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Prognostic factors and survival in malignant pleural mesothelioma

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Prognostic factors and survival in malignant pleural mesothelioma. T. Van Gelder, R.A.M. Damhuis, H.C. Hoogsteden. ©ERS Journals Ltd 1994.

ABSTRACT: Malignant pleural mesothelioma is a lethal disease and little is known about prognostic factors.

The prognostic significance of age, stage of disease, gender and histological subtype was studied in 167 new cases of cytologically (15%) or histologically (85%) proven malignant pleural mesothelioma in the Rotterdam area, during the period 1987–1989.

Median survival of all patients was 242 days. Univariate analysis identified age, stage and histopathological subtype as significant prognostic factors, which was confirmed in multivariate analysis. Median survival rates for patients <65, 65–74 and ≥75 yrs were 359, 242 and 131 days, respectively. Patients with Stage I disease had a median survival of 359 days compared to 147 and 112 days, respectively, for patients with Stage II and the combination of Stages III and IV. Mixed histopathological subtype (190 days) was less favourable than sarcomatous (207 days) and epithelial (252 days) subtypes.

Using a Cox proportional hazard model in patients with malignant pleural mesothelioma, age, histological subtype and stage were identified as independent prognostic factors. These prognostic factors should be taken into account when starting or evaluating treatment studies.

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Asbestos exposure is associated with an increased risk of cancers of the pleura and peritoneum, lung, larynx and several other organs [1]. The incidence of mesothelial tumours is increased among insulators and shipyard-workers [2]. Consequently, areas with large ports and shipbuilding industry have high incidence rates for malignant pleural mesothelioma [3]. Despite regulations to limit the use of asbestos, the incidence of mesothelioma is not expected to fall before the end of this century [4]. Since the Rotterdam area contains the world's largest port, with widespread shipbuilding and ship repair industries, the large number of mesothelioma patients in this area provided an opportunity to study prognostic factors.

Generally, the survival of patients with malignant mesothelioma is less than one year from the onset of symptoms [5]. Various treatment strategies have not been able to improve the prognosis for the majority of patients [6]. We describe the results of a uni- and multivariate analysis of various factors influencing survival in patients with pleural mesothelioma diagnosed in 1987–1989. These prognostic factors are of importance for future therapeutic studies.

Patients and methods

The Rotterdam Cancer Registry started in 1982 and covers the Southwestern part of The Netherlands, an area known for its industrial activities and shipping industry. Data on newly diagnosed cancer patients are collected from hospital and pathology records by specially trained registrars. From 1987, registration is complete in the central part of the region with about 1.5 million inhabitants. The study was confined to patients living in this area.

During the period 1987–1989, 168 patients were diagnosed with cytologically (n=25; 15%) or histologically (n=143; 85%) proven pleural mesothelioma. Thirty four patients with unspecified pleural cancer were not included because the diagnosis was not pathology-based (n=22) or because the pathological diagnosis was indefinite. Autopsy findings of 10 patients were available. When microscopic sections were reviewed by the Netherlands Mesothelioma Panel or the pathology department of the University Hospital Rotterdam, information on subtyping was available. One patient was excluded because the exact date of diagnosis could not be determined.

Tumour extension was classified according to the staging system of BUTCHART *et al.* [7]: Stage I: tumour confined to homolateral pleura, lung and pericardium. Stage II: tumour invading chest wall or involving mediastinal structures, or lymph node involvement within the chest. Stage III: tumour penetrating diaphragm to involve peritoneum directly, or lymph node involvement outside the chest. Stage IV: distant blood-borne metastases.

Classification was performed by the registrars, on the basis of the clinical information available in the hospital records. The extent of clinical staging, however, was variable as it was individually determined by the physicians involved. The medical file was the only source of information regarding asbestos exposure. If available, information about the vital status of patients was obtained up to December 31, 1991. Eight patients were lost to follow-up, but were included in the analyses as censored observations.

Survival was measured from the date of cytological or histological diagnosis, using the method of Kaplan and Meier. Differences in observed survival between groups were tested for statistical significance using the log-rank test. The relative prognostic importance of the various parameters was determined using the Cox multiple regression model for censored survival data.

Only parameters with p-values <0.10 were included in the final model. Missing values were excluded in the univariate analysis but were included in the multivariate model as a separate category.

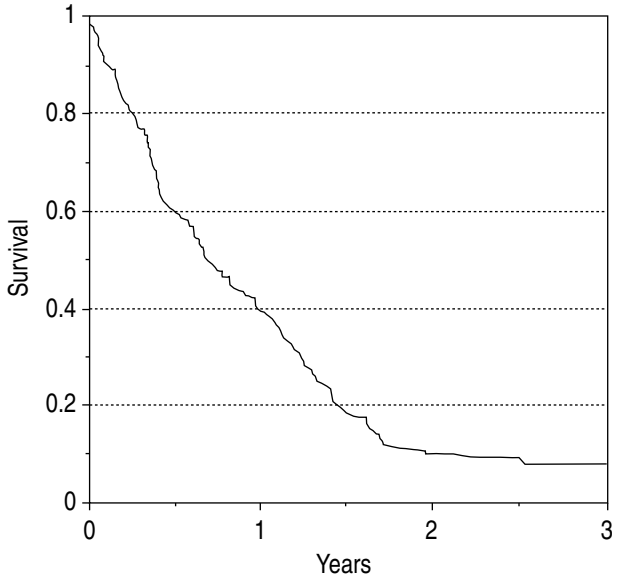

Fig. 1. – Kaplan-Meier survival curve in 167 patients with malignant mesothelioma

Results

In the years 1987–1989, 167 malignant pleural mesotheliomas were diagnosed in the hospitals in the area of the Comprehensive Cancer Centre Rotterdam. Only 13 patients were female (8%). Overall median survival was 242 days (fig. 1). Table 1 shows the results of univariate analysis of variables influencing survival. Survival was significantly longer in younger patients (p=0.004).

Histological subtypes were available in 83 patients; 18 (22%) had sarcomatous type, 30 (36%) epithelial type and 35 (42%) mixed type histology. The histological subtype was a significant prognostic factor (p=0.04), with mixed type histology having shortest survival.

The stage of disease was the most prominent prognostic factor (table 1). Survival in Stage I disease clearly exceeded survival in the other stages (359 *vs* 129 days; p=0.0001). Information on previous asbestos exposure was available for 82 patients, in 68 of whom this was positive (all men). Previous asbestos exposure was not significantly related to prolonged survival (308 *vs* 201 days; p=0.36). Treatment in this series of patients consisted of a mixture of modalities (16 chemotherapy, 16 immunotherapy and 9 radiotherapy). Symptomatic therapy was the main goal in most patients.

According to multivariate analysis, age, stage and histopathological subtype were identified as independent prognostic factors. After controlling for other prognostic factors, mixed type histology had the worst prognosis (table 2).

Table 1. – Univariate analysis of variables influencing survival in 167 patients with pleural mesothelioma

Variable	Categories	Obs. n	Survival* days	p-value log-rank test
Age at diagnosis yrs	<65	70	359 (464)	0.004
	65–74	63	242 (280)	
	>74	34	131 (242)	
Sex	Male	154	271 (369)	0.28
	Female	13	141 (199)	
Year of diagnosis	1987	55	281 (344)	0.22
	1988	55	209 (270)	
	1989	57	326 (329)	
Previous asbestos exposure	Yes	68	308 (429)	0.36
	No	14	201 (266)	
Histopathological type	Sarcomatous	18	207 (375)	0.04
	Epithelial	30	252 (302)	
	Mixed	35	190 (237)	
Butchart Classification	Stage I	108	359 (387)	0.0001
	Stage II	16	147 (237)	
	Stage III + IV	16	112 (131)	

*: median, and mean in parenthesis. Obs: number of observations.

Table 2. – Proportional hazards regression model based on 167 pleural mesothelioma patients, including extra categories for missing or undefined values

Variable	Categories	Coefficient	Standard error	Hazard ratio (95% confidence interval)
Age at diagnosis yrs	<65			1
	65–74	0.38	0.21	1.46 (0.96–2.23)
	>74	0.72	0.24	2.05 (1.58–3.32)
Histopathological type	Undefined			1
	Sarcomatous	-0.12	0.31	0.88 (0.48–1.65)
	Epithelial	0.10	0.24	1.10 (0.68–1.79)
	Mixed	0.54	0.22	1.72 (1.10–2.66)
Butchart classification	Stage I			1
	Stage II	0.66	0.30	1.9 (1.06–3.52)
	Stage III + IV	1.40	0.29	4.1 (2.27–7.24)
	Unknown	0.29	0.23	1.3 (0.84–2.25)

Discussion

The age-standardized incidence rate of mesothelioma in men in the area of the Comprehensive Cancer Centre Rotterdam is 62 per million (world standard population) [8]. This figure is extremely high compared to other regions with high incidence rates, such as Western Australia (28 per million) and Sweden (23 per million) [9]. The large proportion of men in this study (92%) reflects the fact that mesothelioma is mainly an occupational disease.

Data on survival related to the BUTCHART-classification [7] are scarce. In our study, information on stage was available in 141 of 167 patients (84%). Most patients were in Stage I (77%), possibly due to a relatively short patient's and/or doctor's delay, maybe as a result of the high incidence of this tumour in the Rotterdam area. The median survival of Stage I disease was considerably longer than in Stages II, III and IV (359 *vs* 129 days). A similar clear difference was found by others [10]. The overall median survival of 8 months was comparable to other studies [10, 11].

Histological subtype appeared to be a prognostic factor. It is unknown why mixed type histology was related to worse prognosis. In a previous study, we found a higher percentage of mixed type histology when larger amounts of tumour had been obtained [12]. Possibly, the patients with mixed type histology had a larger tumour load, without having a higher stage of disease. In contrast, ANTMAN *et al*. [13] found that mixed type mesothelioma was associated with longer survival than the sarcomatous type. In their study, as well as the reports by CHAHINIAN *et al*. [14] and HILLERDAL [15], patients with epithelial subtype had the longest survival. Since our results were based on only 18 patients with sarcomatous subtype, larger numbers are required for more definite conclusions. Furthermore, international differences in subtype classification may have been of influence. Survival in older patients was significantly worse than in younger patients. Gender and previous asbestos exposure were not of significant influence on survival. The absence of differences may be due to the small numbers of women (13 *vs* 154 men) and patients with negative asbestos history (14 *vs* 68).

In summary, age at diagnosis, histological subtype and stage of disease appear to have a significant independent influence on survival in pleural mesothelioma. Similar results were recently reported by others [16, 17]. Treatment in our series was mainly symptomatic, although several other treatment modalities were used. Effects of treatment should, however, be studied in prospective randomized trials. In such trials, the prognostic factors determined in this study should be taken into account.

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