



Induction chemotherapy, extrapleural pneumonectomy (EPP) and adjuvant hemi-thoracic radiation in malignant pleural mesothelioma (MPM): Feasibility and results[☆]

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Received 10 November 2006; received in revised form 26 January 2007; accepted 3 February 2007

KEYWORDS

Malignant pleural mesothelioma;
Induction chemotherapy;
Radiation therapy;
Surgery

Summary

Background: Trimodality therapy seems to be the best treatment for malignant pleural mesothelioma (MPM). A large experience served to evaluate the efficacy of surgery followed by adjuvant chemo-radiotherapy. Trimodality therapy results have led us to test induction chemotherapy followed by EPP and adjuvant radiotherapy in stages I–III of MPM. The aim of our study was to evaluate the feasibility of this protocol and to estimate survival.

Methods: From 2000 to 2003, 21 patients with MPM (14 males and 7 females, median age 59 years) were enrolled in the prospective study. Induction chemotherapy consisted of Carboplatin (AUC 5 mg/mL/min on Day 1) and Gemcitabine (1000 mg/m² on Days 1, 8, 15) for three to four cycles. EPP was performed 3–5 weeks after induction therapy, while post-operative RT was given 4–6 weeks after operation.

Results: Ten patients received three cycles of chemotherapy, 10 patients received four cycles and 1 patient had two cycles. Grades 3–4 haematological toxicity occurred in eight (38.1%) patients. Chemotherapy response rate was: complete 0%, partial 33.3% and stable disease 66.7%. Seventeen (80.9%) out of 21 patients underwent EPP with no intra or post-operative mortality with an overall major and minor morbidity rate at 52.4%. Median survival was 25.5 months, with an overall 1, 3 and 5-year survival rate of 71, 33 and 19%, respectively.

[☆] Presented at 8th International Conference of International Mesothelioma Interest Group (IMIG), Chicago, October 19–22, 2006.

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Conclusions: In MPM, the combined modality approach using the Carboplatin/Gemcitabine combination as induction chemotherapy is feasible, with good results in terms of survival and morbidity. Our results are similar to those of other studies using a heavier modality treatment.

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1. Introduction

Malignant pleural mesothelioma (MPM) is a relatively rare tumour that is characterized by locally aggressive behaviour which leads to a fatal prognosis mostly due to relative chemo- and radio-resistance and to the difficulty in obtaining a radical excision with surgery. The management of MPM remains controversial and its treatment modalities have yielded poor results: single therapy like chemotherapy, surgery or radiotherapy have not led to improvements in terms of prolonged disease control [1]. Multimodality therapies adopting a combination of surgical resection and adjuvant treatments (chemotherapy, radiotherapy or both) seem to be a better therapeutic option, though only a select group of patients benefits from such treatment [2–5]. A major experience in surgical management of MPM was conducted by Sugarbaker et al. [2] who tested the efficacy of surgery followed by adjuvant chemo- and radiotherapy. In their experience, patients with microscopic negative resection margins, epithelial histo-type and negative lymph-nodes, had a good long-term survival (2 and 5 year survival: 68 and 46%, respectively; median 51 months). Starting in 2000, we adopted a trimodality protocol with neoadjuvant chemotherapy. The rationale behind such choice arises from the positive widespread experience of neoadjuvant chemotherapy in advanced NSCLC (stage IIIA) [6]. Furthermore, since 1996, we have tested the activity of the Gemcitabine/Carboplatin combination in a Phase II study, in patients affected by MPM [7]. Our results indicate a good response rate, an improvement in symptoms and a low toxicity profile—factors that led us to evaluate the pharmacological combination as neoadjuvant treatment in the multimodality approach of MPM. The aim of the study is to determine the treatment feasibility and its results in terms of survival. The present work reports our experience in applying the mentioned multimodality approach.

2. Materials and methods

2.1. Study design

The protocol schema is shown in Fig. 1. Patients with clinical IMIG [8] stages I–III (T1-3, N0-2) of epithelial or mixed histology of MPM, underwent three to four cycles of induction chemotherapy; they were then reassessed with a chest and abdomen CT scan to evaluate the response rate. Patients with complete, partial response or stable disease underwent surgical resection within 4–6 weeks. Adjuvant radiotherapy started 3–5 weeks post-operatively. Written informed consent to participate in our prospective study was obtained from each patient. The study was approved by the Institutional Review Board of our Center.

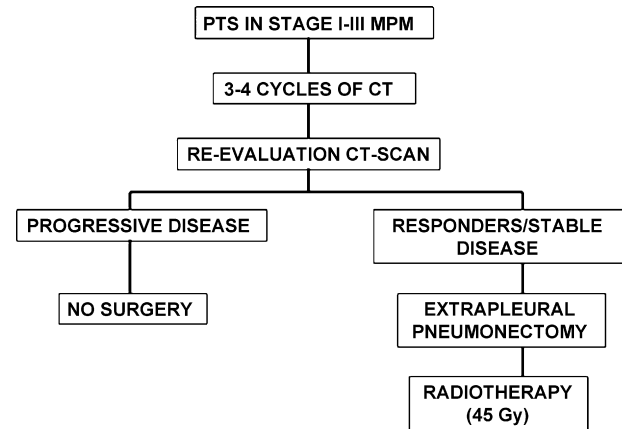


Fig. 1 Protocol scheme.

2.1.1. Eligibility criteria

Patients were eligible if they had:

- (1) A resectable disease confined to one hemi-thorax and not invading the chest wall or mediastinal structures.
- (2) A WHO performance status (PS) score less than or equal to 1.
- (3) Adequate haematological, hepatic and renal functions.
- (4) Adequate cardio-pulmonary function tests.

All patients had: lung functional tests, computed tomography (CT) of the chest and abdomen and echocardiography. Patients with pre-operative FEV1 of less than 2L underwent a ventilation-perfusion scan. In select cases, a cardio-respiratory stress test was performed. Pre-operative mediastinoscopy was done selectively only in patients with radiological suspect of mediastinal contralateral (N3) nodal involvement.

Functional exclusion criteria included:

- (1) A room air arterial $p\text{CO}_2$ greater than 45 mmHg.
- (2) A room air arterial $p\text{O}_2$ less than 65 mmHg.
- (3) A cardiac ejection fraction of less than 45%.
- (4) A predicted post-operative FEV1 of less than 1 L.

2.2. Treatments

Induction chemotherapy comprised of a combination of Carboplatin and Gemcitabine. Carboplatin was delivered to a targeted area under the concentration–time curve (AUC) of 5, diluted in 500 mL normal saline, and infused over 30 min on Day 1. Dosing was based on the Calvert method and the Cockcroft-Gault formula for creatinine clearance was substituted for the glomerular filtration rate. Gemcitabine 1000 mg/m² was diluted in 500 mL normal saline and infused

over 30 min on Days 1, 8 and 15. Treatment was given on an outpatient basis and was repeated at 28-day intervals. Dose modification occurred as follows: Gemcitabine on Days 8 and 15 was reduced to 75% of the planned dose if the absolute neutrophil count (ANC) decreased, having values ranging from 999 to $500 \mu\text{L}^{-1}$ and/or the platelet count decreased to values between 99,900 and $50,000 \mu\text{L}^{-1}$; it was omitted if the ANC was less than $500 \mu\text{L}^{-1}$ and/or the platelet count was less than $50,000 \mu\text{L}^{-1}$ or if Grade 4 non-haematological toxicity occurred. A 50% dose reduction was adopted for Grade 3 non-haematological toxicity. Treatment was recycled on Day 28 if the ANC was greater than or equal to $1500 \mu\text{L}^{-1}$ and the platelet count was greater than or equal to $100,000 \mu\text{L}^{-1}$. Treatment was delayed a week if the ANC and/or platelet counts fell below such levels.

Surgical resection consisted of extrapleural pneumonectomy (EPP) with en-bloc resection of the lung, parietal pleura, hemi-pericardium and diaphragm, as described by Sugarbaker [9]. A systematic hilar and mediastinal lymphadenectomy was done. The prosthesis replacement was accomplished in all patients by Gore-Tex® patch for the pericardium and Dual Mesh Gore-Tex® patch for the diaphragm, in both sides. We prefer to perform a single stitches manual suture for the main stem bronchus with a short stump that we cover when possible with a flap of posterior pericardium or with another tissue (e.g. thymic fat pad or azygous vein bi-valved flap). At the end of surgery we use the argon beam coagulator to achieve an accurate and complete haemostasis on the chest cavity.

Adjuvant radiotherapy was delivered using photons by a 6-MV linear accelerator. A total dose of photon fields of 45 Gy (1.8 Gy/F, 1 F/day for 5 days/week), was delivered to the hemi-thorax, the thoracotomy incision and sites of chest drains. A boost dose of 10–14 Gy (2 Gy/F, 1 F/day for 5 days/week) was delivered to high risk areas (surgical scar and drainages with electron beams 12–15 MeV, pulmonary hilum and areas with macroscopic residual disease marked by surgeon with clips, with photon fields). The radiotherapy planning ensures the coverage of the entire ipsilateral thoracic cavity, from the insertion of the diaphragm to the lung apex, ipsilateral mediastinum and pericardium, and of all surgical incisions. The treatment technique consists of two opposed shielded fields, AP–PA, to the whole hemi-thorax, shielding organs at risk. The dose under the shield is compensated with electron beams, 12–15 MeV, like the technique described by MSKCC team [10].

2.3. Response evaluation, toxicity criteria and follow-up

Change in disease was assessed by measuring the thickness of up to three involved areas of pleural rind at each of three separate levels at least 2 cm apart on computed tomography scan, at baseline, and after three cycles (at least one measurement was >1.5 cm).

Tumour response was defined as: (i) complete response (CR)—disappearance of all known disease, determined by two observations not less than 4 weeks apart; (ii) partial response (PR)—a greater than 50% decrease in the sum of the products of perpendicular diameters of bidimensionally measured lesions on two occasions not less than 4 weeks apart, or a greater than 30% decrease in the sum of linear

tumour measurements on two observations not less than 4 weeks apart; (iii) stable disease (SD)—a decrease in bidimensional tumour area of less than 50% or an increase of less than 25%, or a decrease in the sum of unidimensional measurements of less than 30% or an increase of less than 25%, provided that no new lesions have appeared; (iv) progressive disease (PD)—a greater than 25% increase in the size of the tumour being measured (unidimensional or bidimensional) or the appearance of new lesions [11].

Treatment-related toxicity was recorded according to the World Health Organization criteria [12]. For clinical benefit evaluation tumour-related symptoms were recorded at the start of treatment and reassessed after each course of chemotherapy. Five items were considered, graded as follows: (a) pain was evaluated by the use of analgesics (0: pain absent; 1: controlled with occasional administration of non-opioid analgesics; 2: needs regular administration of non-opioid analgesics; 3: needs occasional administration of opioid analgesics; 4: needs regular administration of opioid analgesics; 5: needs administration of epidural opioid analgesics); (b) dyspnoea (0: absent; 1: by intense effort; 2: by minimal effort; 3: at rest); (c) cough (0: absent; 1: occasional; 2: nocturnal; 3: continuous); (d) fever (0: absent; 1: lower than 38°C ; 2: higher than 38°C); (e) weight loss (0: absent; 1: less than 10%; 2: greater than 10%).

The follow-up evaluation after trimodality treatment required a clinical visit, a thoracic and abdomen CT scan every 3 months; in cases with suspect of recurrence a confirmatory PET scan or Magnetic Resonance Scan (MRI) was done and if possible a biopsy was performed.

2.4. Statistical analysis

Survival time was calculated from the date of the beginning of induction chemotherapy to the date of death or last follow-up (April 2006). Actuarial survival was estimated using the Kaplan–Meier method [13].

3. Results

Between 2000 and 2003, 21 patients with histologically proven MPM were enrolled in the trial. Out of 21 patients who entered the study, 17 (80.9%) received an extrapleural pneumonectomy and 4 (19.1%) received a palliative pleurectomy/decortication. Patient characteristics are summarized in Table 1.

3.1. Response and toxicity profile of induction chemotherapy

No complete response was obtained, while a partial response was observed in 7 (33.3%) patients and 14 (66.7%) patients had a stable disease. The majority of patients had a clinical improvement in one or more symptoms (Table 2). All patients except one, who refused CT after the second cycle, received at least three cycles of chemotherapy (10 patients received three cycles of chemotherapy, 10 patients received four cycles). Chemotherapy was well tolerated and no episodes of Grades 3–4 non-haematological toxicity were observed. Eight (38.1%) patients experienced Grade 3 haematological toxicity, rapidly reversible after treat-

Table 1 Characteristics of patients

Gender	
Male	14 (66.7%)
Female	7 (33.3%)
Age (years)	
Median (range)	59 (37–68)
Asbestos exposure	
Yes	12 (57.1%)
No	9 (42.9%)
Who performance status	
0	5 (23.8%)
1	16 (76.2%)
Location	
Right	10 (47.6%)
Left	11 (52.4%)
Histology	
Epithelial	20 (95.2%)
Mixed	1 (4.8%)
Clinical T stage	
T1	1 (4.8%)
T2	8 (38.1%)
T3	12 (57.1%)
pTNM	
T1	1 (4.8%)
T2	7 (33.3%)
T3	13 (61.9%)
N0	14 (66.7%)
N1	2 (9.5%)
N2	5 (23.8%)
IMIG stage	
I	1 (4.8%)
II	4 (19%)
III	16 (76.2%)

ment and without complications (10 (13.9%) episodes of leucopenia, 6 (8.3%) episodes of thrombocytopenia and 1 (1.4%) episode of anaemia on a total of 72 cycles administered, Table 3). Grade 3 neutropenia was encountered in 12 (16.7%) cases, no episodes of febrile neutropenia were seen. Of 72 delivered cycles, 5 (6.9%) were delayed by 1 week and 3 (4.2%) were delayed by more than 1 week. A 100% dose reduction of Gemcitabine at the 8th day occurred in three (4.2%) cases and at 15th day the 100% dose reduction occurred in eight (11.1%) cases. A reduction of less than or equal to 75% was observed in seven (9.7%) of the 8th day doses and in nine (12.5%) of the 15th day doses.

3.2. Surgery

The median operating time was 3.25 h (range 2–5.5). No intra or post-operative mortality occurred. Major complications were observed in 5 (23.8%) patients: one bronchopleural fistula was treated with open window thoracostomy, one bleeding and three diaphragmatic patch dehiscences required reoperation. Minor complications were observed in six (28.6%) patients. These included three bleedings treated with repeated haemotransfusions and three atrial fibrillations treated with medical therapy. The pathological IMIG stage was: stage I in 1 (4.8%) patient, stage II in 4 (19%) patients and stage III in 16 (76.2%) patients. Lymph nodes metastases were found in seven cases (two N1 and five N2).

3.3. Radiotherapy

Out of 17 patients who received EPP, 15 patients underwent post-operative RT. Adjuvant RT was not received by one patient with broncho-pleural fistula and another patient with poor performance status after surgery. The median dose administered with photon fields to the hemi-thorax was 45 Gy (range 40–45 Gy) and the median boost dose was 10 Gy (range 10–14 Gy). Treatment was well tolerated; 1 patient required the interruption of RT at 40 Gy due to fatigue and 1 patient had Grade 3 skin toxicity.

Table 2 Clinical benefit evaluated as improvement, worsening or stabilization of initial symptoms

Symptom	Initially absent (%)	Equal (%)	Improved (%)	Worsened (%)
Pain	7 (33.3)	4 (19.1)	8 (38.1)	2 (9.5)
Dyspnoea	4 (19)	3 (14.3)	12 (57.2)	2 (9.5)
Cough	12 (57.2)	2 (9.5)	7 (33.3)	0 (0)
Weight loss	11 (52.4)	2 (9.5)	7 (33.3)	1 (4.8)
Fever	15 (71.4)	0 (0)	6 (28.6)	0 (0)

Table 3 Haematological toxicity per cycle

WHO grade	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
Leukocyte count	35 (48.6)	14 (19.4)	13 (18.1)	10 (13.9)	0 (0)
Hb	44 (61.1)	20 (27.8)	7 (9.7)	1 (1.4)	0 (0)
PLT	56 (77.8)	6 (8.3)	4 (5.5)	6 (8.3)	0 (0)

WHO: World Health Organization; Hb: haemoglobin; PLT: platelets.

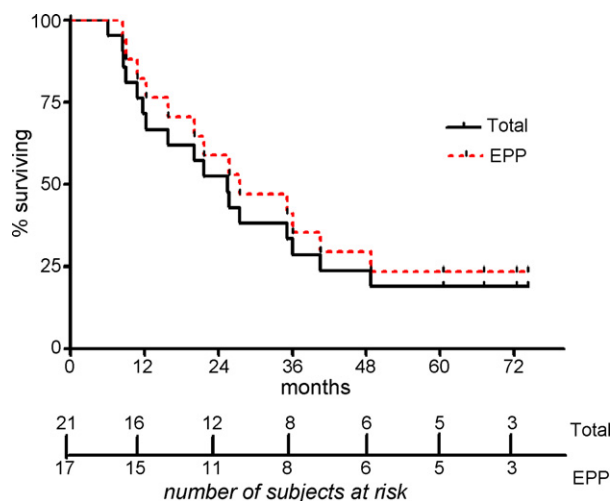


Fig. 2 Overall survival and survival of patients who underwent extrapleural pneumonectomy.

3.4. Survival

Median follow-up was 69 months, median survival was 25.5 months. The overall actuarial survival rates at 1, 2, 3 and 5 years were 71, 52, 33 and 19%, respectively (Fig. 2). Patients without involvement of extrapleural lymph-node and IMIG stages I–II had a better prognosis even if the small number of patients did not permit a statistical evaluation. Median survival was 25.5 and 23.6 months for patients having PR and SD, respectively ($p=0.8$). At the end of the follow-up, four (19%) patients are still alive (over 60 months) with no evidence of relapse. Considering the 17 patients who underwent complete resection (EPP), the survival rate was excellent, with a median survival of 27.5 months and a survival rates at 1, 2, 3 and 5 years of 82, 59, 41 and 24%, respectively (Fig. 2).

3.5. Sites of recurrence

Out of 17 patients with EPP, 13 (76.5%) had recurrence. A 35.2% (6 of 17) local recurrence rate and 64.8% (11 of 17) distant recurrence was found (Table 4). The median time to relapse was 16.3 months (Fig. 3). No difference on distant relapse rate was evidenced between patients with PR or SD after chemotherapy (60% versus 66%, respectively; $p=0.79$).

Table 4 Sites of recurrence

Site of recurrence	n
Intrathoracic omolateral	6
Distant	11
Intrathoracic contralateral	3
Liver	4
Abdomen diffuse	1
Skin	1
Mammary and latero-cervical lymph-nodes	1
Bone	1

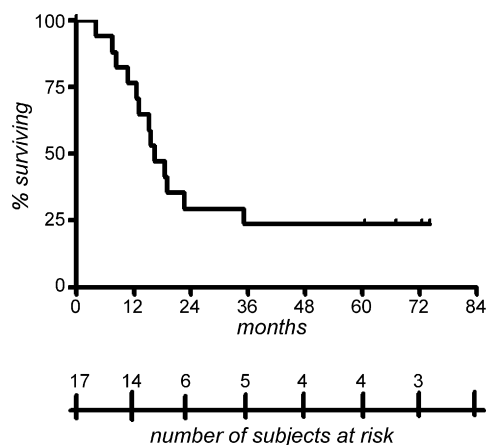


Fig. 3 Relapse free survival.

4. Discussion

The management of MPM is still a main controversial issue in thoracic surgery. Moreover, the increasing incidence in most countries, the poor prognosis for untreated patients (median survival 4–12 months) and the lack of any effective therapies have prompted the search for better treatment [14].

Autopsy studies of patients affected by MPM have demonstrated that more than half of the patients had disseminated MPM [15]. Therefore, systemic chemotherapy seems to be an unavoidable prerequisite in the complex management of MPM. Unfortunately, MPM is a tumour with a high chemo- and radio-resistance. Single-agent chemotherapy has produced response rates below 20% whereas most of the active combined regimens have yielded response rates ranging between 20 and 41% [16,17]. However, the tumour volume in mesothelioma is difficult to accurately assess, so response rates are often not reproducible and more appropriate endpoints should be considered to evaluate biological activity of chemotherapy, e.g. the Progression-free survival rate [18]. The current standard treatment for advanced MPM is the combination of cisplatin and pemetrexed that in a large phase III trial showed a response rate of 41%, a median survival of 12.1 months and a time to progression of 5.7 months. All the parameters were significantly higher than in the cisplatin-alone control arm [17]. A recently published randomized phase III study with raltitrexed and cisplatin versus cisplatin alone confirmed a similar survival advantage; the different response rate (23.6% versus 13.6%), confirmed the difficulty of evaluating and comparing tumour response in MPM [19]. In our previous Phase II study the activity of the Carboplatin/Gemcitabine combination, in a cohort of 50 patients affected by MPM, was 26% (C.I. 15–40%) and the median survival reached 66 weeks. In general, the chemotherapy was well tolerated with a low percentage of haematological toxicity (15% of thrombocytopenia, 11% of leucopenia and 5% of anaemia) and without non-haematological toxicity [7]. The low toxicity profile together with a response rate that is closely related to the response of the cisplatin based combination (33% response rate, 95% CI 20–46%, in the experience of Nowak et al. [20]), has led us to consider the Carboplatin and Gemcitabine combination

as a sound induction treatment for trimodality approach in MPM. The role of Carboplatin was confirmed by a recently published paper [21] that reported, in a large cohort of patients, the combination of pemetrexed and Carboplatin as active and well tolerated. The radiological regression rate of disease was inferior to that reported with the cisplatin combination. However, despite the apparently lower radiological response rate, time to progression and survival in the study were similar to the data reported with the standard cisplatin combination. Therapy was well tolerated, with negligible non-haematological toxicity. That compares favourably with the toxicity profile reported in the cisplatin/pemetrexed trial, in which a higher incidence of nausea and vomiting and fatigue was observed [17]. The haematological toxicity was fairly acceptable, with about 20% of patients experiencing a short-lived neutropenia and a severe and cumulative anaemia (mainly Grade 3) in 11.7% of patients.

A major objection to the use of induction chemotherapy stems from the belief that the rate of mortality and morbidity risk increases in patients who underwent a major operation. Considering these risks, the aim of induction chemotherapy treatment should be to achieve the maximum response with the lower toxicity, in order to minimize the peri- and post-operative complications. In the light of those considerations, the use of a Carboplatin-based combination showing a low toxicity profile combined with a good clinical outcome seems to be attractive; our experience seems to confirm that statement, demonstrating a low rate of post-operative complications.

In recent years advances in surgical and anaesthesiological techniques have resulted in better post-operative outcome, significantly reducing the morbidity and mortality rates compared to the past (30% mortality before 1980) [22]. Sugarbaker et al. [2] on a large number of patients ($n=183$) reported a mortality rate of 3.8%. The use of neoadjuvant chemotherapy in stage IIIA of NSCLC also demonstrated the feasibility of major pulmonary resections with an acceptable mortality and morbidity rate [6]. Clearly, such approach implies important requisites: a careful pre-operative selection of suitable patients based upon the cardio-pulmonary function, a good performance status and the use of chemotherapeutic drugs with an acceptable activity and toxicity.

At present, only few authors have reported data of induction chemotherapy in MPM: Weder et al. [23] reported the results of a pilot study on a group of 19 patients treated with neoadjuvant chemotherapy (three cycles of cisplatin and Gemcitabine) followed by surgery and radiotherapy. The response rate to neoadjuvant chemotherapy was 32%, where 16 patients received EPP and 13 post-operative RT. No fatality occurred and six patients had major complications. Median survival was 23 months and the 1 and 2-year survival rates were 79 and 37%, respectively. De Perrot et al. [24] conducted a similar trial in which induction chemotherapy was followed by surgery and post-operative hemi-thorax radiation therapy. Herein, the operative mortality rate was 6% and the 1-year survival rate was 74%. Our results are akin to the Swiss experience: with no mortality and major complications in five (23.8%) patients who were successfully treated. Comparing our results to those of other authors not using neoadjuvant chemotherapy in the surgical treatment of MPM [4,5,25], the intra and post-operative outcome of

these patients was not significantly influenced by the pre-operative treatment. However, in a recent report, Stewart et al. [26] found that induction chemotherapy is a factor that increases the risk of post-operative complications, as does the right-sided procedure and a prolonged operation. In agreement with Sugarbaker et al. [25], we believe that the key to minimize the post-operative complication is a meticulous surgical technique, a short operative time and a prevention or aggressive management of complications at early stage, when they are easier to treat and before their serious evolution. In our series, only one bronchopleural fistula was recorded: an over scrupulous management of bronchial stump is accomplished by avoiding its devascularization and by covering it with a flap of available tissue. Moreover, the prevention of bleeding by accurate intraoperative haemostasis with argon beam coagulator or its early treatment reduced the risk of acute ischemia of the bronchial stump. Regarding the diaphragmatic patch dehiscence, all cases were seen, at the beginning of our experience, on the left side with evidence of gastric herniation. The main reasons were a technical error in the fixation of the patch in the medial part near the oesophageal hiatus and probably an excessive tension on a too tight patch. On the basis of these considerations we refined our technique: when possible we leave a rim of the diaphragmatic crus on the oesophagus and stomach to fix the patch and to prevent the herniation, moreover the patch is placed loose to avoid tension. If there is a paucity of tissue to anchor the patch at the hiatus we suture the patch to the periaortic tissue and pericardium or pericardial patch. Similarly, if there is not enough diaphragmatic residual tissue, we place the sutures around the ribs inferiorly.

Our good results in terms of survival could in part be explained by the favourable histology (epithelial) of most of our patients and by the low percentage of lymph-nodes involvement. In fact, some authors [2,27] have found these factors to have a positive impact on long-term survival. In our study, patients with a sarcomatoid histology were excluded because of the poor prognosis of this subtype of MPM and the lower response to the chemotherapy.

The use of a high dose of hemi-thoracic radiation after neoadjuvant chemotherapy and EPP has not been evaluated yet in large studies. In the Rusch et al. experience [4], the use of a bimodality approach with EPP and adjuvant high dose hemi-thoracic radiation (54 Gy) has demonstrated the great efficacy in the local control of the disease (87% of local relapse-free survival). Baldini et al. [28] has shown that the concurrent adjuvant chemo/radiotherapy with a low dose of hemi-thoracic radiation (30 Gy) is inadequate to prevent local recurrence, while a high dose of radiation in combination with adjuvant chemotherapy increases toxicity [2,29]. In our protocol, induction therapy followed by surgery enabled us to irradiate the ipsilateral hemi-thorax with a dose of 45 Gy, avoiding the concurrent chemo- and radio-toxicity and leading to a good local control of the disease (35.2% of local recurrence, median relapse-free survival of 16.3 months). The choice in our protocol of an intermediate radiation dose was prudential and justified by the lack of studies on this multimodality treatment. Nevertheless, a recent experience on a small group of patients with advanced stage of MPM at the Memorial Sloan Kettering Cancer Center has also established the feasibility

of induction therapy followed by surgery and higher dose of RT (54 Gy) [30]. In conclusion, despite our small series of patients, we can assert that a multimodal treatment of MPM including induction chemotherapy is feasible and tolerated with acceptable toxicity. Induction treatment, in our experience, has not determined an increased intra or post-operative risk, though a careful selection of patients is fundamental for this treatment. However, to assess the real benefits of this treatment, a multi-institutional controlled clinical trial is needed to estimate the long-term survival and, equally important, the post-treatment changes in health status (quality of life evaluation). Moreover, improvements in survival will probably depend on the availability of new effective chemotherapeutic or biological agents.

Conflict of interest

None declared.

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