

Comparison of Indwelling Pleural Catheters and Chemical Pleurodesis Through Tube Thoracostomy for the Management of Malignant Pleural Effusions.

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Abstract

BACKGROUND: Malignant and paramalignant pleural effusions are important complications of many malignancies. The two main management options debated in the literature are: 1) insertion of an indwelling pleural catheter (IPC) to achieve chronic drainage of the effusion, or 2) hospitalization with tube thoracostomy and subsequent chemical pleurodesis (CP) with talc or doxycycline to prevent fluid reaccumulation. We aimed to describe a large series of patients with malignant pleural effusions managed with an IPC, identify and validate factors identified in the literature as predictors of spontaneous pleurodesis in the IPC group and compare the group managed with IPC to patients managed with CP.

METHODS: We designed a retrospective cohort study comparing patients with malignant and paramalignant pleural effusions managed either with CP between March 1, 2003 and February 28, 2006 or IPC insertion between May 1, 2006 and April 1, 2009. The CP group was identified through the prescription of talc or doxycycline and the IPC group from the IPC clinic database. Data were collected from paper and electronic records and from the Government of Ontario.

RESULTS: We identified 193 consecutive patients with an ECOG performance status of less than 4 (ECOG less than 4 means that the patient is not completely disabled and confined to bed or chair) having undergone IPC insertion and 168 who were managed with CP. None of the variables we tested were significant predictors of spontaneous pleurodesis in the IPC group. Pleural effusion control rates at 6 months were higher in the IPC group than in the CP

group (52.7% vs 34.0%, $p<0.01$) but the rate of freedom from pleural effusion at 180 days and catheter removal at 90 days was not significantly different (25.8% in the IPC group and 34.0% in the CP group $p=0.14$). Patients in the IPC group had a significantly longer median survival (148 days measured from the date of catheter insertion vs 133 days in the CP group, log-rank $p<0.05$).

CONCLUSION: We found an intriguing possible survival benefit favouring management of malignant or paramalignant effusions with an IPC. Given possible biases due to the design of this study and uncertain explanatory mechanism, this needs to be confirmed in a randomized controlled trial. Quality of life, an important measure of success for these palliative procedures, should also be measured.

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Introduction

Malignant pleural effusions are important complications of many malignancies. Dyspnea is present in 50% of patients and quality of life is significantly impaired. Most importantly, the presence of a malignant pleural effusion is a marker for poor survival. There are a few options for management. Hospitalization with tube thoracostomy and subsequent chemical pleurodesis (CP) with talc or doxycycline to prevent fluid reaccumulation is one of the most commonly employed strategies. However, this strategy requires hospitalization and the sclerosing agent which seems to have the highest efficacy may be associated with serious side effects such as acute respiratory distress syndrome (ARDS). There is therefore interest in other options such as the insertion of an indwelling pleural catheter (IPC). These two strategies are the two main options being debated in the literature. Since there is little quality comparative data in the literature on the subject, this thesis will focus on comparing these two options with respect to survival and control of the pleural effusion.

In this section, pleural effusions in general and malignant pleural effusions in particular will be reviewed. We will focus on management options for malignant pleural effusions, discuss their advantages and drawbacks, and review the literature comparing CP and IPC insertion.

1 Definition of pleural effusions

The pleural space is bounded by two membranes, the visceral and parietal pleurae. The visceral pleura covers the lung, while the parietal pleura covers the chest wall and diaphragm. The pleural space has been shown to be a real, not potential space, of about 18-20 μ m in width.¹ Normal pleural fluid is produced from systemic pleural vessels in both membranes and exits through parietal pleural stomata into the pleural lymphatics.² The baseline exit rate in sheep is 0.01 mL/kg/h but increase nearly 30-fold to 0.28 mL/kg/h when artificial effusions were instilled.³ Thus, there is a large lymphatic removal reserve.

Pleural fluid accumulation results from an alteration in transpleural hydrostatic and osmotic pressures, an increase in mesothelial or capillary endothelial permeability or lymphatic drainage impairment.⁴ Traditionally, pleural effusions have been classified into transudates and exudates to help in determining their etiology. In a classic paper, Light et al. defined exudates as effusion presenting any one of three characteristics: a pleural fluid-to-serum protein ratio greater than 0.5, a pleural fluid LDH greater than 200 IU, or a pleural fluid-to-serum LDH ratio greater than 0.6 while transudates do not present any of these characteristics.⁵ Transudates are generally due to an increase in hydrostatic or a decrease in transpleural pressures and suggest intact pleural membranes.²

2 Malignant pleural effusions

2.1 Definition and epidemiology

A malignant pleural effusion is defined by the presence of exfoliated malignant cells in pleural fluid or visualization of malignant cells in pleural tissue obtained by percutaneous pleural biopsy, thoracoscopy, thoracotomy, or at autopsy.⁶ Paramalignant effusions are cytology-negative pleural effusions in patients with established malignancy. Malignant effusions are a common and important clinical problem. An epidemiological study of pleural effusions in a well-defined area of central Bohemia determined the annual incidence of pleural effusions to be 0.32%. Malignant effusions represented 21.8% of these.⁷ Extrapolated to the Canadian population, this would suggest there are in excess of 20,000 new cases affected by malignant pleural effusions yearly in this country. In some series, malignant pleural effusions account for up to 50% of all pleural effusions.⁸

Malignant pleural disease may be primary or secondary. Primary pleural tumours account for about 10% of cases; the most common is malignant mesothelioma.⁹ Secondary involvement of the pleura is much more common. Lung cancer is the most common of secondary tumours, and breast cancer is second with these two tumours account for 50-65% of cases. Lymphomas, genitourinary, and gastrointestinal tumours represent another 25%.⁸ Malignant and paramalignant pleural effusions affect 7-15% of patients with lung cancer during the course of their illness.⁶

2.2 Pathogenesis

Obstruction and disruption of lymphatic drainage by malignant cells is the main mechanism by which malignant pleural effusions occur.⁸ As a matter of fact, mediastinal lymph node involvement by carcinoma is associated with the development of pleural effusions. By contrast, the extent of pleural metastases is not necessarily associated with the occurrence of pleural effusions. For instance, pleural involvement by sarcoma is usually not accompanied by pleural effusions due to the absence of lymphatic metastases.⁶ Vascular endothelial growth factor (VEGF) is also thought to play a role as it is a potent angiogenic mediator and promoter of endothelial permeability.⁸

2.3 Clinical features

Dyspnea is the most common symptom associated with a malignant pleural effusion and is present in 50% of patients.¹⁰ Cough and dull chest pain may also occur.¹¹ Quality of life is often significantly impaired due to these debilitating symptoms.^{12,13} Most importantly, the presence of a malignant pleural effusion (MPE) is a marker for poor survival, with the exception of breast cancer.^{14,15} For instance, median survival is 4.3 months with non-small cell lung cancer, 3.7 months with small cell lung cancer, and 7.4 months with breast cancer.¹⁵

A very recent study examined prognostic factors for survival following management of malignant pleural effusions by a variety of methods.¹⁶ Thoracoscopic talc pleurodesis was employed in 195 of 310 procedures. Pleurodesis through tube thoracostomy accounted for 38

procedures and there were 9 long-term drains. Method of palliation was not a significant predictor of survival, nor was tumour type. While elevated alanine transaminase levels and body-mass index below 18 were associated with decreased survival on single variable Kaplan-Meier analysis, only leukocytosis, hypoxemia and hypoalbuminemia remained significant on multiple variable Cox proportional hazard regression. Factors affecting survival of subjects with malignant pleural effusions previously identified in the literature included tumour cell type, pleural fluid pH and performance status.^{14,17}

2.4 Diagnosis

A pleural effusion as small as 75 mL can be detected on a plain chest-xray lateral view and 175 mL on a postero-anterior view.¹⁸ CT of the thorax can detect pleural effusions of less than 10 mL¹⁹. It can also reveal features suggestive of pleural malignancy, such as pleural thickening, irregularity and nodules as well as detect the presence of a pulmonary mass, mediastinal adenopathy, chest wall involvement, or hepatic metastases.¹¹

Unless the etiology is clear, any pleural effusion of sufficient size should be sampled. Malignant pleural effusions are usually lymphocyte-predominant exudates.⁹ However, from 12 to 24% of eosinophilic effusions are malignant. A pleural pH < 7.30 and glucose < 3.3 mmol/L are also suggestive. Cytology is required for confirmation of the malignant nature of a pleural effusion. However, the sensitivity varies and could be as low as 62%. Further, differentiating between reactive mesothelial cells, mesothelioma and adenocarcinoma, as

well as between lymphoma and reactive lymphocytosis may be difficult and additional studies may be needed.

For instance, when a malignant pleural effusion is still suspected despite negative cytology, pleural biopsy may be indicated⁹, although further testing may be omitted in the setting of a known malignancy. Closed (blind) pleural biopsy is able to diagnose an additional 7-27% of patients only and is therefore not commonly performed.²⁰ CT-guided cutting needle biopsy was directly compared to blind biopsy and was found to be far superior with as sensitivity of 87%.²¹ Pleural biopsies can also be performed through medical or surgical thoracoscopy; the yield is 90-100%.²²

2.5 Management

Despite treatment of the underlying malignancy with chemotherapy or radiation therapy, malignant pleural effusions often recur or do not resolve.²³ However, multiple options are available for the management of malignant pleural effusions. Therapeutic thoracentesis is the removal of a large amount of pleural fluid, allowing the lung to re-expand. However, fluid re-accumulation and recurrence of symptoms occurs in 98 to 100% of patients within 30 days²⁴, requiring repeated procedures. The most common complications associated with thoracentesis are pneumothorax, bleeding and infection. Thus, management of malignant pleural effusions with thoracentesis alone is impractical and subjects patients to complication risks repeatedly.

2.5.1 Chemical pleurodesis

Pleurodesis aims to prevent the reaccumulation of fluid by inducing pleural symphysis. This is achieved by administration of sclerosing agents such as talc, doxycycline, tetracycline, bleomycin or other chemotherapy agents through various routes. In 2006, a meta-analysis found that talc seemed to be the agent with the highest efficacy for preventing recurrence of malignant pleural effusions.²⁵ Nine studies including 341 patients compared talc to other sclerosing agents in this meta-analysis. The relative risk of recurrence for malignant pleural effusions following talc pleurodesis was 0.64 (95% CI, 0.34–1.20) when compared to bleomycin and 0.50 (95% CI, 0.06–4.42) when compared to tetracycline. Results favoured talc but were not statistically significant due to the small size of the available studies.

Talc can be administered as slurry through a standard thoracostomy tube. Tube thoracostomy is usually performed in an inpatient setting and experts recommend waiting for drainage to decrease to less than 150 mL daily before instillation of a sclerosing agent although recent studies have suggested that pleurodesis success rates were similar with sclerosant instillation immediately after tube insertion.²⁴ Hospitalization, often for multiple days, is usually required.

Talc insufflation through medical thoracoscopy or video-assisted thoracic surgery (VATS) also requires hospitalization. Medical thoracoscopy is usually performed under

conscious sedation while VATS is performed under general anesthesia with double-lumen endotracheal intubation to allow for single-lung ventilation. This allows for better visualization of the pleural surfaces. However, many patients' condition may be too poor to permit them to withstand general anesthesia or single-lung ventilation. Both medical thoracoscopy and VATS require a hospital stay since a thoracostomy tube must be left in place after the procedure.²³ A randomized controlled trial comparing talc slurry to talc insufflation²⁶ found no significant difference in the rates of freedom from recurrence of malignant pleural effusion at 30 days (71% vs 78% respectively) although the subgroup with lung or breast cancer fared better with talc insufflation rather than slurry (82 vs 67% respectively).

However, there is controversy about the safety profile of talc. Many North American investigators discourage the use of talc²⁷ as some authors report an association with acute respiratory distress syndrome (ARDS) and even death²⁸⁻³². Nonetheless, other large series have not found any evidence of this association³³⁻³⁷. For instance, in a prospective study of 558 patients who underwent thoracoscopy and talc poudrage with 4 g of calibrated French large-particle talc, there were no cases of ARDS at all.³⁴ Further, in a review of the literature from 1958 through 2001 by Sahn, there were 41 cases of ARDS out of 4030 patients treated with talc pleurodesis for malignant pleural effusions.³⁷ Serious complications were reported in studies from the USA, Brazil and New Zealand but not from Europe or Israel.²⁷ Talc particle size may be the explanation for this discrepancy. Indeed, North American and Brazilian talc, which includes small particles, has been shown to disseminate to virtually all

organs.^{38,39} Small particles are more easily absorbed into the systemic circulation and induce a greater acute inflammatory reaction than talc of mixed-particles.⁴⁰ By contrast, no dissemination occurs with large size-calibrated European talc⁴¹.

In a recent study, Yildirim et al. found that only pleural fluid pH and adenosine deaminase levels were independent predictors of successful chemical pleurodesis.⁴² However, Aelony et al. had found no association between pH and success of pleurodesis⁴³ and a meta-analysis in 2000 found that pH had a modest predictive value.⁴⁴ Other potential predictive factors include pleural fluid glucose, Karnofsky performance status, size of the effusion in chest radiographs, presence of concomitant alterations in chest radiographs, and pleural lactic acid dehydrogenase (LDH) levels.⁴⁵

2.5.2 Indwelling pleural catheter

None of the above options for management of MPEs is ideal. Each has disadvantages ranging from impracticality, limits to feasibility and need for hospitalization to invasiveness and potential for serious complications. Pleural effusion drainage with an indwelling pleural catheter is yet another option. The Pleurx catheter (Denver Biomedical, Cardinal Health, Denver, CO) is an indwelling catheter tunneled under the skin and cuffed to decrease to the risk of infection. It is the only one in common use. Insertion of the catheter can be performed in an outpatient setting. This catheter allows drainage of pleural fluid into vacuum bottles at the patient's home intermittently, usually 2 to 3 times weekly. However, there is relatively little data on this approach. Selected studies are summarized in Table 1. Tremblay et al.

published a series of 250 procedures in 2006;¹³ Warren et al. published a series of 231 procedures in 2008⁴⁶ and Schneider et al. published a series of 107 procedures in 2009.¹² Efthymiou et al. reported on their experience with this catheter in a select population of 116 patients with trapped lung (where the lung fails to re-expand completely, and the visceral and parietal pleurae are not in apposition) confirmed by VATS.⁴⁷ A few smaller series have also been published.⁴⁸⁻⁵¹ Symptom control is complete or partial in the majority of patients.^{13,48,51} Complications are generally minor and infrequent, although empyema occurred in up to 3.7% of procedures in large series.^{12,13,46} In a recent systematic review, symptomatic improvement was reported in 95.6% of patients but quality of life was infrequently reported in the studies reviewed.⁵² In this review, serious complications included empyema (2.8%), pneumothorax requiring a chest tube (5.9%) and unspecified pneumothorax (3.9%). Minor complications included cellulitis (3.4%), obstruction/clogging (3.7%) and unspecified catheter malfunction (9.1%). There were no complications in 87.5% of patients.

Spontaneous pleurodesis is defined as absence of drainage on three consecutive occasions or as drainage of less than 50 cc/day, depending on studies, with absence of pleural fluid reaccumulation. Rates of spontaneous pleurodesis range from 21 to 70% in case series of patients treated with an indwelling pleural catheter.^{12,13,48,50,51,53-56} In the systematic review mentioned above, the rate of spontaneous pleurodesis was 45.6%.⁵² Rates are lowest when patients selected are unsuitable for pleurodesis based on lung re-expansion^{12,50} and highest when patients suitable for pleurodesis are selected.⁵⁶ As a matter of fact, Warren et al. found that spontaneous pleurodesis was more likely with complete re-expansion of the underlying

lung, in patients with breast or gynecologic primary tumours, with cytologic positivity of pleural fluid and absence of chest wall irradiation.⁵⁷ However, Tremblay et al. found that the only predictor of spontaneous pleurodesis was lung re-expansion to the degree that the treated hemithorax contained less than 20% fluid at 2-week follow-up.¹³ Tumour type, side of occurrence, age, and gender were not significant predictors.

2.5.3 Comparison of chemical pleurodesis and indwelling pleural catheter

In a study of 41 patients, Ohm et al. allocated patients into talc pleurodesis through VATS or indwelling pleural catheter insertion based on lung re-expansion.⁵⁸ Only 7 patients were able to undergo pleurodesis. Those in the indwelling pleural catheter group had a higher probability of having a length of stay of less than 2 days as 18 out of 34 of them had the procedure as outpatients.

In the only randomized study comparing the tunneled indwelling pleural catheter to chemical pleurodesis, Putnam et al. randomized 144 patients in a 2:1 distribution to indwelling pleural catheter insertion or doxycycline pleurodesis through tube thoracostomy.⁵⁴ Analysis was per protocol. The primary outcome was not stated. Outcomes included initial pleural effusion control, hospital length of stay, late pleural effusion control failure, quality of life as assessed by measures such as resting and exercise Borg dyspnea scores and, in the indwelling pleural catheter group only, the rate of spontaneous pleurodesis.

Initial treatment was unsuccessful in 13 of 41 patients (32%) in the doxycycline pleurodesis group. For instance, pleurodesis was not attempted in 7 patients randomized to doxycycline pleurodesis as they were having drainage of more than 300 mL / 24h after 4 days of tube drainage. In contrast, amongst patients randomized to the pleural catheter group, chest radiography showed at most a small effusion after the procedure in 91 of 94 patients (97%). Spontaneous pleurodesis occurred in 46% of these 91 patients. The median hospitalization time was significantly shorter in the pleural catheter group (1.0 vs. 6.5 days) even though these patients were kept in hospital for observation for 16 to 24 hours post pleural catheter insertion. Recurrence of the effusion after successful initial control was not significantly different between groups. There was a trend for greater improvement in Borg dyspnea scores at 30, 60, and 90 days in the pleural catheter group; this was significant at 30 days.

In conclusion, a chronic indwelling pleural catheter was found to be an effective treatment for the management of malignant pleural effusion, shortened hospital length of stay compared to doxycycline pleurodesis and could be placed in an outpatient setting. However, doxycycline may be an inferior sclerosing agent compared to talc (see section 2.5.1) and a study comparing talc pleurodesis and indwelling pleural catheter may yield different conclusions. Furthermore, while initial control and late failures were compared between groups, there was no comprehensive measure of successful pleural effusion control and this study did not definitely determine which, if any, of chemical pleurodesis and indwelling pleural catheter insertion is the best approach.

Putnam et al. also conducted a retrospective chart review of 100 patients (60 outpatients, 40 inpatients) who were treated with an indwelling pleural catheter with 68 patients treated with chemical pleurodesis through tube thoracostomy.⁵⁵ Outcomes included survival, hospital length of stay and hospital costs. The primary outcome was not identified.

Median survival did not differ between groups. It was 2.24 months in the chemical pleurodesis group (95% CI, 0.83-3.64) and 4.18 months in the indwelling pleural catheter group (95% CI, 2.14-6.22). Lymphoma patients had a significantly longer survival and the median was not reached at 48 months, while interestingly there was no significant difference between lung cancer, breast cancer and other malignancies. Early and total hospital costs were obtained. As can be expected, early costs were lower for the outpatient indwelling pleural catheter group but total costs were not significantly different between groups. The average cost was USD 32,252 for the chemical pleurodesis group, USD 34,626 for inpatient indwelling pleural catheter group and USD 21,161 for the outpatient indwelling pleural catheter group. In conclusion, costs were lower and hospital length of stay was shorter with the indwelling pleural catheter approach but survival was similar between groups. However, this study has several limitations. For instance, other costs, such as the cost of bottles and home care for the indwelling pleural catheter groups, may not have been included in the hospital costs. Again, doxycycline was used in the chemical pleurodesis group rather than talc. Most importantly, there was no comparison of pleural effusion control or of quality of life measures such as dyspnea scores between groups.

More recently, a cost-effectiveness analysis was conducted employing decision analysis.⁵⁹ Cost data were obtained from the Medicare program reimbursement data from 2008 in the USA and outcome and utility data were estimated from the literature. For instance, the utility for patients with a Pleurx catheter was estimated from another population with an indwelling catheter: patients on peritoneal dialysis. Talc pleurodesis was less costly than the Pleurx catheter (USD 8170.80 vs USD 9011.60) with similar effectiveness (quality adjusted life years of 0.281 for talc pleurodesis and 0.276 for Pleurx catheter). The cost effectiveness of the Pleurx catheter decreased under USD 100,000/quality adjusted life year when life expectancy was less than 6 weeks. In conclusion, talc pleurodesis was, in general, slightly less costly for similar effectiveness. The Pleurx catheter was nonetheless cost-effective when life expectancy was less than 6 weeks. There are several limitations to this study. First, it is only concerned with cost-effectiveness and did not directly assess clinical outcomes. Effectiveness and utility data were estimated from various studies and in some cases assigned empirically. Finally, it does not definitely conclude that any one of the two approaches is superior.

In summary, the indwelling pleural catheter approach has several advantages. It can be performed in the outpatient setting and decreases hospitalization time. It has relatively few complications and there is a possibility for spontaneous pleurodesis allowing for removal of the catheter in a significant proportion of cases. However, in most cases, home care is required, although in one recent study all but 14 of 202 patients were eventually able to care for the catheter themselves without nursing help.⁴⁶ Furthermore, although one clinical trial

and several descriptive studies are available, few studies have compared this approach to other modalities. While it decreases hospitalization time, its impact on other clinical parameters such as successful control of pleural effusions and quality of life is not clear. It may decrease costs due to a decrease in hospitalization, but this may be offset by other costs, especially costs of home care, depending on life expectancy.

Table 1. Selected indwelling pleural catheter studies.

Study	Objectives	N	Major findings	Limitations
Tremblay 2006 ¹³	Describe the use of IPCs in MPE	223 patients 250 procedures	• Partial or complete symptom control after 88.8% of procedures • Spontaneous pleurodesis in 42.9% of procedures	• Descriptive
Warren 2008 ⁴⁶	Describe the use of IPCs in MPE	202 patients 231 procedures	• ‘Symptom palliation’ in all patients • 58% of IPCs removed with only 3.8% rate of fluid re-accumulation	• Descriptive
Ohm 2003 ⁵⁸	Compare IPC to CP through VATS with respect to ‘outcomes, safety and efficacy’	IPC 34 CP 7	• Patients indicated IPC was beneficial to their quality of life • Shorter hospital length of stay in the outpatient IPC group.	• Non-randomized allocation: assigned to IPC group if lung not able to re-expand during VATS and to CP group otherwise • Small CP group
Putnam 1999 ⁵⁴	Compare IPC and doxycycline CP with respect to effectiveness and safety	IPC 99 CP 45	• Similar symptom improvement and quality of life between groups • Rate of late recurrence of pleural effusion (i.e. after successful initial control) not significantly different	• Used doxycycline and not talc • Analysis not intention-to-treat • No comprehensive measure of successful pleural effusion control
Putnam 2000 ⁵⁵	Determine if outpatient insertion of IPC could be performed safely, would eliminate/reduce the need for hospitalization and reduce costs	IPC 100 CP 68	• 60% in the IPC group were inserted in the outpatient setting • No complications in 81% of IPC patients • Similar survival between groups • Costs lowest for outpatient IPC group and highest for CP group	• Used doxycycline and not talc • Did not compare pleural effusion control between CP and ICP groups

Descriptive studies of more than 200 patients and all comparative studies with at least one clinical outcome were included. IPC: indwelling pleural catheter; CP: chemical pleurodesis

3 Summary

Malignant and paramalignant pleural effusions are a common clinical problem with a significant impact on quality of life. Several options are available for management. Repeat thoracentesis exposes patients to complication risks repeatedly and it may need to be performed urgently. In our experience, surgical techniques such as pleurodesis through VATS or pleuroscopy are not commonly performed, as patients are often not able to tolerate such procedures and perhaps because of resource requirements such as access to the operating room. In fact, talc pleurodesis through tube thoracostomy is the most commonly used strategy across Canada. However, there has been ongoing controversy about the safety profile of talc with some investigators discouraging its use and proposing management with indwelling pleural catheters instead. Others still maintain talc pleurodesis should be used. Thus, talc pleurodesis and management with an indwelling pleural catheter are the two main treatment options being debated in the literature. There are few comparative studies in the literature and it is not clear which approach is superior in terms of successful management of malignant pleural effusions, complications, quality of life or costs. Putnam et al. conducted the only randomized trial comparing the indwelling pleural catheter and chemical pleurodesis but used doxycycline, which is less efficacious, rather than talc for chemical pleurodesis.⁵⁴ This group also conducted a comparative retrospective study but only survival and costs were properly compared between groups while the success of managing malignant pleural effusions was not compared between the chemical pleurodesis and indwelling pleural catheter groups.⁵⁵ Our study assesses both survival and procedure outcomes in larger cohorts

of patient who underwent indwelling pleural catheter insertion or chemical pleurodesis almost exclusively with talc.

Aims and objectives

We performed this study to explore the use of indwelling pleural catheters for the management of malignant or paramalignant pleural effusions. Our three main objectives are detailed here.

1. For patients who had insertion of an indwelling pleural catheter (IPC) for management of a malignant or paramalignant pleural effusion:
 - a. Describe the rate of spontaneous pleurodesis, defined as the removal of the catheter less than 90 days after catheter insertion, for any reason, without recurrence or persistence of a moderate or large pleural effusion within 180 days of catheter insertion;
 - b. Describe the rate of pleural effusion control. A failure of pleural effusion control occurred when there was evidence of a pleural effusion at least moderate in size at any time during the period from catheter insertion until 180 days later. Pleural effusion control was considered successful if this did not happen and radiology reports were available at 180 days or later. Subjects who did not have evidence of moderate or large pleural effusion but did not have radiology reports at 180 days or later were considered losses to follow-up and censored. The pleural effusion control rate was calculated as the ratio of success to the total of successes and failures;
 - c. Describe the change in dyspnea scores from baseline;

- d. Describe survival times.
2. For patients who had insertion of an indwelling pleural catheter for management of a malignant or paramalignant pleural effusion, identify factors predicting spontaneous pleurodesis and validate such factors identified in the literature;
 3. Compare clinical outcomes in patients who were treated with an indwelling pleural catheter to historical controls who had undergone talc or doxycycline pleurodesis through tube thoracostomy. Specific clinical outcomes to be compared between the 2 groups will be:
 - a. survival,
 - b. strategy success including pleural effusion control rates and freedom from effusion and catheter,
 - c. the need for subsequent intervention and for re-admission to hospital, and
 - d. complications.

Methods

1 Design and Setting

We conducted a retrospective cohort study comparing non-contemporary groups of patients who underwent either chemical pleurodesis through tube thoracostomy (CP group) or indwelling pleural catheter insertion (IPC group) for management of a malignant or paramalignant pleural effusion at The Ottawa Hospital. IPC insertion is currently the procedure of choice for management of this clinical problem at the Ottawa Hospital. This clinical programme is now well established at The Ottawa Hospital and other modalities are employed only rarely. For this reason, it would be difficult to convince stakeholders to enroll patients in a controlled trial comparing the indwelling pleural catheter to chemical pleurodesis through tube thoracostomy. Furthermore, resource and time constraints also made a prospective randomized controlled trial design undesirable. We therefore chose to conduct a retrospective cohort study.

However, we recognize that a retrospective cohort approach, using data collected via chart review, has several drawbacks. First, as with any use of data initially intended for other purposes, some information may be missing, or may even be inaccurate. Furthermore, some data elements are not available. For instance, in this study of palliative procedures, quality of life would be an important outcome. However, information on quality of life is not recorded in patients' charts. Furthermore, this approach introduces issues with group comparability.

This will be discussed in further detail below. For the purpose of comparing the CP and IPC groups, we elected to address confounding by adjustment in the analysis rather than by matching as this would lead to residual confounding while imposing severe restriction on the sample size.

2 Patient selection and identification

2.1 Indwelling pleural catheter group

IPC cases were identified from the Pleurx programme database. This database references all patients who had an indwelling pleural catheter insertion since this programme began in 2006 (see section 3 for a description). All patients with malignancy who had an IPC insertion between May 1, 2006 and April 31, 2009 were selected for this study. Patients referred to the programme but who did not undergo IPC insertion are not included in the database.

2.2 Chemical pleurodesis group

We identified cases of CP through tube thoracostomy through the prescription of talc or injectable doxycycline, as determined from the Ottawa Hospital data warehouse (see section 3 for a description). This procedure has not been routinely performed at The Ottawa Hospital since the Pleurx programme began. Contemporary cases are therefore unavailable. Cases from other hospitals would not be appropriate comparators for the indwelling pleural catheter group as these hospitals likely serve a population with different characteristics. We therefore opted for historical cases performed at The Ottawa Hospital from 2003-2006, prior to commencement of the Pleurx programme.

As tube thoracostomy for pleurodesis and pleurodesis itself are procedures usually performed at the bedside rather than in the operating room, it can be expected that they

would not be referenced in the discharge abstract. A possible approach to identify patients who underwent talc pleurodesis at The Ottawa Hospital would be to develop a text algorithm to identify the presence of a chest tube from chest radiograph reports. This would require further validation. Moreover, tube thoracostomy is performed for many other reasons than malignant pleural effusions and a cohort identified through such an algorithm would require subsequent narrowing, further complicating this approach. We instead opted to identify cases of pleurodesis through the prescription of talc and injectable doxycycline between March 1, 2003 and February 28, 2006. Pleurodesis is the only medical use of these medications, thus patients who were prescribed either talc or injectable doxycycline would have had these prescriptions specifically for purposes of a pleurodesis procedure. Such information is available through the Ottawa Hospital data warehouse.

2.3 Group comparability considerations

There are potential problems with this approach, since the patients in the two chosen comparator groups may not be easily comparable. For instance, many patients are now undergoing IPC insertion whereas previously their condition would have been deemed too poor to undergo tube thoracostomy and pleurodesis. General condition of cancer patients is evaluated using the Eastern Conference Oncology Group (ECOG) performance scale. ECOG status range from 0 to 5, with 0 referring to normal functioning and 5 referring to death (Table 4). We therefore excluded patients with a status of 4 on the ECOG performance scale from the comparative analysis. This status corresponds to patients that are completely disabled, cannot carry out any selfcare or are totally confined to bed or chair. These patients

would not have been offered tube thoracostomy and CP in the past, but they are now offered IPC insertion. Excluding these patients from the IPC group makes this group more comparable with the historical tube thoracostomy and CP group.

Another limitation is that some patients underwent tube thoracostomy but did not eventually have CP. Thus our study does not compare a management strategy of initial tube thoracostomy with the intent of CP with a strategy of IPC insertion. Rather it compares patients who underwent both initial tube thoracostomy **and** CP to those who underwent IPC insertion.

2.4 Inclusion criteria

1. Patients who had:
 - a. Tube thoracostomy followed by CP with talc or doxycycline between March 1, 2003 and February 28, 2006 inclusive or
 - b. Insertion of an IPC between May 1, 2006 and April 1, 2009.
2. Procedure performed predominantly for management of a pleural effusion, as opposed to pneumothorax.
3. Biopsy-proven diagnosis of malignancy or strongly suspected by the treating physician.
4. Positive pleural fluid cytology or pleural effusion thought to be secondary to malignancy (i.e. malignant or paramalignant pleural effusion). A positive pleural fluid cytology was

not required since this test was not always performed and this test also has a low sensitivity.

2.5 Exclusion criteria

1. ECOG performance status of 4.
2. Previous ipsilateral CP or IPC.
3. Previous or simultaneous contralateral CP or IPC. In the case of simultaneous bilateral procedures, one of the two procedures was excluded. The procedure to be excluded was determined by a computer algorithm using a pseudo-random number generator.
4. The tube thoracostomy, CP or IPC insertion was performed in the setting of another procedure such as medical pleuroscopy or video-assisted thoracic surgery since the success rate of these procedures may be different and the characteristics of patients able to undergo such procedure are different as well.

3 Data collection

3.1 Data sources

Information was obtained from four sources including: the Pleurx Programme Database, The Ottawa Hospital Data Warehouse, hospital patient charts, and the Office of the Registrar General, Province of Ontario.

The Pleurx programme database is maintained prospectively for research purposes and includes all patients who underwent IPC insertion at our centre. Data is entered into the database by the only physician performing this procedure in our centre. We are confident the data is accurate since it is entered into the database by the individual who is responsible for clinical care of subjects and directly ascertains the data.

The Ottawa Hospital data warehouse is a relational database replicating information from several of The Ottawa Hospital's information systems, including clinical data. The data we used was integrated into The Ottawa Hospital data warehouse from clinical information systems whose primary purpose is patient care. Data is entered into The Ottawa Hospital data warehouse automatically and digitally and we are therefore confident the data is accurate.

Most information, particularly for the tube thoracostomy and pleurodesis group, had to be extracted from medical records, whose primary purpose is patient care. Data is written into the paper medical records by health care providers such as physicians and nurses. Since

this data is meant for clinical care of subjects, we are confident of its accuracy. Only prospectively-ascertained data could be more accurate.

Vital status and date of death, if applicable, were obtained from the provincial vital statistics office (Office of the Registrar General, Province of Ontario) if not available from medical records or from the Ottawa Hospital data warehouse. We are confident the completeness of the data is high as few subjects are expected to have passed away outside of the province. Particularly, we expected few patients from Quebec would be included in our series.

The source of each variable is detailed in the next section and in Table 3.

3.2 Variables

3.2.1 Baseline variables and covariates

Sex, age at the time of catheter insertion and the last determination of pleural fluid pH and LDH levels and presence of malignant cells on pleural fluid cytology on or prior to the day of catheter insertion were obtained from the Ottawa Hospital data warehouse. Tumour type and history of previous radiation were obtained from medical records for description, stratification and confounder adjustment. ECOG performance status prior to intervention was determined from medical records for the chemical pleurodesis group and categorized as 4, less than 4 or unknown, based on notes in the paper chart, mostly by nurses but also by other health care providers, on subjects' mobility. For instance, an ECOG score of 4 was assigned

if the patient was noted to be completely confined to the bed or chair. An ECOG score of less than 4 if there was any indication of better mobility. The ECOG score was deemed unknown if there was not enough information to make that determination. The ECOG score was obtained from the Pleurx programme database for the IPC group. It was entered into the database by the physician responsible for clinical care of the IPC group subjects. This physician determined the ECOG score by direct questioning of the subjects. The date and side of catheter insertion was recorded from the Pleurx programme database and medical records for the IPC and CP groups respectively. We also determined if the procedure was performed in the inpatient setting for the IPC group only from the Ottawa Hospital data warehouse, all CP procedures being performed in the inpatient setting. The date of sclerosing agent instillation into the pleural space was determined from medical records for the CP group.

3.2.2 Outcome measures

3.2.3 Rationale for outcome selection

Outcomes in previous indwelling pleural catheter studies include survival, measures of symptom control, measures of spontaneous pleurodesis and measures of pleural effusion control or recurrence.

Survival was generally reported from the time of catheter insertion. The Borg scale and the chronic respiratory questionnaire have been used for quantifying dyspnea⁵⁴, while others have described symptom control on a 3-point scale¹³ (absent, partial or complete) or have simply stated that the intervention “palliated the patient’s symptoms” without further

detail.⁴⁶ Validated outcomes, such as the baseline and transition dyspnea indices available for this study, are preferable.

Spontaneous pleurodesis was usually defined as the removal of the indwelling pleural catheter due to decreased drainage such as less than 50 mL on three consecutive occasions¹³, less than 100 mL every other day⁴⁶, or no drainage on three occasions.^{54,55} One study reported on the proportion of patients still having drainage after 100 days.⁴⁶ None of these definitions specified a time-point at which the proportion would be measured. This is important to avoid duration of follow-up affecting the results. Furthermore, only Tremblay et al. specified that there be no fluid reaccumulation following catheter removal¹³, which is important as removal of the catheter is not desirable if it results in fluid reaccumulation. However, even this group did not specify a follow-up period during which fluid reaccumulation would be assessed and the circumstances in which fluid reaccumulation would be considered significant. Spontaneous pleurodesis has been reported to occur after a median of 29 to 80 days^{12,46,51,54}. Another factor to consider is the generally short survival of patients. For instance, median survival of patients with NSCLC and pleural effusion is only 4.3 months¹⁵ and spontaneous pleurodesis is only beneficial if it occurs a substantial amount of time before death. We therefore required the catheter be removed by 90 days after catheter insertion. A follow-up period of a further 90 days was allowed for fluid reaccumulation such that this was assessed at 180 days after catheter insertion. A small amount of pleural fluid is less likely to be clinically significant and we only considered reaccumulation of a pleural effusion at least moderate in size to be a failure. Since the reason for catheter removal is

irrelevant provided that there is no pleural fluid reaccumulation, we did not require that the catheter be removed due to decreased drainage. This resulted in the following definition of spontaneous pleurodesis: removal of the catheter, for any reason, less than 90 days after catheter insertion with absence of evidence of persistence or recurrence of a moderate pleural effusion within 180 days of catheter insertion (see Table 2). This definition has the additional advantage of being applicable to the CP group as well. For the purpose of comparing the CP and IPC group, we referred to this definition as freedom from catheter and pleural effusion.

Concerning pleural effusion control measures, one study reported on late failure⁵⁴, defined as the recurrence of the effusion after its initial successful control (not defined). Another study reported on the proportion of patients having a recurrence following catheter removal.⁴⁶ Again, recurrence was not further defined. This latter measure fails to acknowledge that a pleural effusion may not be well-controlled despite the presence of a catheter. Furthermore, recurrence needs to be more accurately defined. We therefore considered pleural effusions controlled if there was no pleural effusion, moderate in size or larger, for 180 days starting at the time of catheter insertion (such as both pleural effusion control and spontaneous pleurodesis/freedom from pleural effusion and catheter would be assessed at the same time-point. Radiology reports were required in order to assess pleural fluid, and their absence resulted in exclusion of the patient from the calculation (see Table 2).

For the purpose of comparing the IPC and CP groups, we chose freedom from pleural effusion and catheter as the primary outcome. While survival is a reliable and important

outcome, there is no obvious reason why it would be affected by a palliative procedure. Pleural effusion control is important as well, but does not take into account the nuisance of having an indwelling catheter and ancillary burdens such as care of the catheter and home care visits. The best outcome is therefore freedom from pleural effusion and catheter since it is the best possible situation for the patient.

3.2.3.1 IPC group description

A. Rate of spontaneous pleurodesis

The date and reason for removal of an IPC was determined from the Pleurx programme database to determine if and when spontaneous pleurodesis occurred. Catheters were removed due to spontaneous pleurodesis when drainage was less than 50 mL on 3 consecutive visits. Spontaneous pleurodesis has been reported to occur after a median of 29 to 80 days^{12,46,51,54}. The retrospective nature of this study allowed for a lengthier period of follow-up. We therefore determined the success of management strategies for malignant pleural effusions after 180 days. As indicated above, we defined spontaneous pleurodesis in our study as the removal of the catheter, for any reason, less than 90 days after catheter insertion with absence of evidence of persistence or recurrence of a moderate pleural effusion within 180 days of catheter insertion (Table 2). Pleural effusion status was determined from radiology reports obtained from The Ottawa Hospital Data Warehouse. Subjects who did not have radiology reports at 180 days or later were considered losses to follow-up and censored.

B. Pleural effusion control

A failure of pleural effusion control occurred when there was evidence of a pleural effusion at least moderate in size at any time during the period from catheter insertion until 180 days later. Pleural effusion control was considered successful if this did not happen and radiology reports were available at 180 days or later. Subjects who did not have evidence of moderate or large pleural effusion but did not have radiology reports at 180 days or later were considered losses to follow-up and censored. The pleural effusion control rate was calculated as the ratio of success to the total of successes and failures.

C. Change in dyspnea scores from baseline

For the IPC group, the baseline dyspnea index, transition dyspnea index⁶⁰ at 2 weeks follow-up and amount of initial drainage were also obtained from the Pleurx programme database. This information was not available for the CP group. The baseline dyspnea index (BDI) includes three components: functional impairment, magnitude of task and magnitude of effort (Appendix I). Each component is graded from 0 (severe impairment) to 4 (no impairment). Only the total score formed by adding the grades for each component and ranging from 0 to 12 was recorded. The transition dyspnea index (TDI; Appendix II) rates the change in each of the same three components from -3 (major deterioration) to +3 (major improvement). The total score which ranges from -9 to +9 was recorded. According to a review by the author of these indices⁶¹, the minimal clinically important difference for the TDI is one unit, based on expert opinion, use of another measure (the physician's global

evaluation) as an anchor and on a systematic review that found that the minimal clinically important difference for health-related quality of life measures was close to half of a standard deviation.⁶²

D. Survival

We computed survival time starting at the date of tube thoracostomy or insertion of the indwelling pleural catheter until date of death (Table 2). The date of death was obtained from medical records and from the Ottawa Hospital data warehouse. If unavailable, it was obtained from the provincial vital statistics office. We also performed a secondary analysis of survival, using the start date as the date an Ottawa Hospital chest radiograph or computed tomography of the thorax was first reported to show a pleural effusion (Table 2).

3.2.3.2 Predictors of spontaneous pleurodesis in the IPC group

The definition of spontaneous pleurodesis used for describing the IPC group was also used for the objective of identifying and validating predictors of spontaneous pleurodesis.

3.2.3.3 IPC and CP group comparison

A. Strategy success

The success of CP is not directly comparable with spontaneous pleurodesis occurring in the IPC group. Spontaneous pleurodesis in subjects with an IPC, if it occurs, takes place after some time, while the success of CP is determined shortly thereafter. Consequently,

subjects with an IPC, even those who achieve spontaneous pleurodesis, have to contend with an indwelling catheter, as well as its care and visits from home care personnel, whereas subjects who undergo successful CP are free from all these considerations. We therefore compared the IPC group to the CP group in two different ways.

We examined the rate of control of the pleural effusion (secondary outcome; see Table 2). However, we also examined the rate of freedom from pleural effusion and catheter as a primary outcome. This was defined as the removal of the catheter, for any reason, less than 90 days after catheter insertion with absence of evidence of persistence or recurrence of a moderate pleural effusion within 180 days of catheter insertion (Table 2). This is the same as the definition used to determine the rate of spontaneous pleurodesis, the time to spontaneous pleurodesis in the IPC group and to determine predictors of spontaneous pleurodesis.

Since recurrence of a pleural effusion and death are both undesirable events, and since the analyses described above do not properly take into account

B. Survival

We computed survival time from the time of catheter insertion in the same manner used to describe the IPC group. It is difficult to know when a patient first needed an intervention, or even what the referral date for such an intervention was. We therefore

performed a secondary analysis of the primary outcome of survival as well, using the start date as the date an Ottawa Hospital chest radiograph or computed tomography of the thorax was first reported to show a pleural effusion (Table 2). This alternative survival time calculation was done in order to determine if there was an appearance of lead time bias. This was a feasible approach and the radiology reports were obtained from the Ottawa Hospital data warehouse. While some patients may have had chest radiographs showing pleural effusions at an earlier time at other institutions, this information was not readily available and this phenomenon should have affected both groups equally.

C. Need for subsequent intervention and re-admission to hospital

The need for further interventions within one year of initial catheter insertion such as ipsilateral tube thoracostomy, ipsilateral IPC insertion, CP, pleuroscopy and VATS was also determined from integration of data from medical records, the Pleurx programme database and the Ottawa Hospital data warehouse. The need for re-admission to the Ottawa Hospital within one year was determined through the Ottawa Hospital data warehouse.

D. Complications

Information about complications was obtained from the Pleurx programme database for the IPC group and from medical records for the CP group. The following classification was used to classify complications/adverse effects related to the procedures:

- Symptomatic loculation;
- Empyema;
- Large or moderate pneumothorax;
- Subcutaneous emphysema;
- Bronchopleural fistula;
- Cellulitis;
- Blocked catheter;
- Dislodged catheter;
- Bleeding;
- Tumour seeding;
- Pain requiring removal of catheter;
- Acute respiratory distress syndrome (ARDS);
- Transient respiratory deterioration;
- Fever;
- Fluid leak around the catheter.

Table 2. Summary of outcome definitions.

Primary outcome:	Removal of the catheter, for any reason, less than 90 days after catheter insertion with absence of evidence of
Freedom from pleural effusion and catheter	persistence or recurrence of a moderate pleural effusion within 180 days of catheter insertion. For the CP group this is equivalent to pleural effusion control since all had their catheter removed before 90 days. Pleural effusion status was determined from radiology reports obtained from The Ottawa Hospital Data Warehouse. Subjects who did not have radiology reports at 180 days or later were considered losses to follow-up and censored.
Spontaneous pleurodesis	This term is used for the IPC group only and is defined in the same way as freedom from pleural effusion or catheter: removal of the catheter, for any reason, less than 90 days after catheter insertion with absence of evidence of persistence or recurrence of a moderate pleural effusion within 180 days of catheter insertion.
Pleural effusion control	A failure of pleural effusion control occurred when there was evidence of a pleural effusion at least moderate in size at any time during the period from catheter insertion until 180 days later. Pleural effusion control was considered successful if this did not happen and radiology reports were available at 180 days or later. Subjects who did not have evidence of moderate or large pleural effusion but did not have radiology reports at 180 days or later were considered losses to follow-up and censored. The pleural effusion control rate was calculated as the ratio of success to the total of successes and failures.
Survival since catheter insertion	Computed starting at the date of tube thoracostomy or insertion of the indwelling pleural catheter until the date of death.
Survival since the first report of a pleural effusion	Computed starting at the date an Ottawa Hospital chest radiograph or computed tomography of the thorax was first reported to show a pleural effusion until the date of death.

Table 3. Summary of variable sources.

Data Warehouse	Medical Records	Pleurx programme database	Vital statistics office
Age			
Sex			
pH			
LDH			
Pleural fluid cytology			
Inpatient or Outpatient setting –IPC			
Date of first effusion			
	Tumor type		
	History of thoracic irradiation		
	ECOG – CP	ECOG – IPC	
	Date/Side catheter insertion – CP	Date/Side catheter insertion – IPC	
	Date of sclerosant instillation – CP		
	Complications – CP	Complications – IPC	
		BDI/TDI – IPC group	
	Date of catheter removal – CP	Date/reason of catheter removal – IPC	
Further interventions*	Further interventions	Further interventions	
Date of readmission (s)			
Pleural fluid recurrence/persistence based on radiology reports			
Date of death	Date of death		Date of death

BDI = Baseline Dyspnea Index; TDI = Transition Dyspnea Index; * Further interventions include ipsilateral tube thoracostomy, ipsilateral IPC insertion, CP, pleuroscopy and VATS (video-assisted thoracic surgery).

4 Analysis

4.1 IPC group description

Descriptive statistics were used to describe the IPC groups. Variables described include age, gender, tumour type, previous chest wall irradiation, intervention side, presence of malignant cells on pleural fluid and complications rates. The setting (outpatient or inpatient) of insertion and ECOG performance status were described. The residence time of the catheter was calculated.

The rate of pleural effusion control and the rate of spontaneous pleurodesis were calculated. The time to spontaneous pleurodesis was determined for patients in whom it occurred. The baseline and transition dyspnea indices were also described. We calculated the proportion of patients achieving the minimal clinically important difference for the transition dyspnea index. Survival times computed according to the two approaches outlined above were calculated with Kaplan-Meier survival analysis.

We performed post hoc subgroup Kaplan-Meier survival analyses of subjects with lung cancer and breast cancer. Survival analysis of the effect of ECOG performance score was also conducted. Cox regression was used to adjust for possible confounders such as age, gender, tumour type, ECOG performance status, history of previous radiation to the chest and presence of malignant cells in pleural fluid. These factors have been previously shown or

tested as predictors of either survival or spontaneous pleurodesis. They were used in all adjusted analyses of strategy success rates and survival.

4.2 Predictors of spontaneous pleurodesis in the IPC group

Predictors of spontaneous pleurodesis using that same definition were first assessed through single variable logistic regression. Variables examined included age, gender, tumour type, history of previous radiation, ECOG performance status, intervention side, amount of initial drainage, presence of malignant cells in pleural fluid, pleural fluid pH and LDH and whether the catheter was inserted in the inpatient or outpatient setting. The Wald χ^2 statistic for each parameter was used to determine significance at the 0.05 level. We also examined variables in a multiple variable model. Backward selection was used to determine the best model that could predict the occurrence of spontaneous pleurodesis. The significance level to keep variables in the model was 0.05.

4.3 IPC and CP group comparison

Patient characteristics such as age, gender, tumour type, previous chest wall irradiation, intervention side, presence of malignant cells on pleural fluid were compared between the IPC and CP groups. Proportions were compared between groups using the χ^2 test of independence. Continuous variables were compared using Student's t-test for independent samples.

Unadjusted comparison of the rates of control of pleural effusions between the two groups was performed with a χ^2 test of independence. Logistic regression was then used to adjust for age, gender, tumour type, history of previous radiation, intervention side and presence of malignant cells on pleural fluid cytology. The Wald χ^2 statistic was used to determine significance at the 0.05 level. Freedom from pleural effusion and catheter was analyzed in the same way.

Survival times computed according to the two approaches outlined above were compared with Kaplan-Meier survival analysis and the log-rank test. Cox proportional hazards regression was then performed for adjustment for the confounders expected to affect survival such as age, gender, tumour type, ECOG performance status, history of previous radiation to the chest and presence of malignant cells in pleural fluid. These confounding variables were all determined a priori. The proportional hazards assumption was tested by adding time-dependent interaction terms to the full model. All predictors were tested, including the treatment group and each predictor was tested separately.

The need for further interventions, such as further tube thoracostomy or indwelling pleural catheter insertion, chemical pleurodesis and medical pleuroscopy or VATS were compared with Fisher's exact test, as low expected cell counts in several of these analyses precluded the use of the χ^2 test of independence. The rates of subsequent re-admissions to the Ottawa Hospital were compared between the two groups using Poisson regression. There were very few events and adjustment for confounders, although planned, was not performed.

Complications were compared using Fisher's exact test. The proportion of subjects having at least one complication was also compared between groups using the χ^2 test of independence.

5 Ethical issues

This study was retrospective and did not involve experimentation on humans. We obtained approval from the Ottawa Hospital Research Ethics Board. Consent from subjects was not required or sought. Approval was also obtained from the Ottawa Hospital data warehouse for accessing data as well as for identifying subjects. A confidentiality agreement was signed with the Office of the Registrar General, Province of Ontario in order to obtain subjects' date of death.

A strong identifier, the medical record number was required to link data from the Ottawa Hospital data warehouse with medical records data. The medical record number is not included with the results data. Rather it is included in a separate dataset linking it with the subject study identifier.

The subjects' names and dates of birth were required to obtain the dates of death from the Office of the Registrar General, Province of Ontario. In order to preserve confidentiality, the dataset containing these identifiers was deleted once the date of death was linked into the results datasets.

The results datasets and the master list are stored separately on password-secured accounts on a server of the Ottawa Hospital. They will be kept for a period of 15 years. No paper records were generated.

Table 4. ECOG performance scale

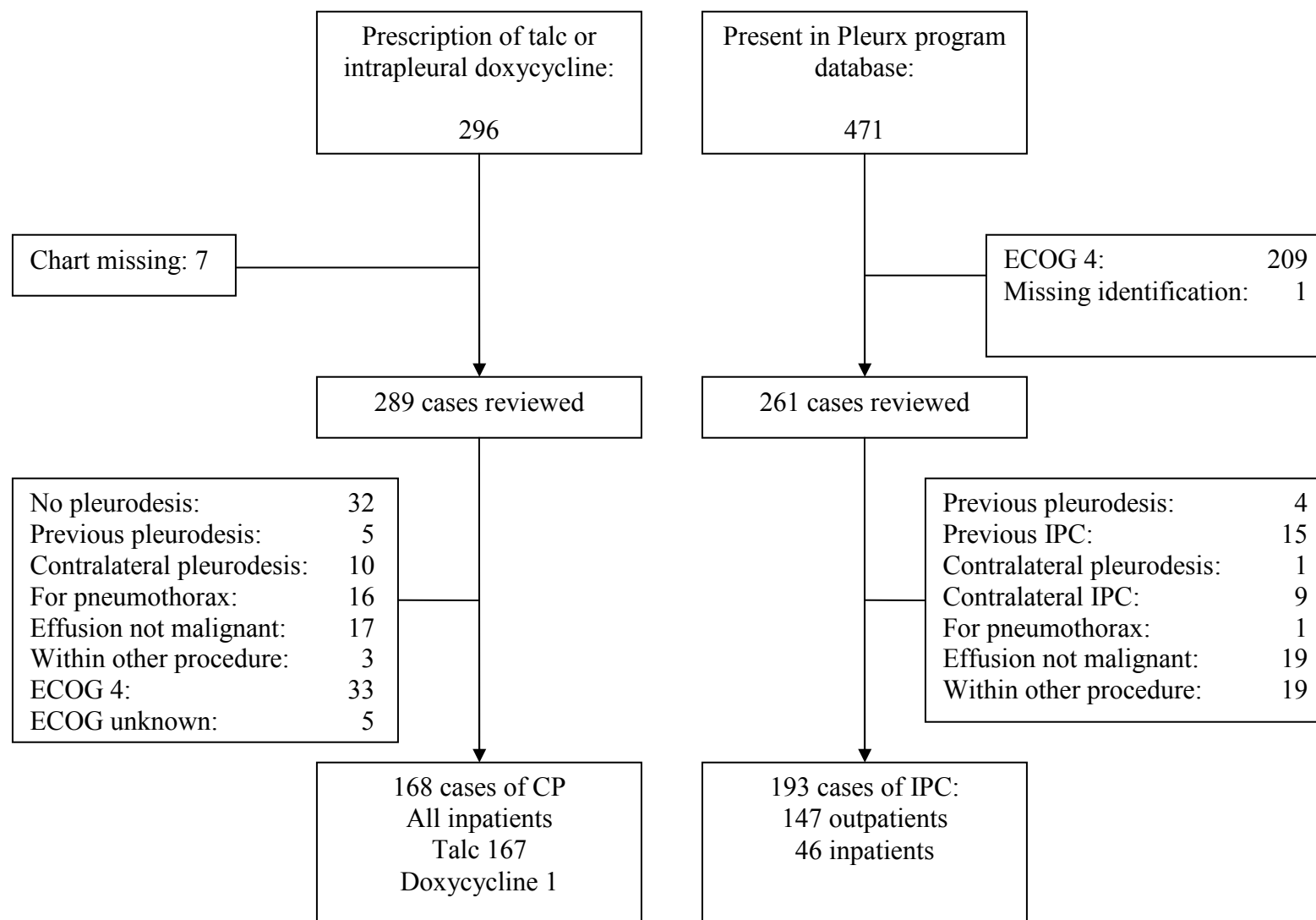
Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Adapted from Oken et al.⁶³

Results

1 Patient selection

Many more subjects were considered for inclusion in the indwelling pleural catheter (IPC) group than the chemical pleurodesis (CP) group during time periods of same duration (Figure 1). The difference was mainly due to the expected higher number of subjects with an ECOG performance status of 4 having underwent IPC than CP. CP cases were identified through prescription of talc or doxycycline. Consequently, many subjects considered for inclusion in that group did not turn out to be cases for various reasons detailed in Figure 1. For instance, some had talc prescribed but did not end up having pleurodesis while others had pleurodesis for a non-malignant effusion or for a pneumothorax rather than for a malignant effusion. IPC insertion is generally not performed for pneumothorax; more cases were therefore excluded for this reason in the CP group. More cases were excluded from the IPC group due to the catheter being inserted in the setting of another procedure, mainly medical pleuroscopy. Comparatively, there were few cases of CP performed during medical pleuroscopy or VATS. Other reasons for exclusion were relatively similar between groups and the IPC group was only slightly larger than the CP group. Most subjects in the IPC group had their catheter inserted in the outpatient setting.

Figure 1. Case selection

2 IPC group description

The mean age in the IPC group was 67.1 years (65.3-68.9) and 56.0% were female (Table 8). Up to 32.6% had a history of previous chest irradiation. Lung cancer was the most frequent underlying malignancy (42.0%) followed by breast cancer (22.3%). Close to half (48.2%) had pleural fluid cytology positive for malignant cells.

The number of subjects increased with worsening ECOG performance status (Table 5). At the time of catheter insertion, a mean of 1.49 L (95% CI 1.42-1.56) of pleural fluid was drained. The baseline dyspnea index was available for 171 of the 193 subjects in the IPC group with a mean value of 3.56 (95% CI 3.28-3.83). The transition dyspnea index 2 weeks after catheter insertion was available for 136 subjects and revealed a mean improvement of 6.71 points (95% CI 6.38-7.04), well above the minimal clinically important difference (MCID) of 1 point. Almost all patients (135/136, 99.3%) achieved the MCID. Dyspnea scores were not available in the CP group patients.

Pleural effusion control (see Table 2 for definition) was achieved in 52.7% of patients in the IPC group (Table 9). However, only 25.8% achieved spontaneous pleurodesis (see Table 2 for definition).

Median survival calculated from the date of catheter insertion was 148 days (95% CI 110-197; see Figure 4 for Kaplan Meier curve). Median survival calculated from the first report of a pleural effusion was 276 days (95% CI 210-335; see Figure 5).

Table 5. Distribution of ECOG performance status in the IPC group.

ECOG performance status	no.	%
0	0	0
1	13	6.74
2	48	24.87
3	132	68.39
4	Excluded	
5	Deceased	

We examined the effect of the ECOG performance status on survival. This analysis could only be performed in the IPC group as the exact status was not available in the CP group. Using Kaplan-Meier survival analysis (Figure 2), the ECOG performance status was a significant predictor of survival calculated from the time of catheter insertion (log-rank $p < 0.01$). Pairwise comparison revealed survival was significantly higher for those with an ECOG performance status of 1 compared to those with a status of 3 (log-rank p with Bonferroni correction < 0.003). In a Cox proportional hazards regression with adjustment for the same potential confounders mentioned above, the ECOG performance status was also a significant predictor of survival calculated from the time of catheter insertion in the type 3

analysis of effects ($p < 0.01$) and similarly to the Kaplan-Meier analysis, survival was higher for those with an ECOG performance status of 1 than for those with a status of 3 ($p < 0.01$).

Similarly, ECOG was a significant predictor of survival calculated from the first report of a pleural effusion on both Kaplan-Meier ($p < 0.04$) and Cox proportional hazards ($p < 0.05$) analyses. Again, those with an ECOG performance status of 3 had poorer survival than those with a status of 1 on both unadjusted ($p < 0.03$) and adjusted ($p < 0.02$) analyses.

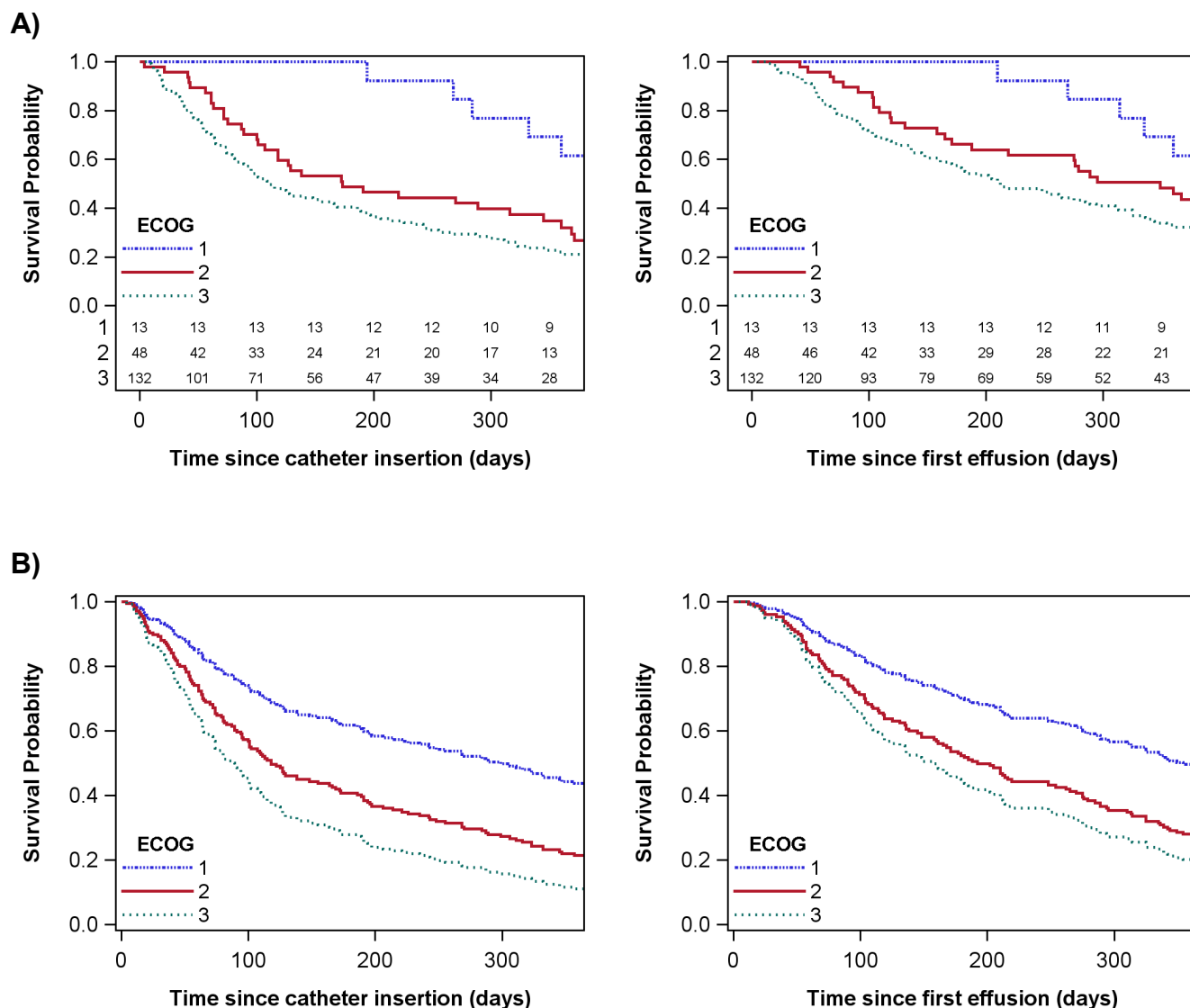


Figure 2. Survival by ECOG performance status in the IPC group.

A) Kaplan-Meier unadjusted analysis; B) Cox regression adjusted analysis. Predicted curves shown are for a male age 50-64 years old, with lung cancer, no history of chest irradiation and a right pleural effusion with malignant cells present on pleural fluid cytology.

3 Predictors of spontaneous pleurodesis in the IPC group

In the IPC group, the catheter was removed due to drainage of less than 50 mL on three consecutive occasions by 180 days after catheter insertion in 78 of 105 patients (74.3%, 95% CI 64.8% - 82.3%). This rate was 52.9% at 90 days (63/119, 43.6% - 61.9%). We defined spontaneous pleurodesis as the removal of the catheter less than 90 days after catheter insertion, for any reason, without recurrence or persistence of a moderate pleural effusion within 180 days of catheter insertion. This occurred in 31 of 120 (25.8%, 95% CI 18.3% - 34.6%) subjects in whom the determination could be made. The mean time to spontaneous pleurodesis was 49.2 days (95% CI 42.2-56.2).

We tested the following variables in univariate logistic regression model to determine if they were predictors of spontaneous pleurodesis, using the same definition: age, gender, tumour type, history of thoracic irradiation, ECOG performance status, intervention side, amount of initial drainage, presence of malignant cells in pleural fluid, pleural fluid pH and LDH and whether the catheter was inserted in the inpatient or outpatient setting. None were significant predictors (Table 6).

We had planned to then examine these variables in multiple variable logistic regression models using a backward selection approach. This was done despite none of the variables being significant predictors on single variable analysis. Unsurprisingly, the backward selection approach did not yield any useful model (Table 7).

Previously identified predictors of spontaneous pleurodesis in the literature include breast or gynecologic primary tumours, cytologic positivity of pleural fluid and absence of chest wall irradiation⁵⁷, although Tremblay et al found there was no impact of tumour cell type.¹³ The degree of lung re-expansion was also found to be a significant predictor of spontaneous pleurodesis.^{13,57} With the exception of the degree of lung re-expansion which would have been difficult to assess, all these factors were included in the above analyses and none were found to be significant predictors of spontaneous pleurodesis.

Table 6. Predictors of spontaneous pleurodesis in single and multiple variable models.

Predictor	Single variable			Multiple variable		
	OR	95% CI	p	OR	95% CI	p
Age (Ref = 49 or less)			0.79			0.56
50-64	1.10	0.25 - 4.89		2.55	0.38 - 17.12	
65-79	0.94	0.22 - 4.07		2.70	0.38 - 19.10	
80 and above	0.53	0.09 - 3.28		1.05	0.12 - 9.20	
Gender (Ref = Male)			0.31			0.69
Female	1.57	0.66 - 3.71		1.30	0.35 - 4.80	
Tumor type (Ref = Other)			0.72			0.55
Breast	1.07	0.34 - 3.34		1.10	0.24 - 5.15	
Lung	0.62	0.22 - 1.80		0.48	0.13 - 1.83	
Lymphoma	0.89	0.19 - 4.25		1.06	0.19 - 5.95	
History of thoracic radiation			0.80			0.79
Positive	0.89	0.36 - 2.18		0.86	0.27 - 2.69	
ECOG (Ref=3)			0.22			0.34
1	2.35	0.68 - 8.12		1.87	0.44 - 7.86	
2	1.99	0.76 - 5.25		2.26	0.70 - 7.34	
Intervention side			0.28			0.17
Right	0.64	0.28 - 1.45		0.50	0.19 - 1.34	
Pleural fluid cytology			0.60			0.23
Positive	1.24	0.55 - 2.82		1.92	0.67 - 5.54	
pH			0.59			0.59
1 unit increase	1.46	0.37 - 5.76		1.55	0.32 - 7.46	
LDH			0.69			0.97
50 U/L increase	1.00	0.97 - 1.02		1.00	0.98 - 1.02	
Amount of initial drainage			0.24			0.25
1L increase	0.61	0.27 - 1.39		0.53	0.18 - 1.57	
Setting (Ref = Outpatient)			0.86			0.65
Inpatient	1.10	0.39 - 3.11		1.34	0.38 - 4.75	

Table 7. Backward selection approach for spontaneous pleurodesis predictors.

Step	Predictor	DF	Multiple variable	
			χ^2	p
1	LDH	1	0.00	0.97
2	History of thoracic irradiation	1	0.07	0.79
3	Inpatient/Outpatient setting	1	0.21	0.65
4	pH	1	0.33	0.56
5	Tumor type	3	1.16	0.76
6	Age	3	1.85	0.60
7	Amount of initial drainage	1	0.26	0.61
8	Pleural fluid cytology	1	1.06	0.30
9	Gender	1	1.06	0.30
10	Intervention side	1	1.68	0.20
11	ECOG	2	3.05	0.22

Predictors are listed in the order they were removed from backward selection multiple variable models. The data indicated in the multiple variable columns are taken from the last model containing the specified predictor and leading to the decision of removing that predictor from subsequent models. Type 3 analysis of effects was used for categorical variables.

4 IPC and CP group comparison

4.1 Patient characteristics

The two groups were comparable with respect to age and intervention side (Table 8). Most subjects were in the seventh decade of life. In agreement with other series such as the study by Tremblay et al.¹³, there were more right than left-sided malignant pleural effusions requiring intervention although the difference was not significant. There were more females in the CP group while gender was approximately balanced in the indwelling pleural catheter IPC group. Although there were generally no differences in tumour types between groups there were more slightly more cases of ovarian or primary peritoneal carcinoma (16.0% vs 8.3%, exclusively females) in the CP group and more cases of mesothelioma in the IPC group (6.2% vs 1.2%, almost exclusively males). This accounts partially for the imbalance in gender distribution between groups. The difference in rates of previous thoracic irradiation between groups was not significant ($p=0.07$). The yield of pleural fluid cytology was low, especially in the CP group, although the difference did not reach the level of significance ($p=0.07$). The yield increases with the number of samples analyzed and indeed there were more samples in the IPC group. As expected from the intended use of the catheters, the residence time of IPCs was much longer than that of catheters inserted prior to CP.

Table 8. Characteristics by group.

Characteristic	CP <i>n=168</i>	IPC <i>n=193</i>	p
Age -- mean in years (95% CI)	65.0 (63.1-66.9)	67.1 (65.3-68.9)	NS
Gender -- n (%)			<0.01
Male	49 (29.2%)	85 (44.0%)	
Female	119 (70.8%)	108 (56.0%)	
History of previous chest irradiation	67 (39.9%)	63 (32.6%)	NS
Diagnosis -- n (%)			NS
Lung	73 (43.5%)	81 (42.0%)	
Breast	45 (26.8%)	43 (22.3%)	
Lymphoma	4 (2.4%)	17 (8.8%)	
Other	46 (27.4%)	52 (26.9%)	
Intervention side -- n (%)			NS
Right	95 (56.6%)	111 (57.5%)	
Left	73 (43.5%)	82 (42.5%)	
Pleural fluid cytology samples -- mean no. (95% CI)	1.29 (1.14-1.43)	1.54 (1.41-1.67)	<0.05
Malignant pleural fluid cytology -- n (%)	65 (38.7%)	93 (48.2%)	NS
Catheter removal -- median residence duration in days (IQR, n)	7 (5-10, n=166)	56 (33.5-96.5, n=96)	<0.0001

95% CI = 95% confidence interval; NS = Not significant; IQR = interquantile range.

4.2 Comparison of strategy success

Overall, there was recurrence or persistence of a pleural effusion, at least moderate in size, in 63 (37.5%) subjects in the CP group and 66 (34.2%) subjects in the IPC group ($p=0.51$). This occurred early in the CP group with a median of 12 days (IQR 7-28). In the IPC group, the median time to recurrence or persistence of a moderate pleural effusion was 43.5 days (IQR 14-126) as good control is expected while the catheter is still present. Despite this, among the 66 cases of recurrence or persistence of a pleural effusion in the IPC group, 40 occurred while the catheter was still in place.

The pleural effusion control rate (see Table 2 for definition) was low at 34.0% (Table 9A) in the CP group. The pleural effusion control rate was higher in the IPC group at 52.7% ($p<0.01$).

It can be argued that while subjects in the IPC group had better control of their pleural effusion, they had to contend with an indwelling pleural catheter and ancillary burdens such as care for the catheter and home care visits. We therefore analyzed the data in a another way, using as a measure of success the removal of the catheter less than 90 days after catheter insertion for any reason with absence of recurrence or persistence of a moderate pleural effusion within 180 days of catheter insertion (freedom from pleural effusion and catheter). For example, a patient who had the IPC removed on day 120 without recurrence of an effusion at or before 180 days would have been considered to have control of the pleural

effusion but not freedom from pleural effusion and catheter. For the CP group, this definition is equivalent to the control of the pleural effusion since all catheters were removed quickly in that group. This analysis of freedom from catheter and pleural effusion showed no difference in success rates between groups (see. Table 9A, CP 34.0%, IPC 25.8%, $p=0.19$).

These analyses were all repeated using logistic regression to account for potential important clinical confounders such as age, gender, tumour type, history of previous chest irradiation, intervention side and presence of malignant cells on pleural fluid cytology (Table 9B). Adjustment for these clinical covariates did not change the conclusions of the analyses.

Table 9. Comparison of strategy success.

A)

Clinical outcome	CP		IPC		p
	no./total no.	%	no./total no.	%	
Pleural effusion control	32/94	34.0%	59/112	52.7%	<0.01
Freedom from catheter and pleural effusion	32/94	34.0%	31/120	25.8%	NS

B)

Clinical outcome	Unadjusted		Adjusted	
	RR	OR	OR	p
Pleural effusion control	1.55 (1.11-2.16)	2.16 (1.23-3.80)	2.29 (1.24-4.22)	< 0.01
Freedom from catheter and pleural effusion	0.76 (0.50-1.15)	0.67 (0.37-1.22)	0.65 (0.34-1.23)	NS

Unadjusted analysis; B) Comparison of adjusted and unadjusted analysis. Adjustment was performed for age, gender, tumour type, history of previous chest irradiation, intervention side and presence of malignant cells on pleural fluid cytology; RR = relative risk; OR= odds ratio; NS = Not significant.

4.2.1 Mortality-Recurrence composite endpoint

Our previous analysis of moderate-size pleural effusion recurrence or persistence 180 days after catheter insertion excluded some patients who died before recurrence. Thus censoring due to death or loss to follow-up is not properly taken into account in that analysis. Furthermore, not only is recurrence of a pleural effusion undesirable but death itself as well. Therefore, we performed a survival analysis of a composite endpoint including moderate pleural effusion recurrence/persistence and death. Patients who did not undergo any of these two events were censored at the time of their last thoracic imaging at The Ottawa Hospital.

This analysis favoured the IPC groups both with unadjusted Kaplan-Meier analysis (log-rank $p < 0.03$) and Cox proportional hazards analysis (HR 0.768; $p < 0.02$). With Kaplan-Meier analysis, the median time-to-event was 55 days (95% CI 40-91) in the CP group and 101 days (95% CI 76-127) in the IPC group.

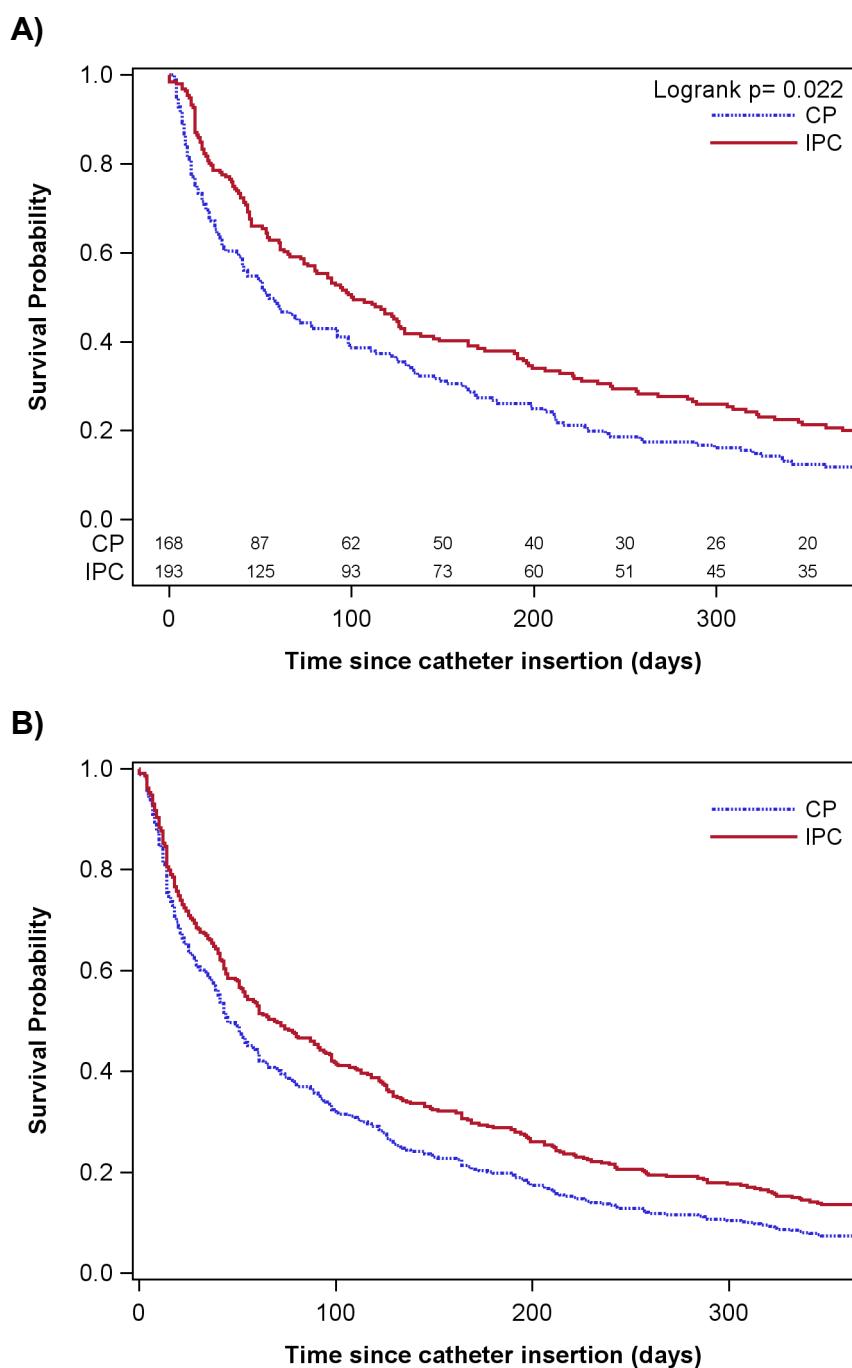


Figure 3. Survival analysis of mortality-pleural effusion recurrence composite endpoint.

A) Kaplan-Meier unadjusted analysis; B) Cox regression adjusted analysis. Predicted curves shown are for a male age 50-64 years old, with lung cancer, no history of chest irradiation and a right pleural effusion with malignant cells present on pleural fluid cytology.

4.3 Survival

4.3.1 Survival calculated from the date of catheter insertion

We examined survival calculated from the date of catheter insertion. The median survival time was 133 days (95% CI 98-168) in the CP group and 148 days (95% CI 110-197) in the IPC group. Survival time significantly favoured the IPC group (Figure 4) with the survival function curves separating progressively (log rank $p=0.042$).

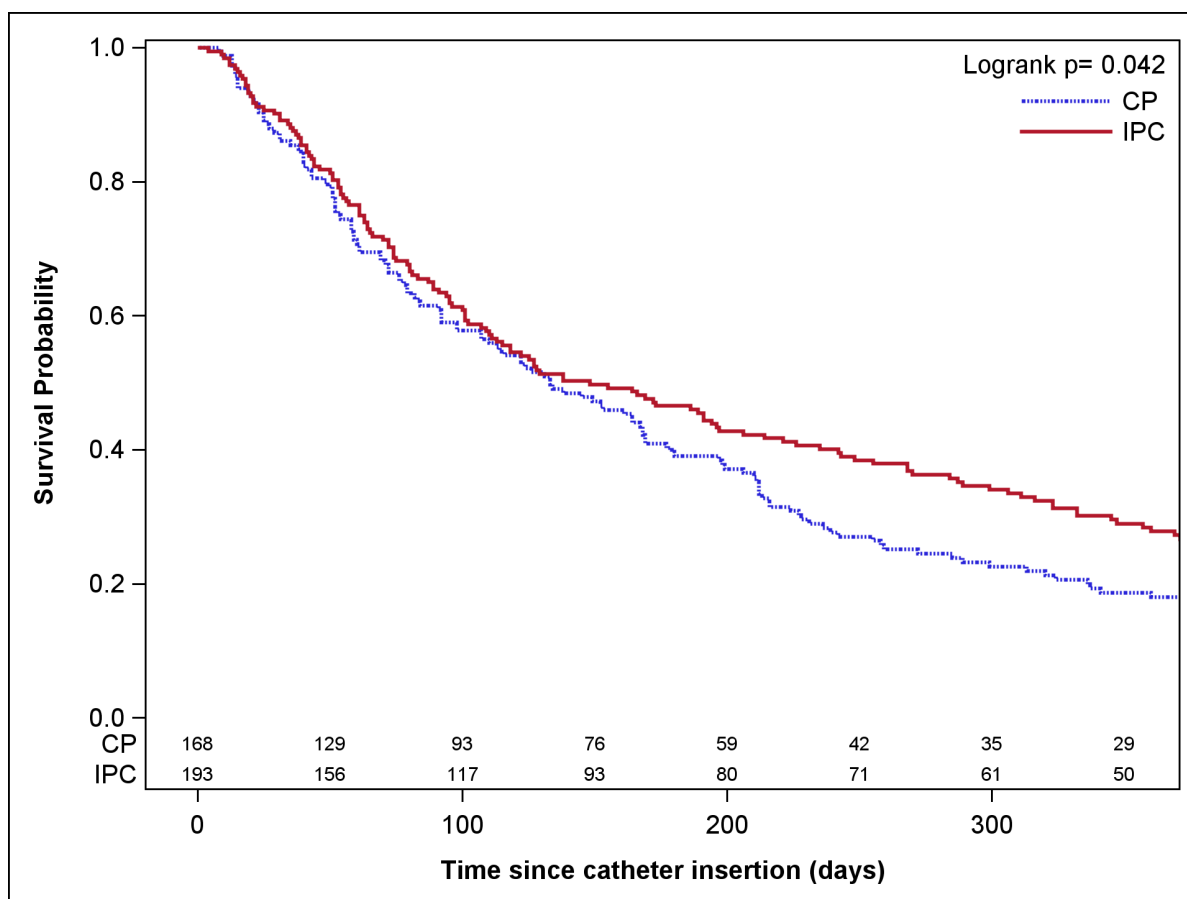


Figure 4. Kaplan-Meier survival curve since time of catheter insertion.

4.3.2 Survival calculated from the date of first report of a pleural effusion

There is a possibility of lead time bias in the previous analysis. For instance, since admission to hospital is needed for CP, subjects in that group may have had their pleural effusion managed later in the course of their disease than those in the IPC group. We therefore elected to analyze survival in an alternative way, using the start date as the date an Ottawa Hospital chest radiograph or computed tomography of the thorax was first reported to show a pleural effusion.

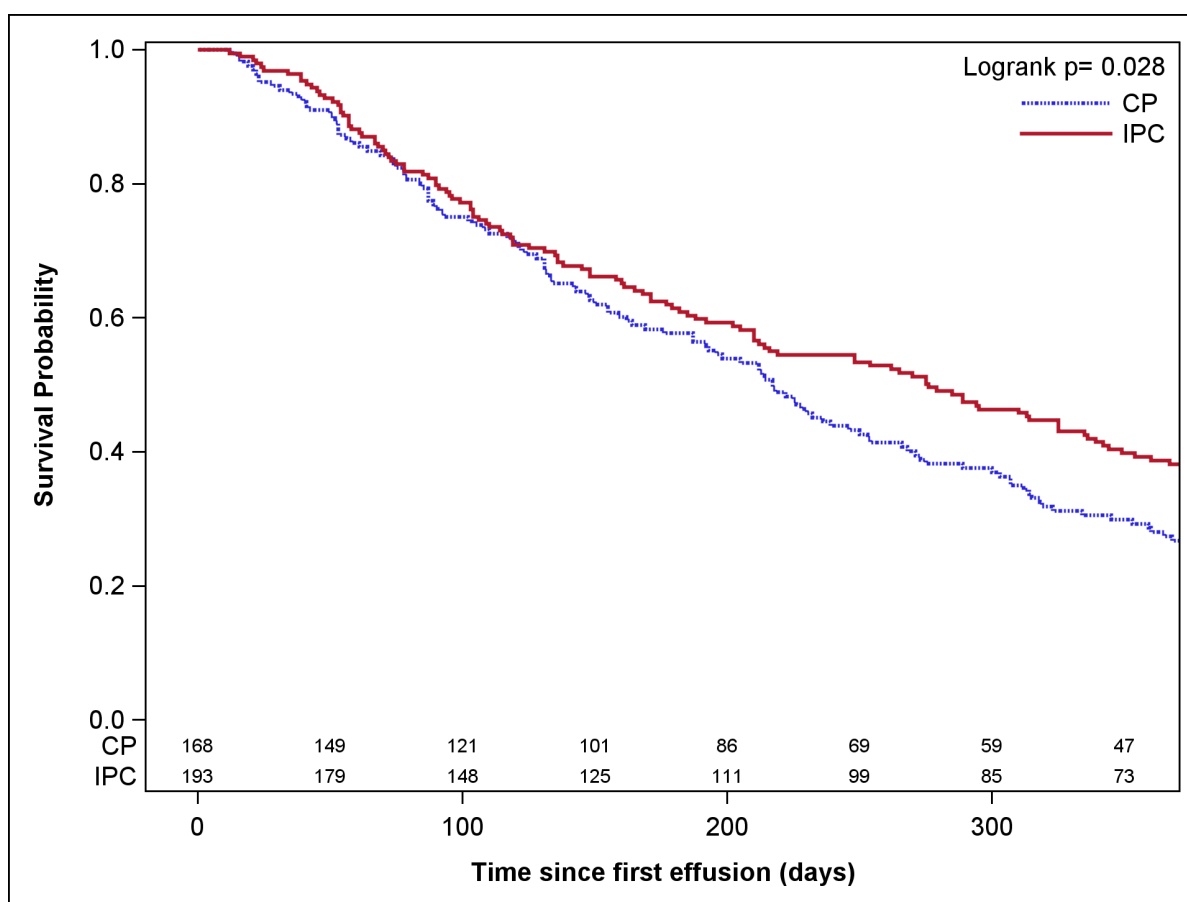


Figure 5. Kaplan-Meier survival curve since the first report of a pleural effusion.

Radiology reports were available for longer before catheter insertion in the IPC group than the CP group ($p=0.001$). The median duration from the first radiology report to catheter insertion was 302.5 days (IQR 31.5 – 776.5) in the CP group and 639 days in the IPC group (IQR 48-1503). Seven subjects in each group (CP: 4.2%, IPC: 3.6%) did not have a radiology report prior to catheter insertion. However, there was no significant difference between the two groups for the duration from the first report of a pleural effusion to catheter insertion. The median for this duration was 24 days (IQR 4-110) in the CP group and 33 days (IQR 7-113) in the IPC group ($p=0.35$). Thirteen subjects in the CP group (7.74%) and 20 subjects in the IPC group (10.36%) did not have a reported pleural effusion prior to catheter insertion.

The median survival since the first report of a pleural effusion was 217 days (95% CI 176-253) in the CP group and 276 days (95% CI 210-335) in the IPC group. Survival significantly favoured the IPC group according to the log-rank test ($p=0.028$) and the survival function curves separated progressively (Figure 5).

4.3.3 Adjusted survival analysis

Cox proportional hazards regression was then used to adjust the analysis for potential confounders such as age, gender, tumour type, history of previous chest irradiation, intervention side, and presence of malignant cells on pleural fluid cytology. Regardless of whether survival time was computed since catheter insertion (HR=0.754; $p<0.02$) or the first report of a pleural effusion (HR 0.735; $p<0.01$), survival time was still greater in the IPC group than the CP group in the adjusted analysis. Figure 6 depicts the survival according to group, using either approach, for a particular set of predictors. Other than treatment group, gender, tumour type and history of previous chest irradiation were significant predictors of survival since catheter insertion, while age, intervention side and presence of malignant cells on pleural fluid cytology were not. Only treatment group and tumour type were significant predictors of survival since the first report of a pleural effusion.

The proportional hazards assumption was tested by adding time-dependent interaction terms to the full model. All predictors were tested, including the treatment group and each predictor was tested separately. Using the approach of computing survival time since catheter insertion, the probability that the interaction term Time*BreastCancer was significant, where BreastCancer indicates that the tumour type is breast cancer, in a model whose reference tumour type was lung cancer, was $p<0.02$. The time-dependant interaction term including lymphoma was also significant with $p<0.04$. However, in a model including these time-

dependent interaction terms, survival was still significantly higher in the IPC group (HR=0.745; $p<0.02$).

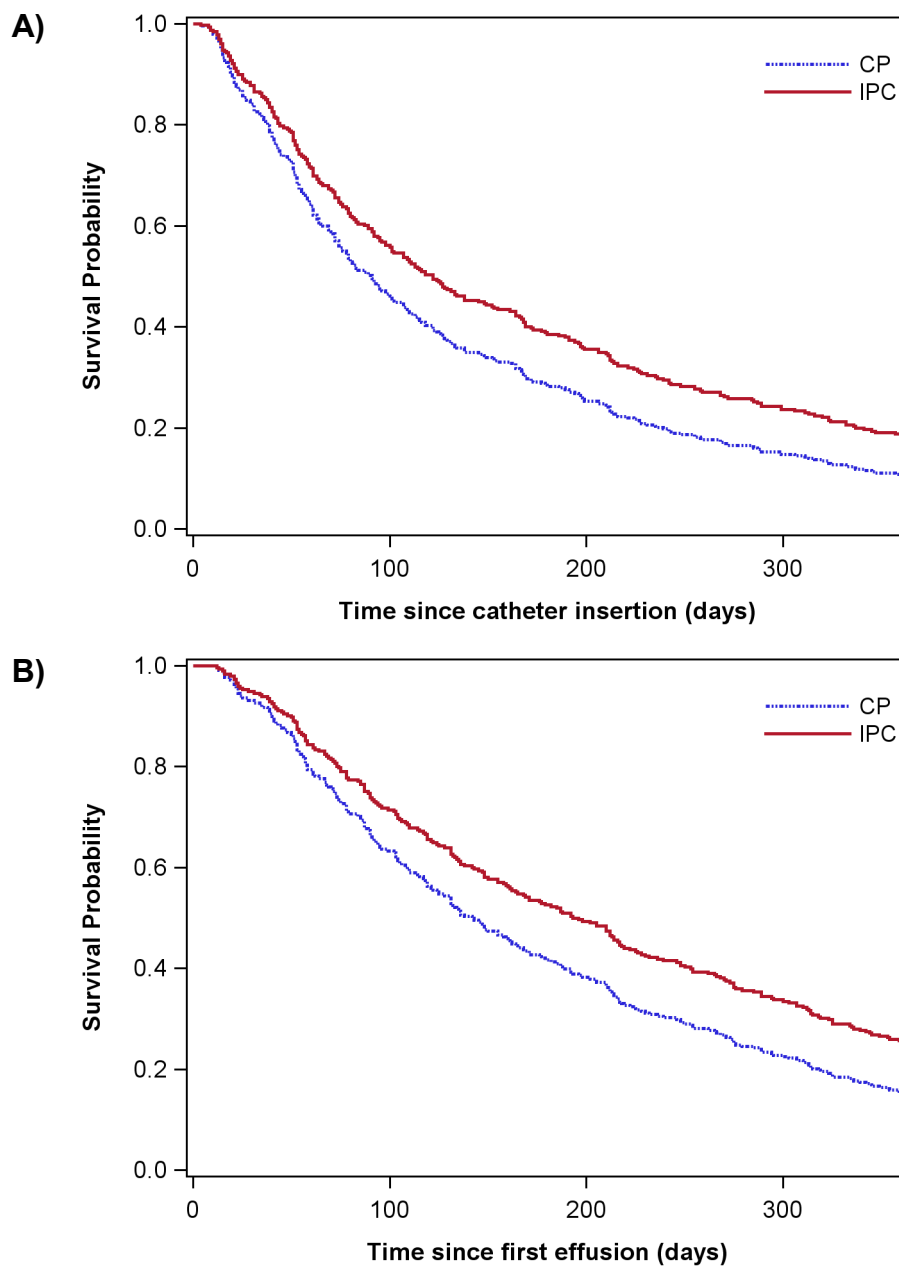


Figure 6. Adjusted predicted survival curves.

Prediction is for a male age 50-64 years old, with lung cancer, no history of chest irradiation and a right pleural effusion with malignant cells present on pleural fluid cytology.

A) Survival time computed since catheter insertion. B) Survival time computed since the first report of a pleural effusion.

4.3.4 Subgroup analysis

4.3.4.1 Tumour type subgroups

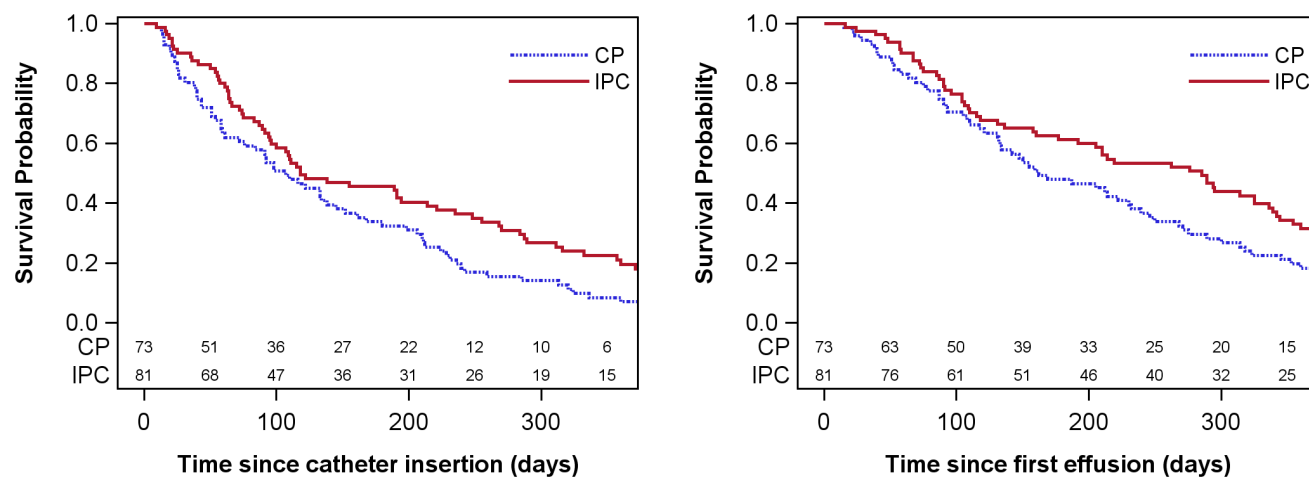
The survival analyses were repeated for 2 subgroups, those subjects with lung or breast cancer. There were few subjects with lymphoma and the subgroup with other malignancies was heterogeneous. These subgroups were therefore not examined.

While there was a trend towards longer survival since catheter insertion favouring the IPC group in the subgroup of subjects with lung cancer (Figure 7), the difference was not statistically significant neither with the Kaplan-Meier analysis with the log-rank test ($p < 0.10$) nor after adjustment for potential confounders with Cox proportional hazards regression (Wald χ^2 $p < 0.10$). The unadjusted median survival for subjects with lung cancer was 107 days in the CP group and 118 days in the IPC group. However, the IPC group did have significantly greater survival times when survival was computed since the first report of a pleural effusion. The unadjusted median survival since the first report of a pleural effusion was 162 days in the CP group and 285 days in the IPC group (Kaplan-Meier analysis log-rank test $p < 0.05$, and adjusted Cox regression analysis Wald χ^2 $p < 0.04$).

In the subgroup of subjects with breast cancer, the survival since catheter insertion was not significantly higher in the IPC group neither on unadjusted analysis nor after adjustment for confounders. Unadjusted median survival was 169 days in the CP group and 242 days in the IPC group. When survival was computed since the first report of a pleural effusion, there was still no significant difference between the two groups in either adjusted or

unadjusted analysis. The median survival since the first report of a pleural effusion in the subgroup of subjects with breast cancer was 315 days in the CP group and 335 days in the IPC group.

A) Lung Cancer Subgroup



B) Breast Cancer Subgroup

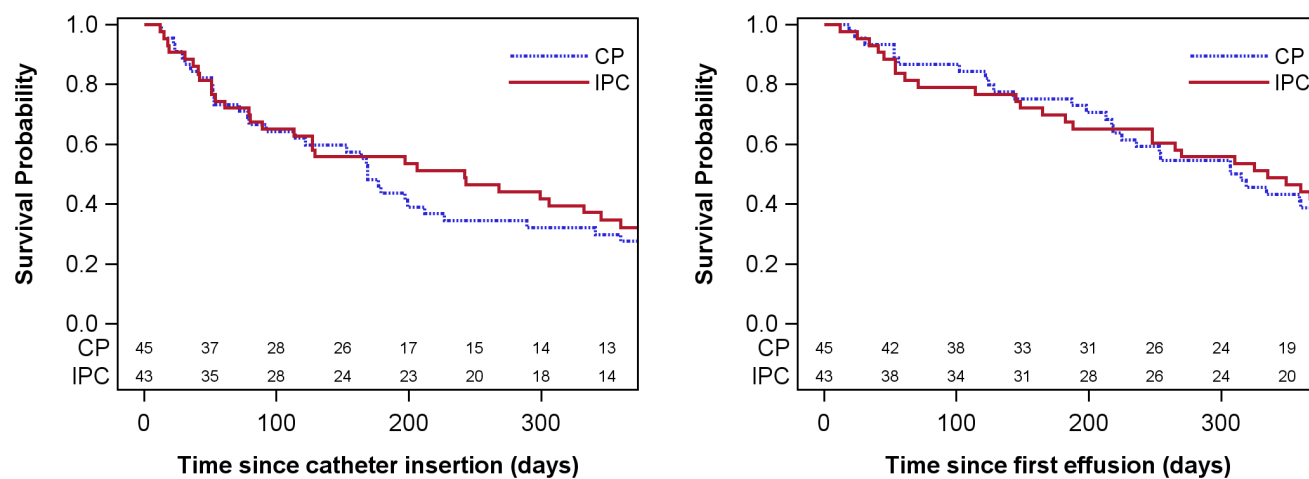


Figure 7. Kaplan-Meier survival curves for subgroups with lung or breast cancer.

4.3.4.2 Sensitivity subgroup analysis by ECOG performance status

Since the ECOG performance status is a significant predictor of survival, a significantly different distribution of ECOG status between the two groups could constitute an important selection bias. We attempted to account for this by restricting the study to patients with an ECOG of 4, as we suspected patients with an ECOG of 4 would have been more likely to be offered IPC insertion than CP. It is possible there would remain a distribution inequality between groups after excluding patients with an ECOG status of 4. Since the exact ECOG status was not available in the CP group, we could not adjust for the ECOG status in the Cox regression models to account for such a potential residual distribution inequality.

We compared the entire CP group to a subgroup of patients in the IPC group who had an ECOG performance status of 3 (Figure 8). We reasoned that the observed apparent survival benefit for the IPC group could not be due to an ECOG status selection bias if those in the IPC group with an ECOG score of 3 still had a survival advantage over those in the CP group who would have ECOG scores between 1 and 3. However, survival from the time of catheter insertion, and survival time from the time of the first pleural effusion were not significantly prolonged in the IPC ECOG 3 subgroup compared to all of the CP group patients (Kaplan-Meier log-rank $p=0.60$ and $p=0.34$, respectively).

Cox regression adjusted analysis (Figure 8B), did show a non-significant trend favouring the IPC ECOG 3 subgroup both when survival was computed since the time of catheter insertion (HR 0.87; 95% CI 0.68-1.12) and since the first report of a pleural effusion (HR 0.83; 95% CI 0.64-1.06).

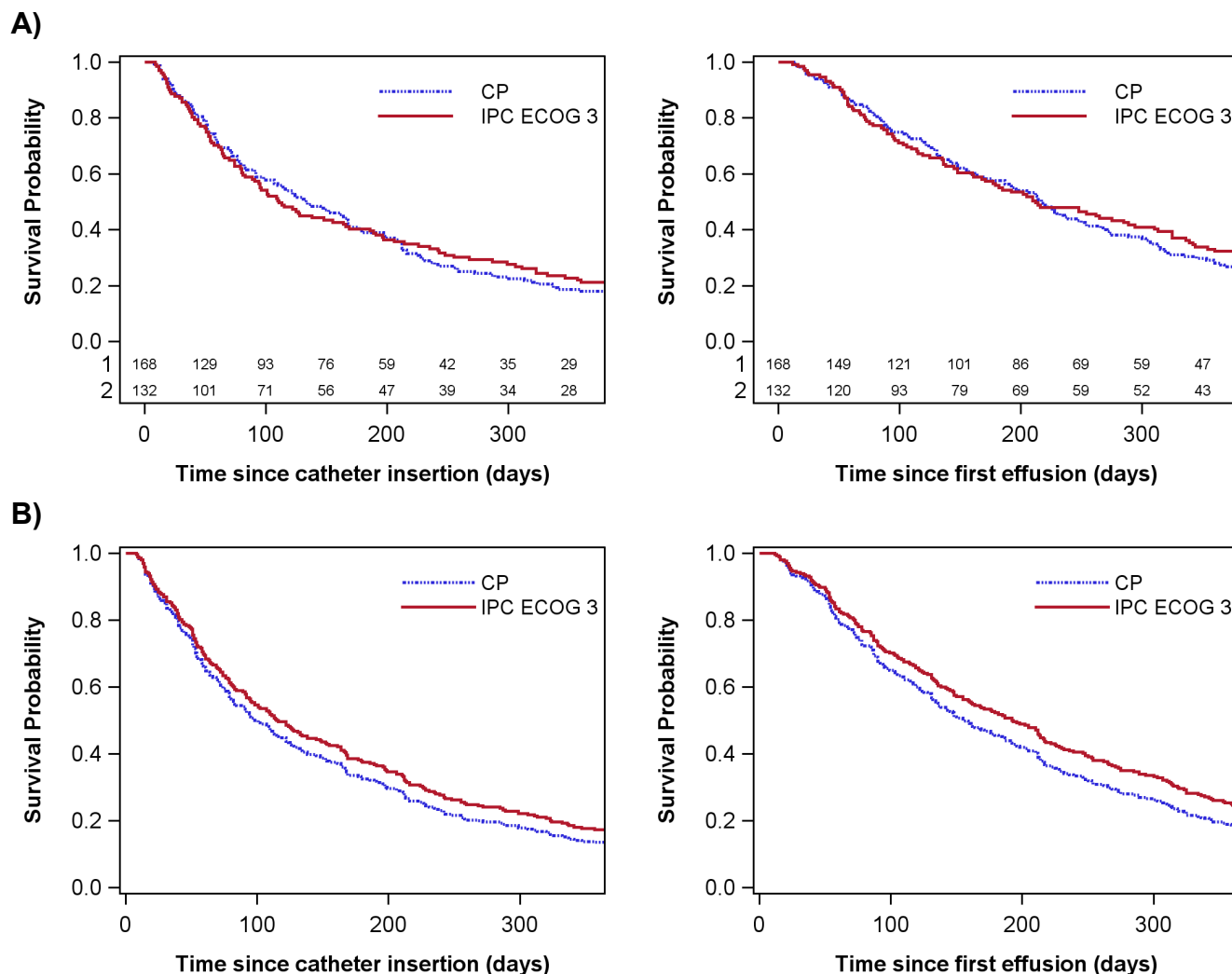


Figure 8. Survival of CP group compared with IPC ECOG 3 subgroup.

A) Kaplan-Meier unadjusted analysis; B) Cox regression adjusted analysis. Predicted curves shown are for a male age 50-64 years old, with lung cancer, no history of chest irradiation and a right pleural effusion with malignant cells present on pleural fluid cytology.

4.4 Requirement for subsequent intervention and readmission

Failure of a management strategy for a malignant or paramalignant pleural effusion may result in the need for further intervention. The most common intervention performed in this setting was repeat insertion of an ipsilateral temporary or indwelling pleural catheter (tube thoracostomy). This occurred with higher frequency in the CP group (Table 10) and was sometimes needed before pleurodesis was performed. Few subjects underwent other procedures and neither the rates of repeat chemical pleurodesis nor the rates of medical pleuroscopy or VATS were significantly different between the two groups. One of the two subjects who underwent CP in the IPC group required CP since management with an IPC was not possible due to absence of appropriate home care in the subject's area of residence.

Table 10. Requirement for subsequent procedures by group.

Procedure	CP		IPC		p
	n	%	n	%	
VATS or pleuroscopy	1	0.6%	2	1.0%	NS
Tube thoracostomy	27	16.1%	14	7.3%	<0.05
Chemical pleurodesis	5	3.0%	2	1.0%	NS

NS = Not significant.

The rate of readmissions to hospital was not significantly different between the two groups. It was 1.18/person-year (95% CI 0.99-1.42) in the CP group and 1.16/person-year (0.99-1.36) in the IPC group (p=0.27).

4.5 Complications

There was a smaller proportion of patients having at least one complication in the IPC group (46 patients, 23.8%) than in the CP group (58 patients, 34.5%, $p < 0.05$). The most common complication of clinical significance was the development of symptomatic loculation of pleural fluid (Table 11). This refers to the development of one or several pockets of pleural fluid that are not free-flowing and communicating with the remainder of the pleural space. This complicates management as these pockets may need to be drained separately. There was no significant difference in the frequency of this complication between the two groups (20 subjects, 11.9% in the CP group and 20 subjects, 10.4% in the IPC group; $p = 0.74$).

Despite concerns of ARDS with talc pleurodesis, there was only one possible case in the CP group and none in the IPC group. There was an increased rate of transient respiratory deterioration (lasting 24-48 hours after chemical pleurodesis) observed in the CP group. Similarly, there was a non-significant trend for higher rates of fever in the CP pleurodesis group.

A small proportion of subjects suffered a moderate or large pneumothorax, at a similar rate between the two groups. Other complications were not as frequent and did not differ significantly between groups. There were no cases of bronchopleural fistula formation.

Table 11. Complications by group.

Complication	CP		IPC		p
	n	%	n	%	
Symptomatic loculation	20	11.9%	20	10.4%	NS
Empyema	3	1.8%	4	2.1%	NS
Moderate or large pneumothorax	9	5.4%	9	4.7%	NS
Subcutaneous emphysema	3	1.8%	0	0.0%	NS
Cellulitis	2	1.2%	5	2.6%	NS
Blocked catheter	4	2.4%	4	2.1%	NS
Dislodged catheter	5	3.0%	2	1.0%	NS
Bleeding	1	0.6%	0	0.0%	NS
Tumour seeding	1	0.6%	0	0.0%	NS
Pain requiring catheter removal	7	4.2%	2	1.0%	NS
Transient respiratory deterioration	6	3.6%	0	0.0%	<0.01
ARDS	1	0.6%	0	0.0%	NS
Fever	7	4.2%	2	1.0%	NS
Fluid leak	0	0.0%	2	1.0%	NS

NS = Not significant.

Discussion

1 IPC group description

This study has identified one of the largest case series of patients treated with an indwelling pleural catheter for malignant or paramalignant pleural effusions. Compared to the largest series published by Tremblay et al. in 2006,¹³ the median age, proportion of right-sided effusion and distribution of underlying tumour cell types were relatively similar. Our series had a slightly higher proportion of females whereas both genders were equally represented in Tremblay's series. More than half of subjects considered for inclusion were rejected due to their ECOG performance status of 4. Most of remaining subjects had a poor ECOG performance status of 3 and very few had minimal limitation (status of 1). Subjects' Baseline Dyspnea Index scores indicated moderate to severe impairment. Although this information was only available for 136 of the 193 subjects in the IPC group, insertion of the IPC led to an improvement in the Transition Dyspnea Index score of 6.71 points after 2 weeks, which indicates moderate improvement and is well above the minimal clinically important difference of 1 point. This is expected, as drainage of a substantial pleural effusion by any means is expected to improve dyspnea. IPC insertion has also been shown to be effective in symptom control in several series.^{13,48,51}

We found the rate of spontaneous pleurodesis using IPC to be 24.8%. We defined spontaneous pleurodesis as the removal of the IPC for any reason less than 90 days after

catheter insertion with absence of recurrence or persistence of a moderate pleural effusion within 180 days of catheter insertion. This is at the lower end of the range of reported spontaneous pleurodesis rates (21-70%) and is likely due to our definition requiring a relatively early removal of the catheter. In fact, most published series did not specify either a time point at which spontaneous pleurodesis rates were computed or a follow-up period. Our definition is more rigorous and would enable better comparability of results. Furthermore our definition is more meaningful by requiring a relatively early removal of the catheter, since removal of the catheter due to spontaneous pleurodesis after a prolonged period of time is of much less interest and benefit to patients. The 90 days time point is not unreasonable since the median time to catheter removal was 59 days (95% CI 46-72) in the Tremblay series and 56 days in the IPC group of our study.

The overall median survival in the IPC group was 148 days (95% CI 110-197) from the time of catheter insertion. Although the confidence interval around it is relatively large, it is relatively close to the reported median survival of patients with malignant pleural effusion due to non-small cell lung cancer (4.3 months) and small cell lung cancer (3.7 months) and is lower than the reported survival of patients with malignant pleural effusion due to breast cancer (7.4 months).¹⁵ This is consistent with lung cancer being the underlying tumour type in 42.0% of patients in the IPC group. In fact, the survival since IPC insertion in the lung cancer subgroup (118 days) is close to the reported median survival as is that of the breast cancer subgroup (242 days). It may be argued that survival should have been higher in our study since we excluded subjects further in the natural course of their disease by excluding

those with an ECOG performance status of 4. However, the requirement for thoracoscopy in the comparative study would also have had a similar effect since debilitated subjects would not have been able to undergo thoracoscopy.

In a retrospective chart review comparing subjects managed with CP and IPC, Putnam et al. found the survival in the IPC group from the date of IPC insertion to be 4.18 months (95% CI 2.14-6.22), also similar to our results.⁵⁵ Subjects in the IPC group in that study were slightly younger with a mean age of 58.2 ± 1.1 years and had a more even gender distribution. Except for a slightly lower proportion of subjects with lung cancer in that study (36% overall vs 42% in our IPC group), underlying tumour cell type distribution was similar. The ECOG performance status was 1.39 (95% CI 1.23-1.55) for the outpatient IPC subgroup and 1.9 (95% CI 1.55-2.25) for the inpatient IPC subgroup while the vast majority of subjects in our study had a status of 3 (mean 2.61; 95% CI 2.53-2.70). Therefore, one might have suspected a higher survival in the Putnam study compared to our study, rather than similar survival.

2 Predictors of spontaneous pleurodesis in the IPC group

Warren et al. had found that spontaneous pleurodesis was more likely in patients with breast or gynecologic primary tumours, with cytologic positivity of pleural fluid and absence of chest wall irradiation.⁵⁷ However, Tremblay et al. found that there was no impact of age, gender, tumour cell type, side of occurrence and size of effusion at baseline.¹³ We tested all these variables, except for the size of effusion at baseline (although we did test a related measure, the amount of initial drainage), and found no significant predictors. Additionally, we tested pleural fluid pH and LDH, ECOG performance status and whether the catheter was inserted in the inpatient or outpatient setting; these variables were not significant predictors either. In all, we tested 11 variables in a population of 193 subjects which should be sufficient, even for a logistic regression model containing all variables. Categories of categorical variables were also sufficiently populated, with the exception of the category of ECOG performance status of 1.

However, it makes intuitive sense that if the lung is unable to re-expand to occupy the full volume of the chest cavity, a phenomenon termed trapped lung, pleural fluid would continue to accumulate in the pleural space between the lung and the chest wall and spontaneous pleurodesis would not occur. In agreement with this, Warren et al. found that those with complete lung re-expansion after 1 week were more likely to have the catheter removed. Tremblay et al. also found that lung re-expansion to the degree that the treated

hemithorax contained less than 20% fluid was a predictor of spontaneous pleurodesis. We did not test this hypothesis as collecting the necessary information would have been difficult.

3 IPC and CP group comparison

3.1 Strategy success

It is difficult to compare the two arms of our study in a meaningful way due to fundamental differences between the two interventions. The outcome of CP is determined early on and those who have good initial response do not tend to experience a recurrence at a later time: the median time to recurrence or persistence of a moderate pleural effusion was 12 days. By contrast, those managed with an IPC can expect better control while the catheter is still in place; the median time to persistence or recurrence of a pleural effusion in this group was 43.5 days. However, these patients have to contend with having the catheter in place attached to their body and leading to the inability to take baths and other burdens such as care of the catheter and home care visits.

To address these issues, we compared success rates between the two groups in two different ways. First, we compared pleural effusion control (see Table 2 for definition). This analysis favoured the IPC group. However, it does not take into account the earlier timing of success in the CP group nor the additional burden in the IPC group of an indwelling catheter. We therefore compared strategies in another way that required removal of the catheter within 90 days with absence of recurrence within 180 days (freedom from pleural effusion and catheter). With this alternative analysis, there no longer was a difference in success between groups.

Thus, using more restrictive definitions of success in the IPC group removes its advantage over the CP group. However, none of the definitions of success used above are ideal. In fact, since these interventions are palliative, the best outcomes are measures of quality of life or of utility. However, this kind of data was not available and this is yet another limitation related to the retrospective design. The pleural effusion control analysis in our study essentially ignored the disutility associated with an indwelling catheter. Conversely, the freedom from pleural effusion and catheter analysis overestimated the disutility associated with an indwelling catheter relatively to dyspnea by putting these two factors at par. The disutility associated with the indwelling catheter is likely not of the same order of magnitude as that associated with dyspnea not being controlled in the case of failed CP. Thus, both approaches are imperfect and we suggest further studies in the matter should either measure quality of life or the utilities associated with both dyspnea and the burdens of an indwelling catheter.

It should be noted that all these calculations were contingent upon the availability of information at the required time points. For instance, subjects who died within 180 days without having had a recurrence would have been excluded from the pleural effusion control analysis. Similarly, subjects in the IPC group who did not have their catheter removed and did not have follow-up for at least 180 days were excluded from the freedom from pleural effusion and catheter analysis. To properly account for censoring due to death or loss to follow-up, we performed a survival analysis from the time of catheter insertion of a composite endpoint including moderate pleural effusion recurrence/persistence and death.

This analysis favoured the IPC group both on unadjusted Kaplan-Meier analysis and Cox regression adjusted analysis.

3.2 Survival

Our data suggests survival time is greater for subjects treated with an IPC than with CP after tube thoracostomy. However, there are many limitations to our study, mainly arising from the retrospective design, although we tried to address several of them. There are several issues with group comparability. For instance, the two groups are not contemporary with the IPC group being selected from a later time period. It is then possible that the enhanced survival in this group is related to better overall management of the underlying malignancy, including better medical treatment or better access to care. For example, EGFR tyrosine kinase inhibitors became available in 2005 for treatment of advanced lung cancer.

There also was a higher proportion of females in the IPC group, partially accounted for by a slightly higher proportion of ovarian and primary peritoneal carcinoma in that group and a slightly higher proportion of mesothelioma (almost exclusively males) in the CP group. Heffner et al. obtained patient-level data on 417 patients from the corresponding authors of 9 studies reporting data on survival and pleural fluid pH in patients with malignant pleural effusions.¹⁴ On univariate Kaplan-Meier analysis, male sex was not found to be a significant predictor of survival with a hazard ratio of 0.95 (95% CI 0.85-1.07). Furthermore, ovarian cancer carried a poor survival similar to lung cancer with a median survival of 3.6 months (IQR 2.4-15.5) while mesothelioma was associated with a median survival of 6.0 months

(3.5-12.0). In a retrospective chart review of 85 patients with malignant pleural effusion, median survival was 135 days (n=13; range 10-330) for ovarian cancer and 180 days (n=20; range 30-690) for mesothelioma while median survival for lung cancer was 75 days (n=20; range 14-680).⁶⁴ The proportion of males was not significantly different between the group of subjects who survived more than 3 months and those who did not. Thus, the overall impact on survival of gender and tumour type imbalance between the IPC and CP group is uncertain and the interpretation of its impact on our findings is unclear.

Since talc pleurodesis is thought to carry higher risk, we surmised that some patients would have been deemed too ill to undergo CP and would have been selected out of that group while patients with similar characteristics would have been included in the IPC group. In an attempt to eliminate this potential selection bias, we excluded from our study patients who were faring poorly, those with an ECOG performance status of 4. Our results support this presumption; while many more patients were considered for inclusion in the IPC group, a large proportion of them were excluded such that the number of patients included in the CP and IPC groups was relatively similar. However, a difference in ECOG determination may also explain the higher proportion of patients excluded from the IPC group due to an ECOG performance status of 4. The exact ECOG status was determined prospectively by the interventionist by direct questioning of the subjects in the IPC group. In the CP group, we determined if the subject had an ECOG performance status of 4 (ie completely disabled, confined to bed or chair) retrospectively from data available in the patient's paper chart. Nonetheless, given the larger number of patients considered for inclusion in the IPC group

with relatively similar numbers of patients included in both groups in the end, our hypothesis of more and sicker patients being offered an IPC than CP is likely a better explanation of our data than a bias due to differential ECOG performance status determination.

There is a possibility that there would remain a differential distribution of ECOG performance scores between the two groups after excluding those with an ECOG status of 4. We could not adjust for ECOG performance status in the Cox regression models as the exact ECOG score was not available in the CP group. We therefore compared the survival of those in the IPC group with an ECOG status of 3 with all patients in the CP group (with an ECOG status between 1 and 3). There was no significant difference in survival for that comparison, both when computing survival since the time of catheter insertion and since the first report of a pleural effusion. However, there was a non-significant trend favouring the IPC ECOG 3 subgroup on adjusted analysis using either method of survival computation. Had these analyses found a significant difference favouring the IPC ECOG 3 subgroup, we could have concluded that there was a survival advantage favouring the IPC group, irrespective of ECOG status imbalance between groups and our results would have been strengthened. However, the fact that these analyses did not uncover a significant difference in survival does not undermine our results as they compared a subgroup of sicker patients (ECOG 3) from the IPC group to the whole CP group which likely contained less sick patients (ECOG 1 and 2) as well as patient with an ECOG status of 3. Furthermore, there were far more ill patients with an ECOG status of 4 considered for inclusion in the IPC group than the CP group.

It should be noted that, due to the method used to identify subjects in the CP group, our study does not compare directly a strategy of standard chest tube insertion followed by chemical pleurodesis with a strategy of indwelling pleural catheter insertion. A CP strategy involves tube thoracostomy first using a standard chest tube followed by CP. Some subjects undergo tube thoracostomy without CP eventually being undertaken. Thus, rather than compare strategies of CP and IPC insertion, our study compares subjects who have in fact undergone CP to those who have undergone IPC insertion. Reasons for not being offered CP after undergoing tube thoracostomy would include technical factors as well as subjects being deemed too ill for the procedure. It is then quite possible that the survival of patients undergoing tube thoracostomy with the view of CP is poorer than the survival of subjects actually undergoing CP. This would reinforce rather than undermine our finding of better survival in the IPC group.

Lead time bias is another potential issue; subjects may have been considered at a different time in the course of their disease for CP as opposed to IPC insertion. It is also possible that delays for the two procedures are not similar. We therefore analysed survival using an alternative approach using the date an Ottawa Hospital chest radiograph or computed tomography of the thorax was first reported to show a pleural effusion as the start date. This approach has its own pitfalls. Although it only considers imaging studies at The Ottawa Hospital, we did not expect this would impact the two groups differentially. Although radiology reports were available for longer in the IPC group, this does not necessarily imply that there was a difference between groups in the timing of detection of pleural effusions by

imaging. Indeed, the earlier studies in the IPC group may have been done at a time when no pleural effusion was present and the longer availability of radiology reports in the IPC group does not provide information about the availability and timing of imaging studies at an opportune time to detect the development of a pleural effusion.

There was no difference between the two groups for the duration from the first report of a pleural effusion to catheter insertion. While it was conceivable that delays for CP would be longer than for IPC insertion due to the requirement of admission to hospital, the longer delays of elective admission are potentially balanced by the shorter delays for urgent admission. Out of 193 subjects, 46 underwent IPC insertion in the inpatient setting, presumably urgently but the proportion of patients in the CP admitted to hospital urgently rather than electively is unknown and difficult to determine. Keeping these caveats in mind, survival since the time of pleural effusion was still significantly better in the IPC group than the CP group.

The potential survival advantage of the IPC strategy is therefore robust to the survival computation method. However, the biological mechanism of such a survival advantage with the IPC strategy is not immediately apparent. Possibly, better symptom control with an IPC delays the time when it is concluded that no further options are available for a patient, and sedating medications, which may lead to an earlier demise, are prescribed.

Among patients with lung cancer, survival since catheter insertion and since the first report of a pleural effusion tended to be longer in the IPC group both with Kaplan-Meier analysis with the log-rank test and with adjustment for potential confounders using Cox proportional hazards models, but the difference was not statistically significant. This may be due to lack of power given the smaller sample size (154 patients). Indeed, when survival was computed since the first report of a pleural effusion, the difference between treatment groups was significant for those with lung cancer, favouring the IPC group.

However, among patients with breast cancer, it is difficult to discern any trend: the survival curves for both treatment groups are close together both when survival is computed since the time of catheter insertion and since the time of the first report of a pleural effusion. It may be argued that the power for survival analysis is even further reduced in the breast cancer subgroup due to the even lower number of patients (88 in all) and overall longer average survival. However, it is possible that the potential survival benefit with the IPC strategy seen in the general study population and possibly in the lung cancer subgroup is not present in the breast cancer subgroup. It is already difficult to conceive why an IPC strategy would lead to a survival benefit, and the mechanism by which it would do so in certain subgroups only is even more elusive.

Survival in our study seemed somewhat longer than reported in the literature in the CP group. Median survival since catheter insertion in the CP group was 133 days (95% CI 98-168, IQR 54-272) while median survival of subjects with malignant pleural effusion in a

retrospective study was 105 days⁶⁴ and 2.8 months (IQR 1.0-5.3) in another study.¹⁴ The reported survival for subjects with a malignant pleural effusion and lung cancer is about 3-4 months^{14,15}, which is similar to the median survival (since catheter insertion) in our study for patients with lung cancer in the CP group of 107 days (95% CI 61-145, IQR 40-224). Therefore, if there truly is a difference in survival for CP patients between our study and the literature, it may be due to different population composition rather than different survival for the same underlying tumour type. If survival in our CP group was poorer than reported in the literature, it could have been argued that the longer survival noted in the IPC group represented a 'regression to the mean' from a poor survival in the CP group rather than a true improvement, but this is clearly not the case.

Factors affecting survival of subjects with malignant pleural effusions previously identified in the literature included tumour cell type, pleural fluid pH and performance status.^{14,17} While we attempted to control for these potential confounders and for other biases, the retrospective, non-randomized design introduces an additional difficulty: the inability to control for unknown confounders. For instance, recently published studies have identified additional factors predictive of survival in subjects with malignant pleural effusions that we did not control for such as low pleural fluid glucose, leukocytosis, hypoxemia and hypoalbuminemia.^{16,64}

3.3 Need for subsequent intervention and re-admission

Few subsequent procedures were employed in the management of pleural effusions in our study and no valid conclusion can be made about the differential requirement of VATS/Pleuroscopy or subsequent chemical pleurodesis between the CP and IPC groups. In any case, the validity of such comparisons can be questioned since, often, no further procedure is offered after the failure of either CP or IPC as the patient may be deemed palliative and too ill for further intervention. The requirement for further tube thoracostomy was higher in the CP group, but this is unsurprising since those in the IPC group often still have the IPC in place and are therefore much less likely to require an additional catheter.

3.4 Complications

Both interventions were relatively safe. The most common adverse event was the development of symptomatic loculations. This occurred at a rate of 10.4% in the IPC group, similar to the rate of 8.4% in the Tremblay series.¹³ While this rate was expected to be higher in the CP group, since the mechanism of chemical pleurodesis is the creation of adhesions, it was not significantly different at 11.9%. The second most common complication in both groups was the development of a moderate or large pneumothorax at a rate of 5.4% in the CP group and 4.7% in the IPC group (not significantly different). This seems somewhat higher than in the Tremblay series where the rate of either pneumothorax, subcutaneous emphysema or bronchopleural fistula was 2.4%. Since we used the size of the pneumothorax on radiology reports rather than clinical data to determine its significance, we may have overestimated the number of clinically significant pneumothoraces.

Other adverse events were relatively uncommon. Although infection is a feared complication with any indwelling foreign body, the rate of cellulitis was only 2.6% in the IPC group and most importantly the rate of empyema was 2.1%. This is similar to the Tremblay series where the cellulitis rate was 1.6% and the empyema rate was 3.2%. The infection rate in the Warren series was 2.2%.⁴⁶

Although some authors advocate against the use of talc due to risk of ARDS, there was only one potential case of ARDS (0.6%) in our CP group. However, there were 6 cases (3.6%) of transient respiratory deterioration lasting less than 48 hours. There were none in the IPC group ($p < 0.01$). Thus talc may be safer than previously suspected. However, the few cases of transient respiratory deterioration may still preclude the use of talc in the outpatient setting.

4 Summary

In this report, we describe one of the largest case series of patients treated with an IPC for malignant or paramalignant pleural effusions. We found a substantial improvement in dyspnea 2 weeks after the insertion of an IPC. The spontaneous pleurodesis rate in our study was 24.8%, in the lower range of reports in the literature, likely due to our strict definition. We could not validate any of the predictors of spontaneous pleurodesis described in previous published case series. Survival in our study was similar to other IPC case series.

Our results suggest an intriguing survival benefit to management of malignant or paramalignant pleural effusions with an IPC rather than CP after tube thoracostomy. This conclusion is robust to the survival computation method but may not apply to all subgroups such as patients with breast cancer. These results are hypothesis-generating rather than confirmatory given difficulties introduced mostly by the retrospective design of this study as well as given the lack of obvious biological plausibility for such an effect. For instance, the retrospective design makes it difficult to account for important confounders such as the ECOG performance status, especially since it could not be measured accurately in the CP group. This design also does not allow us to account for unsuspected or unmeasured confounders. Methodological limitations of the study are summarized in Table 12. One hypothesis is that potentially better symptom control with an IPC delays the time when no other options are available for control of dyspnea than medications that can hasten the dying

process. Certainly, further examination of this potential survival benefit using prospective randomized controlled trials comparing CP to IPC insertion is warranted.

Table 12. Summary of methodological limitations

Limitation	Method used to address limitation
Groups not contemporary	None
Groups differ in composition	Adjusted analysis
Groups may differ in composition: severity of illness	Excluded patients with ECOG 4
Could not measure ECOG score accurately in CP group	Compared survival of IPC patients with ECOG3 to all CP patients
Could not account for unsuspected or unmeasured confounders	None
Possible lead time bias for survival analysis	Alternative analysis with survival calculated from the time of the first report of a pleural effusion
Restricted outcome measure choice: outcome measures chosen are not ideal and could not measure quality of life	None

Appendices

Appendix I- Baseline Dyspnea Index

Done on day 1:

1) Functional Impairment - Questions:

Have you recently had to completely stop any usual activities because of shortness of breath? (Ex. Have you had to stop doing housework, walking, bathing, carrying groceries, lawnwork or shopping because of shortness of breath?)

If yes list up to 3 activities recently stopped.

If patient answers no, ask the next question:

Have you recently had to reduce any of your usual activities because of shortness of breath? (Ex. Have you had to reduce your housework, walking, bathing, carrying groceries, lawnwork or shopping, because of shortness of breath?).

If yes list up to 3 activities recently reduced.

Now ask two more questions related to work activities:

Have had to stop working because of shortness of breath?

If you are retired, do you think that you could still work at your last job, or would you be too short of breath to work at your last job?

1) Functional Impairment - Grading

Based on the answers to the previous questions grade the patient's functional impairment category as follows:

Grade 4 - <i>No impairment</i>	Patient is able to carry out his usual activities and occupation without shortness of breath.
Grade3 - <i>Slight impairment</i>	No activities have been abandoned but some activities have been reduced
Grade 2 - <i>Moderate impairment</i>	Patient has changed jobs <i>or</i> has recently stopped at least one usual activity due to shortness of breath.
Grade 1 - <i>Severe impairment</i>	Patient is unable to work <i>or</i> has given up most usual activities due to shortness of breath.
Grade 0 - <i>Very severe impairment</i>	Patient is unable to work <i>and</i> has given up most usual activities due to shortness of breath.
W: <i>Amount Uncertain</i>	Patient is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.
X: <i>Unknown</i>	Information unavailable regarding impairment
Y: <i>Impaired for reasons other than shortness of breath</i>	For example musculoskeletal problems or chest pain.

2) Magnitude of task- Questions and Grading

Are you currently short of breath sitting, lying down or at rest?

If yes- grade 0. If no, then continue and ask next question>

Do you currently become short of breath walking, washing or standing?

If yes - grade 1. If no, then continue and ask next question>

Do you currently become short of breath walking uphill, climbing less than 3 flights of stairs or carrying a light load on level ground?

If yes- grade 2. If no, then continue and ask next question>

Do you become short of breath walking up a steep hill, climbing more than 3 flights of stairs, or carrying a moderate load on level ground?

If yes- grade 3. If no, then continue and ask next question>

Do you currently become short of breath only when carrying very heavy loads on level ground, running or carrying a light load uphill?

If yes- grade 4.

W: Amount Uncertain - Patient's ability to perform tasks is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.

X: Unknown - Information unavailable regarding limitation of magnitude of task

Y: Impaired for reasons other than shortness of breath - For example musculoskeletal problems or chest pain.

3. Magnitude of effort - Questions and Grading

Ask the patient the most strenuous task he can perform for at least 5 minutes: Write it in here:

Then ask the patient the following questions:

When you _____ (insert task here) can you do it *briskly*, without pausing because of short of breath and without slowing down to rest? **If yes- grade 4.** If no, then continue and ask the question>

When you _____ (insert task here) can you do it *slowly* but without pausing or stopping to catch your breath? **If yes- grade 3.** If no, then continue and ask next question>

When you _____ (insert task here) can you do it *slowly* and do you need to pause once or twice to catch your breath? **If yes- grade 2.** If no, then continue and ask next question>

When you _____ (insert task here) can you do it *slowly* and do you need to pause many times to catch your breath? **If yes- grade 1.** If no, then continue and ask next question>

Can you not do any task, ie. Are you short of breath while lying, sitting or standing? **If yes- grade 0**

W: *Amount Uncertain* - Patient exertional ability is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.

X: *Unknown* - Information unavailable regarding limitation of effort.

Y: *Impaired for reasons other than shortness of breath* - For example musculoskeletal problems or chest pain.

Results:

a) Functional Impairment grade (page 2)

_____ (range 0 - 4)

b) Magnitude of Task grade (page 3)

_____ (range 0 - 4)

c) Magnitude of Effort grade (page 4)

_____ (range 0 - 4)

Total = a+b+c = _____ (range 0-12)

Appendix II - Transition Dyspnea Index

Done on 2 weeks follow-up

1) Change in Functional Impairment - Questions:

Ask the patient to recall his/her breathlessness at the baseline visit in the Emergency Department and provide him with his previous response from page 1: (ex. 10 days ago you had to reduce your housework load and you had to stop carrying groceries and stop taking baths because of your shortness of breath.)

Questions:

Since the last time we spoke 10 days ago have you noticed an improvement in your activity level?

Y____ N____

If patient answers yes then ask:

Are there activities you couldn't do 10 days ago that you now can do again?

Are there activities you had to reduce 10 days ago which you now can do again normally?
Have you been able to go back to work since I last spoke with you 10 days ago?

If the patient answers no ask:

Are there activities you have had to stop doing over the last 10 days because of shortness of breath?

Have you had to reduce doing any activities over the last 10 days because of shortness of breath?

Have you had to stop working because of shortness of breath since I last spoke with you 10 days ago?

1) Change in Functional Impairment- Grading:

Based on the above answers, grade change in functional impairment as:

-3 Major deterioration

Formerly working and has had to stop working and has completely stopped some of usual activities due to shortness of breath.

-2 Moderate deterioration

Formerly working and has had to stop working or has completely stopped some of usual activities due to shortness of breath.

-1 Minor deterioration

Has changed to a lighter job or has reduced activity level due to shortness of breath.

0 No change

No change in activity level.

+1 Minor improvement

Able to resume work at a reduced pace, or has resumed some activities with more vigor than previously due to improvement in shortness of breath.

+2 Moderate improvement

Able to return to work at nearly usual pace or able to return to most activities with moderate restriction only.

+3 Major improvement

Able to return to work at former pace and able to return to full activities with only mild restriction due to improvement of shortness of breath.

Z: Further impairment for reasons other than shortness of breath

Subject has stopped working, reduced work, or given up or reduced other activities for other reasons. For example, other medical problems, being laid off from work, etc.

2) Change in Magnitude of Task - Questions:

Are you currently short of breath sitting, lying down or at rest? **If yes- grade 0.** If no, then continue and ask next question>

Do you currently become short of breath walking, washing or standing? **If yes - grade 1.** If no, then continue and ask next question>

Do you currently become short of breath walking uphill, climbing less than 3 flights of stairs, or carrying a light load on level ground? **If yes- grade 2.** If no, then continue and ask next question>

Do you currently become short of breath walking up a steep hill, climbing more than 3 flights of stairs, or carrying a moderate load on level ground? **If yes- grade 3.** If no, then continue and ask next question>

Do you currently become short of breath only when carrying very heavy loads on level ground, running, or carrying a light load uphill? **If yes- grade 4.**

2) Change in Magnitude of Task - Grading:

Now, record the patient's magnitude of task grade from baseline 10 days ago:

Magnitude of task grade at baseline ten days ago = _____ (from page 3)

Magnitude of task grade today = _____

What has been the patient's change in grade from baseline?

-3: Major deterioration if he has deteriorated 2 grades or greater from baseline.
(ex. If ten days ago he scored a grade 3 on magnitude of task and today he scores grade 1 or 0)

-2: Moderate deterioration: if he has deteriorated 1 grade from baseline.

-1: Minor deterioration: if he has deteriorated within grade, but has not changed grades.

0: No change

+1: Minor improvement: Has improved within grade, but has not changed grades.

+2: Moderate improvement: Has improved one grade from baseline.

+3: Major improvement: Has improved two grades or greater from baseline.

Z: Further impairment for reasons other than of shortness breath. Subject has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problem or chest pain.

3) Change in Magnitude of Effort- Questions:

Remind the patient of the most strenuous 5 minute task which he said that he could do ten days ago and remind him of his score ten days ago.

(ex. 10 days ago the most strenuous 5 minute task you said that you could do was _____ and you indicated you could do it slowly and that you would need to pause once or twice to catch your breath.)

Now ask:

Compared to 10 days ago do you think that you would find _____ (insert the task here) to be easier or harder?

Could you do _____ (insert the task here) faster than you could 10 days ago, or would you have to go slower to avoid shortness of breath?

Would you need to take more pauses now compared to ten days ago, or fewer pauses?

3) Change in Magnitude of Effort-Grading:

Now grade the change in magnitude of effort:

<i>-3: Major deterioration</i>	Patient must perform task much slower to avoid shortness of breath. Task now takes 50 -100% longer to complete than required at baseline.
<i>-2: Moderate deterioration</i>	Patient can do task as quickly as before but requires more pauses compared to baseline.
<i>-1: Minor deterioration</i>	Does not require more pauses, but does task at a slightly slower pace to avoid shortness of breath.
<i>0: No change</i>	No change
<i>+1: Minor improvement</i>	Able to carry out task somewhat more rapidly than previously
<i>+2: Moderate improvement</i>	Able to carry out task with fewer pauses and somewhat more rapidly without shortness of breath.
<i>+3: Major improvement</i>	Task can be performed 50-100% more rapidly than at baseline, few, if any, pauses.
<i>Z: Further impairment for reasons other than shortness of breath.</i>	Subject has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problem or chest pain.

Results:**Transition Dyspnea Index:**

a) Change in Functional Impairment grade (page 7)

_____ (range is from -3 to +3)

b) Change in Magnitude of Task grade (page 9)

_____ (range is from -3 to +3)

c) Change in Magnitude of Effort grade (page 11)

_____ (range is from -3 to +3)

Total score a+b+c = _____ (range is from -9 to +9)

Adapted from Mahler D et al. Chest 1984;85:751-758

References

- 1 Albertine KH, Wiener-Kronish JP, Bastacky J, et al. No evidence for mesothelial cell contact across the costal pleural space of sheep. *J Appl Physiol* 1991; 70:123-134
- 2 Broaddus VC, Light RW. Pleural Effusion. In: Mason RJ, Broaddus VC, Murray JF, et al., eds. *Murray and Nadel's Textbook of Respiratory Medicine*, 2005; 1913-1960
- 3 Broaddus VC, Wiener-Kronish JP, Berthiaume Y, et al. Removal of pleural liquid and protein by lymphatics in awake sheep. *J Appl Physiol* 1988; 64:384-390
- 4 Zocchi L. Physiology and pathophysiology of pleural fluid turnover. *Eur Respir J* 2002; 20:1545-1558
- 5 Light RW, Macgregor MI, Luchsinger PC, et al. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med* 1972; 77:507-513
- 6 Sahn SA. Malignancy metastatic to the pleura. *Clin Chest Med* 1998; 19:351-361
- 7 Marel M, Zrustova M, Stasny B, et al. The incidence of pleural effusion in a well-defined region. Epidemiologic study in central Bohemia. *Chest* 1993; 104:1486-1489
- 8 Antunes G, Neville E. Management of malignant pleural effusions. *Thorax* 2000; 55:981-983
- 9 Lombardi G, Zustovich F, Nicoletto MO, et al. Diagnosis and treatment of malignant pleural effusion: a systematic literature review and new approaches. *Am J Clin Oncol*; 33:420-423

- 10 Chernow B, Sahn SA. Carcinomatous involvement of the pleura: an analysis of 96 patients. *Am J Med* 1977; 63:695-702
- 11 Boylan AM, Broaddus VC. Pleural Effusion. In: Mason RJ, Broaddus VC, Murray JF, et al., eds. *Murray and Nadel's Textbook of Respiratory Medicine*, 2005; 1989-2009
- 12 Schneider T, Reimer P, Storz K, et al. Recurrent pleural effusion: who benefits from a tunneled pleural catheter? *Thorac Cardiovasc Surg* 2009; 57:42-46
- 13 Tremblay A, Michaud G. Single-center experience with 250 tunnelled pleural catheter insertions for malignant pleural effusion. *Chest* 2006; 129:362-368
- 14 Heffner JE, Nietert PJ, Barbieri C. Pleural fluid pH as a predictor of survival for patients with malignant pleural effusions. *Chest* 2000; 117:79-86
- 15 Sanchez-Armengol A, Rodriguez-Panadero F. Survival and talc pleurodesis in metastatic pleural carcinoma, revisited. Report of 125 cases. *Chest* 1993; 104:1482-1485
- 16 Pilling JE, Dusmet ME, Ladas G, et al. Prognostic factors for survival after surgical palliation of malignant pleural effusion. *J Thorac Oncol*; 5:1544-1550
- 17 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; 117:73-78
- 18 Stark P. The pleura. In: Taveras, Ferrucci, eds. *Radiology. Diagnosis Imaging, Intervention*. Philadelphia: Lippincott, 2000; 1-29

- 19 Moskowitz H, Platt RT, Schachar R, et al. Roentgen visualization of minute pleural effusion. An experimental study to determine the minimum amount of pleural fluid visible on a radiograph. *Radiology* 1973; 109:33-35
- 20 Maskell NA, Butland RJ. BTS guidelines for the investigation of a unilateral pleural effusion in adults. *Thorax* 2003; 58 Suppl 2:ii8-17
- 21 Maskell NA, Gleeson FV, Davies RJ. Standard pleural biopsy versus CT-guided cutting-needle biopsy for diagnosis of malignant disease in pleural effusions: a randomised controlled trial. *Lancet* 2003; 361:1326-1330
- 22 Lee YC, Light RW. Management of malignant pleural effusions. *Respirology* 2004; 9:148-156
- 23 Haas AR, Sterman DH, Musani AI. Malignant pleural effusions: management options with consideration of coding, billing, and a decision approach. *Chest* 2007; 132:1036-1041
- 24 Heffner JE, Klein JS. Recent advances in the diagnosis and management of malignant pleural effusions. *Mayo Clin Proc* 2008; 83:235-250
- 25 Tan C, Sedrakyan A, Browne J, et al. The evidence on the effectiveness of management for malignant pleural effusion: a systematic review. *Eur J Cardiothorac Surg* 2006; 29:829-838
- 26 Dresler CM, Olak J, Herndon JE, 2nd, et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest* 2005; 127:909-915
- 27 Noppen M. Who's (still) afraid of talc? *Eur Respir J* 2007; 29:619-621
- 28 Kennedy L, Rusch VW, Strange C, et al. Pleurodesis using talc slurry. *Chest* 1994; 106:342-346

- 29 Marom EM, Patz EF, Jr., Erasmus JJ, et al. Malignant pleural effusions: treatment with small-bore-catheter thoracostomy and talc pleurodesis. *Radiology* 1999; 210:277-281
- 30 Rehse DH, Aye RW, Florence MG. Respiratory failure following talc pleurodesis. *Am J Surg* 1999; 177:437-440
- 31 Rinaldo JE, Owens GR, Rogers RM. Adult respiratory distress syndrome following intrapleural instillation of talc. *J Thorac Cardiovasc Surg* 1983; 85:523-526
- 32 Brant A, Eaton T. Serious complications with talc slurry pleurodesis. *Respirology* 2001; 6:181-185
- 33 Cardillo G, Facciolo F, Carbone L, et al. Long-term follow-up of video-assisted talc pleurodesis in malignant recurrent pleural effusions. *Eur J Cardiothorac Surg* 2002; 21:302-305; discussion 305-306
- 34 Janssen JP, Collier G, Astoul P, et al. Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study. *Lancet* 2007; 369:1535-1539
- 35 Viallat JR, Rey F, Astoul P, et al. Thoracoscopic talc poudrage pleurodesis for malignant effusions. A review of 360 cases. *Chest* 1996; 110:1387-1393
- 36 Weissberg D, Ben-Zeev I. Talc pleurodesis. Experience with 360 patients. *J Thorac Cardiovasc Surg* 1993; 106:689-695
- 37 Sahn SA. Is talc indicated for pleurodesis? Pro: Talc should be used for pleurodesis. *Journal of Bronchology* 2002; 9:223-227
- 38 Kennedy L, Harley RA, Sahn SA, et al. Talc slurry pleurodesis. Pleural fluid and histologic analysis. *Chest* 1995; 107:1707-1712

- 39 Werebe EC, Pazetti R, Milanez de Campos JR, et al. Systemic distribution of talc after intrapleural administration in rats. *Chest* 1999; 115:190-193
- 40 Genofre EH, Vargas FS, Acencio MM, et al. Talc pleurodesis: evidence of systemic inflammatory response to small size talc particles. *Respir Med* 2009; 103:91-97
- 41 Fraticelli A, Robaglia-Schlupp A, Riera H, et al. Distribution of calibrated talc after intrapleural administration: an experimental study in rats. *Chest* 2002; 122:1737-1741
- 42 Yildirim H, Metintas M, Ak G, et al. Predictors of talc pleurodesis outcome in patients with malignant pleural effusions. *Lung Cancer* 2008; 62:139-144
- 43 Aelony Y, King RR, Boutin C. Thoracoscopic talc poudrage in malignant pleural effusions: effective pleurodesis despite low pleural pH. *Chest* 1998; 113:1007-1012
- 44 Heffner JE, Nietert PJ, Barbieri C. Pleural fluid pH as a predictor of pleurodesis failure: analysis of primary data. *Chest* 2000; 117:87-95
- 45 Martinez-Moragon E, Aparicio J, Sanchis J, et al. Malignant pleural effusion: prognostic factors for survival and response to chemical pleurodesis in a series of 120 cases. *Respiration* 1998; 65:108-113
- 46 Warren WH, Kalimi R, Khodadadian LM, et al. Management of malignant pleural effusions using the Pleur(x) catheter. *Ann Thorac Surg* 2008; 85:1049-1055
- 47 Efthymiou CA, Masudi T, Thorpe JA, et al. Malignant pleural effusion in the presence of trapped lung. Five-year experience of PleurX tunnelled catheters. *Interact Cardiovasc Thorac Surg* 2009; 9:961-964
- 48 Musani AI, Haas AR, Seijo L, et al. Outpatient management of malignant pleural effusions with small-bore, tunneled pleural catheters. *Respiration* 2004; 71:559-566

- 49 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; 50:123-127
- 50 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; 35:546-551
- 51 Bertolaccini L, Zamproga C, Barberis L, et al. Malignant pleural effusions: review of treatment and our experience. *Rev Recent Clin Trials* 2007; 2:21-25
- 52 Van Meter ME, McKee KY, Kohlwes RJ. Efficacy and Safety of Tunneled Pleural Catheters in Adults with Malignant Pleural Effusions: A Systematic Review. *J Gen Intern Med*
- 53 Pollak JS, Burdge CM, Rosenblatt M, et al. Treatment of malignant pleural effusions with tunneled long-term drainage catheters. *J Vasc Interv Radiol* 2001; 12:201-208
- 54 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; 86:1992-1999
- 55 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; 69:369-375
- 56 Tremblay A, Mason C, Michaud G. Use of tunnelled catheters for malignant pleural effusions in patients fit for pleurodesis. *Eur Respir J* 2007; 30:759-762
- 57 Warren WH, Kim AW, Liptay MJ. Identification of clinical factors predicting Pleurx catheter removal in patients treated for malignant pleural effusion. *Eur J Cardiothorac Surg* 2008; 33:89-94

- 58 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; 69:198-202; discussion 202
- 59 Olden AM, Holloway R. Treatment of malignant pleural effusion: PleuRx catheter or talc pleurodesis? A cost-effectiveness analysis. *J Palliat Med*; 13:59-65
- 60 Mahler DA, Weinberg DH, Wells CK, et al. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984; 85:751-758
- 61 Mahler DAWJTJ. The MCID of the Transition Dyspnea Index is a total score of one unit. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2005; 2:99-103
- 62 Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003; 41:582-592
- 63 Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5:649-655
- 64 Ozyurtkan MO, Balci AE, Cakmak M. Predictors of mortality within three months in the patients with malignant pleural effusion. *Eur J Intern Med*; 21:30-34