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Survival of peritoneal malignant mesothelioma in Italy: A population-based study

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In some population-based studies, a shorter median survival was observed in peritoneal as compared with pleural, malignant mesothelioma, but in others, longer median survival times or higher proportions of long-term survivors were reported. Statistical instability could have caused these differences. We analyzed survival in peritoneal mesothelioma in a large and unselected population-based case series. Cases (338) registered from 1990 to 2001 by 9 Italian regional mesothelioma registries contributing to the network of the National Mesothelioma Registry were followed until December 31, 2005. Univariate (Kaplan-Meier) and multivariate (Cox proportional hazards regression) analyses of survival were performed according to selected individual characteristics, including limited treatment information in a subset of 194 cases. The results were compared with those obtained in a parallel study on pleural mesothelioma cases. Epithelioid histotype, younger age at diagnosis and, to a lesser degree, gender (women), and being diagnosed in a hospital with a thoracic surgery unit positively and significantly affected survival. The effect of treatment was positive but not statistically significant. No trend in the risk of death according to calendar period of diagnosis was present. Peritoneal mesothelioma cases had shorter median survival time than pleural cases, but a larger proportion of long-term survivors. Survival patterns after peritoneal and pleural mesothelioma differed markedly. Treatment was not associated with a statistically significant improvement in survival, but our study included cases first diagnosed before the introduction of the most recent therapeutic approaches. This provides a large historical comparison for future studies on survival trends at the population level.

Key words: malignant mesothelioma; peritoneum; survival

Malignant mesotheliomas (MM) share the same histopathologic and immunophenotypic features, irrespective of their primary site of origin.[1] However, the peritoneal serous membrane is affected with considerably lower frequency by MM than the pleurae; in Italy, the incidence of peritoneal malignant mesothelioma (PMM) is more than one order of magnitude lower,[2] despite the fact that in selected occupational groups mortality from PMM has been reported to be close to that of its pleural counterpart.[3,4] A recent review on PMM incidence and mortality in occupational cohorts exposed to asbestos has shown a consistent relationship with exposure, once fiber type is taken into account,[5] but the shape of the dose-effect relationship differed from that observed among the pleural mesothelioma cases.[6,7] This feature may account for the differences in both incidence and mortality between the 2 main MM sites in populations where exposure to asbestos was common. Important differences in latency have also been observed.[4]

The clinical manifestations and consequences of PMM are driven by its specific site of origin. In population-based analyses, survival after PMM diagnosis has been observed to be particularly poor. In some studies, a shorter median survival time, as compared with pleural mesotheliomas, was observed[8–10]; however, other researchers reported less unfavorable outcomes in PMM, such as a longer median survival time or a higher proportion of survivors 1 year or more after diagnosis.[11–14] These estimates were based on small numbers of PMM cases and thus were possibly affected by statistical instability. In a highly selected surgical series, considerably longer survival has been found and attributed to improvement in prognosis after aggressive treatment in suitable patients.[15]

The analysis of survival of PMM cases in a large and unselected, population-based, setting, could help to clarify the current prognosis of the disease, compare it with that of pleural MM and provide a basis for assessing the future impact of recent and developing treatment options at the population level.[16] In this article, we present the available data on PMM from the regional sections of the Italian National Registry of Mesotheliomas, obtained in the framework of a study on survival of patients with MM. The results on pleural MM are reported in a separate paper.[17] Some of them will be recalled here, as far as a comparison between peritoneal and pleural MM is appropriate.

Material and methods

Italy was an important producer and importer of raw asbestos until the ban on asbestos production and use was issued in 1992.[18]

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TABLE I – CHARACTERISTICS OF THE REGIONAL OPERATING CENTRES (COR) CONTRIBUTING TO THE STUDY

COR	First year of registration	Population (2001)	Number of cases		Men		Women	
			Total	Mean annual	SIR[1]	95% CI	SIR[1]	95% CI
Piemonte[2]	1990	4,214,677	130	11	2.6	(2.0–3.2)	2.0	(1.5–2.6)
Veneto[2]	1990	4,527,694	64	5	1.4	(0.9–1.8)	1.0	(0.6–1.4)
Liguria[3]	1994	1,571,783	21	3	2.2	(1.1–3.3)	0.6	(0.1–1.2)
Emilia Romagna	1993	3,983,346	45	5	1.2	(0.7–1.7)	1.0	(0.6–1.5)
Toscana	1990	3,497,806	22	2	0.6	(0.3–1.0)	0.3	(0.1–0.5)
Marche	1996	1,470,581	15	3	2.0	(0.7–3.3)	1.2	(0.2–2.2)
Puglia	1993	4,020,707	14	2	0.7	(0.3–1.2)	0.1	(0.0–0.3)
Sicilia[2]	1998	4,968,991	15	4	1.4	(0.6–2.1)	0.3	(0.0–0.7)
Brescia[2]	1992	1,108,776	12	1	1.0	(0.1–1.9)	1.3	(0.3–2.2)

SIR, standardized incidence rate, 95% CI, 95% confidence interval.
[1]Per 1,000,000 person-years. Standard: Italian population at 2001 census.–[2]CORs contributing data on treatment for part of their cases.–[3]Registration limited to the Genoa municipality in 1994 and to the Genoa Province in 1995.

Population-based registration of MM was started independently in the late 1980s at several research institutions, each covering a regional population, to support epidemiological investigations on the etiology of the neoplasm. Based on this experience, a national registry was established in 1993 at the National Institute for Occupational Safety and Health, in compliance with the 1991 Act that made MM registration compulsory.[19] Currently, registration is carried on in 18 regions out of 20 by regional registries—Regional Operating Centres (CORs) of the national registry—covering about 98.5% of the Italian population. Each COR, on the basis of standard guidelines,[20] identifies incident cases, collects the relevant clinical documentation as well as information on exposures, usually through personal interviews based on a standardized questionnaire, and assesses exposures. As incidence estimation and etiology investigation are the primary objectives of the national registry and of its CORs, the follow-up of cases and survival estimation are not mandatory. However, they were carried out on a routine basis by several CORs. Analyses of incidence, asbestos exposure (including latency) and survival have been published.[2,9,21,22]

Our study is based on the data from 9 CORs that provided survival information for PMM cases diagnosed until December 31, 2001. Cases first diagnosed after January 1, 1990, were included in the analysis. The CORs that started their activity after 1990 contributed for part of the study period (Table I). Only CORs that could ensure complete registration of cases for their coverage period and that had followed their cases until December 31, 2005 were included.

Case registration and survival estimate

Notification of new diagnoses of asbestos-related MM is compulsory.[19] However, MM cases, irrespective of their possible causal relationship with asbestos, are mainly identified by active search strategies, according to the national guidelines.[20] Enquiries are made at the most relevant hospital departments, such as chest surgeries and oncology referral centers, the files of all pathology units in public and private hospitals are searched and the records of hospital discharges, available since 1995 at every regional Health Authority, are perused. For every possible case, the relevant clinical information is abstracted and evaluated to assess the confidence in the diagnosis of MM and to establish the date of diagnosis. The diagnosis is classified as: (*i*) "definite" when morphological and, if available, immunophenotypical features were typical of MM, as judged by the referring pathologist; (*ii*) "probable" when they were not typical, but compatible with MM; and (*iii*) "possible" when diagnosis was supported only by clinical assessment and radiological imaging. The date of first diagnosis (incidence date) is established according to the rules adopted by the European Network of Cancer Registries.[23] Exposure assessment has been fully described elsewhere.[21,22] In our study, cases were classified as ever occupationally or nonoccupationally exposed to asbestos, never exposed or unknown.

Vital status is ascertained, following a standard procedure in Italy, by enquiring at the Town Office of the last known municipality of residence and, if the patient moved, by repeating the enquiry until the vital status is known. Date of death or of last follow-up is recorded.

Data on treatment could be provided by 4 CORs (as in Table I) for a fraction of their registered cases. Cases were classified as either ever receiving/not receiving treatment or of unknown status. Data on treatment, abstracted from the original clinical records, were limited to the information that surgical procedures had been carried out (type and date of intervention), or that courses of chemo- and/or radiotherapy had been given (including the treatment start date).

All patients who survived more than 4 years were reexamined by the notifying COR. Cases with a histopathological diagnosis expressed as "well-differentiated papillary mesothelioma" or "malignant mesothelial hyperplasia" (*i.e.*, lesions of uncertain biological behavior) were excluded from analyses.

We excluded 13 cases from our analyses whose diagnosis was classified as possible or that, after revision of their records, had lesions of uncertain biological behavior. The final study dataset consisted of 338 patients.

Statistical analysis

The prognostic effect of the following personal characteristics (predictive variables) have been investigated: gender (men *vs.* women), age at diagnosis (categorized as follows: <55, 55–64, 65–74, 75+), calendar period of diagnosis (4 consecutive 3-year periods, from 1990–1992 to 1999–2001), diagnosis confidence (definite vs. probable), morphology (epithelioid, fibrous/mixed, unspecified), asbestos exposure (ever exposed, never exposed, unknown), type of hospital of diagnosis (hospital with thoracic surgery, without thoracic surgery, unspecified), COR (Piemonte, Veneto, Liguria, Emilia-Romagna, Toscana, Marche, Puglia, Sicilia, Province of Brescia). Information on treatment was used to identify a treated group (*i.e.*, patients receiving (*a*) a surgical procedure of therapeutic, nonpalliative intention, such as radical or cytoreductive exeresis of neoplastic lesions, (*b*) a cycle of chemo- or radiotherapy, (*c*) either treatment (*a*) or (*b*)), an untreated group (consistent information that these patients were never treated) and a group of unknown status (due to incomplete clinical records).

Survival time was computed starting from the diagnosis date up to death or last follow-up date; observations were censored at 72 months after diagnosis because of the very small fraction of individuals surviving longer. Observed survival was assessed using the Kaplan-Meier method (univariate analyses), and differences in survival curves by category of each predictive variable were assessed by the log-rank test. Differences in the distribution of long- and nonlong-term survivors (cut-off: 48 months) across categories of the predictive variables were assessed by the χ^2 test.

TABLE II – CHARACTERISTICS OF ALL CASES AND OF LONG-TERM SURVIVORS (SURVIVAL TIME ≥ 48 MONTHS)

Characteristics		All cases Number (%)	Long-term survivors Number (%)	*p**
Gender	Men	198 (59)	13 (43)	0.076
	Women	140 (41)	17 (57)	
Age at diagnosis	<55	75 (22)	9 (30)	0.068
	55–64	100 (30)	13 (43)	
	65–74	109 (32)	7 (23)	
	≥75	54 (16)	1 (3)	
Calendar period	1990–1992	44 (13)	2 (7)	0.609
	1993–1995	60 (18)	7 (23)	
	1996–1998	111 (33)	11 (37)	
	1999–2001	123 (37)	10 (33)	
Diagnosis	Definite	296 (88)	28 (93)	0.316
	Probable	42 (12)	2 (7)	
Morphology	Epithelioid	187 (55)	15 (50)	0.103
	Mixed	36 (11)	0	
	Fibrous	14 (4)	2 (7)	
	Unspecified	101 (30)	13 (43)	
Asbestos exposure	Yes	111 (33)	54 (28)	<0.001
	No	17 (5)	2 (1)	
	Unknown	210 (62)	138 (71)	
Hospital	With thoracic surgery	108 (32)	16 (53)	0.012
	Without thoracic surgery	174 (51)	8 (27)	
	Unspecified	56 (17)	6 (20)	
COR (residence)	Piemonte	130 (38)	9 (30)	0.465
	Veneto	64 (19)	8 (27)	
	Liguria	21 (6)	3 (10)	
	Emilia Romagna	45 (13)	2 (7)	
	Toscana	22 (7)	4 (13)	
	Marche	15 (4)	2 (7)	
	Puglia	14 (4)	0	
	Sicilia	15 (4)	1 (3)	
	Brescia (province)	12 (3)	1 (3)	
Total		338 (100)	30 (100)	

*p: cases surviving ≥48 months *versus* cases surviving <48 months.

Multivariate analyses were carried out through Cox modeling of proportional hazards, by fitting first the full model, *i.e.*, the model including all the aforementioned variables, with the exception of exposure to asbestos. Exposure to asbestos was not considered because the number of unexposed cases was too small (see Table II). The subsequent search for a simpler model was limited to assessing the effect of deleting those predictive variables that were not in the list of "*a priori*" interest, which included gender, age class, morphology (fibrous and mixed MM were grouped together because of their small number) and calendar period of diagnosis. The effect of model simplification was assessed by testing the log-likelihood ratio. The assumption of hazards proportionality was tested graphically.

Analyses restricted to the 3 subsets (surgery, chemo-/radiotherapy and surgery or chemo-/radiotherapy) of treated *versus* untreated cases were similarly carried out.

Tests for statistical significance were 2-sided. All analyses were performed using Stata 9.2.[24]

Results

Table II shows the general characteristics of the 338 cases with a definite or probable diagnosis of PMM, along with those of the 30 cases with survival time ≥4 years.

Univariate analyses

The overall median survival time was 5.6 months (95% confidence interval: 5.0–6.7), survivors being 48.5% at 6 months, 29.9% at 1 year, 18.6% at 2, 14.8% at 3, 9.1% at 4 and 8.1% at 5 years (Fig. 1). Among the variables of *a priori* interest, gender (Figs. 2 and 3), age-class, morphology and asbestos exposure had statistically significant effects on survival (details not reported). The same occurred for the type of hospital (whether having or not having a thoracic surgery ward). Confidence of diagnosis, calendar period of diagnosis and COR had no statistically significant effect.

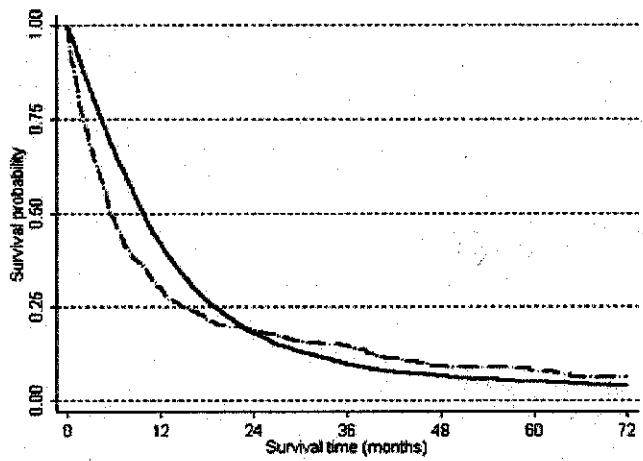

FIGURE 1 – Survival (Kaplan-Meier) of malignant mesothelioma by primary site. Primary site: pleura solid line (——), peritoneum dashed and dotted line (· - - - ·). Men and women.

Main multivariate analysis

The simplest and best data-fitting model included gender, age class, morphology, calendar period of diagnosis and type of hospital as predictive variables, and COR as a stratifying variable (Table III). Male gender, an age at diagnosis of 75 years or more, a fibrous or mixed histological type, and being first diagnosed in a

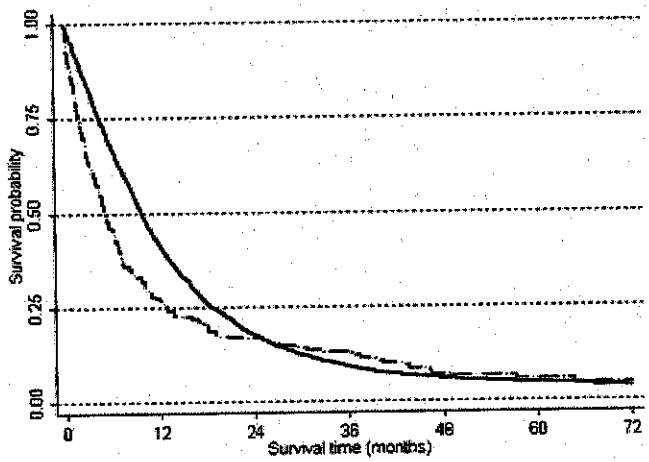

FIGURE 2 – Survival (Kaplan-Meier) of malignant mesothelioma by primary site. Primary site: pleura solid line (——), peritoneum dashed and dotted line (· - · - ·). Men.

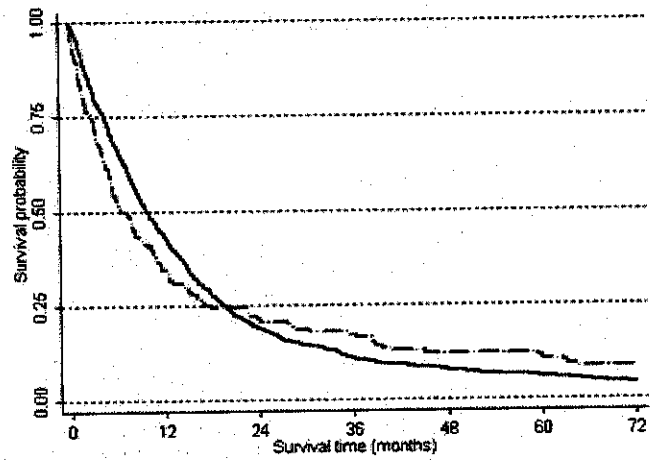

FIGURE 3 – Survival (Kaplan-Meier) of malignant mesothelioma by primary site. Primary site: pleura solid line (——), peritoneum dashed and dotted line (· - · - ·). Women.

hospital without thoracic surgery department were associated with a significantly poorer survival.

Multivariate analysis: Subgroup with data on treatment

Multivariate analysis, restricted to the subgroup of 194 cases that could be classified as definitely ever treated (40) or never treated (154), failed to detect any statistically significant effect of treatment. Considering only patients undergoing surgery (14) or individuals receiving chemo-/radiotherapy (33) gave similar results. For the sake of comparison with the whole dataset, the model shown in Table III included gender, age-class, morphology, calendar period of diagnosis and type of hospital as predictive variables, plus treatment, and used the regional operating centre as a strata defining variable.

Discussion

Estimates of survival from population-based studies on PMM can avoid the selection bias that typically affects observations on hospital-based, and especially surgical, case series. However, at the population level it is impossible to ensure the adoption of strict and consistent diagnostic protocols, so that misclassification of diagnosis may be an issue, and major variations may exist in the possible delay with which diagnosis is established during the natural history of the disease.

As shown in Table IV, previous population-based estimates of survival among PMM cases gave conflicting results as follows: some studies reported shorter median survival time, in comparison with pleural MM, but in others either a longer median survival time or a higher proportion of survivors 1 year or more after diagnosis were observed. Our study partially overlaps with those by Marinaccio *et al.*, Merler *et al.* and Barbieri *et al.*[9,10,14] However, even excluding their results, the heterogeneity of previous survival estimates remains unchanged.

Our study is population-based and considerably larger than all previous investigations, thus overcoming possible difficulties due to selection bias and statistical instability. However, the possibility that the completeness of registration differs between peritoneal and pleural mesotheliomas and/or among CORs must be addressed. As our study is limited to cases with microscopical confirmation of diagnosis and because the CORs consulted the reports of the histological and cytological examinations carried out in all pathological units in their region, selective under-registration of peritoneal mesotheliomas is unlikely, even if under-diagnosis cannot be ruled out. Standardized incidence rates (SIRs) are in the range reported in the literature (Table I).[5] Differences in incidence exist among the CORs. In particular, the high SIRs in Piemonte, Liguria and Marche in men, and in Piemonte in women deserve comment. Peritoneal mesotheliomas had strikingly increased incidence/mortality among workers of the Eternit asbestos-cement production plant in Casale Monferrato[4] and of the SIA asbestos textile factory in Grugliasco,[3] which are relevant for Piemonte, and both industries employed large numbers of women. In Liguria, in particular in Genoa and in La Spezia, there were large shipyards and a high incidence of peritoneal mesothelioma in men has already been reported.[5] The SIR in Marche is based on only 9 observed cases and is affected by considerable statistical uncertainty. Thus, geographical differences in incidence are consistent with the distribution of relevant exposures and do not seem to imply differences in the completeness of registration.

A limitation in our data is that a national panel for revising the evidence in support of diagnosis has not been set up. The evaluation of such evidence is carried out by the CORs, and is generally based on pathological, radiological and clinical reports, but not on the original materials. Thus, some degree of misclassification of diagnosis is possible, even if it is currently impossible to assess. As major geographical variations exist in Italy in mesothelioma incidence, local experience in mesothelioma differential diagnosis may vary accordingly. Similar problems, however, are present in all networks of regional or national cancer registries, such as SEER, and as far as common rules for registration are adopted and complied with, they do not hamper the pooling of data in common databases for survival analysis.[25]

As the population settings, the data sources and the analytical approach were identical, we can compare our findings with those obtained in a parallel investigation of pleural MM.[17] This comparison (Fig. 1) shows that the survival pattern of PMM cases is clearly different from that of pleural MM cases. The median survival time was 5.6 months *vs.* 9.8 months in pleural MM. Only 48.5% of all PMM cases were alive for 6 months after diagnosis *versus* 67% among pleural MM cases, but the proportion of long-term survivors was larger, *i.e.*, 14.8 *vs.* 9.6% at 3 years and 8.1 *vs.* 5.0% at 5 years. Thus, based on our large study, PMM seems to have both a shorter survival in most cases and a larger proportion of long-term survivors; this finding could explain the contradictory results of previous smaller studies.

Gender (women), age at diagnosis (<75 years) and morphology (epithelioid) were the main individual characteristics associated

TABLE III – COX PROPORTIONAL HAZARDS REGRESSION STRATIFIED BY REGIONAL OPERATING CENTRE

Factors		All cases (N = 338)		Cases with information on treatment (N = 194)	
		HR (95% CI)	p	HR (95% CI)	p
Gender	Women*	1		1	
	Men	1.4 (1.1–1.7)	0.017	1.1 (0.8–1.5)	0.493
Age at diagnosis	<55*	1		1	
	55–64	1.1 (0.8–1.6)	0.541	0.9 (0.6–1.4)	0.689
	65–74	1.4 (1.0–1.9)	0.081	1.1 (0.7–1.8)	0.535
	≥75	2.2 (1.5–3.4)	<0.001	2.9 (1.6–5.2)	<0.001
Calendar period	1990–1992	1.4 (1.0–2.0)	0.094	1.5 (1.0–2.5)	0.073
	1993–1995	1.0 (0.7–1.4)	0.952	1.0 (0.6–1.6)	0.949
	1996–1998	1.0 (0.8–1.4)	0.890	1.0 (0.7–1.5)	0.880
	1999–2001*	1		1	
Morphology	Epithelioid*	1		1	
	Unspecified	0.8 (0.6–1.1)	0.131	0.7 (0.5–1.0)	0.083
	Mixed and fibrous	1.8 (1.3–2.5)	0.001	1.9 (1.2–2.9)	0.006
Hospital	With thoracic surgery*	1		1	
	Without thoracic surgery	1.6 (1.2–2.1)	0.003	1.6 (1.1–2.3)	0.027
	Unspecified	1.7 (0.8–3.4)	0.140	1.6 (0.7–3.6)	0.260
Treatment	Treated[1],*	–	–	1	
	Untreated[2]	–	–	1.4 (0.5–3.9)	0.495

HR, hazard ratio, 95% CI, 95% confidence interval, *, reference category. All cases and cases with information on treatment.
[1]Ever treated: chemotherapy and/or nonpalliative surgery.–[2]Definitely never treated.

TABLE IV – SURVIVAL OF PERITONEAL *VERSUS* PLEURAL MALIGNANT MESOTHELIOMAS IN POPULATION-BASED STUDIES

Study and reference	Population	Period	Follow-up	Site	No. cases	Median (months)	% Surviving at (years)			
							1	2	3	5
Janssen-Heijnen *et al.*, 1999[11]	The Netherlands, southeastern	1970–1992	1994	Pleura	119	n.a.	38%	n.a.	n.a.	n.a.
				Peritoneum	15	n.a.	79%	n.a.	n.a.	n.a.
Neumann *et al.*, 2001[12]	Germany	1987–1999	n.a.	Pleura	387	13.2[1]	n.a.	n.a.	n.a.	n.a.
				Peritoneum	16	19.8	n.a.	n.a.	n.a.	n.a.
Desoubeaux *et al.*, 2001[8]	France, Basse-Normandie	1995–1999	2000	Pleura	66	9.0	n.a.	9%	n.a.	n.a.
				Peritoneum	14	5.0	n.a.	14%	n.a.	n.a.
Rosso *et al.*, 2001[13]	Pool of Italian Cancer Registries	1990–1994	1999	Pleura	740	n.a.	34%	n.a.	8%	5%
				Peritoneum	61	n.a.	41%	n.a.	20%	11%
Marinaccio *et al.*, 2003[9]	Italy, 5 regions	1997	2001	Pleura	392	9.2	35%	16%	7%	n.a.
				Peritoneum	34	5.2	29%	27%	18%	n.a.
Barbieri *et al.*, 2004[14]	Italy, Brescia province, men	1982–2000	2001	Pleura	125	7.8	31%	n.a.	n.a.	n.a.
				Peritoneum	11	8.1	36%	n.a.	n.a.	n.a.
	Italy, Brescia province, women	1982–2000	2001	Pleura	66	9.7	41%	n.a.	n.a.	n.a.
				Peritoneum	13	20.8	54%	n.a.	n.a.	n.a.
Merler and Roberti, 2005[10]	Italy, Veneto	1990–2002	2004	Pleura	624	10.0	43%	11%	n.a.	n.a.
				Peritoneum	62	6.9	34%	18%	n.a.	n.a.
This study[2]	Italy, 8 regions and 1 province	1990–2001	2005	Pleura	4100	9.8	42%	18%	10%	5%
				Peritoneum	338	5.6	30%	19%	15%	8%

n.a., not available.
[1]Mean survival time after symptoms onset.–[2]Including microscopically confirmed cases studied by Marinaccio *et al.*, Barbieri *et al.* and Merler *et al.*

with prolonged survival. The poorer general health conditions due to advancing age are an obvious explanation for the effect of the age-class, although a more aggressive clinical approach to diagnosis in younger patients might also have played a role, leading to prompter investigations and earlier diagnosis in some cases. The worse prognosis for the fibrous and mixed histotypes is an often-described feature of MM, so our results from the multivariate analysis are in agreement with previous findings.[8,11,12]

The role of gender deserves a more thorough consideration. A more favorable outcome in women has been reported in some studies.[9,10,14] These findings might reflect a biologically based difference between genders. However, other not uncommon abdominal neoplasms of women (namely, ovarian tumors) could be difficult to distinguish from PMM.[16] Thus, assuming for these malignancies a less unfavorable outcome than for PMM, misclassification as PMM of even a limited proportion of such cases could be at the origin of the effect apparently associated with gender. All possible efforts to avoid diagnosis misclassification have been taken as follows: (*i*) all centers contributing to the study adopted the same standard protocol for classifying the evidence on which diagnoses were based; (*ii*) analyses were limited to cases with morphological confirmation ("definite" or "probable" diagnoses); (*iii*) the original pathology records of each case with survival ≥4 years were reexamined, and cases with lesions of uncertain biological behavior were excluded from the study. However, as no panel of pathologists is currently appointed with the national registry for revising pathologic materials, we cannot rule out that misclassification of diagnosis occurred selectively in women and is at the origin of the difference in survival between genders.

Since chest surgeons have little role, if any, in the diagnosis and treatment of PMM, the observation of longer survival times for cases diagnosed in hospitals where a thoracic surgery department was present may appear surprising. However, these are generally large teaching hospitals including University departments, where advanced diagnostic facilities are available and prompter and more thorough clinical investigations are possible. Thus, a shorter lag between the first symptoms of disease and a definite diagnosis can be expected. More importantly, these hospitals offer all available

treatment options and could be selectively attracting cases whose personal characteristics (age, general condition, stage of disease at presentation) are both strong predictors *per se* of survival, including long-term survival, and factors that make them suitable for treatment.

In multivariate analyses, treatment was associated with prolonged survival, but its effect was not statistically significant. These results applied both when surgically and chemo-/radiotherapy-treated patients were considered separately, and when all treated patients were grouped together. Our findings suggest that, at the population level, treatment for PMM did not significantly improve survival. However, we could not adjust for relevant factors, such as performance status and disease stage, due to a lack of suitable data. Thus, we cannot exclude the possibility that the lack of a statistically significant association between treatment and survival is due to confounding by health status and/or disease stage, even if such confounding would be expected to operate in the opposite direction, as usually severely ill patients do not undergo surgery or chemotherapy.

As detailed data on therapies (as well as on performance status and disease stage) are not systematically available at the population level, population-based studies can assess the impact of treatment on the overall case mix occurring in the population, provided its effectiveness has been established in controlled clinical trials. Therefore, our findings must not be interpreted as evidence of ineffectiveness. Furthermore, in recent years not covered by our survey, some new treatment options have been developed,[15,26–28] and our results could provide a large historical basis for assessing whether their introduction into clinical practice will lead to benefits observable in the whole population of PMM cases.

In conclusion, this is currently the largest study on survival in PMM, including cases registered on a population basis according to homogeneous criteria, with long and recently updated follow-up. Compared with pleural MM, PMM cases revealed a shorter median survival time but a larger proportion of long-term survivors. At the population level, treatment for PMM did not appear to significantly improve survival, but cases were first diagnosed before the introduction of some recent, promising therapeutic approaches. This study will be useful as a historical comparison for future investigations on trends in survival at the population level.

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