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Spontaneous Pneumothorax and Tuberculosis. Long-term Follow-up

AUTHORS

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Abstract

Though spontaneous pneumothorax (SP) is a well-known complication of pulmonary tuberculosis (TB), there are very few reports addressing this topic: For this reason, we retrospectively analyzed the experience of SP in patients diagnosed with TB in our hospital between 1989 and 2010.

Out of 872 patients treated for SP during this period, 47 (5.4%) had TB antecedents, 21 with active TB (0.95% of the 2089 TB cases diagnosed during this period) and 26 with residual inactive TB. 46 cases were treated with pleural drainage (PD): 40 (85%) with only one, 2 with two and 4 with three PD. The average length was 12.9 ± 11.3 days. In 11 cases (23%) a relapse of SP occurred, with no statistical relationship among the different studied variables. In 13 cases (28%) it became necessary to carry out a resection (atypical segmentectomy in all cases) for persistent air leaks with PD. Survival statistics were unfavorable only in elderly patients and those infected with HIV.

We conclude that the treatment of SP secondary to TB with PD is usually a sound response, with a good general prognosis, and low percentage of cases that require another PD and surgical treatment.

Introduction

Spontaneous Pneumothorax is defined as the sudden presence of air in the pleural cavity, without apparent external cause. The majority of cases can be classified as primary spontaneous pneumothorax, ocurring in the young, without associated pulmonary or general disease. Its production mechanism is the rupture of some sub-pleural pulmonary alterations known as blebs[1]. Secondary Spontaneous Pneumothorax (SSP) is associated with clinical or radiological evidence of significant lung disease, most frequenly

consequence of chronic obstructive pulmonary disease (COPD). Pulmonary tuberculosis (TB) has been repeatedly described as frequent cause of SSP[2-6] with a very variable presentation frequency according to the few authors that have studied this matter. Over the past few decades, a clearly growing incidence of SSP caused by TB has been described[4]. The frequency with which SSP can end up complicating the course of TB has also been studied very little, with figures from 0.6% to 1.4%[5]. These figures, although appearing to be very low, can be supremely important if we keep in mind the 9.5 million new cases that the WHO reports are produced in the world every year[7] 80% of these cases occur in countries. In spite of the fact that TB is a frequent cause of SSP, very few series, with very few patients, have been reported. Therefore, the frequency of presentation, the clinical and therapeutical management, and the prognosis of these patients have been poorly studied. There is very little contrasting experience with this type of SSP. With the aim of reviewing our experience and shedding some light on these matters, we present our series of SSP and TB over the past 21 years.

Materials and Methods

The Dr. Negrín General Hospital attends an approximate population of 500,000, corresponding to the northern area of the island of Gran Canaria. There is one Thoracic Surgery Unit in this area where all cases of SP are referred. The average incidence of TB on the island of Gran Canaria was 32.2 cases for 100,000 inhabitants in 1988, over 23/100,000 in 2009[8].

The present study is observational, retrospective and longitudinal analyzing data corresponding to clinical reports of all patients with SSP and TB attended in our hospital between January 1, 1989 and December 31, 2009. The following data were collected from the medical records: age, sex, domicile, comorbidity and past medical history (smoking, alcoholism, drug addiction, social indigence, functional criteria of COPD, previous

respiratory infections, previous TB and other pneumological antecedents), clinical data (dyspnoea, pleuritic pain, fever, cough, expectoration, diagnosis of active TB, bronchopleural fistula, and if the patient was in treatment with anti-TB drugs), diagnostic method for pneumothorax (radiography and computed tomography scan), its location and radiological characteristics (presence of pulmonary infiltrates, pulmonary atelectases, caverns, bronchiectasis, destroyed lung, granulomes, pachypleuritis, calcium plaques, pleural effusion, mediastinal adenopathies), data related to pleural drainage (PD) (duration in days, recurrence of SSP needing PD again), necessity for surgery and type of surgery performed, hospital stay, number of admittances, complications and perioperative mortality (*exitus* during the same admittance), as well as long-term survival. Long-term survival was considered as the period between the performance of the pleural drainage and the death or the date of the last follow-up observation before the analysis if the subjet was still alive. For the follow-up, the hospitals' database was used. The variables considered as "endpoint" were recurrence of SSP and long-term survival after having suffered a pneumothorax.

Diagnosis of SSP was always confirmed through radiological studies, either conventional thoracic radiography or computed tomography. All radiological examinations were evaluated by an independent radiologist.

In all but one case a PD was performed. The procedure was carried out under local anesthesia, inserting a 28F drainage tube in the anterior axillary line, 5th intercostal space. Surgical intervention (thoracotomy or video thoracoscopy) was indicated in the presence of air leaks lasting for more than 10 days and when there was a recurrence of SSP. For this indication, the general performance status of the patient was taken into account as well as pulmonary parenchymal involvement, and the presence of pleural sequelae. In all cases possible, a test of respiratory function was done. If there was any suspicion of endobronchial pathology, bronchoscopy was indicated.

Statistical Analysis

Analyses were done using SPSS version 14.0 (SPSS, Inc. Chicago, Illinois). The placement of PD was considered as the initial date of the study. A descriptive analysis of the sample was done estimating the frequency and the corresponding percentages in the case of categorical variables, and the average (± standard deviation). Afterward, possible relationships among descriptor variables were studied along with those considered "endpoint." In the case of categorical variables, the χ^2 test was used, and in cases where it did not meet the conditions of the application, the Fisher exact test was done. As for numerical variables, in order to compare measurements, Student's t-test was applied.

Survival curves were calculated according to the Kaplan–Meier method. Differences in survival were analyzed with the log rank test and the Hazard ratio was estimated. The relation between the numeric variable age and survival was estimated using Cox regression. In all cases $p<0.05$ was considered significant.

Results

During the study period a total of 872 patients affected with SP were treated in our hospital, 47 (5.4%) of which were SSP secondary to TB. Equally, during this period 2,089 cases of active TB were treated. Of the 47 cases with SSP secondary to TB, 21 presented with active TB at the moment of producing SSP (positive culture for *Mycobacterium tuberculosis*) and 26 with inactive residual TB. This supposes that .95% of active TB cases had this complication. In the other 26 cases, there were clinical data and radiographic evidence to support inactive TB, all with extensive residual lesions considered the cause of the SSP. Of the 47 patients studied, 43 were males (91.5%) and 4 women (8.5%) ($p<0.001$). The average age was 46.6± 15.6 years, ranging between 23 and 92 years.

Personal antecedents are shown in Table 1. Of the total sample, 14 patients (29.8%) had some type of pulmonary antecedent, 11 standing out as meeting the criteria for COPD and

2 having more than one antecedent. As stated, 21 patients (44.7%) had a diagnosis of active TB and were undergoing a complete anti-TB drug therapeutic regimen at the time the SSP occurred.

The clinical manifestations presented by the patients are shown in Table 2: dyspnoea (63.8%) standing out, followed by expectoration (55.3%), cough (48.9%) and pleuritic pain (51.1%). Almost half of the patients with SSP secondary to TB presented no thoracic pain.

Radiological diagnosis was done by simple thoracic x-ray in all patients, and confirmed by CT in the other 15 (32%). In 26 cases, SSP was found on the right side (55.3%), and in 19 cases (40.4%) on the left. In 2 cases it was bilateral (4.3%). Apart from the SSP, all patients had radiological alterations, bilateral in 40 patients (85.1%), limited to the right side in 5 (10.6%), and to the left in 2 (4.2%). Observed radiological alterations accompanying SSP are shown in Table 3. It stands out that 38 of the patients (80.8%) had some form of destroyed lung, and that 33 of them (70.2%) presented infiltrates.

As to PD as treatment for SSP, 40 patients (85%) needed one, 2 (4%) needed two, and in 4 (9%) PD was needed three times. It was decided to wait in only one patient, and the evolution was favorable during his stay. The mean stay for PD was 12.9 ± 11.3 days, ranging between a minimum of 4 and a maximum of 58. There were no complications from this technique.

In 11 patients (23%) SSP recurred. Table 2 shows a univariate analysis that was carried out to study the possible causes associated with the recurrence, without finding any statistical relationship among clinical variables, analyzed radiography and this recurrence. Therefore, not even factors such as suffering active TB, fibrotic TB (radiological infiltrates) or having radiological patterns of destroyed lung are more associated with this recurrence. The treatment for these recurrences was to do another PD in 8 cases (17%), one of them contralateral, and 3 patients needed surgery.

An atypical pulmonary segmentectomy was performed in 13 patients (28%) for persistent air leakage after PD (n=10) and relapses (n=3). Operations were carried out by axillary thoracotomy in 5 cases, lateral thoracotomy in 7 and videothoracoscopy in another. There were 5 postoperative complications (38.4%): persistent air leaks for more than 5 days in 3 cases, pneumonia in one case and surgical wound infection in another. There was no postoperative mortality. The average hospital length of stay was 17.09 ± 17.04 days, ranging between 4 and 73 days. On three occasions Heimlich valves were placed for persistent air leaks (2 postoperatively). Intra-hospital mortality was 4 % (2 patients), in both cases due to severe pneumonia, not SSP.

At the close of the study, 14 patients (30%) had died and 31 (66%) were still alive. Two patients stopped coming to follow-up. Cause of death in 8 cases was respiratory insufficiency, in 3 cases pneumonia, and in 2 cases liver insufficiency. The cause of death could not be determined for 1 patient. Table 3 shows a univariate analysis of the multiple factors analyzed in relation to long-term survival using the log-rank test. Of the different variables analyzed, the only predictors for poor prognosis were the patient's age ($p<0.001$; HR: 1.063; CI95%: 1.026-1.101) - the older the patient, the worse the prognosis -, and HIV infection ($p=0.009$; HR: 6.336; CI95%: 1.301-30.867).

The curve for long term survival for the studied series is reflected in Figure 1. The average survival was 135 months (CI 95%:64.7-205.1), approximately 11 years. The probability of survival at 1, 3, 5, and 10 years was 95.6%, 84.8%, 81.5% and 56.8% respectively.

Discussion

The presence of SP during the evolution of active TB is a well-known situation. However it has not been sufficiently studied up to now, with a 0.6[2] to a 1.4%[4] possibility of occurring, very similar to the .95% found in our study. It would seem, therefore, that we could estimate around 1% of patients with active TB might present this problem[6], a fact that

should be taken into account by all the National Programs for TB Control. It is very likely that many of them go unnoticed, especially in the low income countries, where more of 85% of the TB patients in the world are living.

It is surprising that SSP complication with TB, so accepted for so long, has been the topic of so few publications. There are also very few reports analyzing the place that SSP secondary to TB occupies in the total gamut of SSP occurrences. Moreover, the few works that have analyzed the relationship between TB and SSP are sometimes conflicting. Wilder et al in 1962 published that 78% of SSP studied were due to TB, which supposes that 1.4% of patients with TB suffer this complication. While the data from our study are close to those found by Wilder[6] et al regarding the percentage of patients with TB suffering this type of complication, they are very low when the causes producing SSP are analyzed. Later publications analyzing the etiology of SSP found that TB was decreasing progressively among the causes[9,10], which was linked to earlier diagnosis of TB cases and the the possibility of cure by adequate drug treatment. Nevertheless, in a recently published study by Botianu[11], who retrospectively analyzed all the cases of SSP in his institution between 1985 and 2004, found a marked increase of TB as a cause of SSP along the period of study. Despite these discrepancies regarding whether it is a complication increasing or decreasing frequent, it does seem accepted by most authors that TB is one of the most frequent causes of SSP[2,12,13], being the chronic obstructive pulmonary disease (COPD) the first[14].

In any case, as it has been stated, there are very few series that specifically analyze tuberculous SSP[11,15-17] and up to now the clinical characteristics of this type of spontaneous pneumothorax, as well as treatment, evolution, prognosis and survival, have not been sufficiently studied. In fact, a detailed analysis of the clinical and radiological presentation of these SSP, such as possible factors associated with the recurrence of SSP

and the survival of the patients, has no yet been reported. The present study provides new information that can be very useful for the future and should be tested by other authors.

The definition of SSP to TB is not a clear concept in the published studies adressing this issue. Many authors consider it in cases of active TB. In our study we decided to include patients with TB antecedents, although they did not present activity at the time their SSP appeared. It is our opinion that SSP can occur at any moment of the disease, including at the stage of sequelae because of the associated lung destruction that would be responsible for SSP, as was evident in our patients. Anyway, probably many of the active TB cases have also TB sequelaes, facilitating the possible SSP.

Radiological signs of destroyed lung are very frequent in this group of patients, reflected by the high percentage (53.2%) found in the x-rays. Despite these data, the SSP treatment was not especially conflictive and a resolution of episodes was obtained in most cases. It was only necessary to place more than one PD in 13%, recurrences occurred in 23% and the total of patients that required surgery was 28%. These figures can be considered acceptable and are even lower than in patients with primary spontaneous pneumothorax[18] and for those recognized in general for SSP[19,20]. On the other hand, one cannot conclude that active TB will worsen the evolution of SSP, because there were no significant differences in this issue. The only inference that can differentiate the management of tuberculous SSP with respect to primary is the number of days the PD was left in, prior to indicate surgery for air leakage (12.9±11.3), usually 5-7 days in primary[18]. This is indicative of a more conservative approach in tuberculous SSP. As for surgical interventions, all of them were done with conventional procedures, with segmental resections and complimentary procedures that were, in general, aimed at obtaining a correct pleural abrasion. This suggests that, in our experience tuberculous SSP has a clinical behavior that is not especially aggressive and that can be solved, nearly always, with conventional surgical measures.

There are, however, a small number of cases in our series (4%) with a fatal intrahospital evolution. All of those presented with poor general health and serious respiratory insufficiency that lead to death. As with previous cases, evolution during follow-up years has shown mortality because of respiratory insufficiency, but without demonstrating significant differences in survival. It has been related only to the patients' age and the presence of HIV.

This article analyzes a group of patients affected with SSP and TB in detail, which can allow a better characterization of this type of patient. There are, however, some limitations to this study, which come from its retrospective character and small number of cases, although it has the largest number of cases that have been studied so far.

We conclude that SSP in patients with TB occurs specially in cases that demonstrate destroyed lung. PD is usually a good response, with only a small number of cases that require more than one and surgery, although it requires a high number of days on PD, a longer hospital stay, and mortality in some cases of severe pulmonary affectation. Surgical treatment is standard, in general, and does not require major surgical maneuvers. The survival of this group of patients is dictated more by age and the presence of HIV than by TB.

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Table 1.- Descriptive analysis. Clinical characteristics and radiological findings of the sample studied (n = 47 patients).

	N (%)
Clinical characteristics:	
Active TB	21 (44.7%)
Enolism	19 (40.4%)
Drug addiction	12 (25.5%)
COPD	11 (23.4%)
Social indigence	7 (14.9%)
Pneumonia	5 (10.6%)
HCV	4 (8.5%)
HIV	3 (6.4%)
HBV	1 (2.1%)
Dyspnoea	30 (63.8%)
Expectoration	26 (55.3%)
Cough	23 (48.9%)
Chest pain	24 (51.1%)
Fever	20 (42.6%)
Bronchopleural fistula	10 (21.7%)
Radiological findings:	
Infiltrates	33 (70.2%)
Pleural thickening	26 (55.3%)
Pulmonary destruction	25 (53.2%)
Caverns	21 (44.7%)
Bronchiectasis	17 (36%)
Granulomes	14 (29.8%)
Pulmonary atelectasis	13 (27.7%)
Pleural calcifications	10 (21.3%)
Pleural efusión	6 (12.8%)
Mediastinal adenopathies	5 (10.6%)

Table 2.- Univariate analysis between predictive variables and recidives in TB pneumothorax (Chi-square test).

	N = 47	**Recidive in pneumothorax**		
		Yes (11 cases; 23.4%)	No (36 cases; 76.6%)	
		N (%)	N (%)	p
Sex: Man Woman	 43 4	 10 (90.9%) 1 (9.1%)	 33 (91.7%) 3 (8.3%)	0.670
Age (mean ± SD)	47	42,8 (±14,9)	47,7 (±15,8)	0.717
ADVP	12	2 (18,2%)	10 (27,8%)	0.703
Alcoholism	19	5 (45.5%)	14 (38.9%)	0.737
Smoker	36	7 (63.6%)	29 (80.6%)	0.256
Social indigence	7	3 (27.3%)	4 (11.1%)	0.330
Pneumonia	5	1 (9.1%)	4 (11.1%)	0.668
COPD	11	1 (9.1%)	10 (27.8%)	0.416
HBV	1	0 (0.0%)	1 (2.8%)	0.766
HCV	4	1 (9.1%)	3 (8.3%)	0.670
HIV	3	1 (9.1%)	2 (5.6%)	0.560
Mediastinal adenopathies	5	2 (18.2%)	3 (8.3%)	0.332
Pulmonary atelectasis	13	4 (36.4%)	9 (25.0%)	0.467
Bronchiectasis	17	3 (27.3%)	14 (38.9%)	0.373
Pleural effusion	6	0 (0%)	6 (16.7%)	0.181
Caverns	21	6 (54.5%)	15 (41.7%)	0.505
Active TB	21	5 (45.5%)	16 (44.4%)	0.610
Incomplete TB treatment	26	6 (54.5%)	20 (57.1%)	0.575
Pulmonary destruction	25	6 (54.5%)	19 (52.8%)	0.857
Pulmonary infiltrates	33	9 (81.8%)	24 (66.7%)	0.464
Pleural thickening	26	5 (45.5%)	21 (58.3%)	0.505
Bronchopleural fistula	10	3 (27.3%)	7 (19.4%)	0.430
Granulotes	14	5 (45.5%)	9 (25.0%)	0.177
Pachypleuritis	24	4 (36.4%)	20 (57.1%)	0.229
Calcium plaques	10	4 (36.4%)	6 (16.7%)	0.164
Surgery	13	4 (36.4%)	9 (25.0%)	0.353

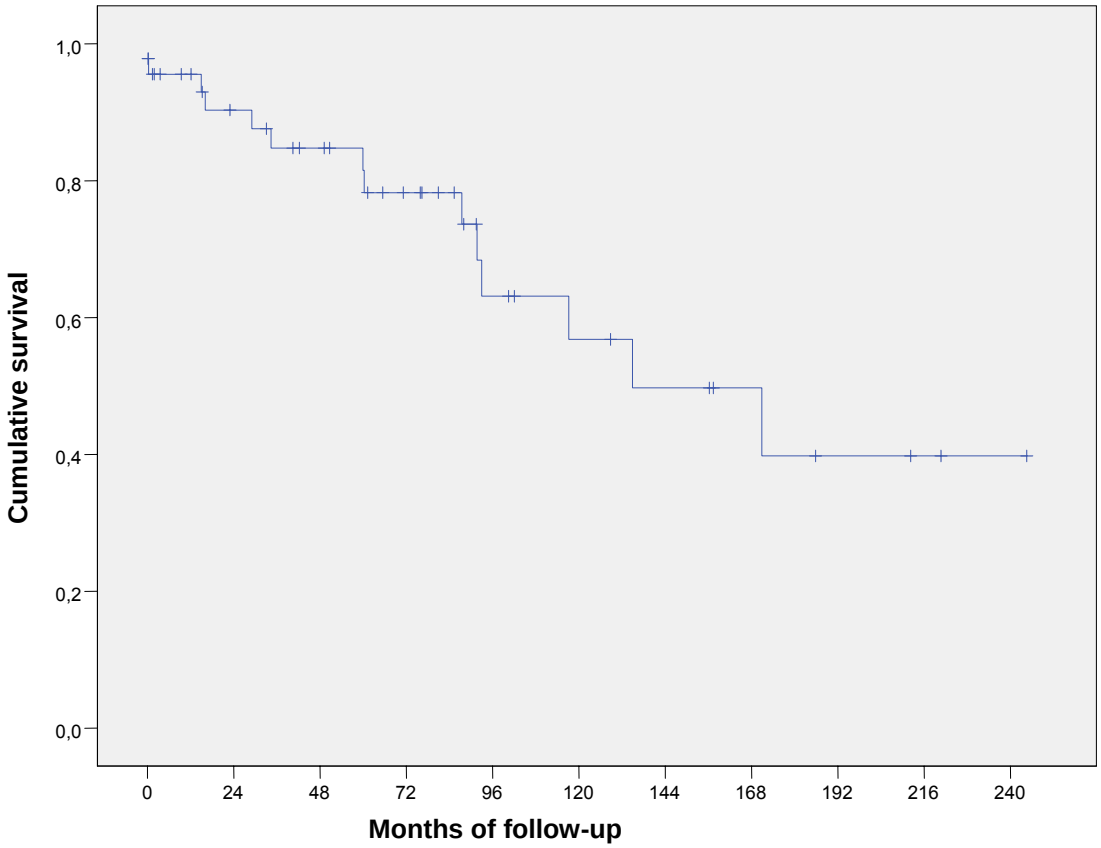
Table 3.- Factors related to long-term survival in TB pneumothorax (Log-rank test, except for variable age). HR: Hazart Ratio. Event: death during the follow-up period. Censored: number of patients who were still alive at the end of the last interval of the follow-up. (*) One patient was lost during the follow-up. (**) Estimated by Cox Regression; (***) Not computable.

	N = 46*	**Number of events (%) N = 14 (30%)**	**Number censored (%) N = 32 (70%)**	**p**	**HR (CI 95%)**
Age ** (mean ± SD)	46	58.5 (±17.1)	41.3 (±41,1)	*0.001*	*1.06 (1.03-1.10)*
Sex					
Men	42	14 (33.3%)	28 (66.7%)	0.102	0.04 (0.00-21.12)
Women	4	0 (0.0%)	4 (100%)		
Drug addiction					
Yes	12	1 (8.3%)	11 (91.7%)	0.088	4.95 (0.65-37.96)
No	34	13 (38%)	21 (61.8%)		
Alcoholism					
Yes	19	8 (42.1%)	11 (57.9%)	0.320	0.586 (0.20-1.70)
No	27	6 (22.2%)	21 (77.8%)		
Smoker					
Yes	36	13 (36.1%)	23 (63.9%)	0.117	0.23 (0.03-1.73)
No	10	1 (10.0%)	9 (90.0%)		
Social indigence					
Yes	7	3 (43.0%)	4 (57.0%)	0.052	0.27 (0.07-1.11)
No	39	11 (28.2%)	28 (71.8%)		
Pneumonia					
Yes	5	2 (30.0%)	3 (60.0%)	0.335	0.48 (0.11-2.19)
No	41	12 (29.3%)	29 (70.7%)		
COPD					
Yes	11	6 (54.5%)	5 (45.5%)	0.064	0.37 (0.12-1.11)
No	35	8 (22.9%)	27 (77.1%)		
HBV					
Yes	1	0 (0.0%)	1 (100%)	0.881	20.76 (N.C.***)
No	45	14 (31.1%)	31 (68.9%)		
HVC					
Yes	4	1 (25.0%)	3 (75.0%)	0.540	0.526 (0.07-4.24)
No	42	13 (31.0%)	29 (69.0%)		
HIV					
Yes	3	2 (66.7%)	1 (33.3%)	*0.009*	*6.34 (1.30-30.87)*
No	43	12 (27.9%)	31 (72.1%)		
Mediastinal adenopathies					
Yes	5	0 (0%)	5 (100.0%)	0.409	23.16 (0.00-2186)
No	41	14 (34.1%)	27 (65,9%)		
Pulmonary atelectasis					
Yes	13	2 (15.4%)	11 (84.6%)	0.453	1.77 (0.39-7.95)
No	33	12 (36.4%)	12 (63.6%)		
Pumonary bronchiectasis					
Yes	17	6 (35.3%)	11 (64.7%)	0.347	0.59 (0.20-1.78)
No	29	8 (27,6%)	21 (72,4%)		
Caverns					
Yes	21	6 (28.6%)	15 (71.4%)	0.957	0.97 (0.33-2.84)
No	25	8 (32.0%)	17 (68.0%)		
Pleural effusion					
Yes	6	2 (33.3%)	4 (66.7%)	0.542	0.62 (0.13-2.91)
No	40	12 (30.0%)	28 (70.0%)		
Pulmonary destruction				0.063	0.34 (0.10-1.12)
Yes	25	9 (36.0%)	16 (64.0%)		
No	21	5 (23.8%)	16 (76.2%)		
Pleural thickening					
Yes	25	8 (32.0%)	17 (68.0%)	0.185	0.46 (0.15-1.48)
No	21	6 (28.6%)	15 (71.4%)		

Bronchopleural fístula Yes No	 10 36	 1 (10.0%) 13 (36.1%)	 9 (90.0%) 23 (63.9%)	0.228	3.26 (0.43-24.98)
Granulomes Yes No	 14 32	 5 (35.7%) 9 (28.1%)	 9 (64.3%) 23 (71.9%)	0.905	0.94 (0.31-2.83)
Pulmonary infiltrates Yes No	 32 14	 10 (31.2%) 4 (28.6%)	 22 (68.8%) 10 (71.4%)	0.936	1.05 (0.33-3.38)
Pachypleuritis Yes No	 24 22	 7 (29.2%) 7 (31.8%)	 17 (70.8%) 15 (68.2%)	0.475	0.67 (0.22-2.05)
Calcium plaques Yes No	 10 36	 3 (30.0%) 11 (30.6%)	 7 (70.0%) 25 (69.4%)	0.806	0.85 (0.23-3.10)
TB active Yes No	 21 25	 5 (23.8%) 9 (36.0%)	 16 (76.2%) 16 (64.0%)	0.951	1.04 (0.34-3.15)
Treatment of TB* Complet Incomplet	 20 25	 4 (20.0%) 9 (36.0%)	 16 (80.0%) 16 (64.0%)	0.772	1.19 (0.36-3.94)
Surgery Yes No	 13 33	 1 (7.7%) 13 (39.4%)	 12 (92.3%) 20 (60.6%)	0.120	4.38 (0.57-35.60
Recidive Yes No	 11 35	 3 (27.3) 11 (31.4%)	 8 (72.7%) 24 (68.6%)	0.782	0.83 (0.23-3.01)

(*) One patient was lost during the follow-up.

Figure 1.- Actuarial Kaplan–Meier survival analysis of patients with pulmonary tuberculosis after pneumothorax (Kaplan-Meier method).



Nº at risk:	46	33	28	21	12	9	7	5	3	2	1