Does Surgery Improve Survival of Patients with Malignant Pleural Mesothelioma?

A Multicenter Retrospective Analysis of 1365 Consecutive Patients

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Background: Surgery with pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP) can be an option for selected patients with resectable malignant pleural mesothelioma (MPM). The aim of this study was to investigate the impact of surgical treatment on the outcome of patients with MPM.

Methods: We retrospectively reviewed data from 1365 consecutive patients with histologically proven MPM, treated from 1982 to 2012 in six Institutions. Patients received chemotherapy alone (n = 172), best supportive care (n = 690), or surgical treatment (n = 503), by either P/D (n = 202) or EPP (n = 301) with or without chemotherapy.

Results: After a median follow-up of 6.7 years (range, 1.1–14.8), 230 patients (16.8%) were alive; median survival for patients who received palliative treatment or chemotherapy alone, P/D, and EPP were 11.7 (95% CI, 10.5–12.5), 20.5 (95% CI, 18.2–23.1), and 18.8 (95% CI, 17.2–20.9) months, respectively. The 30-day mortality was 2.6% after P/D and 4.1% after EPP ($p = 0.401$). According to multivariate analysis (n = 1227), age less than 70, epithelial histology, and chemotherapy were independent favorable prognostic factors. In the subset of 313 patients (25.5%) with all favorable prognostic factors, median survival was 18.6 months after medical therapy alone, 24.6 months after P/D, and 20.9 months after EPP ($p = 0.596$).

Conclusions: Our data suggest that patients with good prognostic factors had a similar survival whether they received medical therapy only, P/D, or EPP. The modest benefit observed after surgery during medical treatment requires further investigation, and a large multicenter, randomized trial, testing P/D after induction chemotherapy versus chemotherapy alone in MPM patients with good prognostic factors, is needed.

Key Words: Malignant pleural mesothelioma, Extrapleural pneumonectomy, Pleurectomy/decortication, Chemotherapy, Palliative treatment.

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Malignant pleural mesothelioma (MPM) is a rare and aggressive disease with approximately 2500 newly diagnosed cases each year in United States and approximately 5000 in Western Europe.[1,2] Median survival is 6 to 9 months from the diagnosis, and 6-month, 1-year, and 5-year overall survival are 55%, 33%, and 5%, respectively.[3]

Medical management of MPM with chemotherapy or radiotherapy has obtained only limited improvement of survival, with pemetrexed and cisplatin chemotherapy reaching a median survival of 12 versus 9 months with best supportive care.[4] Surgery can be an option for patients with good performance status and resectable disease, by either pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP), but patient selection and optimal surgical strategy are still controversial. The aim of surgery is to remove all macroscopic disease, but a complete resection without microresidual disease (R0) is extremely difficult to obtain. Therefore, surgical treatment has been combined with chemotherapy and radiotherapy to improve local control and survival. Encouraging results have been reported for EPP combined with chemotherapy and radiotherapy, with a median survival ranging from 17 to 35 months.[5–7] Recently, several studies comparing the EPP with less invasive surgical procedures, such as P/D, showed similar results in terms of survival, with lower postoperative morbidity and mortality.[8–10] The best treatment for the individual patient remains unknown, because published series are too small and heterogeneous to demonstrate statistically significant differences in survival. In fact,

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surgical patients selected on the basis of best prognostic factors are usually compared with nonsurgical candidates with the poorest prognosis.

At present, there is only one small, prospective, randomized study, the Mesothelioma And Radical Surgery (MARS) trial, which did not show any benefit of EPP after chemotherapy compared with chemotherapy alone.[11] Moreover, the decision to perform either P/D or EPP is on the basis of surgeon's preference rather than scientific data.

The primary aim of this retrospective, multicenter study was to investigate the impact of surgical treatment on the outcome of patients with MPM, having adjusted for independent prognostic factors.

MATERIAL AND METHODS

We retrospectively reviewed data from 1365 consecutive patients with histologically proven MPM, who had undergone thoracoscopic or open pleural biopsy between September 1982 and September 2012 at six Institutions (Spedali Civili Brescia, Ospedale Maggiore della Carità Novara, San Luigi Hospital Orbassano (Torino), Policlinico hospital Milan, IRCCS San Martino Genova, and Fondazione IRCCS Istituto Nazionale dei Tumori Milan; Supplemental Table, Supplemental Digital Content 1, http://links.lww.com/JTO/A517). A common variable database was created. Clinical data were obtained from institutional databases, and variables recorded included age, sex, asbestos exposure, smoking history, histologic subtype, stage, surgical procedure, and chemotherapeutic regimens when available.

In all patients, tissue sampling was achieved by means of thoracoscopy (n = 1282) or open pleural biopsy (n = 83) under general anesthesia. In the absence of pleural effusion, patients underwent open pleural biopsy by lateral minithoracotomy. Three tumor cell types were identified: epithelial, biphasic, and sarcomatous.

Eight hundred sixty-two patients received medical treatment alone, consisting in either chemotherapy (n = 172) or best supportive care (n = 690); 503 patients received surgical treatment with or without chemotherapy, consisting in either P/D (n = 202, 6 patients underwent only pleurectomy) or EPP (n = 301) according to their performance status, histology, and clinical staging of the disease. Before 2004, chemotherapy consisted of cisplatin and/or gemcitabine and after that date a combination of cisplatin and pemetrexed. Patients with histologically confirmed nonsarcomatous MPM, younger than 75 years, with a Eastern Cooperative Oncology Group performance status of 0 to 1, and normal liver and renal function tests were evaluated for surgery with pulmonary function testing, quantitative ventilation–perfusion scanning, echocardiography, and computed tomographic (CT) scanning of the chest and abdomen. Additional imaging studies were performed as clinically indicated.

Patients were considered suitable candidates for multimodality therapy with EPP if the predicted postoperative forced expiratory volume in 1 second was at least 1 liter, and echocardiography showed a grossly normal cardiac function and an ejection fraction of more than 45%, with an estimated normal pulmonary artery pressure. Surgical resectability was defined by tumor confined to one hemithorax without any evidence of metastatic disease, or invasion of the chest wall (preservation of extrapleural fat planes, absence of extrapleural soft-tissue masses, and absence of rib displacement or infiltration) or mediastinum (normal CT attenuation values of mediastinal content), or transdiaphragmatic extension (smooth diaphragmatic undersurface). The decision to perform EPP or P/D was based on the extent of the disease, with locally advanced MPM patients being treated mainly with EPP. EPP was defined as an en bloc resection of the pleura, lung, ipsilateral diaphragm, and pericardium; P/D was defined as an extrapleural dissection from the apex to the diaphragm; decortication of the lung was performed where the visceral pleura was macroscopically involved including the pulmonary fissures down to the pulmonary artery and pleural reflections if involved. The aim of surgery was to obtain a radical macroscopic resection. Postoperatively, patients treated with P/D received adjuvant chemotherapy and/or radiotherapy. Since 1999, after EPP, adjuvant chemo-radiation was carried out according to the scheme by Sugarbaker et al.[5]

Sixty-eight patients (19 in nonsurgical group, 46 in P/D group, and 3 in EPP group) were lost at follow-up. The remaining 1297 patients were followed up until death or for a minimum period of 1 year. Survival was measured from the date of surgical diagnosis; in the surgical groups (P/D and EPP groups), the survival was also analyzed from the data of surgery. In the surgical group, the median interval between diagnosis and surgery was 2.8 months (range, 0.5–4 months).

Patients were followed up with a chest CT arranged every 6 months to monitor response to treatment or disease progression. Those relapsing after multimodality therapy were offered second-line treatment: combination chemotherapy with pemetrexed and cisplatin or single-agent vinorelbine. Radiotherapy was offered as a palliative measure when patients were diagnosed with relapse.

The following characteristics were analyzed: age, sex, asbestos exposure, smoking history, performance status, histology, and treatment options (palliative treatment, chemotherapy, or surgery), dividing patients undergone EPP or PD and chemotherapeutic regimens with or without pemetrexed.

Univariate and multivariate analyses were performed, using the Cox regression model. A two-sided test was used at 5% level of significance. The univariate and multivariate analyses were limited to patients (n = 1227) in whom information on overall survival (OS) was available. Survival functions were estimated using the Kaplan–Meier technique. The subgroup of covariates that best discriminated the prognosis was obtained by means of the classification and regression tree (CART) method. Statistical analysis was performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC); the CART method was applied using R version 2.15.1; the survival plots were performed using STATA version 12.1.

RESULTS

A total of 1365 consecutive patients were enrolled in the study. Most of the patients were male (68.1%) and the most frequent tumor cell type was the epithelial (57.9%); patient characteristics were summarized in Table 1. Clinical and pathological staging were reported in Table 1; the data showed that

TABLE 1. Patient Characteristics (n = 1365, n = 862 Nonsurgical, and n = 503 Surgical)

Characteristics	Nonsurgical Group n = 862 (%)	P/D Group n = 202 (%)	EPP Group n = 301 (%)
Age, yr, median (range)	67.0 (25–95)	62.5 (30–87)	58.7 (33–78)
<70	509 (59.0)	162 (80.2)	287 (95.3)
≥70	353 (41.0)	40 (19.8)	14 (4.7)
Sex			
Male	570 (66.1)	149 (73.8)	225 (74.7)
Female	292 (33.9)	53 (26.2)	76 (25.3)
Smoking			
Smoker	237 (48.0)	97 (49.0)	147 (51.4)
Nonsmoker	257 (52.0)	101 (51.0)	139 (48.6)
Unknown	368 (42.7)	4 (2.0)	15 (5.0)
Asbestos exposure			
No	207 (46.8)	107 (69.5)	96 (49.7)
Yes	235 (53.2)	47 (30.5)	97 (50.3)
Unknown	420 (48.7)	48 (23.8)	108 (35.9)
COPD			
No	51 (92.7)	116 (94.3)	166 (97.6)
Yes	4 (7.3)	7 (5.7)	4 (2.4)
Unknown	807 (93.6)	79 (39.1)	131 (43.5)
CAD			
No	53 (96.4)	165 (94.3)	236 (94.4)
Yes	2 (3.6)	10 (5.7)	14 (5.6)
Unknown	807 (93.6)	27 (13.4)	51 (16.9)
FEV1, liter, median (range)			
<60%	11 (27.5)	27 (28.7)	20 (18.5)
≥60%	29 (72.5)	67 (71.3)	88 (81.5)
Unknown	822 (95.4)	108 (53.5)	193 (64.1)
Chemotherapy			
No	658 (79.3)	43 (21.3)	35 (14.5)
Yes	172 (20.7)	159 (78.7)	206 (85.5)
Unknown	32 (3.7)	0 (0)	60 (19.9)
Clinical stage			
I	34 (14.9)	25 (25.3)	23 (12.5)
II	80 (35.1)	39 (39.4)	100 (54.3)
III	68 (29.8)	34 (34.3)	61 (33.2)
IV	46 (20.2)	1 (1.0)	0 (0)
Unknown	634 (73.5)	103 (51.0)	117 (38.9)
Histology			
Epithelial	385 (44.7)	147 (77.0)	258 (86.6)
Biphasic	105 (12.2)	40 (20.9)	40 (13.4)
Sarcomatoid	60 (7)	4 (2.1)	0 (0)
Unknown	312 (36.2)	11 (5.4)	3 (1.0)
pT			
T1	—	19 (14.4)	13 (4.4)
T2	—	50 (37.9)	84 (28.4)
T3	—	43 (32.6)	181 (61.1)
T4	—	20 (15.2)	18 (6.1)
Unknown		70 (34.7)	5 (1.7)
pN			
N0	—	89 (81.7)	169 (57.1)
N1	—	9 (8.3)	38 (12.8)
N2	—	11 (10.1)	89 (30.1)
Unknown		93 (46.0)	5 (1.7)
Pathological stage			
I	—	19 (14.4)	11 (3.7)
II	—	47 (35.6)	62 (20.9)
III	—	46 (34.8)	206 (69.4)
IV	—	20 (15.2)	18 (6.1)
Unknown	—	70 (34.7)	4 (1.3)

P/D, pleurectomy/decortication; EPP, extrapleural pneumonectomy; FEV1, forced expiratory volume in 1 second; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease.

in both surgical groups, there was a shift of patients with stage I and II to stage III and IV between clinical and pathological staging: in the P/D group the pathological staging showed an increase of 15% of stage III and IV and in the EPP group an increase of 42% of pathological stage III and IV. Five hundred three patients underwent surgical resection by either P/D (n = 202) or EPP (n = 301). The 30- and 90-day crude mortality rate was 2.6% and 6% after P/D, and 4.1% and 6.9% after EPP, respectively (χ^2_{1df} test for difference at 30-day mortality = 0.707, $p = 0.401$; χ^2_{1df} test for 90-day mortality = 0.136, $p = 0.713$). In the P/D group, 21 patients (10.4%) experienced postoperative complications: atrial fibrillation (n = 9), prolonged air leak for more than 7 days (n = 5), bleeding (n = 3; 1 patient required reoperation), myocardial infarction (n = 2), controlateral pleural effusion (n = 1), and paraplegia (n = 1).

In the EPP group, 65 patients (21.6%) developed postoperative complications: atrial fibrillation (n = 32), bleeding (n = 13; 4 patients required reoperation), chest infection (n = 4), bronco-pleural fistula (n = 3), pulmonary embolism (n = 3; 2 fatal), displacement of diaphragmatic prosthesis with herniation (n = 3; 1 patient required reoperation), respiratory insufficiency (n = 2), deep vein thrombosis (n = 2), acute respiratory distress syndrome (n = 1), cerebral ischemia (n = 1), and wound infection (n = 1). The major perioperative morbidity was 7.6%. There was a statistically significant difference in the postoperative complication rate between P/D and EPP (($\chi^2_{1df} = 10.695$; $p < 0.001$).

In the P/D group, 159 patients (78.7%) received chemotherapy, but only 13 (6.4%) received adjuvant radiotherapy. In the EPP group, 206 patients (68.4%) received chemotherapy and 149 patients (49.5%) received also radiotherapy. There was a statistical difference in the number of patients who were able to receive chemotherapy between the two surgical groups ($\chi^2_{1df} = 6.409$; $p = 0.014$).

At the time of analysis, the median duration of observation was 6.7 years (range, 0.1–14.8). Two hundred thirty patients (17.7%) were alive. Five hundred twenty-two patients

(40.3%) died within 1 year. The duration of observation for patients living more than 1 year was 6.7 years (range, 1.1–14.8). Twenty-six patients (3.1%) in the nonsurgical group are still alive, compared with 23 patients (14.8%) in the P/D group and 43 (14.4%) in EPP group. Median survival of the entire study population was 14.5 months (95% CI, 13.5–15.2). Patients who received palliative treatment or chemotherapy alone had an overall median survival of 11.7 months (range, 10.5–12.5 months), a 2- and 5-year survival rate of 19% (95% CI, 0.16–0.22) and 4% (95% CI, 0.03–0.05).

Patients who underwent P/D had a median survival of 20.5 months (95% CI, 18.2–23.1) and a 2- and 5-year survival rate of 40% (95% CI, 0.32–0.48) and 10% (95% CI, 0.06–0.16). Patients who underwent EPP had a median survival of 18.8 months (95% CI, 17.2–20.9), and a 2- and 5-year survival rate of 37% (95% CI, 0.31–0.42) and 12% (95% CI, 0.07–0.17). Median survival of patients undergoing surgical resection with adjuvant therapy was significantly longer than that of patients undergoing chemotherapy only (19.8 versus 11.7 months; $\chi^2_{2df} = 74.541$; $p < 0.0001$; Fig. 1).

Analyzing the three groups before and after the introduction of pemetrexed as first-line chemotherapeutic agent for MPM, there was an improvement in survival after the introduction of pemetrexed in all three groups: in the nonsurgical group, the median survival increased from 10.9 (95% CI, 9.6–11.9) to 15.3 (95% CI, 13.2–17.0) months, in the PD group from 19.5 (95% CI, 16.0–22.2) to 23 (95% CI, 19.5–28.4) months and in the EPP group from 17.2 (95% CI, 15.2–18.8) to 23.3 (95% CI, 19.0–27.0) months; although the prognosis for each group improved before and after the introduction of pemetrexed, it was not detected a statistically significant impact of treatment on the OS hazard ratio before and after the introduction of pemetrexed ($\chi^2_{2df} = 2.198$; $p = 0.333$).

Moreover, analyzing the survival stage by stage in the three groups of patients, no statistically significant interaction was detected between the type of treatment and the clinical stages in terms of overall survival ($\chi^2_{5df} = 2.201$; $p = 0.821$). Among the pathological stages, a statistically significant interaction was detected between the surgical groups, and the pathological stage IV median OS was 28.0 (95% CI, 10.5–73.7) months and 10.9 (95% CI, 5.3–13.6) months for EPP and PD groups, respectively ($\chi^2_{1df} = 9.765$; $p = 0.002$); however, this result should be considered with extreme caution because of the large amount of missing data and the small sample size of stage IV patients (17 patients in EPP group and 20 patients in PD group; see Supplemental Figures 1–7, Supplemental Digital Content 2, http://links.lww.com/JTO/A518).

At univariate analysis, factors that predicted a better prognosis were age, epithelioid histology, chemotherapy, and surgical treatment (Table 2). The cutoff that better discriminated the prognosis for age was 70 years (hazard ratio, 1.63; 95% CI, 1.43–1.86). There was no correlation with sex and survival. The worse prognosis was correlated to the sarcomatoid subtype. Chemotherapy increased the survival both in surgical and nonsurgical patients. Surgery reduced the risk of death compared with chemotherapy or palliative treatment alone.

According to multivariate analysis (Table 3), age, histology, and surgical treatment were independent prognostic factors

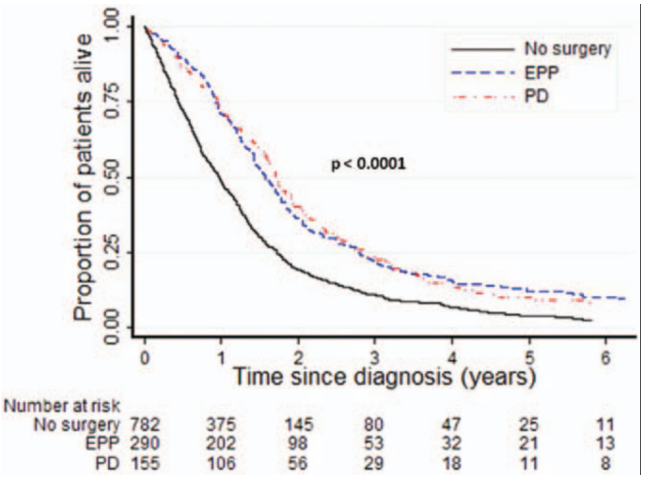

FIGURE 1. Kaplan–Meier survival curves according to the treatment (nonsurgical treatment versus EPP versus P/D). EPP, extrapleural pneumonectomy; P/D, pleurectomy/decortications.

TABLE 2. Univariate Survival Analysis (N = 1227)

Variable	HR	95% CI	*p*
Sex			
Male	1	—	0.309
Female	0.94	0.83–1.06	
Age (yr)	1.02	1.01–1.03	<0.001
Histology			
Epithelioid	1		<0.001
Biphasic	1.58	1.33–1.87	
Sarcomatoid	1.98	1.52–2.58	
Chemotherapy			
No	1		<0.001
Yes	0.59	0.52–0.67	
Treatment			
Nonsurgical	1		<0.001
EPP	0.58	0.50–0.67	
P/D	0.57	0.47–0.69	

Data of potential prognostic factors are expressed in terms of HR and 95% CI.
HR, hazard ratio; CI, confidence interval; EPP, extrapleural pneumonectomy; P/D, pleurectomy/decortications.

associated with survival. Patients younger than 70 years, with epithelioid mesothelioma, who received chemotherapy, had the best prognosis in all surgical and nonsurgical groups.

When the impact of surgery was evaluated in the subset of patients with best prognosis (younger than 70 years, with epithelioid mesothelioma who had received chemotherapy; n = 313), P/D showed the best median survival (24.6 months; 95% CI, 20.5–29.0), followed by EPP (20.9 months; 95% CI, 17.6–23.4 months) and nonsurgical patients (18.6 months; 95% CI, 16.2–24.9). However, this difference was not statistically significant ($\chi^2_{2df} = 1.036$; $p = 0.596$; Fig. 2).

DISCUSSION

The best treatment option for patients with MPM remains controversial, because solid evidence-based results

TABLE 3. Multivariate Survival Analysis (N = 1227)

Variable	HR	95% CI	*p*
Age (yr)	1.01	1.01–1.02	<0.001
Histology			
Epithelioid	1	—	<0.001
Biphasic	1.42	1.18–1.71	
Sarcomatoid	1.99	1.51–2.63	
Chemotherapy			
No	1	—	0.309
Yes	0.91	0.77–1.09	
Treatment			
Nonsurgical	1	—	0.001
EPP	0.77	0.64–0.93	
P/D	0.69	0.55–0.86	

Data of potential prognostic factors are expressed in terms of HR and 95% CI.
HR, hazard ratio; CI, confidence interval; EPP, extrapleural pneumonectomy; P/D, pleurectomy/decortications.

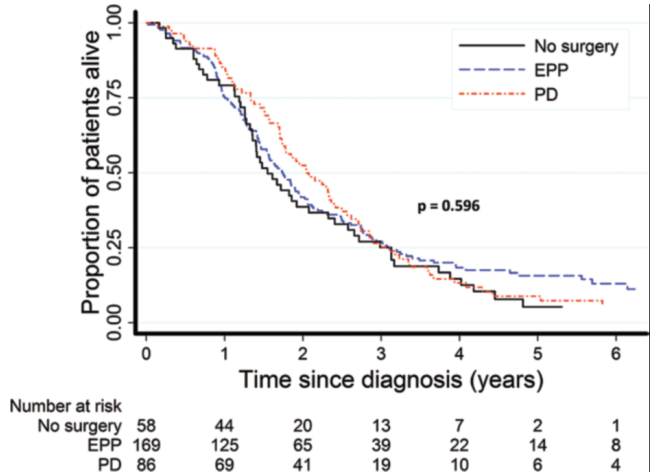

FIGURE 2. Kaplan–Meier survival curves according to the treatment (nonsurgical treatment versus EPP versus P/D) considering only patients with favorable prognostic factors. EPP, extrapleural pneumonectomy; P/D, pleurectomy/decortications.

are lacking. An accurate clinical staging system would be extremely important in assessing the benefit of different treatments. However, clinical evaluation of tumor extent remains poor and the high proportion of understaged patients makes very difficult to select optimal candidates for multimodality treatment or chemotherapy alone.

If pemetrexed-based chemotherapy is generally considered the standard of care for patients with MPM, the role of surgery remains questionable. Moreover, there is a debate among surgeons regarding the role of EPP versus P/D in the multimodality treatment. The aim of surgery is to achieve a macroscopic complete resection to improve the ultimate response to chemo and/or radiotherapy. EPP is performed with an en bloc resection of mediastinal and thoracic parietal pleura, diaphragm, pericardium, and lung. EPP allows higher dose of radiotherapy reducing the local recurrence rate, but this operation leaves patients with major impairment of the postoperative quality of life.[12]

EPP gained wide acceptance after the publications of studies by Sugarbaker et al.[5] and Rusch et al.,[13] showing a favorable outcome in patients with epithelioid histology. The experiences accumulated in patients with best prognostic factors, receiving chemotherapy followed by EPP and adjuvant radiotherapy, showed a 5-year survival rate of more than 40%.[14,15] Although EPP-related mortality is now less than 8% in large-volume centers, less than 60% of the patients complete trimodality treatment because of death or major complications.[16]

In our series, in the EPP group, the overall and major perioperative morbidity were 21.6% and 7.6%, respectively, much lower than the overall morbidity rate of 50% to 68%, and the major complication rate of 23% to 54% reported in several series.[5,9,14,15] In our EPP group, the crude perioperative mortality at 30 and 90 days was 4.1% and 6.9%, respectively, and the overall median survival was 18.8 months, very similar to the results published in the literature, ranging from 12 to 25 months. Most of these literature series are on the basis of retrospective analysis, with only four prospective studies involving patients treated with trimodality therapy and EPP, where the median survival ranged from 16.8 to 25.5 months and the 30-day mortality from 0% to 5%.[14,17–19] These data suggest that EPP can be performed with an acceptable perioperative morbidity and mortality rate in specialized centers.

P/D has long been used in patients with MPM. The P/D is performed removing the visceral and parietal pleura sparing the lung parenchyma. This translates into lower postoperative morbidity and mortality, and a better postoperative quality of life.[12] In 1976, Wanebo et al.[20] reported a median survival of 21 months after pleurectomy, adjuvant radiotherapy, and systemic chemotherapy. More recently, similar outcomes have been reported in patients treated with P/D and adjuvant radiotherapy plus chemotherapy.[21–23] In a systematic review, Teh et al.[24] showed an operative mortality ranging from 0% to 4% and a 3-year survival of 0% to 18% after lung-sparing extirpative surgery. In our series, survival in the entire population was significantly better after surgery and chemotherapy than chemotherapy alone; after P/D, the survival was even better than after EPP, with a median survival of 20.5 months, a postoperative complication rate of 10.4%, and a 30- and 90-day mortality rate of 2.6% and 6%, respectively.

Recently, other authors have reported interesting results after P/D associated with photodynamic therapy[25] or hyperthermic povidone lavage[26] with a median survival of 24 to 30 months, better than patients who underwent EPP. Lang-Lazdunski et al. have shown that survival after incomplete macroscopic resection by P/D is similar to the one of complete macroscopic resection by EPP.

In the present multicenter study, the decision to perform EPP or P/D was left to the individual surgeon, after careful assessment of patient's operative risk, tumor staging, and the possibility to remove all macroscopic tumor. We confirm the results reported by other studies showing similar survival after P/D or EPP with a lower morbidity and mortality after P/D. In our series after the introduction of pemetrexed, our patients showed an improvement of survival in all three groups; surgical patients (P/D and EPP) had a better prognosis than patients undergone palliative treatment or chemotherapy alone, also in the stage by stage analysis,

but this difference lost most of its relevance when other prognostic factors were taken into account. Moreover, the power of each statistical test is drastically reduced in stage by stage analysis, because of the large amount of missing data and the small sample size of pathological stage IV patients (only 37 patients). The variability of MPM populations points out the importance of analyzing surgical data after proper adjustment for clinical prognostic factors that could affect survival, such as age, histology, and staging. In our study, the multivariate analysis showed that age and histology were independent prognostic factors for survival, instead there was no impact of clinical stage and sex. Three large trials had focused on prognostic factors.[27–30] Curran et al. showed that sex had only a moderate significance in the multivariate model, in other series female sex was a significant positive prognostic factor for survival. This uncertainty could be justified by the limited number of females with MPM affecting the prognostic importance of this variable. Among the tumor prognostic factors, the most important was the histology. All trials confirmed the statistical significance of histology, but not of the age. Instead, age was confirmed to be a significant prognostic factor in the series published by Antman.[27–31] Among the tumor prognostic factors, the most important was the histology.[31]

When our analysis was restricted to the subjects with positive prognostic factors, patients showed a similar survival if they had received chemotherapy alone, P/D, or EPP. Overall, our data indicate that survival might be slightly better for surgical patients, with similar outcome for P/D and EPP.

Also, Flores et al.[10] reported that there is still lack of evidence on the real impact of surgery on survival in patients with MPM, showing that other factors influence survival. These data suggest that surgical approach may select a patient population already destined to have a good prognosis even without surgical treatment.

Our series has serious limitations because of its retrospective nature and different therapeutic approaches among the various centers, with biases related also to the different selection criteria and the length of the study period. Whereas, it benefits from including a large number of patients. Our analysis was also limited by the quality of comorbidity data, particularly for the nonsurgical group.

In the literature, there is only one randomized study, the MARS trial, that did not show any advantage of EPP versus chemotherapy alone.[11] This study was not designed to test a survival benefit of multimodality treatment compared with chemotherapy and elicited a strong criticism in the medical community, related to important potential biases in the study design, analysis, and interpretation.[32] As a matter of fact, the trial was an underpowered feasibility study and enrolled a very limited number of patients (50 randomized), and only a fraction of them received the planned therapy; moreover, in the EPP group, the postoperative mortality was 18%, higher than the mortality rate reported in the literature. For all these reasons, the present study, using multivariable analysis, adjusted for possible confounders, on a large population of patients, provides the next best level of evidence.

As a randomized trial of EPP versus P/D is unlikely to be performed, because of the existing data on survival and quality of life after P/D and EPP, it seems that future research efforts should concentrate on the launch of a large multicenter trial comparing P/D after induction chemotherapy versus chemotherapy alone in patients with favorable prognostic factors. To obtain meaningful results, the manner in which surgeons perform P/D needs to be standardized, before testing the impact of P/D versus no-P/D on survival and quality of life. This study could address the fundamental question on the real efficacy of cytoreductive surgery in improving the outcome and survival of patients with resectable malignant mesothelioma.

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