



Predicting survival in malignant mesothelioma

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ABSTRACT: Malignant mesothelioma (MM) of the pleura or peritoneum is a universally fatal disease attracting an increasing range of medical interventions and escalating healthcare costs.

Changes in survival and the factors affecting survival of all patients ever diagnosed with MM in Western Australia over the past five decades and confirmed by the Western Australian Mesothelioma Registry to December 2005 were examined. Sex, age, date and method of diagnosis, site of disease and histological type were recorded. Date of onset of symptoms and performance status were obtained from clinical notes for a sample of cases. Cox regression was used to examine the association of the clinical variables and the 10-yr periods of disease onset with survival after diagnosis.

Survival was inversely related to age, being worse for males (hazard ratio (HR) 1.4, 95% CI 1.2–1.6), and those with peritoneal mesothelioma (HR 1.4, 95% CI 1.1–1.7). Patients with sarcomatoid histology had worse prognosis than patients with epithelioid and biphasic histological subtypes. Survival improved after the 1970s and has made incremental improvements since then. Median (interquartile range) survival by decade, from 1960 until 2005, was 64 (0–198), 177 (48–350), 221 (97–504), 238 (108–502) and 301 (134–611) days; ~4 weeks of this apparent improvement can be attributed to earlier diagnosis.

With increasing resources and treatment costs for MM over the past 40 yrs, there have been modest improvements in survival but no complete remissions.

KEYWORDS: Mesothelioma, survival

Malignant mesothelioma (MM) of the pleura or peritoneum is an invariably fatal disease attracting increasing medical interventions and escalating healthcare costs as novel treatments are tried. Since the first clinical trial of gemcitabine and cisplatin showing partial response rates of 30–40%, and similar stable disease rates [1, 2], and the demonstration of significantly prolonged survival with pemetrexed and cisplatin [3] in selected patients with high enough performance status to tolerate the chemotherapy, as well as claims of improved survival following radical surgery (with chemotherapy and radiotherapy) [4, 5], more patients are submitting to active treatment regimes. “Trimodality therapy” with radical pleuropneumectomy, radiotherapy and chemotherapy still attracts some people with “early” disease [6].

Most reports of survival of patients with MM describe the experience of people referred to secondary or tertiary referral centres for consideration of treatment or for entry into treatment trials [7–13]. As a result, selection of younger patients with higher performance status who have a better

prognosis occurs. Analysis of survival of the first 81 cases on the Western Australian Mesothelioma Registry to 1980 revealed a median survival from the time of diagnosis of only 5.1 months [14]. Since then, other registry-based studies have been published that reveal longer survival times [15–22] and various factors that influence survival. This study is an extension of the earlier study using the Western Australian Mesothelioma Registry [14]. Western Australia has among the highest incidence and mortality rates for MM in industrialised countries for both males and females [23]. The high MM incidence is attributed to the mining of crocidolite at Wittenoom, a now defunct asbestos mining town in the north of the state [24], with wide dissemination of the asbestos state-wide. All cases of mesothelioma in Western Australia are well documented on the registry, which includes all known cases since the first was recognised in 1962. This study describes an improving survival experience and factors influencing survival of all cases of confirmed MM in a general population sample over five decades. It also derives a prediction equation for survival at the time of

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Received:

Jan 04 2011
Accepted after revision:
April 14 2011
First published online:
July 07 2011

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

diagnosis for contemporary cases. The study aimed to examine the effects of calendar period of diagnosis, age, sex, histological subtype, performance status at time of diagnosis and possible earlier diagnosis in recent years, when less invasive diagnostic modalities and more aggressive treatment regimes have been used, on the survival of all cases from Western Australia.

METHODS

All incident cases of cancer in Western Australia since 1980 (except nonmelanotic skin cancer) have been notifiable to the state's Cancer Registry. A separate mesothelioma registry was established in 1962. Patients included in the current Western Australian Mesothelioma Registry were identified from these registries where date and method of diagnosis, site of disease, and histological type have been recorded routinely for every case. All incident cases of mesothelioma in Western Australia are reviewed by a committee comprising the Western Australian Cancer Registry Principal Medical Officer, a pathologist, an occupational physician, a respiratory physician, an epidemiologist and a research assistant to document age, sex, dates and methods of diagnosis, histological type, site of disease, date of death, and available history of asbestos exposure. The written report of the pathologist responsible for the cytological or histopathological diagnosis of each case is considered and, where necessary and if available, the original slides are reviewed to confirm the diagnosis and to classify the disease type as epithelioid, sarcomatoid, biphasic, other or "not specified". Date of onset of symptoms and treatment received has been obtained for a subset of patients in the first and last decades of the study by review of all available clinical records. Performance status at the time of diagnosis has also recorded from the clinical records where sufficient information was available. The study was approved by the Western Australian Department of Health Human Research Ethics Committee (Perth, Australia).

Data in the registry has been supplemented from other sources. These sources include a retrospective study of all cases of MM Australia-wide, which was undertaken by canvassing all pathologists countrywide for MM diagnoses until 1980 [25] and records of the Australian Mesothelioma Registry/Surveillance Program [26]. In addition, the records of the Wittenoom worker and resident cohorts, which were established in 1975 and 1985, respectively, record all employees of the Australian Blue Asbestos Company and all township residents identifiable from available public records, and have allowed identification and complete follow-up of those who have developed MM [23]. A cancer prevention programme for people with previous asbestos exposure has also been conducted in Western Australia since 1990 (with >4,000 participants enrolled at some stage [27–29]). This provides details of their past exposures to asbestos and further improves the quality of the information available to the registry committee.

Statistical analyses

Survival analysis was performed by Cox regression. Prognostic factors used in the survival analysis included age at diagnosis, sex, tumour site, histological type, Eastern Cooperative Oncology Group (ECOG) performance status [30] and calendar year of diagnosis.

Based on the Cox regression findings, a Weibull survival function (accelerated failure time form) was developed using the same

variables, such that an algorithm for predicting survival in newly diagnosed cases of malignant mesothelioma could be constructed. Weibull regression explicitly models the underlying time variable, allowing prediction, whereas Cox regression treats the underlying time variable as a nuisance factor. Both methods assume proportional hazards.

RESULTS

There were 1,362 cases of MM between 1962 and 2005 (1,258 pleural and 102 peritoneal); 260 of these were exposed to asbestos as workers in the Wittenoom asbestos mines and mill, 56 were residents of the Wittenoom town site, 760 had known occupational exposure to asbestos other than in the Wittenoom mine or mill, 87 had residential exposure and only 199 had undetermined exposure. 64 (4.7%) had no known exposure to asbestos.

Survival analysis by age, sex, site, histological type, performance status and calendar year of diagnosis showed that younger females with pleural mesothelioma, epithelioid histology, better performance status and more recent diagnosis have the longest survival (table 1 and figs 1–4).

Survival improved after the 1970s and has made incremental improvements since then. Median (interquartile range) survival by decade from 1960 to 2005 was 64 (0–198), 177 (48–350), 221 (97–504), 238 (108–502) and 301 (134–611) days (fig. 1). The

TABLE 1 Survival times for malignant mesothelioma by prognostic factors

	Subjects	Survival days
Overall	1362	241 (108–515)
Sex		
Male	1181	235 (103–494)
Female	181	323 (137–640)
Calendar period		
1960–1969	8	64 (0–198)
1970–1979	58	177 (48–350)
1980–1989	265	221 (97–504)
1990–1999	568	238 (108–502)
2000–2005	463	301 (134–611)
Age at diagnosis yrs		
20–49	139	362 (195–626)
50–64	454	300 (151–570)
65–74	406	241 (98–537)
≥75	362	147 (49–350)
Histology subtype		
Epithelioid	455	340 (173–622)
Sarcomatoid	113	113 (45–189)
Biphasic	221	221 (101–461)
Site		
Pleural	1258	256 (113–532)
Peritoneal	102	134 (73–262)
ECOG performance status		
≤1	91	335 (219–595)
>1	30	188 (71–404)

Data are presented as n or median (interquartile range). ECOG: Eastern Cooperative Oncology Group.

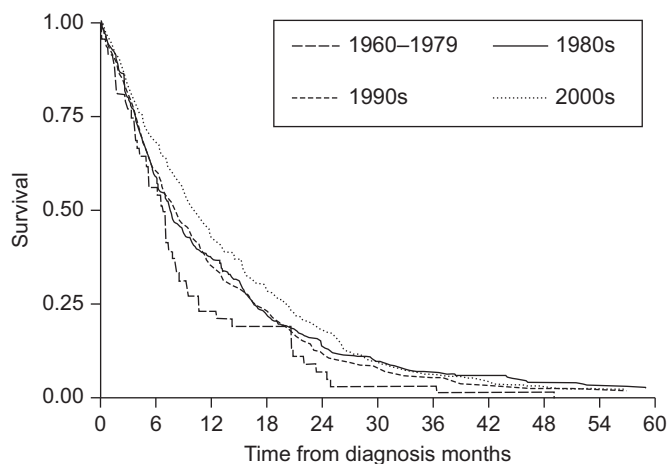


FIGURE 1. Change in survival with mesothelioma by decade of diagnosis.

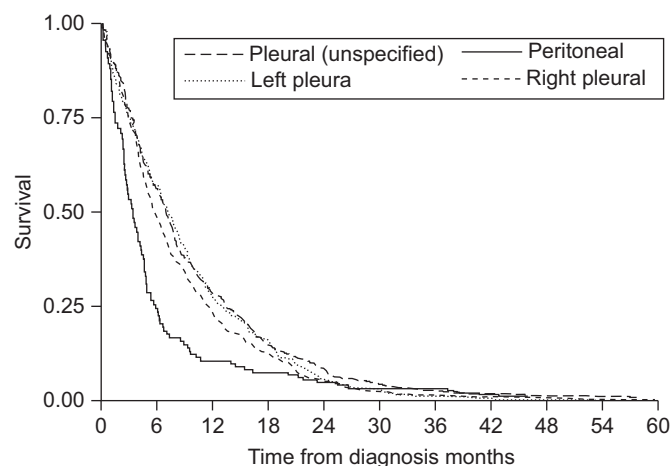


FIGURE 4. Difference in survival according to site of primary mesothelioma.

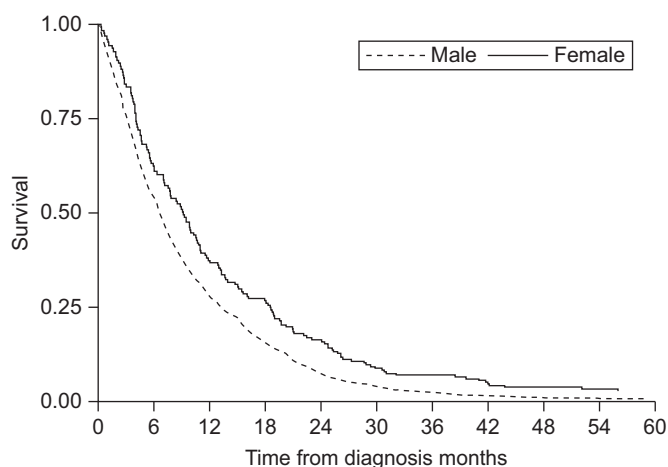


FIGURE 2. Difference in survival with mesothelioma between males and females.

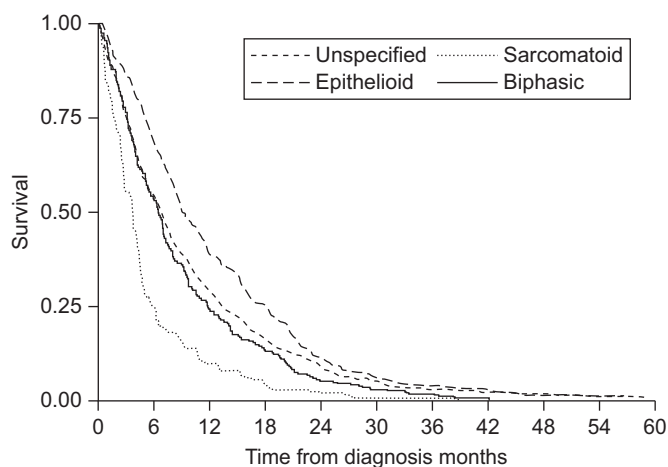


FIGURE 3. Difference in survival for different mesothelioma histological types.

time from presentation to diagnosis has not improved over the past 40 years. However, the time from onset of symptoms to diagnosis has decreased from 63 days in the decade 1971–1979 to 32 days in the period 2000–2005.

Patients who were younger at the time of diagnosis had longer survival. Median survival time ranged from 362 (195–626) days for cases diagnosed before they turned 50 yrs of age to 147 (49–350) days for those diagnosed after the age of 75 yrs (table 1). Females had longer survival time compared with males (table 2 and fig. 2). Patients with ECOG performance status >1 had a hazard ratio of 3.4 (95% CI 1.4–8.7). Patients with MM of the epithelioid histological subtype had a better prognosis for survival than those with biphasic histology who, in turn, had a better prognosis than those with sarcomatoid histology (fig. 3), and peritoneal mesotheliomas had the worst survival for the different sites (fig. 4). There were no significant differences in survival ($p=0.25$) between different exposure groups (Wittemoom, other occupational, residential, none and unknown).

Using the same variables as in table 2, the Weibull survival function indicated that survival in newly diagnosed cases of MM (in weeks) could be predicted as follows.

$$\text{Survival} = \exp(-t^{0.97} \exp((-1.04)(2.36 + 0.004(a/10)^3 - 0.002(a/10)^3 \ln(a/10) + 0.41f - 0.40p - 0.15l - 0.16r - 0.52s + 0.22e - 0.17b + 0.51d_{1980s} + 0.61d_{1990s} + 0.76d_{2000s})))$$

where a is age in years and t is time after diagnosis in months, and the following variables are either 1 (if true) or 0 (if untrue): f (female sex), p (peritoneal MM), l (left pleural MM), r (right pleural MM), s (sarcomatoid subtype), e (epithelioid subtype), b (biphasic subtype), d_{1980s} (diagnosed in 1980s), d_{1990s} (diagnosed in 1990s) and d_{2000s} (diagnosed in 2000s).

An example indicating contrasting expected outcomes is shown (fig. 5).

DISCUSSION

The Western Australian Mesothelioma Registry has collected comprehensive data on all cases of MM in the state over the past 40 yrs, including the first diagnosed case, in 1962. Using these data, this study demonstrates the survival experience of patients with MM from a geographically defined general

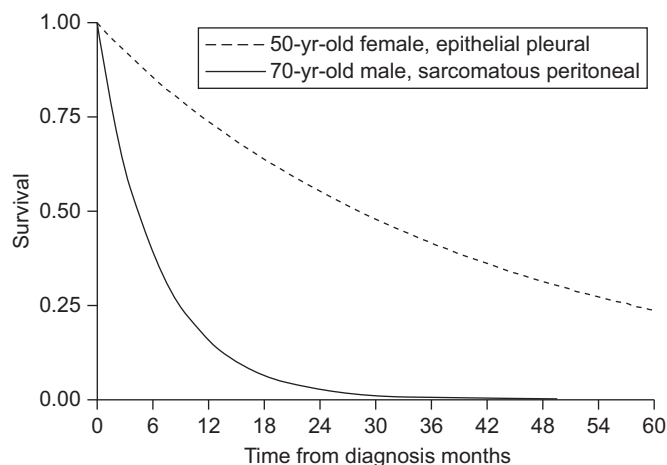
TABLE 2 Determinants of survival using Cox regression

	HR (95% CI)	p-value
Female	0.75 (0.63–0.89)	0.001
Peritoneal	1.53 (1.21–1.94)	<0.0005
Left pleural	1.14 (0.96–1.34)	0.14
Right pleural	1.15 (0.99–1.34)	0.07
Sarcomatoid	1.81 (1.48–2.22)	<0.0005
Epithelioid	0.80 (0.69–0.92)	0.001
Biphasic	1.12 (0.95–1.33)	0.18
1970s	0.61 (0.22–1.71)	0.35
1980s	0.47 (0.17–1.27)	0.14
1990s	0.46 (0.17–1.24)	0.13
2000s	0.41 (0.15–1.09)	0.08

HR: hazard ratio.

Australian population without biases resulting from selection of those who may be fit for some form of treatment or other, or where referral to a tertiary health institution is dependent on age and performance status. It thereby permits an estimate of prognosis to be made at the time of diagnosis, an especially important issue for patients themselves, their families and legal representatives, and compensating authorities.

Survival has improved for each decade from the 1960s to the 2000s. Most other registry-based studies have been conducted since the late 1980s and survival times were longer than reported in our earlier study from the Western Australian registry [14]. Survival times from other registry-based studies were similar for the corresponding decades in the current study. Although we found progressive improvements in survival time for successive decades from the 1960s, calendar period has not been associated with improved prognosis for most studies starting from the late 1980s [16, 17, 19]. However, MONTANARO *et al.* [19] did report a significantly greater proportion of long-term survivors in the period 1999–2001 (8%) compared with the period 1990–1992 (3.7%).

**FIGURE 5.** Predicted survival for two example "patients".

The improved prognosis with time is probably due to earlier presentation and diagnosis, and improved treatment. A review of a subset of cases in the first and last decades of this study showed that, although the time between first presentation and diagnosis of MM did not change, time between reported onset of symptoms and diagnosis did reduce significantly (63 days in the 1970s to 31 days in the 2000s). This suggests that earlier diagnosis is due to patients' greater awareness of their symptoms, leading to earlier presentation in primary care or speedier referral by general practitioners to specialists. Studies involving cases recorded since the late 1980s have often not reported a difference in prognosis between treatment modalities or between treatment and no treatment [16, 19, 31], although in one study of cases from 1973 to 1984, treatment (surgery) was associated with an improved outcome [21]. It is possible that since the early 1990s, there has been little change in treatment efficacy, that treatment effects are restricted to small subgroups of patients [17] or even that treatments have a deleterious effect on almost as many patients as they benefit. However the results are also consistent with there being a treatment effect in the past two decades, attributable to the use of gemcitabine and cisplatin, which improve partial reference rate [1], and pemetrexed and cisplatin, which improved survival in a randomised trial [3].

The registry does not have access to treatment information.

This study again shows that patients with MM of epithelioid histological subtype have a better prognosis for survival than those with either biphasic or sarcomatoid histology [15, 17, 19, 20]. This raises the issue of there being different types of genetic damage, resulting in the different histological forms of disease or different cells of origin of the different mesothelioma cell types. It is also consistent with their being greater chemoresistance in patients with sarcomatoid mesothelioma.

In recent years, subjects with the sarcomatoid subtype of MM have tended to be excluded from published clinical trials of active treatment because they do not respond as well as those with epithelioid or biphasic subtypes. Exclusion of these and older patients from clinical trials tends to bias the overall survival of any study's participants and gives the impression that the prognosis of MM is improving to a greater extent than can be attributed to the increased use of chemotherapy, surgery and radiotherapy.

This study also confirms the better prognosis associated with being female, which was not explained by differences in category of exposure, as well as being younger at time of diagnosis, better performance status and pleural site of disease. Longer survival times for females have been reported previously [18, 20, 31, 32]. Biological reasons for the sex difference are not known and some authors have proposed that some of the difference may be due to misclassification as peritoneal MM of other abdominal neoplasms in females, *e.g.* ovarian cancer, which has a better prognosis [18, 31]. The analysis of the Italian National Mesothelioma Register [18] reported increased survival times in females with peritoneal, but not pleural, MM. In the current study, however, the improved survival time for females was independent of the site of the cancer as well as the other prognostic factors investigated.

Despite increasing resources and treatment costs of MM there have been only modest improvements in survival over the past

40 yrs. The present population-based study shows that median survival overall is still limited to <1 yr from the time of diagnosis. Therefore, primary prevention remains the most urgent priority for MM. The use of asbestos by Australian industry has been declining since the 1980s, and importation and production of all forms has been banned since 2003. Removal, renovation and disposal of *in situ* asbestos are also now tightly regulated (but not well complied with [33]). As a result, the incidence of MM in Western Australia has ceased to rise since the middle of the last decade, reflecting these provisions and the known long latency period characteristic of the disease [23]. In countries where the production and use of asbestos continues, the epidemic of MM will continue unless effective primary preventative measures are enforced or secondary preventative measures discovered [28, 29], and until better cancer treatments emerge for this disease, substantial reductions in mortality will not be made.

STATEMENT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

J. Hui (PathWest Laboratory Medicine WA, Nedlands, Australia) provided assistance with document formatting and preparation.

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