Original Article

Secondary spontaneous pneumothorax in cancer patients

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Background: Malignancy-associated secondary spontaneous pneumothorax (MSSP) poses significant challenges due to limited survival. By assessing risk factors associated with a MSSP recurrence, there is potential to identify patients who could benefit from early intervention intended to prevent recurrence.

Methods: We performed a retrospective cohort study of patients with MSSP. The primary outcome was time to MSSP recurrence. We used a competing risk model to identify risk factors associated with MSSP recurrence.

Results: A total of 2,532 patients were diagnosed with pneumothorax, with 114 having MSSP but only 96 were evaluable for the time-to-recurrence analysis. Of the 96 patients, 9 (9.4%) patients experienced recurrent MSSP, and 58 (60.4%) patients died during the study's follow-up period. The estimated cumulative incidence (CI) of MSSP considering death as a competing risk was 10.1% at 15 months. The univariable model identified the following covariates as associated with MSSP recurrence: mediastinal shift (HR 12.30, 95% CI: 3.44–43.91, P<0.001), distance from lung apex to thoracic cupola (HR 1.02, 95% CI: 1.00–1.03, P=0.003), and distance between visceral and chest wall at the hilum (HR 1.02, 95% CI: 1.00–1.03, P=0.026).

Conclusions: Although the incidence of MSSP recurrence was found to be low, clinical factors such as sarcoma, the associated mediastinal shift, greater distance from lung apex to thoracic cupola, greater distance between visceral and chest wall at the hilum were found to be risk factors for MSSP recurrence.

Keywords: Pneumothorax; malignancy; cancer

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Introduction

Spontaneous pneumothorax is classified as primary (PSP) in the absence of underlying lung disease and secondary (SSP) when it occurs in the setting of known lung disease (1). The most common underlying conditions in patients with SSP are emphysema, cystic fibrosis, infections, and malignancy (1).

Clinicians dealing with patients experiencing SSP are faced with two main treatment decisions: first, whether to drain the pneumothorax, and second, whether to perform a definitive procedure to prevent further recurrences. However, approaches to the initial management of SSP have significant practice variation, with marked differences between pulmonologists and thoracic surgeons (2). In patients with a large pneumothorax who are unstable, these treatment decisions are straightforward. However, in patients with SSP that are clinically stable and asymptomatic the approach varies, with differences arising among published guidelines and consensus statements (3,4).

British Thoracic Society (BTS) guidelines suggest drainage in the majority of patients with SSP, admission for at least 24 hours, and supplemental oxygen for those with small pneumothoraxes with low threshold for drainage (3). On the other hand, the American College of Chest

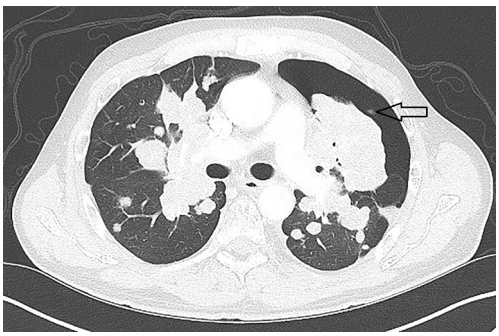

Figure 1 CT chest of a patient with breast cancer and malignancy-associated secondary spontaneous pneumothorax (arrow). CT, computed tomography.

Physicians (ACCP) consensus advises hospitalization, with some panel members being against observation alone because of reports of deaths associated with this approach. Most members of the ACCP panel recommended an intervention after the first occurrence of SSP because of potential for mortality if another pneumothorax occurs (3-5).

Evidence to support these recommendations is scarce and mainly derives from studies involving patients with SSP due to chronic obstructive pulmonary disease (COPD) or infections. Furthermore, although guidelines provide separate recommendations for special subgroups such as patients with cystic fibrosis, HIV-positive status, and pregnancy, SSP in patients with malignancy has not been addressed separately (3).

Compared to other forms of SSP, malignancy-associated secondary spontaneous pneumothorax (MSSP) poses specific challenges due to limited life expectancy of patients (6-8). Additionally, pleural involvement can be significantly more extensive in MSSP than in other pneumothoraxes; therefore, optimal management strategies for MSSP may differ from other forms of SSP. Hence, the decision to perform a procedure in order to prevent further recurrences (e.g., talc pleurodesis) should be based on a careful consideration of the possibility of a second pneumothorax, how well tolerated the pneumothorax would be, and consideration of the competing risk of death given the limited life expectancy of these patients. A high probability of recurrence and/or the inability to tolerate recurrence would favor an aggressive strategy; while conversely, a low probability of a recurrent pneumothorax combined with good tolerance would favor a conservative strategy.

The primary objective of this study was to estimate the cumulative incidence (CI) and to identify risk factors associated with MSSP recurrence. This will help inform clinician decision-making after a first MSSP, specifically whether or not to perform a definitive procedure aimed at preventing recurrence. If the risk of recurrence is high and patients will live long enough to have a recurrence that favors a definitive procedure at the time of first pneumothorax. The secondary objective was to identify risk factors associated with worsening MSSP requiring an intervention among patients who were initially treated with observation. Finally, we evaluated whether our institutional management matched ACCP and BTS guidelines.

Methods

We performed a retrospective review of all patients with spontaneous pneumothorax and an underlying malignancy who were evaluated at MD Anderson Cancer Center between January 2005 and January 2015. The protocol was approved by the Institutional Review Board (IRB protocol number PA15-0761). We identified our patient population by using billing procedure codes for pneumothorax (ICD9codes 512.0, 512.81, 512.82, 512.83, 512.89). We then screened these patients' medical records to assess for inclusion and exclusion criteria. We included patients aged 16 years or older with a diagnosis of MSSP. We excluded patients with iatrogenic pneumothorax such as those patients with pneumothorax after computed tomography (CT) guided or ultrasound guided biopsy and patients with SSP due to other causes.

Definitions

MSSP was defined as a pneumothorax presenting in the absence of trauma or iatrogenic cause in the presence of underlying lung or pleural disease, in this case metastatic lung disease.

Evidence of metastatic disease to the chest was defined as imaging demonstrating multiple nodules or masses in a typical clinical pattern, such as PET or CT with findings sufficiently definitive that the patient was deemed to have metastatic disease to the chest or biopsy/cytology-proven metastatic disease (*Figure 1*).

Initial treatment was defined by the treatment chosen on the day the patient presented with the pneumothorax and categorized into one of two groups:

Invasive procedure group included those patients who underwent any procedure aiming towards draining the pneumothorax, whether it was simple aspiration or a

chest tube.

Observation only group patients were those patients who on presentation with a pneumothorax were observed and not treated with an invasive procedure.

Definitive procedures included any procedure aiming to prevent a recurrence, including chemical pleurodesis using a chest tube or pleurodesis using video-assisted thoracoscopic surgery (VATS) or any other form of surgical procedure aimed to prevent a recurrence.

Size of the pneumothorax

The size of the pneumothorax was evaluated on the initial upright posterior-anterior admission chest radiograph. We measured the distance in millimeters from the visceral pleura to parietal pleura at the level of the hilum, as suggested by the BTS guidelines, and the distance from the lung apex to the ipsilateral thoracic cupola at the parietal surface, as suggested by ACCP guidelines.

Main outcomes

Our primary outcome was time to recurrence of MSSP, measured as days from the diagnosis of the first pneumothorax to the day of diagnosis of the recurrent pneumothorax. Of note, for a recurrence to happen, the first pneumothorax must have resolved. Resolution was defined differently for patients who were in the observation only group as opposed to those whose initial treatment was in the invasive procedure group. In the observation only group, the pneumothorax was considered resolved at 15 days after diagnosis or upon evidence of pneumothorax resolution on imaging, whichever occurred first. This period of 15 days was chosen based on data indicating that total resolution of the pneumothorax occurs within 12 days in the presence of room air and can be accelerated by supplemental oxygen (9,10). In the invasive procedure group, the pneumothorax was considered resolved after chest tube removal with evidence of pneumothorax resolution on imaging. If a patient was in the observation only arm initially, and had to have an intervention, then time originated with removal of the chest tube.

Our secondary outcome was to evaluate time to worsening of pneumothorax requiring an intervention in those patients in the observation only group in order to identify risk factors associated with worsening requiring an intervention. The observation time for this outcome was up to 15 days after the initial presentation of the MSSP; any intervention after that period was considered an intervention for a recurrence and not for treatment of the worsening MSSP.

Finally, we evaluated whether our institutional management matched ACCP and BTS guidelines.

Statistical analysis

Demographic and clinical characteristics were summarized using the mean and standard deviation (SD) or the median and range (min to max) when describing continuous variables. Frequencies and percentages were used to summarize categorical variables. Patient and clinical characteristics, considered categorical, were compared by subgroups of interest using a chi-square test or Fisher's exact test, whiles continuous variables were compared using independent samples *t*-tests or Wilcoxon rank-sum tests.

The CI function of the primary outcome, i.e., the MSSP recurrence, was estimated using the competing risks method of Gooley *et al.* (1999), accounting death as a competing risk for MSSP recurrence. We also use the subdistribution hazard model (Fine & Gray 1999) to estimate the CI for each patient given the baseline risk factors. Estimates of the subdistribution hazards ratio and 95% confidence interval were provided for all potential risk factors.

We used a cause-specific proportional hazard model to analyze time to worsening of pneumothorax, this model identifies risk factors associated with the hazard of pneumothorax worsening. A correlation analysis of all potential risk factors was conducted prior to specifying a full model consisting of covariates of interest. Variables with a P value of less than 0.20 on univariate analysis were considered candidate variables for multivariate regression models. Backward selection with a P value of <0.05 for covariate retention was used to arrive at a multivariable model.

To assess if our institutional management matched ACCP and BTS guidelines we performed a concordance analysis using McNemar's test.

A two-tailed P value <0.05 was considered statistically significant for all analyses. All analyses were conducted using Stata (Release 15. College Station, TX: StataCorp LLC).

Results

We identified 2,532 patients with a diagnosis of pneumothorax who were evaluated in our institution between January 2005 and January 2015. Since we used the ICD9 codes 512.0, 512.81, 512.82, 512.83, 512.89 for all pneumothoraxes

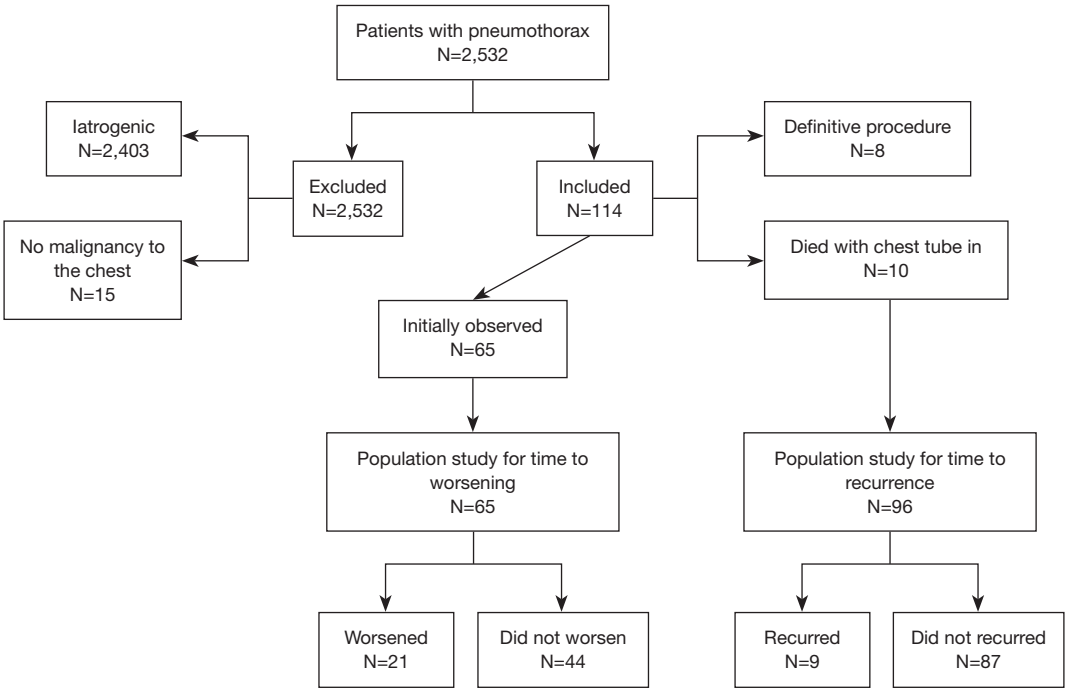

Figure 2 Flow chart of the patients with malignancy-associated secondary spontaneous pneumothorax.

we have a very high number of pneumothoraxes that we reviewed and most associated with an intervention, usually lung biopsy. We excluded 2,418 of the 2,532 patients, 2,403 because they had an iatrogenic pneumothorax and 15 because they did not have metastatic disease in the chest (*Figure 2*). The remaining 114 patients presented with a MSSP.

Risk factors for recurrence of pneumothorax after initial MSSP

Out of 114 patients with MSSP for the outcome of time to recurrence we further excluded 18 patients, 8 patients who had a definitive procedure (5 patients who had talc pleurodesis via VATS and 3 patients who had talc pleurodesis via chest tube) and 10 who died with the chest tube in place. The remaining 96 patients constituted the cohort for analysis. Out of 96 patients, 29 patients had sarcoma, 15 hematological malignancy, 24 lung cancer, and 28 solid non lung cancer. Out of 28 patients with solid non lung malignancy there were 7 patients had gastrointestinal malignancy, 7 patients had head and neck cancer, 3 patients had breast cancer, 2 patients had thyroid cancer, 5 patients had renal cancer, 1 patient had mesothelioma, 1 patient had melanoma, 1 patient had ovarian cancer, 1 patient had endometrial.

Recurrent MSSP occurred in 9 (9.4%) of these patients. The median time to recurrence of MSSP was 0.69 (range, 0.16 to 10.1) months. The median survival time was 7.8 months (95% CI: 4.8–11.1). Clinical and radiological characteristics by MSSP recurrence status are shown in *Table 1*. The estimated CI of MSSP considering death as a competing risk was 8.5% and 10.1% at 10 and 15 months, respectively (*Figure 3*).

The univariable subdistribution hazard model using the method for death as a competing risk analysis identified the associated contralateral mediastinal shift (P<0.001), distance from lung apex to thoracic cupola (P=0.003), and distance between visceral pleura, and chest wall at hilum (P=0.026) as all associated with significantly increasing the CI probability of MSSP recurrence. In addition, compared to all other types of cancer, sarcoma type of cancer was associated with a significantly increased CI of MSSP recurrence (P=0.0011) (*Table 2*).

Risk factors for clinical deterioration requiring intervention among patients initially managed with observation

Out of 114 patients, 65 patients were initially managed with observation only and this constituted the cohort for

Table 1 Clinical and radiological characteristics of patients by recurrence status (n=96)

Characteristics	No recurrence (n=87)	Recurrence (n=9)	P value
Age, years			0.742
Mean ± SD	52.11±17.38	50.08±19.44	
Median (min to max)	55 (16 to 84)	49 (23 to 80)	
Sex, n (%)			0.458
Female	30 (34.48)	2 (22.22)	
Male	57 (65.52)	7 (77.78)	
Smoking status, n (%)			0.320
Never	53 (60.92)	7 (77.78)	
Former/current	34 (39.08)	2 (22.22)	
Cancer type, n (%)			0.077
Sarcoma	23 (26.44)	6 (66.67)	
Hematological malignancy	15 (17.24)	0 (0)	
Solid non-lung	26 (29.89)	2 (22.22)	
Lung cancer	23 (26.44)	1 (11.11)	
Cancer type, n (%)			0.012
Sarcoma	23 (26.44)	6 (66.67)	
Non-sarcoma malignancy	64 (73.56)	3 (33.33)	
Cavitary lung tumor on imaging, n (%)			0.098
No	62 (71.26)	4 (44.44)	
Yes	25 (28.74)	5 (55.56)	
Pleural-based lesions on imaging, n (%)			0.325
No	44 (50.57)	3 (33.33)	
Yes	43 (49.43)	6 (66.67)	
Emphysema on imaging, n (%)			0.639
No	72 (82.76)	8 (88.89)	
Yes	15 (17.24)	1 (11.11)	
Prior radiation chest, n (%)			0.537
No	70 (80.46)	8 (88.89)	
Yes	17 (19.54)	1 (11.11)	
ACCP			0.018
Mean ± SD	29.5±27.11	52.60±30.59	
Median (min to max)	24 (0.00–104.20)	48 (13.40–120.00)	
ACCP recommended intervention, n (%)			0.069
No	47 (54.02)	2 (22.22)	
Yes	40 (45.98)	7 (77.78)	

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	No recurrence (n=87)	Recurrence (n=9)	P value
BTS			0.108
Mean ± SD	19.09±21.55	31.18±17.64	
Median (min to max)	15.4 (0.00–91.90)	25 (9.50–67.00)	
BTS recommended intervention, n (%)			0.017
No	35 (40.23)	0 (0)	
Yes	52 (59.77)	9 (100)	
Associated pleural effusion, n (%)			0.451
No	68 (78.16)	8 (88.89)	
Yes	19 (21.84)	1 (11.11)	
Associated mediastinal contralateral shift, n (%)			<0.001
No	81 (93.10)	4 (44.44)	
Yes	6 (6.90)	5 (55.56)	
Shortness of breath, n (%)			0.051
No	39 (44.83)	1 (11.11)	
Yes	48 (55.17)	8 (88.89)	
Respiratory rate at presentation			0.855
Mean ± SD	19.08±2.28	19.22±1.20	
Median (min to max)	18 (15.00–31.00)	20 (17.00–20.00)	
Heart rate at presentation			0.058
Mean ± SD	89.70 ±19.85	103.33±23.76	
Median (min to max)	91 (54.00–137.00)	100 (75.00–135.00)	
Systolic blood pressure in mmHg			0.808
Mean ± SD	127.75±20.19	129.56±29.73	
Median (min to max)	124 (94.00–186.00)	118(100.00–181.00)	
Diastolic blood pressure in mmHg			0.725
Mean ± SD	73.55±12.39	75.11±14.84	
Median (min to max)	71 (52.00–106.00)	70 (50.00–97.00)	
Oxygen saturation			0.593
Mean ± SD	97.09±2.32	96.67±1.58	
Median (min to max)	98 (89.00–100.00)	97 (94.00–99.00)	

ACCP, distance from lung apex to thoracic cupola; SD, standard deviation; BTS, distance between visceral pleura and chest wall at hilum.

our secondary analysis on time to worsening; clinical and radiological characteristics by worsening status are shown in *Table 3*.

The univariable cause-specific proportional hazard analysis identified patients with sarcomas as having a higher risk of clinical deterioration requiring intervention when compared to solid non-lung tumors (P=0.007) and lung cancer (P=0.022). Other factors associated with increased

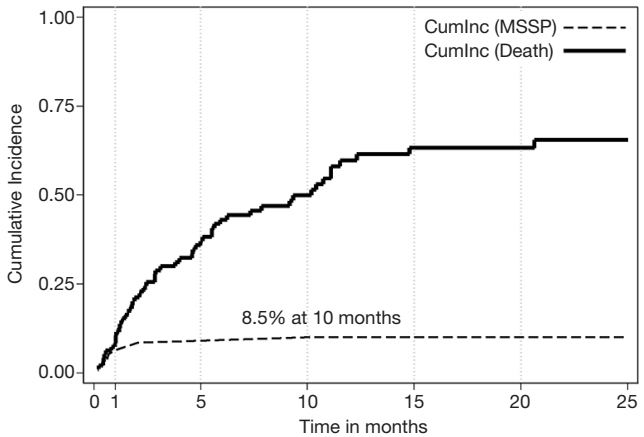

Figure 3 The plot illustrates the cumulative incidence of second pneumothorax with artificial censoring of patients at 25 months. The cumulative incidence of a second pneumothorax considering death as a competing risk (CumInc) was estimated using the method of Gooley *et al.* 1999. Cumulative incidence of death is the solid black line and cumulative incidence of MSSP is the interrupted line. MSSP, malignancy-associated secondary spontaneous pneumothorax.

risk of clinical deterioration requiring interventions were the presence of cavitary lung nodules (P=0.034), mediastinal contralateral shift (P=0.013), shortness of breath (P<0.001), higher respiratory rate (P=0.005), higher heart rate (P=0.016), greater distance from lung apex to thoracic cupola in millimeters (P<0.001), and greater distance between visceral pleura and chest wall at hilum in millimeters (P=0.001) (*Table 4*). On multivariate analysis, only the presence of shortness of breath remained as a significant predictor of worsening and the need for an invasive procedure (P=0.033).

MD Anderson Cancer Center management vs. guidelines

On the basis of the ACCP guidelines, an invasive intervention was recommended in 60 (53%) of 114 patients. This recommendation was followed for 38 (63%) of the 60 patients. Of the 22 patients for whom the ACCP recommended intervention and who were treated with observation, 10 worsened and required an intervention. (*Figure S1*) The BTS guidelines recommended intervention in 78 (68%) of the 114 patients. This recommendation was followed for 48 (62%) of the 78. Only 84 (74%) of the 114 patients were hospitalized for pneumothorax. Of the 30 patients for whom the BTS guidelines recommended intervention and who were treated with observation, 17 worsened and required an intervention. (*Figure S2*) BTS guideline had a higher concordance (83%) with correct outcome (*Table S1*).

Discussion

This is the first study to develop a parsimonious model for time to pneumothorax recurrence in patients with evidence of MSSP. The recurrence rate was low and, of 96 patients, only 9 (9.4%) had a recurrence. The competing risk model showed that associated mediastinal shift, greater distance from lung apex to thoracic cupola, and greater distance between visceral and chest wall at the hilum were associated with a higher hazard of pneumothorax recurrence. In addition, compared to all other types of cancer, sarcoma type of cancer was associated with a significantly increased CI of MSSP recurrence (P=0.0011).

For the outcome of time to worsening in those patients initially observed, we identified multiple risk factors, but due to the sample size only shortness of breath was selected in the multivariate model. It is quite likely that if we had a larger sample size and hence more events we would identify other risk factors.

The low recurrence rate of MSSP (9.6%) observed in this study is in contrast to the recurrence rate of patients with secondary spontaneous pneumothorax due to other causes such as COPD, who with conservative treatment have recurrence rates of 41% to 47% over 2 year. Due to the high recurrence rate and significant associated mortality, recommended treatment for patients with SSP due to COPD is surgery after the first occurrence of SSP to prevent a potentially lethal event (11). However, surgical treatment for SSP is usually planned for patients who have well-preserved respiratory function and a good performance status. This was not the case in our study population with limited survival, and likely at risk for respiratory failure due to high disease burden.

In addition, clinicians have a heterogeneous approach to the management of spontaneous pneumothorax, and the ACCP and BTS have proposed different treatment recommendations (2,4,11,12). ACCP recommends that clinically stable patients with small pneumothorax be hospitalized, whereas BTS guidelines states that observation alone is recommended only in patients with small secondary pneumothoraxes of less than 1 cm depth or isolated apical pneumothoraxes in asymptomatic patients. Hospitalization is recommended in all cases (3,4). In our

Table 2 Pneumothorax recurrence, competing risk model

Parameter	Univariate competing risk			
	SHR	95% CI		P value
Age, in years	0.99	0.95	1.03	0.754
Male	1.82	0.39	8.48	0.445
Smoking				
Current/former	1.00			
Never	2.17	0.45	10.45	0.334
Cancer type				
Sarcoma	1.00			
Liquid tumor	–	–	–	
Solid non-lung	0.32	0.06	1.60	0.167
Lung cancer	0.18	0.02	1.42	0.105
Cancer type				
All others	1.00			
Sarcoma	6.17	1.52	24.98	0.011
Cavitary lung nodules/masses present	2.67	0.73	9.70	0.135
Pleural-based lung nodules/masses present	1.99	0.49	7.92	0.329
Emphysema present	0.59	0.07	4.59	0.621
Prior radiation to the chest	0.50	0.06	3.91	0.512
Associated pleural effusion	0.44	0.05	3.55	0.448
Associated mediastinal contralateral shift	12.30	3.44	43.91	<0.001
Shortness of breath	6.19	0.76	49.88	0.087
Respiratory rate at presentation, breaths/minute	1.02	0.88	1.19	0.744
Heart rate at presentation, beats/minute	1.03	0.99	1.07	0.062
Systolic blood pressure, mmHg	1.00	0.96	1.04	0.847
Diastolic blood pressure, mmHg	1.00	0.95	1.06	0.749
Oxygen saturation, %	0.93	0.79	1.10	0.447
Distance from lung apex to thoracic cupola, mm	1.02	1.00	1.03	0.003
Distance between visceral pleura and chest wall at hilum, mm	1.02	1.00	1.03	0.026

SHR, sub hazard ratio.

patient population, only 84 (74%) of 114 patients were hospitalized for pneumothorax and in just about 60% of cases the ACCP and BTS guidelines were followed in respect to treating the pneumothorax with an intervention. This may be a reasonable approach, especially given that our study found that, in patients with MSSP treated with observation, worsening was seen in 21 (32%) of 65 patients and no patient died with this management strategy. In addition, ACCP and BTS guidelines recommend definitive intervention to prevent recurrence, but since the recurrence rate is low, we recommend against upfront definitive treatment, such as surgical intervention (pleurodesis), in this patient population.

This is the first study to use a Fine-Gray subdistribution

Table 3 Clinical and radiological characteristics of worsening in patients initially observed (n=65)

Characteristics	Worsened (n=21)	Not worsened (n=44)	P value
Age, years			
Mean ± SD	52.11±17.38	50.08±19.44	0.6850
Sex, n (%)			
Male	12 (57.14)	31 (70.45)	0.2890
Smoking status, n (%)			
Former/current	9 (42.86)	17 (38.64)	0.7450
Cancer type, n (%)			
Sarcoma	11 (52.38)	5 (11.36)	
Hematological malignancy	3 (14.29)	6 (13.64)	
Solid non-lung	3 (14.29)	18 (40.91)	
Lung cancer	4 (19.05)	15 (34.09)	0.0030
Cavitary lung tumor on imaging, n (%)			
Yes	6 (28.57)	8 (18.18)	0.2600
Pleural-based lesions on imaging, n (%)			
Yes	15 (71.43)	18 (40.91)	0.0200
Emphysema on imaging, n (%)			
Yes	4 (19.05)	4 (9.09)	0.2260
Prior radiation chest, n (%)			
Yes	2 (9.52)	12 (27.27)	0.0430
Distance from lung apex to thoracic cupola (mm)			
Mean ± SD	41.17±35.34	17.61±14.55	0.0003
Distance between visceral pleura and chest wall at hilum (mm)			
Mean ± SD	23.07±21.82	7.51±11.02	0.0003
Associated pleural effusion, n (%)			
Yes	4 (19.05)	8 (18.18)	0.5910
Associated mediastinal contralateral shift, n (%)			
Yes	2 (9.52)	0 (0.00)	0.1010
Shortness of breath, n (%)			
Yes	17 (80.95)	9 (20.45)	<0.0001
Respiratory rate at presentation (breaths/minute)			
Mean ± SD	19.33±2.22	18.15±1.27	0.0080
Heart rate at presentation (beats/minute)			
Mean ± SD	97.47±21.87	84±23.76	0.0090
Systolic blood pressure in mmHg			
Mean ± SD	116.61±15.92	122±52	0.1760
Diastolic blood pressure in mmHg			
Mean ± SD	72.28±8.82	69.90±9.60	0.3420
Oxygen saturation (%)			
Mean ± SD	96.57±2.03	97.61±2.00	0.0550

SD, standard deviation.

Table 4 Pneumothorax time to worsening, Cox model

Parameter	Univariate Cox model				Multivariate Cox model			
	HR	95% CI		P value	HR	95% CI		P value
Age, in years	0.98	0.96	1.03	0.334				
Male	0.63	0.26	1.48	0.299				
Smoking								
Current/former	1.00							
Never	0.89	0.53	1.50	0.668				
Cancer type								
Sarcoma	1.00				1.00			
Liquid tumor	0.42	0.11	1.53	0.193	0.56	0.09	3.21	0.521
Solid non-lung	0.17	0.47	0.61	0.007	0.45	0.10	2.04	0.303
Lung cancer	0.26	0.82	0.83	0.022	0.42	0.08	2.04	0.285
Cancer type								
All other types	1.00				1.00			
Sarcoma	3.99	1.68	9.45	0.002	2.12	0.64	7.05	0.216
Cavitary lung nodules/masses present	1.37	0.53	3.51	0.512				
Pleural-based lung nodules/masses present	2.79	1.08	7.21	0.034	1.21	0.35	4.23	0.756
Emphysema present	1.73	0.58	5.19	0.321				
Prior radiation to the chest	0.36	0.08	1.54	0.169	0.92	0.14	5.93	0.937
Associated pleural effusion	1.09	0.36	3.25	0.869				
Associated mediastinal contralateral shift	7	1.51	32.39	0.013	0.31	0.02	4.20	0.382
Shortness of breath	8.50	2.83	25.49	<0.001	3.96	1.11	14.06	0.035
Respiratory rate at presentation, breaths/minute	1.27	1.07	1.50	0.005	0.93	0.67	1.28	0.669
Heart rate at presentation, beats/minute	1.03	1.01	1.05	0.016	1.01	0.98	1.04	0.282
Systolic blood pressure, mmHg	0.97	0.95	1.00	0.163	0.98	0.94	1.03	0.630
Diastolic blood pressure, mmHg	1.02	0.97	1.07	0.314				
Oxygen saturation, %	0.84	0.70	1.01	0.080	0.81	0.61	1.05	0.125
Distance from lung apex to thoracic cupola, mm	1.02	1.01	1.04	<0.001	1.02	0.99	1.04	0.06
Distance between visceral pleura and chest wall at hilum, mm	1.04	1.02	1.06	<0.001	1.00	0.97	1.03	0.814

hazard model for MSSP recurrence. Competing risks are particularly good for clinical prediction, compared with conventional Kaplan-Meier and Cox models, because when competing risks are present and occur with high frequency, the Kaplan-Meier survival function will consistently overestimate the crude incidence of the outcome of interest (13).

We recognize that our study has limitations such as the retrospective nature of data collection, which could have led to some misclassification bias (e.g., documentation may have failed to capture SOB that was present. Misclassification bias of this sort would favor the null hypothesis, so while our estimates of the HR may be falsely low, the association is likely to be true. In addition, inaccuracies in billing

diagnoses could have led to bias in identifying all cases.

In conclusion, when MSSP presents, risk factors that predict worsening of the first MSSP requiring an intervention include: having sarcomas, presence of cavitary lung nodules, mediastinal contralateral shift, shortness of breath, higher respiratory rate, higher heart rate, greater distance from lung apex to thoracic cupola, and greater distance between visceral pleura and chest wall at hilum. After the first MSSP resolves, factors that increase the risk of having a recurrence include: contralateral mediastinal shift, distance from lung apex to thoracic cupola, and distance between visceral pleura, and chest wall at hilum. Knowing this will inform our decision as to whether a definitive intervention is used (e.g., talc pleurodesis). The overall incidence of a second MSSP was only 9.4% and median life expectancy was low. This suggests that conservative management strategies for MSSP are reasonable, and this is different than in other forms of SSP such as COPD.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The protocol was approved by the Institutional Review Board (IRB protocol number PA15-0761).

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Supplementary

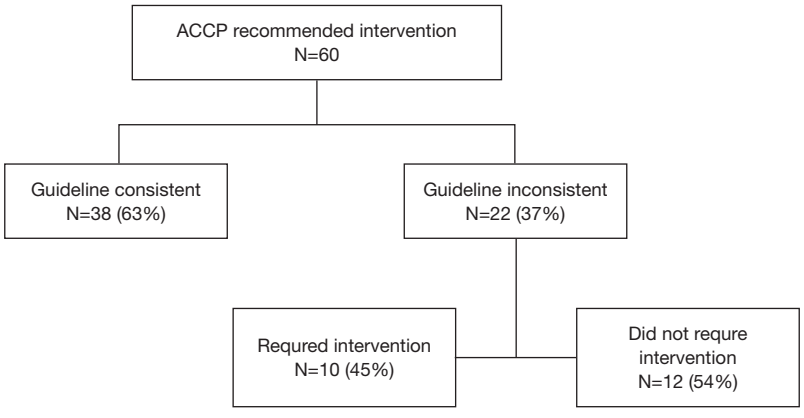

Figure S1 Flow chart of the patients with ACCP recommended intervention. ACCP, American College of Chest Physicians.

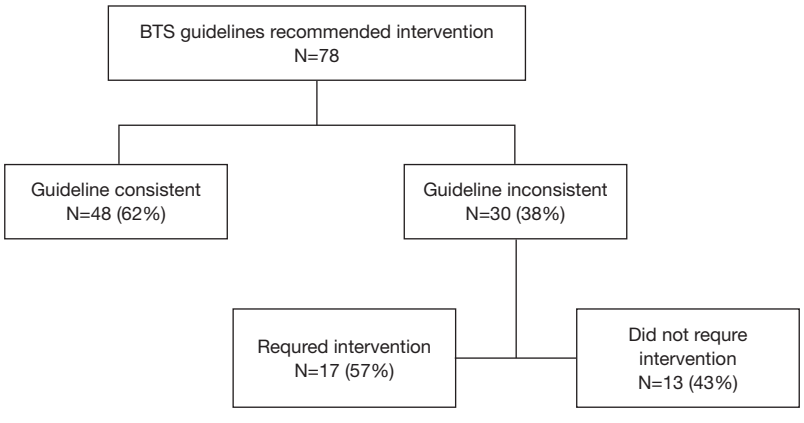

Figure S2 Flow chart of the patients with BTS guidelines recommended intervention. BTS, British Thoracic Society.

Table S1 Institutional management *vs.* guidelines

Guidelines	No. (%)	Concordance	95% CI	McNemar's P value
Guideline concordance				
ACCP *vs.* BTS		70.20%	(60.9%, 78.4%)	0.002
ACCP No/BTS No	28 (24.6)			
ACCP No/BTS Yes	26 (22.8)			
ACCP Yes/BTS No	8 (7.0)			
ACCP Yes/BTS Yes	52 (45.6)			
Outcome concordance				
I ACCP *vs.* Outcome		69.30%	(60.0%, 77.6%)	0.063
ACCP No/Outcome No	31 (27.2)			
ACCP No/Outcome Yes	23 (20.2)			
ACCP Yes/Outcome No	12 (10.5)			
ACCP Yes/Outcome Yes	48 (42.1)			
II BTS *vs.* Outcome		83.30%	(75.2%, 89.6%)	0.108
BTS No/Outcome No	30 (26.3)			
BTS No/Outcome Yes	6 (5.3)			
BTS Yes/Outcome No	13 (11.4)			
BTS Yes/Outcome Yes	65 (57.0)			

ACCP, American College of Chest Physicians; BTS, British Thoracic Society.