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Analysis of survival of mesothelioma cases in the Italian register (ReNaM)

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Abstract

The Italian National Mesothelioma Register (ReNaM) was set up at ISPESL (the National Institute for Occupational Safety and Prevention) in 1993. Five Italian regions (Piedmont, Liguria, Emilia-Romagna, Tuscany and Puglia, with a total of approximately 17 500 000 inhabitants) agreed to record mesothelioma cases according to guidelines established by ISPESL, to define exposure to asbestos and transmit the data to ISPESL. We describe an analysis of survival of 429 mesothelioma cases—392 pleural, 34 peritoneal and 3 in the pericardium—diagnosed during 1997, with variable follow-up from June 1999 to December 2001. The Kaplan–Meier method was used to estimate survival rates, the log rank non-parametric test and Cox proportional hazard model to assess the role of prognostic factors such as age, gender, morphology, level of diagnostic certainty and modality of exposure. Median survival was 275 days (95% confidence interval (CI) 241–309) for pleural mesotheliomas and 157 days (95% CI: 118–196) for peritoneal mesotheliomas. Survival after diagnosis of malignant pleural mesothelioma showed a statistically significant linear trend for age group at diagnosis, for males and females ($P = 0.006$ and 0.008, respectively). The Cox proportional hazard model gave an adjusted relative risk (RR_{adj}), for the fibrous histotype, of 2.96 (95% CI: 1.28–6.81; $P = 0.012$) compared with cases with unspecified morphology; for epithelioid and biphasic morphologies, the risk was lower than unity. There was no significant difference in survival for cases with confirmed exposure (occupational, household or environmental) or without.

Keywords: Mesothelioma; National register; Survival analysis; Prognostic factors

1. Introduction

Malignant mesothelioma (MM) is a highly lethal tumour with a low incidence, selectively induced by exposure to asbestos. It arises most frequently in the serous of the pleura and peritoneum, but cases have been reported in the pericardium and in the *tunica vaginalis* testicular. Incidence rates of mesothelioma, related to the large-scale use of asbestos in many industrial countries up until the 1980s, are rising and in view of the long latency of the disease—on average more than 30 years—this tendency can be expected to continue until at least 2020 [1,2].

In Italy, annual production of asbestos in the 1980s amounted to 100 000–130 000 tons and it was used in numerous industrial applications. Between 1988 and 1997, a total of 9094 deaths from tumours of the pleura were recorded, giving a standardised annual rate of 1.61 per 100 000 inhabitants. The incidence figures recorded by the Italian national tumour register show some parts of Italy, such as the provinces of Trieste and Genoa, where the rates are among the highest in the world (annual rates are 6.4 and 5.0, respectively for males, standardised to the world population) [3,4].

The Italian National Mesothelioma Register (ReNaM) was set up in 1993 at the *Istituto Superiore*

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Prevenzione e Sicurezza Lavoro (National Institute for Occupational Safety and Prevention—ISPESL). Some Italian regions already had a system for active notification of cases and reconstruction of the exposure to asbestos. In 1988, Tuscany set up the *Archivio Regionale Toscano dei Mesoteliomi Maligni* (Tuscan Regional Archives of Malignant Mesotheliomas) which operates throughout that region [5]. In 1989, Puglia set up a regional register for cases of mesothelioma [6], and 1990 saw the start of the Piedmontese Mesothelioma Register [7]. In Liguria and Emilia-Romagna epidemiological surveillance started at municipal level; Genoa followed in 1994, after Reggio Emilia, in 1993, then in 1996 it was extended to the whole region [8,9].

ReNaM published figures for incidence and asbestos exposure for the period from 1993 to 1996 and for the year 1997 for these five regions, which covers approximately 40% of the Italian population and 45% of the annual mortality from pleural tumours [10]. Since then Regional Operational Centers (COR) have been set up in Lombardy, Veneto, Sicily, Basilicata, the Marches and Campania, extending the ReNaM coverage to more than 80% of the resident population.

There is no absolute concordance between published studies of the prognostic factors in malignant pleural mesothelioma and opinions differ on how asbestos exposure influences survival [11–13]. The aim of this study was therefore to present data on survival of incident cases of malignant mesothelioma in 1997 for the five Italian Regions listed, in order to add to the epidemiological picture obtained from clinical studies and to help establish the prognostic role of the main demographic factors (gender, age) and diagnostic and exposure variables (morphology, level of diagnostic certainty, modality of exposure).

2. Patients and methods

Cases are collected by the COR from health care institutions in each region that diagnose and treat cases of mesothelioma. These include pathology and histology units, lung disease and chest surgery wards. Hospital discharge records and death certificates are consulted to check that all available information has been collected. Reference diagnostic protocols are used to standardise the diagnostic criteria for mesothelioma, and cases are classified depending on the level of diagnostic certainty achieved.

Occupational history, lifestyle habits and areas of residence for each case are obtained by interviewing people directly or, if they are not available, someone close to them (indirect interview) who can provide information on the case's work and life history, using a standard questionnaire, administered by a trained interviewer.

Exposure is classified by an industrial hygienist who consults the available documents and applies his own knowledge of industrial conditions to establish whether the subject's work, private life or any particular environmental conditions could have involved exposure to asbestos. Exposure is classified using the standard grid in accordance with national guidelines [10].

We analysed information on survival of 429 cases of malignant mesothelioma diagnosed in 1997 in Piedmont (136), Liguria (135), Emilia-Romagna (72), Tuscany (45), and Puglia (41), with follow- up from June 1999 to December 2001. Of these, 392 were pleural, 34 peritoneal and 3 pericardial. For 20 cases, we could not establish whether they were still alive, and 38 were still alive at the last check (Table 1).

The data presented refer to survival at six months, one, two, three and four years, by site and gender. Survival was calculated by the actuarial method at monthly intervals, and median survival with confidence intervals (CI) was obtained by the Kaplan–Meier method.

We established the significance of differences in the distribution of survival by gender and register using the non-parametric log rank test, adjusted for age. The log rank test was also used to check for a linear trend in survival in relation to age in three brackets (up to 64, 65–74, more than 74 years). We used Cox's proportional hazard model to assess how histotype, level of diagnostic certainty and modality of exposure influenced mesothelioma survival.

We estimated the relative risk (adjusted for all the other variables), for gender, age group, and cases with biphasic, fibrous or epithelioid forms, compared with non-specified ones; for cases with a diagnosis of suspected MM compared with definite mesothelioma, and for cases with exposure to asbestos (definite, probable or possible occupational, household or environmental) compared with those with unknown or unlikely exposure (after reconstructing the working and environmental history by direct interviews or interviews with someone living with the case). The goodness of fit of the model to empirical data was assessed using the log likelihood test. All statistical analyses were done using the Statistical Package for the Social Sciences (SPSS) (version 10.0).

3. Results

Median survival of incident cases in 1997 was 275 days (279 (95% CI: 245–313) for males and 263 (95% CI: 184–342) for females) for pleural mesothelioma ($n = 392$) with 95% CI of 241–309; for peritoneal mesothelioma ($n = 34$) it was 157 days (148 (95% CI: 84–212) for males and 252 (95% CI: 0–551) for females), with 95% CI of 118–196 (Table 2). The difference in the distribution of survival by gender adjusted for age was not significant for pleural mesothelioma (log rank

test = 0.01; $P = 0.91$) and for peritoneal (log rank test = 1.42; $P = 0.23$). There were three cases of mesothelioma of the pericardium (two females and one male) who died less than a year from diagnosis. For Tuscany and Puglia number of cases is too small (4 and 1 respectively) for a reliable estimate.

Survival after a diagnosis of malignant tumour of the pleura showed a significant linear trend for age at diagnosis, for both males and females (log rank test 10.42; $P = 0.006$, and 9.60; $P = 0.008$, respectively); the median survival for pleural mesothelioma in males was 312 days (95% CI: 245–379) for the 0–64 year age group, 286 (95% CI: 216–356) for those aged 65–74 years and 151 (95% CI: 116–186) for those 75+ years (375 (95% CI: 136–615), 225 (95% CI: 130–320), 89 (95% CI: 0–195), respectively in females) (Fig. 1). The trend was not significant for patients with peritoneal mesothelioma.

Table 1
Cases of malignant mesothelioma (MM) in 1997 by gender, age, diagnosis, exposure modality and morphology

Variable	Modality	Males	Females
Site	Pleura	285	107
	Peritoneum	21	13
	Pericardium	1	2
Age (years)	⩽54	33	9
	55–64	72	28
	65–74	127	52
	⩾75	75	33
Diagnosis	MM certain	234	92
	MM suspected	73	30
Exposure to asbestos	Confirmed (occupational, household, environmental)	117	23
	Not confirmed (unknown, unlikely)	37	21
	Not specified	153	78
Morphology	Epithelioid	133	45
	Biphasic	17	12
	Fibrous	18	5
	Not specified	139	60
Vital status	Dead	272	99
	Alive	23	15
	Lost to follow-up	12	8
Total		307	122

MM, malignant mesothelioma.

Analysis by register of origin showed the median survival for pleural mesotheliomas ranged from 225 days (95% CI: 145–303) for Piedmont, to 291 days (95% CI: 242–304) for Tuscany and 296 (95% CI: 247–343) for Liguria, with, in between, 240 days (95% CI: 78–339) for Puglia and 251 (95% CI: 182–320) for Emilia-Romagna. This variability did not reach statistical significance (log rank test adjusted for age = 2.14; $P = 0.71$). For peritoneal mesotheliomas, median survival of the 14 cases in Piedmont was 150 days (95% CI: 10–289), 135 days (95% CI: 0–316) for the 7 cases in Liguria and 120 days (95% CI: 86–153) for 8 cases in Emilia-Romagna.

The histological type of pleural mesothelioma was not specified in 46% of cases (179/392). Most of those specified were epithelioid (162), with 28 and 23 cases of biphasic and fibrous disease, respectively. Peritoneal mesothelioma were epithelioid in 16 of the 17 definite cases. Survival was strongly correlated with morphology (Fig. 2). The log rank test adjusted for age induced us to refute the hypothesis of survival being independent of histological type, with a 0.01% probability of error. For the 1997 incident cases of pleural mesothelioma in the ReNaM, Cox's proportional hazard model gave a relative risk adjusted for fibrous histotype almost three times that for cases with unspecified morphology ($P = 0.012$); the risk for cases with epithelioid or biphasic morphology was lower than unity. Linear trend for age is confirmed by the results of the Cox model.

Exposure to asbestos was not decisive for survival, which for exposed cases (occupational, household or environmental) was much the same as for cases without confirmed exposure (adjusted relative risk (RR_{adj}) = 1.11; $P = 0.6$). The risk was significantly higher for cases with a diagnosis of suspected mesothelioma ($RR_{adj} = 1.85$; $P = 0.01$) than for those with a definite diagnosis (Table 3).

4. Discussion

The ReNaM survival figures give a good representation of the situation, based on an active system of seeking cases, with standard tools and methods, covering a

Table 2
Survival (%) by gender and site at six months, one, two, three and four years and median survival (95% Confidence Interval) by Kaplan–Meier method

	Pleura			Peritoneum		
	Males ($n = 285$)	Females ($n = 107$)	Total ($n = 392$)	Males ($n = 21$)	Females ($n = 13$)	Total ($n = 34$)
6 months	59.0	55.5	58.1	28.6	61.5	41.2
1 year	35.1	36.0	35.3	23.8	38.5	29.4
2 years	16.1	17.3	16.3	19.1	38.5	26.5
3 years	6.2	9.9	7.1	12.7	25.6	17.7
4 years	4.0	8.6	5.3	12.7	25.6	17.7
Median survival in days (95% CI)	279 (245–313)	263 (184–342)	275 (241–309)	148 (84–212)	252 (0–551)	157 (118–196)

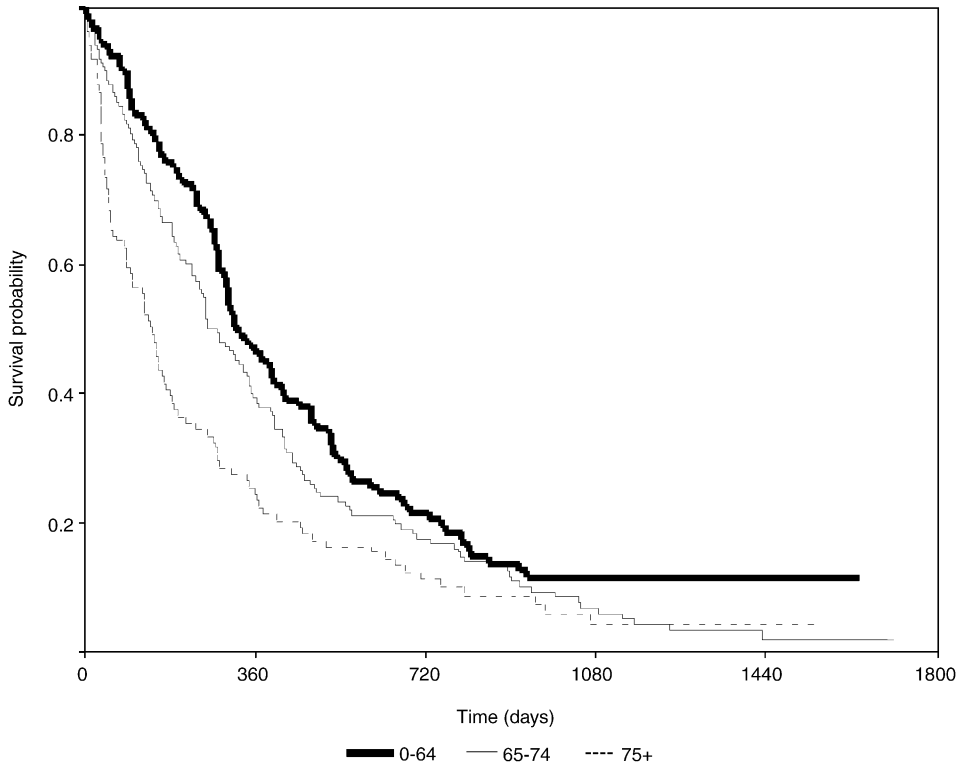

Fig. 1. Kaplan–Meier survival curve for pleural mesothelioma cases by age (0–64, 65–74, 75+ years).

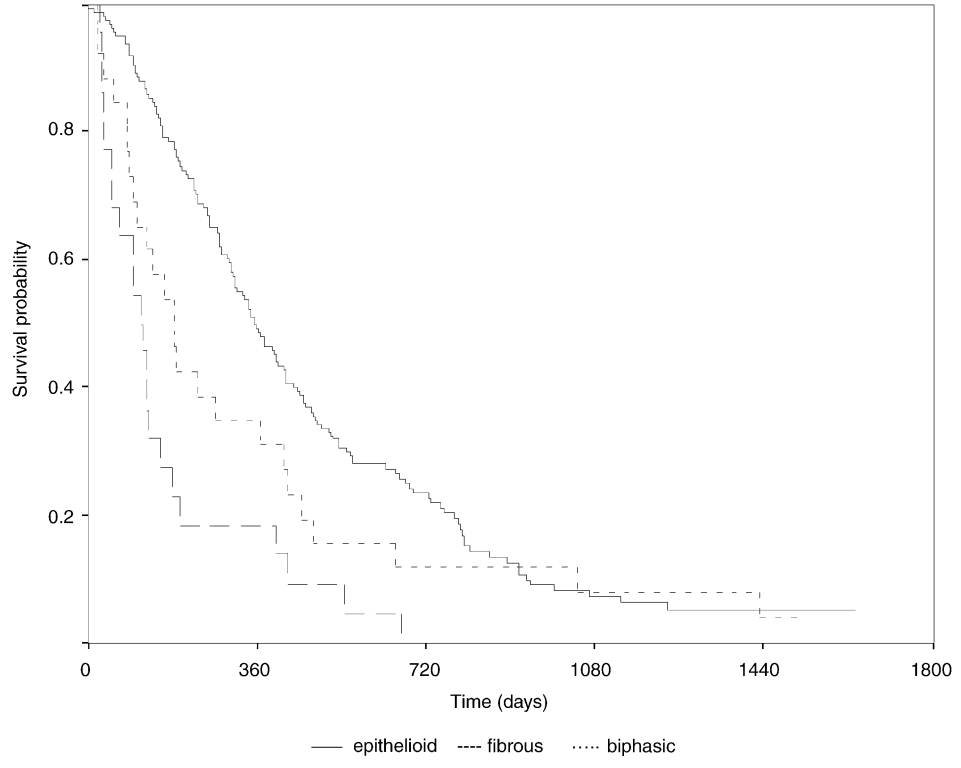

Fig. 2. Kaplan–Meier survival curve for pleural mesothelioma cases by histological subtype (epithelioid, biphasic, fibrous).

good proportion of the country (approximately 17 514 000 residents in 1999). However, it does not allow a complete assessment of its determinants. No information is available on the stage of the disease at diagnosis, or its treatment, and these variables are obviously essential if one is to assess the efficacy of treatment and interpret the factors involved in differences in survival. Quantitative data alone also provides no information on the patient's quality of life.

However, despite these limits the data do permit an estimate of the general level of survival by age, gender and site, and give indications on the possible role of prognostic variables such as histotype and level of diagnostic certainty. In addition, individual reconstruction of the modalities of exposure to asbestos enabled us to test—keeping the contribution of other variables constant—the utility of this historical data, which is rarely available for populations of this size. The completeness of follow-up was satisfactory, with only 5.1% (20/392) of cases lost.

Survival at one and three years from diagnosis of pleural mesothelioma (35.3 and 7.1% in the ReNaM caselist) was very similar to that reported for 740 pleural tumours (ICD-IX 163) collected by the Italian network of population tumour registers between 1990 and 1994 [14–17]. Median survival for pleural mesothelioma was longer than the seven months reported in the USA by the Surveillance, Epidemiology and End Results (SEER) study, for cases diagnosed between 1973 and 1984 [18] and also longer than the eight months in the Australian Mesothelioma Register [12]. The peritoneal mesothelioma survival in our cases is in line with a recent population study on malignant mesothelioma in lower Normandy that reports a median survival of nine months for pleural mesotheliomas and five months for peritoneal disease [19]. The poorer survival for peritoneal tumours could be explained by the later onset of symptoms for this disease [12].

Table 3
Cox's proportional hazard model for pleural mesothelioma. Relative risk adjusted for gender, age and register

Variable	Modality	Cox regression coefficient (β)	Adjusted relative risk $RR_{adj} = e^{\beta}$	95% Confidence Interval
Age (years)	0⩽64		1.00	
	65–74	0.21	1.23	0.86–1.76
	75⩾	0.60	1.82	1.16–2.86
Gender	Male		1.00	
	Female	−0.07	0.93	0.61–1.42
Exposure	Not exposed		1.00	
	Exposed	0.10	1.11	0.76–1.60
Diagnosis	MM certain		1.00	
	MM suspected	0.61	1.85	1.16–2.94
Histological type	Not specified		1.00	
	Biphasic	−0.10	0.90	0.44–1.84
	Epithelioid	−0.01	0.99	0.67–1.47
	Fibrous	1.08	2.96	1.28–6.81

The differences observed for males and females appear marked, although not statistically significant, probably because of the limited numbers, especially for the peritoneum cases. Women with peritoneal mesothelioma survived longer, leading us to consider the possibility of some misclassification of female genital cancers [18]. Univariate analysis showed that age had a significant influence on mesothelioma survival. We classified age in three brackets so as not to unduly reduce the degrees of freedom. The shortening of survival with advancing age is very similar to that found in 167 cases in south-west Holland recorded by the Rotterdam Cancer Registry from 1987 to 1989 [20] and confirms the importance of age as a prognostic factor [18]. The inverse relationship between survival and age has been reported in previous studies; the longer survival in the younger patients could be related to the higher percentage of epithelial subtypes in this group (49% in the 0–64 year age class and 33% in those aged 75+ years).

The differences in survival in the different registers, after adjustment for age, as a whole did not reach statistical significance.

Histological type is therefore a basic prognostic factor, as has already been reported in Refs. [11,20–23]. The risk for cases with epithelioid or biphasic pleural mesothelioma is more than three times lower than for those with fibrous morphology.

Diagnostic certainty also appears to have implications for survival: cases with a diagnosis of suspected MM seemed to have a higher risk—almost double that of cases with a definite diagnosis. In practice, this factor should be viewed as being related to the patient's general conditions, as there is a recognised tendency to avoid invasive instrumental investigations in patients with advanced disease, and precarious health.

In a specialised mesothelioma register, reconstruction of the modalities of exposure to asbestos is fundamental. We were able to rebuild the occupational and residential history for 198 cases out of 429 (46%) which, although not exhaustive, is nevertheless sufficient to verify whether the modality of exposure influences survival. The reconstruction of the modality of exposure is made difficult by the long latency period of the disease (generally more than 30 years) and the variety of occupations involved. Comparing survival of cases with confirmed exposure—occupational, household or environmental—and those with a known occupational and residential history, but not confirmed exposure, we could find no appreciable differences; this finding is remarkable considering the sample size and the modality of reconstruction of exposure by a direct or indirect interview. Our findings therefore do not confirm the shorter survival for cases with previous exposure in naval shipyards which was reported by the USA SEER study.

To conclude, therefore, age at diagnosis, histological type and level of diagnostic certainty (when the stage of disease is not known) appear to be significant prognostic factors for mesothelioma. The assessment of the role of asbestos exposure in this study refers only to the occupational sector in which a case was exposed, and would be more complete if the amount of fibres inhaled could also be estimated. Any judgement on the efficacy of various therapies must take account of these prognostic factors.

References

1. Lanphear B, Buncher C. Latent period for malignant mesothelioma of occupational origin. *Occup Med* 1992, **34**, 718–721.
2. Peto J, Decarli A, La Vecchia C, Levi F, Negri E. The European mesothelioma epidemic. *Br J Cancer* 1999, **79**, 666–672.
3. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, eds. *Cancer Incidence in Five Continents, vol. VII IARC Scientific Publication*. No. 143. Lyon, 1997.
4. Zanetti R, Crosignani P, Rosso S, eds. *Cancer in Italy. Incidence Data from Cancer Registries—Second Volume 1988–1992*. Rome, Il Pensiero Scientifico Editore, 1997.
5. Seniori Costantini A, Chellini E. The experience of the Mesothelioma Registry in Tuscany in assessing health hazard associated with asbestos exposure. *Med Lav* 1997, **88**, 310–315.
6. Musti M, Palamà L, Cavone D, Bufano V. Atti V° Convegno Multidisciplinare di Oncologia I tumori di origine industriale: i mesoteliomi, Bari 1998. *Eur J Oncol*, 1999, 387–390.
7. Ivaldi C, Dalmasso P, Nesti M, Magnani C. Malignant Mesothelioma Registry from Piedmont. Incidence in 1990–1995. *Epidemiol Prev* 1999, **23**, 308–315.
8. Gennaro V, Montanaro F, Lazzarotto A, Bianchelli M, Celesia MV, Canessa PA. Mesothelioma registry of the Liguria region. Incidence and occupational etiology in a high risk area. *Epidemiol Prev* 2000, **24**, 213–218.
9. Mangone L, Romanelli A, Campari C, Candela S. Malignant mesothelioma in Emilia-Romagna: incidence and asbestos exposure. *Epidemiol Prev* 2002, **26**, 124–129.
10. Nesti M, Marinaccio A, Silvestri S, eds. *Italian mesothelioma register: first report*. Rome, ISPESL, 2001.
11. Fusco V, Ardizzoni A, Merlo F, *et al*. Malignant pleural mesothelioma. Multivariate analysis of prognostic factors on 113 patients. *Anticancer Res* 1993, **13**, 683–689.
12. Leigh J, Rogers J, Ferguson AD, Mulder HB, Ackad M, Thompson R. Lung asbestos fiber content and mesothelioma cell type, site and survival. *Cancer* 1991, **68**, 135–141.
13. Ruffie P, Feld R, Minkin S, *et al*. Diffuse malignant mesothelioma of the pleura in Ontario and Quebec: a retrospective study of 332 patients. *J Clin Oncol* 1989, **7**, 1157–1168.
14. Rosso S, Casella C, Crocetti E, Ferretti S, Guzzinati S, eds. Survival of cancer patients in Italy in the nineties: figures from the cancer registries [special issue]. *Epidemiol Prev* 2001, **25**(Suppl.):1–375.
15. Verdecchia, A. and the ITACARE Working Group. Survival of cancer patients in Italy, the ITACARE study. *Tumori* 1997, **83**, 1–507.
16. Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Estève J. *Survival of Cancer Patients in Europe, the EUROCARE Study. IARC Scientific Publication No. 95.* , International Agency for Research on Cancer, 1995.
17. Berrino F, Capocaccia R, Estève J, *et al*. *Survival of cancer Patients in Europe, the EUROCARE2 Study. IARC Scientific Publication No. 151*. Lyon, International Agency for Research on Cancer, 1999.
18. Spirtas R, Connelly R, Tucker M. Survival patterns for malignant mesothelioma: the SEER experience. *Int J Cancer* 1988, **41**, 525–530.
19. Desoubeaux N, Bouvier V, Gervais R, *et al*. Mésothéliomes malins en Basse-Normandie: analyse descriptive, facteurs pronostiques et survie. Une étude de population. *Rev Epidemiol Sante Publique* 2001, **49**, 523–529.
20. Van Gelder T, Damhuis RAM, Hoogsteden HC. Prognostic factors and survival in malignant pleural mesothelioma. *Eur Respir J* 1994, **7**, 1035–1038.
21. Beer TW, Buchanan R, Matthews AW, Stradling R, Pullinger N, Pethybridge RJ. Prognosis in malignant mesothelioma related to MIB 1 proliferation index and histological subtype. *Hum Pathol* 1998, **29**, 246–251.
22. Neumann V, Gunther S, Muller KM, Fischer M. Malignant mesothelioma—German mesothelioma register 1987–1999. *Int Arch Occup Environ Health* 2001, **74**, 383–395.
23. Merritt N, Blewett CJ, Miller JD, Bennett WF, Young JE, Urschel JD. Survival after conservative (palliative) management of pleural malignant mesothelioma. *J Surg Oncol* 2001, **78**, 171–174.