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**

CHEST 2014; 145(6):1347–1356

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.

Manuscript received August 14, 2013; revision accepted December 28, 2013; originally published Online First January 30, 2014.
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Funding/Support: This work was supported by a Comparative Effectiveness Research Grant, Institute for Cancer Care Innovation, The University of Texas MD Anderson Cancer Center.
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DOI: 10.1378/chest.13-1908

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.