

## Population-based survival for malignant mesothelioma after introduction of novel chemotherapy

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## ABSTRACT

Malignant mesothelioma is known for its dismal prognosis and poor response to conventional treatment. Chemotherapy with cisplatin-antifolate combinations recently showed promising response rates and prolonged survival in randomised trials.

To assess the impact of this development on clinical practice and survival at a population-based level, treatment patterns and survival trends were studied for patients diagnosed with mesothelioma in the period 1995-2006. 4731 records were retrieved from the Netherlands Cancer Registry and chemotherapy use and median survival were analyzed.

For the periods 1995-1998 to 2005-2006, chemotherapy use increased from 8% to 36%. Median survival increased over time from 7.1 months to 9.2 months. For pleural mesothelioma, multivariable analysis demonstrated that survival was poorer for elderly patients and sarcomatoid tumours. The prognostic impact of chemotherapy increased with time. Median survival for chemotherapy treated patients improved from 10.1 months (1995-1998) to 13.1 months (2005-2006). For peritoneal mesothelioma, median survival was poor (3.9 months) but better for women and younger patients.

This study demonstrates that chemotherapy use increased at a national level and coincided with an improvement in survival. The novel chemotherapy regimen appears to be more effective but, due to the observational nature of this study, alternative explanations cannot be excluded.

## INTRODUCTION

Malignant mesothelioma (MM) is an aggressive disease, known for its relation with asbestos exposure and its poor prognosis. Long-term survival is rarely seen and local treatment with radiotherapy or surgery tends to be unsuccessful. Response to single agent or combination chemotherapy used to be limited [1] until a novel agent was introduced, pemetrexed, that showed a response rate of 32% in combination with carboplatin [2]. Randomized trials subsequently showed a survival benefit of ten weeks for combination treatment with pemetrexed-cisplatin [3] or raltitrexed-cisplatin [4], compared to single-agent treatment with cisplatin.

At a population level, the impact of new treatment strategies is often difficult to predict or determine. Trials tend to be restricted to young patients with limited disease whereas most patients are diagnosed after age 65, when comorbidity or performance status may preclude cytotoxic treatment [5]. Moreover, availability of new drugs may be restricted due to the costs and some drugs, like raltitrexed, may not even become registered for use in clinical practice.

To assess the application of chemotherapy treatment over time and its impact on survival in a population-based setting, we analysed patient records from the Netherlands national cancer registry for the period 1995-2006.

## METHODS

Electronic records for patients with malignant mesothelioma, diagnosed from 1995 through 2006, were derived from the Netherlands National Cancer Registry (NNCR). This registry covers a nation with 16.6 million inhabitants and approximately 100 hospitals. Newly diagnosed cancer patients are notified to the registry through hospital discharge diagnoses and notes from pathology departments. Due to the high incidence rates in the Netherlands, most pathologists have considerable experience with the differential diagnosis of mesothelioma but still 60% of cases are sent for review to the national mesothelioma panel, mainly to substantiate compensation requests. After notification, trained registration clerks collect data from the clinical records, including gender and age, tumour site and morphology and date of diagnosis. Date of diagnosis is determined by the day of acquiring cytology or histology material for microscopical verification. Annual follow-up information is obtained from the Centralized Civil Register.

Mesothelioma of the pericardium and tunica vaginalis testis were excluded, as were all cases in which diagnosis was based on clinical examination only. As of 2003, TNM stage is recorded by the NNCR but this information was not used because of the absence of a standard staging policy. Stage information based on radiological examinations is considered unreliable and surgical staging is only performed in a minority of cases. Only the initial treatment is recorded, and noted as surgery, radiotherapy and/or chemotherapy. Information on treatment after progression is not recorded. As the surgery code may include diagnostic surgery and radiotherapy may have been applied to prevent tumour invasion into biopsy or drainage intervention sites, both information on surgery (3.7% of cases) and radiotherapy (13% of cases) was ignored in the analyses. Curative surgery as part of multimodality treatment is mainly used in experimental studies and has only been performed in a limited number of highly selected patients [6]. Unfortunately, chemotherapy regimens are not coded in a standard manner by the NNCR. Only for the Rotterdam Registry subset, approximately 20% of all cases, information on type of chemotherapy was available. Year of diagnosis was recoded into four periods: from 1995-1998, 1999-2002, 2003-2004, 2005-2006. The international expanded access program for Pemetrexed [7] enclosed the Netherlands as of 2004 and comprised 181 patients from 12 centres [8], that also included referrals from other hospitals. Pemetrexed became registered at the end of 2005.

Chemotherapy use was tabulated for categorical subgroups and tested for significance with chi-

square analysis and multivariable logistic regression. Results for significant ( $p < 0.05$ ) predictors are reported with odds ratios and 95% confidence intervals. Survival was calculated from date of diagnosis until date of death or censored at January 1 2009, using actuarial analysis. Survival patterns for pleural and peritoneal mesothelioma proved non-proportional. Therefore, multivariable regression using proportional hazards analysis was performed for both sites separately. Prognostic factors were tested for significance using the likelihood ratio test and were included in the model for  $p < 0.05$ . For pleural mesothelioma, a chemotherapy\*period interaction term was introduced to account for the time-dependent effect of chemotherapy.

## RESULTS

This study comprised a total of 4,731 patients with malignant mesothelioma, 4,115 men (87%) and 616 women (13%) [Table 1]. Median age was 68 years, for both pleural as peritoneal mesothelioma, and 35% of patients was aged 70-79 years; 11% was 80 years or older. Peritoneal mesothelioma were uncommon (5.6%) and more frequent in women (10.7%) than in men (4.9%).

In 57% of cases mesothelioma type was specified. Epithelioid tumours were most common (46%) against 5% for sarcomatoid tumours and 6% with mixed tumour type. Incidence increased in time from an average annual number of 344 in the period 1995-1998 to an average number of 486 in 2005-2006.

Chemotherapy use increased in time, from 8% in the period 1995-1998 to 36% in the period 2005-2006 (OR=8.4) [Table 1]. Chemotherapy was less often used in the elderly; from 11% for those aged 70-79 years (OR=0.22) to 3% in patients 80 years or older (OR=0.04). Patients with epithelioid tumours were more often treated with chemotherapy (22%) than those with sarcomatoid tumours (15%) or mixed type tumours (15%). Gender and tumour site had no significant impact on chemotherapy use. The novel antifolate-platinum schedule was introduced in 2003-2004 and became the standard regimen in 2005-2006 [Table 2].

Median survival was 8.1 months for pleural mesothelioma and 3.9 months for peritoneal mesothelioma [Table 3]. Median survival for patients with sarcomatoid tumours was significantly worse (3.6 months) than for patients with mixed type tumours (7.1 months) or those with epithelioid tumours (10.1 months). Elderly patients had half the survival time (5.2 months for those 80 years and older) of younger patients (10.5 months for those aged 20-59 years). For patients who received chemotherapy, median survival improved with time from 10.1 months in the first period to 13.3 months in the last period. Two-year survival was only 13%.

For pleural mesothelioma, multivariable analysis identified age, tumour type and chemotherapy as independent prognostic factors [Table 4]. Gender ( $p=0.44$ ) was not of statistical significance. The prognostic effect of chemotherapy was modified by period and increased with time [Figure 1]. For patients who did not receive chemotherapy, survival did not change over time ( $p=0.23$ ). For peritoneal mesothelioma, only gender (RR for women 0.61) and age were of prognostic significance in multivariable analysis [Table 5]. Tumour type ( $p=0.21$ ), period ( $p=0.27$ ) and chemotherapy ( $p=0.11$ ) were not of statistical significance.

## DISCUSSION

This population-based series presents 4,464 patients with pleural mesothelioma with a median survival of 8.1 months, which is less than the 9.8 months reported by a large study from Italy [9]. The Italian study combined results from 9 regional registries to produce a total number of 4,100 cases, diagnosed in the period 1990-2001. A recent study from Western Australia [10] analysed survival trends for 1,362 patients diagnosed from 1960 to 2005 and reported improvement of median survival up to 10 months for the period 2000-2005. In contrast to the small series from randomized trials or specialized centers, population-based studies are not affected by selection bias, which is reflected by a high proportion of elderly patients. Median age in chemotherapy trials tends to be around 64 years as frail patients get excluded for poor performance status or comorbidity.

Chemotherapy use was inversely related to age but gradually increased in time from 8% in the first period to 36% in the last period. In a population-based study from Leeds, UK, [5] comprising patients diagnosed from 2002 to 2005, 37% were considered fit for chemotherapy but half of those declined. Palliative chemotherapy is now considered standard treatment in Europe [11, 12] even though a recent British trial [13], comparing best supportive care, a platinum combination (MVP) and Vinorelbine, could not demonstrate a benefit with respect to survival or quality of life for the chemotherapy arms. Despite struggles with reimbursement, the antifolate-platinum regimen was quickly adopted as a standard in the Netherlands. The actual chemotherapy use may have been higher than recorded by the cancer registry, especially when treatment was delayed until progression. In several other countries, availability was limited due to financial restrictions [14].

Median survival improved with time from 7.1 to 9.2 months, presumably related to the introduction of the new chemotherapy regimen. For the first period, prognosis seemed better after chemotherapy (10.1 versus 6.8 months) but the survival difference faded after controlling for age and tumour type. This finding confirms the 1998 review on chemotherapy trials [1], which concluded that none of the available agents showed meaningful efficacy. The chemotherapy-period interaction term suggests that chemotherapy became more effective with time but efficacy of chemotherapy cannot be reliably evaluated in observational studies. Lack of information on important prognostic factors such as extent of disease or performance status may introduce residual confounding. Even with modern methodology such as propensity scores and instrumental variable methods [15], selection bias cannot be ruled out.

Immortal time bias [16] poses another problem in non-randomized studies as survival is calculated from day of diagnosis and, by definition, chemotherapy patients cannot die between diagnosis and their first cycle, hence getting a survival head start. The latter bias may also explain why survival appears to be better for patients who receive post-study chemotherapy [17].

Apart from more and better chemotherapy, several alternative explanations may clarify the increase in survival. For example, expertise in palliative care certainly increased within the last decade. Also, tumours may be diagnosed earlier [10], due to wider knowledge of the effects of asbestos exposure, due to a less pessimistic view on the clinical management of mesothelioma patients or due to better prospects for financial compensation after confirmation of the diagnosis [18].

Multivariable survival analysis also identified age and histotype as independent prognostic factors for pleural mesothelioma. At higher age, patients are less able to cope with a disease that is characterised by local tumour progression. In other types of cancer, survival is often determined by progression of distant metastases but in pleural mesothelioma the symptom burden is inflicted by invasion of intrathoracic structures [11]. The prognostic impact of age may, however, be confounded by differences in stage distribution. Diagnostic delay tends to be longer for the elderly, which will produce a higher stage at diagnosis and hence a poorer survival. A staging system for mesothelioma has been developed [19] but current imaging techniques have limited value in predicting local tumour spread or involvement of mediastinal lymph nodes [20]. Surgical staging provides more accurate information but this is only performed when patients are considered eligible for radical surgery. Stage bias may even explain the poor prognosis for sarcomatoid tumours, known for their more invasive growth pattern.

The clinical behaviour of peritoneal mesothelioma is clearly different from its pleural counterpart. Survival was much poorer, probably due to later diagnosis. Similar to the situation for ovarian cancer, symptoms tend to be non-specific and tumour load can be extensive at diagnosis. Women comprise 23% of peritoneal mesothelioma cases against 12% of pleural mesothelioma. The prolonged survival for women may be related to earlier diagnosis or to misclassification of ovarian tumours. Our median survival of 3.9 months is evidently lower than the 5.6 months reported for Italy [21] but difficult to compare because 41% of cases was female in the Italian study. Response rates to antifolate-platinum treatment are similar to those for pleural lesions [22]. Cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy might be a promising treatment alternative given the 47% five-year

survival reported by Yan [23], albeit in selected patients with a mean age of 50 years.

In conclusion, despite introduction of novel chemotherapy regimens, malignant mesothelioma is still a fatal disease with a median prognosis of less than a year. With disease incidence at its peak, now is the time to test new treatment options, preferably in randomized controlled trials. Within ten years, the number of mesothelioma patients will decrease and the ageing of the patient population will make them less suitable for inclusion in trials with toxic treatment. Quality of life should be a major endpoint in these trials and prevention remains the best option to decrease mortality from mesothelioma.

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Table 1. Determinants of treatment with chemotherapy in patients with mesothelioma

		Number	Proportion (%) <sup>1</sup>	Chemotherapy (%) <sup>2</sup>	Odds ratio	95% C.I.
Site	Pleural	4464	94%	17%	-	not significant
	Peritoneal	267	6%	16%		
Tumour type	not specified	2026	43%	13%	1	
	sarcomatoid	226	5%	15%	0.9	0.6 - 1.4
	epitheloid	2194	46%	22%	1.4	1.1 - 1.6
	mixed	285	6%	15%	1.2	0.8 - 1.7
Gender	Men	4115	87%	17%	-	not significant
	Women	616	13%	17%		
Age	20-59	961	20%	29%	1	
	60-69	1624	34%	21%	0.54	0.4 - 0.7
	70-79	1630	35%	11%	0.22	0.2 - 0.3
	80+	516	11%	3%	0.04	0.03 - 0.08
Period	1995-1998	1377	29%	8%	1	
	1999-2002	1542	33%	11%	1.4	1.1 - 1.8
	2003-2004	840	18%	20%	3.1	2.4 - 4.0
	2005-2006	972	21%	36%	8.4	6.5 - 10.8

1 = percentage of the whole population

2 = percentage of the patients in each group

Table 2. Type of chemotherapy used over time (% , Rotterdam region only)

	1995-1998 n=17	1999-2002 n=30	2003-2004 n=26	2005-2006 n=72
Antifolate-platinum	0	0	62	85
Antifolate	0	0	23	1
Platinum	47	77	4	3
Other	53	13	4	3
Not specified	0	10	8	6

Table 3. Determinants of survival in patients with mesothelioma

		Median survival (months)	2-year survival	p-value
Site	Pleural	8.1	13%	<0.001
	Peritoneal	3.9	13%	
Tumour type	not specified	6.1	11%	<0.001
	sarcomatoid	3.6	8%	
	epitheloid	10.1	16%	
	mixed	7.1	9%	
Gender	Men	7.7	13%	0.073
	Women	8.1	15%	
Age	20-59	10.5	19%	<0.001
	60-69	9.0	14%	
	70-79	6.5	10%	
	80+	5.2	6%	
No chemotherapy	1995-1998	6.8	11%	0.125
	1999-2002	7.3	13%	
	2003-2004	6.2	11%	
	2005-2006	7.1	11%	
Chemotherapy	1995-1998	10.1	16%	0.002
	1999-2002	11.9	17%	
	2003-2004	12.7	19%	
	2005-2006	13.3	22%	

Figure 1. Two-year survival for patients with malignant pleural mesothelioma who were treated with chemotherapy, stratified by period of diagnosis

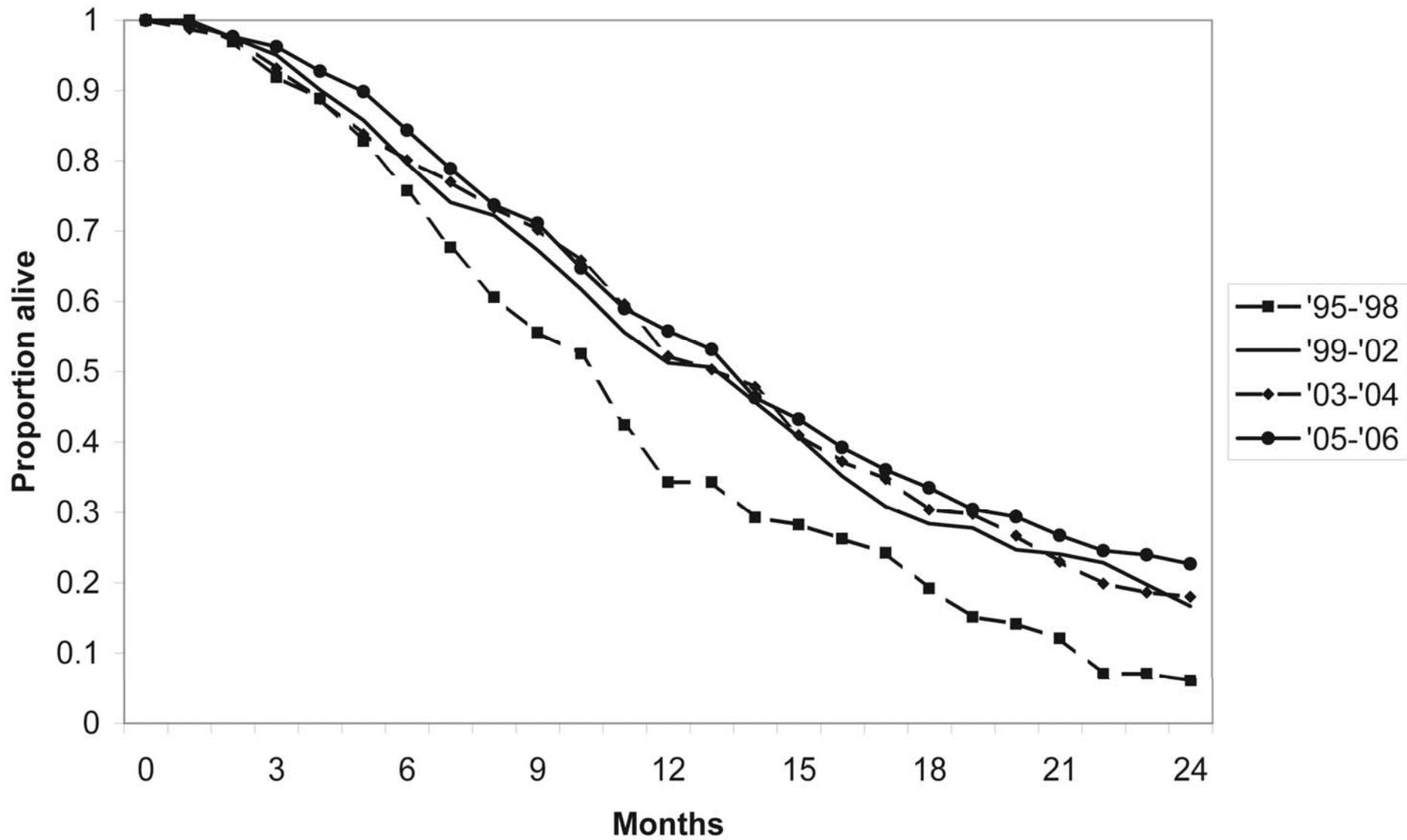


Table 4. Multivariable analysis of survival in patients with pleural mesothelioma

		Risk ratio	95% C.I.
Tumour type	not specified	1	
	sarcomatoid	1.33	1.15-1.53
	epitheloid	0.76	0.71-0.81
	mixed	1.00	0.88-1.13
Age	20-59	1	
	60-69	1.16	1.06-1.26
	70-79	1.41	1.29-1.54
	80+	1.71	1.52-1.92
Chemotherapy versus Period interaction term	None	1	
	Chemo 1995-1998	0.99	0.81-1.21
	Chemo 1999-2002	0.83	0.70-0.97
	Chemo 2003-2004	0.78	0.66-0.92
	Chemo 2005-2006	0.64	0.56-0.73

Table 5. Multivariable analysis of survival in patients with peritoneal mesothelioma

		Risk ratio	95% C.I.
Gender	Men	1	
	Women	0.61	0.45-0.84
Age	20-59	1	
	60-69	1.86	1.27-2.73
	70-79	2.53	1.69-3.79
	80+	2.34	1.36-4.03