Original Article

Malignant pleural mesothelioma: multidisciplinary experience in a public tertiary hospital*

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Abstract

Objective: To evaluate the experience in diagnosing and treating malignant pleural mesothelioma (MPM) accumulated over 5 years in a tertiary public hospital. **Methods:** The medical charts of the patients diagnosed with MPM between January of 2000 and February of 2005 were evaluated retrospectively. **Results:** Of the 17 patients analyzed, 14 were male and 3 were female. The mean age was 54.1 years (range, 13-75 years). The biopsy specimens for histopathological examination were obtained through thoracoscopy in 9 patients (53%), Cope needle in 5 (29.5%), and open pleural biopsy in 3 (17.5%). The following histological types were identified: epithelial, in 14 patients (82%); sarcomatoid, in 1 (6%); and biphasic, in 2 (12%). The therapeutic approaches used were as follows: multimodal (pleuropneumonectomy and adjuvant radiotherapy and chemotherapy) in 6 patients (35%); chemotherapy and radiotherapy in 6 (35%); radiotherapy alone in 3 (17.5%); and chemotherapy alone in 2 (12%). The mean survival was 11 months (range, 1-26 months). **Conclusions:** In the cases studied, an integrated multidisciplinary approach was used, and a highly complex hospital infrastructure was available for the diagnosis and treatment of MPM, as recommended in the literature. However, the mean survival was only 11 months, reflecting the aggressiveness of the disease.

Keywords: Mesothelioma; Pleura; Surgery; Diagnosis.

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Introduction

Despite being rare, malignant pleural mesothelioma (MPM) is the principal primary cancer of the pleura, progressively gaining in notability and importance due to the increased incidence observed in recent decades. In 1973, in the United States, the estimate was 0.5 cases per 100,000 inhabitants, increasing to 1.7 in 1992.[1] Due to its association with the asbestos, especially that of the amphibolic type, and to the long period of latency (30 to 40 years), this increase reflects the greater exposure occurring during the post-war period.[2] These facts explain why, despite the restrictions that have been imposed on asbestos since the 1970s, MPM is expected to regain ground in the coming decade. In Europe, the projections signal an increase in the number of deaths related to the disease, increasing from 5000 in 1998 to 9000 in 2018.[2]

The importance of MPM is not restricted to its increasing incidence alone, but also to the aggressiveness demonstrated by the short survival (mean: 6 to 8 months), even with appropriate treatment.[3] Systemic chemotherapy produces partial response in only 15 to 20% of patients[4] and, even with the introduction of new therapeutic protocols, the response does not exceed 41%, with a mean survival of 12 months.[2] Radiotherapy, as an isolated procedure, also provides little benefit, since the proximity of structures such as the heart, lung, and bone marrow precludes the administration of adequate doses without causing severe toxic effects. The best results are obtained with multimodal treatment that includes surgery (pleuropneumonectomy), radiotherapy, and chemotherapy, resulting in a mean survival of 18 months.[3]

Until recently, only sporadic cases of MPM had been reported in Brazil.[5-8] However, in view of the disheartening nature of the MPM scenario and the perspective of its worsening, due to the expected increase in incidence, there is a need for a better understanding of this disease. Therefore, our objective was to report the experience with MPM accumulated over 5 years in the Pulmonology and Thoracic Surgery Departments of the University of São Paulo School of Medicine *Hospital das Clínicas.*

Methods

A retrospective study was conducted through the analysis of the medical charts of the patients with MPM treated at our institution between January of 2000 and February of 2005. Each chart was reviewed for the following data: gender; age; professional background, especially regarding a history of contact with asbestos; diagnostic method; histological type; clinical and pathological stage; therapeutic approach used (surgery, chemotherapy, radiotherapy, or multimodal treatment); and survival, which was calculated from the date of diagnosis. The study was approved by the Ethics Committee of the Institution.

The definitive diagnosis was established through histological studies of the pleura, and the staging was based on the clinical and imaging evaluation. All patients were submitted to chest X-ray as an initial test and, subsequently, to computed tomography of the chest for the locoregional staging. An individualized approach was used in order to maintain the continuity of the staging. As an additional test, patients with disseminated disease or presenting poor clinical status underwent computed tomography of the skull only, whereas patients with disease located in one hemithorax underwent computed tomography of the skull and positron emission tomography (PET) scanning (available in our facility since 2002).

All patients were initially considered for multimodal treatment (pleuropneumonectomy followed by chemotherapy and radiotherapy to the hemithorax), and were included or excluded based on the staging and on the results of the clinical tests described below. Patients were selected for multimodal treatment if they presented the following characteristics: disease located in one hemithorax, confirmed through tomography of the chest and PET scanning; under the age of 70 years; a Karnofsky performance status > 70; and echocardiogram/ergospirometry results compatible with the procedure proposed. Patients who did not meet these criteria underwent combined treatment (chemotherapy and radiotherapy) or monotherapy with radiotherapy or chemotherapy if their clinical status were insufficient. The chemotherapy regimen used included cisplatin (75 mg/m^2) and doxorubicin (45 mg/m^2), although cyclophosphamide (750 mg/m^2) was added in some cases. The chemo-

therapy drugs were administered in 4 to 6 cycles (according to response) every 3 to 4 weeks. When administered as adjuvant therapy, 4 cycles were performed.

Pleuropneumonectomy, performed as part of the multimodal treatment, consisted of resection of the lung, together with the parietal pleura, mediastinal pleura, ipsilateral diaphragm, and ipsilateral pericardium. The dissection was performed in the extrapleural plane, maintaining the integrity of the parietal pleura (avoiding the cavity containing the tumor). In all cases, the ligation was performed in the intrapericardial portion of the pulmonary vessels. The mediastinal lymph node stations and the ipsilateral mammary lymph node station were emptied. The reconstruction of the diaphragm and pericardium was performed using bovine pericardium. Balanced drainage was maintained for at least 48 h postoperatively.

Results

During the study period (62 months), 17 patients (mean age, 54.1 years; range, 13-75 years) were registered, 14 of whom were male (Table 1). It is important to emphasize that, in 6 patients (35%), there was no reference to occupational history, in 9 (53%), the data were inconclusive, and only in 2 patients (12%) did the information inserted in the medical charts allow to consider asbestos exposure.

As can be seen in Table 2, the pleural fragments required in order to establish the diagnosis were obtained using a Cope needle in 5 patients (29%), by thoracoscopy in 9 (53%), and by minithoracotomy in 3 (18%). The following histological patterns were identified: epithelial, in 14 patients (82%); biphasic, in 2 (12%); and sarcomatoid, in 1 (6%).

Eight patients (47%) presented localized disease, which made them potential candidates for surgery, and were therefore submitted to PET scans. In one of those cases, the radiotracer was detected in supraclavicular lymph node stations and in the superior mesenteric lymph node station. Therefore, the patient was excluded from surgical treatment. One of the 7 remaining patients underwent diagnostic laparoscopy due to the suspicion of peritoneal involvement on the tomography scan. The suspicion was confirmed, and this patient was also excluded from surgical treatment. In that case, the PET scan showed areas of intense detection only in the left costophrenic recess and therefore did not contribute to the diagnosis of intraperitoneal dissemination. In the remaining 6 patients, the PET scans did not provide data that would contraindicate the surgical procedure.

Table 3 summarizes the therapeutic modalities instituted in the patients studied.

Monotherapy

In 3 patients (18%), radiotherapy was the only treatment administered. In 2 of those 3, the entire hemithorax was irradiated with a dose ranging from 40 to 45 Gy. The third patient, following diagnostic thoracoscopy, developed empyema, for which thoracostomy was indicated, and received 5 Gy only to the thoracostomy site, this being considered the only treatment possible, since the clinical status of the patient did not allow the use of chemotherapy or of radiotherapy throughout the hemithorax.

In 2 cases (12%), chemotherapy was the only treatment indicated, and the cisplatin/doxorubicin regimen was used. There was no significant toxicity resulting from the drugs administered.

Combined treatment

In 6 patients (35%), combined treatment with chemotherapy and radiotherapy was administered. In 2 of those 6 patients, doxorubicin was administered in isolation (the clinical status of the patients

Table 1 - Characteristics of the patients studied.

Gender	
Male, n (%)	14 (82)
Female, n (%)	3 (18)
Age, years[a]	54.1 (13-75)
Histological type	
Epithelial, n (%)	14 (82)
Sarcomatoid, n (%)	1 (6)
Biphasic, n (%)	2 (12)

[a]Mean and range.

Table 2 - Methods used for obtaining tissue for the anatomopathological diagnosis.

Diagnostic method	Patients
Biopsy using a Cope needle, n (%)	5 (29)
Biopsy through video-assisted thoracoscopy, n (%)	9 (53)
Open biopsy (minithoracotomy), n (%)	3 (18)

Table 3 - Treatments performed.

Treatment performed	Patients
Multimodal treatment[a], n (%)	6 (35)
Combined treatment[b], n (%)	6 (35)
Monotherapy	
Radiotherapy, n (%)	3 (18)
Chemotherapy, n (%)	2 (12)

[a]pleuropneumonectomy followed by chemotherapy and radiotherapy; and [b]chemotherapy and radiotherapy only.

did not allow them to receive cisplatin), whereas 2 received the doxorubicin/cisplatin combination, and 2 received the doxorubicin/cisplatin/cyclophosphamide combination. There were no significant toxic effects resulting from these treatments.

In these cases, radiotherapy was performed at the incision sites related to the diagnostic procedure and in symptomatic bone metastases, when present.

Multimodal treatment

All 6 of the patients selected for multimodal treatment (35% of the sample) underwent pleuropneumonectomy. In one case, after right pneumonectomy, the patient evolved to noncardiogenic pulmonary edema and died on postoperative day 8. The remaining 5 patients were discharged with good clinical status, on average, 9 days after the surgical procedure. All patients were referred for chemotherapy and radiotherapy (at the incision site and to the hemithorax). The regimen used consisted of the administration of doxorubicin and cisplatin. One patient presented severe cardiotoxicity, and it was necessary to discontinue the chemotherapy. Another one presented a late postoperative complication (in postoperative month 2), evolved to pleural empyema, and therefore underwent classic thoracostomy.

Survival

The mean overall survival, from the time of diagnosis, was 11 months. Of the 17 patients studied, 6 (35%) were still being monitored (mean follow-up period of 13.8 months) at the time of this writing. Of those who underwent the multimodal therapy (5/17, bearing in mind that, of the 6 selected, 1 died during the postoperative period, and therefore only 5 completed the treatment), 4 survived and were still being monitored (mean follow-up period of 16 months, the longest follow-up period being 26 months) at the time of this writing. One patient died after 24 months of follow-up evaluation.

Discussion

It is currently acknowledged that there has been a significant increase in the number of cases diagnosed as MPM. During the 62 months considered in the present study, 17 cases were diagnosed, 9 (53%) in the final 15 months. It is likely that this recent increase reflects not only the increase in the national incidence, in accordance with the worldwide trend, but also an increase in clinical suspicion and an improvement in the diagnostic methods.

Asbestos exposure, classically present in 70 to 80% of the patients with MPM, is usually prolonged and constant, although there have been cases in which such exposure was of short duration or to small amounts of fibers.[9] In our study, asbestos exposure was reported in only 12% (2/17) of the cases. This fact should be noted since, despite its importance, it is frequently ignored during the medical treatment, reflecting a lack of interest and possibly a lack of knowledge. In general, it is indicative of a lack of awareness on the part of physicians regarding the management of occupational diseases. For example, in approximately 35% (6/17) of the medical charts reviewed, there was no information regarding patient occupation (profession). Unfortunately, this bias is also seen in epidemiological studies conducted in Brazil. The largest case series study, which analyzed the State of Rio de Janeiro Mortality Registry (1979-2000) and was published in 2003, identified MPM (confirmed or suspected) in the charts of 73 patients. Information regarding asbestos exposure was included in only 8 (11%) of those 73 charts.[10]

From an anatomopathological point of view, MPM is divided into 3 subtypes: epithelial, sarcomatoid, and biphasic (or mixed). The epithelial subtype is seen in 50 to 60% of the cases and presents a better clinical prognosis. Making the differential diagnosis between MPM and metastatic adenocarcinoma can be difficult, which justifies the need for larger tissue fragments. The sarcomatoid subtype, which consists of spindle cells and is similar to fibrosarcoma or leiomyosarcoma, accounts for 15% of the cases. As shown in Figure 1, the biphasic

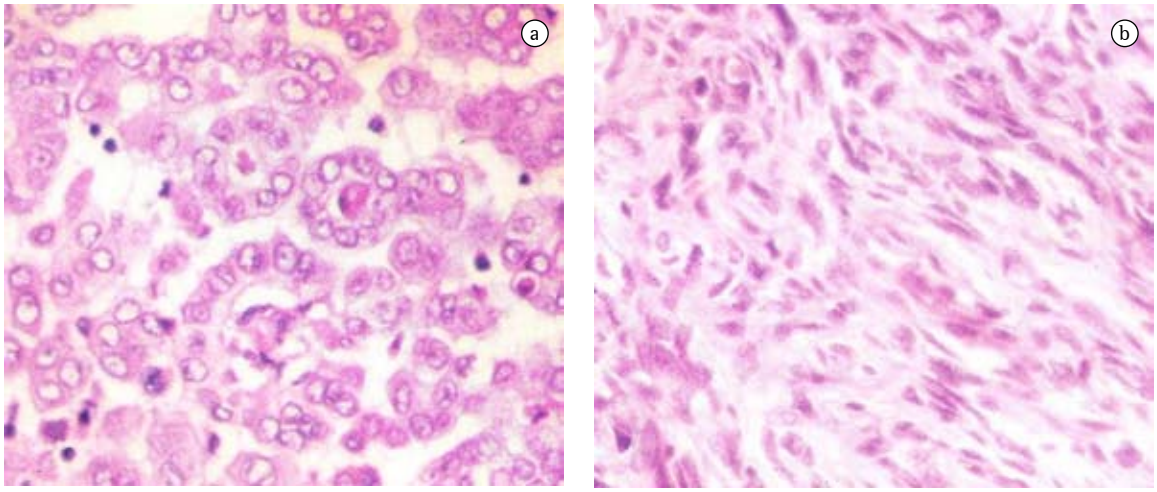

Figure 1 - a) Malignant epithelial mesothelioma (hematoxylin-eosin, ×200, malignant mesothelial cells in detail with discrete anaplasia; and b) Malignant sarcomatoid mesothelioma (hematoxylin-eosin, ×200, note the spindle cells densely grouped in random arrays).

subtype is represented by the co-existence of epithelial and sarcomatoid areas, and multiple sections are needed in order to identify both components.[2] Immunohistochemistry of the fragments complements the histological analysis and is an essential tool for the definitive diagnosis. The most useful markers are calretinin (for the diagnosis of mesothelioma) and carcinoembryonic antigen (for the diagnosis of adenocarcinoma).

Video-assisted thoracoscopy is the best procedure for obtaining fragments, with a yield greater than 90%, since it allows directed biopsies, through which greater amounts of material can be removed.[2] This fact was confirmed in our study. In none of our patients was the diagnosis made through cytology, and in only 29% (5/17, those in which the samples were obtained using a Cope needle) was the histology positive. We can conclude that, in our study, larger and more representative samples of the tumor would have facilitated the diagnosis in 71% (12/17) of the cases.

The choice among the different existing therapies is based on staging and on the analysis of the patient performance status. Consensually, the indication for multimodal treatment is primarily based on the resectability of the tumor, which is evaluated through computed tomography and echocardiogram. Consistent with this premise, the patient clinical status, which includes a Karnofsky performance status > 70 and unaltered renal and liver function, is considered. Exclusion criteria are as follows: arterial carbon dioxide tension > 45 mmHg; arterial oxygen tension < 65 mmHg; ejection fraction (echocardiogram) < 45%; and forced expiratory volume in one second < 1 L.[11,12] As previously mentioned, such criteria were considered in our series in order to select cases for multimodal treatment, combined treatment, or monotherapy.

According to a recently published consensus,[13] the minimal staging for patients who will undergo multimodal treatment is spiral computed tomography of the chest with contrast and PET scanning for appropriate local staging and for ruling out occult metastases. Tomography of the skull or magnetic resonance imaging of the encephalon is suggested only in cases of clinical suspicion of metastases.[13] As for laparoscopy, mediastinoscopy, and contralateral thoracoscopy, there is no consensus, and the procedures are performed according to the routine of a given facility. Of the cases analyzed in the present study, all underwent tomography of the chest for staging. As recommended in the literature, the patients considered for multimodal treatment, underwent PET scanning and, in one of those cases, silent superior mesenteric lymph node metastasis was detected. Laparoscopy was performed in one case in which there was suspicion of peritoneal dissemination. Therefore, appropriate clinical examination

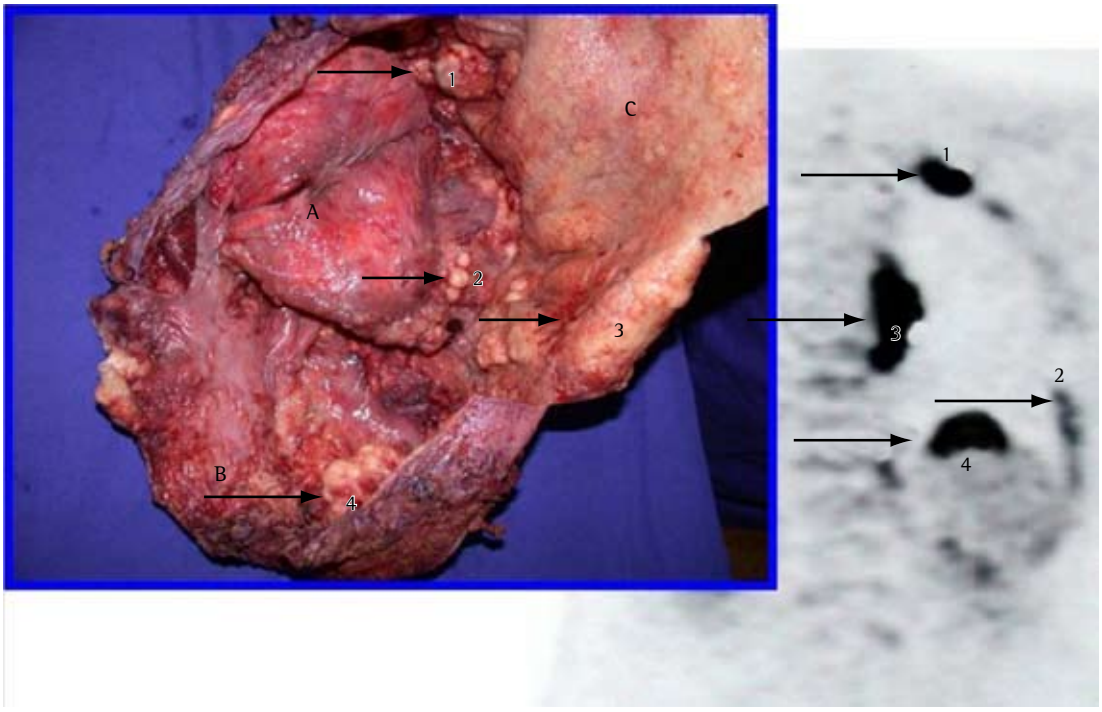

Figure 2 - Correlation between the positron emission tomography (PET) scan and the intraoperative finding. To the left, photograph of the result of the left pleuropneumonectomy (A - left lung; B - diaphragm; and C - parietal pleura) and, to the right, the corresponding PET scan. Note the direct correlation between the areas presenting more intense detection on the PET scan and the areas of greater tumor mass in the sample (Arrows 1 to 4).

and complete staging of the disease are essential for therapeutic decision. An interesting finding in our study was the direct correlation between the areas of more intense detection on the PET scan and the areas that were, intraoperatively, found to be more severely affected (Figure 2).

Although mesothelioma responds to radiotherapy, the large surface to be irradiated, together with the proximity of important elements, such as the heart, bone marrow, and lungs, makes it difficult to administer a sufficient dose of radiation without causing prohibitive toxicity. Therefore, radiotherapy is particularly indicated after puncture, drainage, or surgical incisions, since there is the possibility of dissemination of tumor cells in the chest wall. In such cases, prophylactic irradiation of these points prevents the formation of tumors on the skin. Radiotherapy is also used in other situations: as a means of controlling pain; as a palliative method, especially in bone metastases and in post-pleuropneumonectomy adjuvant treatment; and as part of multimodal treatment.[14] In one of the cases considered in this study, there was tumor formation in the chest wall, at the site where a pleural puncture had been previously performed, and this patient had not received prophylactic irradiation at the site.

Several chemotherapy regimens have been proposed for the treatment of mesothelioma. However, the results are not very encouraging. According to the systematic review made by Berghman in 2001,[14] cisplatin is the drug that shows the best results in isolation, and the regimen with the highest rate of response is the combination of cisplatin and doxorubicin. However, regimens based on cisplatin, anthracycline, or the combination of the two, provide a rate of response of less than 20%, and the mean survival of 6 to 12 months remains unaltered. A large clinical trial comparing the effect of cisplatin used in isolation with that of the pemetrexed/cisplatin combination has been carried out. The combined regimen was more effective in terms of increasing mean survival (12.1 *vs.* 9.3 months), slowing the progression of

the disease (5.7 *vs.* 3.9 months), and increasing the rate of response (41 *vs.* 17%). The patients who received the combined regimen also presented better results in terms of pulmonary function and symptoms such as dyspnea and pain. Despite the toxicity observed, the authors suggest that the pemetrexed/cisplatin regimen be considered as one of the principal therapies for the treatment of unresectable mesothelioma.[2,14] In the present study, the regimen most commonly used was the combination of cisplatin and doxorubicin, although, in some cases, the cisplatin/doxorubicin/cyclophosphamide combination was employed. In patients with poorer clinical status, monotherapy was used.

Surgical treatment with the intent to cure mesothelioma has been developed over the past decades. In the early 1980s, a study involving 170 patients who underwent pleurectomy followed by chemotherapy and external radiotherapy was published, and the authors observed that the main cause of death was local progression of the disease.[15] Subsequent studies conducted by that same group of authors showed that mortality is associated with the volume of residual disease, emphasizing the importance of performing a radical procedure in order to control the disease and increase survival.[16] In the very early stages of the disease, pleurectomy allows complete macroscopic resection of the tumor. However, in the most common forms, in which the disease reaches the visceral pleura and underlying lung, resection is typically incomplete, and, for a more radical procedure, it is necessary to resect the lung together with the pleura. In support of this recommendation, there was a study in which 83 patients with resectable mesothelioma, based on tomography of the chest findings, were submitted to pleuropneumonectomy (resection of the lung together with the pleura, diaphragm, and pericardium), pleurectomy, and decortication, or to surgical treatment not involving resection. Pleuropneumonectomy resulted in the best mean survival (14 months, compared with 10 months for pleurectomy and 7 months for surgical treatment not involving resection).[17]

Due to the high mortality rate, pleuropneumonectomy was regarded with caution for many years. However, with improved surgical techniques and postoperative care, the mortality rate related the procedure is quite reasonable (3.4% in the largest series in the literature, which included 496 cases), and this makes this procedure highly attractive for the treatment of mesothelioma.[18] Although the rate of local recurrence related to pleuropneumonectomy is lower than that related to pleurectomy/decortication, it remains disturbingly high. This has motivated various attempts at combined treatments for local control, such as high-dose external radiotherapy, photodynamic therapy, intrapleural chemotherapy, and gene therapy. Of those, high-dose external radiotherapy following pleuropneumonectomy has provided the most consistent results. In a study involving 54 patients who underwent pleuropneumonectomy and external radiotherapy at 54 Gy, only 2 patients evolved to local recurrence, whereas the remaining patients developed distant metastases.[19] Once local recurrence had been minimized, distant recurrence became a problem. The evolution to metastatic disease justifies the use of chemotherapy as part of the multimodal treatment. There are currently two multimodal treatment trends: neoadjuvant chemotherapy (with cisplatin and gemcitabine or with cisplatin and pemetrexed) followed by pleuropneumonectomy and high-dose adjuvant radiotherapy (45 to 60 Gy); and pleuropneumonectomy followed by chemotherapy (with carboplatin and paclitaxel) and high-dose radiotherapy.[11,12,19,20] In some studies, multimodal treatment resulted in a mean survival of 19 to 23 months (2-year survival rate, 38%; 5-year survival rate, 15%).[11,20] However, in such studies, inclusion criteria are too restrictive, and some authors argue that the evolution of cases thus selected would be favorable regardless of the treatment performed. In our group, we consider the multimodal treatment, despite being controversial, to be the best option currently available, obviously following the selection criteria described above. This therapeutic method was adopted in 5 patients. Although there was one death from disease progression after 24 months, the remaining patients survived to undergo follow-up evaluations at 6, 8, 16, and 26 months.

We can conclude that the treatment of MPM demands an integrated multidisciplinary approach and a highly complex hospital infrastructure that allows the performance of all of the diagnostic and therapeutic steps. In the cases reported, we observed that the multidisciplinary treatment was appropriate, and that the infrastructure currently available allowed the performance of procedures consistent with the trends in the literature. The

recent increase in the number of cases calls for the development of a specific, standardized treatment protocol that will allow treatment outcomes to be compared with those obtained at other mesothelioma treatment centers.

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