

ORIGINAL ARTICLE

Characteristics and long-term outcomes of advanced pleural mesothelioma in Latin America (MeSO-CLICaP)

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Abstract

Background: Malignant pleural mesothelioma (MPM) is an aggressive tumor, associated with poor prognosis. There is a lack of information about the clinical and pathological features related with survival in the Latin American population.

Methods: The MeSO-CLICaP registry identified 302 patients with advanced MPM diagnosed and treated between January 2008 and March 2016. The Cox model was applied to determine the variables associated with survival. A random forest tree model was built to predict the response to first-line chemotherapy among Latin American patients.

Results: The median age was 61.1 years (SD 10.6 years), 191 (63.2%) were men, 65.9% were ever smokers, and 38.7% had previous exposure to asbestos. A total of 237 (78.5%) had epithelioid tumors, and 188 (62.3%) and 114 (37.7%) cases had stage III or IV MPM, respectively. A total of 49 patients (16.2%) underwent pleurectomy, 57 (18.9%) received radiotherapy, and 279 patients received first-line platinum-based chemotherapy. The overall response rate to first-line chemotherapy was 40.4%, progression-free survival to first-line treatment was 5.7 months (95% CI 4.9–6.5), and 63 (20.8%) patients had pemetrexed maintenance. The median overall survival was 16.8 months (95% CI 13.0–20.5), and multivariate analysis found that stage ($P = 0.013$), and pleurodesis ($P = 0.048$),

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Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumor associated with poor outcomes. Considered in the past as a rare disease, it has become more frequent in recent years.¹ Occupational asbestos exposure is the principal risk factor for developing MPM, and explains the rise in incidence since the 1960s.^{1,2} Although the use of asbestos has been banned in most European countries and the USA, it is still used in large amounts in underdeveloped countries, such as in Latin America. In fact, Brazil is one of the world's top asbestos producers, and mortality for MPM in Argentina and Brazil is dramatically increasing, reflecting the absence of regulatory laws in regard to asbestos.^{3,4}

MPM is difficult to treat, because most patients have advanced disease at the time of diagnosis, conferring a poor prognosis. Median overall survival (OS) is approximately one year, and cure is rare.^{5,6} Treatment options for patients with MPM include surgery, radiation therapy, and/or chemotherapy⁷; however, for most patients, only palliative chemotherapy is possible due to the advanced disease at diagnosis.

The palliative effect of combination chemotherapy for patients with MPM has been documented previously.^{8,9} The experience from the Royal Marsden Hospital focused on the palliative benefits of mitomycin C, vinblastine and cisplatin. That study demonstrated an objective response rate of 13.5%, with a median OS of 7 months, and 69% of patients reported some improvement of symptoms.¹⁰ In addition, another trial randomly compared first-line (FL) chemotherapy (either mitomycin, vinblastine, cisplatin [MVP], or vinorelbine) with active supportive care¹¹ although no OS benefit or improvement in quality of life was seen in the intention-to-treat population, exploratory analyses suggested a survival advantage for those treated with vinorelbine, with a two months survival benefit over active supportive care that approached statistical significance. Two large randomized trials have proved the benefit

were independent prognostic factors for first-line overall survival. The model to predict response to first-line chemotherapy obtained a 0.98 area under the curve, a sensitivity of 93%, and a specificity of 95% for detecting responders and non-responders.

Conclusion: This study identifies factors associated with clinical benefit from chemotherapy among advanced MPM Latin American patients, emphasizing the impact of histology and the clinical benefit of chemotherapy on outcomes.

of the addition of a folate antagonist to cisplatin.^{12,13} A large prospective trial including 456 patients comparing cisplatin alone with cisplatin and pemetrexed demonstrated a significantly better response rate (17% vs. 41%) and median OS (9.3 months vs. 12.1 months) with the cisplatin–pemetrexed combination over cisplatin alone.¹²

The role of second-line (SL) chemotherapy in MPM needs to be investigated. Pemetrexed alone or in combination with carboplatin has yielded objective responses of 18–21% in a small series of patients with disease progression after cisplatin chemotherapy.¹⁴ A prospective randomized phase III study enrolling 243 patients examined the role of pemetrexed versus best supportive care.¹⁵ That study demonstrated a better disease control rate for the pemetrexed arm (59% vs. 19%); however, there was no significant survival benefit. The survival results might have been influenced by post-discontinuation chemotherapy, which was given to 28% of patients in the pemetrexed group and 51% of patients in the best supportive care group. The question of how to treat patients with progression after cisplatin and pemetrexed remains unanswered. Gemcitabine, vinorelbine, raltitrexed, oxaliplatin, nintedanib, and nivolumab have demonstrated activity when used in SL therapy and might be reasonable choices.^{16–18} The available scientific evidence about the clinical and pathological features related with survival in the Latin American population is scarce.

In this retrospective analysis, we characterized a group of patients with MPM from nine Latin American countries included in The MeSO-CLICaP registry, describing the main pathological and clinical features, as well as clinical outcomes and factors related with survival.

Methods

The MeSO-CLICaP registry identified 302 patients with advanced MPM from nine Latin American countries (Argentina, Brazil, Colombia, Costa Rica, Panamá,

México, Perú, Nicaragua, and Venezuela) diagnosed and treated between January 2008 and March 2016. An institutional review board and privacy board waiver was obtained to facilitate retrospective collection of clinicopathological data (MeSO-CLICaP Platform, Clínica del Country, Bogotá, Colombia). Data collected included age, sex, asbestos exposure, clinical manifestations, performance status, histology, disease stage, treatment modalities including chemotherapy (FL and beyond), and date of death or last follow up. Outcomes, such as progression free survival (PFS), overall survival (OS), and overall response rate (ORR) were recorded. The Cox model was applied to determine variables associated with survival. As these patients were not participants of a prospective protocol, imaging frequency was variable, and took place on average every two to three months. Patients with incomplete or unknown treatment data were excluded from treatment analyses.

This study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice.

Random forest-tree model design to predict response to FL chemotherapy in pleural mesothelioma among Latin American patients

A random forest tree model was built for the prediction of response to FL chemotherapy among Hispanic patients with MPM. The variables included were sex, age, Eastern Cooperative Oncology Group (ECOG) performance status, smoking history, exposure to asbestos, and histology. Based on these characteristics, patients were classified as responders (partial or complete response) and non-responders (stable disease or disease progression). In order to validate the results, a random subset of 70% of the sample was used to construct the model, and the remaining 30% was utilized as an independent validation cohort. Predictions were compared with each patient's treatment response and operational characteristics for the validation cohort model, and receiver operational curves were computed.

Statistical analysis

For descriptive purposes, continuous variables were summarized as arithmetic means and standard deviations. Categorical variables were reported as frequencies and proportions. Inferential comparisons were performed using Student's *t*-test. The χ^2 -test or Fisher's exact test were used to assess the significance among categorical variables. OS and PFS were estimated using the Kaplan–Meier Method. OS to FL, SL, and third-line (TL) therapy were estimated

since the date of treatment beginning until death or last follow up. PFS to FL, SL, and TL therapy was calculated from the date of treatment initiation until disease progression or last follow up.

Comparison among survival times was performed using the log-rank test or Breslow according to graphical assessment. A multivariate Cox proportional regression analysis was carried out to assess the independently associated factors with either OS or PFS. Statistical significance was considered when $P \leq 0.05$ using a two-sided test. All of the statistical analyses were performed using SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA).

Table 1 General characteristics of patients ($n = 302$)

	% (n/N)
Gender	
Female	36.8 (111/302)
Male	63.2 (191/302)
Age	
Mean (\pm SD)	61.1 (10.6)
<60 years	42.4 (128/302)
\geq 60 years	57.6 (174/302)
Smoking exposure	
Current smoker	23.8 (72/302)
Former smoker	42.1 (127/302)
Never smoker	32.8 (99/302)
NA	1.3 (4/302)
Exposure to asbestos	
Present	38.7 (117/302)
Absent	46.7 (141/302)
NA	14.6 (44/302)
ECOG status	
<2	75.5 (228/302)
\geq 2	23.8 (72/302)
NA	0.7 (2/302)
Histology	
Epithelioid	78.5 (237/302)
Sarcomatoid	5.6 (17/302)
Mixed	10.6 (32/302)
NA	5.3 (16/302)
Pleural effusion	
Present	75.5 (228/302)
Absent	14.2 (43/302)
NA	10.3 (31/302)
Disease stage	
III	37.7 (114/302)
IV	62.3 (188/302)
Main site of metastases*	
Liver	12.8 (24/188)
Bone	12.8 (24/188)
Lung	68.1 (128/188)
Other	5.9 (11/188)

For variables (*) denominator changes and percent is calculated only for those with a metastatic disease (stage IV). ECOG status, Eastern Cooperative Oncology Group performance status; NA, not available; SD, standard deviation.

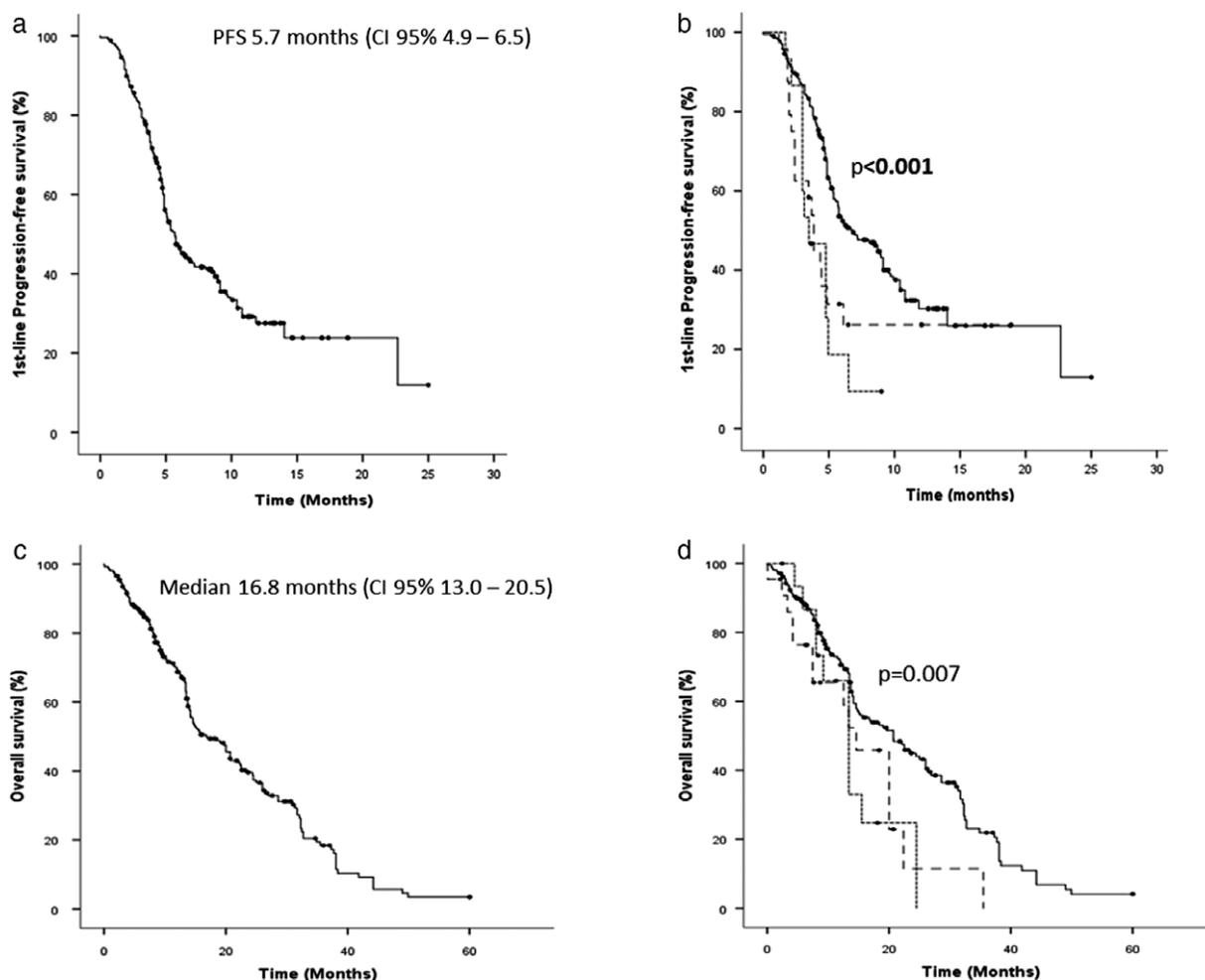


Figure 1 (a) Progression-free survival (PFS) to first-line (FL) therapy. (b) PFS to FL therapy according to histology. Histology, Epithelioid (—) 6.7 months (CI 95% 4.9–8.5), Sarcomatoid (---) 3.5 months (CI 95% 2.1–4.9) and Mixed (· · ·) 3.8 months (CI 95% 3.3–4.4). (c) Overall survival (OS) to FL therapy. (d) OS to FL therapy according to histology. Histology, Epithelioid (—) 20.7 months (CI 95% 14.78–26.6), Sarcomatoid (---) 13.4 months (CI 95% 10.1–16.6) and Mixed (· · ·) 14.7 months (CI 95% 9.7–19.6).

Results

Patient's characteristics

Among the 302 patients included, the median age was 61.1 years (SD 10.6 years), 191 (63.2%) were men, 199 (65.9%) were ever smokers, and 117 (38.7%) had previous exposure to asbestos. A total of 228 patients (75.5%) had a baseline ECOG 0–1, 237 (78.5%) were epithelioid tumors, and 114 (37.7%) and 188 (62.3%) cases had stage III or IV MPM. Table 1 shows the main characteristics of these patients.

FL therapy

Just 49 patients (16.2%) underwent pleurectomy, 57 (18.9%) received radiotherapy, 279 patients received

platinum-based chemotherapy in FL (plus pemetrexed 148/53% and gemcitabine 129/46.2%), and two patients received monotherapy (0.7%; Table 2). A total of 63 patients had pemetrexed maintenance (mean number of cycles 5.6 ± 3). The ORR to FL chemotherapy was 40.4%

Table 2 Diagnosis and therapeutic intervention

	n	%
Pleurodesis for diagnosis and pleural effusion control	112	37.1
Pleurectomy ± tumor decortication of the lungs for debulking and major cytoreduction	49	16.2
Intensity-modulated radiation therapy	57	18.9
First line chemotherapy (platinum base)	279	92.4
Platinum/pemetrexed ± bevacizumab†	148	53.0
Other combinations with platinum (gemcitabine)	129	46.2
Monotherapy	2	0.7

†Three patients received bevacizumab

Table 3 Univariate and multivariate analysis of the clinical factors associated with progression-free survival to first-, second-, and third-line treatment among patients with malignant pleural mesothelioma

	PFS to first line			PFS to second line			PFS to third line		
	Univariate		Multivariate	Univariate		Multivariate	Univariate		Multivariate
	Median, 95% CI	P-value	HR, 95% CI	Median, 95% CI	P-value	HR, 95% CI	Median, 95% CI	P-value	HR, 95% CI
Overall	5.7 (4.9–6.5)			4.8 (3.9–5.6)			5.3 (4.7–5.9)		
Gender									
Female	5.7 (4.8–6.7)			4.8 (3.3–6.3)			5.1 (4.5–5.6)		
Male	5.5 (4.3–6.7)	0.764		4.7 (3.6–5.8)	0.451		6.2 (3.9–8.5)	0.127	
Age									
<60 years	8.7 (4.9–12.5)			6.4 (5.7–7.2)			5.8 (5.2–6.4)		
≥60 years	5.0 (4.3–5.7)	0.005	1.5 (1.0–2.2)	0.039	0.042	1.0 (0.7–1.6)	3.6 (1.9–5.3)	0.79	
Smoking exposure									
Never smoker	4.9 (4.5–5.5)			4.8 (4.4–5.2)			5.9 (1.4–10.3)		
Ever smoker	6.7 (4.2–9.1)	0.039	1.1 (0.7–1.7)	4.8 (3.3–6.4)	0.18	1.0 (0.6–1.7)	5.3 (4.5–6.1)	0.408	
Exposure to asbestos									
Absent	5.7 (4.9–6.6)			5.8 (4.5–7.1)			4.3 (2.6–5.9)		0.001
Present	6.1 (4.5–7.7)	0.455		4.4 (3.9–5.0)	0.418		NR (NR)	0.001	0.2 (0.0–0.7)
ECOG status									0.011
<2	5.5 (4.5–6.6)			4.8 (3.8–5.7)			5.9 (4.1–7.6)		
≥2	5.7 (5.1–6.4)	0.944		4.6 (3.5–5.8)	0.693		5.3 (4.7–5.9)	0.763	
Disease stage									
III	5.4 (4.2–6.5)			5.9 (4.9–6.9)			9.8 (2.7–16.9)		
IV	5.7 (4.5–6.9)	0.437		4.6 (4.1–5.2)	0.528		5.3 (4.7–5.9)	0.048	
Histology									
Epithelioid	6.7 (4.9–8.5)			5.8 (4.9–6.7)			5.9 (5.3–6.5)		
Sarcomatoid	3.5 (2.1–4.9)			4.2 (3.5–4.9)			2.9 (NR)		
Mixed	3.8 (3.3–4.4)	0.001	1.3 (0.9–1.7)	2.1 (0.6–3.6)	<0.001	1.9 (1.3–2.9)	1.4 (NR)	<0.001	6.5 (2.2–19.1)
Pemetrexed maintenance									0.001
Absent	6.1 (4.5–7.6)			4.1 (4.0–4.2)			7.8 (5.8–9.8)		
Present	5.4 (4.7–6.0)	0.353		5.9 (4.7–7.2)	0.001	0.6 (0.4–0.9)	5.3 (4.2–6.4)	0.998	
Pleuroctomy									
Yes	NR (NR)			6.1 (4.9–7.4)			NR (NR)		
No	5.1 (4.5–5.7)	<0.001		4.6 (3.9–5.4)	0.036	1.9 (0.9–3.6)	5.3 (4.5–6.1)	0.072	1.0 (0.3–3.7)
Pleurodesis									
yes	6.7 (4.3–9.1)			6.1 (3.5–8.7)			5.3 (4.7–5.9)		
no	4.9 (4.4–5.6)	0.091	1.3 (0.9–1.8)	4.3 (3.8–4.9)	<0.001	1.7 (1.1–2.8)	5.8 (0.0–12.4)	0.765	
Received radiotherapy									
Yes	10.4 (9.2–11.6)			6.1 (4.7–7.6)			5.3 (4.1–6.5)		
No	4.9 (4.6–5.1)	<0.001	2.1 (1.3–3.4)	4.6 (4.3–4.9)	0.629		4.8 (3.4–6.1)	0.240	
ORR to first line									
Yes	...			8.7 (6.2–11.3)			6.2 (5.7–6.7)		

Table 3 Continued

	PFS to first line			PFS to second line			PFS to third line			
	Univariate		Multivariate	Univariate		Multivariate	Univariate		Multivariate	
	Median, 95% CI	P-value	HR, 95% CI	Median, 95% CI	P-value	HR, 95% CI	Median, 95% CI	P-value	HR, 95% CI	
ORR to second line	4.2 (3.7–4.6)	<0.001	2.9 (1.8–4.7)	<0.001	5.1 (4.0–6.1)	0.239	
Yes	9.8 (5.9–13.6)			
No	3.8 (2.7–4.9)	<0.001	2.5 (1.1–5.7)	0.028
First line TTP ≥12 months										
No				4.6 (4.1–4.9)			5.3 (4.6–5.9)			
Yes				6.1 (4.9–7.4)	0.032		9.8 (6.3–13.2)	0.488		

Bold values represent $P \leq 0.05$, 95% CI, 95% confidence interval; ECOG status; Eastern cooperative Oncology Group performance status; HR, hazard ratio; MPM, malignant pleural mesothelioma; NR, not reached; ORR, overall response rate (includes complete and partial response assessed by RECIST v1.1); TTP, time to progression.

(complete response 4%/partial response 29.7%), and PFS was 5.7 months (95% CI 4.9–6.5; Fig 1a). In the univariate analysis, age <60 years (8.7 vs. 5.0, $P = 0.005$), ever versus never smokers (6.7 vs. 4.9 months, $P = 0.039$), epithelioid versus sarcomatoid or mixed histology (6.7 vs. 3.5 vs. 3.8 months, $P = 0.001$; Fig 1b) and pleurectomy (not reached vs. 5.1; $P \leq 0.001$) were associated with better PFS in FL therapy. In the multivariate analysis age (HR 1.5, 95% CI 1.1–2.2, $P = 0.039$) and histology (HR 1.3, 95% CI 0.9–1.7, $P = 0.001$) were the only factors independently associated with PFS in FL therapy (Table 3). Median OS was 16.8 months (95% CI 13.0–20.5; Fig 1c). In the univariate analysis, ever versus never smokers (22.5 vs. 14.7 months, $P = 0.005$), a better ECOG performance status (<2 vs. >2; 18.4 vs. 13.5 months; $P = 0.048$), disease stage (III vs. IV; 20.7 vs. 14.6 months, $P = 0.025$), epithelioid versus sarcomatoid or mixed histology (20.7 vs. 13.4 vs. 14.7 months, $P = 0.007$; Fig 1d), pemetrexed maintenance (20.7 vs. 14.6 months, $P = 0.051$), and pleurectomy (22.4 vs. 14.9 months) were associated with better OS to FL therapy. Multivariate analysis demonstrated that disease stage (HR 1.6, 95% CI 1.1–2.4, $P = 0.013$) was the only independent prognostic factor for OS to FL treatment (Table 4).

Prediction of response for FL chemotherapy

The validated model obtained a sensitivity of 93% and a specificity of 95% for detecting responders and non-responders to FL chemotherapy (Fig S1). The model yielded a receiver operator curve with a corresponding area under the curve of 0.98 (Fig S2). When predicted responders and non-responders were compared, a survival benefit in terms of OS to FL and SL was observed ($P < 0.001$ for both cases; Fig S3).

SL therapy and beyond

Of the 302 patients included, 126 (41.7%) received some treatment after FL, 98 patients (32.4%) achieved a response (partial response 39/12.9% and SD 59/19.5%), and 18 (5.9%) had a time-to-progression ≥ 8.0 months. Median PFS to SL therapy was 4.8 (95% CI 3.9–5.6; Fig 2a). Median OS to SL therapy was 14.6 months (95% CI 11.4–17.8; Fig 2b).

In the univariate analysis, the factors associated with better PFS to SL therapy were age <60 years (6.4 vs. 4.4 months, $P = 0.042$), epithelioid versus sarcomatoid or mixed histology (5.8 vs. 4.2 vs. 2.1 months, $P \leq 0.001$), pemetrexed maintenance (5.9 vs. 4.1 months, $P = 0.001$), pleurectomy (6.1 vs. 4.6 months, $P = 0.036$), and ORR to FL therapy (8.7 vs. 4.2 months, $P \leq 0.001$). In the

Table 4 Univariate and multivariate analysis of the clinical factors associated with overall survival to first, second and third line treatment among patients with malignant pleural mesothelioma

	OS				OS to second line				OS to third line			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	Median, 95% CI	P-value	HR, 95% CI	P-value	Median, 95% CI	P-value	HR, 95% CI	P-value	Median, 95% CI	P-value	HR, 95% CI	P-value
Overall	16.8 (13.0–20.5)				14.6 (11.4–17.8)				9.9 (7.6–12.3)			
Gender												
Female	18.4 (11.9–24.9)				15.1 (14.2–15.9)				6.8 (6.4–7.2)			
Male	15.5 (10.8–20.2)	0.789			11.3 (7.3–15.4)	0.822			9.9 (7.1–12.8)	0.037		1.3 (0.8–1.9) 0.261
Age												
<60 years	20.7 (16.9–24.4)				15.4 (14.4–16.5)				10.4 (8.6–12.2)			
≥60 years	14.7 (12.7–16.6)	0.222			10.9 (9.0–12.8)	0.204			5.9 (5.1–6.7)	0.09		0.9 (0.6–1.5) 0.901
Smoking exposure												
Never smoker	14.7 (12.6–16.8)				14.0 (10.4–17.7)				9.9 (5.2–14.7)			
Ever smoker	22.5 (14.6–30.4)	0.005	0.7 (0.5–1.0)	0.081	15.1 (11.9–18.3)	0.229			9.9 (6.5–13.4)	0.062		0.9 (0.5–1.4) 0.549
Exposure to asbestos												
Absent	16.8 (9.6–23.9)				14.3 (10.2–18.4)				6.8 (5.9–7.7)			
Present	20.0 (15.7–24.4)	0.285			15.9 (13.9–17.9)	0.521			10.3 (8.3–12.2)	0.08		
ECOG status												
<2	18.4 (14.6–22.2)				13.4 (9.6–17.3)				9.9 (6.5–13.4)			
≥2	13.5 (11.4–15.6)	0.048*	1.4 (0.9–2.2)	0.098	15.1 (13.8–16.4)	0.542			8.1 (0.7–15.5)	0.545		
Disease stage												
III	20.7 (17.9–23.4)				15.9 (14.5–17.3)				10.4 (6.2–14.6)			
IV	14.6 (12.4–16.8)	0.025	1.6 (1.1–2.4)	0.013	11.9 (8.8–15.1)	0.079			8.0 (5.7–10.3)	0.091		1.7 (1.1–2.7) 0.023
Histology												
Epithelioid	20.7 (14.8–26.6)				15.2 (14.1–16.4)				9.9 (7.9–12.0)			
Sarcomatoid	13.4 (10.1–16.7)				9.8 (5.6–13.9)				5.0 (NR)			
Mixed	14.7 (9.7–19.6)	0.007	1.4 (1.0–1.8)	0.187	14.0 (5.2–22.9)	0.024	1.4 (0.9–2.2)	0.157	11.7 (NR)	0.614		
Pemetrexed maintenance												
Absent	14.6 (12.7–16.6)				14.6 (11.9–17.3)				9.9 (9.2–10.7)			
Present	20.7 (14.7–26.7)	0.051*			14.3 (9.5–19.1)	0.217			8.1 (4.2–12.1)	0.962		
Pleurectomy												
Yes	22.4 (14.3–30.5)				11.0 (7.5–14.5)				9.9 (7.5–12.4)			
No	14.9 (11.0–18.9)	0.041	1.4 (0.9–2.3)	0.187	15.1 (12.7–17.5)	0.974			9.2 (6.2–12.2)	0.862		
Pleurodesis												
Yes	22.1 (18.7–25.6)				15.4 (13.1–17.8)				10.3 (5.7–14.8)			
No	14.2 (12.7–15.6)	0.038	1.4 (1.0–2.1)	0.048	11.9 (8.3–15.7)	0.066	1.4 (0.9–2.2)	0.125	8.1 (3.3–12.9)	0.175		1.3 (0.8–2.0) 0.270
Received radiotherapy												
Yes	20.0 (14.5–25.6)				14.6 (9.3–19.8)				6.8 (6.5–7.2)			
No	14.2 (12.6–15.8)	0.420			12.2 (7.7–16.6)	0.925			8.1 (4.4–11.8)	0.815		
ORR to first line												
Yes	31.7 (27.9–35.4)				17.4 (13.2–21.6)				10.3 (8.8–11.7)			
No	13.5 (12.9–14.0)	<0.001			9.9 (9.4–10.3)	<0.001	2.6 (1.6–4.3)	<0.001	6.5 (5.7–7.4)	0.003		2.2 (1.3–3.6) 0.004

Table 4 Continued

	OS				OS to second line				OS to third line			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	Median, 95% CI	P-value	HR, 95% CI	P-value	Median, 95% CI	P-value	HR, 95% CI	P-value	Median, 95% CI	P-value	HR, 95% CI	P-value
ORR to second line												
Yes	32.7 (31.0–34.3)				22.5 (19.1–25.9)				11.4 (9.7–13.1)			
No	14.9 (12.2–17.6)	<0.001		<0.001	10.1 (8.8–11.4)				6.8 (6.2–7.5)	0.009		0.001
First line TTP ≥12 months												
No	14.7 (12.7–16.6)				12.2 (8.8–15.6)				9.2 (5.9–12.5)			
Yes	32.1 (20.5–43.6)	<0.001		0.020*	15.9 (14.6–17.2)				9.9 (7.9–11.9)			0.319

Bold values represent $P \leq 0.05$. 95% CI, 95% confidence interval; ECOG status, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; MPM, malignant pleural mesothelioma; NR, not reached; ORR, overall response rate (includes complete and partial response assessed by RECIST v1.1); TTP, time to progression.

multivariate analysis, the factors independently associated with a better PFS after SL therapy were histology (HR 1.9, 95% CI 1.3–2.9, $P = 0.001$), and pemetrexed maintenance (HR 0.6, 95% CI 0.4–0.9, $P = 0.021$; Table 3). The median OS to SL therapy was 14.6 months (95% CI 11.4–17.8). In the univariate analysis, the factors associated with better OS after SL therapy were histology (epithelioid vs. sarcomatoid vs. mixed) (15.2 vs. 9.8 vs. 14.0 months, $P = 0.024$), ORR to FL therapy (17.4 vs. 9.9 months, $P \leq 0.001$) and a time to progression above one year to FL therapy (15.9 vs. 12.2 months, $P = 0.020$). In the multivariate analysis, the ORR to FL therapy (HR 2.6, 95% CI 1.6–4.3, $P \leq 0.001$) was the only independently associated factor with OS after SL therapy (Table 4).

A total of 81 patients (26.8%) received a TL therapy achieving a disease control rate of 67.4% and a PFS of 5.3 months (95% CI 4.7–5.9). In the multivariate analysis, the factors independently associated with PFS after TL therapy were exposure to asbestos (HR 0.2, 95% CI 0.0–0.7, $P = 0.011$), histology (HR 6.5, 95% CI 2.2–19.1, $P = 0.001$) and achieving an ORR to SL treatment (HR 2.5, 95% CI 1.1–5.7, $P = 0.028$; Table 3). OS to TL therapy was 9.9 months (95% CI 7.6–12.3). The ORR to FL (HR 2.2, 95% CI 1.35–3.6, $P = 0.004$) and ORR to SL (HR 2.6, 95% CI 1.5–4.5, $P = 0.001$) were independently associated factors for OS to TL therapy in the multivariate analysis (Table 4).

Discussion

Several prognostic factors have been identified for MPM, including older age, performance status, male sex, non-epithelioid histology, among others, and prognostic scores systems derived from the combination of them have been proposed and accepted.^{19,20} Meyerhoff *et al.* reviewed the outcomes of a large cohort of patients from the Surveillance, Epidemiology, and End Results Program, USA, database between 2004–2010 identifying that epithelioid tumors had better OS compared with biphasic and sarcomatoid histology types (14, 10, and 4 months, respectively, $P < 0.01$). Similarly, surgical treatment only benefited patients with epithelioid histology (epithelioid MPM HR 0.72, $P < 0.01$; biphasic MPM HR 0.73, $P = 0.19$; sarcomatoid MPM HR 0.79, $P = 0.18$), an outcome that consolidated the use of this intervention in this specific subgroup⁵

In another population-based registry, Linton *et al.* performed an analysis using the New South Wales Dust Diseases Board database during the period 2002–2009, finding 910 patients with MPM. In this large cohort, histology was also related with better survival (13.3 months for epithelioid histology vs. 6.2 months for sarcomatoid or biphasic, $P < 0.001$).⁶ Other series also confirmed the prognostic role of histology.^{21,22} In the present study, we have confirmed

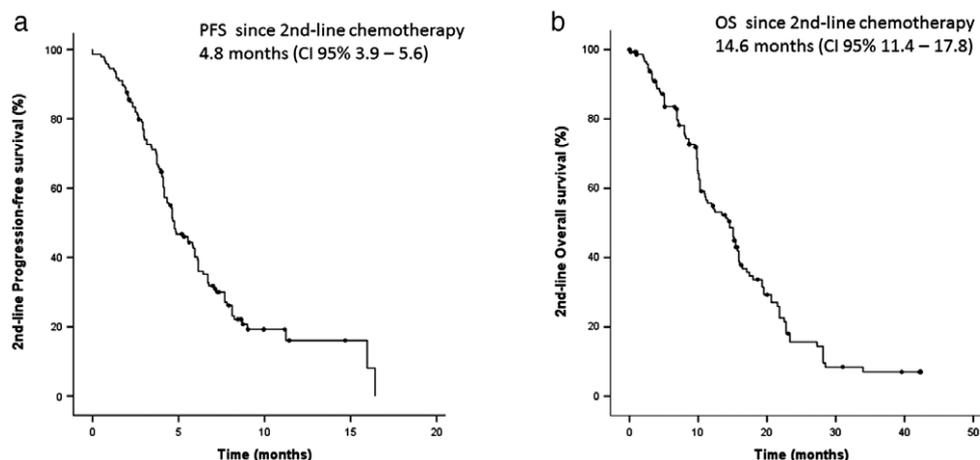


Figure 2 (a) Median progression-free survival (PFS) to second-line (SL) therapy. (b) The median overall survival (OS) to SL therapy was 14.6 months (95% CI 11.4–17.8).

the prognostic relevance of histology, finding a median OS for epithelioid tumors of 20.7 months (95% CI 14.8–26.6). Our survival analysis showed a better outcome compared with other studies, probably because of the selection bias (considering that nearly all of our patients received a FL chemotherapy treatment compared with just 44% in the Linton *et al.* study); however, other series have identified a subgroup of patients with long survival (twice the median of 10 months) regardless of the treatment used, this observation suggests the presence of intrinsic factors that might modify main outcomes.^{6,12,23}

In our series, pemetrexed maintenance in addition to platinum in FL improved PFS, a conclusion previously described by others.^{6,12} Since the Vogelzang *et al.* publication in 2003, platinum-pemetrexed has been a common chemotherapy regimen for MPM; in our series, this was selected for 54% of patients, a frequency similar to data reported by studies from European countries and Australia.¹⁰ In most countries of Latin America, access to medicines for MPM, such as pemetrexed and bevacizumab, is limited. This is why almost half of our population received gemcitabine as part of the FL treatment. More efforts should be made to solve access limitations, and to improve the selection of patients according to the response profile and to the cost-effectiveness of the interventions.

To optimize the selection of Latin American patients who are candidates for medical treatment for MPM in the FL and beyond, we designed and validated a model in our population to predict outcomes. Using age, performance status, and gender, we were able to predict the response and OS to FL chemotherapy with accuracy of 98%. This model has to be validated in other populations as a tool for treatment selection.

The better survival observed in our series can be explained by the proportion of patients treated with radical

surgery (16.2%), or by the chemotherapy treatments, particularly those beyond FL (41.7% of patients received SL or TL chemotherapy) compared with other series. As we mentioned previously, other series have identified a group of patients with prolonged survival irrespective of the type of treatment received. If Latin American patients have genetic variations or molecular subtypes that influence survival, this is an issue that deserves to be further explored. ERCC1, PLK1 and miRNAs are some factors that have been studied and related with prognosis.^{24,25} Furthermore, biomarkers, such osteopontin, mesothelin, and calretinin, may influence prognosis.^{26–28} It would be enriching to evaluate this data in the Latin American population with MPM, and analyze their influence on prognosis or prediction of response to treatment.

To the best of our knowledge, this is the largest series of MPM in the Latin American population, and reflects the real clinical scenario. This study has limitations regarding the selection of patients, and the fact that no molecular or biomarker analyses were performed, which would have been useful to explain some results obtained. In our series, patients had a good response to pemetrexed-based chemotherapy, according to our results we can select patients who could derive more benefit of SL or even TL therapy based on clinical characteristics, such a performance status and response to FL chemotherapy. We advocate for a better treatment selection as a strategy to improve the cost-effectiveness ratio in limited resources scenarios in Latin American countries.

Our study identifies factors associated with a clinical benefit from chemotherapy among Latin American patients with advanced MPM, and emphasizes the impact of histology and clinical benefit from chemotherapy on survival. SL chemotherapy appears to be active in Latin American MPM patients, particularly in younger patients

with good PS and prolonged disease control with FL chemotherapy.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1. Random tree model to predict the response to the first line in Hispanic patients with malignant pleural mesothelioma.

Figure S2. Receiver operator curve for the model to predict response to first line chemotherapy among Hispanic patients with malignant pleural mesothelioma.

Figure S3. (a) Overall survival (OS) for first-line (FL) therapy responders and non-responders. (b) OS for second-line (SL) therapy responders and non-responders.