CHEST

Quality Gaps and Comparative Effectiveness of Management Strategies for Recurrent Malignant Pleural Effusions

David E. Ost, MD, MPH; Jiangong Niu, PhD; Hui Zhao, PhD; Horiana B. Grosu, MD; and Sharon H. Giordano, MD

BACKGROUND: Guidelines for recurrent malignant pleural effusions (MPEs) recommend definitive procedures, such as indwelling pleural catheters (IPCs) or pleurodesis, over repeat thoracentesis. We hypothesized that many patients have multiple thoracenteses rather than definitive procedures and that this results in more procedures and complications.

METHODS: Retrospective cohort study using SEER-Medicare data from 2007 to 2011. Patients 66 to 90 years of age with an MPE were included. The primary outcome was whether patients with rapidly recurring MPE, defined as recurrence within 2 weeks of first thoracentesis, received guideline consistent care. Guideline consistent care was defined as a definitive second pleural procedure.

RESULTS: Thoracentesis for MPE was performed in 23,431 patients. A second pleural procedure because of recurrence was required in 12,967 (55%). Recurrence was rapid in 7,565 (58%) of the 12,967 patients that had a recurrence. Of the 7,565 patients with rapid recurrence, 1,811 (24%) received guideline consistent care. Definitive pleural procedures compared with repeat thoracentesis resulted in fewer subsequent pleural procedures (0.62 vs 1.44 procedures per patient, respectively; $P < .0001$), fewer pneumothoraxes (< 0.0037 vs 0.009 pneumothoraxes per patient, respectively; $P = .001$), and fewer ED procedures (0.02 vs 0.04 ED procedures per patient, respectively; $P < .001$). Repeat thoracentesis and IPCs resulted in fewer inpatient days compared with chest tube or thoracoscopic pleurodesis (0.013 vs 0.013 vs 0.085 vs 0.097 inpatient days per day of life, respectively; $P < .001$).

CONCLUSIONS: Guideline consistent care using definitive procedures compared with repeat thoracentesis was associated with fewer subsequent procedures and complications; however, pleurodesis resulted in more inpatient days. CHEST 2018; 153(2):438-452

KEY WORDS: indwelling pleural catheter; malignant pleural effusion; pleural effusion; pleurodesis; thoracentesis; thoracoscopy

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ABBREVIATIONS: IPC = indwelling pleural catheter; IQR = interquartile range; MPE = malignant pleural effusion; SEER = Surveillance, Epidemiology, and End Results

AFFILIATIONS: From the Departments of Pulmonary Medicine (Drs Ost and Grosu) and Health Services Research (Drs Niu, Zhao, and Giordano), MD Anderson Cancer Center, Houston, TX.

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CORRESPONDENCE TO: David E. Ost, MD, MPH, The University of Texas MD Anderson Cancer Center, Pulmonary Department, 1515 Holcombe Blvd, Unit 1462, Houston, TX 77030; e-mail: dost@mdanderson.org

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More than 150,000 cases of malignant pleural effusions (MPEs) occur annually, and MPEs may be found in as many as 15% of patients who die from malignancy.[1,2] When symptomatic MPEs recur, a second thoracentesis can be performed, but this approach by definition is associated with recurrent dyspnea, which in turn is associated with decreased quality of life.[3] Patients who are treated with multiple thoracenteses may also be at higher risk of pleural adhesions, which can complicate future drainage.[4] For these reasons, the American College of Chest Physicians, the American Thoracic Society, and the British Thoracic Society recommend more definitive options be considered for treatment of recurrent MPEs, such as chemical pleurodesis or placement of indwelling pleural catheters (IPCs) (e-Appendix 1).[4-9]

However, although evidence-based guidelines recommend definitive interventions, we have observed significant variations in practice patterns with respect to the utilization of definitive interventions. By the time patients are referred, some patients have had many thoracenteses over a short time span, which is inconsistent with guidelines. However, to our knowledge there are no large comparative effectiveness studies assessing the impact of practice pattern variations on outcomes from MPE. Most prior studies of MPE management were either surveys of pleurodesis methods,[10] comparative studies of methods to achieve pleurodesis,[11-13] or observational studies of quality of life after procedures.[3,14]

The goal of this study was to compare practice patterns for recurrent MPEs to assess their impact on outcomes and to identify their determinants. We hypothesized that many patients receive multiple thoracenteses rather than having definitive pleural interventions as recommended by guidelines. We further hypothesized that a multiple thoracentesis strategy would result in more pleural procedures and complications.

Methods

We performed a retrospective cohort analysis of the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database. The SEER data was linked to Medicare claims and the 2000 US Census. The study was granted an exemption by institutional review board 4.

Study Participants

The cohort comprised patients 66 to 90 years of age diagnosed with their first primary cancer with histologic confirmation from 2007 to 2011, who had a diagnosis of MPE and had undergone thoracentesis. Patients had to have Medicare A and B coverage and no Health Maintenance Organization enrollment for the 12 months prior to and after the first thoracentesis so that Medicare inpatient and outpatient codes would be complete. The algorithms and search results are shown in Figure 1 (e-Table 1). As per National Cancer Institute policy, strata with $\leq$ 10 patients are reported as $<$ 11 to ensure confidentiality.

Definitions

The first pleural procedure for all patients was thoracentesis. Because our hypothesis involved management of recurrent MPEs, we focused on patients that went on to require at least one additional procedure. Subsequent procedures were defined as definitive if they involved thoracoscopic pleurodesis, chest tube pleurodesis, or an IPC.

To assess guideline compliance, we classified patients that required a second pleural procedure within 2 weeks of the first thoracentesis into groups based on their second pleural procedure. If the second procedure was a definitive procedure, they were considered guideline consistent; conversely, if they had thoracentesis, they were considered guideline inconsistent (e-Appendix 1).[4,5]

Outcomes

The primary outcome was whether patients who required a second pleural procedure within 2 weeks of the first thoracentesis received guideline consistent care. Secondary clinical outcomes included number of subsequent pleural procedures and pneumothorax related to pleural procedures. To define postprocedural pneumothorax, we used a strategy based on previous studies.[15,16] Other secondary outcomes included site of service (ED, inpatient, or outpatient) and inpatient days associated with pleural procedures. Exploratory outcomes included empyema (e-Appendix 1, e-Figure 1, e-Table 1).

Because hospitalization can occur for multiple reasons, we categorized inpatient stays based on when the procedure was done. If the pleural procedure was done within 2 days of admission, we considered the pleural disease as significantly contributing to the hospitalization. If the pleural procedure occurred on the third day or later of hospitalization, these were considered late pleural procedures, and we did not count these days because presumably the patient was already in the hospital for another reason (e-Appendix 1). Because survival time would affect the number of procedures and the number of inpatient days (ie, you live longer, you have more chances to be in hospital and have procedures), we expressed these as incidence rates, dividing each by the total number of days alive.

Contralateral Procedures

One weakness of administrative data is that it does not allow identification of which side a pleural procedure is performed on. It is therefore possible that a subsequent procedure might represent a contralateral procedure. To estimate the probability that the second procedure was a contralateral procedure, we retrospectively reviewed all patients in our hospital from 2011 that had an MPE. We identified which side each procedure was performed on and calculated the percentage of second procedures that were contralateral.

Statistical Analysis

Characteristics of patients and outcomes were compared using the χ^2 test for categorical variables, *t* tests for continuous normally distributed variables, and Wilcoxon rank-sum test for nonnormally distributed variables. We used multivariate hierarchical logistic regression with patient's nested within physicians to analyze factors associated with guideline consistent care. We performed a secondary analysis, excluding patients that died within 30 days of the first thoracentesis

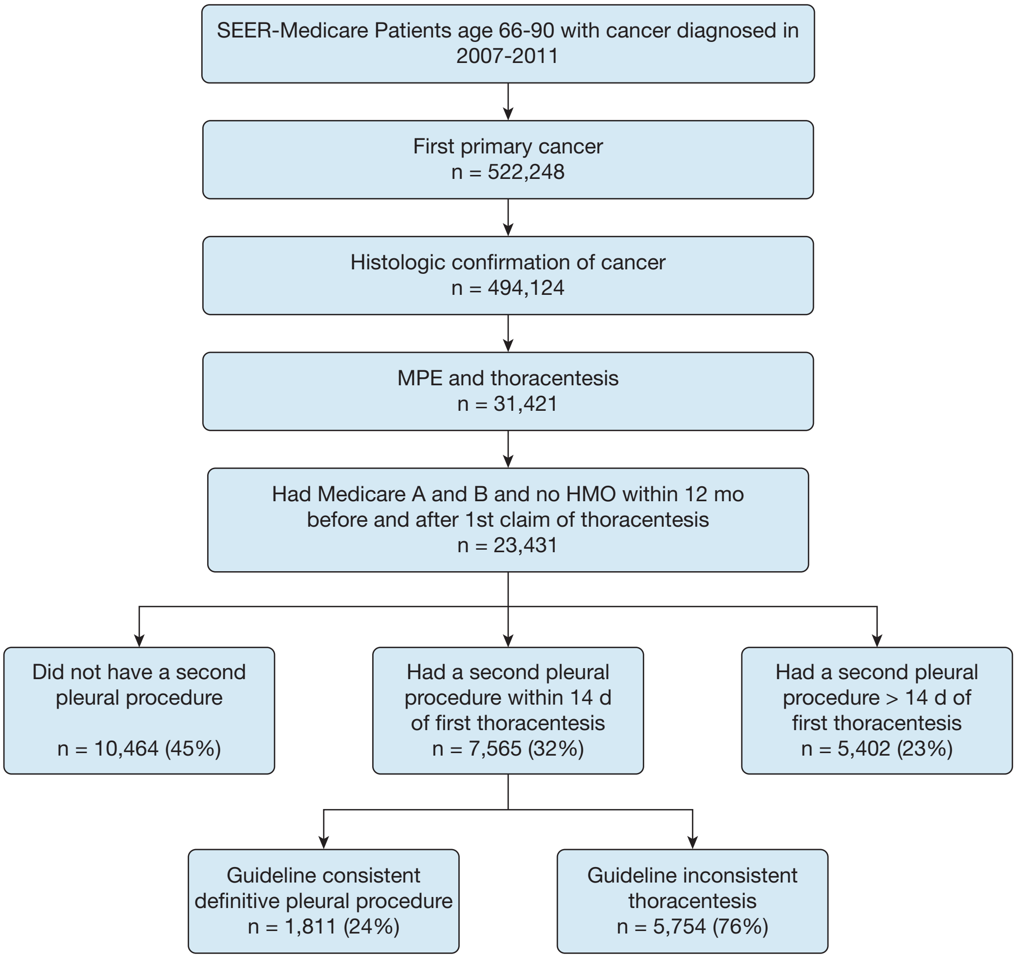

Figure 1 – *Study cohort selection results: SEER Cancer registry 2007-2011. HMO = Health Maintenance Organization; MPE = malignant pleural effusion; SEER = Surveillance, Epidemiology, and End Results.*

because death within 30 days is a factor in deciding whether repeat thoracentesis is a reasonable strategy. We decided a priori that variables significantly associated with outcomes at the 0.2 level in univariate analysis would be considered candidate variables for multivariate analysis. We used backward selection to retain only variables with a level of significance < 0.05.

We used a competing risk model to assess time to second pleural procedure. Time zero was the time of the first thoracentesis, failure time was the time of the second pleural procedure, and death was a competing risk. We performed a similar analysis for time to third pleural procedure, with time zero being the second pleural procedure. All data were analyzed with SAS version 9.3 (SAS Institute).

Results

SEER-Medicare Cohort

A total of 23,431 patients met the inclusion criteria (Fig 1). Patient characteristics are shown in Table 1. There were 46,080 thoracenteses performed. Because of the skewed distribution, the 10.7% of patients receiving ≥ 4 thoracenteses accounted for 31% (14,335) of all thoracenteses (Fig 2). The median number of thoracentesis procedures performed per patient was 1 (25%-75% interquartile range [IQR], 1-2). In addition, there were 1,679 IPCs, 1,799 thoracoscopic pleurodesis procedures, and 4,316 chest tube pleurodesis procedures.

Median survival from first thoracentesis to death was 88 days (IQR, 26-320).

Physician characteristics that performed the pleural procedures are provided in Table 2. Radiologists performed the most pleural procedures, outnumbering all other subspecialties combined.

Second Pleural Procedures

Of the 23,431 patients, 12,967 (55%) eventually required a second pleural procedure, whereas 8,572 (37%) died prior to any other pleural procedure and 1,892 (8%) were alive at last follow-up without recurrence. In a

TABLE 1] Patients Characteristics for the Entire Cohort (N = 23,431)

Variables	Value
Age at diagnosis, y	
Range	66-90
Mean ± SD	76 ± 7
Median	76
66-70	5,368 (22.9)
71-75	5,531 (23.6)
76-80	5,508 (23.5)
>80	7,024 (30.0)
Race	
White	18,900 (80.7)
Hispanic	1,234 (5.3)
Black	1,759 (7.5)
Other	1,538 (6.6)
Sex	
Female	12,042 (51.4)
Male	11,389 (48.6)
Year of diagnosis	
2007	5,338 (22.8)
2008	5,076 (21.7)
2009	4,710 (20.1)
2010	4,380 (18.7)
2011	3,927 (16.8)
Non-high school[a]	
0%-8.71%	5,232 (22.3)
8.71%-15.32%	5,800 (24.8)
15.32%-25.92%	6,325 (27.0)
≥ 25.92%	6,074 (25.9)
Poverty[a]	
0%-4.33%	5,727 (24.4)
4.33%-7.99%	5,748 (24.5)
7.99%-14.8%	5,823 (24.9)
≥ 14.8%	6,133 (26.2)
Marital status	
Married	11,741 (50.1)
Not married	10,406 (44.4)
Unknown	1,284 (5.5)
Charlson comorbidity score	
0	8,104 (34.6)
1	6,373 (27.2)
2	3,673 (15.7)
≥ 3	5,281 (22.5)
Urban/rural county status[a]	
Big metro	13,029 (55.6)
Metro	6,674 (28.5)
Urban	1,307 (5.6)
Less urban	1,947 (8.3)
Rural	474 (2.0)
Cancer type	
Lung	12,389 (52.9)
Lymphoma	1,831 (7.8)
Other solid	9,211 (39.3)
Patients' physician specialty for first thoracentesis	
Pulmonary	4,573 (19.5)
Emergency	378 (1.6)
Internal medicine[b]	5,492 (23.4)
Radiology	12,244 (52.3)
Surgery	401 (1.7)
Thoracic surgery	343 (1.5)
First thoracentesis location	
ED	591 (2.5)
Inpatient	16,669 (71.1)
Outpatient	6,171 (26.3)

Values are No. (%) or as otherwise indicated. Big metro = ≥ 1 million people in a metropolitan county; Less urban = county with an urban population of 2,500 to 19,999; Metro = < 1 million in a metropolitan county; Rural = county with an urban population of > 2,500; Urban = county with an urban population of ≥ 20,000 that is not a metropolitan county.
[a]These are characteristics of the postal code the patient lived in, not the patient's actual educational level or income, which is not in the data set.
[b]Includes all medical subspecialties other than pulmonary.

competing risk model of second pleural procedures vs death as the competing risk, the cumulative incidence of death at 30 days was 14%, which was low relative to the number of patients needing a second pleural procedure (Fig 3). Among all patients who had a second procedure, median time from the first thoracentesis to the second procedure was 9 days (25%-75% IQR, 3-32 days). Patients with solid tumors metastatic to the lung were less likely than patients with primary lung cancer or lymphoma to require a second procedure ($P < .001$) (Fig 4).

The second procedure was a thoracentesis in 10,019 (77%) patients and a definitive procedure in 2,948 patients (23%). When these patients developed recurrences, relative utilization of thoracentesis compared with definitive procedures did not change. The percentage of patients receiving thoracentesis was 74%, 76%, and 77% for the third through fifth recurrences, respectively. Therefore, utilization of

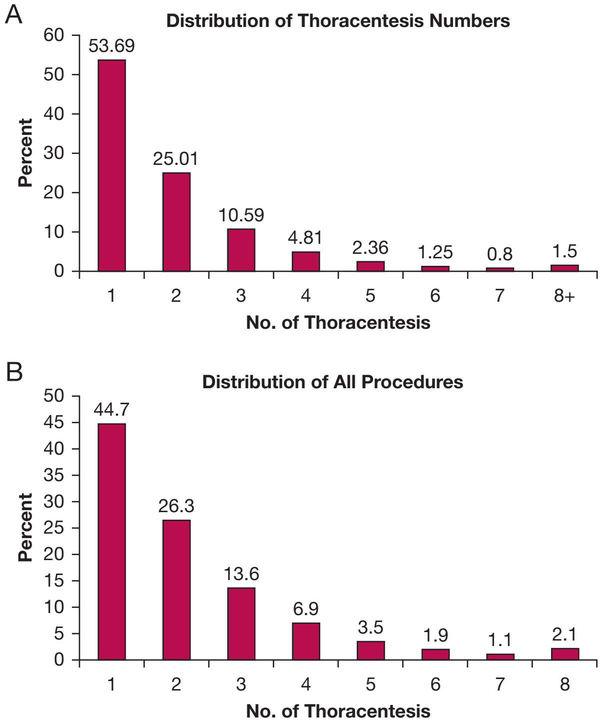

Figure 2 – *A, Histogram showing the number of thoracenteses patients received. B, Histogram showing the total number of pleural procedures (thoracenteses, chest tubes, indwelling pleural catheters, and thoracoscopic procedures).*

definitive pleural procedures was relatively constant, even though we might expect utilization to be higher once a patient had proven themselves to be at high propensity to recur.

However, procedure selection could have been impacted by physician perception of prognosis. According to guidelines, a thoracentesis would be a good alternative if death was likely to occur within 30 days. We therefore analyzed survival among the 12,967 patients that had a second pleural procedure with time zero being the time of the second procedure. If physicians were accurately predicting 30-day survival and recommending thoracentesis for patients with limited prognosis, then presumably survival would be lower in the thoracentesis group. However, we found the thoracentesis group actually had a slightly higher 30-day survival than the definitive procedure group (30-day survival, 0.72 vs 0.68, respectively; log-rank $P = .04$) (Fig 5).

Determinants of Practice Patterns and Guideline Consistency

Of the 12,967 patients who required a second pleural procedure, a total of 7,565 (58%) required it within 14 days of the first procedure. A guideline consistent definitive procedure was performed in 1,811 (24%), whereas 5,754 (76%) had repeat thoracentesis (Table 3). The definitive procedure was an IPC in 310 (17%), thoracoscopic pleurodesis in 420 (23%), and chest tube pleurodesis in 1,081 (60%).

We performed a secondary analysis, excluding all patients who died within 30 days of the first thoracentesis, because in those patients a repeat thoracentesis would have been considered consistent with guidelines. A total of 5,587 patients survived for > 30 days and required a second pleural procedure within 14 days of the first procedure. A guideline consistent procedure was performed in 1,318 (24%), whereas 4,269 (76%) had repeat thoracentesis. Because the results were similar and physicians were either not predicting or not able to predict with accuracy which patients would die within 30 days, we performed subsequent analyses of guideline consistent care using

TABLE 2] Physician Characteristics for Entire Cohort (N = 3,569)

Variables	No.	%
Physician training location		
US trained	2,615	73.3
Not US trained	553	15.5
Unknown	401	11.2
Physician graduation year		
Prior to 1980	902	25.3
1980-1990	1,062	29.8
After 1990	1,165	32.6
Unknown	440	12.3
Physician specialty		
Pulmonary	847	23.7
Emergency	64	1.8
Internal medicine	572	16.0
Radiology	1,823	51.1
Surgery	157	4.4
Thoracic surgery	106	3.0
Physician sex		
Male	2,863	80.2
Female	266	7.5
Unknown	440	12.3
Physician patient volume		
1	1,780	49.9
2-3	860	24.1
≥ 4	929	26.0

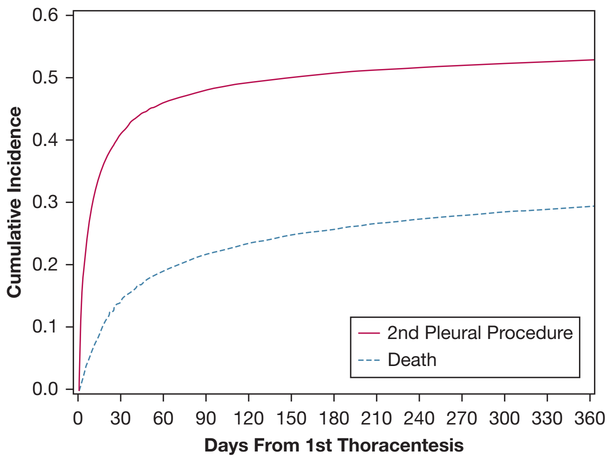

Figure 3 – *Competing risk model: cumulative incidence of recurrent pleural effusion requiring a procedure vs death (n = 23,431).*

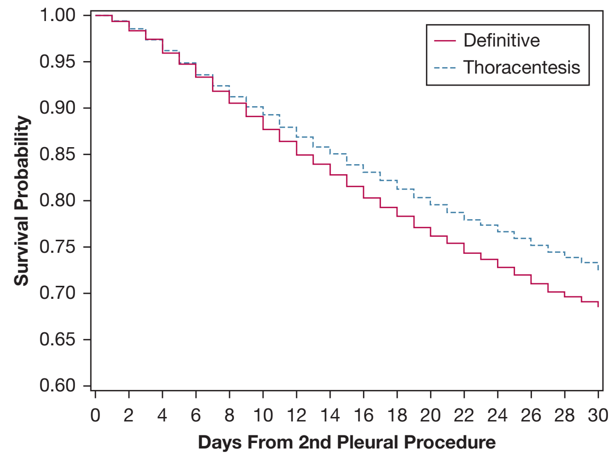

Figure 5 – *Survival time after a second pleural procedure comparing those that had thoracentesis (blue line) with a definitive pleural procedure as their second pleural procedure (n = 12,967). Note that patients with thoracentesis had slightly longer survival times (P = .04), but the absolute magnitude of the difference is small.*

the 7,565 patients that had a recurrence within 14 days of the first procedure.

Univariate analysis of patient and physician factors associated with guideline consistent care is shown in Table 4. On multivariate analysis, younger age; lung cancer; ED setting for first thoracentesis; performance by pulmonologists, radiologists, or thoracic surgeons; and living in a big metropolitan area were associated with guideline consistent care. Guideline consistent care became more frequent in later years (2009 onward).

We performed a competing risk analysis for the 7,565 patients who had a second procedure within 14 days of the first to assess the cumulative incidence of a third procedures vs death (Fig 6). Because guidelines suggest that thoracentesis would be a good alternative if death was likely to occur within 30 days, we analyzed survival probability among these patients to see if there was evidence that patients selected for repeat thoracentesis were more likely to die within 30 days. However, we found similar 30-day survival rates in the thoracentesis and definitive procedure groups (30-day survival, 0.69 vs 0.66, respectively; log-rank $P = .07$) (Fig 7). Therefore, 30-day prognosis was not associated with procedural selection in a manner consistent with guidelines.

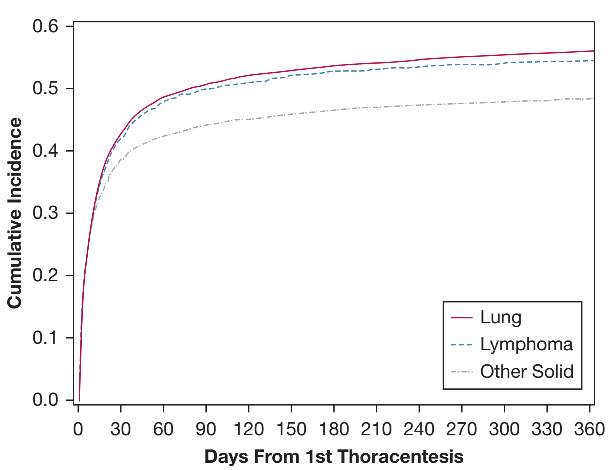

Figure 4 – *Cumulative incidence of second pleural procedures after a first thoracentesis by cancer type (n = 23,431).*

Impact of Physician Referral

In a subset of 5,859 of the 7,565 patients, physician-level data were sufficiently detailed to identify whether the same physician performed both the first and second procedures. When the physician performing the second procedure was different than the first, and the second physician was a specialist (ie, pulmonologist, radiologist, general or thoracic surgeon), guideline consistent care was more likely (e-Table 2).

Pneumothorax

The overall incidence of pneumothorax was 711 out of 46,080 thoracentesis procedures (1.5%) and 22 out of 1,679 IPC procedures (1.3%). Among the 12,967 patients who had a second pleural procedure, 10,019 had a thoracentesis, whereas 2,948 had a definitive procedure. For each group we evaluated the total number of subsequent pleural procedures (third and later) and complications that resulted from them (Table 5). Although per-procedure complication rates were similar, because the definitive group had fewer

TABLE 3] Characteristics of Patients That Had Recurrence Within 14 Days of First Thoracentesis

Variables	Guideline Inconsistent (n = 5,754)	Guideline Consistent (n = 1,811)	*P* Value[a]	Total (N = 7,656)
Age at diagnosis, y			.01	
Range	66-90	66-90		66-90
Mean ± SD	77 ± 7	76 ± 6		76 ± 7
Median	76	76		76
66-70	1,307 (22.7)	460 (25.4)		1,767 (23.4)
71-75	1,355 (23.6)	431 (23.8)		1,786 (23.6)
76-80	1,320 (22.9)	430 (23.7)		1,750 (23.1)
> 80	1,772 (30.8)	490 (27.1)		2,262 (29.9)
Race			.01	
White	4,662 (81.0)	1,435 (79.2)		6,097 (80.6)
Hispanic	315 (5.5)	82 (4.5)		397 (5.3)
Black	438 (7.6)	157 (8.7)		595 (7.9)
Other	339 (5.9)	137 (7.6)		476 (6.3)
Sex			.01	
Female	3,069 (53.3)	904 (49.9)		3,973 (52.5)
Male	2,685 (46.7)	907 (50.1)		3,592 (47.5)
Year of diagnosis			.008	
2007	1,347 (23.4)	388 (21.4)		1,735 (22.9)
2008	1,286 (22.4)	354 (19.6)		1,640 (21.7)
2009	1,130 (19.6)	401 (22.1)		1,531 (20.2)
2010	1,051 (18.3)	345 (19.1)		1,396 (18.5)
2011	940 (16.3)	323 (17.8)		1,263 (16.7)
Non-high school			.60	
0%-8.71%	1,275 (22.2)	413 (22.8)		1,688 (22.3)
8.71%-15.32%	1,399 (24.3)	447 (24.7)		1,846 (24.4)
15.32%-25.92%	1,555 (27.0)	460 (25.4)		2,015 (26.6)
≥ 25.92%	1,525 (26.5)	491 (27.1)		2,016 (26.7)
Poverty			.01	
0%-4.33%	1,329 (23.1)	481 (26.6)		1,810 (23.9)
4.33%-7.99%	1,429 (24.8)	451 (24.9)		1,880 (24.9)
7.99%-14.8%	1,413 (24.6)	428 (23.6)		1,841 (24.3)
≥ 14.8	1,583 (27.5)	451 (24.9)		2,034 (26.9)
Marital status			.11	
Married	2,903 (50.5)	913 (50.4)		3,816 (50.4)
Not married	2,536 (44.1)	821 (45.3)		3,357 (44.4)
Unknown	315 (5.5)	77 (4.3)		392 (5.2)
Charlson comorbidity score			.02	
0	2,060 (35.8)	670 (37.0)		2,730 (36.1)
1	1,516 (26.4)	515 (28.4)		2,031 (26.9)
2	868 (15.1)	273 (15.1)		1,141 (15.1)
≥ 3	1,310 (22.8)	353 (19.5)		1,663 (22.0)
Urban/rural county status			< .0001	
Big metro	3,119 (54.2)	1,085 (59.9)		4,204 (55.6)
Metro	1,609 (28.0)	486 (26.8)		2,095 (27.7)
Urban	369 (6.4)	78 (4.3)		447 (5.9)

(Continued)

TABLE 3] (Continued)

Variables	Guideline Inconsistent (n = 5,754)	Guideline Consistent (n = 1,811)	*P* Value[a]	Total (N = 7,656)
Less urban	536 (9.3)	133 (7.3)		669 (8.8)
Rural	121 (2.1)	29 (1.6)		150 (2.0)
Cancer type			< .0001	
Lung	2,882 (50.1)	1,183 (65.3)		4,065 (53.7)
Lymphoma	542 (9.4)	89 (4.9)		631 (8.3)
Other solid	2,330 (40.5)	539 (29.8)		2,869 (37.9)
Patients' physician specialty			.0001	
Pulmonary	1,572 (27.3)	432 (23.9)		2,004 (26.5)
Emergency	144 (2.5)	27 (1.5)		171 (2.3)
Internal medicine	1,202 (20.9)	406 (22.4)		1,608 (21.3)
Radiology	2,678 (46.5)	880 (48.6)		3,558 (47.0)
Surgery	108 (1.9)	34 (1.9)		142 (1.9)
Thoracic surgery	50 (0.9)	32 (1.8)		82 (1.1)
First thoracentesis location			.09	
Emergency	156 (2.7)	66 (3.6)		222 (2.9)
Inpatient	4,490 (78.0)	1,384 (76.4)		5,874 (77.7)
Outpatient	1,108 (19.3)	361 (19.9)		1,469 (19.4)

Values are No. (%) or as otherwise indicated. See Table 1 legend for expansion of abbreviations.
[a]χ^2 test *P* value; age was treated as categorical here.

procedures, the total incidence of pneumothoraxes per patient was lower with definitive procedures (incidence difference > 0.0053 pneumothoraxes per patient, number needed to avoid one pneumothorax < 190, *P* = .001).

Pleural Procedures Per Patient

Among the 12,967 patients who required a second procedure, those who had a definitive second procedure required fewer subsequent procedures than those who had repeat thoracentesis (0.62 vs 1.44 procedures per patient, respectively; *P* < .0001). Adjusting for survival time by using incidence rates demonstrated that definitive procedures resulted in fewer subsequent procedures than thoracentesis (0.012 vs 0.022 procedures per day of life, respectively; *P* < .0001). Notably, the type of definitive procedure made a difference (Table 6). Thoracoscopic pleurodesis and IPCs had the lowest number of procedures, chest tube pleurodesis was intermediate, and thoracentesis had the most (*P* < .001).

Site of Service

We analyzed site of service and inpatient days. Inpatient location was the most common site of service (e-Table 3). Among the 12,967 patients that had a second procedure, patients who had definitive second procedures required fewer subsequent inpatient and ED procedures than patients who had repeat thoracentesis as their second procedure (Table 7).

Inpatient Days

Patients who had IPCs or thoracentesis as their second pleural procedure had fewer inpatient days associated with pleural procedures per day of life than patients who had chest tubes or thoracoscopic pleurodesis (*P* < .001) (Table 8). From a health-care system perspective, from the time of the second pleural procedure until death, pleural procedures were associated with 5% to 31% of all inpatient days, depending on the type of second procedure performed (lowest was IPC, and highest was thoracoscopy). From a patient perspective, pleural procedures were associated with a median of 3% to 25% of all inpatient days (lowest was IPC, and highest was thoracoscopy).

Relative Use of IPCs and Pleurodesis

IPC utilization increased relative to thoracoscopic and chest tube pleurodesis from 2007 to 2011 (*P* < .0001) (e-Table 4). IPCs accounted for 15% of all definitive pleural procedures performed for cases diagnosed in 2007, with thoracoscopic (23%) and chest tube (62%)

TABLE 4] Hierarchical Multivariable Analysis of Patient, Physician, and System-Level Characteristics Associated With Guideline Consistency

	Univariable		Multivariable	
Variables	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age, y				
66-70	(Reference)	…	(Reference)	…
71-75	0.88 (0.76-1.03)	.12	0.86 (0.73-1.02)	.09
76-80	0.9 (0.77-1.05)	.18	0.89 (0.76-1.04)	.14
>80	0.76 (0.65-0.88)	.0002	0.75 (0.64-0.88)	.0003
Race				
White	(Reference)	…	…	…
Hispanic	0.83 (0.64-1.08)	.17	…	…
Black	1.18 (0.96-1.44)	.11	…	…
Other	1.34 (1.09-1.66)	.007	…	…
Sex				
Female	(Reference)	…	…	…
Male	1.14 (1.02-1.27)	.02	…	…
Year of diagnosis				
2007	(Reference)	…	(Reference)	…
2008	0.98 (0.83-1.16)	.80	1.03 (0.87-1.23)	.72
2009	1.25 (1.06-1.47)	.009	1.30 (1.09-1.55)	.003
2010	1.17 (0.99-1.39)	.07	1.21 (1.01-1.45)	.04
2011	1.23 (1.03-1.46)	.02	1.26 (1.03-1.54)	.02
Non-high school				
0%-8.71%	(Reference)	…	(Reference)	…
8.71%-15.32%	0.95 (0.81-1.11)	.51	1.03 (0.87-1.22)	.72
15.32%-25.92%	0.91 (0.78-1.06)	.22	1.08 (0.90-1.30)	.40
≥ 25.92%	0.97 (0.83-1.13)	.69	1.33 (1.07-1.65)	.01
Poverty				
0%-4.33%	(Reference)	…	(Reference)	…
4.33%-7.99%	0.88 (0.75-1.02)	.09	0.86 (0.73-1.01)	.06
7.99%-14.8%	0.83 (0.71-0.97)	.02	0.80 (0.67-0.97)	.02
≥ 14.8%	0.78 (0.67-0.91)	.002	0.70 (0.57-0.87)	.002
Marital status				
Married	(Reference)	…	…	…
Not married	1.03 (0.92-1.15)	.64	…	…
Unknown	0.83 (0.64-1.08)	.16	…	…
Charlson comorbidity score				
0	(Reference)	…	…	…
1	1.05 (0.91-1.2)	.51	…	…
2	0.94 (0.8-1.11)	.49	…	…
≥ 3	0.83 (0.71-0.96)	.014	…	…
Urban/rural status				
Big metro	(Reference)	…	(Reference)	…
Metro	0.85 (0.74-0.96)	.009	0.84 (0.73-0.96)	.01
Urban	0.59 (0.46-0.77)	.0001	0.57 (0.44-0.75)	< .0001
Less urban	0.7 (0.57-0.87)	.0009	0.68 (0.55-0.85)	.0008
Rural	0.66 (0.43-1.01)	.06	0.64 (0.40-1.00)	.051

(Continued)

TABLE 4] *(Continued)*

Variables	Univariable		Multivariable	
	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Cancer type				
Lung	(Reference)	...	(Reference)	...
Lymphoma	0.41 (0.32-0.52)	< .0001	0.42 (0.33-0.53)	< .0001
Other solid	0.56 (0.5-0.63)	< .0001	0.55 (0.49-0.63)	< .0001
First thoracentesis location				
Emergency	(Reference)	...	(Reference)	...
Inpatient	0.67 (0.5-0.9)	.0074	0.67 (0.48-0.92)	.01
Outpatient	0.77 (0.56-1.05)	.10	0.75 (0.54-1.06)	.10
Patients' physician training location				
US trained	(Reference)	...	(Reference)	...
Not US trained	0.76 (0.62-0.93)	.009	0.83 (0.66-1.05)	.12
Unknown	0.97 (0.86-1.09)	.61	1.13 (0.96-1.33)	.16
Patients' physician graduation years				
Prior to 1980	(Reference)	...	...	...
1980-1990	1.07 (0.87-1.32)	.52	...	...
After 1990	1.04 (0.84-1.29)	.71	...	...
Unknown	1.07 (0.9-1.27)	.45	...	...
Patients' physician specialty				
Pulmonary	(Reference)	...	(Reference)	...
Emergency	0.68 (0.45-1.04)	.08	0.68 (0.42-1.08)	.10
Internal medicine	0.87 (0.74-1.03)	.11	0.84 (0.70-1.01)	.07
Radiology	1.2 (1.05-1.36)	.007	1.18 (1.02-1.37)	.03
Surgery	1.15 (0.77-1.71)	.51	1.32 (0.83-2.09)	.24
Thoracic surgery	2.33 (1.48-3.68)	.0003	2.02 (1.27-3.19)	.003
Patients' physician patient's volume				
1	(Reference)	...	(Reference)	...
2-3	0.89 (0.74-1.08)	.25	0.86 (0.70-1.05)	.14
≥ 4	0.84 (0.73-0.98)	.02	0.73 (0.60-0.88)	.0015
Patients' physician sex				
Male	(Reference)	...	...	...
Female	1.04 (0.73-1.48)	.84	...	...
Unknown	1.03 (0.92-1.15)	.61	...	...

See Table 1 legend for expansion of abbreviations.

pleurodesis accounting for the remainder. IPC use steadily increased over the years, accounting for 28% of all definitive procedures in 2011.

Hospital Cohort for Assessment of Contralateral Effusion Frequency

A retrospective review at MD Anderson Cancer Center identified 205 patients that had a first thoracentesis for MPE. Of these 140 (68%) had one or more subsequent pleural procedures. Of the 140 second procedures, 126 (90%; 95% CI, 84%-94%) were ipsilateral, whereas 14 (10%) were contralateral.

Focusing just on rapid recurrence, we found that 73 of the 205 (36%) patients had a second pleural procedure within 14 days of the thoracentesis: 63 (86%) were ipsilateral and 10 (14%) were contralateral.

Discussion

The data from this study indicate there is a quality gap in terms of the appropriate use of definitive pleural

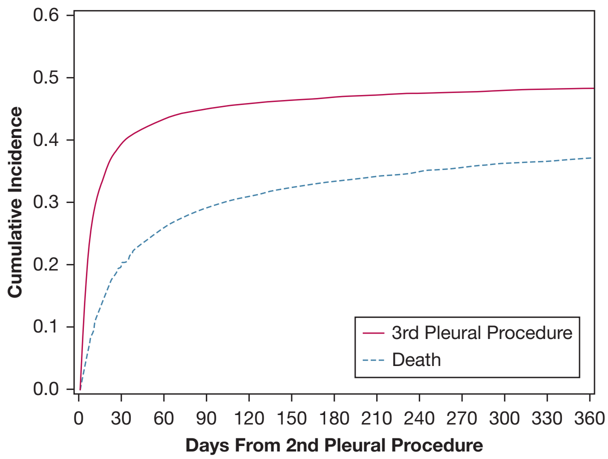

Figure 6 – *Competing risk of pleural fluid recurrence vs death after second pleural procedure in patients that had their second recurrence within 14 days of their first thoracentesis (n = 7,565). Time zero is the time of the second pleural procedure.*

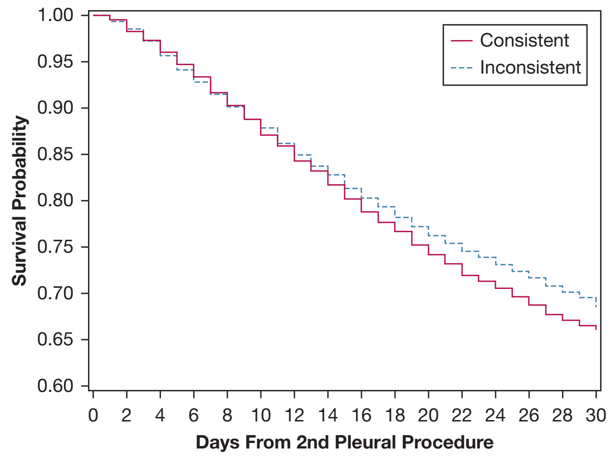

Figure 7 – *Time to death after a second pleural procedure among patients that had their second pleural procedure within 14 days of their first pleural procedure (n = 7,565). Consistent (red line) = guideline consistent, meaning second pleural procedure was a definitive pleural procedure such as an indwelling pleural catheter, a thoracoscopic pleurodesis, or a chest tube pleurodesis; Inconsistent (blue line) = guideline inconsistent, meaning the second pleural procedure was a thoracentesis.*

interventions in patients with rapidly recurrent MPEs. We found that among patients with MPEs that recurred within 2 weeks of initial thoracentesis, only 24% received guideline consistent care and had a definitive procedure, whereas 76% had repeat thoracentesis. The consequence of not using definitive procedures was more pleural procedures per patient, more complications per patient, and more ED procedures. It is also worth considering that additional procedures are associated with at least several preceding days of associated worsening dyspnea and decreased quality of life.[3] Importantly we also found differences in outcomes between definitive pleural procedures. Using IPCs and thoracoscopic pleurodesis to treat recurrent MPEs was superior to chest tube pleurodesis in terms of limiting the need for future procedures; however, all these methods were superior to thoracentesis (Table 6). However, in terms of limiting the need for inpatient stay, thoracentesis and IPCs were equivalent, and both were superior to thoracoscopic or chest tube pleurodesis. This is important because we found that MPE had a large impact on health-care resource utilization, with 5% to 31% of all inpatient days being associated with pleural procedures. The study also provides additional insights into the determinants of practice patterns. We found that patient factors, physician factors, and system-level factors were associated with the probability of guideline consistent care.

Our study is consistent with and builds on prior studies of MPEs by providing information on the comparative effectiveness of different practice patterns across a range of clinically relevant outcomes.[4,5] A recent Cochrane review of interventions for MPEs identified three randomized controlled trials comparing thoracoscopic talc pleurodesis with talc slurry.[17-21] The primary outcome for that review was pleurodesis failure, defined using a hierarchy of preferences, with need for repeat pleural procedure being foremost. Thoracoscopic talc was estimated to be more successful than talc slurry via chest tube, but the evidence was not conclusive (OR for pleurodesis failure, 0.42; 95% CI, 0.13-1.19). Our results are similar in that we found that thoracoscopic pleurodesis was associated with fewer subsequent pleural procedures than chest tube pleurodesis (0.006 vs 0.016 procedures per day of life, respectively; relative risk, 0.38; $P < .001$).

The Cochrane review found insufficient data to perform network meta-analysis for important patient-centered outcomes, including hospital length of stay.[17,18] Our finding that IPCs and thoracentesis are associated with fewer inpatient days due to pleural procedures per day of life than thoracoscopic or chest tube pleurodesis provides useful additional information in this area. No prior studies have, to our knowledge, evaluated total number of lifetime pleural procedures or inpatient hospital days associated with pleural procedures after MPE treatment. Because treatment of MPE is essentially palliative, eliciting patient preferences through discussion is an important aspect of management. Patient-centered outcomes, such as length of stay, are important factors to consider in this context

TABLE 5] Complications According to Type of Pleural Procedure Chosen at Time of First Recurrence of Malignant Effusion (n = 12,967)

Pleural Procedure Chosen to Treat First Recurrence of Malignant Pleural Effusion	No. (%)	Subsequent Thoracenteses or IPC	Pneumothoraxes From Subsequent Thoracenteses or IPC	Complication Rate Per Procedure	Complications Per Patient
Thoracentesis	10,019 (77)	11,793	89	0.008	0.009[a]
Definitive procedure	2,948 (23)	1,031	< 11[b]	< 0.01[b]	< 0.0037[b]

Definitive procedures = thoracoscopic pleurodesis, chest tube pleurodesis, or IPCs; IPC = indwelling pleural catheter.
[a]$P = .001$.
[b]Strata with ≤ 10 patients were suppressed as per National Cancer Institute policy and are reported as < 11 to ensure confidentiality.

because management decisions will need to be individualized according to each patient's values and preferences. We think these data can be useful to help inform the decision process by making the trade-offs involved clearer.

We think sharing these data can also help address the quality gaps that are evident. Part of the reason for the low rate of guideline compliance may be that although physicians are aware that recurrence is common, they may be unaware of how fast it happens. We observed that 32% of patients with MPE had a second pleural procedure within 14 days of their first thoracentesis. Proper disease management requires knowledge of time to recurrence, which is a rate, rather than the simpler question of whether something will eventually recur, which is a proportion. If providers are not aware of the rapid rate, there is less urgency to arrange follow-up, for example 1-month follow-up might be considered as sufficient, resulting in subsequent ED visits for dyspnea which could have been avoided.

Consistent with physician knowledge being a determinant of whether guideline consistent care was delivered, we found that the specialty of the physician providing initial treatment of MPE was predictive of whether guideline consistent care was provided in the future. The probability of future guideline consistent care was higher when initial treatment was provided by pulmonologists, thoracic surgeons, radiologists, and general surgeons than by ED and internal medicine physicians. Of note, our data do not provide insight into how interventional pulmonologists perform relative to other specialties because they are not classified as a distinct specialty in the database. However, no specialty did particularly well (guideline consistency range, 14%-37%).

The data from this study also provide insight into how physician factors and system-level factors interact. This is highlighted by the association between site of service where the first pleural procedure was performed and whether guideline consistent care was provided in the future. Initial treatment in the ED was predictive of guideline consistent care during subsequent visits. This is interesting, given the concurrent finding that having the first pleural procedure performed by an emergency physician was associated with a lower probability of guideline consistent care.

We think what this highlights is two different dimensions that both impact quality—physician training

TABLE 6] Procedures Per Patient According to Pleural Procedure Chosen at Time of First Recurrence of Malignant Pleural Effusion (n = 12,967)

Pleural Procedure Chosen to Treat First Recurrence of Malignant Pleural Effusion	No. (%)	Subsequent Pleural Procedures Per Patient[a]	Subsequent Pleural Procedures Per Patient Day of Life[a]
Thoracentesis	10,019 (77)	1.44	0.022[b]
IPC	496 (4)	0.45	0.006[b]
Thoracoscopic pleurodesis	673 (5)	0.42	0.006[b]
Chest tube pleurodesis	1,779 (14)	0.75	0.016[b]

See Table 5 legend for expansion of abbreviation.
[a]Subsequent procedures include all procedures beginning with the third procedure and later.
[b]Chest tube pleurodesis vs thoracoscopy, $P < .001$; chest tube vs IPC, $P < .001$; chest tube vs thoracentesis, $P < .001$; and thoracentesis vs IPC, $P < .001$.

TABLE 7] Site of Service According to Pleural Procedure Chosen at Time of First Recurrence of Malignant Pleural Effusion (n = 12,967)

Pleural Procedure Chosen to Treat First Recurrence of Malignant Pleural Effusion	Subsequent ED Pleural Procedures Per Patient	Subsequent Inpatient Pleural Procedures Per Patient	Subsequent Outpatient Pleural Procedure Per Patient	Subsequent Pleural Procedures Per Patient
Thoracentesis	0.04[a]	0.85[a]	0.55[a]	1.44[a]
IPC	0.02[a]	0.31[a]	0.13[a]	0.45[a]
Thoracoscopic pleurodesis	0.01[a]	0.33[a]	0.08[a]	0.42[a]
Chest tube pleurodesis	0.02[a]	0.57[a]	0.16[a]	0.75[a]

All patients had a first thoracentesis and malignant pleural effusion and had a subsequent recurrence. Subsequent procedures include all procedures beginning with the third procedure and above. See Table 5 legend for expansion of abbreviation.
[a]Nonparametric $P < .001$ for each category compared with thoracentesis group.

and the organizational context within which care is provided. We think it is not the physician doing the first procedure that matters, but rather whether follow-up care is being arranged with a care team that is capable of performing timely definitive interventions. When an emergency physician does the procedure, this is just a risk marker that a good follow-up plan has not necessarily been put in place, because a pulmonary/thoracic surgery referral probably was not made, because if it had been made that specialist probably would have done the first procedure. Consistent with this hypothesis, we found that when the second physician was a specialist and was not the same as the first physician, guideline consistent care was more likely (e-Table 2). Also consistent with this hypothesis, we found no difference in per-procedure complication rates between guideline consistent and inconsistent groups. Therefore, it is not technical performance that is lacking, but rather recognition and referral to effective longitudinal disease management teams that needs improvement.

System-based solutions to this problem will need to be locally designed. However, the data from this study can help identify the performance characteristics that solutions will require. Our data suggest systems will need to be able to handle a relatively high percentage of early recurrences and have readily available definitive procedures because roughly one-third of all patients will recur within the first 2 weeks.

Although we think the data are useful in highlighting opportunities for improvement, it is also important to recognize its limits. Because this is SEER-Medicare data, one inherent limitation is that it does not distinguish between ipsilateral vs contralateral procedures. Therefore, some second procedures are no doubt occurring on the contralateral side. Our clinical data suggest that probably 10% to 14% of all second procedures are contralateral. In addition, repeat thoracentesis might have been because of patient preference or other valid reasons. We can conceive of circumstances when a second thoracentesis within 2 weeks would be appropriate, such as to obtain molecular markers or to provide terminal support at the end of life. Therefore, the true rate of guideline consistent care is probably higher than our data suggest. However, given that only 24% of patients received guideline consistent care, even if half of the other procedures were contralateral procedures or because of patient preference, the remaining quality gap would be substantial. Similarly, pneumothorax ex vacuo cannot be distinguished from other pneumothorax complications in our dataset. This might impact selection of subsequent treatments. However, the overall pneumothorax rate per procedure was similar in both groups and it was fairly low; therefore, even if all the pneumothoraxes were ex vacuo, this would not be sufficient to explain the quality gap.

In addition, although the data can help to quantify changes in practice patterns and the consequences of those changes, we cannot determine the exact reason why these changes are occurring. As an example, similar to previously published reports,[22] we found that use of pleurodesis decreased over the period of the study. However, although previous studies did not measure IPC use,[22] we found that IPC utilization relative to chest tube and thoracoscopic pleurodesis increased from 2007

TABLE 8] Inpatient Days Associated With Early Pleural Procedures According to Pleural Procedure at Time of First Recurrence of Malignant Effusion (n = 12,967)

Pleural Procedure Used for First Recurrence of Malignant Pleural Effusion	No. (%)	Inpatient Days Associated With Early Pleural Procedure[a]	Survival Time	Inpatient Days Associated With Pleural Procedures Per Day of Life	Total Inpatient Days[b]	Inpatient Days Associated With Early Pleural Procedures/Total Inpatient Days
Thoracentesis	10,019 (77)	1 (1-1)	79 (24-276)	0.013 (0.002-0.05)	31 (15-67)	0.03 (0.01-0.07)
IPC	496 (4)	1 (1-1) $P < .0001$	63[c] (22-170) $P = .0008$	0.013 (0.002-0.044) $P = .90$	23[c] (12-51.5) $P < .0001$	0.03[c] (0.01-0.07) $P = .10$
Thoracoscopic pleurodesis	673 (5)	7 (6-7) $P < .0001$	79.5 (27-260) $P = .64$	0.085[c] (0.021-0.23) $P < .0001$	25[c] (15-42) $P < .0001$	0.25 (0.14-0.41) $P < .0001$
Chest tube	1,779 (14)	7 (7-7)[c] $P < .0001$	62[c] (18-271.5) $P = .0004$	0.097[c] (0.021-0.37) $P < .0001$	34 (18-68) $P < .0001$	0.18[c] (0.08-0.33) $P < .0001$

Values are median (interquartile range) or as otherwise indicated. Distributions are not normal with a heavy right-sided tail. Time zero for all measurements is the day of the procedure used to treat first recurrence of malignant pleural effusion. See Table 5 legend for expansion of abbreviation.

[a]Inpatient days were only counted for early pleural procedures, defined as procedures occurring on the first or second day of hospitalization (e-Appendix 1).

[b]Total inpatient days is the sum of all days spent in hospital from the time of first recurrence onward, irrespective of whether a pleural procedure was done.

[c]Nonparametric $P < .001$ for that group compared with the thoracentesis group.

to 2011 (e-Table 4), such that use of definitive interventions overall was fairly stable. Whether this relative increase in IPC use was because of improved physician training, availability, patient preferences, an emphasis on keeping patients out of hospital, or system-based factors such as early specialist referral cannot be determined from the data.

Finally, although inpatient days clearly have significant economic and quality of life implications, attributing inpatient days to a diagnosis is difficult because patients are often hospitalized for multiple reasons. By counting only inpatient days in which a pleural procedure was done early, we tried to capture this attributable fraction. However, our definition of early pleural procedures (2 days) is such that a patient admitted on a Saturday that had a thoracentesis on Monday would be considered late, and the days for that admission would not be counted in the analysis. Arguably these would constitute real inpatient days related to pleural disease and should be counted. However, such a misclassification would affects all groups in a proportional manner, such that each group would lose the same proportion of inpatient days. The consequence would be that the relative ratios between groups would be unchanged and correct, but the absolute difference in days between groups would decrease, favoring the null hypothesis. Therefore, our estimates of inpatient days are conservative in this regard. In addition, the finding that ED procedures paralleled inpatient procedures supports our findings. However, although we think the observed association is valid, the magnitude of the effect is difficult to precisely quantify, and this should be kept in mind when interpreting the results.

In summary, we found that definitive pleural procedures were underused among patients that had rapid recurrence of MPEs. A strategy of repeat thoracentesis was associated with more future procedures, more complications, and more ED procedures. However, in terms of allowing patients to stay out of the hospital, thoracentesis and IPC were superior to thoracoscopic and chest tube pleurodesis. The public health burden from MPEs was significant, with 5% to 31% of all subsequent inpatient days being associated with pleural procedures.

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Additional information: The e-Appendix, e-Figure, and e-Tables can be found in the Supplemental Materials section of the online article.

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