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Managing malignant pleural effusion with an indwelling pleural catheter: factors associated with spontaneous pleurodesis

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ABSTRACT

Introduction: Malignant pleural effusion can be recurrent despite active anti-cancer treatment. Significant malignant pleural effusion leads to debilitating dyspnoea and worsening quality of life in patients with advanced cancer. An indwelling pleural catheter offers a novel means to manage recurrent malignant pleural effusion and may remove the need for repeated thoracentesis. Spontaneous pleurodesis is another unique advantage of indwelling pleural catheter placement but the factors associated with its occurrence are not clearly established. The aims of this study were to explore the safety of an indwelling pleural catheter in the management of symptomatic recurrent malignant pleural effusion, and to identify the factors associated with spontaneous pleurodesis.

Methods: This case series with internal comparisons was conducted in the Division of Respiratory Medicine, Department of Medicine, Queen Mary Hospital, Hong Kong. All patients who underwent insertion of an indwelling pleural catheter from the initiation of such service from January 2010 to December 2014 were included for data analysis. Patients were monitored until December 2014, with the last catheter inserted in July 2014.

Results: Between 2010 and 2014, a total of 23 indwelling pleural catheters were inserted in 22 consecutive patients with malignant pleural effusion, including 15 (65.2%) cases with malignant pleural

effusion as a result of metastatic lung cancer. Ten (43.5%) cases achieved minimal output according to defined criteria, in five of whom the pleural catheter was removed without subsequent re-accumulation of effusion (ie spontaneous pleurodesis). Factors associated with minimal output were the absence of trapped lung ($P=0.036$), shorter time from first appearance of malignant pleural effusion to catheter insertion ($P=0.017$), and longer time from catheter insertion till patient's death or end of study ($P=0.007$).

Conclusions: An indwelling pleural catheter provides a safe means to manage symptomatic malignant pleural effusion. Potential clinical factors associated with minimal output were identified along with the occurrence of spontaneous pleurodesis, which is a unique advantage offered by indwelling pleural catheter.

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New knowledge added by this study

- An indwelling pleural catheter (IPC) offers a new and safe management option for symptomatic malignant pleural effusion (MPE).
- Potential clinical factors associated with spontaneous pleurodesis were identified.

Implications for clinical practice or policy

- IPC is a safe management option for MPE.
- In addition to drainage of effusion, the use of an IPC may be followed by spontaneous pleurodesis that obviates the need for any additional chemical sclerosant.

Introduction

Malignant pleural effusion (MPE) develops in up to 50% of patients with advanced lung cancer¹ and can also develop in metastatic pleural involvement from non-pulmonary cancers. Such complication can be recurrent despite active anti-cancer treatment and thus difficult to manage.¹ Significant

MPE leads to debilitating dyspnoea and worsening quality of life in patients with terminal cancer.² Conventional management options of MPE include thoracentesis, chest tube drainage, and chemical and surgical pleurodesis.³ Nonetheless, MPE often recurs and necessitates repeated thoracentesis or chest tube drainage.⁴ Chemical pleurodesis via

an intercostal chest tube may entail prolonged hospitalisation and despite initial ‘success’, MPE often recurs a few months later.⁵ Surgical pleurodesis is often too invasive for frail cancer patients.⁶ Systemic anti-cancer treatment may reduce MPE but there is no guarantee of success.⁷ To secure symptom relief and to minimise repeated interventions and hospitalisation in refractory MPE was a constant challenge, until an indwelling pleural catheter (IPC) became more commonly used.⁸

An IPC is intended to be left in situ in the pleural cavity permanently in patients with advanced cancer. Insertion is under local anaesthesia, and supplemented with conscious sedation if needed. An IPC is a silicon catheter with a polyester cuff for anchoring the catheter at the subcutaneous tunnel that serves to reduce infection. At the end of the external portion of the catheter is a silicone valve that remains closed unless connected to a designated drainage line or vacuum bottle. Vacuum bottles are not reusable and are discarded after each episode of drainage. Patients are usually advised to have IPC drainage every 1 or 2 days, especially when output remains substantial. In addition, drainage should be done whenever symptoms of MPE occur (Fig).

The guidelines for management of MPE published by the British Thoracic Society suggest

持續胸腔引流治理惡性胸腔積液：與自發性胸膜固定相關的因素

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引言：儘管積極進行抗癌治療，惡性胸腔積液的情況仍會復發。惡性胸腔積液會導致晚期癌症患者呼吸困難，使其生活質量下降。持續胸腔引流（IPC）為惡性胸腔積液提供一種嶄新的治理方法，並可能減低重複胸腔穿刺的需要。IPC有可能引致自發性胸膜固定，這亦是引流的另一項優勢，可惜自發性胸膜固定出現的因素尚未確定。本研究探討IPC治理有症狀的惡性胸腔積液的安全性，並找出與自發性胸膜固定相關的因素。

方法：這個具群組內部比較的病例系列在香港瑪麗醫院的呼吸內科部進行。我們於2010年1月開始引入IPC的技術。本研究把2010年1月至2014年12月期間所有接受IPC的病人列入研究範圍；研究期間的最後一次IPC於2014年7月進行，病人數據更新至2014年12月。

結果：2010年至2014年間共有23例（22名病人）IPC，其中15例（65.2%）因肺癌轉移出現惡性胸腔積液。根據治療準則，10例（43.5%）達到最小輸出，其中5例被移除導管而沒有積液（即自發性胸膜固定）。與最小輸出有關的因素包括：沒有萎陷肺（ $P=0.036$ ）、從發現惡性胸腔積液至導管插入的時間較短（ $P=0.017$ ），以及從導管插入至病人死亡或研究結束的時間較長（ $P=0.007$ ）。

結論：使用IPC治理有症狀的惡性胸腔積液是安全的。本研究找出與最小輸出和自發性胸膜固定（IPC的一項獨特優勢）有關的潛在臨床因素。

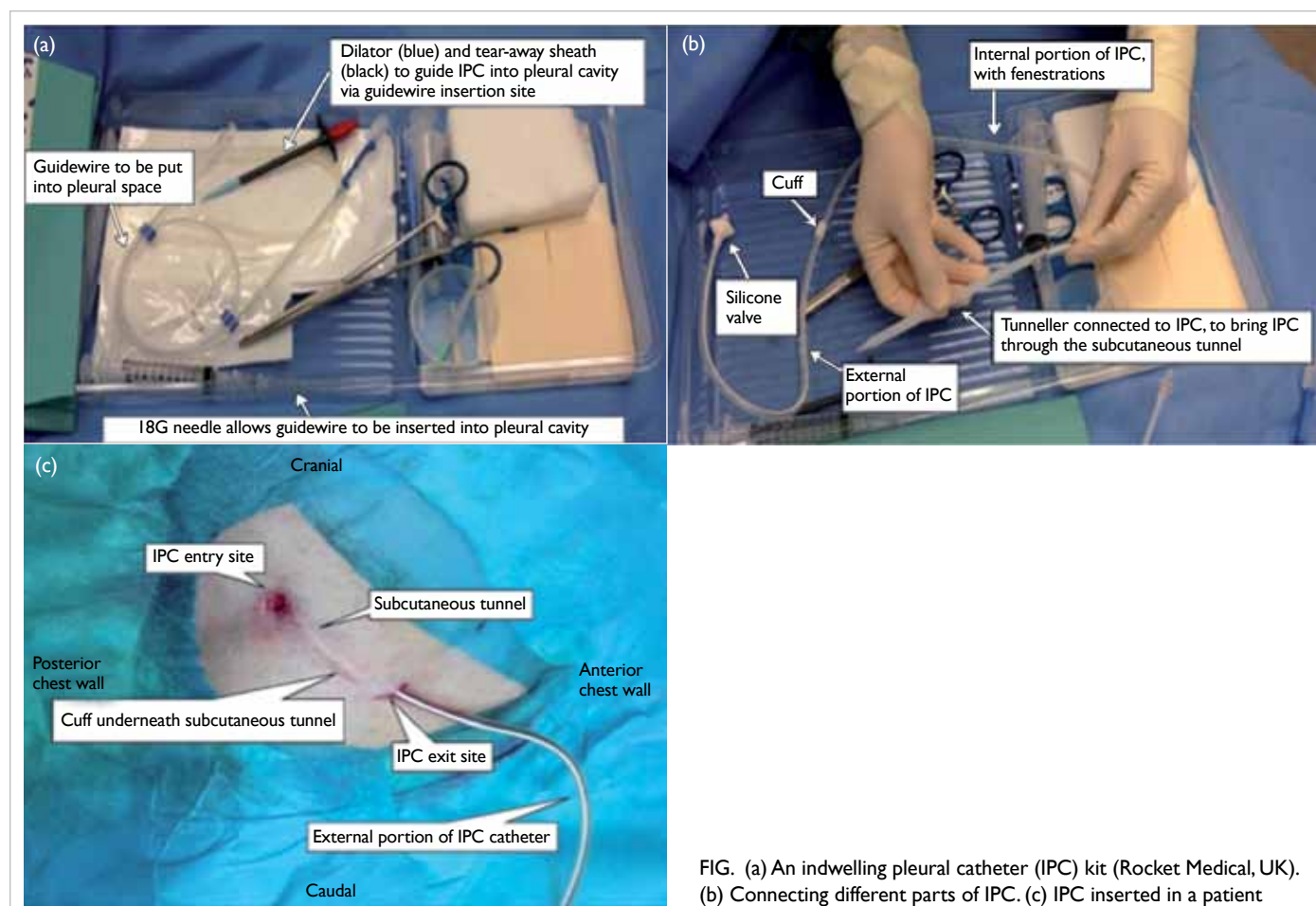


FIG. (a) An indwelling pleural catheter (IPC) kit (Rocket Medical, UK). (b) Connecting different parts of IPC. (c) IPC inserted in a patient

that IPC is an alternative option for patients whose estimated survival exceeds 1 month and who have either a trapped lung or recurrent pleural effusion following a trial of pleurodesis.³ First-line use of IPC in patients who have no previous trial of pleurodesis has also been shown to be superior to talc pleurodesis with subjects being less dyspnoeic at 6 months, and less likely to need further pleural procedures, and reduced hospital stay by 3.5 days.⁹ Another prospective open-label trial that compared IPC with talc slurry pleurodesis as first-line treatment for MPE also demonstrated that first-line use of IPC conferred non-inferior improvement in dyspnoea and quality of life, reduced effusion-related hospital stay by 7 to 11 days, and required less subsequent pleural procedures compared with talc slurry pleurodesis.¹⁰ Research has shown that IPC is a safe procedure, with no complications in 87.5% (range, 54.5–100%) of patients.¹¹ Although the IPC is designed to be left permanently in situ in the pleural cavity in patients with advanced cancer, one unique advantage of IPC is the occurrence of autopleurodesis or spontaneous pleurodesis (SP)—ie pleurodesis achieved following IPC insertion without the use of sclerosant. The achievement of SP may enable consequent removal of the IPC. The pooled rate of SP in MPE patients has been reported to be 45.6%,¹¹ achieved after a mean duration of 26 to 56 days after IPC insertion.^{11–20} The possibility of SP is attractive as there is a chance that an IPC will no longer be required. The aims of this study were to review our single-centre experience of the safety of IPC in the management of symptomatic MPE and to explore the potential clinical factors associated with SP. To our knowledge, this is the first IPC study published in Hong Kong.

Methods

All patients who underwent IPC insertion at the Division of Respiratory Medicine, Department of Medicine, Queen Mary Hospital since initiation of the IPC service in January 2010 up to December 2014 were included for data analysis. Patients and data were followed up until December 2014, with the last IPC inserted in July 2014. The study was approved by the University of Hong Kong/Hong Kong Hospital Authority Hong Kong West Cluster Institutional Review Board/Ethics Committee (HKU/HAHO HKWC IRB/EC UW13-581) and informed consent was obtained from patients.

An IPC was inserted in patients with MPE who had trapped lung or prior failed pleurodesis or persistent high effusion output from a chest drain and a high chance of pleurodesis failure, or in patients who preferred IPC as their first-line management of MPE. The IPC kits (Rocket Medical, UK) were used and IPCs were inserted in the endoscopy room under local anaesthesia supplemented with conscious sedation if needed.

The electronic patient records, in-patient records, chest radiographs, and drainage diaries were retrospectively reviewed. Data regarding patient demographics, primary malignancy, cancer treatment, history of thoracic irradiation, number and type of prior pleural procedures, indications for IPC, serum albumin level before IPC insertion, laboratory analysis of pleural fluid obtained prior to IPC insertion, and IPC-related complications and admissions were collected and evaluated. 'Massive effusion' was defined as more than two thirds of the hemithorax. Effusion less than or equal to two thirds of the hemithorax was defined as 'non-massive effusion'. Trapped lung was clinically diagnosed when chest X-ray showed an incompletely re-expanded lung despite adequate drainage and suction, together with a compatible tumour status predisposing to trapped lung (eg endobronchial tumour). The number of IPCs inserted, instead of the number of patients, was used for analysis in this study unless otherwise specified.

Although IPC removal could be considered when SP was achieved clinically, there were patients who achieved minimal IPC output in whom IPC was not removed due to other clinical considerations or patient preference. Hence, the rate of SP would be underestimated if only IPC removal of the basis of minimal output was considered to reflect SP. Therefore, in this study patients were deemed to have achieved 'minimal output' if there was a persistently reduced IPC output of ≤ 50 mL per day on average that was not secondary to IPC complications, and regardless of whether the IPC was removed or kept in situ. Patients who persistently had an average IPC output that exceeded 50 mL per day, or had little output due to IPC complications (eg blocked IPC or significant pleural loculation) were defined as the 'persistent output' group. As achievement of SP did not necessarily infer IPC removal, because of patient preference and/or other considerations, the endpoint 'minimal output' was used for analysis of factors associated with SP.

The IBM PASW statistical software version 20 was used for data analysis. Association of clinical factors with outcome was analysed with Fisher's exact test, independent sample *t* tests, and Mann-Whitney test where appropriate. Shapiro-Wilk tests were used to check for normal distribution of individual continuous variables. As minimal output was a dichotomous variable, the point-biserial correlation method was used for association analysis between minimal output and other factors that were continuous variables. The *P* values were two-sided and were considered statistically significant if < 0.05 .

Results

A total of 23 IPCs were inserted in 22 consecutive patients with symptomatic MPE. Insertion of 15

(65.2%) IPCs were in patients with MPE from metastatic lung cancer. A further six were inserted for MPE from metastatic breast cancer and two in patients with MPE from metastatic colon cancer. The characteristics of patients are shown in Table 1. The mean (\pm standard error of the mean) duration of follow-up was 33.3 ± 28.1 weeks.

Patients were admitted for symptomatic MPE or elective IPC insertion. Patients were able to be discharged with a mean of 4 days following IPC insertion. Ambulatory IPC drainage via vacuum bottles was performed by patients and/or their carers, except one patient who was attended by outreach nurses of the palliative care team.

Complications related to IPC occurred in 10 (43.5%) cases (Table 2). Site infection and wound infection following IPC removal were minor and all resolved after a course of oral antibiotics without the need for hospitalisation. Tumour seeding at the IPC tract was successfully treated by local radiotherapy. Two patients had symptomatic loculated effusion following IPC insertion and required intrapleural fibrinolytics: only one of them improved. Complications necessitated removal of two IPCs. One patient developed empyema 6 months after IPC insertion. *Pseudomonas aeruginosa* was persistently isolated from pleural fluid despite appropriate antibiotics; infection resolved following IPC removal. Another patient developed intractable cough and it was suspected that her IPC was trapped at the right oblique fissure causing irritation. Cough improved following IPC removal. There were six IPC complication-related hospitalisations (either clinical or emergency admissions) in three patients: the two patients with symptomatic loculations on the IPC requiring fibrinolytics and the patient with empyema mentioned above.

A total of 10 patients achieved minimal output: IPC was removed in five (21.7%) without subsequent effusion re-accumulation and the other five patients achieved minimal output but retained their IPC. In another two patients, IPC was removed because of complications as mentioned before. No difficulties were encountered during any IPC removal.

Significant factors associated with minimal output were the absence of trapped lung ($P=0.036$), shorter time from first appearance of MPE to IPC insertion (24.5 ± 24.2 weeks in persistent output group vs 5.75 ± 4.91 weeks in minimal output group; $P=0.017$), and longer time from IPC insertion till patient's death or end of study (whichever was earlier; 20.2 ± 19.5 weeks in persistent output group vs 50.3 ± 29.2 weeks in minimal output group; $P=0.007$; Table 3).

Discussion

In this small series of 22 patients with 23 IPCs, mainly minor complications were encountered.

TABLE 1. Summary of characteristics of subjects included in this study (n=23)

Characteristic	Data*
Gender	
Male	6 (26.1%)
Female	17 (73.9%)
Age (years)	59.3 ± 14.3
Smoking habit	
NS	18 (78.3%)
Current/ex-smoker	5 (21.7%)
Cancer	
Lung primary	15 (65.2%)
Non-lung primary	8 (34.8%)
Presence of trapped lung	
No	12 (52.2%)
Yes	11 (47.8%)
Effective anti-cancer treatment on IPC	
No treatment/PD	16 (69.6%)
PR/SD on treatment	7 (30.4%)
History of pleural tappings ≥ 2	
No	8 (34.8%)
Yes	15 (65.2%)
History of pleurodesis	
No	20 (87.0%)
Yes	3 (13.0%)
Pleural fluid cytology	
Negative	5 (21.7%)
Positive	18 (78.3%)
Non-massive pleural effusion	
Small-to-moderate initial MPE	5 (21.7%)
Massive initial MPE	18 (78.3%)
Drainage schedule†	20 (87.0%)
Every 1-2 days	8 (34.8%)
>Every 2 days	12 (52.2%)
Duration from first appearance of MPE to IPC insertion (weeks)	16.4 ± 20.5
Duration from IPC insertion to hospital discharge (days)	4.4 ± 3.0
Duration from IPC insertion to IPC removal due to SP (weeks)‡	19.0 ± 9.8
Duration from IPC insertion till death or end of study (weeks)	33.3 ± 28.1

Abbreviations: IPC = indwelling pleural catheter; MPE = malignant pleural effusion; NS = non-smoker; PD = progressive disease; PR = partial response; SD = stable disease; SP = spontaneous pleurodesis

* Data are shown as No. (%) of insertions or mean \pm standard error of the mean

† Three patients did not keep drainage diary and hence drainage frequency not traceable

‡ No. of patients = 5 (21.7%)

A serious IPC complication, namely empyema, occurred in one (4.3%) case who was successfully treated with antibiotics and removal of IPC without serious consequences. Insertion of IPC is considered a relatively safe procedure: up to 87.5% (range, 54.5-

TABLE 2. Complications related to indwelling pleural catheter (IPC) in this study (n=23)

Complication	No. (%) of cases
IPC-related complication	
Tumour seeding at IPC tract	1 (4.3)
Symptomatic loculated effusion after IPC	2 (8.7)
Undrained effusion due to malpositioned IPC	1 (4.3)
Pleural infection	1 (4.3)
IPC entry- or exit-site cellulitis	4 (17.4)
Infection at wound of IPC removal (n=7)	1
IPC-related hospitalisations	Total of 6 admissions in 3 patients
IPC removal due to complications	2 (8.7%)

TABLE 3. Association of clinical factors with minimal output by bivariate analysis

Clinical factor	Point-biserial correlation coefficient	P value
Duration of IPC from insertion to death or end of study	0.567	0.007
Trapped lung	-0.472	0.036
Duration from first appearance of MPE to IPC insertion	-0.473	0.017

Abbreviations: IPC = indwelling pleural catheter; MPE = malignant pleural effusion

100%) of patients have no complications following the insertion.¹¹ Complications reported in the literature include local pain (0.4-13%), bleeding (0-0.9%), pneumothorax (0-38%), cellulitis at exit site (1.3-25%), pleural infection (0-16.7%), asymptomatic loculations (4-7.3%), symptomatic loculations (2-13.5%), IPC tract metastasis (0-13.6%), clogged catheter (0-17.6%), IPC dislodgement (1.3-17.7%), and fractured IPC during removal (9.8%). Previous studies suggest that up to 20.6% (range, 1.6-20.6%) of IPCs need to be removed due to complications.^{9-11,14,15,21,22} Nonetheless, serious complications are uncommon; the most common being pleural infection (0-16.7%).²³ The TIME2 study reported that the risk of pleural infection was 13.4% in the IPC group compared with 1.9% in the talc slurry pleurodesis group.⁹ Chemotherapy is not regarded as a contra-indication to IPC, or vice versa. No increased risk of pleural infection has been observed in patients who receive chemotherapy with an IPC in situ.²⁴ Symptomatic loculations following IPC insertion is another relatively significant complication, as they often necessitate admission for management such as intrapleural fibrinolysis or other pleural procedure.

When the daily IPC output reduces to a certain level (the exact 'amount' remains arbitrary), IPC removal can be considered and SP is achieved if there is no significant re-accumulation following IPC removal. In reality, some patients had little IPC output but the catheter was left in situ due to

other clinical considerations. The rate of SP could be underestimated if it was solely reflected by the ultimate rate of IPC removal, hence 'minimal output' was used in this study as the surrogate of SP during analysis of factors that contributed to SP.

We determined that absence of trapped lung, shorter time from first appearance of MPE to IPC insertion, and longer time from IPC insertion till patient's death or end of study were associated with minimal output. Trapped lung unsurprisingly led to a higher chance of persistent output. Nonetheless, it has been observed that patients with IPC inserted for trapped lung can still achieve SP,^{12,15,17,18,20} or their lung expansion will improve after IPC.¹⁷ In our cohort, two patients had their trapped lung re-expanded after IPC insertion; one of whom had IPC removed successfully without re-accumulation of effusion.

It appears from this study that a shorter time from MPE to IPC insertion could be associated with the achievement of a minimal output state. This could imply that the earlier an IPC is inserted, the better chance of achieving minimal output or even SP. Both a history of multiple pleural procedures (which was arbitrarily defined in this study as requiring two or more episodes of pleurocentesis or chest drainage) and a history of failed pleurodesis were usually indicative of refractory or difficult-to-manage MPE.²⁵ It has never been ascertained whether earlier IPC insertion rather than repeated attempts at pleurocentesis or pleurodesis will

increase the chance of SP with IPC. Both factors were not significantly associated with minimal output in our small cohort. Further studies are required to investigate whether prompt insertion of IPC as soon as possible after development of MPE will improve the likelihood of SP.

Patients who achieved minimal output had a longer time from IPC insertion until death or end of study (20.2 ± 19.5 weeks in the persistent output group vs 50.3 ± 29.2 weeks in the minimal output group; $P=0.007$). Minimal output may be a marker of overall disease control. Lung cancer was the underlying pathology in eight of the 10 subjects who achieved minimal output, of whom six had adenocarcinoma and were prescribed targeted therapy and chemotherapy. Whether the concomitant use of anti-cancer treatments for these lung cancer patients contributed to longer survival following IPC insertion could not be established from this small cohort of lung cancer patients. Comparison with non-lung cancer patients with IPC in this study could not be made as patients with metastatic breast or colorectal tumour with MPE had different treatment strategies. As at December 2014, only four of the 22 patients were still living. They were patients with adenocarcinoma of the lung on palliative chemotherapy/tyrosine kinase inhibitors. Among these four patients, one had her IPC removed earlier due to SP achievement, two had IPC removed earlier due to IPC-related complications, and one still had IPC in situ with persistent output.

Minimal output was used as a surrogate of SP in this study rather than actual IPC removal in the hope that it would better reflect what clinical factors contribute to SP. Comparison of time from IPC insertion to minimal output achievement in those five patients whose IPCs were ultimately removed and the five patients in whom IPC remained in situ despite minimal output revealed no significant difference (30 [interquartile range, 15-59] days vs 23 [standard error of the mean, 6.63] days). Nonetheless, one must not ignore the reasons for non-removal of IPC despite minimal output since they impact the ultimate goal of IPC removal. In this study, there were five patients who achieved minimal output but in whom IPCs remained in situ due to various reasons: poor performance state and short life expectancy, undergoing cycles of chemotherapy, or patient preferences.

This study was limited by the very small sample size and its retrospective nature. There were missing data and the dichotomous groupings, eg IPC drainage every 1 to 2 days versus less frequent, were crude and arbitrary. For example, more-frequent IPC drainage to increase the chance of pleural apposition may theoretically increase the chance of SP, although in this study IPC drainage every 1 to 2 days versus less frequent was not associated with

minimal output. This could be related to the crude grouping of the IPC drainage frequency due to the retrospective design of this study that did not allow us to properly allocate the IPC drainage schedule. Further studies to identify modifiable clinical factors that may facilitate SP would be particularly meaningful.

Conclusions

Insertion of IPC was shown to be a safe technique in the management of symptomatic MPE. Potential factors associated with minimal output, which may predict SP, were absence of trapped lung, shorter time from first appearance of MPE to IPC insertion, and longer time with IPC. Validation by further studies is required owing to the small number of subjects in this study. More data are needed regarding modifiable factors that contribute to achievement of minimal output, as the removal of IPC offers further enhancement of quality of life.

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Declaration

All authors have disclosed no conflicts of interest.

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