

Pleurodesis for malignant pleural effusions: A survey of physicians in South and Central America*, **

Pleurodese nos derrames pleurais malignos:
Um inquérito entre médicos em países da América do Sul e Central

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Abstract

Objective: Pleurodesis is an effective alternative for the control of malignant pleural effusions. However, there is as yet no consensus regarding the indications for the procedure and the techniques employed therein. The objective of this study was to evaluate how pleurodesis is performed in South and Central America. **Methods:** Professionals who perform pleurodesis completed a questionnaire regarding the indications for the procedure, the techniques used therein, and the outcomes obtained. **Results:** Our sample comprised 147 respondents in Brazil, 49 in other South American countries, and 36 in Central America. More than 50% of the respondents reported performing pleurodesis only if pleural malignancy had been confirmed. However, scores on dyspnea and performance status scales were rarely used as indications for the procedure. Nearly 75% of the respondents in Brazil and in Central America preferred to perform pleurodesis only for recurrent effusions and stated that lung expansion should be 90-100%. Talc slurry, instilled via medium-sized chest tubes, was the agent most often employed. Thoracoscopy was performed in less than 25% of cases. Fever and chest pain were the most common side effects, and empyema occurred in $\leq 14\%$ of cases. The mean survival time after the procedure was most often reported to be 6-12 months. **Conclusions:** There was considerable variation among the countries evaluated in terms of the indications for pleurodesis, techniques used, and outcomes. Talc slurry is the agent most commonly used, and thoracoscopy is the technique of choice in Brazil. Pleurodesis is an effective procedure that has few side effects, as evidenced by the low complication rates and high survival times.

Keywords: Pleural effusion, malignant; Pleura; Pleurodesis.

Resumo

Objetivo: A pleurodese é uma alternativa eficaz no controle dos derrames pleurais malignos, mas existem controvérsias a respeito de sua indicação e técnica. O objetivo deste estudo foi avaliar como é realizada a pleurodese em países da América do Sul e Central. **Métodos:** Profissionais que realizam pleurodese responderam um questionário sobre critérios de indicação para pleurodese, técnicas utilizadas e desfechos. **Resultados:** Nossa amostra envolveu 147 profissionais no Brasil, 49 em outros países da América do Sul e 36 em países da América Central. Mais de 50% dos participantes realizavam pleurodese somente se confirmada a malignidade no derrame pleural. Entretanto, escalas de dispneia e de status de performance eram raramente utilizadas para indicar o procedimento. Aproximadamente 75% dos participantes no Brasil e na América Central preferiam realizar a pleurodese somente no caso de recidiva do derrame, e a expansão pulmonar deveria variar de 90% a 100%. O talco *slurry* foi o agente mais utilizado, instilado via drenos de calibre intermediário. A toracoscopia foi realizada em menos de 25% dos casos. Febre e dor torácica foram os efeitos adversos mais comuns, e empiema ocorreu em $\leq 14\%$ dos casos. A média de sobrevida após o procedimento variou entre 6 e 12 meses. **Conclusões:** Há variações consideráveis quanto aos critérios de indicação para pleurodese, técnicas utilizadas e desfechos entre os países. Talco *slurry* é o agente mais frequentemente utilizado, e a toracoscopia é a primeira escolha no Brasil. Os baixos índices de complicações e o tempo de sobrevida elevado indicam que a pleurodese é efetiva e causa poucos efeitos adversos.

Descritores: Derrame pleural maligno; Pleura; Pleurodese.

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Introduction

Malignant pleural effusion is a common complication of malignant diseases.⁽¹⁾ Lung and breast neoplasms are responsible for 75% of all malignant effusions.⁽²⁾ However, in as many as one out of every ten cases, the primary site goes unidentified.⁽²⁾

Among patients with malignant effusions, the mean survival time is 3-13 months.^(3,4) Although many patients respond to adjuvant treatments, which can control the primary disease, the great majority improve only after palliative therapy designed to avoid recurrence of the effusion.

Pleurodesis is still the most efficient alternative for the palliative treatment of malignant effusion.⁽²⁾ Various authors have attempted to determine which pleurodesis technique is the best. Although many well-established guidelines provide general recommendations,⁽⁵⁻⁹⁾ there are still a wide variety of practices.⁽¹⁰⁾

The objective of the present study was to determine how pleurodesis has been performed in South and Central America. We speculated that significant differences might facilitate future multi-institutional studies and inform decisions regarding the establishment of policies designed to improve practice.

Methods

Professionals working in South and Central American countries were contacted via e-mail and invited to complete a questionnaire related to pleurodesis. The e-mail addresses of the professionals contacted were kindly provided by respiratory medicine and thoracic surgery societies in Brazil and in Latin American countries (the Brazilian Thoracic Association; the Sao Paulo State Society of Pulmonology and Phthysiology; and the Latin American Thoracic Society-Union of Latin American Respiratory Societies).

The questionnaire was sent to 2,500 professionals, 915 of whom responded. The questionnaire was also made available for reference online. Due to a greater number of respondents, Brazil was analyzed separately. Two months after the questionnaires had been circulated, the answers were compiled and analyzed.

The compiled data were divided into three main parts: indications for pleurodesis;

techniques and agents employed; and outcomes (including complications).

The data, presented in absolute values and percentages of respondents (by country or region), were analyzed with SigmaStat 3.5 (Jandel Scientific, San Rafael, CA, USA). The differences among the groups (Brazil, other South American countries, and Central America) were analyzed with Kruskal-Wallis ANOVA on ranks test or Mann-Whitney rank sum test, complemented by Dunn's test for the analyses of subgroups. The level of significance was set at $p < 0.05$.

Results

Of the 915 respondents, 232 stated that they routinely perform the procedure: 147 in Brazil; 49 in other South American countries; and 36 in Central America. In Brazil, pleurodesis is most often performed by surgeons (86% vs. 14% for pulmonologists), whereas, in other countries, this procedure is more often performed by pulmonologists (South America: 64% vs. 26%; and Central America: 69% vs. 29%).

Number of procedures per year

The majority of the respondents reported performing ≤ 25 procedures/year (73% in Brazil; 70% in other South American countries; and 83% in Central America). The proportion of respondents who reported performing > 25 procedures/year was 27% in Brazil, 30% in other South American countries, and 17% in Central America. However, in Central America, 49% of the respondents reported performing ≤ 10 procedures/year, which was significantly different than the 17% who reported performing > 25 procedures/year ($p < 0.05$). If we consider an estimated annual mean of 15 pleurodesis procedures per professional who completed the questionnaire, we can calculate that the number of procedures/year performed by the participants of this study was 3,500 (Table 1).

Confirmation of pleural malignancy

As can be seen in Table 1, the majority of the respondents (61% in Brazil; 73% in other South American countries; and 74% in Central America) stated that pleurodesis is not indicated unless there is confirmation of pleural effusion malignancy ($p < 0.05$ vs. no confirmation).

Use of dyspnea and performance status scales

The majority of the respondents stated that they do not use scores on dyspnea and performance status scales (Karnofsky or Eastern Cooperative Oncology Group scales) as criteria for the indication of pleurodesis. Nearly 70% of the respondents reported performing pleurodesis without taking dyspnea into consideration. Likewise, nearly 65% of the respondents reported performing pleurodesis without taking performance status into account (Table 1).

When to perform pleurodesis

In Brazil and in Central America, respectively, 71% and 77% of the respondents stated a preference for treating the first episode of malignant pleural effusion in a conservative way

(without pleurodesis). In contrast, 60% of the respondents in other South American countries reported that they recommend pleurodesis at the first episode of malignant pleural effusion (Table 1).

Lung expansion

The majority of the respondents reported that they take lung expansion after pleural drainage into consideration before recommending pleurodesis. In Brazil, the preference was for lung expansion of 75-90%, compared with 100% in other South American countries and in Central America. However, approximately 20% of the respondents reported having performed pleurodesis without consideration for the degree of lung expansion after pleural drainage (Table 1).

Table 1 – Questions regarding the number of procedures performed per year and the indications for pleurodesis according to the respondents in Brazil, in other South American countries, and in Central America.

Question	Respondents, n (%)			Total respondents, n
	Brazil	South America (other)	Central America	
Procedures per year				
≤ 10	40 (37)	20 (45)	17 (49)*	188
11-15	39 (36)	11 (25)	12 (34)	
> 25	30 (27)	14 (30)	6 (17)	
Total	109 (100)	44 (100)	35 (100)	
Confirmed malignancy (prerequisite)				
Yes	73 (61)**	32 (73)**	26 (74)**	198
No	46 (39)	12 (27)	9 (26)	
Total	119 (100)	44 (100)	35 (100)	
Employs dyspnea score				
Yes	38 (32)	13 (29)	9 (26)	199
No	82 (68)***	31 (71)***	26 (74)***	
Total	120 (100)	44 (100)	35 (100)	
Employs performance status score				
Yes	44 (37)	16 (38)	12 (33)	196
No	74 (63)****	26 (62)	24 (67)****	
Total	118 (100)	42 (100)	36 (100)	
Timing of pleurodesis				
First episode of pleural effusion	34 (29)	27 (60)*****	8 (23)	199
Recurrence	85 (71)*****	18 (40)	27 (77)*****	
Total	119 (100)	45 (100)	35 (100)	
Lung expansion (prerequisite)				
No	21 (18)	9 (20)	6 (17)	198
≤ 75%	9 (7)	4 (10)	4 (11)	
75-90%	66 (56)*****	20 (45)*****	10 (28)	
100%	22 (19)	11 (25)	16 (44)*****	
Total	118 (100)	44 (100)	36 (100)	

*p < 0.05 vs. > 25 procedures/year; **p < 0.05 vs. malignancy not confirmed; ***p < 0.05 vs. positive response; ****p < 0.05 vs. positive response; *****p < 0.05 vs. first episode; *****p < 0.05 vs. Brazil and Central America; and *****p < 0.05 vs. other groups.

Pleurodesis agents

In general, the pleurodesis agent of choice is talc, especially in Brazil, where it is preferred by 76% of the respondents, compared with 53% of those in other South American countries and 43% of those in Central America (Brazil vs. the other groups, $p < 0.05$). Most of the respondents reported using 2-5 g of talc in each procedure, a significantly greater number than that of those who choose not to use a pre-defined quantity of talc ($p < 0.05$).

In South American countries other than Brazil, as well as in Central America, there was a tendency toward using agents other than talc. The most common agents were tetracycline, silver nitrate, and iodopovidone, followed by methylprednisolone, doxorubicin, sodium hydroxide, cyclophosphamide, bleomycin, mitomycin, and autologous blood. Tetracycline is more commonly used in Brazil and in other South American countries than it is in Central America (58% and 48% vs. 19%; $p < 0.05$). In Central America, the preferred agent is iodopovidone (48%; Figure 1 and Table 2).

Chest tube size

Most of the respondents stated a preference for medium-sized chest tubes (16F to 28F) over those of other sizes ($p < 0.05$). However, small-bore chest tubes (< 14 F) are becoming popular

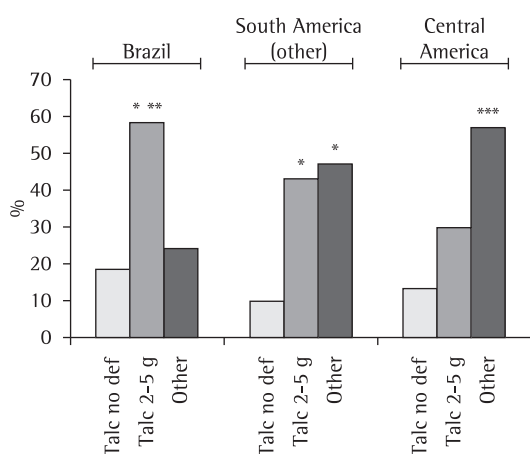


Figure 1 - Pleurodesis agents used according to the respondents in Brazil, in other South American countries, and in Central America. * $p < 0.05$ vs. talc no defined dose (No def). ** $p < 0.05$ vs. other agents. *** $p < 0.05$ vs. talc No def and talc 2-5 g.

in Brazil, although not in other South American countries or Central America (22% vs. 9% and 8%; $p < 0.05$). Large-bore chest tubes (> 28 F) are less often used in Brazil and in Central America than in other South American countries (18% and 16%, respectively, vs. 35%; $p < 0.05$; Table 2).

Thoracoscopy

In Brazil, 31% of the respondents stated that thoracoscopy is the pleurodesis technique of choice, compared with 20% of those in other South American countries ($p < 0.05$) and 3% of those in Central America ($p < 0.001$). Approximately 56% of the respondents in Central America stated that they never use thoracoscopy. In all three groups, thoracoscopy was reported to have been used sparingly. As can be seen in Table 2, 54% of the respondents in Brazil stated that they used thoracoscopy in $< 25\%$ of cases, as did 65% of those in other South American countries and 77% of those in Central America.

Use of intrapleural anesthetics

In Central America, 97% of the respondents reported the routine use of intrapleural anesthetics prior to the instillation of the pleurodesis agent ($p < 0.001$ vs. no intrapleural anesthetic use). The respondents in Central America more often reported using intrapleural anesthetics than did those in Brazil and in other South American countries (97% vs. 51% and 59%, respectively; $p < 0.05$; Table 2).

Chest tube removal

Table 2 shows that 72% of the respondents in Brazil and 58% of those in other South American countries remove chest tubes within 3-10 days after pleurodesis. In Central America, 53% of the respondents reported removing the chest tube within less than 3 days. In the comparison within groups, the difference between later chest tube removal and earlier chest tube removal was significant only for Brazil ($p < 0.05$).

Side effects

The leading pleurodesis-related side effects were fever and chest pain. Fever was reported by approximately 30% of the respondents in the three groups, with no significant difference

Table 2 – Questions regarding pleurodesis agents and techniques according to the respondents in Brazil, in other South American countries, and in Central America.

Question	Respondents, n (%)			Total respondents, n
	Brazil	South America (other)	Central America	
Pleurodesis agent employed				
Talc				
2-5 g	79 (58)*	24 (43)*	11 (30)*	149
No defined dose	24 (18)	6 (10)	5 (13)	
Total	103 (76)**	30 (53)	16 (43)	
Non-talc				
Tetracycline	19 (14)***	13 (23)***	4 (11)	81
Silver nitrate	8 (6)	0 (0)	0 (0)	
Iodopovidone	1 (1)	5 (9)	10 (27)***	
Other	5 (3)	9 (15)	7 (9)	
Total	33 (24)	27 (47)	21 (57)	
Overall total	136 (100)	57 (100)	37 (100)	230
Chest tube size				
< 14F	32 (22)****	4 (9)	3 (8)	229
16-28F	88 (60)*****	25 (56)*****	29 (76)*****	
> 28F	26 (18)	16 (35)*****	6 (16)	
Total	146 (100)	45 (100)	38 (100)	
Thoracoscopy use				
Never	23 (20)	13 (28)	19 (56)*****	194
< 25% of cases	39 (34)	17 (37)	7 (21)	
25-50% of cases	17 (15)	7 (15)	7 (21)	
> 50% of cases	35 (31)	9 (20)	1 (3)	
Total	114 (100)*****	46 (100)	34 (100)	
Intrapleural anesthetic use				
No	56 (49)	17 (41)	1 (3)	184
Yes	54 (51)	25 (59)	31 (97)*****	
Total	110 (100)	42 (100)	32 (100)	
Chest tube removal				
≤ 3 days after pleurodesis	31 (28)	18 (42)	19 (53)	191
3-10 days after pleurodesis	81 (72)*****	25 (58)	17 (47)	
Total	112 (100)	43 (100)	36 (100)	

*p < 0.05 vs. no defined dose; **p < 0.05 vs. South America (other) and Central America; ***p < 0.05 vs. other agents; ****p < 0.05 vs. South America (other) and Central America; *****p < 0.05 vs. chest drain of other sizes; *****p < 0.05 vs. Brazil and Central America; *****p < 0.05 vs. Brazil and South America (other); *****p < 0.05 vs. South America (other) and p < 0.001 vs. Central America; *****p < 0.05 vs. Brazil, p < 0.05 vs. South America (other), and p < 0.001 vs. no intrapleural anesthetic use; and *****p < 0.05 vs. ≤ 3 days.

among the groups. Chest pain was more often reported in Central America (54%) than it was in Brazil and other South American countries (54% vs. 29% and 32%, respectively; p < 0.05). Empyema was reported by no more than 14% of the respondents, with no significant differences among the groups (Figure 2 and Table 3).

Evaluation of pleurodesis

The most common tool for the postoperative evaluation of pleurodesis results is chest X-ray. Less than 20% of the respondents reported using other diagnostic tools, such as ultrasound and CT (Table 3).

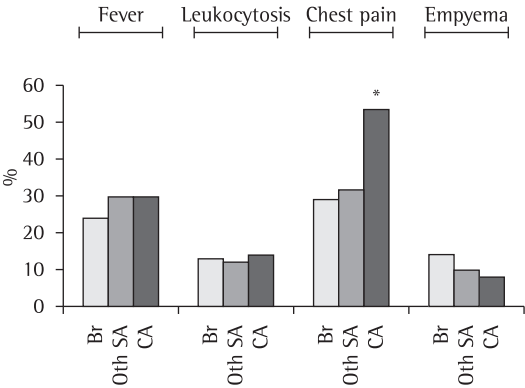


Figure 2 – Pleurodesis-related side effects according to the respondents in Brazil (Br), other South American countries (Oth SA), and Central America (CA).

Pleurodesis outcome

According to the great majority of the respondents, pleurodesis is defined as successful when there is no recurrence of pleural effusion within the first 30 days after the procedure. Only 17% of the respondents in Brazil and 12% of those in Central America used a reduction in the degree of dyspnea as a measure of success, compared with 33% of those in other South American countries ($p < 0.05$; Table 3).

Survival

Of the respondents, 55-66% reported the mean postpleurodesis survival time to be 6-12 months ($p < 0.05$ vs. other mean survival

times). Less than 2% of the respondents reported a mean survival time of < 30 days, whereas 14-19% of the respondents reported a mean survival time of > 12 months (Table 3).

Discussion

Pleurodesis is considered an efficient method for controlling malignant pleural effusion. However, for reasons unknown, 10-20% of patients do not adequately benefit from the procedure.

The appropriate timing of pleurodesis remains controversial, as does the choice of agents and techniques.⁽⁴⁾ Although guidelines have been established,⁽⁵⁻⁹⁾ there have been few

Table 3 – Questions regarding side effects and pleurodesis outcomes according to the respondents in Brazil, in other South American countries, and in Central America.

Question	Respondents, n (%)			Total respondents, n
	Brazil	South America (other)	Central America	
Side effects				
Fever ($> 38^{\circ}\text{C}$)	86 (24)	30 (30)	17 (26)	522
Leukocytosis	46 (13)	12 (12)	7 (10)	
Chest pain	104 (29)	31 (32)	36 (54)*	
Empyema	50 (14)	10 (10)	3 (5)	
Skin incision infection	26 (7)	2 (3)	1 (2)	
Other	46 (13)	13 (13)	2 (3)	
Total	358 (100)	98 (100)	66 (100)	
Imaging employed				
AP chest X-ray	90 (61)**	35 (54)**	19 (42)**	257
AP + D chest X-ray	26 (18)	11 (17)	15 (33)**	
Ultrasound	7 (5)	8 (12)	6 (13)	
CT	24 (16)	11 (17)	5 (12)	
Total	147 (100)	65 (100)	45 (100)	
Indicator of pleurodesis success				
Dyspnea improvement	24 (17)	21 (33)***	5 (12)	245
No effusion after pleurodesis:				
Day 30	69 (49)****	21 (33)	22 (54)****	
Day 60	18 (13)	14 (22)	6 (15)	
Day 90	30 (21)	7 (12)	8 (19)	
Total	141 (100)	63 (100)	41 (100)	
Mean survival time				
< 1 month	1 (1)	1 (2)	0 (0)	181
1-6 months	20 (19)	10 (24)	11 (30)	
> 6 and < 12 months	68 (66)*****	23 (55)*****	20 (56)*****	
> 12 months	14 (14)	8 (19)	5 (14)	
Total	103 (100)	42 (100)	36 (100)	

AP: anteroposterior; and D: decubitus. * $p < 0.05$ vs. Brazil and South America (other); ** $p < 0.05$ vs. other variables within groups; *** $p < 0.05$ vs. Brazil and Central America; **** $p < 0.05$ vs. other variables within groups; and ***** $p < 0.05$ vs. other variables within groups.

large-scale controlled studies comparing the various pleurodesis techniques.

There is no consensus as to whether pleurodesis is indicated only in cases of confirmed malignancy of the effusion.⁽⁸⁾ However, in the present study, most of the respondents reported the pleurodesis is not indicated unless there is such confirmation. Nevertheless, when there is evidence of systemic disease with symptomatic pleural effusion, the use of the procedure is totally justified.

In our study, over 60% of the respondents recommended pleurodesis regardless of the degree of dyspnea or even when the performance status was considered inadequate. This is in contrast with the findings of previous reports, which strongly recommended using these parameters as criteria for pleurodesis candidacy.^(4,5,7,8) If we consider the mean survival time reported in our study, we can speculate that the respondents choose patients with average or good general health status, even if they reported not having taken these parameters into account. However, the lack of precise information regarding the degree of dyspnea and performance status prevented us from investigating this in greater detail.

Regarding the timing of pleurodesis, over 70% of the respondents in Brazil and in Central America preferred to treat the first episode of pleural effusion in a conservative manner, recommending pleurodesis only when the effusion is recurrent. In contrast, 60% of the respondents in other South American countries preferred to perform pleurodesis at the first episode of pleural effusion. This aspect remains controversial. According to various authors, when malignant pleural effusion is minimally symptomatic, of small volume, nonprogressive, and nonrecurrent, only clinical observation is required.^(6,7) Other authors argue that this might be the ideal time at which to perform pleurodesis, because the risk is low for patients with few symptoms, good performance status, and adequate lung expansion, and because there is a high probability of success (definitive control of the effusion).⁽⁸⁾

In controlled studies, lung expansion has been used as a criterion for determining the efficacy of pleurodesis.⁽¹¹⁾ In the present study, most of the respondents stated that pleurodesis should not be performed unless there is proper

lung expansion, preferably > 90%. However, approximately 20% of the respondents performed pleurodesis without consideration for the degree of lung expansion after pleural drainage. Future studies should address the question of whether adequate lung expansion after pleural drainage is relevant to pleurodesis results in cases of malignant effusions. Likewise, it remains unclear whether investigative tools that are more accurate, such as ultrasound and CT, which can show pleural thickening, loculation, and atelectasis, are predictive of better pleurodesis results.

Talc (2-5 g) was the pleurodesis agent most often employed. Professionals in Brazil used talc more often than did those in other South American countries and in Central America, who stated a preference for tetracycline or iodopovidone. This might be due to the lack of proper talc preparations for pleurodesis, as reported by the respondents in those countries. Our data are in agreement with those of previous studies showing that talc is the pleurodesis agent of preference.⁽¹⁰⁻¹³⁾ Other agents, such as bleomycin and doxycycline, are not routinely used in South or Central America. However, approximately 10% of the respondents in Brazil reported using silver nitrate.⁽¹⁴⁾

In our study, the pleurodesis technique most often reported was instillation of a slurry using medium-sized chest tubes, with a trend toward the use of small-bore tubes in Brazil and large-bore tubes in other South American countries. If we consider the need for techniques that produce rapid results and are minimally aggressive (because the patients are already suffering from the primary disease), the use of small-bore chest tubes for pleurodesis seems to represent a meaningful step in the evolution of this procedure.⁽¹³⁾

The majority of the respondents reported using thoracoscopy sparingly (in < 25% of cases). In Brazil, 31% of the respondents reported using thoracoscopy in > 50% of cases, a finding that is likely attributable to the fact that Brazilian surgeons are responsible for the majority of the procedures. There is no consensus in the literature regarding the best pleurodesis technique. However, the results achieved with talc slurry instillation seem to be comparable to those achieved with thoracoscopy.⁽¹¹⁾

The use of intrapleural anesthetics is also controversial. In our study, over 50% of the respondents reported the routine use of anesthetics prior to the instillation of the pleurodesis agent. Nearly 100% of the respondents in Central America reported using intrapleural anesthetics. We can conclude that the use of intrapleural anesthetics depends mostly on the experience of each professional or department. There is a lack of data in the literature regarding the effectiveness of intrapleural anesthetics in alleviating pleurodesis-related pain.

In Brazil and in other South American countries, the mean time to chest tube removal after pleurodesis was most often in the 3 to 10 days range, whereas it was most often less than 3 days in Central America. In Brazil, the later removal of the chest tube might be due to the wider use of thoracoscopy or to the use of silver nitrate, which can provoke more exudation than does talc.⁽¹⁴⁾ We conclude that chest tube removal is also dependent on the personal experience of each professional.

In the present study, the respondents reported the most common pleurodesis-related side effects to be fever and chest pain. Postpleurodesis respiratory failure, which can be fatal,⁽¹⁵⁻²⁰⁾ was not reported by the respondents in our study, and the reported incidence of empyema after pleurodesis ranged from 5% to 14%. However, we could not determine whether the occurrence of empyema was associated with a specific pleurodesis agent or whether it occurred in patients with poor performance status or inadequate lung expansion. Future studies might clarify this aspect.

The majority of the respondents reported that the pleurodesis results were evaluated solely on the basis of the chest X-ray findings. This is in agreement with the findings of previous studies showing that the success of pleurodesis is defined as definitive control of the effusion, as evaluated by chest X-ray, with no recurrence within the first 30 days after the procedure.^(5,6)

The mean survival time after pleurodesis has been reported to range from 3 to 13 months.^(3,4) In the present study, 50% of the respondents reported that the mean survival time after pleurodesis was between 6 and 12 months. Less than 2% of the respondents reported a mean survival time of < 30 days, showing that candidates for the procedure have generally been

well selected. It is of note that approximately 15% of the respondents reported a mean survival time of > 12 months, although it remains unclear whether this is related to any specific primary neoplasia.

In conclusion, the indications for and techniques employed in pleurodesis vary considerably throughout South and Central America. In view of this, future prospective randomized trials, using the variables evaluated in the present study, should be aimed at defining the most efficient pleurodesis techniques.

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