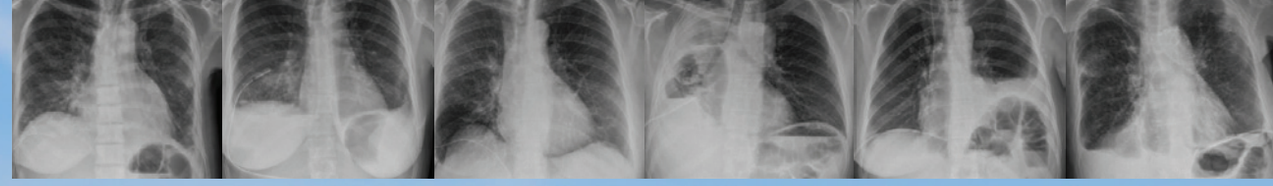
Management of malignant pleural effusion

Boshuizen, R.C.



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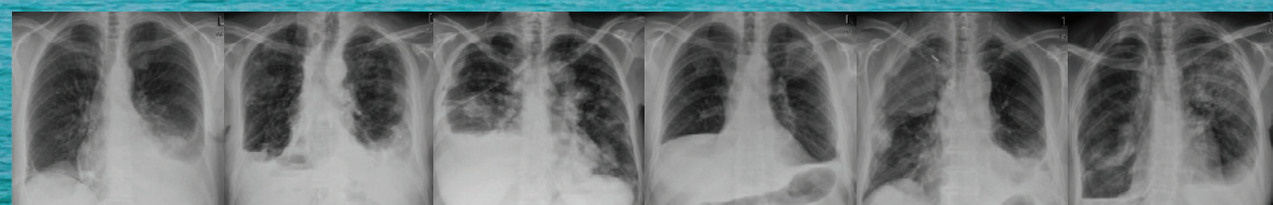

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Rogier Christiaan Boshuizen

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MANAGEMENT OF MALIGNANT PLEURAL EFFUSION

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Introduction and outline of this thesis

Pleural Effusion

Pleural effusion is fluid that accumulates between the parietal and visceral pleura. In a physiologic balance, this fluid is 'produced' by the parietal and visceral pleura and absorbed by the parietal pleura. [1] Increased production, decreased breakdown and a combination of both disturbs this equilibrium.

Pleural effusion can be a manifestation of a variety of diseases. [2] Differentiation between those causes can be made on past medical history, radiologic examination and fluid analysis. In 1972, doctor Richard Light demonstrated that a combination of LDH and protein levels in both pleural and serum samples differentiated more accurately between transudate and exudate (**Table 1**) than these values individually. [3] Pleural fluid is not likely to be caused by malignancy in patients without a medical history of cancer; in a large study reviewing almost 6000 pleural effusions, less than 10 percent of effusions were caused by malignancy. [4] Differentiation between transudate and exudate contributes to the diagnosis even without a history of malignancy, since most MPEs are exudates. [5;6] It must be emphasized that differential diagnosis for exudative pleural effusion is broader than MPE alone.

	Protein PF/ serum ratio	**LDH PF/ serum ratio**	**LDH ULN**
Transudate	< 0.5	< 0.6	< 2/3
Exudate	≥ 0.5	≥ 0.6	≥ 2/3

TABLE 1 - Light's criteria

PF= pleural fluid; ULN= upper limit of normal; LDH= lactate Dehydrogenase

Symptoms

MPE can cause a variety of symptoms. Most common complaint is dyspnea, followed by coughing and chest discomfort. [7] The differential diagnosis of dyspnea in end-stage cancer patients is more diverse than in healthy people and fluid aspiration helps to assess the impact of MPE on dyspnea. Pleural involvement of (metastasized) malignancy means that curation is no longer an option. The presence of malignant pleural effusion has a negative impact on the quality of life of patients with metastasized malignancy. Treatment of malignant pleural effusion should therefore focus on symptom relief rather than survival improvement. More than other endpoints, patient reported outcomes should be used to monitor treatment effect of pleural interventions.

Diagnosis

The sensitivity of cytopathologic examination increases with the number of pleural taps. ([8,9,10]) Thoracoscopy is often performed when pleural fluid recurs and no malignant cause is demonstrated. An alternative for a thoracoscopy is a closed pleural biopsy, which can also identify the nature of the origin of the effusion. [8] There is an on-going debate on the optimal volume of pleural fluid needed for cytopathologic examination. [10-12] More importantly, the sensitivity of cytopathologic examination varies by tumor type. [9;13] It is clear that the probability that a pleural effusion is of malignant origin rises when patients suffer from any malignancy. In a post-mortem series of patients with malignancy, 28% of patients had pleural metastases and approximately half of them (15%) presented with MPE. [14] MPE is most frequently seen in patients suffering from malignant mesothelioma, lung cancer or breast cancer and lymphoma. [15]

Both special radiology and nuclear medicine are not standard of care in diagnosing MPE and their role might be underestimated. Pleural involvement can be demonstrated by a Chest X-ray (CXR), Computed Tomography (CT-scan) and 18-FluoroDeoxyGlucose-Positron Emission Tomography ([18]FDG-PET). [16;17] Ultrasonography enables the pulmonologist to diagnose malignant pleuritis and to perform pleural interventions safely simultaneously. [18-21] Ultrasound examination of the thorax has now become standard in most countries to facilitate the examination of MPE.

Prognosis

Patients with malignant pleural effusion have a poor prognosis. [15] Moreover, patients with metastasized malignancy due to pleural involvement have even worse prognosis than patients with metastases to other organs. [22;23] Since 2007, NSCLC with pleural involvement is considered as metastasized disease. Predicting overall survival is hard, as was illustrated by the largest study on talc pleurodesis comparing thoracoscopic talc instillation with bedside administration of talc sludge by chest drain. [24] Despite the inclusion criteria of an estimated life expectancy of at least 2 months, approximately half of patients died within those 2 months making MPE a symptom of a grave prognosis.

Treatment

Malignant pleural effusion can be treated by either local or systemic treatment. Some primary tumors and their pleural metastases respond very well to systemic treatment, preventing patients from repeat pleural interventions. Recurrence rates of MPE are determined by a number of factors. One of them is the tumor type. MPE in chemo-sensitive tumors like small cell lung cancer (SCLC), ovarian cancer or lymphoma is mostly responsive to systemic treatment. Patients with these malignancies in particular can be treated with systemic antitumor therapy.

Therapeutic thoracenteses were traditionally limited to drain 1-1.5 L in order to prevent *re-expansion pulmonary edema* (RPE). [25] However, RPE in MPE is a rare phenomenon [26], but has been reported in the literature. [27] To avoid RPE, pleural manometry might be of additional value in predicting lung expansion and pleurodesis success. [28] Therapeutic drainages can be performed repetitively, necessitating the patients to visit the hospital regularly on an outpatient basis. The down side of this approach is that each single thoracentesis is an invasive intervention with risk of bleeding, infection, pneumothorax or the development of a tract metastasis.

More definitive pleural treatments are talc pleurodesis (via either bedside chest drain, or thoracoscopy) and insertion of an *indwelling pleural catheter* (IPC, **Figure 1A**). According to most guidelines, talc pleurodesis can be performed when the lung can still expand and patient's life expectancy is at least one month. [15] The physician's assessment of lung expansion and survival guides decisions on talc administration.

Talc pleurodesis vs indwelling pleural catheter

In general, patients who undergo pleurodesis are admitted to the hospital for 5-7 days. [29-31] Results of a Dutch multicenter study show that talc was injected in only 75% of patients. [29] In approximately 15% of patients no talc was instilled due to poor lung expansion. Other reasons for withholding talc were: persisting high fluid production (n=3), rapid clinical deterioration (n=3), absence of malignant cells in pleural effusion (n=3), technical drain problems (n=2), chylothorax and empyema (both n=1). Success rate in an intention-to-treat analysis was 32 percent. Success rate in this study increased when patients in whom no talc was instilled were omitted from analysis. Regarding only patients who were alive at 6 weeks after performed talc instillation, pleurodesis success increased further to 71%. [29] The reported success rates of pleurodesis are also influenced by the elastance of the lung, the pH, tumor type and possible systemic treatment, and performance status. [28;32-34]

Fluid recurrence following pleurodesis can be invasively treated by repetitive aspirations, repeat talc pleurodesis, insertion of an indwelling pleural catheter. Those drains are also called *tunneled pleural catheters* (TPCs), but will be consequently named IPCs in this thesis. Vacuum bottles (**Figure 1B**) can be connected to these IPCs. These catheters enable the patient and caregivers to drain the fluid themselves on an 'as needed' basis. Since an IPC is an effective MPE treatment following failed pleurodesis or in patients with a trapped lung syndrome, [35-37] studies have been initiated to investigate whether IPCs would adequately manage MPE in a frontline setting as well.

Outline of this thesis

The first part of this thesis focuses on IPCs in MPE management. In an invited review, the (dis)advantages and prejudices of IPCs are described (**Chapter1.1**). Since costs and reimbursement issues are the main reasons in the Netherlands to withhold patients from IPCs, we performed a retrospective analysis of a prospectively collected database. In this database, we registered patient characteristics (gender, tumor type), survival data and IPC supplies. Material costs of IPC treatment were calculated and are presented in **Chapter 1.2**. Results of a multicenter randomized controlled trial comparing *talc pleurodesis* (TP) with IPC as first line treatment in The Netherlands are presented in Chapter **1.3**.

In part two of this thesis therapeutic thoracenteses are evaluated. Since lung expansion is one of the most important predictors for lung expansion, we focused on lung expansion. Results of a survey on the interpretation of Chest X-rays (CXRs) are discussed in **Chapter 2.1**. Chest physicians of The Netherlands and Belgium were asked to review 50 CXRs from consecutive patients previously treated for MPE. For each CXR, they were asked whether they considered the lung to be expanded; whether they would instill talc and to estimate the success rate. In the next chapter (**Chapter 2.2**), pleural manometry was used for early recognition of lung expansion or trapped lung. In contrast to more frequently used methods, we used software to monitor/ record pleural pressure with a high frequency. We observed pleural pressure swings during respiration. In **Chapter 2.3** we show patient reported outcomes (PROs) after therapeutic thoracentesis and correlate these scores to re-interventions. Finally, in a letter-to-the-editor we comment on a predictor study for definitive MPE treatment. (**Chapter 2.4**)

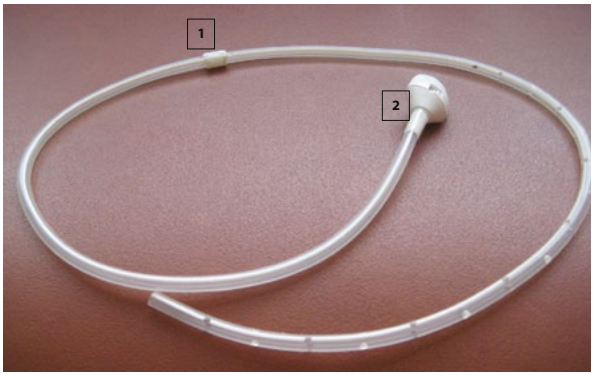

FIGURE 1A - Inwelling pleural catheter

An IPC with drainage holes (visible on the right side of the picture). The subcutaneous tunneled cuff (1) provides fixation. A vacuum bottle (Figure 2B) can be attached to a valve (2) at the end of the external part.

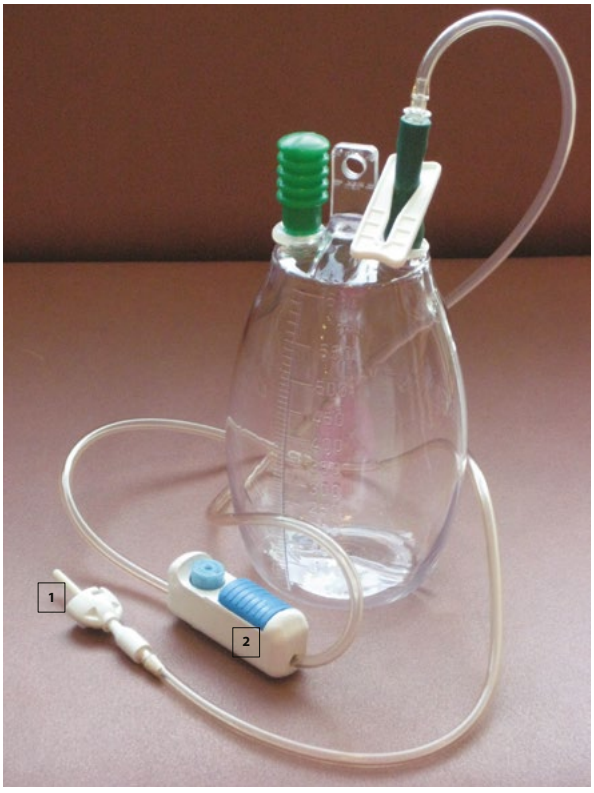

FIGURE 1B - Vacuum bottle

A vacuum bottle with an access tip (1) which can be inserted into the valve. The flow of pleural fluid can be controlled by the blue button. Full flow can be generated when the slider (2) is pushed over the button.

PART ONE

Indwelling Pleural Catheters for Malignant Pleural Effusion

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Chapter 1.1

Advantages of Indwelling Pleural Catheters for Management of Malignant Pleural Effusions

First line treatment for recurrent malignant pleural effusion

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Abstract

The use of indwelling pleural catheters (IPC) has an established place in the management of malignant pleural effusion (MPE) when pleurodesis has failed or is unsuitable. The use of IPC as a front line therapy in place of pleurodesis is also gathering momentum. Recent studies confirmed that IPCs provide similar improvement in symptoms and quality of life, and requires fewer hospital days, when compared against talc pleurodesis. Adverse events related to IPC treatment are uncommon and generally mild. Comparing the cost-effectiveness of IPC and pleurodesis is difficult and remains a contentious issue. Patients with a MPE are a heterogeneous group; it is likely some patients may benefit more from IPC and others from pleurodesis. How best to identify these subgroups is of high priority in MPE research. In the meantime patients should be offered both options of IPC and pleurodesis (if no contraindication) and patient preference incorporated into the decision process.

Introduction

Malignant pleural effusion (MPE) is a common clinical problem with a growing incidence. Talc pleurodesis, first reported in 1935, [38] remains a mainstay practice, testifying to a serious lack of progress in the clinical management in MPE. Studies in recent years have also raised concerns of the suboptimal efficacy and safety of talc pleurodesis. [29;39;40]

Success of talc pleurodesis was often defined, in older literature, as no radiological evidence of fluid re-accumulation after 28-30 days, and reported as 90+%. Large randomized studies however failed to reproduce such figures and instead showed a 30-day success of approximately 75% even in selected patients with no significant trapped lung. More importantly, the failure rate of talc pleurodesis increases the longer the patients survives; by six months only ~50% patients still have adequate fluid control. [24]

The advent of indwelling pleural catheters (IPCs) allows clinicians to question the wisdom of pleurodesis. The majority of patients with MPE have an incurable malignancy. The aim of management should be optimal palliation, especially against the associated breathlessness, which is often disabling, frightening and reduces quality of life (QoL). The median survival for MPE patients is 3-4 months. Evacuation of the MPE often requires spending precious days of the patients' remaining life in hospital and can be associated with significant health care costs.

The ideal therapy for MPE patients should offer effective fluid control, improve dyspnea and QoL, be safe, minimally invasive and affordable and limit time in hospital.

Advantages of Indwelling Pleural Catheter (IPC)

The use of IPCs has grown exponentially, especially in the management of malignant pleural effusions, since the Food and Drug Administration approved their use in 1997. Commonly used commercially-available devices include PleurX® catheter (CareFusion, USA) and Rocket® IPC (Rocket Medical, England) which have similar designs, and will hereafter be discussed generically as an IPC.

IPCs are 15.5 to 16 French silicone catheters and approximately 65 cm in length with a fenestrated section. The catheters are designed to remain *in situ* indefinitely for the remaining lifespan of the patient. The polyester cuff in the tunneled portion of the catheter promotes tissue fibrosis and avoids inadvertent catheter dislodgement. Tunneling of the catheter is believed to reduce infection risks though this has not been formally tested. The one-way valve at the distal end of the catheter permits ambulatory drainage of pleural fluid: the catheter can be 'opened' and connected to

drainage devices when needed whilst at other times the patient can continue usual daily activities with the catheter capped off.

Insertion of the catheter is a minor intervention usually requiring only local anesthesia or conscious sedation. It can be performed as an outpatient day procedure and the patient is ambulant promptly afterwards. Two incisions are made between which the polyester cuff is tunneled into the subcutaneous tissue. The fenestrated part is inserted into the pleural space using Seldinger's technique via the cranial incision.

The frequency of drainage can be determined by the patient depending on the rate of fluid re-accumulation and severity of symptoms, mainly dyspnea. It thus provides greater control and flexibility to the patients in managing their condition. Drainage itself can be performed by a trained carer or health care worker, removing the need of repeated invasive pleural drainage procedures, and the associated risks, costs and hospitalizations.

Effective fluid control

An estimated 50% of patients with a MPE will develop symptomatic re-accumulation requiring more definitive therapy to control fluid recurrence. Pleurodesis, either mechanically (via surgery), eg pleurectomy, or chemically using a sclerosing agent has been the treatment of choice for decades. Surgical pleurodesis is costly, carries anesthetic risks and is associated with post-procedural intercostal neuralgia, [41] and is not appropriate in the majority of MPE patients who have advanced malignancies with a limited life expectancy. Pleurodesis, especially via bedside instillation of a sclerosant, is the most common procedure worldwide to control MPE recurrence.

Talc has been shown to be the most cost-effective sclerosant. [42] However, recent studies have confirmed that talc pleurodesis (either by thoracoscopic poudrage or instillation as a slurry) is effective in around 75% of cases at one month. [24] More importantly, the longer the patient survives, the more likely there will be fluid re-accumulation necessitating further interventions. In the largest randomized trial of MPE to date, only 50% of patients will still have adequate fluid control by six months post-talc pleurodesis. [24] The median survival of patients with a metastatic pleural carcinoma is around 4 months, and those with a primary pleural mesothelioma about 9-12 months. Thus the lifetime control of fluid re-accumulation by pleurodesis is suboptimal.

In addition, pleurodesis is only appropriate when the patient has full lung expansion after fluid drainage. The incidence of trapped lung varies among studies. Even for patients admitted to the hospital with the intent to perform pleurodesis, approximately 25% were found to be unsuitable, most often due to insufficient lung expansion, as shown in a study in the Netherlands. [29;43]

IPC is now accepted as the preferred management in patients with failed pleurodesis or in whom pleurodesis is inappropriate (eg trapped lung). IPCs function as a continuous access to the pleural cavity, through which pleural fluid can be drained without the need for repeat invasive procedures. A wealth of literature has testified to the effectiveness of IPCs in pleural fluid drainage. In most studies, over 90% of patients treated with an IPC do not require any further effusion-related pleural intervention. [44-46]

It is therefore logical to examine if IPC can be used as the frontline treatment in place of pleurodesis, rather than only when the latter is contraindicated or fails. Several key studies have now established that IPC has at least an equivalent benefit when compared with pleurodesis, thus challenging the conventional treatment paradigm, [47] since the first randomized controlled trial comparing IPC with (doxycycline) pleurodesis was published in 1999, [30] including a UK multicenter randomized trial, [44] and a small study from the USA. [48] Additional randomized studies on the benefits of IPC over pleurodesis are also underway in the Netherlands and Australasia.

Two schools of thoughts exist in the clinical application of IPC. In many centers it is advocated as an alternative to pleurodesis (see below) and a strong focus of the drainage regime is to keep the pleural cavity dry, eg via daily or alternate day fluid drainages. [31;49-52] Others believe that the goal of MPE management is symptom palliation, and evacuation of fluid should only need to be performed as guided by patient symptoms. [37;53;54] Often, complex drainage schedules are described. [30;46;55-57]

In either case, spontaneous pleurodesis, if it occurs, is an added advantage as it allows removal of the catheter, thus negating the associated risks of IPC-related complications, inconvenience and costs. Spontaneous pleurodesis associated with IPC use has varying definitions in published literature, **Figure 1.** Rates of spontaneous pleurodesis range from 26% to 76% in most large series, [44-46;58;59] and the median time to spontaneous pleurodesis varies from one to three months. [30;46;58] Numerous factors may confound the incidence of pleurodesis, including the incidence of trapped lung in the study cohort, duration of patient survival, underlying types of malignancy and if pleurodesis [46] has been attempted before.

The amount of fluid drained in the first week has also been suggested as a predictor of spontaneous pleurodesis as the median drainage is significantly less in the group that achieves pleurodesis as compared to the group that does not. [30] Studies are underway to investigate the influence of drainage schedules on pleurodesis rates. Whether these different regimens will lead to reliably better pleurodesis rates in real world setting will also depend on the patient's compliance with the prescribed drainage schedules.

The rate of spontaneous pleurodesis may be lower in cases of lung cancer compared to other malignancies and in the presence of a trapped lung. [57] Even in patients unsuitable for talc pleurodesis who undergo IPC insertion, most patients have symptomatic benefit and spontaneous pleurodesis has been reported. [50;51]

Reference	Criteria for inclusion	Incidence
Ref 31	Pleural symphysis	21/100
Ref 51	Pleural fusion with subsequent IPC removal	11/51
Ref 60	IPC removal	19/82
Ref 46	IPC removal*	110/418
Ref 54	Drainage 3x<50mL, without progressive symptoms or fluid on CXR	22/63
Ref 64	No drainage for 1 month and no significant effusion on CXR	37/90
Ref 79	No definition provided	13/31
Ref 50	Drainage <10mL	22/52
Ref 58	Drainage 3x<50mL, without progressive symptoms or fluid on CXR	103/240
Ref 30	No definition provided	42/91
Ref 44	Cessation of fluid*	26/51
Ref 49	Long term relief with absence on CXR until death	11/19
Ref 57	IPC removal following tapered drainage	173/295
Ref 48	Drainage 3x<30mL in 3 consecutive days	17/26
Ref 63	No definition provided	95/125
Total	-	722/1734

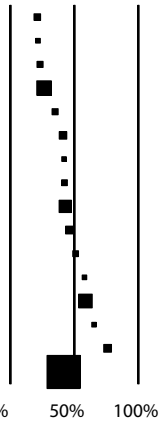

FIGURE 1 - Rates of spontaneous pleurodesis

A literature summary of published rates of spontaneous pleurodesis in IPC patients, and the different definitions used.

** the inclusion criteria of Ref 44 and 46 included no clinical or radiological re-accumulation of fluid, IPC removal, and no subsequent need for further pleural interventions*

Quality of Life (QoL)

It is increasingly realized by clinicians and patients that the primary goal of MPE management is palliation and thus QoL is an essential measurement in assessing any therapy for MPE. However, studying QoL is difficult in this patient population. To date, there are no validated instruments specific for QoL assessment in MPE patients. The patients' sense of well-being is often influenced by numerous factors not directly related to the MPE. Confounding co-morbidity from the underlying cancer and/or its treatment, as well as psychological issues such as uncertainty about prognosis, produce significant study 'noise' that hinders reliable assessment of the impact of MPE therapy in QoL of any individual patient.

The same difficulties apply even if the study endpoint is restricted to the impact of MPE therapy on dyspnea. Differential diagnosis of dyspnea in patients with end-stage cancer is broad and may not always be directly related to MPE alone. No dyspnea score has been validated for the use in patients suffering from MPE.

Withstanding these limitations, important attempts have been made to decipher the benefits of IPC management in QoL and symptom control.

In 1999, Putnam and colleagues showed in a randomized controlled trial with 144 patients (45 pleurodesis: 99 IPC) that at 30 days the modified Borg scale (MBS) dyspnea scores were significantly improved in the IPC group compared to those who received doxycycline pleurodesis. [30]

A recent randomized study of 106 MPE patients (54 pleurodesis: 52 IPC) employed the Visual Analog Scale (VAS) for dyspnea assessment. The study showed that IPC provided equivalent improvement in dyspnea compared with pleurodesis at six weeks after randomization. [44] Dyspnea control at 6 months after randomization was superior in the IPC group. Quality of Life Questionnaire (QLQ-30) did not show significant differences at any time point between the two treatment arms.

Another randomized trial of 57 patients (29 pleurodesis: 28 IPC) employed multiple instruments for QoL assessment (distress score, number of symptoms, the Memorial Symptom Assessment Scale, changes in function form, performance status, dyspnea score, physical function, emotional state, and social life). Overall, patients randomized for IPC treatment had better dyspnea scores than those pleurodesed, especially in patients with trapped lungs. [48]

Allowing patients the choice between IPC and pleurodesis may also provide a sense of control over their palliation treatment. In a non-randomized, patient-choice study, patients who chose to have IPC (n=34) were significantly more likely to report improvement in QoL (recorded on a visual analog scale) than those who elected to receive talc pleurodesis (n=31), p=0.02. [45] Interestingly, in this study when patients were given a choice, approximately equal number of patients chose IPCs and talc pleurodesis. [45]

Concluded from FACIT-TS-G questionnaires, the majority of patients treated with IPC was satisfied, would recommend it to others with MPE and would choose it again. [60] In a non-randomized observational study (82 IPCs), patients reported significant improvements QoL and dyspnea assessed by QLQ-C30 and QLQ-LC13, at 2 and 14 weeks after IPC insertion. [60]

Despite the limitation of the study tools and the variations in trial protocols, the overall picture that has emerged from the published data would support that IPC is at least as efficient as (talc) pleurodesis in relieving dyspnea and/or improving QoL.

Safe treatment for MPE

The overall safety of IPC use has been confirmed in many observation series as well as randomized and non-randomized trials. Wrightson et al summarized the reported complication rates in published literature [61] and showed that common reported adverse events are mild and easily controlled. Post-insertion pain was the most common reported side effect, affecting about one-third of patients, but

is transient (<72 hours) and usually required only simple analgesia. More significant complications e.g. symptomatic loculation (<10%), infection or catheter tract metastases do occur but at low and very acceptable incidences (<5%), **Figure 2A/B.**

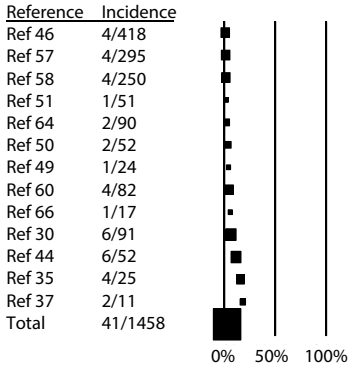

FIGURE 2A - Rates cellulitis after IPC placement

A literature summary of published rates of (a) cellulitis and in IPC patients, showing a low incidence in all series.

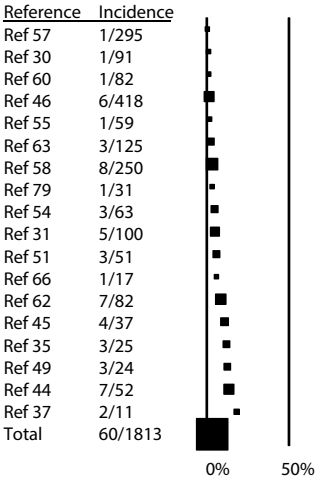

FIGURE 2B - Rates of empyema after IPC placement

A literature summary of published rates of empyema in IPC patients, showing a low incidence in all series.

Infections

The fear of pleural infection from a long-term implanted device is the most significant deterring factor for the uptake of IPC. This concern is understandable considering that most of these patients are elderly and with advanced malignancy (some of whom may undergo chemotherapy).

To date, all literature series suggest IPC infection rates are low. Morel and colleagues showed that 7 out of 82 IPCs developed a pleural infection. [62] The incidence rate was actually lower (one of 23) in patients treated with chemotherapy compared with 6 out of 59 patients who did not receive chemotherapy (4% vs 10%). In the TIME2 randomized study of 106 patients, five had a significant pleural infection of which only one received chemotherapy. The risk of any IPC related pleural infection must also be analyzed in the context of the cumulative risks of alternative management which often involves multiple pleural interventions (eg repeated drainages for trapped lung patients).

It is likely that infection was acquired during the course of the use of IPC, rather than at the time of insertion. Having reviewed 18 publications on IPC and pleural infections, only Sioris reported to have used antibiotic prophylaxis (Cephalexin, 750mg BID for 5 days) at the time of insertion, and showed an infection rate similar to other series. [51] As the majority of patients treated with IPC and chemotherapy does not develop pleural infections, routine prophylactic antibiotics (even during immunosuppressed phase) appear unwarranted.

Tract metastasis

Fifteen tract metastases were reported in 13 studies with a combined number of nearly 1000 IPC insertions. [30;31;35;49-51;54;58;63-66] Tract metastases are more often described in mesothelioma patients but have been described for metastatic carcinomas as well. There is a suspicion that tract metastases occur more frequently the longer the IPC is *in situ*, though the incidence is too low to allow meaningful analyses. [65] Importantly, catheter tract metastases respond very promptly to radiotherapy which can be performed with the IPC *in situ*.

The value of prophylactic radiotherapy in pleural puncture sites in mesothelioma patients remain a contentious issue. [67] The protective value of radiotherapy is even more doubtful in the setting of IPC as the risk of tumor invasion of the catheter tract is ongoing, which differs from the risks from one-off pleural interventions (such as thoracotomy). [67] Thus, radiotherapy should be reserved for patients with symptomatic tract metastases only.

Mechanical defects

Mechanical faults of the IPC drainage system can arise infrequently but most can be corrected without removal of the catheter. For example, catheter clogging occurs in a minority of cases and can be successfully treated with instillation of fibrinolytics. Rarely, mechanical defects (eg incompetent one-way valve) can occur but most can

easily be replaced. [68] Removal of IPC can be difficult and fracture of the catheter leaving residual portions in situ has been reported. This should not raise concerns as the IPC is intended to remain for the remaining lifespan of the patient and retained segments have not been shown to increase morbidity. [69]

Reducing hospitalization

Most patients with a MPE have advanced diseases and the prognosis is grave. Allowing patients to remain ambulatory outside hospital is one of the main goals in palliative care. IPCs are predominantly placed on an outpatient (or day case) basis, or at most requiring an overnight stay. Pleurodesis however requires inpatient care that can commonly take up about six days (the commonest quoted figure for talc slurry pleurodesis). Given a median survival of 3-4 months in patients suffering from a MPE, the hospital time for pleurodesis represents a significant proportion of the patients' remaining lifespan. When pleurodesis fails or is contraindicated, repeated pleural drainage requires further (often multiple) hospital admissions.

Hospitalization time for pleurodesis differs among centers, and with various methods of pleurodesis. Comparison of inpatient care time by pulled data from different studies is therefore inappropriate. Direct comparison of hospital days between patients treated with IPC and pleurodesis is the subject of a randomized trial in Australasia. It should be emphasized that it is the cumulative hospital admission days (till death) that matter most to the patient, not just the initial hospital stay for the IPC or pleurodesis.

Putnam and coworkers retrospectively reviewed hospital durations for patients with an inpatient chest drain (n=68), as well as inpatient (n=40) and outpatient (n=60) indwelling pleural catheter. The latter group has significantly shorter hospitalization time (median 0 vs 7 days) for the initial procedure. [31]

In the patient choice study described before, [55] patients who chose to receive an IPC spent significantly fewer days in hospital for admissions due to effusion-related reasons or overall hospital days from procedure till death (median 3 vs 10 days; $p<0.001$ and 6.5 vs 18 days; $p=0.002$, respectively), as compared with the bedside pleurodesis group. [45] In the TIME2 study patients randomized to the IPC group spent a median of 1 day in hospital (vs 4.5 days in the pleurodesis group, $p<0.001$) for drainage or drain-related complications after 12 months. [44]

A recent pilot study also suggested that the insertion of an IPC immediately following thoracoscopic poudrage would decrease the hospital days significantly. [56]

Cost-effectiveness

The cost-effectiveness of IPC (vs conventional pleurodesis) has provoked considerable discussions. No studies have performed thorough cost analyses comparing IPC and pleurodesis, in part because of the significant difficulties in such analyses. Most published works are retrospective or described only the costs of IPC (without direct head-on comparison with pleurodesis). Other papers rely on mathematical models comparing IPC against alternative treatments; the data have significant shortcomings and often cannot be extrapolated to other healthcare settings.

IPC and pleurodesis involved very different cost items and the quantity needed for each item varies widely among patients. There are also many factors such as survival, likelihood of success of pleurodesis, complication rates etc which either vary significantly in the literature and/or differ considerably among individual patients.

For example, IPC predominantly requires outpatient care, and most of the costs depend on the catheter and drainage kits, the latter depends on the frequency of drainage regime which can vary from daily to as required only (see above). Whether the drainage is performed by a family member or require home visits from community nurses, and how often the patient is reviewed by medical staff will also drastically alter the costs. The duration of IPC drainage also varies widely depending on patient survival, and if spontaneous pleurodesis develop. Complications are uncommon, as discussed, but in those small proportion of patients the costs can rise sharply (eg inpatient for intravenous antibiotics for IPC related pleural infection). The longer the IPC is *in situ*, the more drainage devices the patient will consume, the higher the risks of complications and the more healthcare resources (eg community nurse visits) are needed.

On the other hand, pleurodesis costs vary significantly among centers, and the price for hospital bed days vary greatly around the world. Surgical pleurodesis are generally more expensive than bedside pleurodesis. If pleurodesis fails, subsequent costs will have to include additional intervention procedures.

In 2000, Putnam showed that early (7-days) hospital charges were lowest when IPC was inserted on an outpatient basis, compared with both inpatient IPC insertion and chest tube doxycycline pleurodesis. Total (long term) hospital charges did not differ significantly between these groups, neither did overall survival. [31]

Puri and colleagues compared four pleural interventions for MPE management in their cost-effective analysis: repeated thoracentesis, IPC, bedside pleurodesis and thoracoscopic pleurodesis. Based on projected figures the paper concluded that IPC is most cost-effective in providing Quality Adjusted Life Years (QALYs) for patients with limited (ie <3 months) survival. If the patient is to survive 12 months or more,

bedside pleurodesis was the most economical.[70]

Another study also showed that IPCs appeared to be more cost-effective in patients with a life expectancy of less than 6 weeks compared to those with longer survival. Effective treatment was defined as resolved effusion following survival of all potential life threatening complications caused by either IPC insertion or talc pleurodesis. Resolution of effusion was assumed to be higher from talc pleurodesis than IPC insertion (based on figures of 80% vs 45%, respectively). The IPC complication rate was estimated at 7.5%, and 1.5% for talc pleurodesis. IPC induced pleural adherence was estimated to occur after 10 weeks, and patients were assumed to be visited by a nurse thrice weekly for drainage. [71] Caution must be exercised in adopting these conclusions as even small changes in the figures used for calculation (eg pleurodesis success rate) can profoundly alter the cost-effectiveness ratios [72] and the figures used for analysis are sometimes contestable.

Clinicians are also notoriously poor in predicting patient's life expectancy in MPE. For example, the CALGB study (n=482 MPE patients) had a recruitment criterion of a life expectancy of at least 2 months; however almost 50% of the recruited patients died within 30 days.[24] Treatment decisions based on prognosis may be difficult to implement until better means of assessing survival is available for MPE patients.

The concept of combined use of IPC as well as pleurodesis is now being explored, either by implanting IPC post-thoracoscopic pleurodesis, [56] or to instill talc slurry via an IPC. Successful combination of both management strategies may help reduce costs.

The price of drainage catheters and bottles varies among countries and vendors, and are subjected to market competitions. A change in the pricing of these consumables will also dramatically alter the results of the cost-effectiveness assessments. Other forms of less expensive devices (such as reusable Surgivac pumps in Egypt) are also being tried in various centers which will influence healthcare costing. [73]

Conclusion and Future Directions

The use of IPC is gathering momentum around the world, more than a decade after it gained FDA approval. Its efficacy is well proven as a rescue treatment of MPEs when pleurodesis has failed or is contraindicated. In addition, the use of IPC as a front line therapy in place of pleurodesis is growing in popularity. IPC provides improvements in QoL and dyspnea scores at least similar to talc pleurodesis. No major safety issues have been identified. IPCs significantly reduce pleural interventions, hospital admissions and inpatient expenses. The use of IPC also highlights the priorities of MPE management, ie improving symptoms and QoL rather than to create pleural symphysis.

The precise benefits of IPC, especially in its cost-effectiveness and impact on QoL, require further investigations. It is likely that different subsets of patients may benefit from using IPC or pleurodesis as first line of management for their MPE. Future studies are needed to help identify criteria to guide the choice of therapy in individual patients. Combining both pleurodesis and IPC treatments may further increase effectiveness. [56] In the meantime patients should be offered both options of IPC and pleurodesis (if no contraindications) and patient preference should be incorporated into the decision process on clinical management.

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Chapter 1.2

The Use of Indwelling Pleural Catheters for Management of Malignant Pleural Effusion- Direct costs in a Dutch hospital

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Abstract

Background

Indwelling Pleural Catheters (IPCs) are increasingly used in the treatment of Malignant Pleural Effusion (MPE). In general, these catheters have been reported to manage MPE efficiently. Unfortunately, insurance companies in the Netherlands do not reimburse these catheters in either first line treatment or following failed talc pleurodesis.

Objectives

Investigation of direct costs of Indwelling Pleural Catheters

Methods

Retrospective analysis of a prospective collected database. Direct costs for both catheters and vacuum bottles were calculated. Indicators for indirect costs such as adverse events and complications and need for additional home care for drainage were registered.

Results

Mean costs for IPC amounted to €2173 and were different between tumor types; Mesothelioma €4028, Breast €2204, Lung €1146 and other €1841; p=0.017. Four patients were admitted to hospital for treatment of complications. Mean costs for IPCs was similar when inserted as frontline treatment and after failed pleurodesis. Approximately 75% of patients did not need any help from specialized home care.

Conclusion

Direct costs for IPC placement turn out to be acceptable when compared with estimated hospitalization costs for pleurodesis treatment. Randomized controlled trials have to be performed to compare the (cost-) effectiveness of IPCs compared to pleurodesis

Background

Malignant Pleural Effusion is a common complication of malignancy. The prognosis is poor with patients having a median survival of 3 to 12months. [15] MPE can cause significant shortness of breath, and therefore treatment focuses mainly on palliation. In general, recurrent MPE is treated with the instillation of sterile talc into the pleural space, according to current guidelines. [24;74-76] Mean hospitalization duration for pleurodesis is 4-8 days. [77] The percentage success rate of pleurodesis is approximately 80%, according to the guidelines of the British Thoracic Society. [15] This percentage decreases over time [24;29;43] and depends on definition.

When talc pleurodesis fails, insertion of an Indwelling Pleural Catheter (IPC) can be considered. [37] An IPC is a subcutaneously tunneled catheter, which enables patients and their caregivers to perform drainages at home. Alternative treatment options for recurrent pleural effusion range from the very invasive (pleurectomy) to no intervention (abstination). More frequently, a second pleurodesis or repeat therapeutic drainages are undertaken.

Recently, results of two randomized controlled trial comparing the effectiveness of IPC to talc pleurodesis as frontline treatment for MPE were published. [44;48] in the TIME2 study, patients reported dyspnea equally in both treatment arms, six weeks after randomization. Incidences of serious adverse events were also comparable. Patients who were randomized to talc pleurodesis had a longer hospital stay (median 4 vs 0 days, $p<0.001$). [44] This difference was also seen when patients chose either IPC or talc pleurodesis. [49] Patients who had been treated with an IPC would choose it again. [60]

In 2000, Putnam and colleagues demonstrated that total hospital charges were reduced when patients were treated with an IPC instead of doxycycline pleurodesis. [31] An IPC rather than talc pleurodesis was shown to be most cost-effective when patients survived less than 6 weeks. [71] Two years later repeat thoracenteses, IPC and pleurodesis were compared in another cost-effective analysis. IPC was considered most cost-effective when patient's survival was 3 months. [70]

Indwelling pleural catheters appear cost-effective in managing MPE. Unfortunately, in the Netherlands, reimbursement is organized in such a way that the costs of vacuum bottles (direct costs) have to be paid by the respiratory department of the hospital. This might prevent optimal use of IPCs. In this article we describe the direct costs of IPCs in a Dutch hospital.

Materials and Methods

Indwelling Pleural Catheter

Between September 2009 and April 2012 65 IPCs were inserted for symptomatic malignant pleural effusion in the Netherlands Cancer Institute. Insertion technique has been described previously. [35]

Database

Patient and intervention related details such as age, gender, past medical history, and systemic anti-tumor treatment were recorded in a prospective database. Use of a prospective database was approved by the Medical Ethical Committee of the Netherlands Cancer Institute. All interventions for malignant pleural effusions, motivation for IPC insertion and complications were documented. It was also recorded who performed the domiciliary drainages; patient, family or nurses. Vacuum bottles were ordered by the respiratory department. These data were compared to distribution data provided by the supplier.

Direct costs

Since 2009, costs for an IPC insertion set are €255 (Tax excluded), costs per 5 vacuum bottles (600 mL) €310 (Tax excluded) and per 5 peritoneal drainage bags €195 (Tax excluded). No other costs had to be made to perform drainages at home. Direct costs were calculated using the costs of insertion sets and vacuum bottles or peritoneal drainage bags.

Statistics

Groups were compared using the ANOVA-test. P-values below 0.05 were considered to be significant. In general, mean costs were displayed representing the daily practice. Median values were used for survival times. Unless otherwise mentioned, variables were reported per inserted catheter and not per patient.

Results

Patient characteristics

Sixty patients underwent 65 IPC insertions. Eleven patients were treated by their referring pulmonologist elsewhere. These patients were excluded from analysis, due to the absence of proper follow-up data. In four patients an IPC was inserted for reasons other than MPE (infection following an extrapleural pneumonectomy,

radiation pleuritis, yellow nail syndrome, and terminal heart failure) and were also not included in this overview. Five patients underwent bilateral IPC insertion. In total 50 IPCs in 45 patients were used in this analysis (**Table 1**). Reasons for IPC insertion were failed ipsilateral pleurodesis (n=20). Thirty patients had an IPC placed as frontline treatment: failed contralateral pleurodesis (n=10), explicit demand by medical oncologists/ patient (n=8). Twelve patients were treated with an IPC as frontline treatment in trial.

	50 IPCs	**45 patients***
Age		
mean (years)		57
range (years)		(30-83)
Side		
left	27	
right	23	
Gender		
Female		26
Male		19
Previous admissions for pleurodesis		
No	30	
Yes, talc instillation	10	
Yes, no talc instillation	10	
Tumor type		
Breast	15	13
Lung	8	8
Mesothelioma	7	6
Gastro-intestinal	5	4
Urogenital	5	5
Ovarian	4	4
Other[1]	6	5

TABLE 1 - Patient characteristics

** 5 patients had bilateral IPCs*

[1] Other tumors: 2 patients suffered from a Head-and-Neck malignancy, 2 patients from an adenocarcinoma of unknown primary, and one patient had bilateral pleural effusion caused by melanoma.

Four patients also had an indwelling peritoneal catheter in situ for ascites drainage. Four patients underwent pericardial drainages for malignant pericardial effusion. During this analysis two patients were still alive at 301 and 265 days after IPC insertion. IPCs had been removed 183 and 94 days after placement, respectively. Overall survival was 51 days (95%CI 63-150 days) and was not different between patients with an IPC as frontline treatment (n=30) (67 days, 95%CI 62-129) and

patients who previously underwent an ipsilateral pleurodesis (n=20) (39 days, 95% CI 24-221; p=0.551). Patients suffering from mesothelioma had longest median overall survival (time between IPC placement and death) (294 days), followed by patients suffering from breast cancer (58 days), lung cancer (45 days) and patients with other tumors (44 days, p= 0.002).

Pleural intervention prior to IPC insertion

Prior to IPC insertion patients underwent 2.4 ipsilateral therapeutic thoracenteses (median 2; range 0-8). Twenty patients were admitted to the hospital for ipsilateral pleurodesis previously, and in 10 patients no talc was instilled due to insufficient lung expansion following drainage. These 20 patients had a mean hospitalization time of 6.1 days (median 6; range 2-19 days). Median time from IPC insertion to death was similar for patients with and without talc instillation (43 vs 35 days; p=0.621).

Pleural interventions following IPC insertion

No patient required a re-intervention for MPE management following IPC insertion. Nine IPCs were removed, in the majority, due to decreased fluid production.

Direct costs of the IPC

Direct cost per IPC was amounted to €2137 (median €1495; range €379-€8315). IPC costs were not different when comparing first-line inserted IPCs with IPCs inserted following ipsilateral pleurodesis (€1888 vs. €2512, p=0.259). Costs for the use of an IPC were higher when patients also had an Indwelling Peritoneal Catheter (€4518 vs. €1931; p=0.008, bottles or bags for peritoneal uses have been excluded from the analysis). Pericardial effusion did not influence the direct costs for using an IPC. IPCs had lowest costs when inserted in patients suffering from lung carcinoma (€1146) in contrast to mesothelioma (€4028). Patients suffering from breast cancer and other tumors had IPC costs between (€2204 and €1841; p=0.017). Using an IPC for a time period under six weeks significantly lowered costs compared to longer use (€1100 vs €2273; p=0.002). Patients who were treated with systemic anti-tumor therapy (n=24) had a better median survival (104 vs 39 days; p= 0.00714) and IPC costs were therefore higher (€2916 vs €1481; p=0.008). Daily costs (total costs divided by drainage duration) was not different between tumor types (lung €36.9, other €40.5, mesothelioma €45.9 and breast €50.7; p=0.842)

Complications

Approximately 75% of IPC insertions were without complications (**Table 2**). Four patients were admitted for 1, 3, 12 and 14 days with painful drainage, pneumothorax and empyema (2 admissions), respectively. One empyema developed while patient was treated with antitumor therapy (1 out of 24 patients). One patient out of 26 patients who did not receive any systemic antitumor treatment developed an empyema.

One IPC had to be re-inserted following dislocation during a coughing episode and one IPC was damaged during removal of stitches and had to be replaced. One patient had a leaking drainage valve, which was easily repaired. One patient developed a tract-metastasis 11 months after IPC insertion, and was successfully palliated with radiotherapy.

Complication	Intervention	50 IPCs
Major complications		**5**
Empyema	Intravenous antibiotics	2
Dislocation	Replacement	1
Mechanical	Replacement	1
Tract metastasis	Radiotherapy	1
Minor complications		**9**
Loculations	Drain removal	3
Superficial skin infection	Oral antibiotics	2
Mechanical	Reparation	1
Pain during drainage	Peritoneal drainage bags	1
Leakage	Wait and see	1
Pneumothorax after insertion	Extra drain	1
No complications	**Not applicable**	**36**

TABLE 2 - Complications

Complications following IPC placement. Approximately 75% was without complications.

Drainages

Most patients did not require the help of nurses with drainages. Four patients performed the drainages themselves and 17 patients (20 IPCs) performed the drainages with help of their family. The drainages of 12 patients (24%) were performed by family alone. Twelve patients (14 IPCs, 28%) had the drainages performed by home visiting nurses or during hospital visits.

Discussion

In this overview we showed that the mean direct costs per IPC amounted to €2137. With the current re-imbursement structure in the Netherlands, these costs have to be paid by the hospital.

The mean price of one hospitalization day in the Netherlands in 2010 was €1400. [78] This leads to €5600-€11200 for a 4 to 8 hospital stay for pleurodesis. These prices vary between hospitals and are not transparent due to closed negotiations between hospitals and insurance companies. Compared to these figures, costs for the use of an IPC are acceptable, especially considering the limited success rate of talc pleurodesis.

In this overview all material costs are summed, but the total costs for using an IPC also include costs of complications, re-interventions, and daily care during the drainages. None of the patients required re-interventions related to recurrent ipsilateral malignant pleural effusion. The complication rate was comparable to previously reported studies [58;79] and 4 patients needed complication related hospitalization. Two patients needed IPC replacement. Replacement of a defective valve has previously been described. [68] One patient developed a tract metastasis. This is a rare complication, with a higher incidence rate in mesothelioma. [65] The benefit of prophylactic radiotherapy for prevention of tract metastasis in mesothelioma is debatable. [80] National guidelines for mesothelioma treatment do not recommend prophylactic radiotherapy. [81] These and other costs (e.g. radiology, theatre) are not included, since they do not contribute to the hospital expenses.

Other indirect costs (e.g. loss of income, travel costs, and home care visits) are also not included in this overview. The vast majority of patients no longer worked due to advanced disease. Travel costs for patients using an IPC should be less than repeat thoracentesis costs. Costs for home care were excluded too, since it remains unclear whether these patients needed to be visited by nurses when they did not have an IPC. However, the percentage of patients in whom drainages were performed by home care was low.

In contrast to two cost-effective analyses, we chose to avoid assumptions about alternative treatments. [70;71] Small differences in assumptions can have significant consequences for cost-effectiveness. [72] In our opinion, pleurodesis success rates of 80% in these analyses are too optimistic as intention to treat analysis has not been taken into consideration. According to our data 32-71% is a more realistic percentage. [29;43] It was assumed that patients required home care three times a week. [71] Our patient selection might have been biased by their ability to perform drainages themselves, but the majority did not need professional help. Furthermore, we realize

that drainage without professional help might differ from other centers.

The costs of vacuum bottles are a major factor in the total costs of IPC usage. In an Egyptian hospital, the safety of reusable Surgivac pumps was investigated. [73] A vacuum was created manually and caregivers had to clean the pump system after drainage. Complication rates were acceptable with substantially lower costs. Hopefully, this won't be necessary in the Netherlands since patients and family are now able to perform drainages themselves. In some patients, usage of (peritoneal) drainage bags could also be an alternative to the (more expensive) vacuum bottles. At this time at least two brands of IPCs: PleurX (Denver-Carefusion) and Rocket (Rocket Medical) are available. Competition might reduce vacuum bottle prices.

Conclusion

To the best of our knowledge, this is the first study showing direct costs of IPC treatment. Costs are dependent on tumor type and survival time. No differences in costs were seen when IPC was used as frontline treatment or following failed pleurodesis. Comparing these material costs to estimated costs for pleurodesis, IPC treatment seems reasonably priced. Complication rates appear acceptable.

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Chapter 1.3

A Randomized Controlled Trial comparing Indwelling Pleural Catheters with Talc Pleurodesis (NVALT-14)

First line treatment for recurrent malignant pleural effusion

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ABSTRACT

Background

Symptomatic malignant pleural effusion (MPE) occurs frequently in patients with metastatic cancer. The associated prognosis is poor and the success rate of talc pleurodesis (TP) is low. Indwelling pleural catheters (IPCs) are commonly inserted when TP has been unsuccessful.

Methods

We compared talc pleurodesis with the use of an indwelling pleural catheter in patients with recurrent MPE in a multicenter randomized controlled trial. The primary endpoint was improvement from baseline in Modified Borg Score (MBS) 6 weeks after randomized treatment. Secondary endpoints were hospitalization days, re-interventions, and adverse events.

Results

Dyspnea improved significantly ($p< 0.01$) after either treatment, but the magnitude of this improvement did not differ significantly between arms (median 3 and 1 for TP, IPC respectively in rest, p = 0.22, and 2 and 1 during exercise, p = 0.96). There was no difference in dyspnea during exercise between TP and IPC at week 6 following treatment, while at rest TP patients reported less dyspnea than IPC patients (median 0 vs 1, $p=0.002$). Compared to TP, patients with an IPC had significantly less hospital days during randomized treatment (median: 0 vs 5, $p< 0.0001$), and total hospitalizations for all causes (median: 1.6 vs 1.0, $p=0.0035$). Fewer IPC patients underwent more than one re-intervention (7/45 vs 15/43, $p= 0.09$). The mean number of re-interventions was lower following IPC (0.21 vs 0.53, $p=0.05$). Equal number of adverse events occurred.

Conclusions

IPC was not superior in primary endpoint, improvement of the modified Borg scale (MBS). However, IPC patients had lower hospital stay, fewer admissions and fewer re-interventions. The IPC is an effective treatment modality in patients with symptomatic malignant pleural effusion.

Background

Approximately 15% of patients with cancer develop symptomatic malignant pleural effusion (MPE) [14] and the prevalence of MPE is increasing.[82] MPE may cause a variety of symptoms, [83] of which dyspnea is the most common. A therapeutic thoracentesis may relieve dyspnea temporarily, but pleural fluid often recurs, necessitating more permanent treatment options. The recurrence rate of MPE depends on tumor type, and the necessity to drain larger volumes is predictive of earlier pleural re-interventions.[84]

Talc pleurodesis (TP) is the current standard treatment when MPE recurs and patient's life expectancy is at least 3 months.[15] However, TP success rate in an intention-to-treat analysis (ITT) is low. [29;43] Failure rates increase with longer patient survival. [24] Talc can be administered again, after failed pleurodesis, or an Indwelling Pleural Catheter (IPC) can be inserted. [37]

In this randomized controlled trial, we compared TP with IPC as first line treatment for recurrent MPE. Modified Borg scale (MBS) dyspnea scores (**Figure 1**) [84] were chosen for primary endpoint evaluation. We hypothesized that patients who randomized for IPC, reported a better improvement in dyspnea.

Material and Methods

This study is a multicenter open label randomized clinical trial, conducted in the Netherlands between February 2011 and December 2013. Approval was obtained from the Medical Ethical Board of the Netherlands Cancer Institute and the trial was registered at the Dutch Trial Registry. (NTR 2518).

After written informed consent was obtained, patients with symptomatic MPE were enrolled. Patients were eligible for the trial if they had a histologically or cytologically confirmed MPE, as were patients with a progressive malignancy and pleural effusion after exclusion of alternative diagnoses. Patients previously treated with either TP or IPC for ipsilateral MPE, and patients with impaired immunity or thrombocytopenia (thrombocytes $<50*10^9$/ L) were excluded. At registration, patients underwent a therapeutic thoracentesis.

Patients were randomized using Alea randomization software between TP and IPC in a 1:1 ratio if and when fluid recurred within 6 months. Stratification was performed based on type of malignancy (Lung vs Breast vs other) and WHO performance score (0-1 vs >1). IPC's (Rocket Medical, England) were inserted on an outpatient basis. Patients and caregivers were instructed to drain on an as-needed basis. Patients randomized for TP were admitted to the hospital. Talc (large particles, 3-5 mg at

investigators discretion) was instilled through a chest tube (size 15-20 Ch) according to the Dutch guidelines (NVALT) for MPE management.

Primary endpoint

Primary endpoint was improvement in MBS score at rest and during exercise. (**Figure 1**) [84] The improvement in MBS scores was defined as the difference between the MBS score after 6 weeks and the MBS score before randomization. All analyses were done in both an intention-to-treat analysis and in a per-protocol analysis. The intention-to-treat analysis evaluates all randomized patients. The per-protocol analysis excludes patients who had no talc instilled or underwent an ipsilateral re-intervention within 6 weeks.

	Shortness of breath	At rest	During activity
0	Nothing at all	□	□
0.5	Very very slight	□	□
1	Very slight	□	□
2	Slight	□	□
3	Moderate	□	□
4	Somewhat severe	□	□
5	Severe	□	□
6		□	□
7	Very severe	□	□
8		□	□
9	Very very severe	□	□
10	Maximal	□	□

FIGURE 1 - Modified Borg Scale (MBS)

MBS dyspnea score at rest and during exercise. Activities were not defined, but were considered to require any effort.
Dyspnea scores were completed before and after randomized treatment daily for 14 days. Also after 6 weeks, 3 and 6 months.

Secondary endpoints

Patients were asked to report the MBS daily, at a vast time point, at rest and during exercise for 2 weeks following the randomized treatment. The mean MBS score from randomization until either re-intervention occurred or until two weeks after randomization (whichever came first) was calculated. Other secondary endpoints were number of hospital visits, pleural re-interventions, hospital stay and time-to-failure. Success was defined as complete when no pleural fluid recurred either by symptoms or radiologically (by chest X-ray). Fluid re-accumulation without

symptoms or need for re-intervention was defined as partial success. Treatment was considered to have failed when fluid re-accumulation led to ipsilateral re-interventions, when no talc was instilled despite drain placement, or when patients survived less than 6 weeks. Adverse events were registered. For long-term follow up, PROs as well as treatment outcomes were evaluated at 3 and 6 months.

Power calculation

Patients in the IPC arm were expected to report a mean improvement of 4-6 points on MBS, and TP patients a 1-2 points. This expectation was further specified to the assumption that the improvements in both arms (defined as the difference between the MBS scores at six weeks and at baseline) would be distributed normally with a mean of 2 and 4 for TP and IPC respectively and a common standard deviation of 2. It was calculated that when each arm contained 26 evaluable patients, the power to detect a difference in improvement of MBS between arms at the 95% confidence level in a two-sided Wilcoxon-Mann-Whitney test would be 93% in the scenario above.

We expected that the response rate of PRO forms at six weeks would be 60%-70% and that two third of the registered patients would present with recurrent MPE within 6 months. Based on these assumptions an initial sample size of 120 registered patients was chosen, with the aim of obtaining 80 randomized patients of which 26 patients per arm would be evaluable.

After registration of 105 patients, it turned out that both assumptions were too optimistic. Permission from the Medical Ethical Board for the inclusion of an additional 35 patients was sought and granted. After 155 patients had been registered and followed for 6 months we had to conclude that the percentage of patients that were subsequently randomized was as expected but the percentage of evaluable patients had fallen even further than anticipated.

Statistical analysis

Evaluation of the primary endpoint and secondary endpoints were done in all randomized patients by randomization arm. Improvements in MBS scores absolute difference between the scores at six weeks and just before randomization) were compared between arms using a Wilcoxon-Mann-Withney test. Absolute MBS scores at six weeks (as well as those at 3 and 6 months) were compared between arms using Mann-Whitney tests. Within each arm, scores at six weeks were compared to those at randomization using a paired t-test. Percentages of patients experiencing more, equal or less dyspnea at six weeks than at randomization were compared between arms using Fisher's exact test.

Count endpoints such as the number of re-interventions were compared between arms using Poisson regression. Linear regression was used to assess the influence of treatment arm, presence or absence of ipsilateral interventions and MBS at baseline on MBS at six weeks after treatment.

Time-to-event endpoints such as time-to-re-intervention and overall survival were described by the Kaplan-Meier method and compared across arms the log-rank test, both unstratified and stratifying for tumor type and performance score at the start of treatment. Analysis of the primary endpoint was repeated in the subgroups used in this stratification.

Overall survival was calculated for both time since randomization and registration. In the latter group the prognostic and predictive value of several patient and tumor characteristic was assessed using cox-models.

Based on the LENT-score, a recently developed predictor for mortality, [85] we compared overall survival since study enrolment between the LENT-risk groups for all registered patients. Since information on pleural neutrophil-leukocyte ratio was not available in our patient cohort, our LE(N)T score was calculated using LDH levels in pleural fluid, performance score and tumor type for each patient.

Known predictors for the recurrence of MPE after first therapeutic thoracentesis were evaluated in enrolled patients using univariate and multivariate logistic regression
The incidence of adverse events in treated patients since the start of treatment were compared between arms (by event type) using Fisher's exact test.

Mean PRO scores over time periods were calculated by dividing the area under the score vs time curve by the length of the time period, where said curve was constructed by linearly interpolating between measurements.

Results

Ninety-four patients experienced recurrent MPE and were randomized between TP and IPC (48:46). The last patient was randomized in December 2013. Patient characteristics were balanced between treatment arms. (**Table 1)**. At time of analysis, September 2015, a total number of 18 randomized patients were still alive. Median follow up was 193 days (95% CI 189-247 days, range 4-1269 days). Median overall survival since randomization was 72 days.

Primary endpoint

Patients who initiated TP treatment more frequently had an incomplete treatment *(7/45 vs 0/43, p=0.012*, **Table 2**). Seven patients in the TP arm had no talc instilled

due to incomplete lung expansion (n=4) or no cessation of fluid drainage (n=3). Three patients refused further trial participation after TP randomization, of which one patient insisted on an IPC. Two patients didn't get randomized treatment, since complete lung opacification was noted due to total atelectasis (1 TP, 1 IPC).

	TP N=48 (%)	**IPC** N=46 (%)
Gender		
Male	27 (56)	19 (41)
Female	21 (44)	27 (59)
Age (year)		
Median	60	64
Range	35-81	30-84
Performance score*		
0-1	21 (44)	22 (48)
>1	27 (56)	24 (52)
Performance score		
0	3 (6)	3 (6)
1	18 (38)	19 (40)
2	18 (38)	19 (40)
3	8 (17)	4 (8)
4	1 (2)	1 (2)
Tumor Type*		
Breast	10 (21)	10 (22)
Lung	16 (33)	15 (33)
Other	22 (46)	21 (45)

TABLE 1 - Patient characteristics of randomized patients

TP= talc pleurodesis
IPC= Indwelling Pleural Catheter
*=stratification factor

One patient randomized for IPC, but the treating pulmonologist decided to insert a normal chest drain since a prior thoracentesis was complicated by a hemothorax. One patient withdrew after IPC randomization. Finally, one patient underwent a TP for logistic reasons, despite IPC randomization. Six (out of 7) patients in the TP arm who had no talc instilled after drain placement had an ipsilateral re-intervention or died within 6 weeks compared to 20 out of 38 patients who completed TP *(p=0.21)*. Because of this no meaningful comparison of MBS at six weeks could be made between patients in the TP arm that did and did not have talc instillation. Treatment failure as defined in the *methods* section was not different between groups *(67% vs 59%, p=0.52)*.

Thirty-five (out of 94) randomized patients died within 6 weeks. Thirty-one (13:18) patients were eligible for per-protocol (**Figure 2, Appendix 1**), and forty (20:20)

for intention-to-treat primary endpoint analysis. The majority of patients reported lower MBS 6 weeks after randomized treatment **(Appendix 2)**. These improvements in dyspnea were observed in either treatment arm, and at rest as well as during exercise (mean improvement (ITT) 2.2 and 1.5 MBS points for TP and IPC at rest and 1.3 and 1.7 MBS points for TP and IPC during exercise, $p<0.01$ in all four cases). Improvement in dyspnea 6 weeks after randomization was similar in both treatment arms (*PP*: mean 2.2 and 1.5 MBS point for TP and IPC at rest *(p=0.22)*, and during exercise (1.3 vs 1.7; *p=0.96), ITT:* mean 2.2 and 1.6 MBS point for TP and IPC at rest ($p = 0.25$), and 2.1 vs 1.8 during exercise ($p = 0.44$)). Absolute MBS dyspnea scores did differ between arms in rest but not during exercise and are shown in **Appendix 2.**

Secondary endpoint by treatment received	TP	IPC	p-value
Number of patients with incomplete treatment	7/45	0/43	0.012
Number of patients with > 1 re-intervention	15/45	7/43	0.09
Number of re-interventions per patient (mean)	0.51	0.37	0.06
LOS randomized treatment (days, median)	5	0	<0.0001
Total all-cause LOS (days, median)	7	2	0.0016
Number of hospitalizations since randomization (mean)	1.6	1.0	0.0035

TABLE 2A - Summary of secondary endpoints

Secondary endpoints in per-protocol analysis.

Secondary endpoint by randomization arm	TP	IPC	p-value
Number of patients with treatment of opposite arm	1/48	1/46	1
Number of patients with no treatment	3/48	3/46	1
Number of patients with incomplete treatment	7/48	0/46	0.012
Any of the above	11/48	4/46	0.09
Number of patients with > 1 re-intervention	15/48	7/46	0.09
Number of re-interventions per patient (mean)	0.5	0.2	0.05
LOS randomized treatment (days, median)	4	0	<0.0001
Total all-cause LOS (days, median)	6	3	0.002
Number of hospitalizations since randomization (mean)	1.5	1.1	0.07

TABLE 2B - Summary of secondary endpoints

Secondary endpoints in an intention-to-treat analysis.

AUC= Area under the curve. Daily MBS scores reported. Without re-interventions: MBS scores after re-intervention are excluded.
LOS= Length of Stay

In a previous study it was found that the maximum increase in dyspnea since the lowest dyspnea level measured in the first two weeks after treatment (increase since nadir) could be used to predict which patients would need a re-intervention due to dyspnea symptoms. [84] We could not reproduce this finding in our cohort. We did find however increase since nadir in the first two weeks was positively correlated with dyspnea at six weeks (R = 0.5, p = 0.01 both during exercise and in rest). This finding was independent of treatment arm and whether or not the patients had an ipsilateral re-intervention.

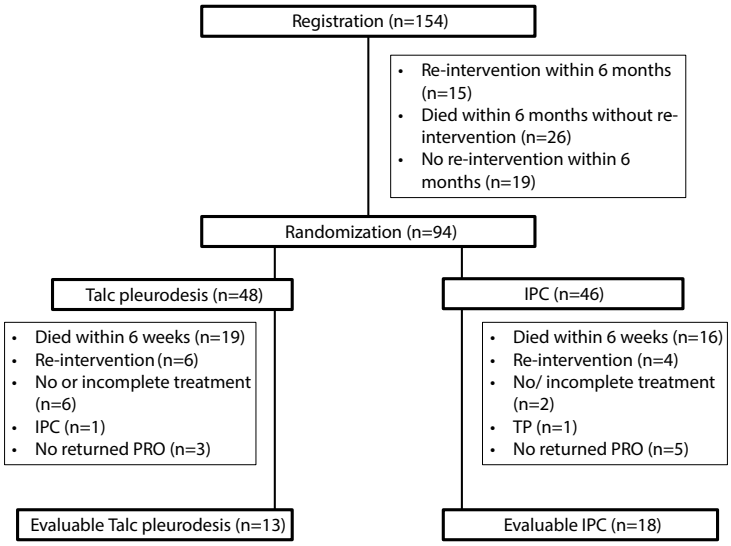


FIGURE 2 - Consort diagram

Per-protocol analysis (TP 13: IPC 18). In an intention-to-treat analysis 40 patients (20:20) were evaluable.

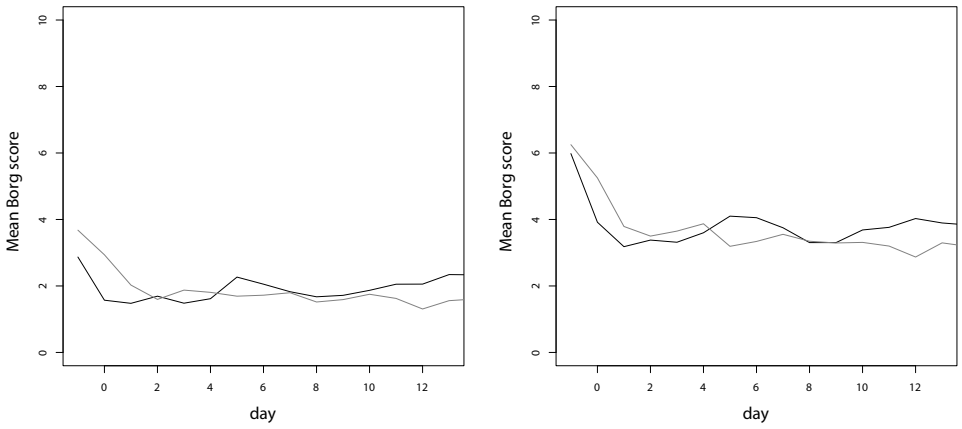
Re-intervention: intervention at the same site as the randomized treatment.
IPC= Indwelling Pleural Catheter; PRO= Patient Reported Outcome; TP= Talc Pleurodesis

Secondary endpoints

Fifty-seven patients (60% of randomized patients) completed the dyspnea diaries in the first two weeks after randomization. Average MBS (calculated via AUC) until re-intervention was similar in both treatment arms *(at rest: 1.8 vs 1.8; p=0.95, and during exercise: TP 3.6 vs IPC 3.3; p=0.7)*. Average improvement (calculated as difference between MBS before treatment and average MBS) was also similar *(at rest: TP 1.6 vs IPC 2.1; p=0.15, and during exercise TP 2.6 vs IPC 2.5; p=0.59)*.

Initial hospitalization duration was significantly longer when patients were treated with TP, compared to IPC *(median 5 days vs 0 days, p<0.0001)*. Median hospitalization

days since randomization *(7 days vs 2 days, p=0.0016)* and the number of hospital admissions per patient since randomization *(1.6 days vs 1.0 days, p= 0.0035)* were different, favoring the IPC arm. Mean number of re-interventions was higher for TP patients *(0.53 vs 0.21, p=0.05)*.



(a) Atrest **(b)** During excercise

FIGURE 3 - Mean MBS

Mean MBS per day since treatment (at rest and during exercise). Patients are excluded after re-intervention. Black is TP, grey is IPC. Day 0 is after randomized treatment. MBS before start are pictured at D-1, even if though most of them were measured at the day of treatment. Patients that underwent TP reported slight increase in dyspnea after talc instillation.

MBS= Modified Borg Scale

Equal number of patients had at least one re-intervention *(TP 15 vs IPC 7, p=0.09)*. All secondary endpoints are listed in **Table 2**. Time to first re-intervention was significant longer in IPC arm (*p=0.045;* **Figure 4**). At 6 weeks, 34% of the TP patients required a re-intervention compared to 11% of IPC patients. **(Figure 4)** Improvement in dyspnea wasn't different between both treatments at 3 and 6 months. **(Appendix 2)** Adverse events were rare, and no difference was seen between groups. **(Table 3)** Median overall survival since randomization was 70.5 days (95% CI: 40 – 138 days) in the TP arm and 72 days (49 – 111 days) in the IPC arm. No differences in survival were seen between both treatment arms (p = 0.62 in a log-rank test).

Median overall survival since registration was 85.5 days (95% CI 57 - 119) in the randomized patients vs 123 days (84 - 201) in the not-randomized patients. (p = 0.28). Median overall survival in the LE(N)T risk groups was 23 days (95% CI: > 17) for the high risk group, 106 days (95% CI: 73 – 140) for the intermediate risk group and 148 days (95% CI: > 77) for the low risk group *(p=0.01)*. **(Appendix 3)**

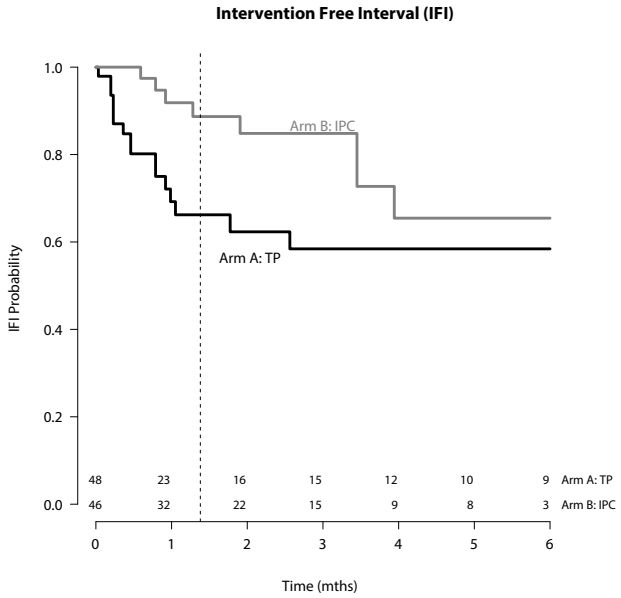


FIGURE 4 - Intervention Free Interval

Kaplan Meier curve depicting time from randomization to first re-intervention. Re-interventions are ipsilateral pleural interventions needed for fluid evacuation. Patients are censored at death or last followup. Dotted line denotes 6 weeks. Estimated free interval proportion at six weeks in the IPC arm is 88.7% (95%CI 78.8%-99.8%) and in the TP arm 66.2% (95%CI 53%-82.7%). The curves show longer intervention free interval for IPC (log-rank test; p=0.045)

IPC= Indwelling Pleural Catheter; TP= Talc Pleurodesis

	TP (45)	IPC (43)	p-value
Pain	1	2	0.61
Dyspnea	2	3	0.67
Infection	2	2	1
Cardiovascular events	1	1	1
General malaise	1	0	1

TABLE 3 - Adverse events of at least grade 3, and related to (received) treatment and MPE.

TP = talc pleurodesis
IPC= indwelling pleural catheter

Discussion

In this clinical trial, we found that dyspnea scores improved in both treatment arms similarly at 6 weeks after randomization. Thus, both TP and IPC are effective treatments for recurrent MPE. We note however that this may be subject to some selection effect as the improvement could not be measured for patients dying within six weeks. Patients treated with IPCs required fewer re-interventions and completed their treatment more often.

Three prior trials have compared IPC with chemical pleurodesis. [30;44;48] While these studies all favored IPC over chemical pleurodesis, none showed any significant difference in reported dyspnea. In 1999, Putnam and colleagues compared IPCs with doxycycline pleurodesis. [30] Change in dyspnea during exercise quantitated by MBS 30 days after randomization favored IPC. Their finding IPCs require shorter hospitalization time (1 vs 6.5 days, $p<0.001$) was confirmed by our study. They concluded an IPC to be an effective treatment for patients with symptomatic, recurrent MPE. [30] Doxycycline is considered inferior to talc for pleurodesis and no randomized controlled trial comparing talc and IPC was published until 2012. In the TIME2 study Visual Analog Scale (VAS) scores for dyspnea observed after 6 weeks were similar between arms. [44] Patients treated with IPC reported less dyspnea after 6 months. Also, patients spent fewer days in hospital when they were treated with an IPC. This TIME2 study is the only trial to really have the robustness of design and methods required to draw meaningful conclusions. The third RCT, comparing TP with IPC (530 patients intended), was closed early after inclusion of only 67 patients. [48] Primary endpoint was a combined success after 30 days. Treatment was considered to be successful when patient was alive, no fluid recurred, lung expanded for at least 90% following drainage, and intervention was completed within 2 weeks. Success rate, evaluated in 57 patients, was equal in both treatment arms (62% IPC vs 46% TP; *p=0.064*).

Patients suffering from MPE have a poor prognosis and performance status. Predicting life expectancy in MPE patients is difficult, emphasized by the study conducted by Dresler. Despite a life expectancy of 2 months, a significant 30-day mortality rate was observed.[24] In our study, 37% of patients died within 6 weeks after randomization, and median survival after randomization was only 72 days, emphasizing the frailty of the patient cohort. Our survival rates are lower than those in the trials mentioned earlier, which can be explained by a lower proportion of patients with malignant mesothelioma [44;85] and a poorer performance score of our patients. In contrast to the LENT-study, we did not restrict to first presentations of MPE. [85] Besides, no patients were excluded based on their performance score, [30;44;48] and neither were

patients with bilateral effusion. [48] We believe that not excluding patients with lower performance scores led to a more realistic representation of the target population. Even without data on pleural neutrophils and leukocytes, we were able to reproduce Clive's study on survival predictors. [85] **(Appendix 3)**.

A weakness of the study is the low number of evaluable patients. In part this is due to the study design: as only part of the registered patients will be randomized and only part of the randomized patients will be evaluable (due to high mortality rates) it was hard to estimate the number of patients needed to include.

Moreover, a big proportion of the surviving patients who completed randomized treatment needed a re-intervention within 6 weeks. This resulted in a high drop-out rate for the per-protocol primary endpoint analysis. Secondary endpoints such as hospitalization duration and numbers of re-intervention can be evaluated in all 94 randomized patients.

One of our secondary endpoints: treatment failure, was defined as incomplete treatment, ipsilateral re-intervention or death within 6 weeks. Reason to exclude patients that needed an ipsilateral re-intervention for symptom relief from the per-protocol analysis was our expectation that their PRO would mostly measure the effect of the re-intervention rather than that of the randomized treatment. However it turns out that people who underwent an ipsilateral intervention within the first 6 week have considerably worse dyspnea at six weeks when compensating for MBS at baseline and treatment arm (difference in mean MBS score 1.8 points, p= 0.002 in rest and 1.3 MBS score, p = 0.121 during exercise). One could argue that death within 6 weeks should not be part of this definition as the treatments under consideration are not given with curative intent. This is why **Figure 4** (time from randomization to re-intervention) doesn't count death as an event. Its counterpart, depicting time from randomization to re-intervention or death is given in **Appendix 4**. As can be seen from comparing the two figures, leaving death out of the definition of failure increases the advantage of IPC over TP in the time to failure outcome.

We observed that approximately half of patients preferred either treatment, in line with the non-randomized study by Fysh. [45] According to current Dutch guidelines, IPCs are not recommended as first line treatment outside of a clinical trial. In general, only patients who preferred IPC or either treatment participated in our RCT. For that reason, it is not surprising that 3 patients refused further trial participation after being randomized for TP. One patient changed from IPC randomization to TP because a treatment with chemotherapy was considered to be a risk by the treating oncologist. However, previous studies indicate that there is no increased risk of complications (pleural infections) when an IPC is used. [44;62] In our study, pleural

infection rate was low, and not different between treatment arms. As was previously reported by Davies [44], pleural infections may occur late after IPC insertion. The relative high number of drop-outs in our study prevents us to make any conclusions about the incidence in our group.

Initial hospitalization duration for randomized treatment was significantly shorter when patients were treated with an IPC, as was previously demonstrated.[44] We expect that TP costs are at least as high as IPC costs. The main costs of a TP treatment are related with hospitalization. This might exceed cost for no or minimal hospital stay in case of IPC placement together with costs of vacuum bottles. Moreover, IPCs were found to have a lower re-intervention rate. In a previous analysis, mean direct costs for IPC in the Netherlands were reported to be €2,173. No significant difference in IPC-related costs was observed between insertion as first line treatment and after failed pleurodesis. [86] These data indicate that the total health care cost for an IPC placement after failed pleurodesis will be the highest. IPCs have been considered and proven to be cost-effective.[87;88] Despite the fact that significant shorter length of stay for IPC patients was reported several times, hospitalization time was never investigated as primary outcome in a RCT. [30;44;45;48] Currently, hospitalization as primary endpoint will be evaluated in a RCT comparing IPC with TP. [89;90]

A few weaknesses of the trial need to be addressed. No information on drainage frequency of IPCs was available. Daily or other prescribed drainage protocols might have caused a more prominent decrease in dyspnea. Currently, symptom-guided and aggressive drainage protocols are compared in a randomized controlled trial. [91] Third, as patients were instructed to drain their IPCs on an as needed basis it is not clear whether reported dyspnea scores reflect dyspnea before or after draining and this may even vary from patient to patient.

Our study would suggest that an IPC as first line treatment for MPE is not superior to talc pleurodesis in improving dyspnea. Moreover, adverse events were comparable between both methods. Initial hospitalization duration was significantly shorter for IPC patients, because IPC can be placed in an outpatient setting. Patients treated with IPC needed fewer re-interventions and time to re-intervention was longer. Based on our results, and the observation that patients preferred either treatment, patients should be involved in the decision about treatment modality for recurrent MPE.

Appendix

	Evaluable TP N=13 (%)	**TP** N=48 (%)	**Evaluable IPC** N=18 (%)	**IPC** N=46 (%)
Gender				
Male	6 (46)	27 (56)	5 (28)	19 (41)
Female	7 (54)	21 (44)	13 (72)	27 (59)
Age				
Median	59	60	66	64
Range	35-78	35-81	32-84	30-84
Performance score*				
0-1	8 (67)	21 (44)	12 (71)	22 (48)
>1	5 (33)	27 (56)	6 (29)	24 (52)
Performance score				
0	1 (8)	3 (6)	2 (11)	3 (8)
1	7 (54)	18 (38)	10 (56)	19 (40)
2	4 (31)	18 (38)	5 (28)	19 (40)
3	1 (8)	8 (17)	0 (0)	4 (8)
4	0 (0)	1 (2)	1 (6)	1 (2)
Tumor Type				
Breast*	2 (15)	10 (21)	4 (22)	10 (22)
Lung*	7 (54)	16 (33)	4 (22)	15 (33)
Other:				
Mesothelioma	2 (15)	3 (6)	3 (17)	3 (7)
Gastro-Intestinal	1(8)	7 (15)	4 (22)	9 (20)
Genito-Urinary	0 (0)	6 (12)	2 (11)	8 (17)
Melanoma	0 (0)	3 (6)	1 (6)	1 (2)
Other	1 (8)	3 (6)	0 (0)	0 (0)

APPENDIX 1- Patient characteristics of evaluable patients

*=stratification factor

IPC= Indwelling Pleural Catheter; TP= Talc Pleurodesis

Absolute MBS dyspnea score	TP:IPC	TP (median/mean)	IPC (median/mean)	p-value
MBS rest (1 weeks)	(28:30)	2/ 2.3	2/ 1.9	0.75
MBS exercise (1 weeks)	(28:31)	4/ 3.9	4/ 3.8	0.66
MBS rest (2 weeks)	(18:27)	3/ 2.2	1/ 1.7	0.14
MBS exercise (2 weeks)	(18:28)	4/ 3.9	3/ 3.2	0.16
Average MBS rest	(27:29)	1.8/ 1.8	1.7/ 1.7	0.95
Average MBS exercise	(27:30)	3.6/ 3.6	3.3/ 3.5	0.7
MBS rest (6 weeks)	(13:18)	0/ 0.42	1/ 1.75	0.0015
MBS exercise (6 weeks)	(13:18)	3/ 3.3	3.5/ 3.9	0.31
MBS rest (3 months)	(9:9)	0/ 0.39	0.5/ 1.28	0.22
MBS exercise (3 months)	(9:8)	3/ 2.9	3.5/ 3.5	0.43
MBS rest (6 months)	(8:4)	0.25/ 0.56	0.5/ 1	0.66
MBS exercise (6 months)	(8:4)	3/ 3	4.5/ 4	0.26

APPENDIX 2A - Absolute MBS scores at 1,2 and 6 weeks and after 3 and 6 months

Absolute MBS scores reported at different time points. *(per-protocol analysis)*

Improvement in MBS dyspnea score	TP:IPC	TP (median/mean)	IPC (median/mean)	p-value
MBS rest (1 weeks)	(24:26)	1.2/ 1.1	1.2/ 1.8	0.49
MBS exercise (1 weeks)	(24:28)	2.5/ 2.4	2.2/ 2.4	0.96
MBS rest (2 weeks)	(18:24)	1/ 0.72	1.5/ 1.85	0.21
MBS exercise (2 weeks)	(18:26)	2/ 1.9	2.5/ 2.9	0.25
Average MBS rest	(27:28)	1.6/ 1.2	2.1/ 2	0.15
Average MBS exercise	(27:30)	2.6/ 2.4	2.5/ 2.8	0.59
MBS rest (6 weeks)	(13:16)	3/ 2.4	1/ 1.6	0.16
MBS exercise (6 weeks)	(13:17)	3/ 1.8	1/ 1.7	0.72
MBS rest (3 months)	(8:8)	2.2/ 2	2.2/ 1.8	0.96
MBS exercise (3 months)	(8:8)	1/ 1	1/ 1.6	0.75
MBS rest (6 months)	(7:4)	2/ 2.1	1.8/ 2	1
MBS exercise (6 months)	(7:4)	2/ 1.4	1/ 1.2	0.85

APPENDIX 2B - Improvement in MBS scores at 1,2 and 6 weeks and after 3 and 6 months

Improvement in MBS scores at different time points. A positive number corresponds with less dyspnea after treatment than before treatment. *(per-protocol analysis)*

Absolute MBS dyspnea score	TP:IPC	TP (median/mean)	IPC (median/mean)	p-value
MBS rest (6 weeks)	20:20	0.25/ 1	1/ 1.8	0.038
MBS exercise (6 weeks)	20:20	4/ 4	4/ 4	0.75
MBS rest (3 months)	13:10	0.5/ 0.92	1.2/ 1.35	0.56
MBS exercise (3 months)	13:9	4/ 3.8	4/ 3.9	0.92
MBS rest (6 months)	10:5	0.25/ 0.75	0.5/ 1.4	0.37
MBS exercise (6 months)	11:5	3/ 3.8	5/ 5.4	0.39

APPENDIX 2C - Absolute MBS scores at 6 weeks and after 3 and 6 months

Absolute MBS scores reported at different time points. *(intention-to-treat analysis)*

Improvement in MBS dyspnea score	TP:IPC	TP (median/mean)	IPC (median/mean)	p-value
MBS rest (6 weeks)	18:18	3/ 2.2	1.2/ 1.6	0.25
MBS exercise (6 weeks)	18:19	3/ 2.1	2/ 1.8	0.44
MBS rest (3 months)	12:9	2/ 2	3/ 2	0.91
MBS exercise (3 months)	12:9	1/ 1.6	1/ 1.6	0.94
MBS rest (6 months)	9:5	2/ 2.2	2/ 2.2	1
MBS exercise (6 months)	10:5	2/ 1.9	2/ 1.6	1

APPENDIX 2D - Improvement in MBS scores at 6 weeks and after 3 and 6 months

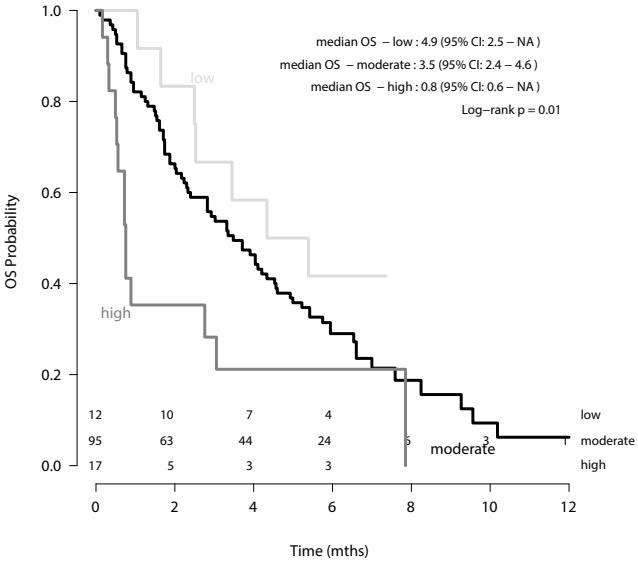
Improvement in MBS scores at different time points. A positive number corresponds with less dyspnea after treatment than before treatment. *(intention-to-treat analysis)*

MBS dyspnea score after six weeks vs just before treatment	**TP (n = 20)** number of patients (%)	**IPC (n = 20)** number of patients (%)	**All (40)** number of patients (%)
More dyspnea in rest	1 (6%)	4 (22%)	5 (14%)
Equal or less dyspnea in rest	17 (94%)	14 (78%)	31 (86%)
More dyspnea during exercise	4 (22%)	3 (16%)	7 (19%)
Equal or less dyspnea during exercise	14(78%)	16 (84%)	30 (81%)

APPENDIX 2E - Number of patients reporting more or equal/less dyspnea after 6 weeks compared to baseline

Numbers of patients reporting increased or stable/decreased dyspnea after 6 weeks, by treatment arm. *P*-values (Fisher's exact test) are 0.34 in rest and 0.69 during exercise.

IPC= Indwelling Pleural Catheter; MBS= Modified Borg Scale;TP= Talc Pleurodesis



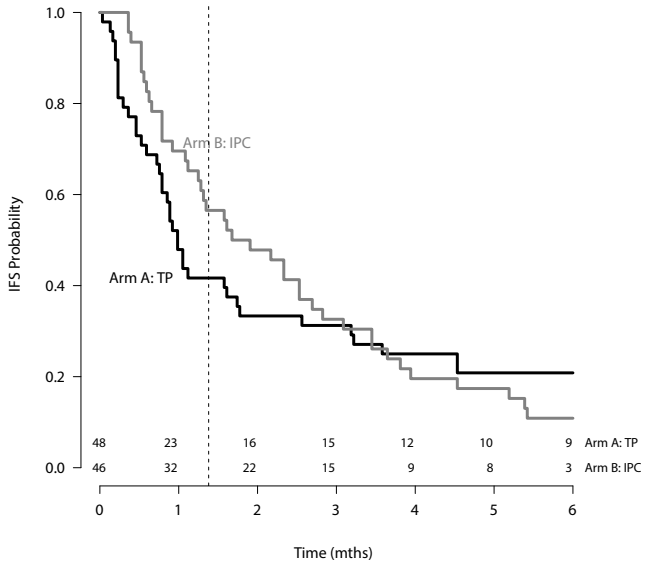
APPENDIX 3 - Overall Survival by LE(N)T Score

Kaplan Meier curve for the three LENT risk groups, depicting overall survival since registration in the study (both randomized and non-randomized patients).

LENT is an acronym for (LDH *(<1500: 0; >1500:1); ECOG (0:0; 1:1; 2:2; 3-4:3);* Neutrophil-Leukocyte Ratio *(>9: 1),* and Tumor *(Mesothelioma, Hematologic malignancies: 0; Breast, Gynaecological, and Renal cancer:1; Lung and other cancer:2).* In our patient cohort no data was available on Neutrophil-Leukocyte Ratio, limiting the LENT-score to 6 instead of 7.

Based on the LENT score (without NLR), patients were categorized into low (LENT ≤1; N=12), moderate (LENT=2-4; N=96), and high risk (LENT ≥5; 17) patients. Based on NLR, eleven low risk patients and 31 moderate patients could be reclassified as moderate risk and high risk, respectively.

ECOG= Eastern Cooperative Oncology Group; LDH= Lactate DeHydrogenase; NLR= Neutrophil-to-Lymphocyte Ratio



APPENDIX 4 - Time to intervention or death

Kaplan Meier curve depicting time from randomization to first re-intervention or death, whichever comes first. Re-interventions are ipsilateral pleural interventions needed for fluid evacuation. Patients are censored at last followup. Dotted line denotes 6 weeks. Estimated re-intervention free survival proportion at six weeks in the IPC arm is 56.5% (95%CI 43.9%-72.8%) and in the TP arm 41.7% (95%CI 29.8%-58.2%). Measured over the entire period the treatment do not differ significantly in intervention free survival. (log-rank test; p=0.88)

PART TWO

Predictors for pleurodesis success and pleural re-interventions

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Chapter 2.1

Talc instillation consensus aids differentiating successful from unsuccessful pleurodesis

A survey on the interpretation of pleural approximation after chest tube placement

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Respiration, 2013;85(1):85-6

To the editor,

Pleural approximation is the most important predictor for successful pleurodesis. [28] We performed an online survey to investigate variation in pulmonologists' opinions regarding 1) lung expansion, 2) talc instillation and 3) the expected success rate of pleurodesis after conventional pleural fluid drainage. Chest X-rays of patients suffering from malignant pleural effusion (n=50), made after full drainage and used to decide whether or not to instill talc, were reviewed by experienced pulmonologists. All patients had been treated prior to this questionnaire. Pulmonologists from 30 out of 100 hospitals responded. When pulmonologists reported that the lung was expanded, they recommended pleurodesis in 89% of the cases. When they reported the lung not to be expanded, they still advised pleurodesis in 38% of cases. Pulmonologists disagreed more frequently on lung expansion than they did recommending pleurodesis (**Figure 1A&B**). Agreement was not related to either patient (gender, age, tumor type) or pulmonologist characteristics (age, gender, personal experience or ultrasound usage).

In this patient cohort, which was previously reported as part of a prospective trial on pleurodesis efficacy, talc slurry had been instilled in approximately 75% (38 patients). [29] Sixty-one percent of these patients (intention to treat analysis: 46%) had a successful pleurodesis (as defined by the absence of fluid recurrence, or re-intervention, and survival for > 2 months after talc instillation). In 7 out of 38 patients talc was instilled despite the fact that in this online survey no consensus was reached between pulmonologists about whether to treat these patients or not (i.e. less than 75% agreement). However, in 4 of these patients (57%) the pleurodesis was successful (**Figure 1C**), and this equals the overall success rate. When 2 pulmonologists independently gave the same assessment, the ability to accurately predict the success of pleurodesis increased from 75% to 81% ($p<0.0001$).

Thus, the most reliable predictor for the outcome of pleurodesis is prone to heterogeneous interpretation. Our results suggest that talc pleurodesis may be successful in cases of incomplete lung expansion.

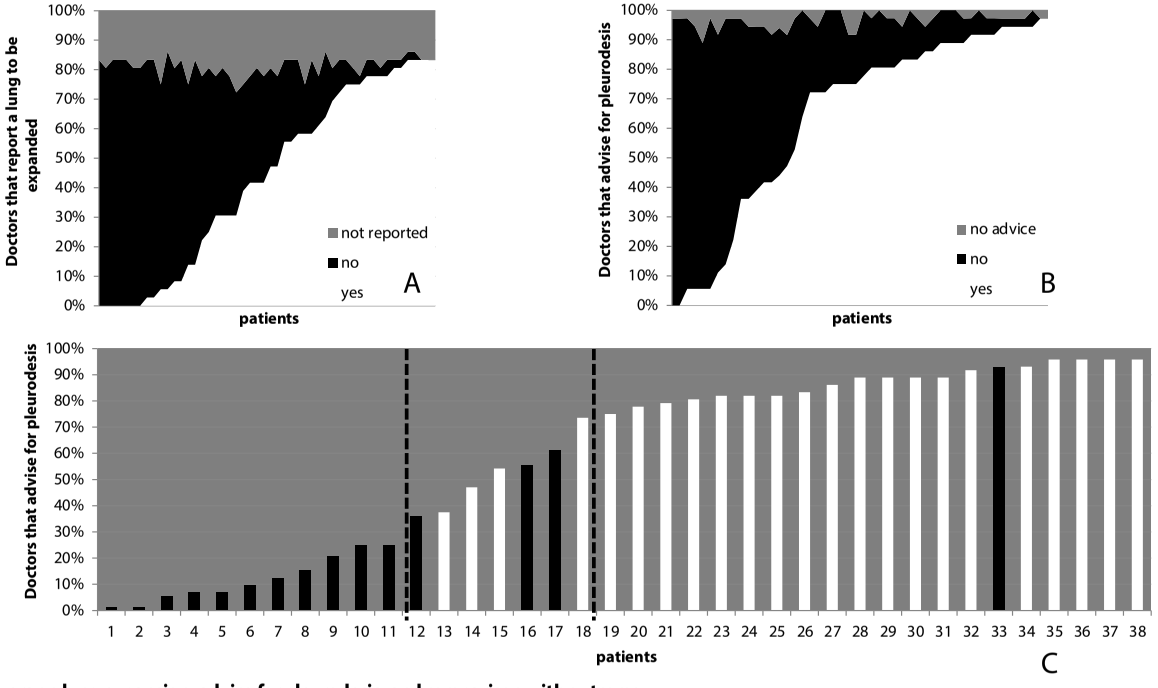

FIGURE 1 - Answers on lung expansion, advice for pleurodesis, and comparison with outcome

Survey on interpretation of lung expansion in patients with malignant pleural effusion after complete pleural fluid evacuation:

A - *"Do you report this lung to be expanded?"*
Percentage of pulmonologists that report a lung to be expanded (white bars).

B - *"Would you perform pleurodesis?"*
Furthermore, more often agreement was reached (ie either yes or no was answered by at least 75% of the pulmonologists). More positive answers (white bars) were given for pleurodesis advice.

C - *Advice for pleurodesis compared with the real outcome*
Thirty-eight pleurodeses had been performed, of which 23 were considered to be successful (white bars) and 15 were considered to be failures (black bars). In 31 patients consensus (ie less than 25% or greater than 75% of doctors recommending pleurodesis) about treatment was reached to either instil talc or to remove the drain. There was no agreement for treatment of 7 patients (between dotted lines).

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Chapter 2.2

Pleural Pressure Swing and Lung Expansion After Malignant Pleural Effusion Drainage

The benefits of high temporal resolution pleural manometry

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Abstract

Background

Malignant pleural effusion is a common complication in end stage cancer patients and can cause severe dyspnea. Therapeutic thoracentesis is often limited to 1-1.5 L. Pleural manometry can be used to recognize a not-expanded lung.

Methods

Interval pleural pressure measurements with a high temporal resolution were performed after each removal of 200 ml of fluid in order to observe pleural pressure swings. Pleural elastance was defined as the difference in pleural pressure divided by the change in volume. Chest X-rays were performed to evaluate lung expansion, re-expansion pulmonary edema, and fluid residue.

Results

Thirty-four procedures in 30 patients were eligible for analysis. Four patients had incomplete lung expansion following drainage. No re-expansion pulmonary edema was observed. Pleural pressure swing after 200 mL drainage was higher when lung did not expand. Pleural elastance after removal of 500 mL was higher in the not-expanded subgroup.

Conclusions

We demonstrated that a high pleural pressure swing after removal of only 200 ml was related to incomplete lung expansion. We confirmed the association between pleural elastance and lung expansion.

Introduction

Approximately 50% of patients with metastatic disease develop malignant pleural effusion (MPE). [92] Depending on primary pathology, median life expectancy is only a few months. [93] Most patients suffer from dyspnea, chest discomfort or cough. Pleurodesis is the standard of care in case of fluid recurrence but intention-to-treat analysis shows that it is only effective in 46% of patients. [43] A common reason for pleurodesis failure is the presence of a non-expanded lung. [28;94]

Therapeutic thoracentesis is a frequently performed medical intervention and aims to improve quality of life. Pleural pressure (P_{pl}) is related to lung expansion [28] and pleural pressure drops below -20 cm H_2O are used as cut-off to avoid re-expansion pulmonary edema (RPE). [95] Development of chest discomfort during drainage is associated with a drop in pleural pressure and a reason to terminate drainage, in contrast to cough. However, pleural pressures below -20 cm H_2O also occur in patients without any complaints. [96] Despite the benefits of large volume removal, these concerns have let to limit fluid drainage to 1-1.5 liters in the absence of pleural manometry. [26;97]

Pleural pressure changes during respiration and is usually read at end-expiration. [98] Since changing pleural pressure during respiration might be affected by stiffness of the lung, we hypothesized that these changes during respiration would be increased in not-expanded lungs. This might be used to select patients at risk for pleurodesis failure who would preferentially benefit from indwelling catheters. We therefore developed high temporal resolution pleural manometry to observe pleural pressure changes during respiration.

Materials and Methods

Consecutive patients presented for therapeutic thoracentesis were asked to participate in the study. The study was approved by the Medical Ethical Board. Since pleural manometry is optional in standard treatment, no special written informed consent procedure was deemed necessary. There was no predefined maximum volume of drained fluid, since large volume thoracenteses are deemed to be safe even without pleural manometry. [99;100] MPE diagnosis was defined by the presence of malignant cells or histologically proven pleural involvement. Massive pleural exudative effusion in patients with progressive malignant disease was also considered to be MPE following exclusion of alternative diagnoses.

Therapeutic Thoracentesis and pleural manometry

Patients were placed in an upright position. The presence of pleural fluid was confirmed by ultrasound. After local anaesthesia with Lidocain (1%), an 8 Ch (2.7 mm) pleural catheter (Rucomed) was inserted, and connected to a three-way stopcock. One arm of the stopcock was attached to a fluid tube connected to a modified Thopaz vacuum pump, [101] which was set at -40 cm H_2O during the procedure. The other arm of the stopcock was connected to an electronic pressure transducer (BD DTXplusTM disposable pressure transducer sets), positioned in alignment with the catheter insertion point. A measurement unit was developed in order to be able to measure negative pressures. This unit consisted of a Wheatstone bridge and an analog-to-digital converter (USB 6009 from National Instruments). Signals were recorded using in-house developed software (Labview National Instruments). The system was designed to measure pressure signals with a temporal resolution of less than 100 milliseconds. This was calibrated against a water manometer and enabled us to observe pressure change during respiration. Drainage was terminated when flow ceased or the patient experienced chest discomfort or persistent cough despite pausing drainage. In particular, no predefined maximum for drained volume or pleural pressure was set.

Interval pleural pressure was measured before drainage (*baseline pressure*) and after each 200 mL of drained fluid. The *closing pressure* was defined as the last interval measurement after drainage was terminated and was repeated when disturbed by cough. During interval measurements, pleural pressure was recorded 40 times per second for approximately 13 seconds, which was arbitrarily chosen.

Analyses

In the test phase for this analysis we found that pleural pressure during interval measurements fluctuated during inspiration and expiration (**Figure1**). During each interval, inspiratory and expiratory pleural pressures were determined per breath. The average of these values was used to calculate the pleural pressures representative of each interval ($P_{pl\text{-}insp}$ and $P_{pl\text{-}exp}$). Subsequently for each interval the mean pleural pressure was calculated as ($P_{pl\text{-}insp} + P_{pl\text{-}exp}$)/2. Total pleural pressure drop was defined as the difference between mean baseline and mean closing pleural pressure. Pleural elastance (E_{pl}) was calculated at intervals of 200 mL and defined by the change in mean pleural pressure divided by the change in volume ($\Delta P_{pl} / \Delta V$). E_{pl} after removal of 500 mL, as used in previous studies, was defined as the mean of elastances after 400 mL and 600 mL. Pleural pressure swing during respiration ($P_{pl\text{-}swing}$) was defined as the difference between the $P_{pl\text{-}insp}$ and $P_{pl\text{-}exp}$.

Evaluation

Chest X-rays (CXRs) were performed within 24 hours post thoracentesis and were evaluated by two experienced chest physicians blinded to thoracentesis details such as volume and complaints. The amount of remaining pleural fluid was estimated, and both lung expansion and radiographically RPE were reported. Patients were grouped based on lung expansion and presence of pleural fluid after thoracentesis.

Statistical analysis

The association between pleural pressure values (baseline, closing, total drop, swing after 200 mL, and elastance at 500 mL) and lung status (expanded vs. not-expanded, and expanded empty vs. expanded not empty vs. not-expanded) were tested using ANOVA.

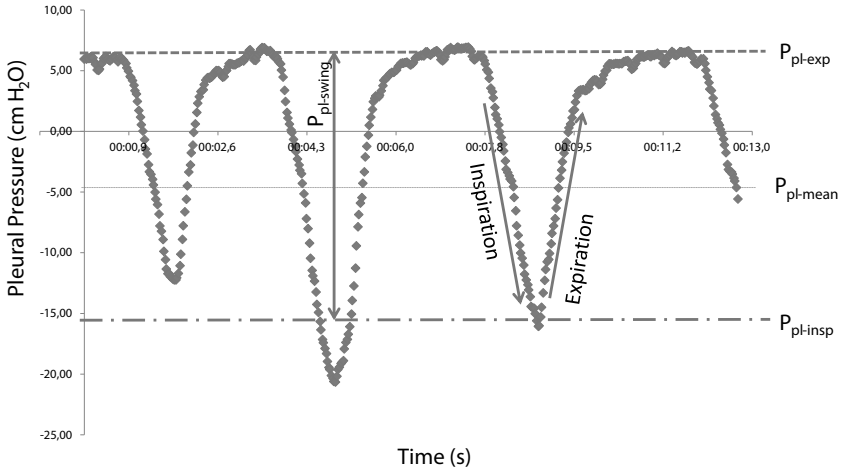

FIGURE 1- Interval measurement. Illustrative explanation of the calculations

(In this particular example, lung did not expand.)

Ppl-exp *Average of pleural pressures measured at end-expiration*
Ppl-insp *Average of pleural pressures measured at end-inspiration*
Ppl-mean *Mean of Ppl-exp and Ppl-insp*
Ppl-swing *Difference in Ppl between Ppl-exp and Ppl-insp*
Ppl *Pleural pressure*

Results

Patient and Effusion characteristics

Forty-five serial measurement series were performed during therapeutic thoracenteses in 40 patients. Ten patients were not evaluable since no CXR was performed within 24 hours and were therefore excluded from analysis. Thirty-four drainages in 30 patients were eligible for this analysis. Mean age was 59 years (range 35-88 years). Twenty-two out of 34 patients were female. Both two male and two female patients were analyzed twice because of recurrent effusion. Most common malignancy was breast cancer (n=14), 8 patients suffered from lung cancer, and as much patients suffered from ovarian cancer as mesothelioma (n=3). The remaining patients suffered from other malignancies, such as renal cell carcinoma (n=2), melanoma, lymphoma, sarcoma and ACUP (all n=1).

Therapeutic thoracentesis

The mean amount of fluid removed was 1300 mL (range 190-3190 mL). Half of the aspirations were performed in the left pleural space (50%). No patient developed either clinical or radiological signs of RPE. Half of the patients (n=17) were considered to have expanded lungs without (residual) pleural fluid after the intervention. No significant difference was found in the amount of fluid removed between patients with expanded or not-expanded lungs. In 13 patients the lung was expanded following incomplete drainage (no hydropneumothorax). Four Chest X-rays were reported to show incomplete drainage and a not expanded lung. The combination of a not-expanded lung with complete fluid evacuation was not reported. Sixteen patients experienced pain during drainage and 20 patients started coughing during the procedure.

Pleural pressure

Mean baseline pleural pressure was 7.10 cm H_2O (SD 5.45 cm H_2O) and mean closing pressure was -3.51 cm H_2O (SD 8.89 cm H_2O). The mean drop in pleural pressure was 10.62 cm H_2O (SD 10.06 cm H_2O). The mean pleural pressure swing after the first 200 mL drained was 3.54 cm H_2O (range 0.73 to 8.36 cm H_2O). A difference was observed between the volume/pressure curves of the expanded group and the not-expanded group (**Figure 2**). Two out of four patients in the not-expanded group showed a pressure drop of more than 25 cm H_2O whereas this did not occur in the expanded group.

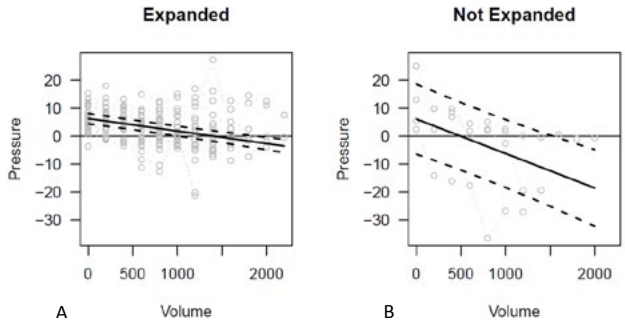

FIGURE 2 - Relation between pleural pressure and lung expansion

Thirty patients were considered to have expanded lungs (A) and in four patients lungs did not expand (B). In contrast to the data from the expanded lungs (A), a significant drop in pleural pressure is observed in the not-expanded lungs (B). The observed data are presented (grey circles) along with the estimated mean (black solid line) pressure and 95% confidence bands (black dashed lines).

Analysis

The not-expanded subgroup showed an insignificant higher opening pressure, a lower closing pressure (not significant), and a larger total drop in pressure. Pleural pressure swing (after removal of 200 mL) was significantly higher in patients with not-expanded lungs. Also elastance (after removal of 500 mL) was significantly higher when the lung was reported to be incompletely expanded (**Table 1**). No associations between pleural pressure and complaints were found.

	***Expanded n=30*[1] (95% CI)**	***Not-Expanded n=4* (95% CI)**	***p-value***
Mean baseline P_{pl} (cm H_2O)	6.52 (4.84 - 8.20)	11.45 (-4.66 – 27.56)	0.09
Mean closing P_{pl} (cm H_2O)	-2.50 (-5.38 – 0.38)	-11.15 (-34.10 – 11.79)	0.067
Total P_{pl} drop (cm H_2O)	9.02 (6.13 – 11.91)	22.61 (-5.70 – 50.91)	0.009
$P_{pl\text{-}swing}$ after 200 ml (cm H_2O)	3.23 (2.64 – 3.84)	5.90 (1.27 – 10.53)	0.007
E_{pl} after 500 mL (cm H_2O/L) [2]	9.79 (7.48 – 12.11)	24.89 (-5.75 – 55.53)	0.002

TABLE 1 - Pleural pressure and lung expansion

Total P_{pl} drop Difference between mean baseline P_{pl} and mean closing P_{pl}

$P_{pl\text{-}swing}$ Difference between inspiratory P_{pl} and expiratory P_{pl} (as explained in Figure 1)

E_{pl} Difference between mean baseline P_{pl} and mean P_{pl} after removal of 500 mL, divided by the amount of fluid removed (500 mL)

P_{pl} Pleural pressure

E_{pl} Pleural elastance

[1] *Four patients had two therapeutic thoracenteses. These patients had expanded lungs.*

[2] *In two patients (both had expanded lungs) drainage was less than 500 ml. These patients have been excluded for analysis of E_{pl} after 500 ml drainage*

p-value less than 0.05 was considered to be significant

Conclusion

To our knowledge, this is the first report where pleural pressures were measured with high temporal resolution. This enabled us to calculate pleural pressure swings. We have shown that changes in pleural pressure during respiration are higher when the lung fails to expand. One single (high resolution) pleural pressure measurement provides sufficient information about expected lung expansion. This might increase pulmonologist's interest in performing pleural manometry.

In physiological state, pleural pressure is a result of in- and outward forces changing during respiration. Inspiration will cause increased intra-thoracic volume. This increased intra-thoracic volume is accompanied by an increased negative pleural pressure. The expansion of the lung during inspiration is primarily the result of an increase in negative pleural pressure in the thoracic cavity as result of the expansion of the rib cage. Impairment of complete lung expansion will therefore cause greater differences between pleural pressures measured during inspiration and expiration. Ideally, lung function tests would have been performed during drainage to observe changes in tidal volume as well.

There were two changes introduced in the procedure that increase the accuracy of the intermittent pleural pressure measurements. Firstly, in previous reports of pleural pressure measurements, water manometer measurements were performed after removal of a fixed amount of fluid. [28;95;98;102;103] Use of water manometers is prone to errors since they have to be read at a certain point (most often at end-expiration) of the respiratory cycle. This is considered to be a real issue because pleural pressure differences can be observed during respiration that range up to 20 cm H_2O. It is even more challenging in dyspneic patients. Calculating the mean pleural pressure using high frequency recordings is therefore considered to be more reliable. Secondly, in contrast to those previous studies, [28;95;98;102;103] a pump was used that creates a constant negative pressure of 40 cm H_2O. In laboratory setting, with manual suction using the same catheter and a 50 mL syringe, negative pressures over 100 cm H_2O can easily be reached (data not shown). Therefore, we believe that a pump regulates the pressure in the patient's chest more accurately, preventing patients from dramatic pleural pressure falls. This might also impact on the intermittent pleural pressure measurements as the tissue recoil after suction and removal of the fluid is not an instantaneous process but takes time.

Removal of large volumes was without complications such as RPE. As Feller-Kopman et al have previously reported, [26] RPE might be rare and independent of the volume of drained effusion. In our study, only three patients had pleural pressures below -20 cm H_2O, and all were without any pain or discomfort during drainage. In a large

series Feller-Kopman concluded that development of chest discomfort was, in contrast to cough, associated with a potentially unsafe fall in pleural pressure. Chest discomfort should be a reason to terminate drainage. However, like in our cohort, pleural pressures below -20 cm H_2O were also shown to occur in patients without causing any symptoms. [96] Elastance was associated with lung status and the extent of drainage. As previously demonstrated by Lan et al, elastance higher than 19 cm H_2O / L was associated with both a not-expanded lung and pleurodesis failure. [28] As proof of concept, we reproduced relationship between pleural elastance (after 500 mL) and lung expansion. Although we identified only four patients with not expanded lungs, its incidence (12%) seems in line with earlier observations. [29] Only a few patients underwent pleurodesis later on and association between pleural pressure swing and pleurodesis success could thus not be studied.

A few weaknesses of this study need to be addressed. Firstly, we have chosen for a Chest X-ray within 24 hours after drainage as the endpoint, since it can be reviewed independently. The use of ultrasound would be incorporated in further studies as well since it informs instantly about lung expansion and is sensitive too. In most patients (n=32) CXR was performed immediately following drainage. CXR was obtained one day afterwards in only two patients, and was reported to show one expanded lung after complete drainage and one not expanded lung after incomplete drainage. The latter might have been drained completely initially, and the fluid might have re-accumulated in the time between drainage and CXR. Secondly, besides an expanded lung and a trapped lung, a third entity has been described: lung entrapment. [104] Pleural pressure curves of those patients are biphasic. Initial parts of these curves are similar to expanded lungs. The second phase of those curves show a steep decline in pleural pressure. These patients can therefore not be identified at the earliest phase of drainage. Serial pleural pressure swing measurements would help to identify lung entrapment as well, but this contrasts the purpose of this study (i.e. early recognition of the not-expanded lung)

Further studies are required before a validated cut-off level of pleural pressure swing can be used to predict lung expansion. In contrast to previous studies in which series of interval measurements were performed, only one single measurement can be associated with a not-expanding lung. Whether high temporal pressure measurements are predictive for pleurodesis success and RPE identification should also be tested in a larger cohort. Reducing the number of required interval measurements makes pleural manometry a more attractive procedure.

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Chapter 2.3

Comparison of Modified Borg Scale and Visual Analog Scale Dyspnea scores in predicting re-intervention after drainage of Malignant Pleural Effusion

An observational study on Patient Reported Outcomes

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Supportive Care Cancer (2013) 21:3109-3116

Abstract

Background

Dyspnea is the most common symptom in patients with malignant pleural effusion (MPE). Treatment decisions are primarily based on the perception of dyspnea severity.

Aims

To study dyspnea perception following therapeutic thoracentesis using the Visual Analog Scale (VAS) dyspnea score and Modified Borg Scale (MBS). To investigate whether Patient Reported Outcome (PRO) measures can predict pleural re-interventions.

Patients en methods

Consecutive patients presenting with symptomatic MPE, and planned for therapeutic thoracentesis were asked to complete MBS and VAS dyspnea scores (both at rest and during exercise) daily for 14 consecutive days. Physicians, unaware of the results of these PRO measures, decided on the necessity of a re-intervention, according to routine care. PRO measures were analysed and correlated with performed re-interventions and the volume of removed fluid.

Results

Forty-nine out of 64 consecutive patients returned the diaries. Twenty-eight patients (57%) had a re-intervention within 30 days. Patients who required a re-intervention reported significantly higher MBS than patients who did not. The extent of increase in MBS during exercise was related to the need for re-intervention. Regarding the MBS during exercise, median time to maximal relief was 2 days. Re-intervention was required sooner when larger volumes were drained.

Conclusion

Patient reported outcomes are useful tools to assess treatment effect of therapeutic thoracentesis. Median time to maximal relief is 2 days. MBS rather than VAS dyspnea score appears to be more prognostic for repeat pleural drainage within 30 days.

Background

The space between the inner layer of the thoracic cavity (parietal pleura) and the outer surface of the lungs (visceral pleura) is filled with a small amount of pleural fluid. Production and breakdown of this pleural fluid is balanced in physiologic state.[1] Disturbance of this equilibrium results in fluid accumulation up to several liters. Pleural effusion can be a manifestation of a variety of diseases of which less than 10 percent is caused by malignancy. [2;4] In a post-mortem series of patients with malignancy, 28% of patients had pleural metastases. [14] These pleural metastases can result in fluid formation: malignant pleural effusion (MPE). Approximately 50% of patients with metastasized disease develop MPE. [92] Patients suffering from MPE have a worse survival than patients with metastases to other organs. [22]

MPE can cause diverse symtoms: pain, chronic cough, and even abdominal complaints. [83] Dyspnea, perception of breathing impairment or shortness of breath, is the most common symptom of MPE. MPE due to its incidence and impact on quality of life (QoL) is considered a major problem. MPE can develop in most malignancies but is most frequently seen in patients suffering from either mesothelioma, lung or breast cancer.

Therapeutic thoracentesis aims to remove as much fluid as necessary to relieve symptoms. When life expectancy is greater than one month, talc pleurodesis is advised in cases of early recurrence. [15] Any treatment decision related to the effusion is based on the reported perception of symptoms.

Dyspnea perception differs when assessed by patients and physicians. [105] PRO measures have shown their value in dyspnea evaluation in diseases such as chronic obstructive pulmonary disease (COPD) and asthma. [106;107] Several scales or scores proved to be accurate in describing treatment effect. [108] VAS dyspnea score and MBS are the two most commonly used methods recording dyspnea perception, and may be potentially useful for the evaluation of pleural interventions. These scales have never been validated for dyspnea evaluation in MPE patients. However, (PRO) measures such as Visual Analog Scale (VAS) dyspnea score and Modified Borg Scale (MBS) have been used as (primary) endpoint in studies on management of MPE. [30;44]

Few studies have reported on dyspnea relief following pleural interventions. One such study reported dyspnea perception, as scored by Modified Borg Scale, decreased significantly following therapeutic thoracentesis. [109] Given that six minute walk test (6MWT) also had improved, it was concluded that this dyspnea score reflected a physiologic improvement due to the pleural intervention. [110]

Since most treatment decisions are based on dyspnea perception, we set up a study to measure patients reported dyspnea perception following therapeutic thoracentesis,

using the most common used PRO measures. Furthermore, we investigated whether these PRO measures were predictive for fluid recurrence, as represented by a re-intervention within 30 days.

Patients and methods

Patients

Consecutive patients with symptomatic pleural effusion in the Netherlands Cancer Institute – Antoni van Leeuwenhoek hospital, a comprehensive cancer center, were asked to participate in this observational study. Patients with symptomatic brain metastases, illiterate patients or visually disabled patients were not asked to participate. All patients signed informed consent for storage of pleural fluid samples. The Medical Ethical Committee approved patient participation in this observational study without the need for an additional written informed consent. Patients were allowed to withdraw from the study at any time.

Patients with suspicion of MPE consulted a resident, specialized nurse or chest physician. The procedure was explained, contra-indications were checked for and patients were asked to report dyspnea on a daily basis for two consecutive weeks. MBS and VAS dyspnea score (both at rest and during exercise) were scored before therapeutic thoracentesis and for 14 days on a daily basis following therapeutic thoracentesis, or until re-intervention. Both scales, printed in a patient diary, were explained before the intervention (see below). Results of a pilot study of 10 patients, not included in this report, indicated that VAS dyspnea score was more likely to be completed incorrectly. This pilot resulted in a patient guideline on the use of the VAS dyspnea score in the current report and resulted in a higher rate of correctly completed VAS dyspnea scores. Patients were not subjected to exercise, but they were told to consider activities of daily living as exercise when these activities increased the dyspnea. Patients were asked to send completed diaries to the hospital, and were reminded by phone within 7 days after completion. Scores were analysed by persons blinded for the clinical outcome. Physicians who made treatment decision regarding the pleural effusion were unaware of the results of the PRO measures.

Modified Borg Scale (MBS) dyspnea score [111]

This modified 12- point scale consists (0; 0,5; 1-10) corresponds with increasing shortness of breath **(Figure 1)**. Patients were asked to mark the most appropriate description or number of their shortness of breath at rest and during exercise.

	Shortness of breath	At rest	During activity
0	Nothing at all	□	□
0.5	Very very slight	□	□
1	Very slight	□	□
2	Slight	☒	□
3	Moderate	□	□
4	Somewhat severe	□	□
5	Severe	□	□
6		□	☒
7	Very severe	□	□
8		□	□
9	Very very severe	□	□
10	Maximal	□	□

FIGURE 1 - Modified Borg Scale dyspnea score

This scale consists of both verbal (10) and numerical (12) descriptions for dyspnea assessment. Patients are asked to tick the boxes that reflect their dyspnea perception best.

Visual Analog Scale (VAS) dyspnea score [111]

VAS is a horizontal line, 100 mm in length, anchored by word descriptors at each end. The VAS dyspnea score uses: 'No shortness of breath at all' and 'Maximum shortness of breath'. **(Figure 2)** The patient marks on the line the point that they feel represents the perception of their current state. The distance (mm) between the beginning of the horfizontal line and this mark represents the degree of dyspnea perception.

FIGURE 2 - Visual Analog Scale dyspnea score

Patient is requested to draw a vertical line on the horizontal one (as shown). Distance (in mm) from the left-side of the horizontal line to the vertical line represents extent of dyspnea.

Drainage

Therapeutic thoracentesis was performed under ultrasound guidance, according to the in-house protocol. Drainage was stopped when flow ceased or when patients experienced discomfort. In particular, there was no predefined maximum volume of fluid to be drained.

Therapeutic thoracentesis was evaluated by phone call to the patient within a week. Patients were instructed to contact the respiratory department whenever they experienced increased symptoms. Decisions regarding re-interventions were based on the presence of symptoms and the recurrence of pleural effusion as assessed by ultrasound, Chest X-ray or computed tomography.

Statistical methods

The association between patient reported dyspnea, as assessed by both MBS and VAS dyspnea score (at rest and during exercise), and the time until re-interventionwas assessed using Cox proportional hazard regressions. The dyspnea measures included the baseline score and three measures of the change in dyspnea score: the cumulative decrease, the nadir value (defined as best value in either MBS or VAS dyspnea score, maximal relief) and the cumulative increase over time. Cumulated increase was calculated from nadir. The changes in dyspnea scores were included as time dependent variates. The strength of association was compared using Log-likelihood ratios (LLRs) and only patients completing all four scores were included in the analysis. As the number of degrees of freedom is equal for all models a comparison of LLRs is equivalent to using Akaike information criterion (AIC). For each PRO measure two Cox models were constructed; one univariable, and one multivariable adjusting for the volume of liquid removed and when assessing the change in PRO, the baseline measure.

A subsequent analysis was performed to address the clinical question: what is the value of the MBA and VAS in predicting re-intervention within 30 days. This was assessed using receiver operating characteristic (ROC) curves with the area under the curve (AUC) used as the measure of discrimination.

The association between patients reported improvement in dyspnea due to the removal of fluid and the actual quantity of fluid removed was assessed using Spearman's correlation. The association between the quantity of volume drained and the risk of re-intervention was assessed using Cox proportional hazard regression. The Kaplan-Meier technique was used to present the probability of no re-intervention over time.

Results

Patients

Between April 2011 and April 2012 64 consecutive patients were invited to participate in the study; all patients consented and were registered. Forty-nine diaries (77%) with patient reported outcomes were returned. Fifteen patients did not return their diaries for various reasons (6 patients died within 2 weeks, 4 patients refused further participation, 3 patients underwent a planned thoracoscopy within 14 days, and 2 patients underwent further treatment in another hospital). Patient characteristics are listed in **Table 1**. Thirty-three out of 49 patients (67%) underwent ipsilateral pleural re-interventions. Median time to re-intervention was 20 days (95% CI 13-92 days). Twenty-eight patients (57%) required an ipsilateral re-intervention within 30 days.

Patient	**N=49**
Male/ Female	27 / 22.
Age (median)	58; range (29-77)
Side	17 left/ 32 right
Primary Tumor	
Breast	13 (27%)
Lung	12 (24%)
Melanoma	5 (10%)
Mesothelioma	3 (6%)
Ovary	3 (6%)
Colon	2 (4%)
Kidney	2 (4%)
Pancreas	2 (4%)
Bladder	2 (4%)
Other	5 (10%)

TABLE 1 - Patient characteristics

Patient Reported Outcome (PRO)

MBS dyspnea scores were correctly completed in all 49 cases, while 46 VAS dyspnea scores were correctly completed. Median time to maximal dyspnea was different depending on which scale was used and ranged from 1.9 days (MBS at rest) to 4.8 days (VAS during exercise). As expected, dyspnea scores before intervention were lower at rest than during exercise. Maximal increase in both MBS and VAS dyspnea

score following maximal relief was also reported higher during exercise than at rest (**Table 2**).

	MBS (rest)	MBS (exercise)	VAS (rest)	VAS (exercise)
	N = 49	**N = 49**	**N = 46***	**N = 46***
Baseline				
Median	3	5	021	0.73
(Range)	(0-8)	(3-10)	(0.02 - 0.8)	(0.23 - 0.97)
Mean	2.9	5.8	0.3	0.68
(St.Dev.)	(2)	(2)	(0.24)	(0.2)
Nadir				
Median	0.5	2	0.04	0.21
(Range)	(0-3)	(0 - 7)	(0 - 0.38)	(0 - 0.82)
Mean	0.69	2.1	0.066	0.28
(St.Dev.)	(0.76)	(1.3)	(0.074)	(0.22)
Time To Nadir (days)				
Median	1	2	3	4
(Range)	(0 - 13)	(0 - 13)	(0 - 14)	(0 - 14)
Mean	1.9	2.8	3.7	4.8
(St.Dev.)	(2.8)	(2.7)	(3.4)	(3.6)
Max Increase				
Median	1.5	2	0.15	0.27
(Range)	(0 – 5.5)	(0 - 8)	(0 - 0.68)	(0 - 0.66)
Mean	1.6	2.5	0.21	0.28
(St.Dev.)	(2)	(1.4)	(0.17)	(0.17)

TABLE 2 - MBS and VAS scores at rest and during exercise

* 3 patients did not complete the VAS

Nadir Maximal relief, lowest reported dyspnea score

PRO and need for re-intervention

A comparison of the time dependant Cox proportional hazard regressions using AIC indicated that, of the changes in the patient reported outcomes, an increase in MBS following maximal relief was most prognostic for re-intervention. MBS assessed during exercise was more prognostic than when assessed at rest. (**Table 3**) Patients who required a re-intervention reported a higher increase in MBS during exercise (**Figure 3**). Patients, who reported higher increases in either PRO measure following maximal relief, were more likely to undergo a re-intervention. For example, only

29% of patients experiencing small increases in MBS during the first two weeks required re-intervention within 30 days, as compared to 80% who experienced large increases. (**Appendix 1**) Likewise increases in MBS assessed during exercise had the highest discrimination between patients who required intervention within 30 days and those who did not, with a concordance index (ROC-AUC) of 0.75.

		Cox univariable		Cox multivariable		ROC	
		LLR Chi sq	**ΔAIC**	**LLR Chi sq**	**ΔAIC**	**AUC**	**95% CI**
Baseline							
MBS	exercise	6.24	28.78	12.38	27.68	0.66	(0.51 - 0.66)
MBS	rest	3.30	31.72	8.84	31.22	0.65	(0.5 - 0.65)
VAS	exercise	0.62	34.40	10.22	29.84	0.63	(0.48 - 0.63)
VAS	rest	6.28	28.74	14.38	25.68	0.73	(0.59 - 0.73)
Nadir							
MBS	exercise	3.14	31.88	14.30	25.76	0.63	(0.48 - 0.63)
MBS	rest	12.84	22.18	19.96	20.10	0.71	(0.58 - 0.71)
VAS	exercise	0.62	34.40	11.08	28.98	0.62	(0.43 - 0.62)
VAS	rest	8.92	26.10	18.80	21.26	0.69	(0.55 - 0.69)
Cumulative decrease							
MBS	exercise	1.28	33.74	14.30	25.76	0.45	(0.6 - 0.45)
MBS	rest	0.58	34.44	19.96	20.1	0.55	(0.4 - 0.55)
VAS	exercise	0.06	34.96	11.08	28.98	0.52	(0.36 - 0.52)
VAS	rest	3.46	31.56	18.80	21.26	0.68	(0.53 - 0.68)
Cumulative increase							
MBS	exercise	35.02	0	40.06	0	0.75	(0.62 - 0.75)
MBS	rest	29.00	6.02	29.38	10.68	0.71	(0.58 - 0.71)
VAS	exercise	4.46	30.56	11.46	28.6	0.59	(0.43 - 0.59)
VAS	rest	14.48	20.54	27.08	12.98	0.61	(0.45 - 0.61)

TABLE 3 - Results of the time dependent Cox regressions and ROC analyses

Multivariable Cox regressions included baseline value and volume removed as covariates. The change in AIC (ΔAIC) is relative to cumulative increase in MBS (during exercise).

LLR = log-likelihood ratio; Chisq = Chi-square statistic; AIC = Akaike information criterion; ROC = Receiver operating characteristic; AUC = Area under the curve; CI=Confidence intervals.

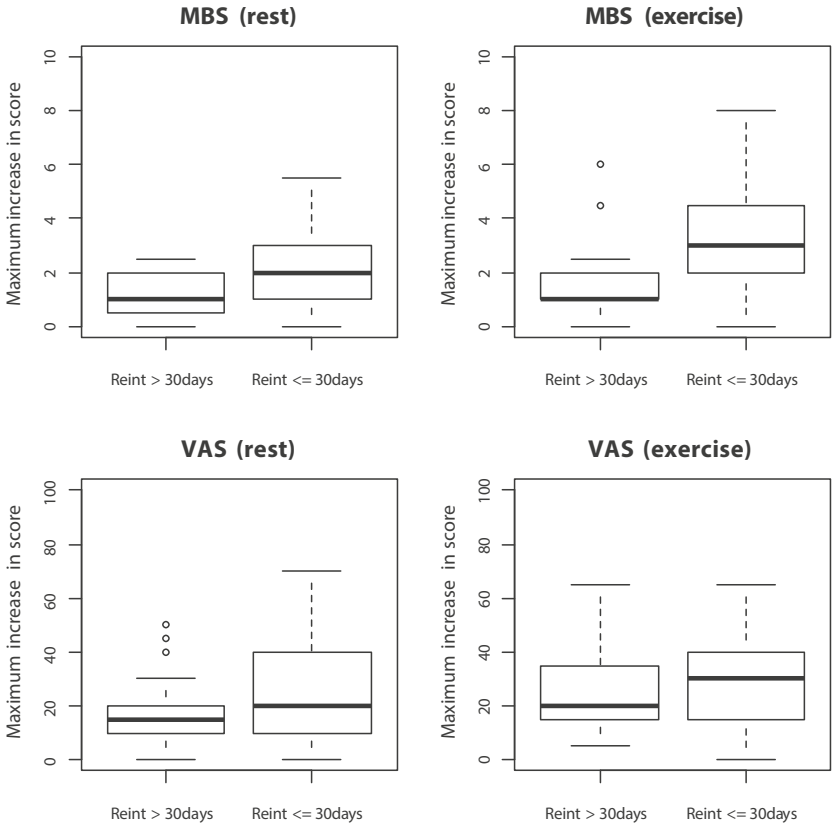


FIGURE 3 - Association between need patient reported outcomes and re-intervention within 30 days
(MBS (rest): *p=0.02*; MBS (exercise): *p=0.001*; VAS (rest): *p=0.23*; VAS (exercise): *p=0.27*)

PRO and drained volume

Median volume drained during thoracentesis was 1500 mL (range 300-3000 mL; mean = 1600, SD = 730). The correlation between amount of fluid removed and both MBS and VAS dyspnea score was weak. Spearman's rho for MBS during rest and exercise was 0.24 and 0.23 (p=0.10 and P=0.12, respectively) and for VAS dyspnea score during rest and exercise the correlation was even lower: rho=0.07 (p=0.65) and rho =-0.07 (p=0.66), respectively. The volume of fluid drained was prognostic for re-intervention, with patients from whom larger volumes were drained being at higher risk for re-intervention (p=0.04; **Figure 4**).

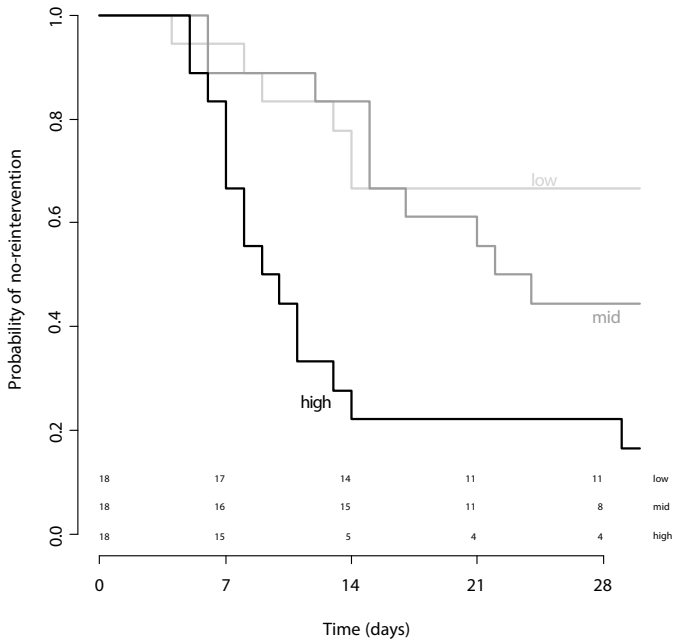


FIGURE 4 - Incidence proportion curves for re-intervention

Volume is divided into tertiles: low (<1300mL), mid (1300mL-1870mL), high (>1870mL).

Discussion

The current results suggest that PRO measures such as the Modified Borg Scale are useful tools to observe dyspnea relief following thoracentesis and to predict the risk on re-intervention within a month. To the best of our knowledge, this is the first study showing that dyspnea perception is associated with the need for re-intervention. We believe that these results may prove useful in the optimization of palliative care.

Currently, patients are informed that the major improvement in dyspnea following therapeutic thoracentesis will occur within 24 hours. However, we observed that the median time to maximal relief following drainage was up 2 days, regarding the MBS during exercise. Patients in the final 6 months of their lives tend to visit emergency departments frequently for symptoms such as chest pain, dyspnea and pleural effusion. [112;113] A better understanding of symptom relief following therapeutic thoracentesis by patients may reduce the number of last-minute presentations at emergency departments.

The second aim of this study was to investigate whether patient reported outcomes predict when patients require re-interventions for recurrent pleural effusion. Patients who underwent a re-intervention within 30 days reported a higher maximal

increase in MBS following maximal relief compared to patients who did not require a re-intervention. The MBS was a successful tool in differentiating between patients with a high and low risk for re-intervention within 30 days. Based on the maximal increase in MBS during the first two weeks, the percentage of patients requiring re-intervention within 30 days ranged from 29% in patients with small maximal increases to 80% in patients with large increases (**Appendix 1**). Therefore, we hypothesize that daily dyspnea assessment may provide sufficient data to plan re-interventions.

The volume of fluid drained appears not to be associated with dyspnea improvement. Some patients had small volume pleural effusions causing dyspnea while others had massive pleural effusions. All volumes of pleural effusion were drained until patients started coughing or flow ceased. The lack of association between volume and symptom relief is therefore most likely related to the approach of "maximal" drainage. In other words, the maximum relief is patient-specific, and achieved when a majority, if not all, of the fluid present is drained. In contrast the amount of fluid removed was strongly related to the time to re-intervention. This suggests that quantity of fluid present in a patient is related to the accumulation rate.

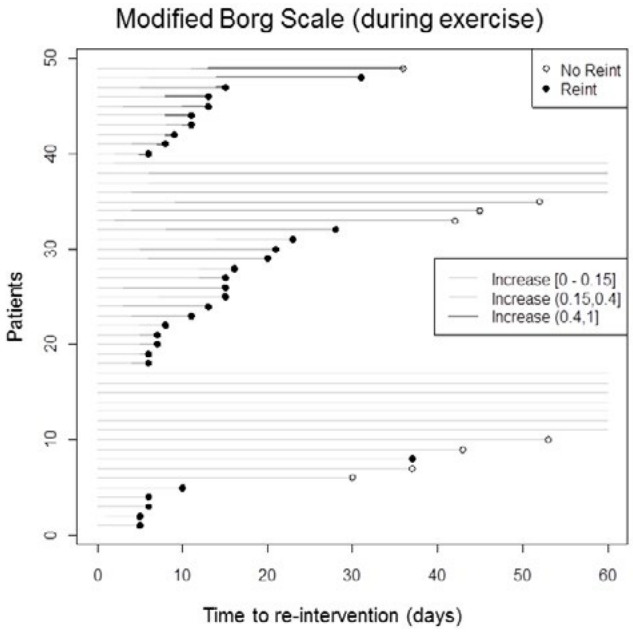
In this series MBS rather than VAS appears to be a potential tool to predict fluid recurrence. MBS and VAS dyspnea scores in healthy subjects represented dyspnea without any preferred method. [114-116] Currently, MBS is favoured over VAS dyspnea scores in healthy subjects, as the test is more reliable and reproducible. [111] Even in illiterate COPD patients no difference between the two scales was observed. [107] Since perception of dyspnea is subjective, PRO measures might be influenced by emotional status. [116] In our study all subjects were diagnosed with cancer, and pleural fluid was expected to be of malignant origin. Patients were aware of this, and furthermore the majority of patients had proven metastatic disease, and were aware of prognostic implications. Dyspneic patients will understandably minimise their activities. Therefore, all patients were told to report when they experienced an increase in shortness of breath during non-defined activities or exercise. Although patients with advanced disease have multiple reasons for shortness of breath, we assumed that only pleural fluid contributed to dyspnea, since no intervention other than thoracentesis was performed and all patients reported dyspnea relief.

As more than 75% of the diaries were returned, we concluded that these PRO measures are a patient friendly tool to assess the need for pleural intervention evaluation, without the need for lung function tests or functional tests such as 6MWT. After a re-intervention, most people realise that they suffered from dyspnea complaints for too long and regretted not contacting the respiratory department at an earlier time.

Thus, such PRO measures may result in patient empowerment by providing a tool for early recognition of symptoms. As a result, earlier recognition of fluid recurrence will enable pulmonologists to plan re-interventions before 'air hunger' occurs. We realise that some of the diaries may have been filled in retrospectively by the patient, or after checking the score on the day before. This limitation is common to all PRO protocols, which may be addressed with the development of electronic diaries.

In conclusion, MBS was rather than VAS dyspnea useful to predict the need for re-intervention. Using the score that correlates best with need for re-intervention (MBS during exercise) we demonstrated that the median time to maximal relief was two days. Based on these results, patients can be informed more accurate on the expected relief and recurrence of fluid. Further, daily dyspnea assessments may provide an early indication for re-intervention thereby improving the quality of life of these patients.

Appendix



APPENDIX 1 - Relation between increase in MBS and re-intervention

The maximum cumulative increase in MBS during exercise is indicated by the weight of the lines. Patients are grouped according to the maximum reported increase in MBS, and ordered within each group by the time to re-intervention.

Note: Patients whose MBS does not increase (i.e. the first 17 patients) had a much lower risk of re-intervention, with 5 (29%) requiring re-intervention within 30 days. In patients who have large increases in MBS (the last 10 patients), 8 (80%) require a re-intervention within 30 days (and one just after). From the remaining 22 patients who have moderate increases in MBS, 15 (68%) require re-interventions within 30 days.

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Chapter 2.4

Comments on: Predictors of Clinical Use of Pleurodesis and/or Indwelling Pleural Catheter Therapy for Malignant Pleural Effusion

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To the editor,

With great interest we read the study by Fysh et al. [117] Using both patient and fluid characteristics they have been able to select patients who are likely to undergo definitive pleural therapy. The authors claim that this knowledge allows early selection of patients avoiding repeated pleural procedures.

As Fysh commented, these results are "a real-life prescription behavior of clinicians regarding definitive therapy". Decisions to undertake definitive therapy are made by physician together with patient.

We question the use of a treatment modality as primary endpoint as it is influenced by the physician himself. Decisions whether to perform pleurodesis, insert an Indwelling Pleural Catheter (IPC) or not are not solely based on pH, large size pleural effusion, mesothelioma or age. For instance, we demonstrated prospectively that changes in patient reported dyspnea scores after therapeutic thoracentesis were related to the need for reintervention too. [84] Thus, these predictors can be used together with the objective need for definitive pleural therapy.

We prospectively collected a database from patients with pleural effusions. Over 500 patients with pleural effusions were included. As is expected from a comprehensive cancer center, the majority of patients suffered from malignant pleural effusion. After excluding non-malignant effusions, 381 patients were enrolled for this analysis. In this cohort, the majority was female (232/381). Median age of patients was 61 years. Pleural effusion was predominantly right-sided (213/381). In contrast to the population described by Fysh, our database consisted of more patients suffering from breast cancer (103/381), as previously reported.[85] At the time of analysis 42 patients were still alive without either pleurodesis or IPC insertion, 170 patients (45%) underwent definitive treatment for recurrent MPE, and 169 patients died without a definitive treatment for pleural effusion. No data was available on recurrent thoracenteses.

Inspired by the referred study, univariate analysis of our data showed also a significant correlation with age (OR 0.979, p= 0.017). Besides, patients with higher protein levels were more likely to undergo definitive treatment for pleural effusion at some stage during their disease (OR 1.021, p=0.048). No information was available on pleural fluid pH.

We identified one other variable. Patients with bilateral pleural effusion (52/381) were more prone for definitive pleural treatment than patients with unilateral pleural effusion. (OR 3.884, p< 0.0001).

Understanding their own clinical decisions, clinicians may be able to inform patient more detailed on future therapies.

D

Discussion/ Future perspectives

General aspect MPE/ Prognosis

Malignant pleural effusion caused by any primary tumor is considered to be metastasized malignancy, and is accompanied with worse prognosis compared with metastatic spread to other organs. [22] Prognosis of MPE is poor and dependent on tumor type, performance score, and the presence of malignant cells in the pleural fluid. [118] MPE patients from an international cohort study had a median estimated life expectancy of 136 days. [85] A prognostic score (LENT) was developed: LENT is an acronym for pleural fluid LDH level (L), ECOG performance status (E), pleural fluid neutrophil-to-lymphocyte ratio (N), and tumor type (T) (**Table 1**). Based on these parameters patients were divided into 3 categories (low, moderate and high risk for mortality). [85] In general, patients suffering from MPE due to mesothelioma have the longest survival while patients with lung cancer and other tumors have the shortest. (**Figure 1)** [85;118] Comparable studies confirmed those parameters: NLR ratio, ECOG, and tumor type were also identified as predictive factors for 30 day mortality. [119;120]

Recurrent malignant pleural effusion

MPE is likely to recur within several days following (maximal) drainage. Using MBS scores, patients reporting a bigger increase in dyspnea following initial relief after drainage are more prone for pleural re-interventions within 30 days. Maximal benefit in dyspnea after thoracentesis was not reported immediately, but 1-2 days later. Larger volumes of pleural drainage are related with sooner re-interventions as well. [84] We assume that drainage of larger effusion doesn't induce earlier recurrence by itself, but that the active malignancy causes a more rapid fluid formation: large volumes of pleural fluid can be drained, but recurs fast, requiring earlier re-interventions.

Besides repeat thoracenteses, or palliation with oxygen/ opiates, patients can be treated with a more definitive pleural therapy. Even pleurectomy has been reported for recurrent MPE, but this is considered to be too invasive. To date, talc pleurodesis and IPC insertion are common definitive pleural treatments. The decision for definitive pleural treatment (e.g. TP or IPC insertion) is made by the doctor together with the patient. Not only pulmonologists, but also medical oncologists (in case of non-thoracic primary malignancies) are involved in this clinical decision. Fysh and colleagues identified predictors for definitive MPE treatment, and reported that patients with a lower pleural pH, a larger pleural effusion, and patients suffering from mesothelioma were more likely to undergo definitive pleural treatment. Mesothelioma patients are often treated by pulmonologists for systemic treatment

as well. So, it could be suggested that mesothelioma patients undergo earlier definitive therapy since they are not treated by medical oncologists. [117] Inspired by this analysis, we demonstrated that in our patient cohort younger patients and patients with higher pleural protein levels were more likely to undergo definitive pleural treatment. In our patient cohort, 45% out of 381 MPE-patients underwent definitive treatment, and patients with bilateral MPE underwent definitive pleural treatment most frequently. [121] We realize that those predictors are not necessarily valid for each individual hospital, but it should be encouraged that doctors analyze their previous decisions and results.

	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	0
	- Mesothelioma	
	- Hematological malignancy	
	Moderate risk tumor types	1
	- Breast cancer	
	- Gynaecological cancer	
	- Renal cell carcinoma	
	Highest risk tumor types	2
	- Lung cancer	
	- Other tumor types	
Risk categories	**Total score**	
Low risk	0-1	
Moderate risk	2-4	
High risk	5-7	

TABLE 1 - The LENT score calculation [85]
ECOG PS: eastern cooperative oncology group performance score; LDH: lactate dehydrogenase; NLR neutrophil-to-leukocyte ratio

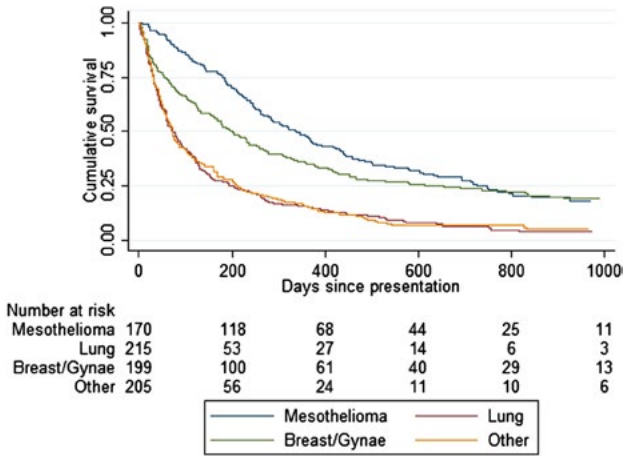

FIGURE 1 - Kaplan-Meier survival curves according to cell type for the UK, Australian and Dutch cohorts combined. [85]

Success of pleural drainage

When the pleura are involved in malignant disease, curation is no longer an option. Therefore, MPE treatment focuses on palliation. Dyspnea is the most common symptom, and pleural treatment aims to decrease shortness of breath. Success of symptom control in MPE patients should not be measured by radiologic absence of effusions or lung expansion but by patient's experience of dyspnea. Regarding (the need for) pleural re-intervention as surrogate for unsuccessful pleural treatment, patient reported outcomes (PRO) were used to assess drainage success. Increase in MBS scores (both at rest and during exercise) rather than VAS scores was indicative for pleural re-intervention. Maximal benefit after therapeutic thoracentesis was not reported immediately, but up to 5 days (dependent on the use of either MBS or VAS).

Definitive pleural therapy

In the Netherlands, talc pleurodesis is standard of care when definitive pleural therapy is given. IPCs are barely mentioned In the current national guidelines on MPE treatment, dating from 2003: *"IPCs are an ambulatory option for patients in a poor condition whose talc pleurodesis failed."* [122]

Talc pleurodesis

Talc has been proven to be safe [123], the most efficient, and cost effective sclerosant for chemical pleurodesis. [15] Definition changes can alter pleurodesis success rates.

Burgers et al. demonstrated that their patient population had a 35% success rate (35 out of 100 patients). Exclusion of the 25 patients in whom talc instillation was omitted raised the success rate to 47%. This percentage was even increased when only patients were included in the denominator who survived at least 70 days. [29] Timing of chemical pleurodesis can affect success rates as well. In a retrospective cohort study, MPE patients suffering from breast cancer had better pleural effusion control when they underwent talc pleurodesis before systemic therapy than when they were treated with systemic therapy alone. [34] These authors posed that earlier/ sooner talc pleurodesis led to a better pleurodesis success rate. Absence of pleural effusion can be defined as treatment success, but could be a result of biologic behaviour of the tumor as well. Pleural fluid doesn't necessarily recur after first presentation. Thus, the higher success rate of immediate definitive pleural treatment might not be due to a better timing or efficacy of the talc, but due to the fact that MPE doesn't recur at all.

Predicting outcome (lung expansion)

Lung expansion is one of the most important predictors for pleurodesis success. In our pleural pressure study, drainage was terminated when patients started coughing or experienced chest discomfort. No radiologic or clinically RPE was observed during follow up. We were able to monitor pleural pressure with high resolution. Only after drainage of 200 mL, the difference between pleural pressure during expiration and during inspiration was higher in patients whose lungs were reported to be not expanded. Despite minimal time consumption of our pleural manometry method, thoracentesis with separate pleural monitoring is still more exhaustive than without. Only two pleural pressure measurements were necessary to differentiate between expandable and not-expandable lungs. Another advantage of this method is that patients were allowed breath "normally" instead of holding their breath at in- or expiration during pressure monitoring. The high temporal resolution method is more patient friendly, since holding breath (especially for research purposes) is inacceptable for patients who dyspneic. Based on our results and results from previous studies, thoracic drainage devices are currently optimized to drain pleural fluid and monitor pleural pressure simultaneously. More patients, also patients with not-malignant pleural effusions, are needed to better understand the mechanism of pleural effusion. Future studies may investigate whether these electronic devices are able to predict lung expansion and pleurodesis success.

Decisions about talc instillation depend mainly on radiologic evaluation. In an online survey Dutch and Belgian pulmonologists examined 50 chest X-rays of consecutive patients (admitted for talc pleurodesis, after drain placement, and before the decision

whether to instill talc). Asked whether they reported the lung to be expanded, and if they would instill talc, they agreed more often on the second question. Lung expansion, as assessed by CXR interpretation, seemed doctor dependent. In our survey, doctors were informed about gender, age and tumor type of the consecutive patients. Those patient characteristics might have influenced their answers. Mixing (or even hiding) these data would have unmasked the impact of these data.

Questioning colleagues what they would have done after the patients had been treated provided us with unique data. Normally, talc administration should not be performed when the doctor would not advise to do so. When doctors agreed on not instilling talc, all patients who had undergone talc instillation had an unsuccessful pleurodesis. When doctors agreed on talc administration, success rate was nearly 100%. Without consensus in advice, slightly more than half of patients had a pleurodesis success (defined as no recurrence of fluid or re-intervention, and survival of at least 2 months after talc instillation).

Indwelling pleural catheters

The Food and Drug Administration approved the use of IPCs in 1997. Originally, IPCs were inserted after failed pleurodesis. Currently, IPCs are also inserted as frontline treatment for malignant pleural effusion, but also for refractory not-malignant pleural effusion. Majority of our patients didn't require help from specialized nurses to perform drainages. [86] There have been some concerns about IPCs which are discussed below.

Costs of IPCs

IPCs are considered to be expensive, especially the costs for vacuum bottles or drainage bags. We demonstrated that mean direct costs (IPC and vacuum bottles**)** in a dutch hospital for IPC were €2137, and were different between tumor types. [86] Mean IPC costs for patients suffering from Mesothelioma were €4028; Breast cancer €2204; lung cancer €1146, and other malignancies €1841. These differences in costs follow a similar pattern as survival data of MPE (**Figure 1**), and it is therefore not surprising that IPC costs per day was not different between tumor type. [86] IPCs were considered to be cost-effective when patients had a life expectancy shorter than 6 weeks. [71] In our direct cost overview patients who survived less than 6 weeks had also significant lower cost for IPC treatment. [86] In another study, IPC were considered to be cost-effective in providing QALY's (Quality Adjusted Life Years) when patients survived less than 3 months. [70] In a randomized comparison, costs calculated from data derived from the TIME2 study weren't different between treatment arms. [87]

Since costs for IPC as first line treatment equal IPC costs after failed pleurodesis, man can imagine that failed TP followed by IPC placement causes highest treatment costs. Unfortunately, use of IPCs is still considered to be expensive, necessitating physicians to be inventive.[124]

Infection

Infection is a major concern in IPC patients. Pleural infection rates after IPC placement are reported to be low. [125] It can be concluded from international multicenter study that IPC-related pleural infections are not common. [126] Less than 5% of patients had an IPC-related pleural infection, which occurred at a median of 62 days after placement. This suggests that prophylactic antibiotics during placement won't decrease infection rate, since infections seem more related to the usage than to the insertion of the IPC. This also may be an explanation for the lower pleural infection incidence rates in our RCT: patients in the NVALT14-trial had shorter survival. (**Chapter 1.3**) As was demonstrated in several other studies, there was no difference in pleural infection rate in patients treated with and without systemic treatment. [44;62;86] In the large multicenter study described above (50 pleural infections in 1021 IPCs) only 20% was treated with chemotherapy in the preceding month. [126] Ninety-four percent of those patients with empyema were successfully treated with antibiotics. [126] Pleural infections are complications of pleural interventions, but have sclerosing capacities as well: even 62% (31 out of 50 patients with pleural infections) had successful pleurodesis.

Talc pleurodesis vs. IPC

As previously mentioned, TP (by chest drain) is the gold standard for recurrent malignant pleural effusion in the Netherlands. Worldwide, IPCs are not only used after failed pleurodesis, but as frontline treatment as well. A randomized controlled trial comparing TP with IPC was performed to study the efficacy of both treatments.

Effective treatment

Both talc pleurodesis and IPC are effective treatments, as was reported by patients in our RCT. Improvement in dyspnea wasn't significantly different between treatment arms 6 weeks after randomization. Unfortunately, number of evaluable patients was low. (**Chapter 1.3**) Two previous RCTs compared IPCs with TP for MPE management. [44;48] (**Table 2**) The TIME2 study is the only one to really have the robustness of design and methods required to draw meaningful conclusions.[44] In 1999, Putnam compared IPCs with doxycycline pleurodesis. [30] Superiority of IPC was proven in none of those

randomized comparisons, neither was inferiority. [30;44;48] (**Chapter 1.3**) As far as we know, TP or IPC has never been compared with therapeutic thoracentesis in a randomized controlled trial. Patients are satisfied with an IPC as definitive pleural treatment. In an observational study, patients were asked whether they would choose an IPC again, and if they would recommend it to others. Majority of patients did. [60] Unfortunately, TP patients weren't included in this study.

	Putnam [30]	**Davies [44]**	**Demmy [48]**	**NVALT14**
IPC vs	Doxycycline	Talc (4 gram)	Talc (4-5 gram)	Talc (3-5 gram)
Randomized patients	144	106	67	94
Male/ Female	61/ 83	46/60	33/24	46/48
Tumor Type				
Lung	58 (40%)	25 (24%)	36 (63%)	31 (33%)
Breast	39 (27%)	27 (26%)	7 (12%)	20 (21%)
Mesothelioma	Unknown	11 (10%)	0 (0%)	7 (7%)
Other	47 (33%)	42 (40%)	14 (25%)	36 (40%)
Stratification factors	NA	Mesothelioma/	In/ outpatient Breast/lung/other Syst. chemoTx	PS 0-1 vs >1 Breast/lung/other
Exclusion criteria	Karnofsky < 50	PS 4	PS >2 Bilateral MPE	No PS
Treatment				
IPC	99	52	33	46
Stand.	45	54	34	48
Pleurodesis, no talc/ docycycline	13/41 (32%)	6/54 (11%)	Unknown/29	7/48 (15%)
Reasons	7 pers. Fluid 3 incompl drainage 1 (trapped lung, death < 3 days, rec large eff)	3 trapped lung 3 drain displacement	Unknown	4 trapped lung 3 persistent fluid
Prim. Endpoint				
At	Unknown	6 weeks	30 days	6 weeks
Alive	Unknown	86/106 (81%)	51/57 (89%)	59/94 (63%)
Score	MBS	VAS	Combined succ	MBS
Hospitalization				
IPC	1	0	Unknown	0
Stand.	6.5	4	Unknown	5
FU	90 days	6.1 month (med)	Unknown	6.3 month (med)
Survival				
IPC	87 days	153 days	147 days	70.5 days
Stand.	90	200 days	147 days	72 days

TABLE 2 - Overview of randomized controlled trials comparing IPC with chemical pleurodesis

Hospitalization, re-interventions and complications

Median hospitalization for TP is 4-5 days. [44] (**Chapter 1.3**) Initial hospitalizations for definitive pleural treatment were significant shorter when patients had an IPC inserted. [30;44;45] (**Chapter 1.3**) In up to 15% of these admitted patients, no talc was actually instilled. Combining the data of three RCTs comparing TP with IPC [44;48] (**Chapter 1.3**) 7% of TP patients didn't receive talc due to a trapped lung. In the TIME2 study, 16 percent of patients treated with TP had to be readmitted to the hospital for repeat drainage or drain related complications. [44] Demmy et al. reported that 52% patients were alive without recurrence 30 days after TP treatment. [48] In the dutch RCT, 15 (out of 45 TP patients) needed at least one pleural re-intervention compared to 7 out of 43 IPC patients. This wasn't significantly different. An average of 0.51 pleural re-interventions was needed after each talc pleurodesis, and an average of 0.37 pleural re-interventions after each inserted IPC. In an intention to treat analysis, these differences (0.5 vs 0.2) were significant. (**Chapter 1.3**) Adverse events were acceptable. [44;45] (**Chapter 1.3**)

Definitive pleural treatment in the Netherlands

In our RCT patients preferred either IPC or TP, which was also described in an Australian prospective multicenter study. [45] IPC is not yet a well-accepted treatment in the Netherlands, mainly caused by reimbursement issues. Patients only had the opportunity to get an IPC inserted via trial participation. Only patients who preferred IPC or patients who had no preference for either treatment entered our RCT. Patients who preferred TP were advised to undergo talc pleurodesis as standard treatment. When both TP and IPC were available to patients, our study population should have been more homogenous. On the other hand, patients would not participate in the trial when they preferred either treatment. The short overall survival in our patient cohort might be a result of an unintentional selection of patients: patients who might benefit most from an IPC were proposed to participate in the trial.

Future directions

Several agents have been tested to be administered intrapleurally. Talc administration, first reported in 1935 [38], has been proven to be the most (cost) effective. We don't expect other agents to be more successful, and improvements in pleural treatments should be found in innovative therapies. In most developed countries, IPCs are considered as effective as talc pleurodesis. However, there is some room for optimizing IPC treatment.

Optimize TP or IPC treatment

IPCs have demonstrated their efficacy in recurrent MPE both as frontline treatment and after failed pleurodesis. However, more studies are warranted to select those patients who benefit most of IPC, to determine the best timing for IPC insertion. To date, in Australasia the role of drainage schedules on the efficacy of IPC is investigated. [91] In a 1:1 randomization, patients are instructed to drain either aggressively (usually daily) or when symptomatic (often weekly to monthly). In a patient-blind multicenter study, IPC patients are randomized between talc administration and normal saline via IPC. Primary endpoint in this study is successful pleurodesis (defined as collection of ≤ 50 ml pleural fluid on 3 consecutive occasions in combination with opacification of ipsilateral chest side less than 25%) 5 weeks after randomization. [127] In a pilot study was suggested that combination of talc pleurodesis with IPC placement might reduce hospital stay and duration of IPC use. [56] In a retrospective case series, another strategy was reported. [128] Three days after IPC insertion lung expansion and resolution of pleural fluid was assessed with thoracic ultrasound. If the lung was expanded and fluid resolved, talc was administered and patients were instructed to drain daily at least for 3 days. This study started initially with 57 IPCs insertions, and only 22 out of 24 talc instillations were said to be successful. In 33 patients no talc was administered for reasons of trapped lung, and PS>1. This high number of excluded patients emphasizes the necessity to predict lung expansion.

IPC and complications

Despite pleural infections are complications of treatment, iatrogenic pleural infections are even suggested to be related with longer survival. It was hypothesized that pleural infections may stimulate antitumor effects by activation of local immune response. [129] IPC placement as first line treatment will lead to longer IPC use, which will raise questions how long IPCs can be tolerated in situ. Histologic examination of IPCs didn't reveal any breakdown of the catheter or tumor invasion in removed IPCs. [130] Removal of IPCs can be hard due to tissue fibrosis around the polyester cuff. [69;131] When catheters break during removal, and fragments stay intrathoracally, no adverse events were seen in small case series. [69]

Permanent access

Permanent access to the pleural cavity in order to avoid repeat invasive procedures has been applied for years. [132-135] IPCs can be used for longitudinal sampling, enabling us to observe biochemical changes in MPE for a longer period of time. [136] Intraperitoneal chemotherapy (via a peritoneal catheter) in ovarian cancer has

shown survival benefits. [137] Intrapleural administration of antitumor agents should be investigated as well. Hyperthermic Intrathoracic Chemotherapy (HITHoC) has been associated with high morbidity and mortality rates [138], but administration via an IPC and possibly targeted therapy might be beneficial. [139-142]

In conclusion,

Life expectancy of malignant pleural effusion is mainly determined by primary malignancy. Curation of pleural metastasized malignancy is not realistic, and treatment focusses on palliation. Except for chemo-sensitive tumors, fluid often recurs following drainage. Recurrence rate (or pleural re-intervention within 30 days) can be predicted using daily PROs following drainage. Improvement in dyspnea after MPE drainage is the most important factor to decide to perform future pleural interventions. In a prospectively collected MPE-database we observed that 45% underwent definitive pleural treatment. Patients with bilateral MPE underwent definitive treatment most frequently. One of the most important predictors for pleurodesis success is lung expansion. However, lung expansion on CXR is subject to doctor's interpretation. When doctors agree on advice for talc instillation pleurodesis success rate will increase. Traditionally, IPC was considered after failed talc pleurodesis, and turned out to be an effective treatment in this stadium. In a randomized controlled trial, patients reported IPCs as first line treatment as effective as TP. Hospitalizations after IPC placement are significantly shorter, complication rate is low, and costs are acceptable. Patients who need definitive treatment for recurrent MPE should have the choice between TP and IPC. Patients with expected limited survival (for example based on LENT-score) can be advised to get an IPC inserted to avoid a relatively long hospitalization.

"Om 11 uur in de ochtend haal ik Marie met de auto op in haar huis in de Michelangelostraat. Ze heeft het thoraxteam van het AvL gebeld en kan vandaag langskomen voor een punctie. 'Ga je met me mee?' vraagt ze. 'Is het toch een beetje alsof pap ook bij me is.' Midden in de zin hapt ze een paar keer naar lucht. In haar rechterlong is twee weken geleden een permanente thoraxdrain geplaatst. Door middel van een punctie wordt vandaag de linkerlong ontlast, zodat ze gemakkelijker kan ademen. Genezing is uitgesloten, maar ze reageert goed op een chemomiddel dat haar uitstel van executie kan geven. In haar botten en klieren slinken de tumoren. De longen doen nog niet mee en herstellen zich het traagst."

Uit: Connie Palmen, Logboek van een onbarmhartig jaar

S

Nederlandse samenvatting

Maligne pleuravocht

Pleuravocht is vocht dat zich ophoopt tussen het parietale (borstvlies) en viscerale pleurablad (longvlies). Dit vocht wordt door het borstvlies en longvlies geproduceerd, en geabsorbeerd door het borstvlies. Toegenomen productie, afgenomen afbraak of een combinatie van beiden verstoort dit evenwicht.

Pleuravocht kan een uiting zijn van verschillende ziekten. Medische voorgeschiedenis, radiologisch onderzoek en analyse van het vocht kan differentieren tussen de verschillende oorzaken. In 1972 toonde dokter Richard Light aan dat een combinatie van LDH en eiwit in pleuravocht en serum het onderscheid tussen transudaat en exsudaat nauwkeuriger maakte dan de bepalingen afzonderlijk. Het is onwaarschijnlijk dat pleuravocht wordt veroorzaakt door een maligniteit wanneer de patient niet bekend is met een tumor; in een groot onderzoek van meer dan 6000 pleuravochtsamples was minder dan 10% veroorzaakt door een maligniteit. In het algemeen is maligne pleuravocht een exsudaat, en differentiatie tussen transudaat en exsudaat kan dus een toegevoegde waarde in de diagnostiek hebben. Aan de andere kant is de differentiaal diagnose van exsudatief pleuravocht breder dan maligne pleuravocht alleen.

Maligne pleuravocht wordt, onafhankelijk van de primaire tumor, beschouwd als uitgezaaide maligniteit, en gaat gepaard met een nog slechtere prognose dan wanneer sprake zou zijn van uitzaaiingen elders. De prognose van maligne pleuravocht is afhankelijk van tumor type (patiënten met een mesothelioom de beste overleving, en longkankerpatiënten de slechtste), conditie van de patiënt, en aanwezigheid van maligne cellen in het pleuravocht. In een internationaal cohort onderzoek was de mediane overleving van patiënten met maligne pleuravocht 136 dagen. Een predictor voor overleving werd ontwikkeld: de LENT-score. LENT is een acroniem voor Lactaat dehydrogenase, ECOG performance score, Neutrofielen-leukocyten ratio, en Tumor type. Op grond van deze parameters konden patiënten worden ingedeeld in drie categorieën (laag, gemiddeld, en hoog risico voor overlijden).

Recidiverend maligne pleuravocht

Maligne pleuravocht recidiveert gewoonlijk binnen enkele dagen na (maximale) drainage. Patiënten die grotere toename in Modified Borg Scale (MBS) dyspneu score na initiële verbetering rapporteren, hebben vaker een re-interventie binnen 30 dagen. Maximaal effect op de dyspneu werd niet onmiddellijk na een drainage gerapporteerd, maar 1-2 dagen later (en afhankelijk van gebruikte dyspneu score

zelfs tot 5 dagen). Wanneer grotere volumes werden gedraineerd, hadden patiënten eerder een pleurale re-interventie nodig. Het draineren van grotere volumes zal niet zozeer een vroeger recidief induceren, maar de mogelijkheid een groter volume te kunnen draineren weerspiegelt de tumoractiviteit (en daarmee snellere vochtproductie).

Naast herhaalde thoracenteses, of palliatie middels zuurstof/ opiaten kunnen patiënten met recidiverend pleuravocht een meer definitieve pleurale therapie (talkpleurodese; of een thoracale verblijfsdrain) ondergaan. Een thoracale verblijfsdrain wordt ook wel indwelling pleural catheter (IPC) genoemd. Zelfs pleurectomie is geopperd als behandeling voor recidiverend maligne pleuravocht, maar wordt doorgaans als te invasief beschouwd. De beslissing om talkpleurodese te verrichten danwel een thoracale verblijfsdrain te plaatsen, wordt genomen door de behandelend arts en patiënt. Niet alleen longartsen, maar ook medisch oncologen (in het geval van niet-pulmonale maligniteiten) zijn betrokken bij deze besluitvorming. Fysh identificeerde samen met collega's predictoren voor definitieve behandeling van maligne pleuravocht: patiënten met zuurder pleuravocht, grotere pleuravocht volumes, en mesothelioompatiënten ondergingen vaker definitieve pleurale behandelingen. De systemische behandeling van mesothelioompatiënten wordt vaker ook door longartsen gedaan. Het is dus niet ondenkbaar dat mesothelioompatiënten vaker een pleurodese of IPC-plaatsing ondergaan omdat ze door longartsen worden behandeld (of juist niet door medisch oncologen). Naar aanleiding van Fysh' analyse toonden wij aan dat in onze patiëntengroep met name jongere patiënten, en patiënten met hogere pleurale eiwitgehaltes vaker definitieve behandeling ondergingen. Patiënten met bilateraal maligne pleuravocht overigens het vaakst. Uiteraard zullen deze predictoren niet zondermeer geldig zijn voor andere artsen en ziekenhuizen, maar dokters zouden moeten hun eigen beslissingen en resultaten vaker moeten analyseren. Op deze manier kunnen de toekomstige patiënten het best worden geïnfomeerd.

Pleuradrainage succes

Een maligniteit met pleurale betrokkenheid is niet te genezen, en palliatie is dan ook het doel. Omdat kortademigheid het meest voorkomende symptoom is, richt behandeling zich met name hierop. Effect van pleuradrainage zou niet moeten worden beoordeeld aan de hand van radiologische afwezigheid van maligne pleuravocht, of longexpansie, maar door de dyspneu-beleving van de patiënt. Met behulp van patient reported outcomes (PROs) observeerden we het succes van de pleuravochtdrainage. Toename in MBS scores (zowel in rust als tijdens inspanning)

was meer gecorreleerd met een pleurale heringreep dan VAS (Visual Analog Scale) scores.

Definitieve pleurale behandeling

In Nederland is talkpleurodese standaardbehandeling wanneer maligne pleuravocht recidiveert. IPCs worden nauwelijks genoemd in de landelijke richtlijn, daterend uit 2003. Daarin wordt enkel vermeld dat na een gefaalde talkpleurodese ambulante opties (zoals subcutaan getunnelde drains) tot de mogelijkheden behoren.

Talkpleurodese

Talkpleurodese is veilig, en de meest effectieve sclerosant voor chemische pleurodese. Succespercentages van pleurodese zijn definitie-afhankelijk en variëren tussen 35% en 71%. Burgers onderzocht 100 patiënten die pleurodese ondergingen; 35 waren met succes. Na exclusie van 25 patiënten die überhaupt geen talk ingepoten hadden gekregen, steeg dit percentage naar 47%. Als patiënten die binnen 70 dagen na pleurodese overleden niet in de analyse werden meegenomen, steeg dit percentage verder door. Er wordt ook wel gesuggereerd dat de slagingskans van pleurodese afhankelijk zou zijn van het moment in het ziekteproces waarop deze wordt toegepast. In een retrospectief cohortonderzoek hadden borstkankerpatiënten met maligne pleuravocht betere pleuravochtcontrole wanneer systemische behandeling werd voorafgegaan door pleurodese dan wanneer alleen systemische behandeling plaatsvond. De auteurs van dit onderzoek concludeerden dat vroege talkpleurodese tot een hoger succespercentage leidde. Uit eigen data blijkt dat pleuravocht weliswaar in de meerderheid van de gevallen recidiveert, maar dat een niet onaanzienlijk deel van de patiënten geen re-interventies nodig heeft na een eerste drainage. Afwezigheid van pleuravocht kan worden geduid als pleurodesesucces, maar kan dus ook het biologische gedrag van een tumor zijn. Het wegblijven van pleuravocht na een vroege talkpleurodese hoeft dus niet direct te worden toegeschreven aan de talkpleurodese.

Voorspellen van pleurodese succes (longexpansie)

Longexpansie is één van de belangrijkste voorspellers van pleurodesesucces. Van longexpansie wordt gezegd dat het middels pleurale drukmetingen te voorspellen is. We beeindigden standaard de drainage wanneer patiënten hoestklachten of thoracale pijnklachten ontwikkelden. Radiologisch of klinisch re-expansie longoedeem werd tijdens follow-up niet gezien. Het bleek mogelijk om pleurale

drukken met hoge resolutie te monitoren. Verschil tussen in- en expiratoire pleurale druk na drainage van 200 mL pleuravocht was groter wanneer de long niet zou ontplooien. Ondanks de minimale moeite die onze pleurale manometrie methode kost, vergt het meten van drukken uiteraard meer tijd dan het niet meten. Slechts twee pleurale drukmetingen waren nodig om ontplooiende van niet-ontplooiende longen te kunnen onderscheiden. Een ander voordeel van deze patiëntvriendelijke methode is dat patiënten tijdens de metingen niet hun adem hoefden vast te houden, maar gewoon door mochten ademen. Mede dankzij onze resultaten worden momenteel electronische pompen verder ontwikkeld om gelijktijdig pleuravocht te kunnen draineren en pleurale drukken te meten. Het aantal patiënten met pleuravocht (ook niet-maligne) moet fors worden uitgebreid om het mechanisme van maligne pleuravocht en pleurale druk beter te kunnen begrijpen. Toekomstige studies moeten uitwijzen of deze electronische pompen óók in staat zijn longexpansie en pleurodesesucces te kunnen voorspellen.

Beoordeling van de longfoto speelt een belangrijke rol in de beslissing om talkpleurodese toe te passen. In een online onderzoek werden Belgische en Nederlandse longartsen gevraagd 50 longfoto's te beoordelen van opeenvolgende patiënten die eerder waren opgenomen voor talkpleurodese. De foto's waren gemaakt na drainplaatsing, op het moment dat er besloten moest worden of er talk zou worden toegediend. Er werd gevraagd of ze de long ontplooid vonden en talk zouden inspuiten. Longartsen waren het vaker eens over de tweede vraag dan de eerste. Longexpansie beoordeeld middels een X-thorax was dokter afhankelijk. Longartsen werden geïnformeerd over geslacht, leeftijd, en tumor type. Wellicht hebben deze gegevens hun antwoorden beïnvloed, hetgeen getest zou kunnen worden door de enquete nogmaals af te nemen (met blindering of verwisseling van de data).

De vraag wat collega's zouden doen nadat beslissingen in werkelijkheid genomen waren, gaf ons unieke data. Normaal gesproken zou namelijk nooit talk worden ingespoten na een overwegend negatief talkadvies. Wanneer ondervraagde longartsen adviseerden geen talk in te spuiten, hadden patiënten een niet succesvolle pleurodese. De helft van de patiënten had een succesvolle pleurodese wanneer de longartsen niet eenduidig in hun advies waren. Succesvolle pleurodese was overigens voor deze studie gedefinieerd als: geen recidiverend pleuravocht (of nieuwe interventie), en overleving van minimaal 2 maanden na talkinjectie.

Thoracale verblijfsdrains

De Food and Drug Administration heeft het gebruik van IPCs goedgekeurd in 1997. Oorspronkelijk werden thoracale verblijfsdrains ingebracht na mislukte pleurodese. Momenteel worden IPCs niet alleen ingebracht als eerstelijnsbehandeling voor maligne pleuravocht, maar ook voor refractair niet-maligne pleuravocht. De meerderheid van onze patiëntenpopulatie had geen hulp van gespecialiseerd verpleegkundigen nodig voor drainages thuis. Zoals bij elke nieuwe ontwikkeling zijn er wat twijfels over de IPC, welke hieronder worden besproken.

Kosten van thoracale verblijfsdrains

Het gebruik van IPCs worden als kostbaar beschouwd, met name het gebruik van de vacuümflessen en drainagezakken. De gemiddelde prijs voor het gebruik van IPC en vacuümflessen in een Nederlands ziekenhuis bedroegen €2137, en de kosten waren afhankelijk van tumor type. Gemiddelde kosten voor mesothelioompatiënten (€4028) waren het hoogst, die voor longkankerpatiënten (€1146) het laagst. Patiënten met borstkanker (€2204) en andere tumoren (€1841) zaten daar qua kosten tussen in. Het patroon van deze kosten lijkt veel op het patroon in overleving, en het is dan ook niet verwonderlijk dat de gemiddelde gebruikskosten per dag gelijk voor de verschillende tumor types. In kosteneffectiviteits analyses werd eerder al aangetoond dat IPCs kosteneffectief zijn waneer patiënten korter dan 6 weken leven. In ons overzicht verschilden de kosten significant tussen patiënten die korter en langer dan 6 weken leefden. In een andere studie waren IPCs kosteneffectief wat betreft QALYs wanneer patiënten korter dan 3 maanden leefden. In een RCT met data van de TIME2 studie waren de kosten van talkpleurodese en IPCs niet verschillend. Omdat de IPC-kosten van eerstelijnsbehandeling en na gefaalde pleurodese even hoog zijn, is het logisch te denken dat de kosten voor gefaalde pleurodese gevolgd door IPC-plaatsing het hoogst zullen zijn. Helaas wordt de IPC nog steeds gedacht duur te zijn, waardoor longartsen heel inventief worden om kosten te besparen, met mogelijk een toename van infecties of andere complicaties.

Infectie

Artsen zijn bang voor Infecties door IPCs, hoewel pleurale infecties weinig voor lijken te komen. In een grote multicenter studie had minder dan 5% een pleurale infectie, wat na een mediane tijd van 62 dagen na plaatsing optrad. Profylactische antibiotica zal dan ook geen toegevoegde waarde hebben, aangezien de complicatie met name gerelateerd lijkt te zijn aan het gebruik dan de plaatsing van de drain. Dit zou ook een verklaring kunnen zijn waarom in onze gerandomiseerde studie

minder pleurale infecties voorkwamen dan in vergelijkbare studies: patiënten in de NVALT-14 studie hadden in het algemeen een kortere overleving. Zoals ook reeds werd gemeld in andere onderzoeken, was het aantal infecties onafhankelijk van eventuele gelijktijdige systemische behandeling. In de grote bovengenoemde studie (50 pleurale infecties in meer dan 1000 IPCs) had slechts 20% van de patiënten in de voorafgaande maand chemotherapie ondergaan. Vier-en-negentig procent van de patiënten met een empyeem werd succesvol behandeld met antibiotica. Pleurale infecties zijn niet alleen complicaties van pleurale ingrepen, maar hebben tegelijkertijd ook scleroserende eigenschappen, getuige de 62% van de patiënten met een pleurale infectie die een succesvolle pleurodese had. Hoewel pleurale infecties uiteraard complicaties zijn, wordt van iatrogene pleurale infecties zelfs gesuggereerd dat ze een langere overleving veroorzaken. Verondersteld wordt dat deze infecties het locale immuunrespons activeren, en daarmee het antitumoreffect. IPC plaatsing als eerstelijnsbehandeling zal leiden tot langer gebruik. Men zal gaan zich afvragen hoe lang de IPC in situ kan blijven. Histologisch onderzoek van IPCs toonde geen enkele afbraak na verwijdering. Het verwijderen van IPCs is trouwens best lastig, aangezien de cuff door fibrose omgeven zal zijn. Wanneer IPCs tijdens de verwijdering breken, waarbij delen intrathoracaal achterblijven, leidde dat niet tot meer bijwerkingen.

Talkpleurodese of thoracale verblijfsdrain?

Talkpleurodese is in Nederland dus eerstekeus behandeling. Wereldwijd worden IPCs niet alleen na gefaalde pleurodese gebruikt, maar ook als eerstelijnsbehandeling. Een gerandomiseerde studie werd uitgevoerd om de effectiviteit van talkpleurodese met die van IPCs te vergelijken. De meeste patiënten die voor onze RCT werden gescreend, hadden een voorkeur voor één van de behandelarmen. Dit was ook beschreven in een Australische multicenter studie. In Nederland is een thoracale verblijfsdrain momenteel (nog) geen algemeen geaccepteerde behandeling, voornamelijk door vergoedingsproblemen. Patiënten konden eigenlijk alleen een IPC krijgen door studiedeelname. Patiënten met een sterke voorkeur voor talkpleurodese werd geadviseerd niet aan de studie deel te nemen en gewoon de standaard behandeling te ondergaan. Wanneer zowel talkpleurodese als IPC toegankelijk voor al onze patiënten zouden zijn geweest, zou onze patiëntenpopulatie mogelijk meer homogeen zijn geweest. Aan de andere kant, wanneer patiënten voorkeur voor één van de behandelarmen zou hebben, en beide toegankelijk voor patiënten zouden zijn, zouden er wellicht minder patiënten deelgenomen hebben aan de studie. De korte overleving in onze studie is mogelijk het gevolg van de onbedoelde selectie

van patiënten: patiënten waarvan de hoofdbehandelaar dacht dat ze het meest baat zouden hebben bij een IPC (een behandeling die zonder studiedeelname nagenoeg onmogelijk was).

Effectieve behandeling

Zowel talkpleurodese als het inbrengen van een thoracale verblijfsdrain blijken effectieve behandelingen. Verbetering van de dyspneu was gelijk tussen beide behandelarmen 6 weken na randomisatie. Helaas was het aantal evalueerbare patiënten laag. Twee eerdere RCTs vergeleken ook talkpleurodese met IPCs, waarvan de TIME2 studie de enige studie is waaruit betrouwbare conclusies getrokken mogen worden. In 1999 vergeleek Putnam IPCs met doxycycline. Superioriteit van de IPCs werd in geen van deze drie eerdere studies aangetoond, noch inferioriteit. Wij zijn niet op de hoogte van studies die talkpleurodese of IPC met herhaalde thoracenteses vergelijken. Patiënten zijn over het algemeen zeer tevreden met een IPC. In een observationele studie werd aan patiënten gevraagd of ze opnieuw voor een IPC zouden kiezen, en ze een IPC aan anderen zouden aanbevelen. De meerderheid van de patiënten deed dat. Helaas werd dezelfde vraag niet gesteld voor talkpleurodese.

Ziekenhuisopname, re-interventies en complicaties

De mediane ziekenhuisopname voor talkpleurodese bedraagt 4-5 dagen. De opnameduur was significant korter patiënten voor IPC patiënten. Vijftien procent van de patiënten opgenomen voor talkpleurodese kregen uiteindelijk geen talk ingespoten. In ee drie RCTs over talkpleurodese en IPC samen kreeg 7% geen talk vanwege een trapped lung. In de TIME2 studie moest 16% van de talkpleurodese patiënten opnieuw worden opgenomen voor herhaalde drainages of complicaties van de eerdere behandeling. Demmy toonde aan dat 52% van de talkpleurodese patiënten 30 dagen nadien nog in leven waren zonder recidief. In onze studie had een-derde van de talkpleurodese patiënten tenminste één re-interventie nodig vergeleken met 7 van de 43 IPC patiënten. Dit was overigens niet significant verschillend. Gemiddeld werd 0.51 pleurale re-interventie verricht na elke talkpleurodese, en 0.37 na elke IPC. In een intention-to-treat analyse waren deze verschillen significant (0.5 vs 0.2). Bijwerkingen waren acceptabel voor beide behandelarmen.

Toekomstplannen

Thoracale verblijfsdrains hebben wereldwijd hun waarde bewezen in de behandeling van maligne pleuravocht, zowel als eerstelijnsbehandeling als na mislukte pleurodese. Uiteraard zijn er meer studies nodig om te onderzoeken welke patiënten het meeste profiteren van een IPC, en wat de beste timing is een IPC te plaatsen. Momenteel wordt in Australië en Azië het belang van drainageschema's onderzocht. Na een 1-op-1 randomisatie worden patiënten geïnstrueerd om agressief (meestal dagelijks) danwel op geleide van de klachten (wekelijks tot maandelijks) te draineren. In een andere (voor de patiënt geblindeerde) multicenter studie worden IPC patiënten gerandomiseerd tussen toediening van talk en fysiologische zout via de IPC. Primaire eindpunt van deze studie is een succesvolle pleurodese (gedefinieerd als drainage van hooguit 50 mL pleuravocht tijdens 3 opeenvolgende drainages, en opacificatie van de ipsilaterale thoraxhelft van minder dan 25%) 5 weken na randomisatie. In een pilot-studie werd gesuggereerd dat het combineren van talkpleurodese met een IPC wellicht de ziekenhuisopname en gebruik van IPC reduceert. In een retrospectieve case serie was een andere strategie beschreven: drie dagen na IPC-plaatsing werd echografisch longexpansie en resolutie van het pleuravocht geschat. Als de long ontplooid was, en het vocht verdwenen, werd talk toegediend en de patiënten geïnstrueerd dagelijks te draineren gedurende minimaal 3 dagen. In deze studie, oorspronkelijk gestart met 57 IPCs, werden uiteindelijk 22 van de 24 talkinstillaties omschreven als succesvol. In 33 patiënten werd wegens een trapped lung, en een PS>1 geen talk toegediend! Dit hoge aantal trapped lungs bevestigt weer eens de noodzaak aan om longontplooiing te kunnen voorspellen.

Permanente toegang

Permanente toegang tot de pleuraholte, met als doel het vermijden van herhaaldelijke invasieve ingrepen, wordt reeds jaren toegepast. Door middel van IPCs kunnen ook biochemische veranderingen in het pleuravocht voor langere tijd kan worden bestudeerd. Recent werd in een grote meta-analyse aangetoond dat intraperitoneale chemotherapie (middels een peritoneale verblijfsdrain) in ovariumcarcinoom tot overlevingswinst leidt. Eerder werd Hypertherme IntraThoracale Chemotherapie (HITHoC) onderzocht, en bleek geassocieerd met een hoge morbiditeit en mortaliteit. Intrapleurale toediening van antikanker middelen zou nogmaals moeten worden onderzocht. Zowel toediening van klassieke chemotherapie als targeted therapie via een IPC zou een meerwaarde kunnen hebben, aangezien de ingreep zelf minder invasief is.

Concluderend,

De levensverwachting van patiënten met maligne pleuravocht is voornamelijk afhankelijk van de primaire tumor en performance status. Er zijn geen curatieve mogelijkheden voor pleuraal gemetastaseerde maligniteiten, en behandeling richt zich dan ook op palliatie. Afgezien van chemosensitieve tumoren recidiveert pleuravocht vaak na drainage. Recidiefkans (of re-interventie binnen 30 dagen) kan worden voorspeld met behulp van patient reported outcomes na drainage. Verbetering van de kortademigheid is de belangrijkste factor in de beslissing omtrent nieuwe pleurale ingrepen. Vijf-en-veertig procent van de patiënten kreeg uiteindelijk een definitieve behandeling (talkpleurodese of IPC) voor het maligne pleuravocht ondergingen. Patiënten met bilateraal pleuravocht werden het vaakst behandeld met talkpleurodese of IPC. Het succes van talkpleurodese is sterk afhankelijk van longexpansie. Longartsen zijn het vaker oneens over longexpansie dan of er daadwerkelijk talk ingespoten moet worden. Pleurodese succes neemt toe naarmate de longartsen het eens zijn om daadwerkelijk talk toe te dienen. Oorspronkelijk werd een IPC geplaatst na een mislukte talkpleurodese, wat een effectieve behandeling bleek te zijn. In een RCT bleken IPCs en talkpleurodese even effectief als eerstelijnsbehandeling. Ziekenhuisopnames na IPC plaatsing zijn significant korter dan voor talkpleurodese, complicaties zeldzaam, en kosten acceptabel. Patiënten die in aanmerking komen voor een definitieve pleurale behandeling zouden dan ook moeten kunnen kiezen tussen talkpleurodese en een thoracale verblijfsdrain. Patiënten met een te verwachten korte overleving (bijvoorbeeld op basis van de LENT-score) zou een IPC kunnen worden aangeraden om relatief lange ziekenhuisopnames te voorkomen.

D

Dankwoord

"Es ist vollbracht!" Zonder hulp was het nooit gelukt om dit proefschrift af te ronden. Ongetwijfeld zal ik mensen vergeten te bedanken, hetgeen zeker niet persoonlijk is. De grootste dank ben ik verschuldigd aan de patiënten die vrijwel allemaal meewerkten om de kwaliteit-van-leven van patiënten na hen te verbeteren.

Vele patiënten lieten een onuitwisbare indruk achter. Zo onderging een patiënte op vijdagmiddag een ontlastende drainage, en was de week erna helaas al weer terug. Haar echtgenoot bedankte me meteen voor het weekend. Dit moest hij wel even aan me uitleggen: voor het eerst in weken had hij het aangedurfd even boodschappen te doen en zijn vrouw kort alleen te laten. Zijn vrouw was namelijk tijdelijk minder kortademig. Toen hij met de boodschappen thuiskwam, hoorde hij op de galerij harde muziek. Zijn vrouw danste op dat moment op de muziek van Willy Alberti. Ze vierde een feestje, en danste van geluk omdat ze weer lucht had. Ook de jonge vrouw die op vrijdagochtend een drainage onderging om die avond naar de balletvoorstelling van haar dochter te gaan, zal ik me altijd blijven herinneren.

Geachte professor Baas, beste Paul, één van onze belangrijkste momenten was het biertje in ''Gent aan de Schinkel''. Je vroeg me of ik niet liever naar Perth in plaats van San Diego zou willen gaan voor een paar maanden. Oorspronkelijke idee was namelijk dat ik in San Diego onderzoek naar circulerende tumorcellen zou doen. Ik begreep meteen dat je een fellowship bij professor Gary Lee voor ogen had, en dacht eerlijk gezegd dat het grootspraak was. Enkele dagen later al had ik een uitnodiging voor Australië. Mede door het verblijf in Australië is dit proefschrift uiteindelijk afgekomen. Enerzijds doordat ik geen klinische werkzaamheden kon verrichten, anderzijds door de contacten met toonaangevende onderzoeksgroepen, hetgeen leidde tot gezamenlijke publicaties in Chest en Thorax. Als ik in het ziekenhuis in Perth vertelde uit Amsterdam te komen, reageerde vrijwel iedereen met "Paul Baas" (en daarna pas met Johan Cruijff). Naast mijn opleiding tot longarts had ik weinig tijd voor het afronden van mijn promotie, maar het is uiteindelijk toch zover gekomen. Dank je voor je geduld.

Michel, je had een arts nodig voor je immunotherapiestudie, iets waar je 10 jaar geleden al heilig in geloofde. Daarnaast zou ik nog een paar kleine andere projecten zou kunnen doen. Via omwegen en zijpaden met circulerende tumorcellen belandde ik uiteindelijk bij maligne pleuravocht, wat mijn rode draad werd. Na mijn proefschrift zou ik de landelijke richtlijn moeten gaan aanpassen, en in zekere zin komt ook die voorspelling uit. Net als jouw voorspellingen over immunotherapie. Aangestoken door jouw nooit aflatende bereikbaarheid en verantwoordelijkheidsgevoel behandelde ik vele patiënten. Artikelen volgden eigenlijk pas tijdens het verblijf in Perth. Ook nu we niet meer in hetzelfde ziekenhuis werken, is het erg fijn om met jou een lastig oncologisch

probleem te bespreken. Hoewel je mijn mails aanzienlijk minder snel beantwoordt dan ik van je gewend was, kunnen er slechts weinig mensen aan die snelheid tippen. Het lijkt me gezellig om in de toekomst af en toe een biertje te blijven drinken. Ik denk dat je gelijk hebt dat jij de leukste baan hebt die je je kunt wensen!

Beste Sjaak, jij was het die mij als zaalarts mijn eerste drainage liet doen. Een patiënte met een KNO-tumor ontlastte ik van meer dan 2 liter pleuravocht. Na de drainage stelde ze zich voor; eerder was ze daar vanwege de kortademigheid niet toe in staat. Jouw droge humor, kennis, maar ook relativeringsvermogen maakt je tot een voorbeeld voor mij. Onopgemerkt ben je daarnaast ook erg kritisch. Het is voor mij dan ook een eer en leerzaam onder andere samen met jou de landelijke richtlijn voor behandeling van pleuravocht te mogen vernieuwen. Net als Paul en Michel heb je me altijd onvoorwaardelijk gesteund als ik ''aan het klussen'' was op de behandelkamer. Zodra ik iemand van jullie nodig had, waren jullie direct beschikbaar. Ik kan alleen maar hopen dat ik ook zo word.

Geachte promotiecommissie. Dank voor jullie aanwezigheid op mijn promotie. Jullie werden opgezadeld met een tijdsdruk, maar het is jullie wel gelukt om op tijd de benodigde formulieren in te vullen. Ik kijk er naar uit, en zie er tegelijkertijd tegen op, om fysiek tegenover jullie te staan. Dear professor Maskell, thanks for your willingness to come over for my PhD-ceremony. I'm really flattered that you, as one of the most important pleural researchers, assessed my thesis.

Dear Gary, Ed, and Rajesh, thanks for the wonderful time in Perth, and for all valuable advices you gave me then and later on. To be honest, I do respect your heaps of publications on pleural effusions (and I'm jealous of it too). I'm proud of having been a member of your Pleural Interest Group, and to review your results for journals like BMJ Open, Thorax and JAMA.

Beste Vincent, jij was begonnen in het AvL toen ik in Australië zat. Doordat ik bij terugkomst in Nederland niet meer in het AvL werkte, was afspreken lastig te plannen. Ik bewonder je geduld van de afgelopen jaren. Toen ik je voorafgaand aan de analyses van de NVALT14-studie een uitgebreide uitleg gaf over maligne pleuravocht, merkte je halverwege mijn ongetwijfeld te lange monoloog zeer terecht op: "maar dat is toch verschrikkelijk". Toen was voor mij duidelijk dat ik de ernst van het maligne pleuravocht goed had over weten te brengen. Het was fijn met iemand de statistiek door te nemen die zich de impact van maligne pleuravocht zo goed kon inbeelden, en daarnaast met mijn onmogelijke planningen kon omgaan..

Beste Michiel, het is al weer een paar jaar geleden dat we pleurale drukken maten. Ik denk dat jouw opslagruimte tijdens de testfase meerdere malen onder water is gelopen. Sorry nog daarvoor. Als een meting bij een patiënt dreigde te mislukken, was je binnen enkele seconden op de behandelkamer om hulp te bieden. De doktersjas die je in de haast wist aan te trekken, was werkelijk geen gezicht (had ik misschien eerder tegen je moeten zeggen). In jouw aanwezigheid zou ik bijna vergeten dat we met serieuze zaken bezig waren, zo vrolijk en opgewekt was je altijd. Dank voor je support, en enthousiasme.

Wieneke en Josine, jullie hebben mij veel patiënten laten draineren, en daardoor veel onderzoeken kunnen laten doen. De belofte dat ze dezelfde dag nog geholpen konden worden, heb ik gelukkig altijd na kunnen komen. Zo verschillend, maar ook zoveel overeenkomsten hebben jullie. Ik denk dat jullie even enthousiast kunnen vertellen over de voetballende kids als over mesotheliomen. Veel succes met jullie promoties! Wieneke, ik zie jou eigenlijk nog het meest: tot het eerstvolgende MDO in het OLVG. Ik kan veel leren van je nuchtere kijk op de oncologische problematiek, al moest ik in het begin wel wennen aan je directheid. Ook dank voor alle wijze adviezen!

Wilma, Suzanne en Erica, jullie zijn een hele belangrijke steun geweest in de behandeling en begeleiding van vele (studie)patiënten. Het was fijn met jullie te kunnen samenwerken. Dat Wilma van Pauls promovendi uiteindelijk als eerste zou promoveren, heeft me nooit verbaasd.

Marieke, jij was nooit te beroerd om de helpende hand te bieden. De logistiek van de immunotherapiestudie, honderden envelopes vullen: niets was jou te veel. Dank nog daarvoor.

Linda-Maria, opeens was jij daar op het secretariaat. Jouw opgewektheid maakt vele dagen goed. Bea, we hebben met name contact gehad via de mail, maar het was een geruststellende gedachte te weten dat er iemand orde in de chaos schept, en het overzicht bewaakt.

Het OBC van het AvL (met name Henk, Vera en Sophie) ben ik uiteraard ook veel dank verschuldigd. Jullie was nooit iets teveel, officieus had ik gewoon altijd een behandelkamer (met eigen opslagruimte) tot mijn beschikking. Helaas is het me niet gelukt om daar Mozart pianoconcerten te laten klinken, het enige minpuntje.

Peter Jordan, zonder jou en met name je vader was de NVALT14 studie minder soepel verlopen. Het overlijden van Alwin is een groot gemis, hij was oprecht en zeer begaan met het lot van de patiënten met maligne pleuravocht. Als ik wilde dat er ergens dezelfde dag materiaal werd bezorgd, werd dat altijd geregeld.

Alle longartsen die hebben meegeschreven aan de NVALT-14 studie: Jos Stigt, Jeroen Hiltermann, Judith Herder, Sayed Hashemi. Peter Kunst, ik ben heel blij dat ik van jou kan leren scopiëren. Ik denk dat weinig longartsen zo scopie-vaardig zijn als jij. Ik hoop dat je nog lang in het OLVG blijft werken.

Vicky Goldfinger, en Sheima Farag, zonder jullie was de pleurale drukken studie nooit mogelijk geweest. Dankzij jullie had ik altijd assistentie, en konden we veel drainages doen. Ook als er geen drukmetingen werden verricht, hielpen jullie mee. Heel veel dank nog daarvoor.

Longartsen OLVG, dank voor jullie begrip dat ik naast de opleiding ook mijn promotie wilde afronden. Uiteraard had ik ook niet gedacht dat het nog zó lang zou duren. Hopelijk zal binnen enkele maanden de richtlijn voor de behandeling van maligne pleuravocht worden aangepast. Vanaf dat moment zal hopelijk ook in het OLVG de IPC (vaker) worden gebruikt in de behandeling van recidiverend (maligne) pleuravocht. Tot die tijd heb ik veel respect voor jullie zelfbeheersing als ik de optie weer eens aandraag.

Berber, Brigitte, Coen, Hilde, Jan Willem, Josien, Laurens, Liesbeth, Marlise, Melanie, Sannemarije, Sylvia, (Bart, Eva, Joris, en uiteraard Pieter). Hierbij beloof ik plechtig dat ik na mijn promotie minder over thoraxdrains, verblijfskatheters en pleuravocht zal praten. Ik hoop dat jullie vrijdag na mijn promotie lekker komen drinken! Ik ben meestal degene die niet mee gaat borrelen op vrijdag, maar op 3-2-2017 ben ik zeker van de partij. Het is fijn onderdeel te zijn van een groep die elkaar alles gunt. Fijnere collega's kan ik me niet wensen.

Mijn paranimfen Paul en Geertje, heel fijn dat jullie aan mijn zijde wilden staan tijdens deze dag. Van oorsprong waren de paranimfen de stand-in van de promovendus. Gelukkig voor ons drie is dat niet meer zo, al zou ik jullie blind vertrouwen! Jullie hebben gelukkig nooit iets te maken gehad met maligne pleuravocht. Als dit achter de rug is, gaan we gezellig naar het concertgebouw!

Jan-Willem, vaak kon ik nog een artikel naar jou sturen, wat jij dan niet alleen inhoudelijk, maar ook op Engels "nakeek". Hoewel dat altijd erg handig is (geweest), zou ik het veel gezelliger hebben gevonden als je niet zover weg was gaan wonen. Sil, nu gaat het er toch op lijken dat we allebei gepromoveerd zijn. Tijd voor bier en wijn!

Pa, aan jouw onvoorwaardelijke trouwe zorg voor ma kan ik alleen maar een voorbeeld nemen. Het geeft veel rust te weten dat er met veel liefde voor haar wordt gezorgd! Bedankt! Ma, vergeet nooit hoeveel ik van je hou! Gabrielle, John, Michiel, Stephan en Arjan: hier ben ik dus lange tijd mee bezig geweest. Robert en Marijke: een goede buur

zou beter zijn dan een verre vriend, maar de opa en oma van mijn kinderen als overbuur overtreft alles! Ik kan mij geen betere schoonouders wensen.

Lieve Marjolein, allerliefste, soms denk ik dat het proefschrift wel eerder af was geweest als ik jou nooit had ontmoet, maar waarschijnlijk was het helemaal nooit afgekomen. Dank voor je geduld. Ik houd ontzettend veel van je, en kijk er ook naar uit meer tijd met jou en onze lieve kinderen door te brengen! Het is mijn droom om met zijn allen nog een keer terug te gaan naar Australië. Olivier en Philine, geen enkel woord kan mijn liefde voor jullie omschrijven. Een kus voor jullie, een hele grote!

C

Curriculum vitae / List of publications

Curriculum Vitae

Rogier Boshuizen werd op 19 juli 1978 in Delft geboren. Na zijn Gymnasium diploma aan het sint Stanislascollege (1997), begon hij in 2000 met de studie Geneeskunde aan de Universiteit van Amsterdam. Naast zijn studie speelde hij viool in vele studentenorkesten. Zijn oudste co-schap liep hij in het Antoni van Leeuwenhoek ziekenhuis, waar hij direct na zijn afstuderen in 2007 als arts-assistent begon. In het najaar van 2009 begon hij aan zijn promotie-onderzoek op de afdeling thoraxoncologie onder leiding van Michel van den Heuvel (en Paul Baas). Het onderwerp van dit promotietraject eindigde via immunotherapie en circulerende tumorcellen uiteindelijk in de behandeling van maligne pleuravocht. Als onderdeel van dit promotietraject deed hij In 2012 een fellowship ''pleural diseases'' bij professor Gary Lee in Perth, Australië. Bij terugkomst in Nederland werkte hij als ANIOS ouderengeneeskunde in verpleeghuis de Bolder (Huizen) tot hij in mei 2013 met zijn vooropleiding interne geneeskunde in het Onze Lieve Vrouwe Gasthuis begon. In mei 2015 startte hij met zijn opleiding tot longarts (opleider: Jaring van der Zee/ Paul Bresser). Sinds najaar 2016 maakt hij deel uit van de NVALT-commissie die de landelijke richtlijn voor behandeling van pleuravocht zal herzien.

List of Publications

2012

Fuid biopsy for circulating tumor cell identification in patients with early- and late-stage non-small cell lung cancer: a glimpse into lung cancer biology
Wendel M; Bazhenova L; ***Boshuizen R****; Kolatkar A; Honatti M; Cho EH; Marrinucci D; Sandhu A; Perricone A; Thistlewaite P; Bethel K; Nieva J; Heuvel Mv; Kuhn P*
Physical Biology (2012 Feb;9(1):016005

Kortademigheid en hoestkachten na radiofrequente ablatie van levermetastasen
RC Boshuizen*; APE Besnard; H Boot; MM van den Heuvel*
Nederlands Tijdschrift voor Oncologie (2012;9:77-80)

Circulating Tumor Cells in non-small cell lung carcinoma
Boshuizen R*; Kuhn P; van den Heuvel M*
Journal of Thoracic Disease (2012 Oct;4(5):456-8

2013

Talc instillation consensus aids differentiating successful from unsuccessful pleurodesis: a survey on the interpretation of pleural approximation after chest tube insertion
Boshuizen RC*; Vincent AD; Kunst PW; Burgers JA; van den Heuvel MM*
Respiration 2013;85(1):85-6

Advantages of indwelling pleural catheters for management of malignant pleural effusions
Rogier C Boshuizen*; Rajesh Thomas; YC Gary Lee*
Curr Respir Care Rep (2013) 2:93–99

Pleural pressure swing and lung expansion after malignant pleural effusion drainage; the benefits of high resolution pleural manometry
Boshuizen RC*; Sinaasappel M; Goldfinger V; Vincent AD; Farag S; van den Heuvel MM*
J Bronchology Interv Pulmonol. 2013 Jul;20(3):200-5

The use of Indwelling Pleural Catheters for the management of Malignant Pleural Effusion; direct costs in a Dutch hospital
Boshuizen R*; Onderwater S; Burgers SJ; van den Heuvel MM*
Respiration. 2013;86(3):224-8

Comparison of Modified Borg Scale and Visual Analogue Dyspnea Scores in predicting re-intervention after drainage of Malignant Pleural Effusion; An observational study on Patient Reported Outcomes
Boshuizen RC*; Vincent AD; van den Heuvel MM*
Support Care Cancer. 2013 Nov;21(11):3109-16

Clinical outcomes of Indwelling Pleural Catheter-Related Pleural Infections: an international multicenter study
Fysh, ET; Tremblay, A; Feller-Kopman, D; Mishra, EK; Slade, M; Garske, L; Clive, AO; Lamb, C; ***Boshuizen, R****; Ng, BJ; Rosenstengel, AW; Yarmus, L; Rahman, NM; Maskell, NA; Lee, YC*
Chest. 2013 Nov;144(5):1597-602

2014

Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score
Clive AO; Kahan BC; Hooper CE; Bhatnagar R; Morley AJ; Zahan-Evans N; Bintcliffe OJ; ***Boshuizen RC;*** *Fysh ET; Tobin CL; Medford AR; Harvey JE; van den Heuvel MM; Lee YC; Maskell NA*
Thorax. 2014 Dec;69(12):1098-104

2015

NHS-IL2 combined with radiotherapy: preclinical rationale and phase Ib trial results in metastatic non-small cell lung cancer following first-line chemotherapy.
van den Heuvel MM, Verheij M, ***Boshuizen R****, Belderbos J, Dingemans AM, De Ruysscher D, Laurent J, Tighe R, Haanen J, Quaratino S.*
J. Translational Med. 2015 Jan 27;13:32

Comments on Predictors of Clinical Use of Pleurodesis and/or Indwelling Pleural Catheter Therapy for Malignant Pleural Effusion
Boshuizen RC*, Burgers JA, van den Heuvel MM*
Chest. 2015 Jun; 147(6):e232

2016

Tumorlysissyndroom bij kleincellig longcarcinoom
Boshuizen RC, *Smit AA, Moons-Pasic A, Bresser P*
Nederlands Tijdschrift voor de Geneeskunde 2016: 160(0);A9823

R

References

1 Light RW, Lee YC. Textbook of Pleural Diseases. 2 ed. 2008; 45.

2 Villena G, V, Ferrer SJ, Hernandez BL et al. Diagnosis and treatment of pleural effusion. Arch Bronconeumol 2006; 42(7):349-372.

3 Light RW, MacGregor MI, Luchsinger PC et al. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med 1972; 77(4):507-513.

4 Johnston WW. The malignant pleural effusion. A review of cytopathologic diagnoses of 584 specimens from 472 consecutive patients. Cancer 1985; 56(4):905-909.

5 Assi Z, Caruso JL, Herndon J et al. Cytologically proved malignant pleural effusions: distribution of transudates and exudates. Chest 1998; 113(5):1302-1304.

6 Ryu JS, Ryu ST, Kim YS et al. What is the clinical significance of transudative malignant pleural effusion? Korean J Intern Med 2003; 18(4):230-233.

7 Thomas JM, Musani AI. Malignant pleural effusions: a review. Clin Chest Med 2013; 34(3):459-471.

8 Bhattacharya S, Bairagya TD, Das A et al. Closed pleural biopsy is still useful in the evaluation of malignant pleural effusion. J Lab Physicians 2012; 4(1):35-38.

9 Bielsa S, Panades MJ, Egido R et al. Accuracy of pleural fluid cytology in malignant effusions. An Med Interna 2008; 25(4):173-177.

10 Abouzgheib W, Bartter T, Dagher H et al. A prospective study of the volume of pleural fluid required for accurate diagnosis of malignant pleural effusion. Chest 2009; 135(4):999-1001.

11 Swiderek J, Morcos S, Donthireddy V et al. Prospective study to determine the volume of pleural fluid required to diagnose malignancy. Chest 2010; 137(1):68-73.

12 Thomas SC, Davidson LR, McKean ME. An investigation of adequate volume for the diagnosis of malignancy in pleural fluids. Cytopathology 2011; 22(3):179-183.

13 Rakha EA, Patil S, Abdulla K et al. The sensitivity of cytologic evaluation of pleural fluid in the diagnosis of malignant mesothelioma. Diagn Cytopathol 2010; 38(12):874-879.

14 Rodriguez-Panadero F, Borderas NF, Lopez MJ. Pleural metastatic tumours and effusions. Frequency and pathogenic mechanisms in a post-mortem series. Eur Respir J 1989; 2(4):366-369.

15 Roberts ME, Neville E, Berrisford RG et al. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. Thorax 2010; 65 Suppl 2:ii32-ii40.

16 Alkhawaldeh K, Biersack HJ, Henke A et al. Impact of dual-time-point F-18 FDG PET/CT in the assessment of pleural effusion in patients with non-small-cell lung cancer. Clin Nucl Med 2011; 36(6):423-428.

17 Gupta NC, Rogers JS, Graeber GM et al. Clinical role of F-18 fluorodeoxyglucose positron emission tomography imaging in patients with lung cancer and suspected malignant pleural effusion. Chest 2002; 122(6):1918-1924.

18 Diacon AH, Brutsche MH, Soler M. Accuracy of pleural puncture sites: a prospective comparison of clinical examination with ultrasound. Chest 2003; 123(2):436-441.

19 Gordon CE, Feller-Kopman D, Balk EM et al. Pneumothorax following thoracentesis: a systematic review and meta-analysis. Arch Intern Med 2010; 170(4):332-339.

20 Qureshi NR, Rahman NM, Gleeson FV. Thoracic ultrasound in the diagnosis of malignant pleural effusion. Thorax 2009; 64(2):139-143.

21 Rahman NM, Singanayagam A, Davies HE et al. Diagnostic accuracy, safety and utilisation of respiratory physician-delivered thoracic ultrasound. Thorax 2010; 65(5):449-453.

22 Morgensztern D, Waqar S, Subramanian J et al. Prognostic impact of malignant pleural effusion at presentation in patients with metastatic non-small-cell lung cancer. J Thorac Oncol 2012; 7(10):1485-1489.

23 Wu SG, Yu CJ, Tsai MF et al. Survival of lung adenocarcinoma patients with malignant pleural effusion. Eur Respir J 2012.

24 Dresler CM, Olak J, Herndon JE et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. Chest 2005; 127(3):909-915.

25 Trapnell DH, Thurston JG. Unilateral pulmonary oedema after pleural aspiration. Lancet 1970; 1(7661):1367-1369.

26 Feller-Kopman D, Berkowitz D, Boiselle P et al. Large-volume thoracentesis and the risk of reexpansion pulmonary edema. Ann Thorac Surg 2007; 84(5):1656-1661.

27 Woodring JH. Focal reexpansion pulmonary edema after drainage of large pleural effusions: clinical evidence suggesting hypoxic injury to the lung as the cause of edema. South Med J 1997; 90(12):1176-1182.

28 Lan RS, Lo SK, Chuang ML et al. Elastance of the pleural space: a predictor for the outcome of pleurodesis in patients with malignant pleural effusion. Ann Intern Med 1997; 126(10):768-774.

29 Burgers JA, Kunst PW, Koolen MG et al. Pleural drainage and pleurodesis: implementation of guidelines in four hospitals. Eur Respir J 2008; 32(5):1321-1327.

30 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; 86(10):1992-1999.

31 Putnam JB, Jr., Walsh GL, Swisher SG et al. Outpatient management of malignant pleural effusion by a chronic indwelling pleural catheter. Ann Thorac Surg 2000; 69(2):369-375.

32 Bielsa S, Hernandez P, Rodriguez-Panadero F et al. Tumor type influences the effectiveness of pleurodesis in malignant effusions. Lung 2011; 189(2):151-155.

33 Heffner JE, Nietert PJ, Barbieri C. Pleural fluid pH as a predictor of pleurodesis failure: analysis of primary data. Chest 2000; 117(1):87-95.

34 Hirata T, Yonemori K, Hirakawa A et al. Efficacy of pleurodesis for malignant pleural effusions in breast cancer patients. Eur Respir J 2011; 38(6):1425-1430.

35 Burgers JA, Olijve A, Baas P. Chronic indwelling pleural catheter for malignant pleural effusion in 25 patients. Ned Tijdschr Geneeskd 2006; 150(29):1618-1623.

36 Ohm C, Park D, Vogen M et al. Use of an indwelling pleural catheter compared with thorascopic talc pleurodesis in the management of malignant pleural effusions. Am Surg 2003; 69(3):198-202.

37 Pien GW, Gant MJ, Washam CL et al. Use of an implantable pleural catheter for trapped lung syndrome in patients with malignant pleural effusion. Chest 2001; 119(6):1641-1646.

38 Bethune N. Pleural poudrage: new technique for deliberate production of pleural adhesions as preliminary to lobectomy. J Thorac Cardiovasc Surg 1935; 1935(4):251-261.

39 Brant A, Eaton T. Serious complications with talc slurry pleurodesis. Respirology 2001; 6(3):181-185.

40 Lee YC, Light RW. Management of malignant pleural effusions. Respirology 2004; 9(2):148-156.

41 Brims FJ, Davies HE, Lee YC. Respiratory chest pain: diagnosis and treatment. Med Clin North Am 2010; 94(2):217-232.

42 Ong KC, Indumathi V, Raghuram J et al. A comparative study of pleurodesis using talc slurry and bleomycin in the management of malignant pleural effusions. Respirology 2000; 5(2):99-103.

43 Boshuizen RC, Vincent AD, Kunst PW et al. Talc instillation consensus aids differentiating successful from unsuccessful pleurodesis: a survey on the interpretation of pleural approximation after chest tube placement. Respiration 2013; 85(1):85-86.

44 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; 307(22):2383-2389.

45 Fysh ET, Waterer GW, Kendall PA et al. Indwelling pleural catheters reduce inpatient days over pleurodesis for malignant pleural effusion. Chest 2012; 142(2):394-400.

46 Suzuki K, Servais EL, Rizk NP et al. Palliation and pleurodesis in malignant pleural effusion: the role for tunneled pleural catheters. J Thorac Oncol 2011; 6(4):762-767.

47 Lee YC, Fysh ET. Indwelling pleural catheter: changing the paradigm of malignant effusion management. J Thorac Oncol 2011; 6(4):655-657.

48 Demmy TL, Gu L, Burkhalter JE et al. Optimal management of malignant pleural effusions (results of CALGB 30102). J Natl Compr Canc Netw 2012; 10(8):975-982.

49 Musani AI, Haas AR, Seijo L et al. Outpatient management of malignant pleural effusions with small-bore, tunneled pleural catheters. Respiration 2004; 71(6):559-566.

50 Qureshi RA, Collinson SL, Powell RJ et al. Management of malignant pleural effusion associated with trapped lung syndrome. Asian Cardiovasc Thorac Ann 2008; 16(2):120-123.

51 Sioris T, Sihvo E, Salo J et al. Long-term indwelling pleural catheter (PleurX) for malignant pleural effusion unsuitable for talc pleurodesis. Eur J Surg Oncol 2009; 35(5):546-551.

52 Stather DR, Tremblay A. Use of tunneled pleural catheters for outpatient treatment of malignant pleural effusions. Curr Opin Pulm Med 2007; 13(4):328-333.

53 Bertolaccini L, Zamprogna C, Barberis L et al. Malignant pleural effusions: review of treatment and our experience. Rev Recent Clin Trials 2007; 2(1):21-25.

54 Cases E, Seijo L, Disdier C et al. Use of indwelling pleural catheter in the outpatient management of recurrent malignant pleural effusion. Arch Bronconeumol 2009; 45(12):591-596.

55 Hunt BM, Farivar AS, Vallieres E et al. Thoracoscopic talc versus tunneled pleural catheters for palliation of malignant pleural effusions. Ann Thorac Surg 2012; 94(4):1053-1057.

56 Reddy C, Ernst A, Lamb C et al. Rapid pleurodesis for malignant pleural effusions: a pilot study. Chest 2011; 139(6):1419-1423.

57 Warren WH, Kalimi R, Khodadadian LM et al. Management of malignant pleural effusions using the Pleur(x) catheter. Ann Thorac Surg 2008; 85(3):1049-1055.

58 Tremblay A, Michaud G. Single-center experience with 250 tunnelled pleural catheter insertions for malignant pleural effusion. Chest 2006; 129(2):362-368.

59 Tremblay A, Mason C, Michaud G. Use of tunnelled catheters for malignant pleural effusions in patients fit for pleurodesis. Eur Respir J 2007; 30(4):759-762.

60 Sabur NF, Chee A, Stather DR et al. The impact of tunneled pleural catheters on the quality of life of patients with malignant pleural effusions. Respiration 2013; 85(1):36-42.

61 Wrightson JM, Fysh E, Maskell NA et al. Risk reduction in pleural procedures: sonography, simulation and supervision. Curr Opin Pulm Med 2010; 16(4):340-350.

62 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; 66(5):448-449.

63 Bazerbashi S, Villaquiran J, Awan MY et al. Ambulatory intercostal drainage for the management of malignant pleural effusion: a single center experience. Ann Surg Oncol 2009; 16(12):3482-3487.

64 Bertolaccini L, Viti A, Gorla A et al. Home-management of malignant pleural effusion with an indwelling pleural catheter: ten years experience. Eur J Surg Oncol 2012; 38(12):1161-1164.

65 Janes SM, Rahman NM, Davies RJ et al. Catheter-tract metastases associated with chronic indwelling pleural catheters. Chest 2007; 131(4):1232-1234.

66 van den Toorn LM, Schaap E, Surmont VF et al. Management of recurrent malignant pleural effusions with a chronic indwelling pleural catheter. Lung Cancer 2005; 50(1):123-127.

67 Davies HE, Musk AW, Lee YC. Prophylactic radiotherapy for pleural puncture sites in mesothelioma: the controversy continues. Curr Opin Pulm Med 2008; 14(4):326-330.

68 Bower C, Mahmood K. Re: Noninvasive repair of broken tunneled pleural catheters. J Vasc Interv Radiol 2011; 22(2):255-256.

69 Fysh ET, Wrightson JM, Lee YC et al. Fractured indwelling pleural catheters. Chest 2012; 141(4):1090-1094.

70 Puri V, Pyrdeck TL, Crabtree TD et al. Treatment of malignant pleural effusion: a cost-effectiveness analysis. Ann Thorac Surg 2012; 94(2):374-379.

71 Olden AM, Holloway R. Treatment of malignant pleural effusion: PleurX catheter or talc pleurodesis? A cost-effectiveness analysis. J Palliat Med 2010; 13(1):59-65.

72 van den Berg M, Hamberg-van Reenen HH, Schoemaker CG. Cost-effectiveness: euros per QALY is not enough. Ned Tijdschr Geneeskd 2012; 156(5):A3817.

73 Al-Halfawy A, Light R. Safety and efficacy of using a surgivac pump for the drainage of chronic indwelling pleural catheters in malignant pleural effusions. Respirology 2008; 13(3):461-464.

74 Chen H, Brahmer J. Management of malignant pleural effusion. Curr Oncol Rep 2008; 10(4):287-293.

75 Haddad FJ, Younes RN, Gross JL et al. Pleurodesis in patients with malignant pleural effusions: talc slurry or bleomycin? Results of a prospective randomized trial. World J Surg 2004; 28(8):749-753.

76 Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database Syst Rev 2004;(1):CD002916.

77 Goodman A, Davies CW. Efficacy of short-term versus long-term chest tube drainage following talc slurry pleurodesis in patients with malignant pleural effusions: a randomised trial. Lung Cancer 2006; 54(1):51-55.

78 Financial Statistics. 2013.

79 Pollak JS. Malignant pleural effusions: treatment with tunneled long-term drainage catheters. Curr Opin Pulm Med 2002; 8(4):302-307.

80 Lee C, Bayman N, Swindell R et al. Prophylactic radiotherapy to intervention sites in mesothelioma: a systematic review and survey of UK practice. Lung Cancer 2009; 66(2):150-156.

81 Burgers JA, Schlósser NJJ, Aertz JGVV et al. Mesothelioma: diagnostics and treatment (dutch guideline). 2011.

82 Rodriguez-Panadero F. Malignant pleural diseases. Monaldi Arch Chest Dis 2000; 55(1):17-19.

83 Erasmus JJ, Patz EF, Jr. Treatment of malignant pleural effusions. Curr Opin Pulm Med 1999; 5(4):250-255.

84 Boshuizen RC, Vincent AD, van den Heuvel MM. Comparison of modified Borg scale and visual analog scale dyspnea scores in predicting re-intervention after drainage of malignant pleural effusion. Support Care Cancer 2013; 21(11):3109-3116.

85 Clive AO, Kahan BC, Hooper CE et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. Thorax 2014; 69(12):1098-1104.

86 Boshuizen RC, Onderwater S, Burgers SJ et al. The use of indwelling pleural catheters for the management of malignant pleural effusion--direct costs in a Dutch hospital. Respiration 2013; 86(3):224-228.

87 Penz ED, Mishra EK, Davies HE et al. Comparing cost of indwelling pleural catheter vs talc pleurodesis for malignant pleural effusion. Chest 2014; 146(4):991-1000.

88 Shafiq M, Frick KD, Lee H et al. Management of Malignant Pleural Effusion: A Cost-Utility Analysis. J Bronchology Interv Pulmonol 2015; 22(3):215-225.

89 Fysh ET, Thomas R, Read CA et al. Protocol of the Australasian Malignant Pleural Effusion (AMPLE) trial: a multicentre randomised study comparing indwelling pleural catheter versus talc pleurodesis. BMJ Open 2014; 4(11):e006757.

90 Fysh ET, Thomas R, Read CA. Correction. Protocol of the Australasian Malignant Pleural Effusion (AMPLE) trial: a multicentre randomised study comparing indwelling pleural catheter versus talc pleurodesis. BMJ Open 2015; 5(5):e006757corr1.

91 Azzopardi M, Thomas R, Muruganandan S et al. Protocol of the Australasian Malignant Pleural Effusion-2 (AMPLE-2) trial: a multicentre randomised study of aggressive versus symptom-guided drainage via indwelling pleural catheters. BMJ Open 2016; 6(7):e011480.

92 Chernow B, Sahn SA. Carcinomatous involvement of the pleura: an analysis of 96 patients. Am J Med 1977; 63(5):695-702.

93 Burrows CM, Mathews WC, Colt HG. Predicting survival in patients with recurrent symptomatic malignant pleural effusions: an assessment of the prognostic values of physiologic, morphologic, and quality of life measures of extent of disease. Chest 2000; 117(1):73-78.

94 Aydogmus U, Ozdemir S, Cansever L et al. Bedside talc pleurodesis for malignant pleural effusion: factors affecting success. Ann Surg Oncol 2009; 16(3):745-750.

95 Light RW, Jenkinson SG, Minh VD et al. Observations on pleural fluid pressures as fluid is withdrawn during thoracentesis. Am Rev Respir Dis 1980; 121(5):799-804.

96 Feller-Kopman D, Walkey A, Berkowitz D et al. The relationship of pleural pressure to symptom development during therapeutic thoracentesis. Chest 2006; 129(6):1556-1560.

97 Antunes G, Neville E, Duffy J et al. BTS guidelines for the management of malignant pleural effusions. Thorax 2003; 58 Suppl 2:ii29-ii38.

98 Doelken P, Huggins JT, Pastis NJ et al. Pleural manometry: technique and clinical implications. Chest 2004; 126(6):1764-1769.

99 Abunasser J, Brown R. Safety of large-volume thoracentesis. Conn Med 2010; 74(1):23-26.

100 Jones PW, Moyers JP, Rogers JT et al. Ultrasound-guided thoracentesis: is it a safer method? Chest 2003; 123(2):418-423.

101 Rathinam S, Bradley A, Cantlin T et al. Thopaz portable suction systems in thoracic surgery: an end user assessment and feedback in a tertiary unit. J Cardiothorac Surg 2011; 6:59.

102 Feller-Kopman D, Parker MJ, Schwartzstein RM. Assessment of pleural pressure in the evaluation of pleural effusions. Chest 2009; 135(1):201-209.

103 Villena V, Lopez-Encuentra A, Pozo F et al. Measurement of pleural pressure during therapeutic thoracentesis. Am J Respir Crit Care Med 2000; 162(4 Pt 1):1534-1538.

104 Feller-Kopman D. Therapeutic thoracentesis: the role of ultrasound and pleural manometry. Curr Opin Pulm Med 2007; 13(4):312-318.

105 Shumway NM, Wilson RL, Howard RS et al. Presence and treatment of air hunger in severely ill patients. Respir Med 2008; 102(1):27-31.

106 Hareendran A, Leidy NK, Monz BU et al. Proposing a standardized method for evaluating patient report of the intensity of dyspnea during exercise testing in COPD. Int J Chron Obstruct Pulmon Dis 2012; 7:345-355.

107 Martinez JA, Straccia L, Sobrani E et al. Dyspnea scales in the assessment of illiterate patients with chronic obstructive pulmonary disease. Am J Med Sci 2000; 320(4):240-243.

108 Bausewein C, Booth S, Higginson IJ. Measurement of dyspnoea in the clinical rather than the research setting. Curr Opin Support Palliat Care 2008; 2(2):95-99.

109 Marcondes BF, Vargas F, Paschoal FH et al. Sleep in patients with large pleural effusion: impact of thoracentesis. Sleep Breath 2012; 16(2):483-489.

110 Cartaxo AM, Vargas FS, Salge JM et al. Improvements in the 6-min walk test and spirometry following thoracentesis for symptomatic pleural effusions. Chest 2011; 139(6):1424-1429.

111 Wilson RC, Jones PW. A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnoea during exercise. Clin Sci (Lond) 1989; 76(3):277-282.

112 Barbera L, Taylor C, Dudgeon D. Why do patients with cancer visit the emergency department near the end of life? CMAJ 2010; 182(6):563-568.

113 Wallace EM, Cooney MC, Walsh J et al. Why do palliative care patients present to the emergency department? Avoidable or unavoidable? Am J Hosp Palliat Care 2013; 30(3):253-256.

114 Morris NR, Sabapathy S, Adams L et al. Verbal numerical scales are as reliable and sensitive as visual analog scales for rating dyspnea in young and older subjects. Respir Physiol Neurobiol 2007; 157(2-3):360-365.

115 von LA, Dahme B. Differentiation between the sensory and affective dimension of dyspnea during resistive load breathing in normal subjects. Chest 2005; 128(5):3345-3349.

116 von LA, Ambruzsova R, Nordmeyer S et al. Sensory and affective aspects of dyspnea contribute differentially to the Borg scale's measurement of dyspnea. Respiration 2006; 73(6):762-768.

117 Fysh ET, Bielsa S, Budgeon CA et al. Predictors of clinical use of pleurodesis and/or indwelling pleural catheter therapy for malignant pleural effusion. Chest 2015; 147(6):1629-1634.

118 Zamboni MM, da Silva CTJ, Baretta R et al. Important prognostic factors for survival in patients with malignant pleural effusion. BMC Pulm Med 2015; 15:29.

119 Abrao FC, de Abreu IR, Fogarolli M et al. Prognostic Factors of 30-Day Mortality After Palliative Procedures in Patients with Malignant Pleural Effusion. Ann Surg Oncol 2015; 22(12):4083-4088.

120 Abrao FC, Peixoto RD, de Abreu IR et al. Prognostic factors in patients with malignant pleural effusion: Is it possible to predict mortality in patients with good performance status? J Surg Oncol 2016; 113(5):570-574.

121 Boshuizen RC, Burgers JA, van den Heuvel MM. Comments on predictors of clinical use of pleurodesis and/or indwelling pleural catheter therapy for malignant pleural effusion. Chest 2015; 147(6):e232.

122 Groen HJM, Welling A, Postmus PE et al. Diagnostics and treatment of MPE (dutch guideline). 2003.

123 Janssen JP, Collier G, Astoul P et al. Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study. Lancet 2007; 369(9572):1535-1539.

124 Mehta D, Gupta A, Singhal S et al. Indwelling pleural drain for mobile management of malignant pleural effusion-combining benefits of both methods. Lung India 2015; 32(1):64-66.

125 Boshuizen RC, Thomas R, Lee YC. Advantages of indwelling pleural catheters for management of malignant pleural effusion. Curr Respir Care Rep. 2013: 93-99.

126 Fysh ET, Tremblay A, Feller-Kopman D et al. Clinical outcomes of indwelling pleural catheter-related pleural infections: an international multicenter study. Chest 2013; 144(5):1597-1602.

127 Bhatnagar R, Kahan BC, Morley AJ et al. The efficacy of indwelling pleural catheter placement versus placement plus talc sclerosant in patients with malignant pleural effusions managed exclusively as outpatients (IPC-PLUS): study protocol for a randomised controlled trial. Trials 2015; 16:48.

128 Ahmed L, Ip H, Rao D et al. Talc pleurodesis through indwelling pleural catheters for malignant pleural effusions: retrospective case series of a novel clinical pathway. Chest 2014; 146(6):e190-e194.

129 Bibby AC, Clive AO, Slade GC et al. Survival in Patients With Malignant Pleural Effusions Who Developed Pleural Infection: A Retrospective Case Review From Six UK Centers. Chest 2015; 148(1):235-241.

130 Tobin CL, Thomas R, Chai SM et al. Histopathology of removed indwelling pleural catheters from patients with malignant pleural diseases. Respirology 2016; 21(5):939-942.

131 Palmen C. Logboek van een onbarmhartig jaar. 2011

132 Abouzgheib W, Bartter T, Dagher H et al. A prospective study of the volume of pleural fluid required for accurate diagnosis of malignant pleural effusion. Chest 2009; 135(4):999-1001.

133 Hussain SA, Burton GM, Yuce M. Symptomatic loculated malignant pleural effusion treatment with indwelling Tenckhoff catheter. Chest 1990; 97(3):766-767.

134 Leff RS, Eisenberg B, Baisden CE et al. Drainage of recurrent pleural effusion via an implanted port and intrapleural catheter. Ann Intern Med 1986; 104(2):208-209.

135 Mitnick HJ, Tunick P, Boyd A et al. Subcutaneous thoracentesis utilizing an Ommaya reservoir in amyloid cardiomyopathy. JAMA 1986; 255(9):1170-1171.

136 Thomas R, Cheah HM, Creaney J et al. Longitudinal Measurement of Pleural Fluid Biochemistry and Cytokines in Malignant Pleural Effusions. Chest 2016; 149(6):1494-1500.

137 Jaaback K, Johnson N, Lawrie TA. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database Syst Rev 2016;(1):CD005340.

138 van Sandick JW, Kappers I, Baas P et al. Surgical treatment in the management of malignant pleural mesothelioma: a single institution's experience. Ann Surg Oncol 2008; 15(6):1757-1764.

139 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. J Thorac Oncol 2010; 5(1):75-81.

140 Lombardi G, Nicoletto MO, Gusella M et al. Intrapleural paclitaxel for malignant pleural effusion from ovarian and breast cancer: a phase II study with pharmacokinetic analysis. Cancer Chemother Pharmacol 2012; 69(3):781-787.

141 Shoji T, Tanaka F, Yanagihara K et al. Phase II study of repeated intrapleural chemotherapy using implantable access system for management of malignant pleural effusion. Chest 2002; 121(3):821-824.

142 Tohda Y, Iwanaga T, Takada M et al. Intrapleural administration of cisplatin and etoposide to treat malignant pleural effusions in patients with non-small cell lung cancer. Chemotherapy 1999; 45(3):197-204.