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Progress in Radical Surgery for Malignant Pleural Mesothelioma

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Abstract: *Aim*: Stages I and II malignant pleural mesothelioma (MPM) can be satisfactorily treated with extended extrapleural pneumonectomy (EPP). We modified our diagnostic methods and surgical techniques to improve outcome.

Methods: 74 patients were treated with EPP, 33 from 1988 to May 2000 (first group), and 41 from June 2000 to 2010 (second group) and all underwent thoracoscopy without mediastinoscopy or laparoscopy prior to EPP. We began to make changes in surgical management in group 2 (2000-2010). Staging was improved using 3D CT scan and Standard Uptake Values (SUV) provided by 2-[Fluorine-18]fluro-2-deoxy-D-glucose positron emission tomography (FDG PET) scan. Talc pleurodesis was used preoperatively in 15 cases. Double unilateral thoracotomy, performed on 24 patients, facilitated dissection of the diaphragm and made alterations in the reconstructive phase possible. Polytetrafluoroethylene (PTFE) prostheses were used instead of biological materials. In 10 cases the pericardium was not reconstructed on the left side after the previous negative experience of functional pericardial concretio that needed the prosthesis removal (Table **1**). Topical thrombin was used to reduce postoperative complications whereas posterior prosthetic packing was used to prevent paraprosthetic evisceration and reduce postoperative bleeding.

Results: Patients of group 2 experienced less morbidity. Fourteen of the 71 patients who survived beyond the immediate postoperative period lived at least 3 years. Potential positive prognostic factors were identified at follow-up.

Conclusions: The innovations we adopted, especially the reconstruction procedures, improved the outcome for our series of patients who underwent extended EPP for MPM. Follow-up results suggest that the MIB-1 index, stage 1 disease, prosthetic diaphragmatic replacement, adjuvant radiotherapy and control are important positive prognostic factors.

Keywords: Double thoracotomy, extrapleural pneumonectomy, malignant pleural mesothelioma, PET staging, reconstruction procedures, adjuvant tomotherapy.

INTRODUCTION

Over the past 10 years, it has been shown that extrapleural pneumonectomy extended to the pericardium and diaphragm (EPP) can achieve satisfactory results in the treatment of stage I-II malignant pleural epithelial mesothelioma (MPM), especially as part of trimodality therapy [1,2]. Neoadjuvant pemetrexed (Eli Lilly and Company, Indianapolis, IN) plus cisplatin (Cadila Pharmaceuticals Ltd., Ahmedabad, India) chemotherapy followed by EPP and radiotherapy [3], surgery combined with intraoperative hyperthermic chemotherapy [4], photodynamic therapy [5], and immunotherapy [6] have all been found to have limited long term efficacy. Based on these data and the results we achieved from the first part of our case series (1988-2000), using surgery plus adjuvant

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Table 1. Case Series Divided into 2 Groups with the Relative Morbidity and Mortality

Major Surgical Morbidity	01/1988-05/2000 33 cases (27,2%)	05/2000-07/2010 41 cases (14,6%)
Consumation coagulopathy	3	2
Hemorrhage	1 (+)	
Paraprosthetic evisceration	2	
Concretio pericardii	1	1
Thoracotomy dehiscence	1	
ARDS		1 (+)
IMA		1 (+)
Pleural empyema	1	1
Perioperative Mortality	3%	4,9%

+Cause of death.

radiotherapy [7] and by other [8] studies, we gradually modified our clinical approach. We have made technical innovations to correct any possible errors (such as the use of posterior packing to prevent paraprosthetic evisceration and avoiding the placement of pericardial prosthesis on the left side) and to move beyond previous limitations while continuing to use EPP plus adjuvant radiotherapy and chemotherapy whenever possible.

PATIENTS AND METHODS

Clinical data from 1988-2010 are presented on the radical treatment with EPP of 74 patients (63 men and 11 women; aged 29-74 years), suffering from preoperative stage I and stage II MPM. There were 67 cases of epithelial MPM and 7 cases of biphasic MPM.

Histology was always carried out using a thoracoscopic biopsy from a port, except for two patients in the first group (1988-2000) and two in the second group (2001-2010), in whom a diagnostic sample could be obtained only after extrapleural dissection during thoracotomy. Nonetheless, ten biopsies on various pleural specimens through one access point, to avoid parietal diffusion of tumor cells, were performed in these four patients who were not diagnosed preoperatively. All four of these patients were stage I. Staging was performed up until 2005 through pleuroscopy, CT and MRI in order to evaluate costal, pericardium and diaphragmatic limits without having to carry out mediastinoscopy and laparoscopy to establish stage III in the absence of suspicious or confirmatory radiological elements. Starting in 2007, FDG PET scan, together with three-dimensional (3D) CT, were used to establish stage II. In two patient's thoracoscopic biopsy was performed after pulmonary collapse using a Carlens tube under general anesthesia due to lack of pleural fluid.

Group 1 consisted of 33 patients who underwent radical *en bloc* EPP *via* extrapleural separation of the cupola, with pericardial exeresis, intrapericardial vascular suturing, manual suturing of the bronchi at their origin, and, in most cases, subtotal exeresis of the right hemidiaphragm followed by autologous reconstruction.

Group 2 consisted of 41 patients and is characterized by innovations we made in diagnostic procedures and surgical techniques.

The criteria of cardiorespiratory function in patients undergoing surgery were based on a predicted ideal forced expiratory volume (FEV1) > 1.3 L and an ejection fraction >45% on cardiac ultrasound. Increasing importance was given to the diffusion level of carbon dioxide (DLCO) in patients with bronchial obstruction and to echocardiography results in patients with coronary artery disease. Imaging used for staging was improved in the last 19 cases, through use of 3D CT scan of the pericardium, border of the aorta, diaphragm, and chest wall (Fig. **1**). This technique was also used in restaging.

In the last 16 cases another contribution to clinical imaging, was made with FDG PET scan which defined tumor aggressivity by means of standard uptake value (SUV), calculated according to standard methods based on the uptake of FDG in grams per millimeter corrected for the injected FDG dose and adjusted for the patient's weight, in

relation to hyperfixation in areas of pathological metabolic activity and grading. SUV was also used to evaluate mediastinal, cervical, and retroperitoneal lymph nodes, and the retroperitoneum and diaphragm (Fig. **2**).

Fig. (1). 3D-CT scan of the chest showing the borders of the mediastinum, diaphragm, pleura, pericardium, aorta and chest wall.
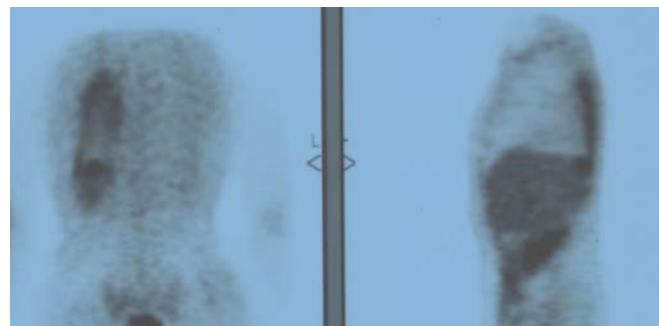
Fig. (2). FDG PET scan of a patient with stage I epithelial MPM showing the involvement of the mediastinal posterior and right parietal pleura.

The preoperative, resective and reconstructive phases of treatment changed significantly. In the last 16 cases preoperative talc pleurodesis was performed. Two to three weeks before surgery, talc was administered through a chest tube or during pleuroscopy, to patients examined in other institutions. Twenty-four of the 41 patients in group 2, underwent a double unilateral thoracotomy, the last 16 consecutively : first a classic thoracotomy by posterolateral incision along the 6th rib, and then a thoracotomy by posterior incision along the 11th rib. This technique greatly facilitated the dissection of the diaphragmatic insertions without causing functional or organic damage. The last ten left EPP procedures were performed without reconstruction of the pericardium, leaving the heart free in the chest cavity, since double unilateral thoracotomy permitted more caudal anchoring of the diaphragmatic prosthesis, resulting in better positioning of the heart. In right EPP procedures a 0.1 mm thick PFTE pericardial prosthesis was always applied, anchored to the posterior, paraesophageal, and anterior retrosternal remnants of the pericardium, leaving the cranial and caudal parts of the pericardial sac free. The homolateral diaphragm was removed in all 41 patients and replaced by a 2mm thick 20x30 cm PFTE prosthesis, the most recent version of which has a corrugated antibacterial surface (W. L. Gore, Flagstaff, AZ). All diaphragmatic prostheses benefit

from a more solid anchorage with interrupted sutures in a U shape at the level of the 10th rib and the base of the pericardium.

RESULTS

Three (4.3%) of the 74 patients (63 men and 11 women) who underwent EPP died in the early postoperative phase. One died of hemorrhagic shock caused by dehiscence of the sutures on the left subclavian artery at its origin on postoperative day 1, the second of massive myocardial infarction on day 2, and the third of left-sided acute respiratory distress syndrome (ARDS), possibly due to pulmonary microemboli identified by angio CT scan and echocardiography, 40 days after surgery. The average mortality rate (excluding the above 3 cases) was 4.2%; 1 patient out of 33 (3%) in the first part of the series and 2 out of 41 (4.9%) in the second part. Surgical morbidity was greater in the first 33 patients (27.2%) than in the other 41 (14.6%). This overall improvement permitted us to administer adjuvant therapy according to Sugarbaker's criteria [8] in a higher number of operated patients.

Major surgical complications included posterior paraprosthetic evisceration into the left hemithorax in 2 cases (in the first group), hemothorax from consumption coagulopathy in 5 cases (3 in the first group, 2 in the second group), pleural empyema in 2 cases (1 in each group), and thoracotomy dehiscence in 1 case (first group).

A frequent complication is bleeding, which has been reduced by the use of topical thrombin, (FloSeal; Baxter Inc, Deerfield, IL), a novel matrix hemostatic sealant composed of collagen-derived particles and topical bovine-derived thrombin applied to all bleeding areas of the chest wall. Thrombin cannot be used in patients who are allergic to materials of bovine origin and is ineffective in patients who suffer from coagulation defects. Bleeding was dramatically reduced in the second group of patients: average blood loss during the first 24 hours after surgery was 900-1400 ml in group 1 patients, but only 300-500 ml in group 2, and the number of patients with consumption coagulopathy declined from 3 out of 33 to 2 out of 41 patients. Atrial fibrillation, considered a minor morbidity, was the most frequent complication (33%) but also the easiest to resolve. All cases except 1 which required electrical cardioversion, were successfully managed with pharmacological cardioversion. Another, less frequently encountered complication which occurs more often in the left hemithorax is intrathoracic herniation of abdominal contents. In the first part of our series this complication occurred twice, and in both cases required another thoracotomy to replace the viscera in the abdominal cavity. Since then we have used a simple procedure to prevent intrathoracic herniation: a second prosthesis is positioned and packed into the reconstruction defect between the vertebral bodies and the posterior costal arch (Figs. **3**, **4**).

The oncological follow-up of the 71 survivors, divided into two subgroups with 6 patients with biphasic MPM and 65 patients with epithelial MPM, indicated that 14 out of 71 patients survived at least 3 years. The details regarding survivors are below.

-2 patients are alive at >10 years: one had postoperative pleural empyema and is currently undergoing

radiochemotherapy for retroperitoneal recurrence, the other was operated on for mesothelioma *in situ* and remained disease-free.
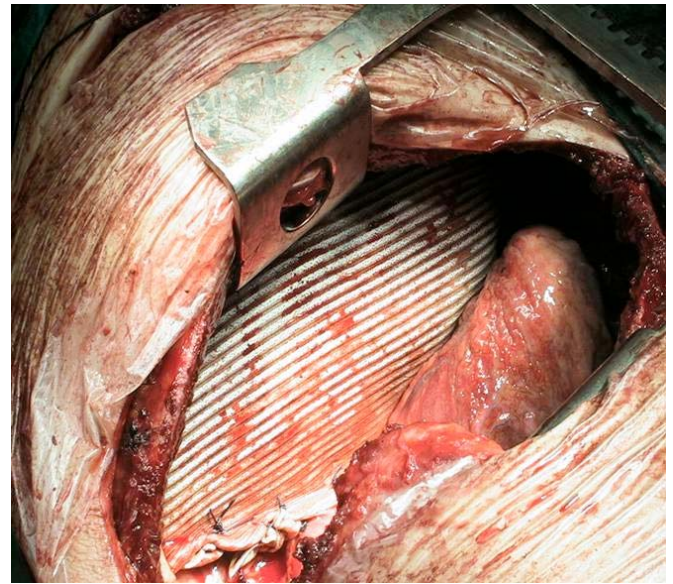
Fig. (3). Left pleuro-pneumo-phreno-pericardiectomy without pericardioplasty and with posterolateral prosthetic packing to prevent intrathoracic herniation of abdominal contents.

Fig. (4). CT scan of the same patient showing posterolateral prosthetic packing.

-2 patients are alive at >3 years. One is undergoing chemotherapy for resected retroperitoneal recurrence (identified as sarcomatoid MPM), after EPP and radiotherapy for epithelial MPM.

-2 patients died of peritoneal recurrence at 7 and 8 years respectively.

-8 patients survived 3 years.

In 36 cases (50.7%) it was possible to administer complete standard adjuvant radiotherapy to the hemithorax and retroperitoneum with an average dose of 50Gy and since 2007 we have used helical tomotherapy. Fifteen (21%) of the 71 survivors tolerated three additional cycles of

chemotherapy to complete trimodal therapy (11 of the 39 in the second group).

The MIB-1 tumor indices were used to help determine prognosis. Patients whose tumors showed an interaction between monoclonal antibodies and the nuclear protein Ki 67 were started on more intensive adjuvant therapy.

The impact of adjuvant radiotherapy on overall survival was investigated and statistically significant survival benefits ($p=0.03$) were observed within the first 40 months (30% versus 15%) (Fig. **5**). The patients with the most favorable prognosis were those who received the fewest transfusions (20% survival at 5-7 years and 10% at 10 years in those with only two transfusions and death at 20 months in those given three to five transfusions; Fig. **6**), those with MIB-1 positive cancer cells (20% versus 10% at 30 months with $p=0.03$), those who were diagnosed with stage I epithelial MPM (Fig. **7**), and those who received diaphragmatic prostheses (Fig. **8**). Differences in patients' sex, age, preoperative talc poudrage, postoperative chemotherapy and SUV in the two groups were not statistically significant.
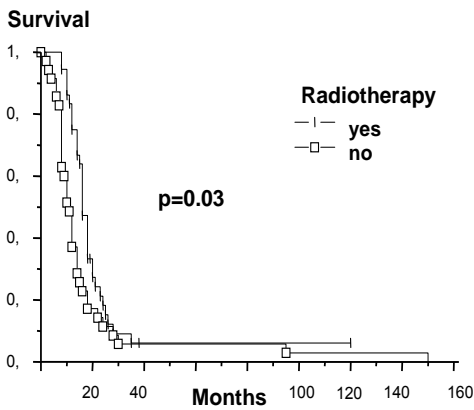

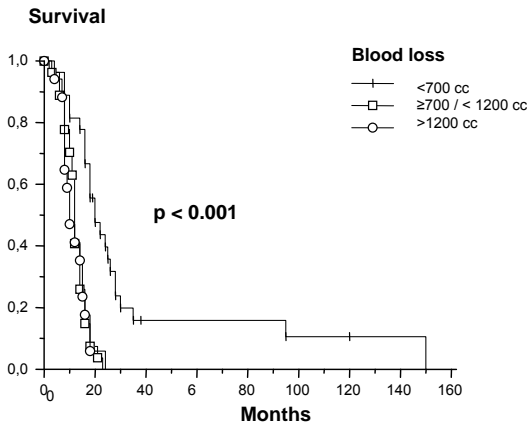**Fig. (5).** Follow-up of the 71 survived patients according to postoperative radiotherapy status.

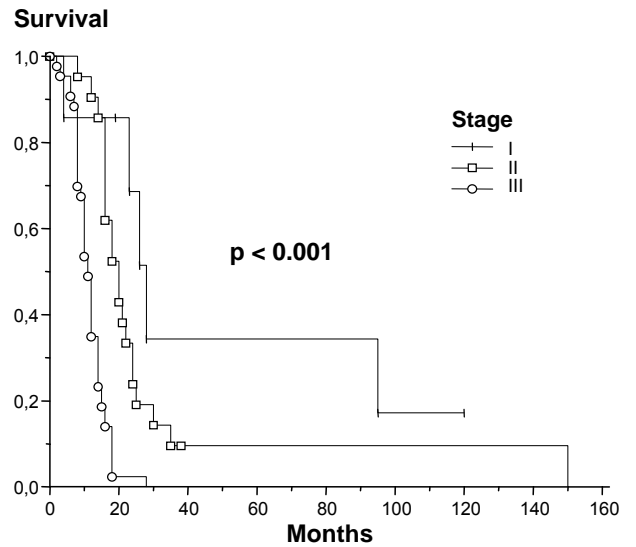**Fig. (6).** Follow-up of the 71 survived patients according to blood loss.

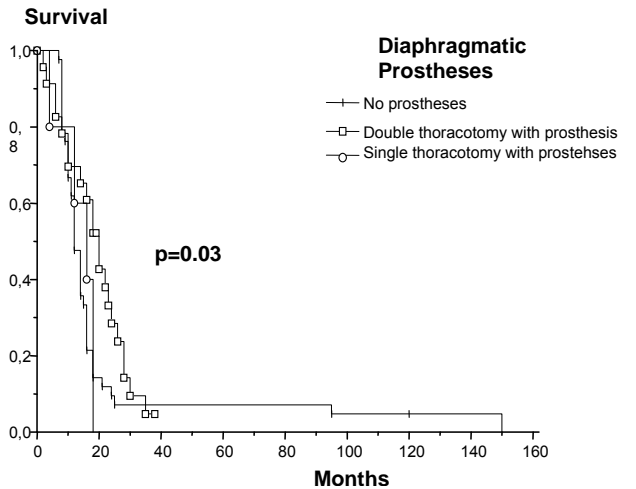**Fig. (7).** Follow-up according to TNM stage in 66 survived epithelial mesothelioma.

Fig. (8). Follow-up of the 71 survived patients according to diaphragmatic prostheses status.

DISCUSSION

EPP appears to be the most effective form of therapy in the treatment of stage I and II malignant pleural epithelial mesothelioma [1]. Both intraoperative radiotherapy with 4-15Gy (9), and palliative surgery (simple pleurectomy) alone [7] or associated with intrathoracic hyperthermic chemotherapy [2], photodynamic therapy [4], or immunotherapy [5], do not favor long term survival and in some cases have led to serious morbidity [2].

Since the patients in our series did not easily tolerate trimodal therapy and only 15 out of 71 patients (21%), who were all in stage II, considered advanced disease, completed it. Another study (a multicenter phase II trial) of the same neoadjuvant chemotherapy (pemetrexed plus cisplatin) followed by EPP showed that initial clinical stage at the time of surgery was improved in 15.8%, unchanged for 42.1% and worsened in 28.1% [3].

EPP is a high risk procedure [2]. Increased risk is associated with cardiorespiratory function, length of operative time, extent of blood loss, and use of preoperative chemotherapy or intraoperative procedures such as thermotherapy. Undoubtedly the most important risk evaluation parameters are echocardiography, stress echocardiography, the predicted FEV1, the PCO2, PO2 and renal function values. In our experience lung perfusion values in the affected lung were especially important, with values <20% indicating high risk. We believe that a predicted FEV1 >1.3L can be associated with a favorable postoperative course and tolerance of trimodal therapy [8].

In our series oncological indications for EPP were primarily based on staging both by thoracoscopy and CT scan, (3D CT scan in our last 15 patients to define more precisely the borders of the diaphragm, pericardium, ribs and aorta). Preoperative cytology of pleural liquid was positive in only 15% of cases and the indications for EPP were primarily based on clinical and diagnostic elements, especially on thoracoscopic evaluation and histopathology. In 4 patients, 2 from each group, the indications were provided by thoracotomy since 10 preoperative pleural biopsies were negative although there was strong radiological suspicion of MPM. After preoperative functional evaluation and adequate staging of these 4 patients, we proceeded to perform an EPP when the intraoperative histopathology report identified epitheliomorphic MPM, and we resected four stage I tumors. The last 16 EPP procedures were preceded by talc pleurodesis, a technical decision based on the intraoperative observation that dissection was usually easier on the chest wall and diaphragm in patients who had undergone palliative talc pleurodesis in another institution, before transfer to our department. As a result the pleural cavities of our 16 patients were free of residual liquid and the chance of contamination of the pleural cavity was reduced to a minimum [9]. After 1 year the patients' condition has remained unchanged. SUV played an important role in patients of group 2. A low SUV (<4), indicating low metabolism, sometimes induced us to take into consideration borderline cases or even patients suffering from biphasic MPM [10]. Patients with this type of MPM, besides not being indicated for elective surgery, usually have an SUV >10 [7].

In the literature, the PET scan is not recognized as having an important role in extrathoracic staging, rather than locoregional staging [11, 12]. However, the PET scans induced us to perform a thoracoscopy which enabled us to diagnose MPM in 2 of our patients who were otherwise indeterminate and without pleural effusion according to chest CT scan.

We also modified our surgical technique, using double unilateral thoracotomy instead of a classic thoracotomy by posterolateral incision along the 6th rib. We performed 24 double thoracotomies in the second part of our series, with a second, smaller incision along the 11th rib, which we initially used only for the exeresis of large talc granulations and for pachypleuritic forms of mesothelioma [7]. This permitted optimal dissection of the costal insertions of the hemidiaphragm, control of the abdominal and retroperitoneal viscera, and most importantly, easy anchoring of the diaphragmatic prosthesis at the level of the 10th rib, with interrupted sutures in a U shape.

A second thoracotomy along the 8th rib, as suggested by other authors [7], seemed too cranial and likely to cause difficulties in anchoring the prosthesis caudally on the chest wall, keeping the cardiac axis raised and inclined with respect to the root of the aorta.

In the median sternotomy approach sometimes used in EPP, the exeresis of the posterior diaphragmatic insertions and anchoring of the prosthesis are technically complex. It does not seem attributable purely to chance that, as reported in the literature, some patients undergo as many as 7 additional thoracotomies after this procedure [13,14].

Evolving surgical experience induced us to omit pericardial prostheses in the last 10 left EPP procedures, as suggested by some authors [8], because in 2 cases this type of prosthesis caused adhesive pericarditis and a severe pumping defect of the right heart which obliged us to perform another thoracotomy. Leaving the heart free in the chest cavity and lowering the diaphragmatic prosthesis by anchoring it to the 10th rib did not cause hemodynamic problems except for a higher incidence of atrial fibrillation, (40% in the first group versus 33% of the second group), and in 2 cases the appearance of a right pleural effusion of about 700ml which had to be drained after CT scan showed infiltration of the anterior mediastinum.

An additional technical improvement in EPP is the application of thrombin to the decorticated chest wall and the bleeding areas of the mediastinum. Topical application of thrombin has been shown to be especially effective in patients without coagulation defects and without significant intraoperative blood loss [15]. Postoperative blood loss, which was controlled in the usual way with both thoracic and subdiaphragmatic drains, was significantly reduced in our patients, (from 900-1400ml to 300-500ml in the first 24 hours), and as a result perioperative morbidity also declined (from 27.2% to 14.6%). The use of thrombin did not prevent 2 cases of hemothorax due to consumption coagulopathy in patients who had been given multiple transfusions and had a past medical history of non-steroidal anti-inflammatory drug (NSAID) abuse. We do not yet have sufficiently definitive data to determine whether limiting transfusions affects follow-up positively, but follow-up data on 5 of our patients who were reoperated for consumptive coagulopathy and who survived <6 months, points in this direction.

Our series will permit us to evaluate patients at follow-up to determine the prognostic efficacy of various survival factors such as those having had a low number of transfusions. Follow-up at 24 months shows that 51.8% of our patients were free of disease after trimodal therapy, including a positive MIB-1 index [16], those with helical tomotherapy [17, 18], stage I tumor, presence of epitheliomorphic cells, the use of prostheses, and double unilateral thoracotomy.

CONCLUSIONS

In recent years the role of radical surgery in the treatment of MPM has become progressively more important because of improved indications, fewer complications, and better long term results. 3D-CT scan of the pericardium, diaphragm

and chest wall and FDG PET scan of the chest and abdomen, provide significant improvement in clinical imaging. Preoperative talc pleurodesis facilitates extrapleural dissection although this did not improve follow-up in our experience. The use of diaphragmatic prostheses permits more radical surgery. Double unilateral thoracotomy has made it possible to control the costophrenic space and correctly anchor the diaphragmatic prosthesis which remains well attached caudally without compressing the heart on the left. Topical application of thrombin results in less postoperative bleeding.

The innovations described above, especially the new reconstruction procedures, have reduced patient morbidity. Adjuvant radiotherapy and especially helical tomotherapy [18] have improved the follow-up for patients with epithelial MPM, (although unfortunately only 11 out of 39 patients (28%) in group 2 were able to tolerate trimodality therapy) [1]. To further improve the understanding of long-term results after radical surgery for MPM, we believe that based on our experiences to date and the currently available data, that it is not premature to add the following new clinical factor the MIB-1 index, to the well-known prognostic factors for MPM (stage I TNM classification, presence of epitheliomorphic cells, and adjuvant therapy). This indicates the utility of screening asbestos workers since only patients with MPM at stage 1 TNM have a favorable follow-up and, for this purpose, we have found that the FDG-PET scan is currently the most specific and practical clinical procedure.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

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