluid on a patient's nutritional status. A retrospective study on the effect of IPC drainages on patients with hepatic hydrothoraces, found a mean decrease between pre-IPC and post-IPC values of 0.3 g/dL (p .005) after mean follow-up of 29.6 days [35]. However, the statistically significance does not necessarily confer clinical significance, or indeed prove that IPC drainages were the causative factor. It is presently unclear whether the more rapid pleurodesis, and IPC removal, in the accelerated regime, offsets the protein loss associated with the more aggressive drainages.

The IPC Plus study investigated whether instilling talc sclerosant via the IPC would induce a pleurodesis reaction, thereby combining the ambulatory aspect of the IPC with the pleurodesis action of talc. The study randomly assigned instilling 4g talc pleurodesis via an IPC 10 days post insertion, compared to placebo. The talc arm had significant higher rates

of pleurodesis, at 43% at day 35 compared with 23% in the placebo group, with no difference in mortality, adverse events or days in hospital [36].

It must be noted the that the rate of spontaneous pleurodesis in these recent randomized trials for patients managed with IPCs was much lower than previously found in retrospective studies. The incidence for spontaneous pleurodesis for IPC alone ranged from 24%, 28.8%, 16.9% and 23% in the ASAP, AMPLE, AMPLE 2 and IPC Plus trials respectively [6, 32, 33, 36], compared to an average of 45% found in earlier non-randomized studies [8]. This implies that the actual rate of spontaneous pleurodesis associated with IPC is much lower than previously thought.

6.0 Summary

IPCs are a simple, safe and effective option for the relief of symptoms associated with MPE. The TIME 2 and AMPLE trial demonstrated comparable efficacy in managing breathlessness when compared to the first-line treatment of talc-pleurodesis[6, 16]. They should be considered and discussed with all patients suffering with MPE as they offer an ambulatory pathway to managing refractory effusions, with low risk of serious complications. They have advantages in patients who have trapped lung, failed previous talc-pleurodesis or in circumstances where minimizing time in hospital is an important outcome. The ASAP and AMPLE 2 trial demonstrated that daily drainages are superior in terms of provoking early pleurodesis reaction[32, 33]. The IPC Plus study demonstrated that instillation of talc via the IPC was safe and increased likelihood of pleurodesis[36].

7.0 Expert Opinion

Indwelling pleural catheters are an effective method of managing dyspnea in patients with refractory malignant pleural effusions. It offers an outpatient ambulatory management pathway for patients, which controls symptoms as well as talc pleurodesis and should be considered alongside this approach as a 1st line option. Patient can be advised that with an IPC they are likely to have a lower length of hospital stay, and require on average, fewer ipsilateral pleural procedures. Conversely IPCs, are associated with an increased risk of cellulitis, although this can be typically managed with antibiotics, without requiring removal of the IPC. IPCs should be the treatment of choice in patients with trapped lung and patient who have previous failed pleurodesis. Patients should be advised the main aim of the IPCs is to control dyspnea, but that approximately 20% of patients will achieve spontaneous pleurodesis, with subsequent catheter removal. For patients who desire early catheter removal, it would be reasonable to offer them either a more aggressive drainage regime (daily regime) or instillation of talc via their IPC. The later approach doubles the likelihood of pleurodesis with no increased in adverse events. Whilst considering the theoretical impact of increased protein loss with regular drainages.

The last 5 years has provided a wealth of randomized evidence demonstrating indwelling pleural catheters (IPCs) as a safe and effective way of managing malignant pleural effusion

and explored how best to optimize its potential. The next 5 years will see the publication of several exciting trials which will expand on the role of the IPC. There are two trials further examining the utility of instilling talc via the IPC to provoke early pleurodesis. The currently recruiting Optimum study is comparing quality of life outcomes in patients managed with IPCs and talc pleurodesis versus standard inpatient treatment with chest drain and talc pleurodesis(7). The AMPLE-3 trial (https://www.anzctr.org.au/ ACTRN12618001013257) is currently randomly allocating patients with MPE between IPC and talc pleurodesis therapy or Video-Assisted Thoracoscopic Surgery (VATS). Further trials will focus on use of IPCs in specific phenotypes of MPE, including trapped lung. MesoTRAP is a feasibility study examining IPCs versus surgical video-assisted thoracoscopic partial pleurectomy/decortication in patients with trapped lung with malignant pleural mesothelioma (MesoTRAP https://clinicaltrials.gov NCT03412357).

Drug eluting catheters are another possibility for future development in the management of MPEs, with studies in rabbit and lamb models demonstrating increased rates of pleurodesis [37]. Silver Nitrate coated IPCs are the only drug eluting IPCs so far tested in humans showing a favorable safety profile and patient tolerability [38] and is currently under investigation in a large phase 3 randomized control trial , the SWIFT study (NCT02649894). This device is coated with silver nitrate an inert agent which facilitate controlled release into the pleural space to provoke pleural inflammation and subsequent pleurodesis. This trial has finished recruiting, and the results are anticipated in 2019.

Perhaps most exciting is the opportunity that IPCs provide for improved delivery of intrapleural oncological therapies. Studies examining the efficacy of infusing intrapleural chemotherapies via IPCs for lung cancer have so far demonstrated mixed outcomes [39, 40, 41] . There are case studies examining its use in other cancers, including non-Hodgkin's B-cell lymphoma [42]. There has been a lot of recent interest in the use of intrapleural immunological therapies to promote adaptive immune response against cancer[43, 44, 45]. This has the advantage of anticipated increased local effects, as well as enabling the dissemination of memory T-cells capable on controlling disease systemically[39]. It is anticipated that there will be increasing number of trials investigating the use of intrapleural immunotherapies. These include the currently recruiting feasibility study examining the use of intra-pleural Streptococcus Pyogenes and BCG in mesothelioma (TILT trial https://www.isrctn.com ISRCTN10432197). Additionally, the use of the IPC will enable serial evaluation of tumor and immune cells during immunotherapy, which may identify clinically actionable targets present within the tumor and immune cells, allowing for development of effective patient-specific treatments[39].

8.0
Article Highlights

- The presence of a Malignant Pleural Effusion (MPE) is a marker of advanced disease and associated with a poor prognosis
- Care should focus on palliating symptoms, reducing hospital stay and reducing pleural interventions.
- Indwelling pleural catheters (IPCs) offer a simple, effective method of managing MPEs as an outpatient.
- IPCs are associated with a shorter length of hospital stay and fewer ipsilateral pleural procedures than standard talc pleurodesis.
- IPCs are, however, associated with increased frequency of adverse events than standard talc pleurodesis, particularly infection
- Aggressive daily drainage regimes lead to increased pleurodesis rates.

- Instilling talc via the IPC doubles the likelihood of pleurodesis
- The IPC can be used as a port for intrapleural oncological therapies, as well as enabling serial monitoring of tumor and immune response.
- Future trials will further define the role of IPCs in MPE, as well as investigating the role of more sophisticating drug-eluting catheters.

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References

1. Management of malignant pleural effusions. American journal of respiratory and critical care medicine. 2000 Nov;162(5):1987-2001.
2. Roberts ME, Neville E, Berrisford RG, et al. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010 Aug;65 Suppl 2:ii32-40.
3. Lui MM, Fitzgerald DB, Lee YC. Phenotyping malignant pleural effusions. Current opinion in pulmonary medicine. 2016 Jul;22(4):350-5.
4. Rahman NM, Pepperell J, Rehal S, et al. Effect of opioids vs NSAIDs and larger vs smaller chest tube size on pain control and pleurodesis efficacy among patients with malignant pleural effusion: the TIME1 randomized clinical trial. JAMA : the journal of the American Medical Association. 2015;314(24):2641-2653.
5. Dresler CM, Olak J, Herndon JE, 2nd, et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. Chest. 2005 Mar;127(3):909-15.
6. Thomas R, Fysh ET, Smith NA, et al. Effect of an indwelling pleural catheter vs talc pleurodesis on hospitalization days in patients with malignant pleural effusion: The AMPLE randomized clinical trial. 2017;318(19):1903-1912.
   * Patients required less days in hospital with IPCs versus talc-pleurodesis
7. Clive AO, Jones HE, Bhatnagar R, et al. Interventions for the management of malignant pleural effusions: a network meta-analysis. The Cochrane Library. 2016.
8. Van Meter ME, McKee KY, Kohlwes RJ. Efficacy and safety of tunneled pleural catheters in adults with malignant pleural effusions: a systematic review. Journal of general internal medicine. 2011 Jan;26(1):70-6.
9. Gilbert CR, Feller-Kopman DJCPR. Adjunct strategies to enhance the efficacy of indwelling pleural catheters. 2015;4(1):28-33.
10. Argento AC, Schembri F. The Evolving Role of the Indwelling Tunneled Pleural Catheter. A Means to an End. American Thoracic Society; 2017.

11. Warren WH, Kalimi R, Khodadadian LM, et al. Management of malignant pleural effusions using the Pleur(x) catheter. The Annals of thoracic surgery. 2008 Mar;85(3):1049-1055.
12. Fysh ET, Tremblay A, Feller-Kopman D, et al. Clinical outcomes of indwelling pleural catheter-related pleural infections: an international multicenter study. Chest. 2013 Nov;144(5):1597-602.
13. Lui MM, Thomas R, Lee YC. Complications of indwelling pleural catheter use and their management. BMJ open respiratory research. 2016;3(1):e000123.
14. Mekhaiel E, Kashyap R, Mullon JJ, et al. Infections associated with tunnelled indwelling pleural catheters in patients undergoing chemotherapy. Journal of bronchology & interventional pulmonology. 2013 Oct;20(4):299-303.
15. Morel A, Mishra E, Medley L, et al. Chemotherapy should not be withheld from patients with an indwelling pleural catheter for malignant pleural effusion. Thorax. 2011 May;66(5):448-9.
16. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. Jama. 2012 Jun 13;307(22):2383-9.
** Showed no significant difference in dyspnea score between IPCs and talc-pleurodesis.
17. Thomas R, Budgeon CA, Kuok YJ, et al. Catheter tract metastasis associated with indwelling pleural catheters. Chest. 2014 Sep;146(3):557-562.
18. Boutin C, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma. A randomized trial of local radiotherapy. Chest. 1995 Sep;108(3):754-8.
19. O'Rourke N, Garcia JC, Paul J, et al. A randomised controlled trial of intervention site radiotherapy in malignant pleural mesothelioma. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2007 Jul;84(1):18-22.
20. Bydder S, Phillips M, Joseph DJ, et al. A randomised trial of single-dose radiotherapy to prevent procedure tract metastasis by malignant mesothelioma. British journal of cancer. 2004 Jul 5;91(1):9-10.
21. Clive AO, Taylor H, Dobson L, et al. Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial. The Lancet Oncology. 2016;17(8):1094-1104.
22. Wrightson JM, Fysh E, Maskell NA, et al. Risk reduction in pleural procedures: sonography, simulation and supervision. Current opinion in pulmonary medicine. 2010 Jul;16(4):340-50.
23. Wilshire CL, Louie BE, Aye RW, et al. Safety and Efficacy of Fibrinolytic Therapy in Restoring Function of an Obstructed Tunneled Pleural Catheter. Annals of the American Thoracic Society. 2015 Sep;12(9):1317-22.
24. Vial MR, Ost DE, Eapen GA, et al. Intrapleural Fibrinolytic Therapy in Patients With Nondraining Indwelling Pleural Catheters. Journal of bronchology & interventional pulmonology. 2016 Apr;23(2):98-105.
25. Thomas R, Piccolo F, Miller D, et al. Intrapleural Fibrinolysis for the Treatment of Indwelling Pleural Catheter-Related Symptomatic Loculations: A Multicenter Observational Study. Chest. 2015 Sep;148(3):746-751.
26. Fysh ETH, Wrightson JM, Lee YCG, et al. Fractured indwelling pleural catheters. Chest. 2012 Apr;141(4):1090-1094.
27. Putnam JB, Jr., Light RW, Rodriguez RM, et al. A randomized comparison of indwelling pleural catheter and doxycycline pleurodesis in the management of malignant pleural effusions. Cancer. 1999 Nov 15;86(10):1992-9.
28. Maskell NA. Treatment options for malignant pleural effusions: patient preference does matter. Jama. 2012 Jun 13;307(22):2432-3.
29. Demmy TL, Gu L, Burkhalter JE, et al. Optimal management of malignant pleural effusions (results of CALGB 30102). Journal of the National Comprehensive Cancer Network : JNCCN. 2012;10(8):975-982.
30. Boshuizen RC, Vd Noort V, Burgers JA, et al. A randomized controlled trial comparing indwelling pleural catheters with talc pleurodesis (NVALT-14). Lung cancer (Amsterdam, Netherlands). 2017 Jun;108:9-14.
31. Feller-Kopman DJ, Reddy CB, DeCamp MM, et al. Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical Practice Guideline. 2018;198(7):839-849.

32. Wahidi MM, Reddy C, Yarmus L, et al. Randomized trial of pleural fluid drainage frequency in patients with malignant pleural effusions. The ASAP trial. American journal of respiratory and critical care medicine. 2017;195(8):1050-1057.
* Daily drainage regime increased rates of auto-pleurodesis with no change in quality of life or adverse events
33. Muruganandan S, Azzopardi M, Fitzgerald DB, et al. Aggressive versus symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters (AMPLE-2): an open-label randomised trial. 2018;6(9):671-680.
34. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. Clinical nutrition (Edinburgh, Scotland). 2017 Feb;36(1):11-48.
35. Kniese C, Diab K, Ghabril M, et al. Indwelling Pleural Catheters in Hepatic Hydrothorax: A Single-Center Series of Outcomes and Complications. Chest. 2019 Feb;155(2):307-314.
36. Bhatnagar R, Keenan EK, Morley AJ, et al. Outpatient Talc Administration by Indwelling Pleural Catheter for Malignant Effusion. 2018;378(14):1313-1322.
** Instillation of talc through an IPC system significantly increases pleurodesis rates
37. Tremblay A, Dumitriu S, Stather DR, et al. Use of a drug eluting pleural catheter for pleurodesis. Experimental lung research. 2012 Nov;38(9-10):475-82.
38. Bhatnagar R, Zahan-Evans N, Kearney C, et al. A Novel Drug-Eluting Indwelling Pleural Catheter for the Management of Malignant Effusions. 2018;197(1):136-138.
39. Murthy P, Ekeke CN, Russell KL, et al. Making cold malignant pleural effusions hot: driving novel immunotherapies. 2019:1-24.
40. Du N, Li X, Li F, et al. Intrapleural combination therapy with bevacizumab and cisplatin for non-small cell lung cancer-mediated malignant pleural effusion. 2013;29(6):2332-2340.
41. Jones DR, Taylor MD, Petroni GR, et al. Phase I trial of intrapleural docetaxel administered through an implantable catheter in subjects with a malignant pleural effusion [Clinical Trial, Phase I Research Support, N.I.H., Extramural]. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2010 Jan;5(1):75-81.
42. Islam A, Takita H. Malignant Pleural Effusion and Advanced Stage Low-Grade Non-Hodgkin's Lymphoma Successfully Treated with Intrapleural Instillation of Rituximab. 2012;120(21):4891-4891.
43. Sterman DH, Recio A, Haas AR, et al. A phase I trial of repeated intrapleural adenoviral-mediated interferon-beta gene transfer for mesothelioma and metastatic pleural effusions. Molecular therapy : the journal of the American Society of Gene Therapy. 2010 Apr;18(4):852-60.
44. Aggarwal C, Haas AR, Metzger S, et al. Phase I Study of Intrapleural Gene-Mediated Cytotoxic Immunotherapy in Patients with Malignant Pleural Effusion. 2018;26(5):1198-1205.
45. Ren S, Terman DS, Bohach G, et al. Intrapleural staphylococcal superantigen induces resolution of malignant pleural effusions and a survival benefit in non-small cell lung cancer. 2004;126(5):1529-1539.

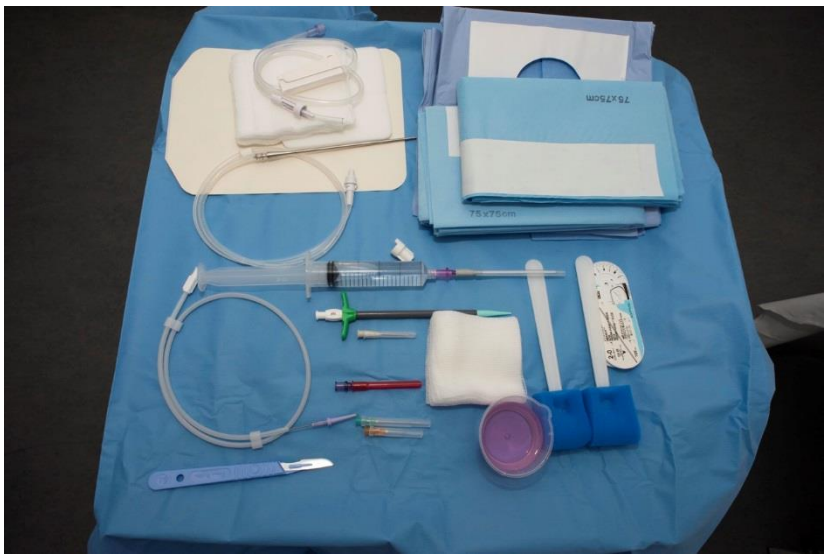

Figure 1a. Example of Indwelling Pleural Catheter set

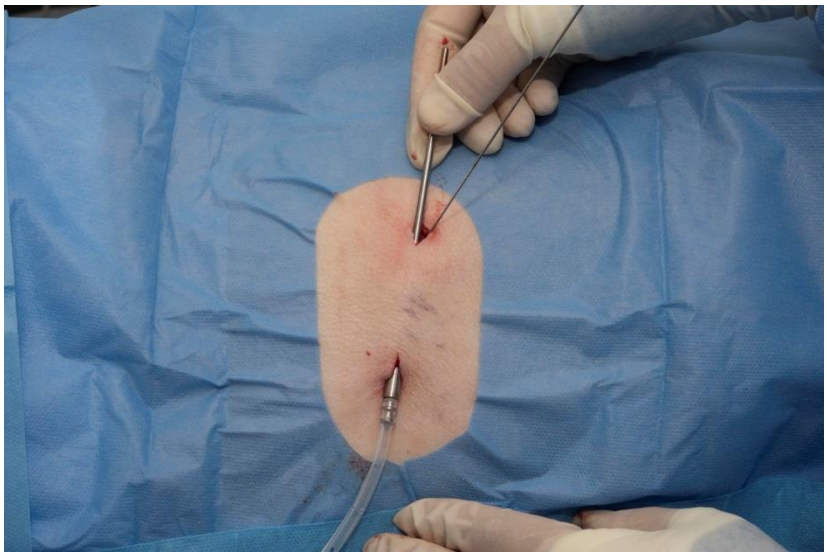

Figure 1b. Tunnelling of Indwelling Pleural Catheter, with guide-wire situ

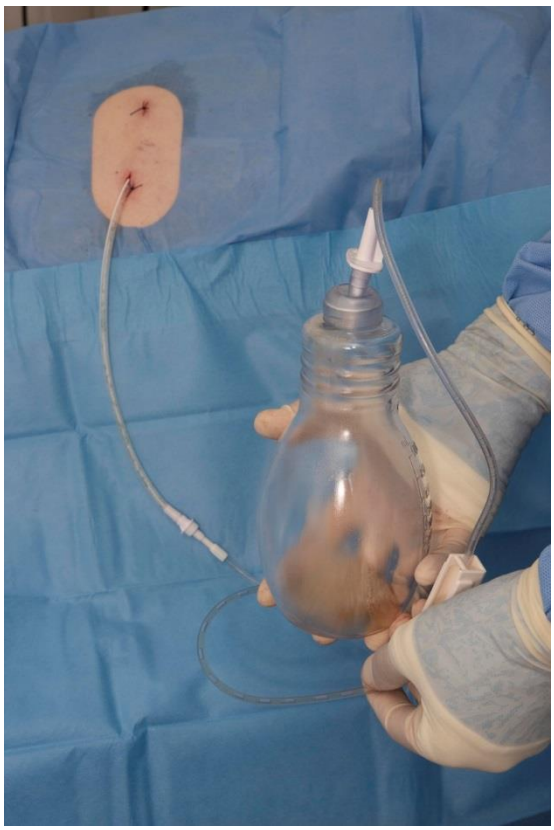

Figure 1c. Drainage of IPC with vacuum bottle

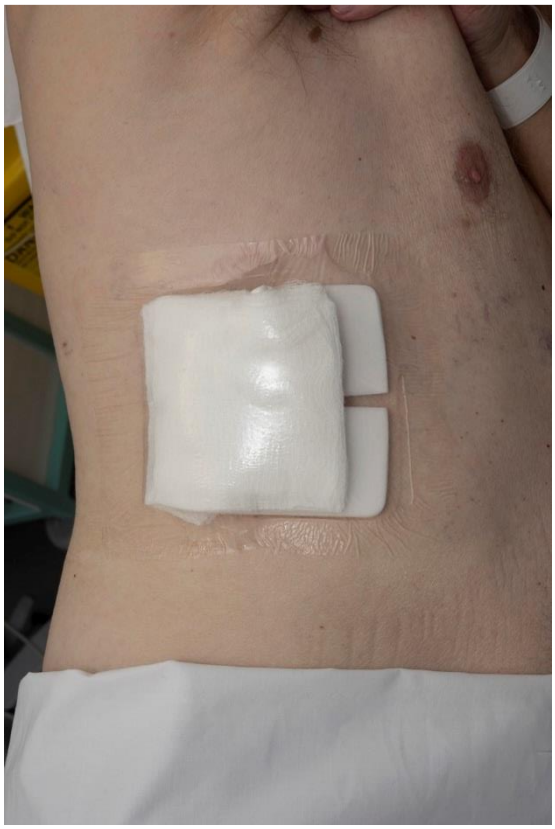

Figure 1d. IPC with dressing