Pleurodesis in follow-up and treatment of malignant pleural mesothelioma patients

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ÖZET

Malign plevral mezotelyomalı hastaların takip ve tedavisinde plörodezis

Bu çalışmada plörodezis uygulamasının endikasyonları, etkinliği ve güvenilirliğini belirleyerek, malign plevral mezotelyomalı hastaların takibinde ne kadar gerekli olduğunu ve yaşam süresine katkısı olup olmadığını tartışmayı amaçladık. Yüz doksan bir hasta retrospektif olarak değerlendirildi ve bunların 69 (%36)'una plörodezis endikasyonu konuldu. Plörodezisi kabul eden 42 hastada plörodezis başarısı değerlendirildi. Plörodezis başarısını etkileyen faktörler ve plörodezisin sağkalıma olan etkisi belirlendi. Plörodezis 42 hastanın 26 (%62)'sında başarılıydı. Plörodezisin başarılı olduğu grupta Kornofsky permons skoru (KPS) ve plevral sıvı pH'sı daha yüksekti (sırasıyla; p= 0.030, p= 0.032). KPS ≥ 80 olan hastalarda duyarlılık %76.9, özgüllük %50.0, pozitif prediktif değer %71.4 ve negatif prediktif değer %57.1 olarak belirlendi. Plevral sıvı pH > 7.27 olan hastalarda duyarlılık %92.9, özgüllük %50.0, pozitif prediktif değer %76.5 ve negatif prediktif değer %80.0 olarak belirlendi. Plörodezisin başarılı olduğu grupta median sağkalım daha uzundu (Log-rank: 11.2; p= 0.0008). Kemoterapiden bağımsız olarak, plörodezisi başarılı olan hastaların diğerlerine göre daha uzun yaşama şansları 2.6 kat daha fazlaydı. İşlem sırasında şiddetli bir komplikasyon gözlenmedi. Malign plevral mezotelyomalı hastalarda plörodezis düşünüldüğünden daha az sıklıkta uygulanmaktadır. KPS ≥ 80, plevral sıvı pH > 7.27 olan ve endikasyon doğan hastalarda plörodezis yapılmalıdır. Uygun hastalarda talk ile başarılı plörodezis malign plevral mezotelyomalı hastaların sağkalımını artırır ve güvenle uygulanabilir.

Anahtar Kelimeler: *Malign plevral mezotelyoma, talk plörodezis, sağkalım.*

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SUMMARY

Pleurodesis in follow-up and treatment of malignant pleural mesothelioma patients

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We analyzed the necessity of pleurodesis in the follow-up of the patients with malignant pleural mesothelioma (MPM), and how much it contributes to the survival period by determining the indications, efficiency, and reliability of the pleurodesis application. 191 patients were assessed retrospectively and 69 (36%) of them were established with a pleurodesis indication. In 42 patients accepting pleurodesis, the pleurodesis success was evaluated. Factors affecting the success of pleurodesis and the effect of pleurodesis on survival were assessed. Pleurodesis was a success in 26 (62%) of the 42 patients. In the group in which the pleurodesis process was a success, it was observed that KPS and pleural fluid pH were higher (p= 0.030, p= 0.032, respectively). In case of KPS ≥ 80, the sensitivity was: 76.9%, specificity: 50.0%, PPV: 71.4%, and NPV was established as 57.1%. In case of pleural fluid pH > 7.27, the sensitivity was: 92.9%, specificity: 50.0%, PPV: 76.5%, and NPV was observed as 80.0%. In the group in which pleurodesis was a success, the median survival was longer (Log-rank: 11.2; p= 0.0008). Independently from chemotherapy, the chance of living longer for patients whose pleurodesis was a success was 2.6 times higher. A severe complication concerning the process was not observed. Pleurodesis is performed less frequently than it is assumed on patients with MPM. In patients with KPS ≥ 80, pleural fluid pH > 7.27, and with indication, pleurodesis must be administered. In feasible patients, a successful pleurodesis with talc increases the survival of patients with MPM, and it can be safely administered.

Key Words: *Malignant pleural mesothelioma, talc pleurodesis, survival.*

Although the aetiology and clinical course of malignant pleural mesothelioma (MPM) is well known, therapeutic success with this disease has as of yet been unsatisfactory. Standard MPM therapy is still deficient, and decisions regarding surgery, radiotherapy or multimodal procedures are made on a case-by-case basis. For a considerable number of patients, a palliative treatment approach remains the only choice. Palliative treatment applications are a necessity in almost all of the patients during the course of disease. The most prevalent symptoms in patients with mesothelioma are pain, dyspnea and weight loss. Dyspnea generally occurs due to the pleural fluid. For malignant pleural fluids, a reasonable approach is to perform pleural symphysis using a chemical agent administered intrapleurally. Palliation of dyspnea is completed by drainage of the pleural effusions via tube thoracostomy or thoracoscopy, and then introduction of a sclerosing agent into the pleural space by injection or insufflation.

There exists a broad range of information on pleurodesis concerning its use for the palliation of patients with malignant pleural effusion (1-7). Pleurodesis is also recommended for the course of MPM treatment as a palliative treatment method (8). But, despite this recommendation and a wide range of acceptance, we do not yet have sufficient information on its necessity for patients with MPM, when it should be administered, its success and complication ratios, and whether it contributes to the prognosis of the patients. In the light of this view, in an MPM series comprised of 254 cases undergoing a follow-up in our clinic, we analyzed the necessity of pleurodesis in the follow-up of the patients with MPM, and how much it contributes to the survival period by determining the indications, efficiency, and reliability of the pleurodesis application.

MATERIALS and METHODS

Patients diagnosed as MPM have been followed up in our clinic since January 1990 by means of a predetermined program including registration of demographic features, clinical and laboratory parameters, radiological findings, diagnostic approaches, histopathology, stage, treatment, and prognosis.

In the present study, from January 1990 to January 2006, 254 consecutive patients with MPM were diagnosed. Since 41 of these patients did not accept any other processes following the diagnosis, and 22 patients are still alive, these patients were not included in the study. As a result, 191 patients were assessed in line with the study objectives (Table 1).

In accordance with the protocol applied in our clinic, the indications of pleurodesis applications for patients with MPM were as follows,

1. In patients with repeating massive or moderate free pleural effusion and at the same time having dyspnea complaints, an improvement of dyspnea after therapeutic thoracentesis;

2. Karnofsky Performance Score (KPS) ≥ 60,

3. Life expectancy > 1 month.

Talc (Laborsan; Eskisehir, Turkey) was used as the sclerosing agent. Pleurodesis was administered in two ways: 1. in patients that had undergone a diagnostic thoracoscopy and decided to be malignant by observation during the process, "thoracoscopic talc poudrage" was utilized; 2. in patients whose mesothelioma was diagnosed by computerized tomography (CT)-guided biopsy or was unable to be ascertained during diagnostic thoracoscopy by observation but mesothelioma was diagnosed after the procedure, a "talc slurry" via chest tube was utilized. Thoracoscopy was done by pulmonologists in accordance with a standard technique, which could be done under local anaesthesia in an endoscopy suite. An average of 4 g of sterile asbestos-free talc powder was administered into the intrapleural space. After removal of the thoracoscope, a chest tube (24 French) was inserted. The chest tube was clamped for 2 h. The patients were followed up every day and the chest tube was removed when the amount of fluid collected in the previous 24 h was < 100 mL. In patients who were not observed to have reexpansion 48 hours after the release of the clamp and with drainage of no less than 100 mL, suction was conducted with -20 cmH_2O. In case of the continuation of the same condition at the end of the 72^{nd} hour following the suction, the process was repeated as a slurry via the tube with the same amount.

A 14 or 24 French catheter was inserted into the patients who were administered talc slurry. Pleurodesis was administered to patients whose pulmonary reexpansion was achieved and whose daily fluid drainage was below 100 mL. Also, the process was conducted in patients who had previously undergone thoracoscopy via the present chest tube. Talc slurry was administered in 100 mL of saline solution through a chest tube at the bedside. The chest tube was clamped for 2 h,

Table 1. The distribution of malignant pleural mesothelioma patients.

Patients	No	%
Patient number	191	
Early death (≤ 1 month)	12	6.3
Surgical or multimodal treatment	33	17.3
Open biopsy via thoracotomy for diagnosis	7	3.7
Karnofsky Performance Score < 60	6	3.1
Less or no pleural fluid	53	27.8
Moderate pleural fluid but no dyspnea	11	5.7
Patients with indication of pleurodesis	69	36.1

MPM: Malignant pleural mesothelioma.

and the patient was placed in the prone, supine, and right and left decubitus positions for periods of 15 min. The chest tube was removed when the amount of fluid collected in the previous 24 h was < 100 mL. In 24 chest tube patients with no reexpansion and a decrease in drainage below 100 mL after 48 hours of the intubation, suction was applied with -20 cmH_2O and talc slurry was administered at the end of the 72^{nd} hour following the suction. In case of a continuance of this condition, the process was repeated with the same dosage. The side effects and procedure-related complications were documented. No patient received systemic corticosteroids or a non-steroid anti-inflammatory drug including pure analgesic medication during the study.

Chest X-rays were obtained immediately following tube removal, once after 3 and 10 days and at their monthly follow-up visits. The success of pleurodesis was assessed at the end of the 3^{rd} month. Successful pleurodesis was described as an absence of fluid reaccumulation with symptom relief. Unsuccessful pleurodesis was described as a recurrent symptomatic effusion that needed to be drained (9).

The average age, gender, histopathologic subtypes, stages, KPS, conditions of undergoing chemotherapy, preprocess pleural fluid amount (moderate, massive), therapeutic thoracentesis necessities, and median survivals of the patients were established. Staging was done according to the International Mesothelioma Interest Group staging system. The size of the pleural effusion in a chest X-ray was classified as moderate when extending from the diaphragm to the pulmonary hilum, and massive when exceeding the hilar region. Of the 69 patients diagnosed with pleurodesis indication, patients who did or did not undergo pleurodesis were compared in terms of the above-mentioned parameters. Later on, a pleurodesis success rate was established. Patients treated with or without successful pleurodesis were compared in terms of age, KPS, histopathologic subtype, stage, condition of undergoing chemotherapy, a full reexpansion of lungs before the process, mean total fluid drainage, mean duration of chest tube drainage, haemoglobin, white blood cell (WBC), serum lactic dehydrogenase (LDH), platelet count, pleural fluid LDH, pleural fluid glucose, pleural fluid pH, median survival times, and side effects. In addition, the predictive accuracy of pleural fluid pH and KPS in predicting failure of pleurodesis was assessed and we attempted to determine the optimal pH and KPS threshold for clinical use. Haemoglobin, WBC, serum LDH, platelet count, fluid LDH, glucose and pH levels were obtained before the process. The survival times were calculated bearing in mind the date of diagnosis. Finally, the effect of chemotherapy and a successful pleurodesis on median survival was assessed.

Statistical Analysis

All analyses were calculated using software program (SPSS, version 13.0; SPSS; Chicago, IL). Univariate analysis was used to compare data. Survival was calculated as median survival using the Kaplan-Meier curve with 95% confidence intervals (CI). Comparisons of survival were done using the log-rank test to evaluate the equality of Kaplan-Meier survival distributions. Cox proportional hazards regression model was used to identify independent predictors of survival. Continuous predictors were examined by Receiver Operating Characteristic (ROC) analysis. A p value of < 0.05 was considered to be statistically significant.

RESULTS

Of the 191 patients in follow-up after being diagnosed, 122 did not have a pleurodesis indication, and the remaining 69 (36%) patients were diagnosed with a pleurodesis indication (Table 1). 38 of the patients with a pleurodesis indication were observed to have massive pleural effusion, and 31 of them moderate pleural effusion. 69 patients with a pleurodesis indication had undergone therapeutic thoracentesis once or twice. Of these, 7 out of 38 patients with massive effusion and 20 out of 31 with moderate effusion did not require pleurodesis because of diminishing and not repeating complaints following therapeutic thoracentesis. Consequently, only 42 (61%) of 69 patients were treated with pleurodesis (Table 2).

The age average of 69 patients with a pleurodesis indication was 61.5 ± 10.3 years (range: 33-

Table 2. The distribution of the patients according to the size of pleural effusion.

Patients	No	%
Patients with indication of pleurodesis	69/191	36
Moderate effusion	31/69	45
Massive effusion	38/69	55
Patient accepted pleurodesis	42/69	61
Moderate effusion	11/31	35
Massive effusion	31/38	82

80), 33 (47.8%) of them were females, 36 (52.2%) of them were males. 50 (72.5%) of the patients had epithelial, 7 (10.1%) of them had mixed, and 3 (4.3%) had sarcomatous type histopathology. 9 (13.0%) patients were unable to undergo a type distinction. 5 (7.2%) of the patients with pleurodesis indications were stage 1, 15 (21.7%) of them were stage 2, 37 (53.6%) were stage 3, and 12 (17.4%) were stage 4.

Pleurodesis was successfully assessed in the 3rd month in 26 (62%) of the 42 patients. Table 3 manifests the distribution of demographic and clini-

Table 3. Characteristics of patients with successful pleurodesis, and the factors affected the success of pleurodesis.

Patients characteristics	Successful pleurodesis (n= 26)	Unsuccessful pleurodesis (n= 16)	p
Mean age, years (range)	63.0 ± 10.1 (36-80)	60.5 ± 11.2 (33-78)	0.70
Mean Karnofsky Performance Score (range)	78.8 ± 9.0 (60-90)	72.5 ± 8.6 (60-80)	**0.030**
Histopathology, n (%)			
Epithelial	19 (73.0)	11 (68.8)	0.801
Mixed	-	-	
Sarcomatous	3 (11.6)	3 (18.7)	
Unidentified	4 (15.4)	2 (12.5)	
Stage, n (%)			
I-II	10 (38.5)	2 (12.5)	0.071
III-IV	16 (61.5)	14 (87.5)	
Chemotherapy, yes/no (%)	21/5 (80.1)	7/9 (43.7)	0.088
Patients number of full reexpansion of the lung at procedure, n (%)	22 (84.6)	3 (18.8)	**< 0.0001**
Mean total fluid drainage, mL (range)	2246.2 ± 1051.9 (600-4000)	3618.7 ± 1889.7 (900-7000)	**0.015**
Mean duration of chest tube drainage, days (range)	5.1 ± 3.7 (2-18)	10.4 ± 6.1 (2-25)	**0.009**
Mean serum haemoglobin level (g/dL)	13.9	13.2	0.298
Mean serum white blood cell count (n/mL)	9211	10.256	0.421
Mean serum LDH level (IU)	345	380	0.504
Mean serum platelet count (n/mL)	335.461	383.125	0.218
Mean pleural fluid LDH level (IU)	1099	1148	0.903
Mean pleural fluid glucose level (mg/dL)	84.7	76.6	0.651
Mean pleural fluid pH (range)	7.35 ± 0.9 (7.25-7.50)	7.27 ± 0.5 (7.06-7.40)	**0.032**

LDH: Lactic dehydrogenase.

cal characteristics of patients undergoing pleurodesis in accordance with the pleurodesis success.

It was observed in the group containing patients with successful pleurodesis that KPS was higher (p= 0.030), the ratio of patients with a full reexpansion before the procedure was higher (p< 0.0001), the mean total drainage amount was smaller (p= 0.015), chest tube drainage duration was shorter (p= 0.009), and the pleural fluid pH level was higher (p= 0.032).

We used decision thresholds for pleural fluid pH and KPS that were determined by ROC analysis. When the KPS threshold was determined as 75, areas under the curve (AUC) were established as 0.692, 95% CI 0.532-0.852. In case of KPS ≥ 80, the established values were: sensitivity, 76.9%; specificity, 50.0%; positive predictive value (PPV), 71.4%; and negative predictive value (NPV), 57.1% (Figure 1). When the pleural fluid pH threshold was determined as 7.27, AUC was observed as 0.808, 95% CI 0.600-1.016. In case of pleural fluid pH > 7.27, the established rates were: sensitivity, 92.9%; specificity, 50.0%; PPV, 76.5%; and NPV, 80.0% (Figure 2).

The median survival of 26 patients of which pleurodesis was a success was 12 months (8.7-15.3), and the median survival of 16 patients of which pleurodesis was not a success was 6 months (5.1-6.9). The median survival of the group in which pleurodesis was a success was found to be significantly longer (Log-rank: 11.2; p= 0.0008) (Figure 3).

When the effect of chemotherapy and the success of pleurodesis on survival periods of 42 patients was assessed by "cox regression analysis", OR: 1.39 (95% CI: 0.64-3.04); p= 0.403 was observed for undergoing chemotherapy,

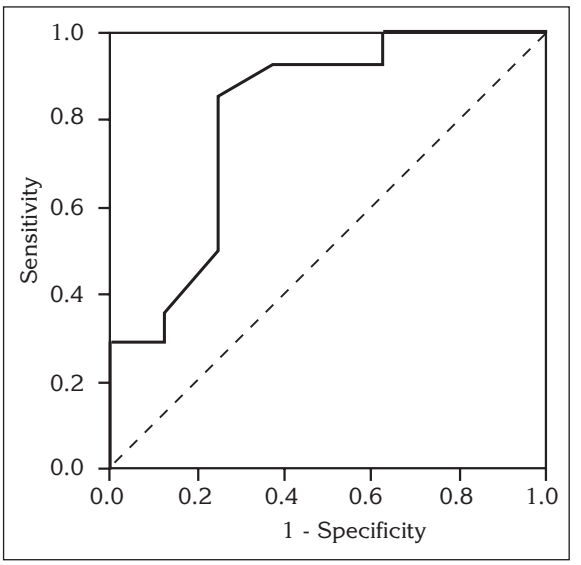

Figure 2. ROC plots describing the predictive accuracy of pleural fluid pH for predicting successful pleurodesis.

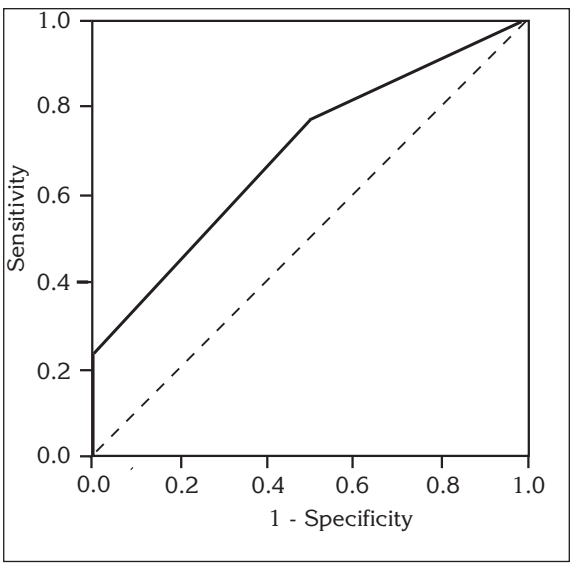

Figure 1. ROC plots describing the predictive accuracy of KPS for predicting successful pleurodesis.

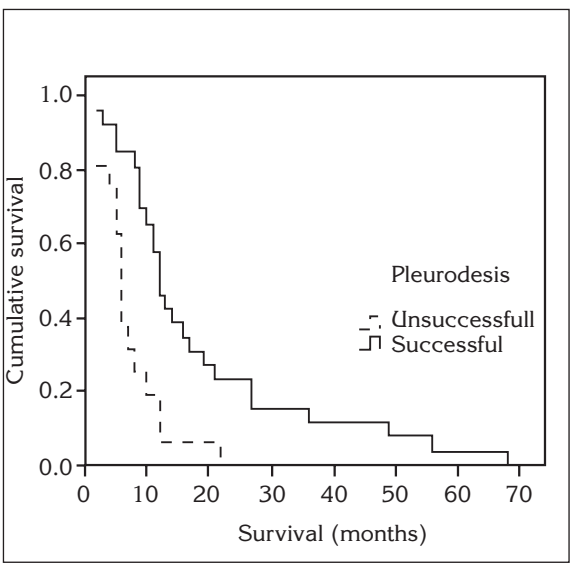

Figure 3. Kaplan-Meier survival curve for successful and unsuccessful pleurodesis.

and OR: 2.596 (95% CI: 1.20-5.61); p= 0.0015 for successful pleurodesis. Therefore, patients with successful pleurodesis had a 2.6 fold chance of a longer survival time compared to others, independent of chemotherapy.

Early complications due to the procedure were observed in 8 (19%) patients, and the local spread of the tumour over the insertion spot where late complications occurred were seen in 8 (19%) patients. A difference was not observed between the two groups of which pleurodesis was or was not a success in terms of early and late side effects (p= 0.348). The distribution of side effects according to pleurodesis success is given in Table 4.

Severe pain was not present in the patients because routine analgesics such as paracetamol were given. Serious complications such as acute respiratory distress syndrome were not presented. There was no procedure related death.

DISCUSSION

The mainstay of treatment for most patients with mesothelioma is best supportive care. Pleurodesis is a recommended approach for the palliation of dyspnea, which is one of the major symptoms observed in patients with mesothelioma (8). Yet, widely-accepted clear cut recommendations do not exist regarding when pleurodesis needs to be administered and for which patients. Some authors report that the rate of pleurodesis success is lower in advanced malignant pleural disease, therefore it is necessary to perform pleurodesis immediately, if possible, at the time of diagnosis (10). On the other hand, most of the clinicians do not carry out the pleurodesis procedure during the diagnosis, contemplating whether effusion could be controlled by antitumoral treatments and considering the recurrence rate. In quite a broad series containing 191 consecutive patients with MPM, we assessed the necessity and success of pleurodesis for patients to which we applied widely-accepted indications. Our results in the primary assessment revealed that during the diagnosis and follow-up only 36% of these patients required pleurodesis. This rate might be received as low at first, but we should bear in mind that mesothelioma has a beginning, pleural spread, and a course of progression different than that of metastatic malignant fluids. In a study comprised of 99 cases of mesothelioma assessed by CT findings during diagnosis, it was observed that 30% of the patients had massive sized fluid and 28% had moderate sized fluid, and that 28% of the patients had lungs surrounded by tumoural masses generated from pleura. Furthermore, in 70% of the patients, pleura had an entire involvement (11). This distribution suggests that, during diagnosis, only 58% of patients have massive and moderate sized effusions, and fundamentally, pleurosis indications are open for discussion in these patients. In some of these patients, relief indicating pleurodesis would not occur following the fluid drainage due to the tumour load causing entire involvement of the pleura and spread. Considering the CT findings of mesothelioma patients in the aforementioned study, the rate of pleurodesis indications presented in this study must be received as reasonable (11). However, the tumour load in metastatic malignant pleural involvements are observed less frequently due to differences in the development

Table 4. Side effects of pleurodesis.

Complications, n (%)	Successful pleurodesis (n= 26)	Unsuccessful pleurodesis (n= 16)	p
Early			
Fever	3 (11.5)	2 (12.5)	Kolmogrof- Smirnov
Empyema	0	2 (12.5)	
Nausea	1 (3.9)	0	p= 0.348
Late			
Local invasion at intervention site	6 (23.1)	2 (12.5)	

and spread of metastatic tumours, and the fact that pleural fluid is seen more significant than mesothelioma (12). Thus, pleurodesis indications might be higher in such a group of patients.

On the other hand, in patients undergoing surgery and responding to chemotherapy following the diagnosis, pleural fluid does not pose an issue. But, the tumour may spread in the pleura, and fill the entire pleural cavity of patients undergoing supportive care, leaving them unable to respond to the treatment or subject to a recurrence (13). Therefore, even though it is the pleural fluid that accompanies this condition, and relief is not observed in patients following the fluid drainage necessitating the pleurodesis, dyspnea continues due to the tumour load. Thus, the need for pleurodesis decreases during the follow-up of the patients.

A commonly accepted opinion does not exist concerning the timing of pleurodesis assessment, and different time periods are determined in different studies (1). Pleurodesis success is assessed at the end of the 1st month in some studies, 3rd in some studies, and 6th in some other studies; and the success rate ranges from 71% to 96% depending on the adopted method and agent (3-5,7,14). In our study, the success rate was observed to be 62% at the end of the 3rd month. This rate might seem lower compared to previous studies. There might be several reasons for such a low rate. In previous studies, the success rate of pleurodesis may be lower than reported in cases where the lungs of the patients did not entirely come into contact with the chest wall, or pleural layers did not come in contact with each other, as such cases were excluded from the study (4,5,14). Additionally, different methods were suggested for the palliation of dyspnea due to pleural fluid in these patients (10). In some other studies, patients with a total fluid amount of more than 3 L were excluded from the study (5). Furthermore, in some other studies, suction was performed by -20 cmH_2O routinely following the procedure (3-5). In our study, when the mid and lower pulmonary areas came in contact with the chest wall, the fact that the lungs were 2 cm closer to the chest wall was deemed sufficient for pleurodesis, and suction was utilized whenever the lungs were not expanded as desired, not routinely in early period of time. As a matter of fact, the lungs were not entirely in contact with the chest wall in 16 (81.2%) out of 19 cases of which pleurodesis was not a success. These results suggest that pleurodesis should be performed on cases in which the lungs are in contact with the chest wall.

KPS, a well-known prognostic factor in patients with MPM and commonly used in patient selection for treatments, also plays an important role in patient selection for pleurodesis in patients with malignant pleural effusion (2-4,7,18). Since life expectancies are low in patients with low KPS, pleurodesis is avoided in consideration of comorbidity and mortality risks. In one study, the effect of pleural fluid pH, glucose, advanced stage of the disease, and KPS obtained during thoracoscopy were assessed on the survival of patients with malignant pleural fluids undergoing pleurodesis, and only KPS was observed to be an effective prognostic factor (16). Thus, this parameter needs to be taken into account before the procedure (16). In our series, pleurodesis was not administered to patients with a KPS level lower than 60. KPS was established to be higher in the group in which pleurodesis was a success. This suggests that KPS needs to be taken as a criterion in deciding whether to treat patients with the pleurodesis procedure. In our study, we observed successful pleurodesis treatments in patients with KPS $\geq$ 80; sensitivity, 76.9%; specificity, 50.0%; PPV, 71.4%; and NPV, 57.1%.

In previous studies, it was reported that some parameters affected the success of pleurodesis, and thus, these factors need to be considered in selecting patients for pleurodesis (17,18). Of these parameters, in the light of the fact that pleural fluid pH would reflect the tumour load in the pleural cavity and in turn affect the pleurodesis success and survival, pleural fluid pH was assessed in patients with malignant pleural fluid. Sanchez-Armengol and Rodriguez-Panadero established that the rate of failure in patients with < 7.20 pleural fluid pH was 43%, and that prognosis was worse in patients with pH level < 7.20 and glucose level < 60 mg/dL (18). In another study that analyzed the data obtained from previous studi-

es, the effect of pleural fluid pH, glucose, LDH and age on pleurodesis success was assessed by a logistic regression model. pH was found to be the only independent determinant of pleurodesis, and it was observed that the rate of pleurodesis failed to increase when the pH value decreased (19). However, in another study, thoracoscopic talc poudrage was effective despite the low pH (20). In patients with epithelial type malignant mesothelioma followed up only by palliative treatment after throacoscopic talc poudrage, the basal pleural fluid pH value was found to be correlated with survival, and the survival period was longer in patients with a value of pH > 7.32 (21). In our study, the pleural fluid pH in patients of which the pleurodesis was a failure was lower compared to patients with a successful pleurodesis. It was observed for the success of pleurodesis that pleural fluid pH > 7.27 had following values: sensitivity, 92.9%; specificity, 50.0%; PPV, 76.5%; and NPV, 80.0%. Preprocedure pleural fluid pH might be assessed as another determinant in establishing the pleurodesis success.

Talc is known to induce apoptosis in malignant cells and to improve survival and quality of life in those who have had successful pleurodesis (5,22,23). A recent study demonstrated that an angiogenic environment is present in the pleural space in malignant pleural effusion. The addition of talc results in an increase in the amount of endostatin released by normal pleural mesothelial cells, with a resultant shift in the balance to angiostasis. Also, this change in the angiogenic balance was reported to cause an improvement in the clinical condition of patients with successful pleurodesis (24). In our series, the median survival of 26 patients (12 months) with successful pleurodesis was found to be significantly longer compared to the median survival of 16 patients (6 months) with unsuccessful pleurodesis. In the cox regression analysis performed to free this condition from the effect of chemotherapy, it was observed that the chance of longer survival patients with successful pleurodesis was 2.6 times higher compared to others, independent of chemotherapy. This might arise from pleurodesis preventing early deaths due to pleural fluids, or from the effect of talc on angiogenesis, as mentioned in previous studies. Consequently, we could say that a successful pleurodesis positively contributes to the survival of patients with malignant mesothelioma all by itself. Thus, pleurodesis must at all times be performed in patients with mesothelioma having a pleurodesis indication.

Talc is the most recommended and used agent for pleurodesis (1-3,5,7,14,20). Talc is so widely used is because it is more effective compared to other agents, and it is easily available and cheap (6,25). But, there are discussions over its safety, and especially over its life-threatening side effects. The quality of talc, including the particle size and dose used for pleurodesis, has shown to vary the effects on the morbidity of patients with malignant pleural effusion. It has been reported that a high dose of smaller-particle talc might cause respiratory failure, whereas large-particle talc can safely be used (2,26-28). In addition, side effects such as pain, fever, empyema, nausea and pulmonary infection following talc pleurodesis are observed with varied rates (1,3,5,7,14,20). Severe co-morbidity or mortality such as acute respiratory distress syndrome was not observed in our study. Both of the 2 patients that developed empyema had unsuccessful pleurodesis. This brought to mind a prolonged drainage period. The fact that severe pain was not reported was thought to be due to routine analgesic administration or the retrospective characteristic of the study. In the long run, 19% of the patients were found to have a local tumour spread at the insertion spot. None of the patients had any local preventive radiotherapy. This rate was not high, and it correlated with another study of us in which the observation that prophylactic radiotherapy should suffice to be applied only to a selected patient group (29).

In conclusion, pleurodesis is performed less frequently than it is assumed on patients with malignant pleural mesothelioma. Pleurodesis should be administered on patients with levels of KPS ≥ 80, pleural fluid pH > 7.27, and with indication. Successful pleurodesis with talc on appropriate patients increased the survival of patients with MPM and can safely be applied.

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