Tumori, 98: 215-219, 2012

Effects of combined therapies on the survival of pleural mesothelioma patients treated in Brescia, 1982-2006

Pietro Gino Barbieri[1], Alessandro Marinaccio[2], Pierpaolo Ferrante[2], Alberto Scarselli[2], Valentina Pinelli[3], and Gianfranco Tassi[3]

[1]Occupational Health Unit, Local Health Authority, Brescia; [2]Department of Occupational Medicine, Epidemiology Unit, Workers' Compensation Authority (INAIL), ex-ISPESL research area; [3]Lung Diseases Department, General Hospital of Brescia, Italy

ABSTRACT

Aims and background. During the 1990's, the traditional unimodal treatments (surgery, radiotherapy, chemotherapy, immunotherapy) for malignant pleural mesothelioma started to be combined in bimodal or multimodal strategies. However, recent population-based analyses of the survival of patients with malignant pleural mesothelioma indicate that even these treatments have not led to significant improvements in prognosis, which remains very poor. The present study assessed the survival of patients given combined treatments and multimodal therapies in a specialized hospital department.

Methods. The study population comprised 530 patients diagnosed with malignant pleural mesothelioma from 1982 to 2006: 343 of them were residents in the province of Brescia (Lombardy, Northern Italy) and 187 were residents outside the province, with a follow-up to 12 December 2009. Kaplan-Meier survival analyses and Cox proportional risks model were used to test sex, age at diagnosis, histological type and treatments, as prognostic factors.

Results. The estimated median survival for the whole group of patients was 317 days (257 for residents and 398 for non-residents), and respectively 310 and 340 days in the groups diagnosed in the periods 1982-2000 and 2001-2006. Multivariate analysis confirmed that the prognosis was better for younger patients and cases of epithelioid type malignant pleural mesothelioma, whereas for patients receiving any single treatment the prognosis was not significantly better than for those given palliative care alone. However, patients receiving combined treatments or the multimodality approach had significantly longer median survival and the relative risk of death was respectively 0.57 and 0.61 compared to untreated patients (or those only given symptomatic therapy).

Conclusions. This is the first study in Italy to assess the effectiveness of different treatment approaches in a significant number of patients treated in one hospital. Further studies are needed to confirm the improvement in prognosis – even if modest – on larger numbers of patients and taking into account the different stages of the disease.

Key words: pleural malignant mesothelioma, survival, therapy.

Correspondence to: Dr Pietro Gino Barbieri, Occupational Health Unit, Local Health Authority, Corso G. Matteotti 21, 25122 Brescia, Italy.
Tel +39-030-3838677;
fax +39-030-3838540;
e-mail: pietro.barbieri@aslbrescia.it

Received June 2, 2011;
accepted December 6, 2011.

Introduction

Pleural malignant mesothelioma (MPM) is a disease with a rapid, dismal prognosis, causally associated with asbestos exposure. Progressive increases in incidences rates and mortality in the general population[1-5] have boosted the search for new and more effective therapeutic approaches, in view of the substantial failure of treatments used until the 1990s, particularly unimodal therapy.

Between 1993 and 2004, 92.5% of the 9166 incident cases recorded in the Italian national mesothelioma register were in the pleural site[6]. On the basis of epidemiologi-

cal surveillance system findings and active searches for cases, published population-based survival analyses have estimated the median survival as 8-9 months[7-10].

During the 1990's new therapeutic approaches gradually replaced traditional palliative treatments. In the second half of that decade, most patients were treated with chemotherapy, immunotherapy and surgery (singly to start with, then in combinations), but on the basis of treatment protocols that were not always standardized and whose effectiveness was frequently not properly assessed[11-14]. In more recent years, these initial therapeutic approaches have been boosted by multimodal therapy (extra-pleural pneumonectomy, with chemotherapy and radiotherapy) which – it is hoped – will be more effective[15,16], though clearly still limited[17].

One of the most active Italian centers for the treatment of pleural mesothelioma has been working for a long time in Brescia. It is a reference and focal point for many patients from different parts of Italy. The Brescia Mesothelioma Registry was the basis for a first assessment of the population-based survival of 353 patients diagnosed from 1982 to 2000 (215 residents in the province and 138 from other areas), all treated in the same hospital[18]. This first analysis found no improvement in the prognosis for the patients treated in recent years, except for a selected group whose longer survival needed to be confirmed.

The present study checked the improvement in the prognosis for MPM patients who received specific or combined therapies after 2000 and examined the survival times in relation to specific therapies.

Methods

The analysis considered 530 cases of MPM observed from 1982 to 2006, of which 343 were residents in the province of Brescia and 187 came from outside the province, all treated in the Brescia hospital. Brescia is the largest province in Lombardy (a region in the northwest of Italy), covering 4,784.36 sq. km, with 1,112,628 inhabitants (49.2% male).

The level of diagnostic confidence was based on the standards adopted in Italy following the Italian national mesothelioma register guidelines[19]. There are three categories of MPM diagnostic confidence: *definite*, *probable* and *possible*. *Definite* and *probable* are cases with a diagnosis supported by histology and/or cytology and possibly also immunohistochemical tests. The *possible* category is assigned to cases with only a clinical diagnosis supported by radiological findings. The incidence date of cases was the date of histological and/or cytological analysis, when available; otherwise it was the date of clinical diagnosis at first hospital admission. We excluded cases with extra-pleural sites and 2 cases with a histopathological diagnosis of "well-differentiated papillary mesothelioma" because of the different clinical pathological connotation from MPM[20]. The analysis also excluded 3 patients who received only radiotherapy and 4 cases, not resident in the province, for whom there was no information on treatments. The vital status was reconstructed for all cases on 31 December 2009, retrieving mortality data from the National Statistics Institute (ISTAT).

In view of the wide variety of therapeutic combinations employed in the period and taken from hospital records, the treatments administered were grouped under six headings: (group 1) palliative therapy (e.g. pleural poudrage, radiotherapy of drainage channels or thoracocentesis tracts (RTT) or pleural poudrage and RTT); (2) chemotherapy; (3) surgery (pleurectomy/decortication or extra-pleural pneumonectomy); (4) immunotherapy; (5) bi-modality or tri-modality approaches (every possible combination of chemotherapy, surgery, immunotherapy, radiation therapy, except treatments in group 6); (6) multimodality approach (extra-pleural *pneumonectomy plus chemotherapy plus* radiotherapy). The median survival and its confidence interval were obtained with the Kaplan-Meier method[21]. The median and observed rates of survival were evaluated after one and three years for the 530 patients enrolled, by sex, level of diagnostic confidence, residence (Brescia province or elsewhere), morphology and calendar period of diagnosis. The assumption of hazards proportionality was assessed both graphically (adjusted log-log plots) and by the formal tests (Schoenfeld residuals and Wald tests). Three factors (diagnosis, therapy and residence in Brescia) violated the proportional assumption and for each one a term of interaction with time was included in the model.

The Cox proportional-hazards regression model[22] was used to test the role of explanatory variables on survival in a multivariate context considering, as categorical variables, sex, age, level of diagnostic confidence, histological type, calendar period of incidence and treatment received. The baseline categories of the model were the following: women, <55 years for age, *possible* for diagnostic confidence, absence of treatment or symptomatic therapy only for treatment, and epithelioid for morphology. The goodness of fit of the model was assessed by testing the log-likelihood ratio. All statistical analyses were done with SAS software (version 9.1).

Results

Table 1 shows the sex, age at diagnosis, diagnostic confidence, morphology, vital status at the end of follow-up and treatment received for the 530 patients. Two thirds were males (66.8%), and the residents in the province of Brescia add up to 64.7%. More than half (56.2%) were older than 65 years. The diagnosis of MPM was *definite* for 86.7% and 94.4% if cases with a *probable* diagnosis were included. The histological diagnoses

Table 1 - Cases of malignant pleural mesothelioma treated in Brescia (Italy) in 1982-2006 by sex, age, diagnosis, morphology, residence, calendar period and therapy

		Men	Women	All
Age at diagnosis (years)	≤55	29	60	89
	56-65	38	105	143
	66-75	51	119	170
	≥75	58	70	128
Diagnosis	Definite	312	147	459
	Probable	25	16	41
	Possible	17	13	30
Residence	Brescia	226	117	343
	Elsewhere	128	59	187
Vital status	Alive at follow-up	7	6	13
	Deceased	347	170	517
Morphology	Epithelioid	220	125	345
	Biphasic	56	16	72
	Fibrous	30	4	34
	Unspecified	31	18	49
	Unknown	17	13	30
Calendar period of diagnosis	1982-2000	221	96	317
	2001-2006	133	80	213
Treatment	Chemotherapy	31	22	53
	Surgery	27	10	37
	Immunotherapy	48	9	57
	Combined	30	12	42
	Multimodal	18	6	24
	Symptomatic	200	117	317
Total		354	176	530

were made by expert pathologists, using an immunohistochemical test in 86% of cases. Two thirds of the patients with a histological diagnosis had epithelioid histology (69%).

Just over half the patients (59.8%) were given only palliative therapies in the selected period. The remaining 40.2% received chemotherapy, surgery and immunotherapy, singly or in combinations, with a substantially uniform distribution. Only 24 were given multimodality therapy and 42 combination therapies. Table 2 shows the median survival and survival rates at one and three years, separately by sex, morphology, calendar period, and level of diagnostic confidence. Median survival was slightly longer for women and so were the survival rates at one and three years. There was a clear gradient in the duration of survival in relation to diagnostic confidence, with a median of only 56 days for cases with a *possible* diagnosis. Survival was significantly longer for non-residents than residents (logrank test, P <0.001).

Figure 1 compares the survival of MPM cases given palliative and symptomatic treatments and those receiving single or combination therapies. Figure 2 shows the survival of patients in relation to the treatments received.

Table 2 - Kaplan-Meier median survival (days) and observed survival one and three years from diagnosis (%)

		Median (d)	One yr	Three yr
Sex	Men	294	0.43	0.09
	Women	362	0.50	0.13
Diagnosis	Definite	351	0.49	0.11
	Probable	130	0.22	0.05
	Possible	56	0.20	0.03
Residence	Brescia	257	0.40	0.11
	Elsewhere	398	0.55	0.09
Morphology	Epithelioid	421	0.54	0.14
	Biphasic	279	0.39	0.03
	Fibrous	109	0.09	0.03
	Unspecified	130	0.29	0.02
	Unknown	56	0.20	0.03
Calendar period	1982-2000	310	0.43	0.08
	2001-2006	310	0.49	0.13
Total		317	0.45	0.10

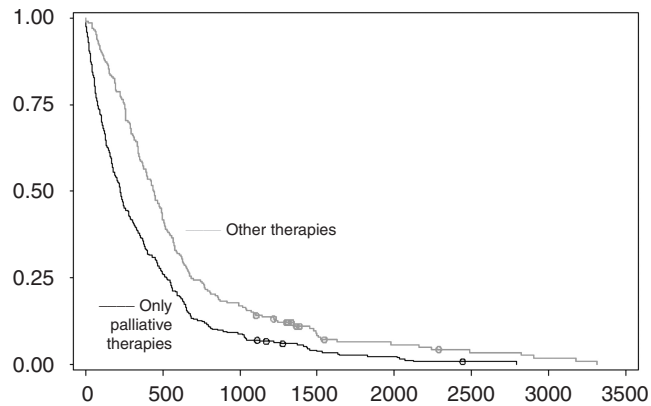

Figure 1 - Survival (Kaplan-Meier model) of malignant pleural mesothelioma by therapy (palliatives or other).

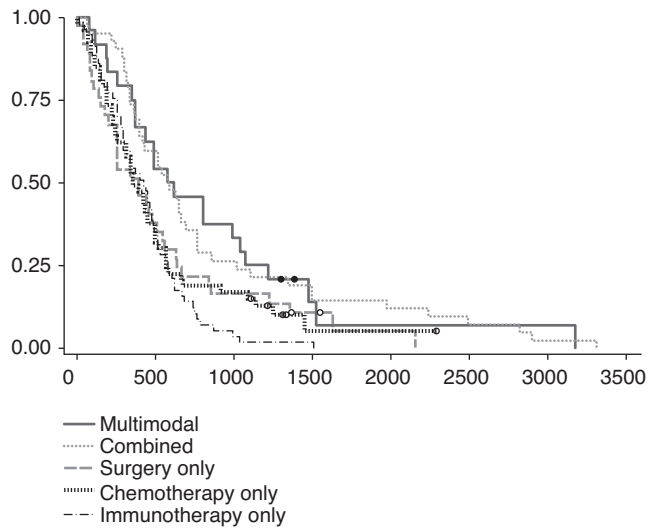

Figure 2 - Survival (Kaplan-Meier model) of malignant pleural mesothelioma by therapy.

Table 3 gives the results of the multivariate Cox regression model. Older patients (at diagnosis) had a significantly higher risk than those younger than 55 years of age. Patients with biphasic or fibrous type pleural mesothelioma had a significantly higher risk of death than those with the epithelioid type.

Survival was significantly longer for patients receiving combinations and multimodality therapy (P <0.05); there was no appreciable effect for the single-modality approach. In detail, immunological therapies had no constant effect on survival over time, but compared with a short-term survival advantage, the effect over the longer period was negative, with shorter survival and a significantly higher risk of death. In contrast, the improvement of prognosis with the combinations and multimodality therapies remained stable over time.

Discussion

Previous analyses of the survival of MPM in hospital case series showed the lowest overall survival of patients and indicated the role of age, clinical stage and histological type as factors affecting the prognosis, in agreement with the findings of the present study[23-25]. Analyses of population-based MPM surveillance systems confirmed these results and helped formulate more solid estimates of survival, based on larger numbers of patients[7,8]. An analysis of survival on a broad case series in Italy also confirmed the earlier findings, though it could not assess the effectiveness of patient-administered therapies[10].

Table 3 - Cox's proportional hazard regression model in patients with pleural malignant mesothelioma (mostly Brescia residents). Relative risks adjusted by sex, age, residence, diagnosis, incidence period, morphology and therapy

Variable	Modality	Adjusted relative risk $RR_{adj} = e^{\beta}$	Confidence interval %	*P*
Sex	Women	1		
	Men	1.14	0.94-1.38	ns
Age	≤55	1		
	56-65	1.27	0.96-1.69	ns
	66-75	1.47	1.11-1.95	<0.05
	≥75	1.91	1.33-2.51	<0.05
Residence	Brescia	1.44	1.10-1.90	<0.05
	Elsewhere	1		
Calendar period	1982-2000	1.26	1.03-1.54	<0.05
	2001-2006	1		
Morphology	Epithelioid	1		
	Fibrous	3.02	2.07-4.40	<0.05
	Biphasic	1.62	1.24-2.11	<0.05
	Unspecified	1.38	0.95-2.02	ns
Treatment	Symptomatic	1		
	Chemotherapy	0.95	0.69-1.32	ns
	Surgery	0.84	0.59-1.20	ns
	Immunotherapy	Time-related	-	-
	Combined	0.57	0.40-0.81	<0.05
	Multimodal	0.61	0.37-0.99	<0.05

Between 2001 and 2006, there was an annual increase in the number of MPM cases diagnosed and treated in Brescia, and a substantial proportion of patients came from other Italian provinces. The latter were a selected sample – they were generally younger patients, with cancer at an early stage – and had a significantly better survival profile, confirming previous analyses.

As repeatedly observed in previous studies, the present findings confirm that the main determinants of survival are age at diagnosis and cancer morphology (with a better prognosis for younger patients and epithelioid histology). The poor survival of patients with a diagnosis of *possible* MPM is consistent with their higher age and with the stage of cancer development, which makes it impossible to complete full diagnostic investigations. The association between level of diagnosis certainty and age has been repeatedly reported[6].

A limitation of the present study is the lack of assessment of the clinical stage of the disease, which is a determinant of prognosis; staging was done for only about 25% of MPM diagnosed from 1982 to 2000 and for about 50% from 2001 to 2006. This information was too incomplete to be usefully included in the analysis.

The median survival for the Brescia residents was significantly better in the 2001-2006 period than in the earlier years (1982-2000), probably on account of new therapeutic approaches. The survival rates at one and three years were comparable to the figures given in earlier analyses. Starting in the mid-90s, it was acknowledged that the conventional single-modality treatments (surgery, radiotherapy, chemotherapy, immunotherapy), which had been proposed and administered to a limited number of patients, had no real impact on survival. New therapeutic approaches started to be tested, such as combination therapy, two-, three- or multi-modality approaches, suggested as alternatives to conventional therapy to selected patients. A significant proportion of the patients considered herein was treated with these protocols, which were thoroughly assessed in a Consensus Conference in 2008[26]. Subsequently, the Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons (2010), while stating that the multimodality approach was probably more appropriate, concluded that the data available to date were still too limited to indicate the best possible combination therapy and suggested that candidates for a this approach should be included in prospective clinical trials organized in specialized centres[27].

The present analysis of the expected effects on survival since the introduction of newer therapies must still be interpreted with caution since this was not a prospective population-based study and was based on a heterogeneous group of cases. Furthermore, a selection bias could be possible as patients in better general health status were considered eligible for therapy. However, for those patients who were assigned to non-traditional treatment protocols, particularly with combination or multimodality therapies, survival was longer

than with single therapy. The relative risks of death for patients treated with combination therapies and the multimodality approach were respectively 0.57 and 0.61, against a baseline of 1 for symptomatic therapy.

The present study is, to our knowledge, the only one in Italy that has evaluated the efficacy of different therapeutic approaches, in terms of survival of patients with MPM treated in one specialized structure.

In conclusion, compared to the previous figures, survival analysis of MPM patients in this update shows that life expectancy was significantly better for those treated in the most recent period (2001-2006), and that combination therapies, including multimodality treatments, appeared to significantly improve survival, although it is still poor. Further confirmation is clearly needed in order to strengthen this evidence on a larger group of patients, introducing an analysis of disease staging.

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