CHEST

Original Research

PULMONARY PROCEDURES

Quality-Adjusted Survival Following Treatment of Malignant Pleural Effusions With Indwelling Pleural Catheters

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Background: **Malignant pleural effusions (MPEs) are a frequent cause of dyspnea in patients with cancer. Although indwelling pleural catheters (IPCs) have been used since 1997, there are no studies of quality-adjusted survival following IPC placement.**
Methods: **With a standardized algorithm, this prospective observational cohort study of patients with MPE treated with IPCs assessed global health-related quality of life using the SF-6D to calculate utilities. Quality-adjusted life days (QALDs) were calculated by integrating utilities over time.**
Results: **A total of 266 patients were enrolled. Median quality-adjusted survival was 95.1 QALDs. Dyspnea improved significantly following IPC placement ($P < .001$), but utility increased only modestly. Patients who had chemotherapy or radiation after IPC placement ($P < .001$) and those who were more short of breath at baseline ($P = .005$) had greater improvements in utility. In a competing risk model, the 1-year cumulative incidence of events was death with IPC in place, 35.7%; IPC removal due to decreased drainage, 51.9%; and IPC removal due to complications, 7.3%. Recurrent MPE requiring repeat intervention occurred in 14% of patients whose IPC was removed. Recurrence was more common when IPC removal was due to complications ($P = .04$) or malfunction ($P < .001$) rather than to decreased drainage.**
Conclusions: **IPC placement has significant beneficial effects in selected patient populations. The determinants of quality-adjusted survival in patients with MPE are complex. Although dyspnea is one of them, receiving treatment after IPC placement is also important. Future research should use patient-centered outcomes in addition to time-to-event analysis.**
Trial registry: **ClinicalTrials.gov; No.: NCT01117740; URL: www.clinicaltrials.gov**

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Abbreviations: ECOG = Eastern Cooperative Oncology Group; IPC = indwelling pleural catheter; MPE = malignant pleural effusion; QALD = quality-adjusted life day; QALY = quality-adjusted life year

Malignant pleural effusions (MPEs) are a common problem, occurring in up to 15% of patients with advanced malignancies.[1] Management options include chemical pleurodesis either through chest tube or thoracoscopy and placement of indwelling pleural catheters (IPCs).[2] Although randomized controlled studies have compared chest tube drainage with chemical pleurodesis vs IPCs,[3,4] no definitive randomized control studies have demonstrated the superiority of one technique over others.

Part of the difficulty in evaluating the comparative effectiveness of MPE treatments has to do with how outcomes are defined and measured in this population, which is particularly true of IPC studies. A systematic review identified 19 studies of 1,370 patients with IPCs.[5] Symptomatic improvement was reported in 95% of patients, but the method of assessing symptomatic improvement varied widely, with some studies simply stating that patients experienced "symptomatic improvement" without further details.[5] Similarly, although some studies used Borg scores to quantify dyspnea,[4] most did not use validated instruments. Quality-of-life assessments were also infrequent, and again, these were not done with validated

instruments.[5-7] No study has reported on quality-adjusted survival.

Outcome definitions, such as that for pleurodesis, have varied among studies.[5] For example, most studies used the term "pleurodesis" to describe enduring pleural symphysis, defined radiographically as the absence of pleural fluid at 4 to 8 weeks, which facilitated subsequent IPC removal. However, absence of fluid recurrence at 4 weeks does not necessarily imply that an effusion will not return subsequently. Unfortunately, long-term data on incidence rates of fluid recurrence after IPC removal are lacking, and the duration of follow-up after IPC removal varied widely among studies or was not reported.

Another aspect to consider is the type of clinically relevant outcomes. As clinical trials move more toward patient-centered outcomes, measuring the success of interventions for MPE in terms of the need for repeat pleural interventions while maintaining improvements in dyspnea is recommended.[8]

A multidimensional, patient-centered approach to defining and measuring outcomes of MPE treatments is needed. Because these treatments are essentially palliative, any construct that measures MPE treatment success should include a validated measure of quality-adjusted survival. When operationalizing this construct, it is important that outcomes be assessed with validated instruments and that an appropriate time-to-event methodology be used for analysis rather than incidence proportions taken at arbitrary time points.

The goal of this study was to prospectively describe patient-centered outcomes and their associated risk factors for patients with MPE undergoing IPC placement. The primary outcome was quality-adjusted survival. Secondary outcomes were dyspnea, complications, and time to repeat pleural interventions.

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Materials and Methods

Design

This was a prospective observational cohort study of patients with MPE undergoing IPC placement at The University of Texas MD Anderson Cancer Center from April 2010 to January 2013. Institutional Review Board Committee 4 approval was obtained under protocol 2010-0103, and all patients gave informed consent. Inclusion criteria were age ≥ 18 years, sufficient mental capacity to answer SF-6D and Borg questionnaires, and a willingness to follow-up for a minimum of 1 year. Exclusion criteria were previously attempted pleurodesis, previous IPC placement, chylous effusions, pleural space infection, bilateral effusions requiring interventions, or respiratory failure requiring mechanical ventilation (e-Fig 1 for CONSORT [Consolidated Standards of Reporting Trials] flow diagram).

Patients

The clinical diagnosis of MPE was established either by cytology or histology or by the presence of a recurrent large exudative pleural effusion in the context of histologically proven malignancy with proven metastatic disease elsewhere.[3] Our definition of MPE was based on the Second Therapeutic Intervention in Malignant Effusion Trial (TIME2) randomized trial.[3] Because this definition includes patients who do not have definitive pleural fluid cytology, we further subclassified patients according to whether there was definitive pathologic proof of pleural involvement. Patients with positive pleural fluid cytology or histology were categorized as having pathology-proven MPEs. Patients with recurrent exudative effusions by thoracentesis with proven metastatic disease elsewhere but without positive pleural fluid cytology by thoracentesis were categorized as having a clinical diagnosis of MPE if no other cause of exudative effusions could be identified and at least one prior thoracentesis was performed. Patients with negative pleural fluid cytology results and a normal thoracoscopy were considered as true negatives for MPE and, thus, excluded from the study (ie, not counted as a clinical diagnosis of MPE).

IPC Placement, Management, and Follow-up

All patients underwent ultrasound-guided IPC placement using the PleurX system (CareFusion Corp). Large-volume drainage was performed the day of the procedure. Relatives or community nurses provided subsequent drainage. Drainage frequency, management of IPC malfunctions, and management of IPC infections followed standardized algorithms (Fig 1, e-Figs 2-3). Patients were followed up at 2 weeks, 4 weeks, and every month thereafter until death.

Outcomes

Self-reported global quality of life was measured using the SF-6D,[9] which provides a means to estimate a preference-based single-index measure for health using general population data. The SF-6D generates a measure of utility ranging from 0 to 1 utiles. Integrating utilities over time allows for calculation of quality-adjusted life years (QALYs). In the present analysis, we express quality-adjusted survival in quality-adjusted life days (QALDs) because of the short survival times.

Dyspnea was measured with the Borg score, and performance status was measured with the Eastern Cooperative Oncology Group (ECOG) score. SF-6D, Borg, and ECOG data were collected at each visit. Complications were documented by mid-level providers using standardized definitions. All IPC removals were classified as being elective either due to decreased drainage or due to complication.

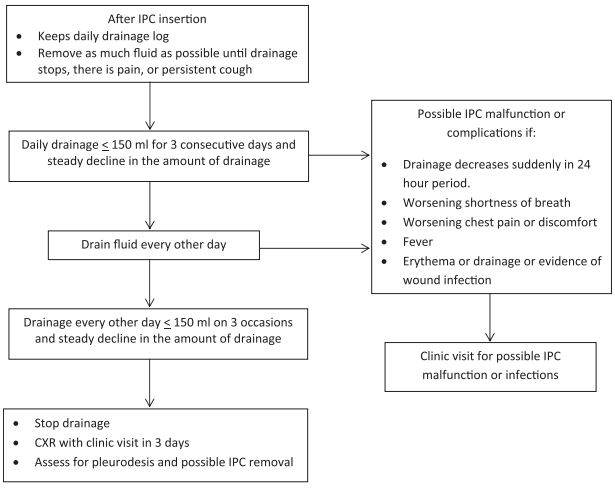

FIGURE 1. Drainage algorithm of pleural fluid after IPC insertion. CXR = chest radiograph; IPC = indwelling pleural catheter.

Statistical Analysis

Paired *t* tests were used to compare baseline and 1-month utilities and Borg scores. A generalized linear model was used to evaluate whether other variables had any impact on the pairwise difference of utility between baseline and 1-month scores.

QALDs were calculated as the area under the utility curve with time as the x-axis. For patients who were lost to follow-up, utility ended at the last follow-up date. Additional details on measuring utility and QALDs are available in e-Appendix 1. The Kaplan-Meier product-limit method was used to estimate median QALDs. Patients alive at study completion or lost to follow-up were censored. For time to complications, the patient was also censored if the IPC was electively removed due to decreased drainage without complications.

Univariate Cox proportional hazards models were fit to determine the association of patient and clinical characteristics with time-to-event outcomes. Variables that had statistical significance at the $P = .1$ level from univariate analyses were candidates in multivariate-extended Cox models. In the multivariate models, backward elimination was used to retain only variables with $P < .05$. We used time-dependent covariates to represent repeated measurements, such as utility and Borg score. The last observation-carried-forward method was used to impute missing utility or Borg scores. We used a competing risk model to plot the cumulative incidence of death without catheter removal, catheter removal due to decreased drainage, and catheter removal due to complications.

$P < .05$ was considered statistically significant; all tests were two sided. Statistical analyses were carried out using SAS 9.3 (SAS Institute, Inc), S-Plus 8.2 (TIBCO Software Inc), and the contributed package CMPRSK in R 2.15.2.[10]

RESULTS

Patients

A total of 266 patients were included. Pathologic proof of MPE was present in 196 patients, whereas a clinical diagnosis of MPE based on the presence of a recurrent large exudative nonchylous effusion in the context of proven metastatic disease outside the pleura was present in 70 patients. Patient characteristics are summarized in Table 1. There was no significant difference between patients with pathologically proven MPE and those with a clinical diagnosis of MPE in terms of the types of cancer present ($P = .40$) (e-Table 1).

Table 1—*Patient Characteristics*

Characteristic	Value
No. patients	266
Age, y	
Median (range)	61 (18-89)
Mean ± SD	59.9 ± 12.3
Sex	
Female	166 (62.41)
Male	100 (37.59)
Race	
White	204 (76.69)
Black	36 (13.53)
Hispanic	16 (6.02)
Asian	10 (3.76)
Location of procedure	
Inpatient	81 (30.45)
Outpatient	185 (69.55)
Cancer type	
Breast cancer	67 (25.19)
Lung cancer	79 (29.70)
Liquid tumor	34 (12.78)
Other solid tumor	86 (32.33)
Method of MPE diagnosis	
Pathology proven	196 (73.7)
Clinical diagnosis[a]	70 (26.3)
ECOG at baseline	
0	10 (3.76)
1	107 (40.23)
2	84 (31.58)
3	63 (23.68)
4	2 (0.75)
No. prior thoracenteses	
0	16 (6.02)
1	175 (65.79)
2	56 (21.05)
3	10 (3.76)
4-11	9 (2.38)
Prior radiation	
No	233 (87.59)
Yes	33 (12.41)
Prior chemotherapy	
No	65 (24.44)
Yes	201 (75.56)
Chemotherapy or radiation after procedure	
No	78 (29.32)
Yes	188 (70.68)
Reason for catheter removal (n = 148)	
Decreased drainage	127 (85.81)
Complication	15 (10.14)
Other	6 (4.05)

Data are presented as No. (%) unless otherwise indicated. ECOG = Eastern Cooperative Oncology Group; MPE = malignant pleural effusion.
[a]Clinical diagnosis: recurrent exudative nonchylous effusions with proven metastatic disease elsewhere.

Utility and Quality-Adjusted Survival

There was no significant improvement in utility at 1 month after IPC placement compared with baseline

(difference, 0.023; 95% CI, −0.004 to 0.05; $P = .10$). Long-term trends in utility over time are shown in Figure 2.

On univariate and multivariate analysis, patients who had chemotherapy or radiation after IPC placement and those who were more short of breath at baseline had greater improvements in utility from baseline to 1 month than those who did not (Table 2). Median quality-adjusted survival using the Kaplan-Meier method was 95.1 QALDs (95% CI, 73.3-116.5).

Time to Death

One hundred fifty-six patients (58.6%) died (median follow-up, 3.5 months; range, 0-14.5 months). The median Kaplan-Meier estimate of overall survival was 171 days (95% CI, 130-192 days). Extended Cox models are shown in Table 3. On multivariate analysis, older patients ($P < .001$), outpatients ($P < .001$), patients receiving chemotherapy or radiation after IPC placement ($P < .001$) (Fig 3), patients experiencing less shortness of breath ($P = .003$), and patients experiencing better quality of life lived longer ($P < .001$). In terms of quantifying the association between quality of life and risk of death, for every 0.1 increase in utility, the risk of death decreased by 36%.

Dyspnea

Dyspnea as assessed by the Borg score was significantly better at 1 month than at baseline (difference, −2.31; 95% CI, −2.66 to −1.95; $P < .0001$). Borg scores decreased from a median of 4 at baseline, to 2 at 2 weeks, to ≤ 1 thereafter (Fig 4).

Complications

There were 26 patients (9.7%) who had 31 complications (Table 4). Median time to any complication was 1.4 months (range, 0-13.6 months). On univariate and multivariate analyses, no factor had a significant impact on the time to any complication (Table 5). Receiving chemotherapy or radiation after IPC placement did not affect complication rates ($P = .74$) (Fig 5).

Fifteen patients (5.6%) had complications that required removal of the IPC. Median time to complications that required removal of the IPC was 1.4 months (range, 0-13.6 months). On univariate analysis, no factor had a significant impact on the time to complications that required removal of the catheter (e-Table 2).

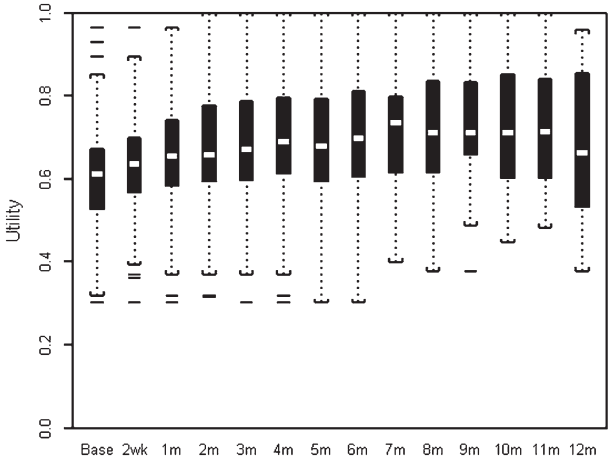

FIGURE 2. Box plot of utilities for patients alive with an IPC for malignant pleural effusions. See Figure 1 legend for expansion of abbreviation.

Time From Removal of Catheter to Fluid Recurrence Requiring Intervention

IPC removal occurred in 148 patients (55.6%). Of these patients, fluid recurrence requiring intervention developed in 21 (14%). Interventions included thoracentesis in 11 patients, IPC replacement in seven, and chest tubes in three. Median time from removal of IPC to fluid recurrence was 3.8 months (range, 0-13.8 months). No patients with an IPC in place and functioning required repeat interventions. On univariate and multivariate analyses, patients whose IPCs were removed due to complications or catheter malfunction rather than decreased drainage had a markedly increased risk of fluid recurrence requiring intervention (Fig 6, Table 6). Overall, recurrences requiring repeat interventions developed in 9% of patients whose IPCs were removed electively due to decreased drainage.

Competing Risks: Death or Catheter Removal Due to Decreased Drainage or Complications

Eighty-five patients died, 33 were lost to follow-up without IPC removal, 127 had their IPC removed due to decreased drainage, and 21 had their IPC removed due to complications or other reasons. The 1-year cumulative incidence of death without catheter removal was 35.7% (95% CI, 29.5%-42.0%); the 1-year cumulative incidence of catheter removal due to decreased drainage was 51.9% (95% CI, 45.4%-58.3%); and the 1-year cumulative incidence of catheter removal due to complications or other reasons was 7.3% (95% CI, 4.2%-10.5%) (Fig 7).

DISCUSSION

Clinical and comparative effectiveness research is contingent on having validated and clinically relevant outcome measures that are analyzed properly. The goal of this study was to quantify patient-centered outcomes for patients with MPE undergoing IPC placement. We chose to focus on three domains: (1) health-related quality of life, including utility, quality-adjusted

Table 2—*Risk Factors Associated With the Pairwise Difference of Utility Between 1 Mo and Baseline*

Variable	Estimate	SE	*P* Value
Univariate analysis			
Chemotherapy or radiation after procedure: yes vs no	0.113	0.035	.001
Cancer type			
Lung vs breast	−0.033	0.038	.39
Liquid tumor vs breast	−0.024	0.047	.62
Other solid tumor vs breast	−0.045	0.038	.24
Pathology-proven MPE vs clinical diagnosis[a]	0.008	0.031	.80
Baseline ECOG: 2-4 vs 0-1	−0.044	0.027	.11
Baseline Borg score	0.016	0.006	.009
Multivariate analysis			
Chemotherapy or radiation after procedure: yes vs no	0.121	0.033	< .001
Baseline Borg score	0.017	0.006	.005

See Table 1 for expansion of abbreviations.

[a]Clinical diagnosis: recurrent exudative nonchylous effusions with proven metastatic disease elsewhere.

survival, and dyspnea; (2) time to recurrent MPE requiring repeat pleural interventions; and (3) complications. Although dyspnea improved significantly, median quality-adjusted survival was only 95 QALDs, and there were only modest improvements in utility, with the greatest improvements being observed in patients who were more short of breath at baseline and in those who received radiation or chemotherapy after IPC placement. Only 19 of the 266 patients (7%) required a repeat pleural intervention. All of these occurred after the IPC was removed. When IPCs were removed electively due to decreased drainage according to protocol, recurrence was rare. When IPCs were removed prematurely due to complications or

Table 3—*Extended Cox Models for Time to Death*

Variable	Hazard Ratio	95% CI	*P* Value
Univariate analysis			
Age (continuous)	0.99	0.97-0.999	.035
Male vs female sex	1.13	0.82-1.56	.47
Race			
Black vs white	1.43	0.95-2.17	.09
Hispanic vs white	0.76	0.37-1.56	.45
Asian vs white	0.51	0.19-1.38	.18
Location of procedure: outpatient vs inpatient	0.43	0.31-0.60	< .001
Cancer type			
Lung vs breast	1.00	0.65-1.54	1
Liquid tumor vs breast	0.63	0.34-1.17	.15
Other solid tumor vs breast	1.46	0.96-2.2	.07
Pathology-proven MPE vs clinical diagnosis[a]	0.93	0.66-1.32	.69
Baseline ECOG: 2-4 vs 0-1	2.23	1.6-3.12	< .001
Days between first pleural procedure and IPC	1.00	1-1	.77
Prior radiation: yes vs no	1.12	0.69-1.81	.65
Prior chemotherapy: yes vs no	1.22	0.84-1.78	.29
Chemotherapy or radiation after procedure: yes vs no	0.21	0.15-0.30	< .001
10 times baseline utility	0.71	0.62-0.82	< .001
10 times wk 2 utility	0.69	0.59-0.81	< .001
Wk 2 Borg score	1.24	1.13-1.36	< .001
10 times utility from baseline to 12 mo (time dependent)[b]	0.57	0.52-0.61	< .001
Borg score from baseline to 12 mo (time dependent)	1.36	1.26-1.47	< .001
Multivariate analysis			
Age, y	0.97	0.95-0.99	< .001
Location of procedure: outpatient vs inpatient	0.38	0.24-0.62	< .001
Chemotherapy or radiation after procedure: yes vs no	0.17	0.11-0.26	< .001
10 times utility from baseline to 12 mo (time dependent)[b]	0.64	0.54-0.76	< .001
Borg score from baseline to 12 mo (time dependent)	1.16	1.05-1.27	.003

IPC = indwelling pleural catheter. See Table 1 legend for expansion of other abbreviations.

[a]Clinical diagnosis: recurrent exudative nonchylous effusions with proven metastatic disease elsewhere.

[b]Utility is derived from the SF-6D and ranges from 0 (dead) to 1 (perfect health). Integrating utility over time allows the analyst to calculate quality-adjusted life years. The way to interpret the coefficients in this case is that for every 0.1 increase of utility, the risk of death will decrease by 36%.

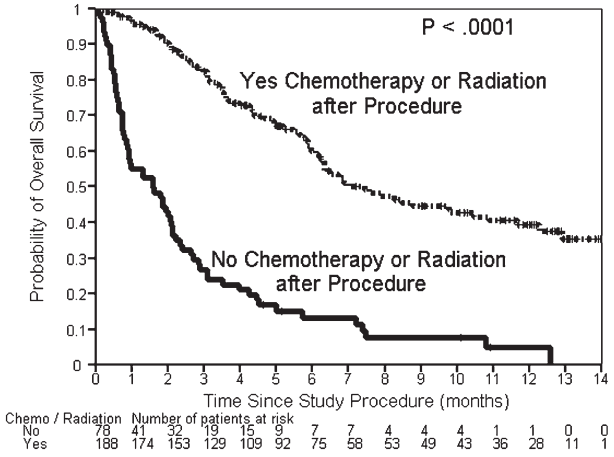

FIGURE 3. Kaplan-Meier plot of time to death based on whether patients received chemotherapy or radiation after IPC placement. Chemo = chemotherapy. See Figure 1 legend for expansion of other abbreviation.

malfunctions, recurrence was more frequent. In a competing risk model, the 1-year cumulative incidence of complications serious enough to warrant IPC removal was 7.3%.

To our knowledge, this study is the first to report quality-adjusted survival following IPC placement. Although other studies have reported on quality of life, the only study to use a validated instrument to report on global health status was the TIME2, but quality-adjusted survival was not reported.[3] QALYs have been recognized as the most important indicator of health-care intervention effectiveness, which is reflected by the position statements and guidelines of the National Institute of Clinical Excellence,[11] the Agency for Health Care Research and Quality, and the US Public Health Service.[12-14] QALYs are particularly relevant for treatment of MPE because all interventions are currently palliative in nature. However,

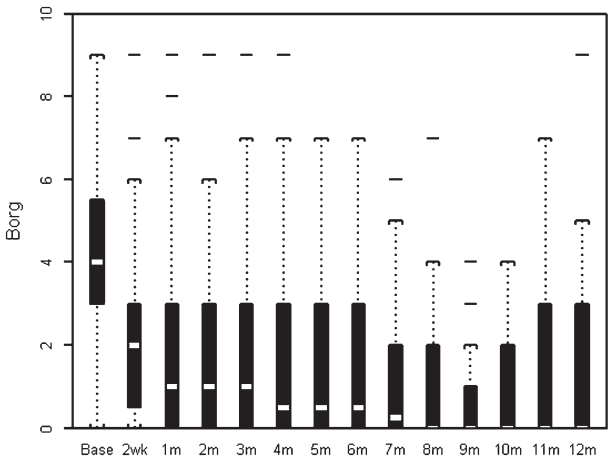

FIGURE 4. Box plot of Borg score for patients alive with IPC for malignant pleural effusions. See Figure 1 legend for expansion of abbreviation.

Table 4—*Complications Associated With IPC*

Complication	No. (%)[a]
Wound site infection	10 (4)
Empyema	3 (1)
Trapped lung with hydropneumothorax	5 (2)
Clogged IPC	7 (3)
Dislodgement of IPC	2 (1)
Leakage around catheter	1 (0.4)
Pain and severe discomfort	1 (0.4)
Kinked IPC	1 (0.4)
Decreased drainage due to subpulmonic IPC location	1 (0.4)

See Table 3 legend for expansion of abbreviation.
[a]Patients could have more than one complication; total number of patients was 266.

most studies reporting QALYs use modeling. A systematic review in 2006 identified only 70 studies that reported QALYs based on pretreatment and posttreatment measurements, and none of these involved MPE.[15] As a result, insufficient information exists to compare the efficacy of various interventions in terms of quality-adjusted survival. Knowledge of baseline QALY distributions is also important in terms of clinical study design because the various interventions may affect mortality and quality of life differently.[16] The present findings are consistent with those in the literature, which demonstrated that for non-small cell lung cancer, utilities for various health states for cancer-related outcomes range from approximately 0.33 (end of life) to 0.70 (responding to therapy), with progressive disease being approximately 0.47 utiles.[17]

We observed that utility did not improve much following IPC placement, whereas dyspnea did improve, suggesting that many determinants affect quality of life in patients with MPEs. Although dyspnea certainly is one of these, other factors related to the underlying malignancy are also pivotal. This is consistent with the present finding that the two factors associated with greater improvements in utility were more severe baseline dyspnea and treatment with chemotherapy or radiation following IPC placement.

The second domain we focused on was time to recurrent MPE requiring repeat intervention. Previous systematic reviews have focused on pleurodesis, reporting an overall incidence proportion of 46%.[5] Of the 19 studies included, only 10 reported on catheter duration and only 12 on pleurodesis.[5] In all studies, the investigators reported pleurodesis as something achieved at some arbitrary time point, and this was defined radiographically. However, being fluid free does not guarantee that fluid will not recur at some future time. Similarly, defining successful treatment of MPE by radiographic criteria at one time point is problematic because some patients may still have IPCs in place and yet may truly have achieved pleurodesis. From a patient-centered perspective, so long as there is no

Table 5—*Univariate Cox Proportional Hazard Model for Time to Any Complication*

Variable	Hazard Ratio	95% CI	*P* Value
Age (continuous)	0.97	0.94-1.003	.08
No. prior thoracenteses: 2-11 vs 0-1	1.90	0.87-4.13	.11
Location of procedure: outpatient vs inpatient	1.52	0.57-4.04	.4
Cancer type			
Lung vs breast	1.49	0.55-4.05	.43
Liquid tumor vs breast	1.04	0.26-4.17	.96
Other solid tumor vs breast	0.81	0.26-2.51	.71
Pathology-proven MPE vs clinical diagnosis[a]	0.62	0.28-1.36	.23
Baseline ECOG: 2-4 vs 0-1	0.86	0.4-1.86	.7
Days between first pleural procedure and IPC	1.00	0.997-1.001	.32
Prior radiation: yes vs no	0.57	0.14-2.43	.45
Prior chemotherapy: yes vs no	0.59	0.26-1.32	.20
Chemotherapy or radiation after procedure: yes vs no	0.73	0.32-1.69	.46

See Table 1 and 3 legends for expansion of abbreviations.

[a]Clinical diagnosis: recurrent exudative nonchylous effusions with proven metastatic disease elsewhere.

symptomatic recurrence of MPE, it matters little whether there was pleurodesis or an IPC was in place. From a methodology standpoint, this arbitrary time point is also problematic because patients who die before it cannot be counted in either group.

Thus, rather than measuring the occurrence of pleurodesis radiographically at one moment in time and arbitrarily defining this as success, it is more effective to measure time to failure. In this case, failure is defined as the time to symptomatic MPE recurrence requiring repeat pleural interventions. By operationalizing the constructs in this manner, we can use survival analysis methods to gain insights into clinically relevant outcomes, eliminating all the methodology problems described previously. This is not possible if we define success as an incidence proportion measured at any one moment in time radiographically. The present study adds to the existing body of evidence in this area by more systematically defining the outcome of recurrent MPE in a clinically meaningful way.[8]

With this approach, we were able to describe and quantify the incidence of recurrent MPEs requiring repeat interventions using survival analysis. Overall, 7.8% of patients required a repeat intervention, which is similar to the overall 7.7% incidence proportion reported in a systematic review.[5] Patients whose IPCs were removed due to decreased drainage required a repeat pleural intervention far less frequently than those whose IPC was removed due to complications. Clinicians should be aware of the higher likelihood of recurrence following IPC removal due to complications and should closely follow these patients for recurrence. If there are no complications, IPCs can be removed electively once drainage decreases. We used a standardized algorithm for IPC management, but it is possible that if we had left the IPCs in longer after drainage decreased that recurrence following elective removal would have been less frequent. In terms of future research, using standardized algorithms is important because they

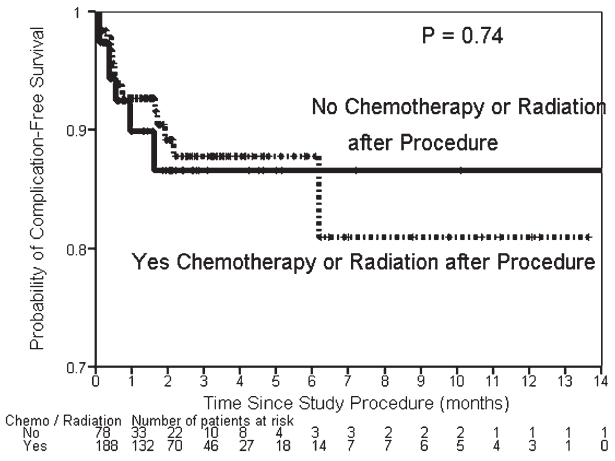

FIGURE 5. Kaplan-Meier plot of time to any complication stratified by whether patients received chemotherapy or radiation after IPC placement. See Figure 1 and 3 legends for expansion of abbreviations.

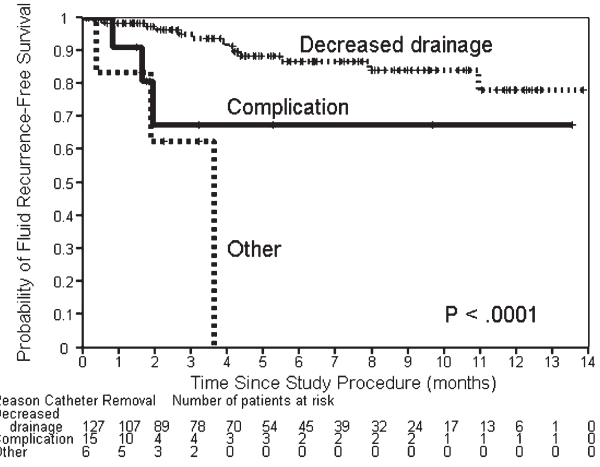

FIGURE 6. Kaplan-Meier plot of time to fluid recurrence requiring intervention following IPC removal stratified by reason for removal. See Figure 1 legend for expansion of abbreviation.

Table 6—*Cox Proportional Hazards Model for Time From Removal of Catheter to Fluid Recurrence Requiring Intervention*

Variable	Hazard Ratio	95% CI	*P* Value
Univariate analysis			
No. prior thoracenteses: 2-11 vs 0-1	0.35	0.08-1.5	.16
Cancer type			
Lung vs breast	0.83	0.21-3.32	.79
Liquid tumor vs breast	1.53	0.38-6.15	.55
Other solid tumor vs breast	1.74	0.51-5.97	.38
Pathology-proven MPE vs clinical diagnosis[a]	1.43	0.48-4.33	.52
Days between first pleural procedure and IPC placement	1.00	0.99-1	.80
Days the pleural catheter was in place	0.98	0.97-1.005	.15
Prior radiation: yes vs no	0.23	0.002-1.67[b]	.32
Prior chemotherapy: yes vs no	1.51	0.5-4.57	.46
Chemotherapy or radiation after procedure: yes vs no	0.42	0.12-1.46	.17
Reason for catheter removal: complication vs decreased drainage	3.73	1.05-13.22	.042
Reason for catheter removal: other vs decreased drainage	11.52	3-44.28	< .001
Multivariate analysis			
Reason for catheter removal: complication vs decreased drainage	3.73	1.05-13.22	.042
Reason for catheter removal: other[c] vs decreased drainage	11.52	3-44.28	< .001

See Table 1 and 3 legends for expansion abbreviations.

[a]Clinical diagnosis: recurrent exudative nonchylous effusions with proven metastatic disease elsewhere.

[b]Firth correction was applied when estimating the hazard ratio and the profile-likelihood confidence limits for the hazard ratios were provided.

[c]Other reasons for removal were defined as IPC malfunctions that were not true complications but did prevent the tube from functioning. For example, an IPC that was clogged and could not drain would have been defined as other.

allow us to compare various IPC management strategies.

The final domain we evaluated was complications. Each physician must balance competing concerns when managing IPCs. On the one hand, removing an IPC too early may lead to recurrent MPE, requiring a second intervention. On the other hand, leaving an IPC in longer than necessary may lead to infectious complications. We capture the two sides of this coin in Figures 5 and 6. The incidence proportion of wound site infections (4%) and empyema (1%) was similar to that previously reported.[5]

In this study, we analyzed the risk of complications using survival analysis methods, which provide additional insights that incidence proportions cannot.[5,18] By examining the time-to-event curves (Figs 5, 7), we see that most of the risk of complications occurs early, within 1 month of IPC placement. When physicians have to decide whether to remove a catheter, they are making a decision based on a contingent probability, not on the baseline incidence proportion. For example, if a patient has had an IPC in place for 3 months and now has decreased drainage, the physician must consider the risk of complications when deciding whether to remove the IPC. But the risk of complications at that time point is not the same as the incidence proportion of infections at baseline (ie, 5%) because the patient has already passed through the period of highest risk, which is the first 1 to 2 months. This is important because the decision to remove an IPC involves a contingent probability that is far lower than the baseline incidence proportion of 5%. If physicians incorrectly use the baseline incidence proportion to inform their decisions, they are more likely to prematurely remove IPCs because of the perceived risk of infection. Instead, they should use these data to estimate the hazard function and recognize that the marginal risk of leaving the IPC in longer is actually much lower than 5%. Thus, studying IPC management algorithms that allow IPCs to remain in longer once drainage is decreased, provided that the IPC has been in place for ≥ 2 months, are warranted because the marginal risk of complications is low. Conversely, if drainage decreases early when the IPC has been in place for only a short while, the marginal risk of complications is still high such

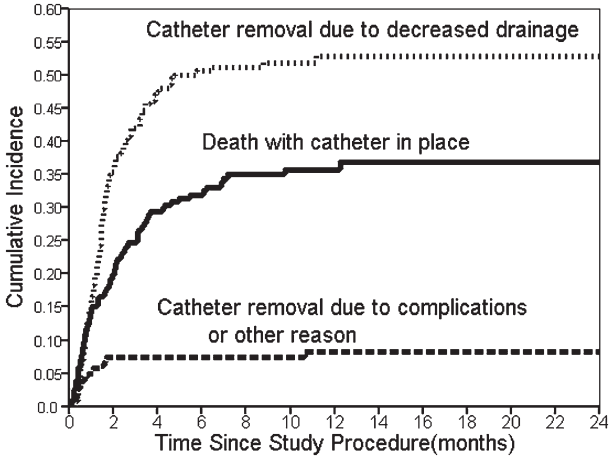

FIGURE 7. Cumulative incidence of competing risks.

that early IPC removal benefits may outweigh the risks.

Although these findings are useful, it is important to recognize the limitations of this study. We used a definition of MPE similar to that used in other studies,[3] but this definition allows inclusion of patients who do not have pathologic proof of MPE. Some of these patients might have paramalignant effusions due to lymphatic obstruction. However, we did not find any significant difference in outcomes between pathologically proven and clinically diagnosed MPEs, and there was no difference in types of underlying cancer. This finding is not surprising because all the patients with a clinical diagnosis of MPE had other distant metastatic disease present. The definition used provides some distinct advantages in terms of clinical applicability. Specifically, thoracoscopy is not always feasible (eg, a patient with breast cancer with proven bone metastasis and a recurrent exudative nonchylous effusion with negative cytology and limited performance status). Pursuing a thoracoscopy for a tissue diagnosis in the palliative setting for patients with a low performance status when there is already known metastatic disease often is not warranted. Yet, physicians need data on outcomes for these difficult-to-manage patients. As such, the generalizability of the findings is better because this study provides physicians with patient outcome data that are most relevant to clinical practice. In addition, if we had required pathologic proof, it would have created bias because patients with negative initial cytology would only be enrolled if they were deemed fit enough for pleuroscopy, whereas those with poor performance status would not be enrolled. This selection bias would lead to a false-positive association between improved QALDs and thoracoscopy and negative initial cytology and would similarly result in a falsely high overall estimate of QALDs in the population overall because those with negative cytology and low performance status would be excluded. The results of such a study would be internally valid but would not necessarily be generalizable to clinical practice. For similar reasons, because many patients in this study were not candidates for thoracoscopy due to poor performance status and comorbidities, the outcomes of patients in this study cannot necessarily be compared with the outcomes of patients undergoing thoracoscopy with talc pleurodesis.

Another limitation is the IPC management algorithm. Because the same algorithm was used for all patients, the outcomes observed are linked to this algorithm, presenting both an advantage and a disadvantage. It allows us to design future comparative effectiveness studies of various management algorithms and provides a baseline for future sample size calculations, but the results may not be generalizable to other populations in which the management algorithm is very different. Additionally, we could not empirically measure the cost of care for these patients because the patients received care from multiple providers using multiple payers in multiple sites. As such, collection of total costs would have required access to different fee schedules for many providers outside of our system. Finally, although this is the largest prospective study of IPCs reported,[5] it is a single-center trial. Future studies of quality-adjusted survival in this population and the trade-offs involved ideally should involve multiple centers.

In conclusion, this study is the first, to our knowledge, to prospectively measure quality-adjusted survival following IPC placement for MPEs. We found that IPCs were associated with large improvements in dyspnea but relatively modest improvements in utility. Patients who had more dyspnea at baseline and who were able to receive treatment after IPC placement had the greatest improvement in utility. Consistent with the existing literature, complications were infrequent, and recurrent MPE requiring repeat intervention was rare when a standard management algorithm was followed. Repeat interventions were more common when the IPC had to be removed early due to complications or malfunction. Careful analysis of time-to-event data shows that the hazard of complications is highest in the first month following IPC placement. As such, the marginal benefit of leaving IPCs in longer to prevent recurrence may be warranted in select patients, depending on how long the IPC has been in place and how much drainage there is. In the broader context, our hope is that this study provides a template for future studies of treatments for MPE by helping to standardize outcomes, definitions, and methods of analysis. The focus should be on using patient-centered outcomes and the proper use of time-to-event analysis rather than radiographic outcomes and incidence proportions.

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Dr Ost: contributed as principal investigator and to the study oversight and design; patient recruitment; performance of procedures; data auditing, analysis, and management; and writing and editing of the manuscript.

Dr Jimenez: contributed to the patient recruitment, performance of procedures, and review and editing of the manuscript.

Dr Lei: contributed to the study design, data analysis, and review and editing of the manuscript.

Dr Cantor: contributed to the study design, data analysis, and review and editing of the manuscript.

Dr Grosu: contributed to the patient recruitment, performance of procedures, and review and editing of the manuscript.

Dr Lazarus: contributed to the patient recruitment, performance of procedures, and review and editing of the manuscript.

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