Original Article

ISSN: 1735-0344 *Tanaffos 2014; 13(2): 6-12*

TANAFFOS

Clinicopathologic and Survival Characteristics of Malignant Pleural Mesothelioma Registered in Hospital Cancer Registry

Kosar Najmi [1], Adnan Khosravi [1], Sharare Seifi [1], Habib Emami [2], Samira Chaibakhsh [1], Golnar Radmand [3], Kian Khodadad [4]

[1] Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [2] Tobacco Prevention and Control Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3] Department of Epidemiology and Biostatistics, NRITLD, Shahid Beheshti University Of Medical Sciences, Tehran, Iran, [4] Department of Internal Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

Received: 25 February 2014
Accepted: 29 May 2014

Correspondence to: Emami H
Address: Tobacco Prevention and Control Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email address: emamihabib@yahoo.com

Background: Malignant pleural mesothelioma (MPM) is a rare but fatal thoracic tumor, which in the majority of patients is caused by prolonged exposure to asbestos fibers. We aimed at presenting clinicopathological and treatment outcomes of 60 patients of MPM registered in our hospital cancer registry.

Materials and Methods: Demographic characteristics of patients, exposure to asbestos, smoking habit, their clinicopathologic characteristics and survival analysis were described.

Results: Sixty patients had MPM. Forty patients (66.7%) were men. The mean age of patients was 55.8±11 years. Chest pain and dyspnea were the most prevalent symptoms (31.7%, and 30%, respectively). Thirty-six (61.7%) patients reported asbestos exposure. The median survival and Progression free survival (PFS) were 10.5 months (0.95CI=9.22-11.78) and 7.57 months (0.95CI=5.68-9.45), respectively. In multivariate analysis, exposure to asbestos and epithelioid subtype significantly extended the survival time. Bilateral involvement, high blood level of LDH and platelet count ≥400,000 significantly shortened the overall survival.

Conclusion: MPM is still an important health problem in Iran. Given the aforementioned results, developing a national program to eliminate asbestos-related diseases according to the world health organization (WHO) recommendation is necessary.

Key words: Cancer registry, Malignant pleural mesothelioma, Survival

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare but fatal thoracic malignancy (1, 2). The incidence of MPM in the industrial world is increasing (3-5). The life expectancy of MPM is low and its median overall survival is 9 to 12 months (6). It is caused by prolonged occupational or environmental exposure to mineral fibers including asbestos and/or Erionite (7). The time period between the first exposure to asbestos fibers and overt disease is between 30-40 years (8, 9).

Asbestos is still used by brake and clutch manufacturers in Iran (10, 11). About 55,000 tons of asbestos is imported to Iran annually most of which is used in cement industries (12). Also, about 2,000 tons of asbestos is used in production of friction materials in the country

annually and about 3,000 workers are exposed to asbestos fibers in brake and clutch production industries (13).

In 2010, a hospital-based cancer registry was established in Masih Daneshvari Hospital to collect thoracic cancer data to be used for treatment monitoring and survival assessments. This is the first article using the registry data. In this study, we aimed at presenting clinico-epidemiological and treatment specifications of MPM cases whose data were registered. Reporting the survival rate and discussing its determinants such as sex, chemotherapy regimen, chief complaint, exposure to asbestos and histologic subtype was our other objective.

MATERIALS AND METHODS

In this chart review study, 60 patients with MPM registered from 2010 to 2013 in our cancer registry were studied. Their demographic and behavioral data (age, gender, history of exposure to occupational or environmental asbestos, smoking habit, and opium use) and their clinical and pathological characteristics [side of pleural involvement, sub-type of mesothelioma, types of treatment, platelet count, Hemoglobin (Hb), ESR and LDH] were assessed.

Their survival time and its predictors were described using Kaplan-Meier method and Cox proportional hazard. All cases of thoracic cancers are reported to the cancer registry unit by the thoracic surgery, oncology and outpatient wards. A registry staff member, who is also a physician, interviews patients and fills out the data sheets. The physician systematically monitors the patient status. In case the patient dies, the exact time of death is reported by the first-degree relatives. Based on the history of exposure to asbestos, four categories were defined: (i) Occupational exposure, (ii) Environmental exposure, (iii) No exposure, (iv) Unknown. Also, history of asbestos exposure was reported as (i) Yes or (ii) No.

History of smoking was categorized as smoker (currently smoking up to the time of diagnosis or ex-smoker) and non-smoker (those who had never smoked). According to the pathology results, patients' diagnoses were divided into four groups of (i) Epithelioid, (ii) Sarcomatoid, (iii) Mixed and (iv) Unspecified cell type. The staging was determined according to the AJCC seventh edition (14). Multimodality was defined as surgery (extra pleural pneumonectomy) + chemotherapy ± radiotherapy (15,16).

Descriptive statistics were applied to present all the clinical and pathological variables. Univariate and multivariate analyses were used to determine the prognostic effect of all variables on survival time (the period between the onset of the disease and death or last visit). Survival time of all the patients was described using Kaplan-Meier. PFS was also described. Log-rank test was used to compare the survival time between groups. Cox proportional hazard was used to test the independent effect of the variables on survival. All the statistical comparisons were performed considering type one error equal or lower than 0.05. All the data were analyzed using SPSS version 22.

RESULTS

Of 600 cases of thoracic malignancies registered in our hospital, 60 (10%) were MPM. All patients were diagnosed based on open or closed pleural biopsy. Forty patients (66.7%) were men. The mean age of the patients was 55.8±11 years (range 34 to 79 years). Most cases (61.7 %) were in the age range of 51 to 70 years. Chest pain and dyspnea were the most prevalent symptoms (n=19, 31.7% and n=18, 30%, respectively). Forty-nine patients (81.7%) had stage IV disease. Thirty-six (61.7%) patients reported history of asbestos exposure for an average of 36.1 years. Bilateral involvement was found in 11 cases (18.33%). All the demographic and clinicopathological characteristics are presented in Table 1.

Table 1. Descriptive characteristics of 60 cases of MPM in Masih Daneshvari Hospital registered in the cancer registry center.

	Variables	No	%
Gender	Male	40	66.7
	Female	20	33.3
Asbestos exposure	Yes	37	61.7
	No	22	36.7
	unknown	1	1.7
Asbestos exposure type	Occupational	12	32.43
	Environmental	12	32.43
	Both	13	35.14
Smoking history	Yes	22	36.7
	No	38	63.3
Platelet count	<400,000	38	63.33
	400,000≥	20	33.33
	unknown	2	3.34
Site of involvement	Right Pleura	26	43.33
	Left Pleura	21	35.3
	Bilateral	11	18.33
	unknown	2	3.34
Histology subtype	Epithelial	29	48.3
	Biphasic	4	6.66
	Sarcomatous	5	8.33
	Unidentified	22	36.7
Death	Yes	45	75
Multimodality therapy	Yes	6	10
Chemotherapy	Yes	55	91.7
	No	5	8.3

The mean Hb, ESR, WBC, platelet count and LDH were 12.72 ± 1.93g/dl, 67.9±34.3 mm/h, 10814 ± 5616K/µL, 360155±127 555 K/µL and 428±250U/L, respectively.

The median overall survival (OS) for all cases was 10.5 months (0.95 CI= 9.22-11.78). The median PFS was 7.57 months (0.95CI=5.68-9.45) (Figures 1 and 2).

In univariate analysis, none of the differences were statistically significant except for the variable platelet count. The median OS in patients with platelet count less than 400,000 was significantly more than that in subjects with platelet count ≥400,000 (10.8 vs. 7.4 months, P<0.05). In multivariate analysis, the Cox proportional hazard model was applied. Variables such as gender, treatment, asbestos exposure, platelet count, age group, symptoms, histology subtype, Hb, chemotherapy protocol, surgical treatment, cigarette smoking, site of involvement, WBC count, LDH, ESR and stage of the disease were entered into the model as independent variables.

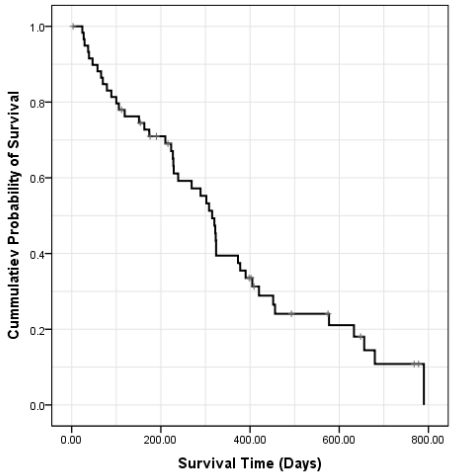

Figure 1. Kaplan Meier's overall survival plot

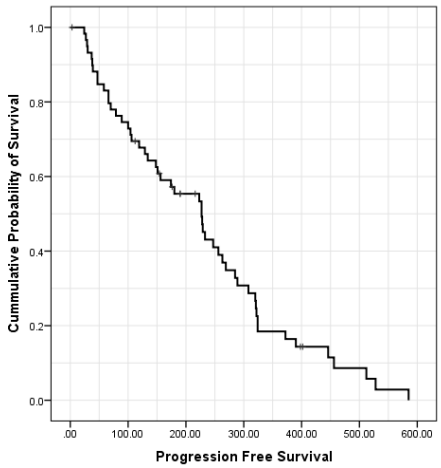

Figure 2. Kaplan Meier's PFS plot

Exposure to asbestos (HR=0.194, 0.95CI=0.072-0.522) (Figure 3a) and epithelioid histology subtype (HR=0.121, 0.95CI=0.017-0.881) (Figure 3c), were significantly associated with extended survival time. Bilateral involvement (HR=9.486, 0.95CI=2.466-36.485) (Figure 3b), high LDH (HR=1.006 for one unit increase, 0.95CI=1.001-1.011) and platelet count ≥400,000 (HR=3.523, 0.95CI=1.212-10.237) (Figure 3d) significantly shortened overall survival (Table 2).

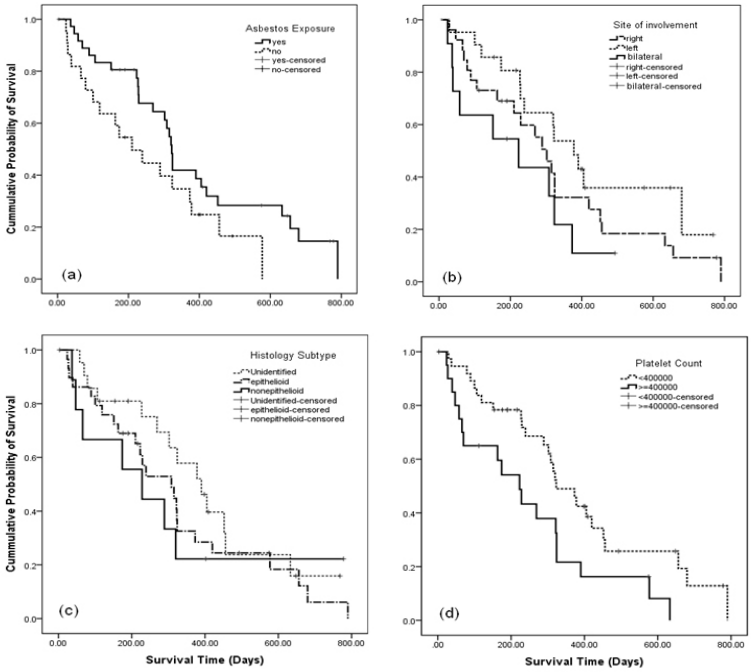

Figure 3. Kaplan Meier's plots for significant predictors; (a): Asbestos exposure; (b): Site of involvement; (c): Histology subtype; (d): Platelet count

Table 2. Cox proportional hazards regression.

Independent Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender				
Male/Female[1]	1.250 (0.654-2.389)	NS	2.18(0.475-10.02)	NS
Treatment				
Chemotherapy/Chemotherapy+Surgery[1]	0.754 (0.385-1.479)	NS	3.45(0.12-94.91)	NS
Asbestos exposure	0.577 (0.310-1.073)	NS	0.19 (0.07-0.52)	0.001
Platelet count				
≥400,000/<400,000[1]	2.021 (1.088-3.755)	0.026	3.52 (1.21-10.24)	0.021
Age group				
≥55 / <55[1]	1.110 (0.608-2.028)	NS	2.53 (0.65-9.83)	NS
Symptoms				NS
Chest Pain/Dyspnea[1]	0.563 (0.268-1.185)		0.21 (0.05-0.83)	0.026
Other/Dyspnea[1]	0.412 (0.158-1.069)		0.23 (0.03-1.84)	NS
Unknown/Dyspnea[1]	0.903 (0.394-2.070)	NS	1.16 (0.25-5.38)	NS
Histology subtype				NS
Unidentified/Non-Epithelial[1]	0.631 (0.253-1.575)	NS	0.22 (0.04-1.28)	NS
Epithelial/Non-Epithelial[1]	0.888 (0.380-2.075)		0.12 (0.02-0.88)	0.037
Hemoglobin				
Normal/Abnormal[1]	1.197 (0.642-2.233)	NS	0.38 (0.14-1.07)	NS
Chemotherapy protocol				
Pemetrexed+ Carboplatin/ Gemcitabine+Carboplatin[1]	0.336 (0.103-1.092)	0.07	0.17 (0.01-3.18)	NS
Surgical treatment				
Without thoracic surgery/Thoracic surgery[1]	0.656 (0.337-1.278)	NS	0.50 (0.02-10.94)	NS
Cigarette smoking	1.390 (0.748-2.581)	NS	0.91 (0.21-4.04)	NS
Site of involvement				0.003
Left/Right[1]	0.648 (0.324-1.298)		0.72 (0.24-2.20)	NS
Two-sided/Right[1]	1.617 (0.730-3.584)	NS	9.49 (2.47-36.49)	0.001
WBC				
≤10,000 / >10,000[1]	0.562 (0.299-1.056)	0.073	1.23 (0.31-5)	NS
LDH	1.001 (1.000-1.002)	NS	1.01 (1-1.01)	0.014
ESR	1.005 (0.994-1.016)	NS	1.02 (1-1.04)	NS
Stage				
IV / Less than IV[1]	1.396 (0.587-3.324)	NS	3.5 (0.75-16.35)	NS

1: References Category

DISCUSSION

According to our findings, MPM is still a serious health problem in Iran and a national commitment is required to eliminate this and other asbestos-related diseases. Since the establishment of our hospital-based cancer registry in 2010, about 600 cases with different thoracic malignancies were registered who were all referred to our hospital from other health centers in Iran. Sixty cases were MPM which ,means one out of 10 cases of thoracic cancers. Comparing with previous similar studies (17,18) in Iran, the prevalence of MPM is increasing. In the first study, which was a joint project between three university hospitals in Tehran and Mashhad conducted between 1996 and 2008, only 40 cases of MPM were detected and in the next one conducted between 2001 and 2008 in our hospital, 66 cases were found. Based on our study, 60 cases were diagnosed within three years and we can speculate that this difference indicates an increasing trend in the incidence of disease or improvement of diagnosis.

The prevalent symptoms were chest pain and dyspnea, similar to other studies (19). The most common histology subtype was epithelial, which is in accordance with other researches (15,20). Only 6 (10%) patients were eligible to undergo multimodality therapy and lived longer (22.7 months vs. 10.3 months). This is consistent with the findings of other researches (16).

Asbestos is still used in different industries in Iran (8). Exposure to asbestos significantly extended the survival time. It could be due to clear history of past exposure and early diagnosis resulting in early treatment (21). The relationship between exposure to asbestos and developing mesothelioma has been documented earlier (22). About 61.7% of our patients reported exposure to asbestos, and only 32.43% of them were occupationally exposed. It means that source of exposure is not limited to work environments. Different studies report different history of asbestos exposure among cases of MPM. This could be due to different techniques used to assess exposure. Some investigators use lung tissue biopsy to detect asbestos fibers and some others perform patient interviews (7). The other reason relies on the fact that a substantial portion of exposures are non-occupational such as exposure to asbestos released from car brakes and clutches (13,23), exposure from living near industries where asbestos is used for manufacturing products, or even incidental exposure as occurred in two female cases who were contaminated by asbestos from their husbands' clothing (19). Males outnumbered females (7,24), which could be due to higher occupational exposure among men. More than two-thirds of the cases were between 51 and 70 years of age, which is consistent with other studies (7,15). The median overall survival of the patients who underwent therapy was 10.5 months (0.95CI, 9.22-11.78) (15, 17,25). Those with WBC count less than 10,000, non-smokers, subjects with left lung involvement (17), and those who underwent chemotherapy + surgery lived longer but not significantly. Patients treated with Pemetrexed+ Carboplatin lived longer than those treated with Gemcitabine+ Carboplatin (26.3 months vs. 10.3 months). Although statistically not significant, the obtained P-value was borderline (0.056). One reason could be the small sample size. The overall survival time of patients with stage < IV and females (17) was longer but this difference was not statistically significant. It could partly be due to small sample size.

CONCLUSION

Our study describes the main clinicopathologic characteristics of 60 Iranian patients with MPM. Epithelial histology subtype, exposure to asbestos, platelet count less than 400,000, and unilateral involvement confer better overall survival. High LDH and ESR as well as stage IV disease are prognostic factors of survival time. Female gender and chemotherapy administration along with surgery were associated with prolonged survival although not significantly. Further studies on a larger number of patients with MPM are warranted to validate our finding.

In our study, approximately 60% of patients had a history of asbestos exposure. We speculate that environment is potentially an important source of

exposure to asbestos; possibly due to asbestos released by car brakes, clutch and manufacturing companies. Given the aforementioned findings, developing a national program to eliminate asbestos exposure and consequently asbestos-related diseases according to the WHO recommendation seems necessary (26).

Acknowledgement

The authors wish to thank the personnel of Oncology and Thoracic Surgery wards and the Epidemiology and Biostatistics Department of Masih Daneshvari Hospital for their kind cooperation.

REFERENCES

1. Henderson DW, Rantanen J, Barnhart S, Dement JM, De Vuyst P, Hillerdal G, Huuskonen MS, et al. Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. *Scand J Work Environ Health* 1997; 23(4): 311-6.
2. McDonald JC, McDonald AD. The epidemiology of mesothelioma in historical context. *Eur Respir J* 1996; 9(9): 1932- 42.
3. Girardi P, Bressan V, Merler E. Past trends and future prediction of mesothelioma incidence in an industrialized area of Italy, the Veneto Region. *Cancer Epidemiol* 2014; 38 (5): 496-503.
4. Jennings CJ, Walsh PM, Deady S, Harvey BJ, Thomas W. Malignant pleural mesothelioma incidence and survival in the Republic of Ireland 1994-2009. *Cancer Epidemiol* 2014; 38 (1): 35- 41.
5. Delgermaa V, Takahashi K, Park EK, Le GV, Hara T, Sorahan T. Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008. *Bull World Health Organ* 2011; 89 (10): 716- 24, 724A- 724C.
6. Robinson BW, Musk AW, Lake RA. Malignant mesothelioma. *Lancet* 2005 ; 366 (9483): 397- 408.
7. Yang H, Testa JR, Carbone M. Mesothelioma epidemiology, carcinogenesis, and pathogenesis. *Curr Treat Options Oncol* 2008; 9 (2-3): 147- 57.
8. Toyokuni S. Mechanisms of asbestos-induced carcinogenesis. *Nagoya J Med Sci* 2009; 71 (1-2): 1- 10.
9. Marinaccio A,Binazzi A, Marzio DD, Scarselli A, Verardo M, Mirabelli D et al. Pleural malignant mesothelioma epidemic :Incidence ,modalities of asbestos exposure and occupations involved from the Italian National Register. *Int J Cancer* 2012; 130 (9): 2146- 54.
10. Kakooei H, Sameti M, Kakooei AA. Asbestos exposure during routine brake lining manufacture. *Ind Health* 2007; 45 (6): 787-92.
11. Kakooei H, Yunesian M, Marioryad H, Azam K.Assessment of airborne asbestos fiber concentrations in urban area of Tehran, Iran. *Air Qual Atmos Health* 2009; 2: 39–45.
12. Panahi D, Kakooei H, Marioryad H, Mehrdad R, Golhosseini M. Evaluation of exposure to the airborne asbestos in an asbestos cement sheet manufacturing industry in Iran. *Environ Monit Assess* 2011; 178 (1-4): 449- 54.
13. Kakooei H, Marioryad H. Evaluation of exposure to the airborne asbestos in an automobile brake and clutch manufacturing industry in Iran. *Regul Toxicol Pharmacol* 2010; 56 (2): 143- 7.
14. Pleural mesothelioma. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 271-7.
15. Borasio P, Berruti A, Billé A, Lausi P, Levra MG, Giardino R, Ardissone F. Malignant pleural mesothelioma: clinicopathologic and survival characteristics in a consecutive series of 394 patients. *Eur J Cardiothorac Surg* 2008; 33 (2): 307- 13.
16. Budroni M, Cossu A, Paliogiannis P, Palmieri G, Attene F, Cesaraccio R, Tanda F. Epidemiology of malignant pleural mesothelioma in the province of Sassari (Sardinia, Italy). A population-based report. *Ann Ital Chir* 2014; 85 (3): 244- 8.
17. Bagheri R, Haghi SZ, Rahim MB, Attaran D, Toosi MS. Malignant pleural mesothelioma: clinicopathologic and survival characteristic in a consecutive series of 40 patients. *Ann Thorac Cardiovasc Surg* 2011; 17 (2): 130- 6.
18. Cheraghvandi A, Fallah Tafti S, Karimi Sh, Kosari H. Malignant Mesothelioma: A Study of Sixty-Six Cases. *Tanaffos* 2006; 5(4): 59- 63 .
19. Spirtas R, Heineman EF, Bernstein L, Beebe GW, Keehn RJ, Stark A, Harlow BL, Benichou J. Malignant mesothelioma:

attributable risk of asbestos exposure. *Occup Environ Med* 1994; 51 (12): 804- 11.

20. Ahn S, Choi IH, Han J, Kim J, Ahn MJ. Pleural mesothelioma: an institutional experience of 66 cases. *Korean J Pathol* 2014; 48 (2): 91- 9.
21. Montanaro F, Rosato R, Gangemi M, Roberti S, Ricceri F, Merler E, et al. Survival of pleural malignant mesothelioma in Italy: a population-based study. *Int J Cancer* 2009; 124 (1): 201- 7.
22. Moore AJ, Parker RJ, Wiggins J. Malignant mesothelioma. *Orphanet J Rare Dis* 2008; 3: 34.
23. Olsen NJ, Franklin PJ, Reid A, de Klerk NH, Threlfall TJ, Shilkin K, et al. Increasing incidence of malignant mesothelioma after exposure to asbestos during home maintenance and renovation. *Med J Aust* 2011; 195 (5): 271- 4.
24. Mensi C, Sieno C, De Matteis S, Consonni D, Riboldi L, Bertazzi PA. Incidence of malignant mesothelioma and asbestos exposure in the Lombardy region, Italy, 2000-2008. *G Ital Med Lav Ergon* 2011; 33 (3 Suppl): 96- 8.
25. Sugarbaker DJ, Wolf AS, Chirieac LR, Godleski JJ, Tilleman TR, Jaklitsch MT, et al. Clinical and pathological features of three-year survivors of malignant pleural mesothelioma following extrapleural pneumonectomy. *Eur J Cardiothorac Surg* 2011; 40 (2): 298- 303.
26. WHO [internet]. Outline for the Development of National Programmes for Elimination of Asbestos-Related Diseases. Switzerland; 2007 [cited 2 July 2012]. Available from: http://www.WHO.int/occupational_health/publications/Out_NPEAD_ENG.pdf