Original articles

Malignant mesothelioma in south east England: clinicopathological experience of 272 cases

D H Yates, B Corrin, P N Stidolph, K Browne

Abstract

***Background* – Malignant mesothelioma is a rare pleural tumour associated with asbestos exposure. The proportion of malignant mesothelioma unrelated to asbestos exposure, and any differentiating features between exposed and unexposed cases, are not well described. This study describes occupational, clinical, and pathological features in a large cohort of cases of malignant mesothelioma from south east England.**

***Methods* – All 272 cases from this region were studied, either in life or after death when necropsy examination suggested malignant mesothelioma. Detailed information was gathered regarding the occupational history, clinical course, and mode of death. Necropsies were performed in 98% of cases. Lung tissue was examined histologically to confirm the diagnosis, subtype of tumour, presence or absence of asbestosis and asbestos bodies.**

***Results* – Exposure to asbestos was documented in 87% of cases, while in the remainder, no asbestos exposure was found nor were asbestos bodies seen; 94.5% were pleural, 5.1% peritoneal, and 0.4% pericardial. Right sided tumours were more common than left sided tumours (ratio 1.6:1). Patients usually presented with breathlessness and chest pain, but 33% presented with pleural effusion in the absence of chest pain. The mean (SD) time from first exposure to asbestos to symptoms was 40 (12) years with a median (interquartile range (IQR)) survival of 14 (12.5) months. The median (IQR) survival time in sarcomatous, epithelial, and mixed cell type malignant mesothelioma was 9.4 (10) months, 12.5 (18) months, and 11 (14) months, respectively, and was significantly greater in cases detected by chance. Clinical features were similar in asbestos related and non-asbestos related malignant mesothelioma.**

***Conclusions* – In south east England most cases of malignant mesothelioma are associated with asbestos exposure. Clinical features do not differentiate between asbestos related and non-asbestos related disease.**

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Keywords: mesothelioma, asbestos, pleural tumour.

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Malignant mesothelioma is an uncommon tumour usually attributable to asbestos exposure, which is rising in incidence in the UK.[1] Clinical and pathological features of malignant mesothelioma have been previously well described.[2–4] In many published series, however, numbers are small and complete clinical, occupational, and pathological details have been difficult to obtain. The proportion of tumours not related to asbestos, survival with different tumour subtypes, and features of non-asbestos related tumours are also uncertain. This report provides complete documentation of 272 cases where mesothelioma was the cause of death within a defined geographical area in the south east of England for the calendar year 1987.

In the UK a system of compensation for occupational lung disease has existed since 1931,[5] and a regional network of Pneumoconiosis Panels (now called Medical Boarding Centres (MBCs)) assesses live and posthumous claims. The London MBC area covers all of the industrial south east.

In England all deaths suspected of being due to industrial disease must be reported to the coroner and a necropsy performed. Until April 1988 it was mandatory for coroners to refer all cases of malignant mesothelioma to MBCs for special examination of the lungs. A report by specialist physicians as to cause of death and presence or absence of an occupational lung disease was then made to the coroner.

Although only cases where there was any suspicion of industrial causation were legally required to be reported to the coroner, in practice – because of compensation issues – almost all cases diagnosed as malignant mesothelioma were referred. It is, however, possible that a small number of cases remained unreported because of the extreme improbability of any asbestos exposure. Clinical information was supplemented by verification of occupational exposure to asbestos, as government offices carefully verified potential asbestos exposure. This system resulted in the gathering of complete information on all cases of malignant mesothelioma in the region, but ended in 1988 with the abolition of industrial death benefit. 1987 was therefore the last year of complete registration of all cases of malignant mesothelioma in which any suspicion of asbestos causation had arisen.

Methods

CASE GATHERING

All deaths from malignant mesothelioma occurring in 1987 were studied. These included

patients examined in life for industrial disablement benefit or on appeal, those where such a diagnosis had been considered in life or discovered after death, and those confirmed at necropsy.

OCCUPATIONAL HISTORY

Occupational histories were obtained from multiple sources. Where a claim had been made for benefit, a detailed employment history was available. Where no claim had been made, occupational details were obtained from widows, hospital case notes, and coroners' reports from inquests. In each such case the available employment history was examined by experienced occupational respiratory physicians, and further details regarding each and any employment which might have entailed contact with asbestos were obtained. Those employments involving contact with asbestos in the south east region had been previously documented by the MBC over a period of 30 years by the collation of results from periodic asbestos examinations in asbestos manufacturing and other industries and by claims for asbestos related diseases. These records were consulted where no history of asbestos exposure was obtained. In addition, employment records were searched. Occupational details were verified by local government officers who confirmed contact with asbestos from previous employers, work mates, and relatives by obtaining written confirmation that the person had worked in the relevant employment, and the dates of such employment.

Cases were categorised into four groups on the basis of occupational history and histological findings: (1) definitely exposed, (2) probably exposed, (3) non-occupationally exposed, and (4) non-exposed. Thus, a case where few occupational details were available but asbestos bodies were easily seen on histological examination of necropsy material was classified as asbestos exposed. Where no asbestos bodies were seen but the decedent had worked in an occupation where asbestos exposure was likely, the case was classified as probably asbestos exposed. Probable exposure was also recorded when the decedent had worked in a less likely but recognised industry with no or very few asbestos bodies seen. Non-occupational exposure included a history of exposure outside the workplace. Non-exposure was only accepted where no asbestos bodies were seen and the complete occupational history indicated that exposure to asbestos was unlikely. These criteria resulted in a case being more likely to be classified as asbestos exposed than otherwise.

CLINICAL FEATURES

Clinical features were identified from regular examinations made by the MBC in life, hospital records, chest radiographs, coroners' inquests, and necropsy records.

HISTOPATHOLOGICAL EXAMINATION

Lungs were examined macroscopically and three blocks were taken of both the tumour and the uninvolved lung. Histological examination was performed by one of the authors (BC) without knowledge of the occupational history. When only a glandular pattern was evident, haematoxylin and eosin staining was supplemented by diastase periodic acid Schiff and alcian blue staining with hyaluronidase control for mucous substances and by immunocytochemistry for carcinoembryonic antigen. To identify asbestos bodies three unstained sections of the contralateral lung, 30 μm thick, were scrutinised in their entirety. Asbestos bodies were documented as absent, occasional, scanty, easily found, or numerous and asbestosis was diagnosed only when interstitial fibrosis was accompanied by numerous asbestos bodies. In two cases where the histological findings were doubtful the clinical and radiological features were considered carefully before inclusion in the series.

ANALYSIS OF DATA

Differences in proportions within groups were examined by χ^2 tests and differences in age were examined by unpaired two-sided Student's t tests. All calculations were performed with a Dell PC and the NCSS statistical software program. Results are reported as mean (SD) and survival data as medians with interquartile ranges. Significance levels were taken at $p<0.05$.

Results

AGE, SEX DISTRIBUTION, AND SMOKING HABITS

From a total of 285 cases referred, 272 (252 men) were accepted as being malignant mesothelioma. The mean (SD) age at death was 65.2 (9.5) years, ranging from 39 to 92 years (fig 1), with no difference between men (65 (10) years) and women (66 (9.6) years).

The median survival from time of symptom onset was 14 (12.5) months (range 0–91 months) with survival of women not significantly different from that of the men. Most patients survived less than nine months and survival beyond 40 months was very rare (4%). Survival was significantly shorter in peritoneal

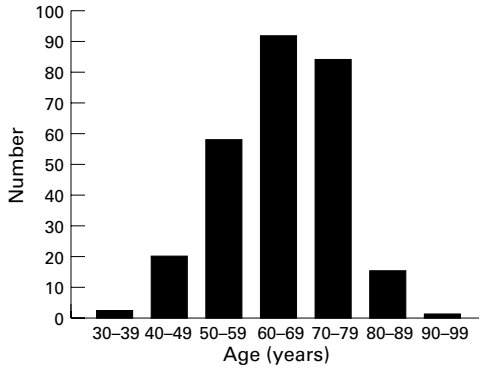

Figure 1 Frequency distribution of malignant mesothelioma by age (n=272).

Table 1 Exposure to asbestos by cases of malignant mesothelioma (n=272)

	Number of cases	*(%)*
Occupational exposure		
Definite	212	(77.9)
Probable	24	(8.8)
Possible non-occupational	4	(1.5)
No exposure	30	(11)
Unclassified	2	(0.7)
Total	272	(100)

Table 2 Occupational exposure to asbestos by cases of malignant mesothelioma (n=272)

	Number of cases	*(%)*
Certain or probable occupational exposure:		
Shipbuilding and repair	42	(15.4)
Boiler, pipe and heating	40	(14.7)
Carpenters	30	(11.0)
Electricians	27	(9.9)
Construction and demolition	23	(8.5)
Asbestos manufacturing and sales	14	(5.1)
Insulation work, laggers	13	(4.8)
Electricity generation	11	(4.0)
Stevedores and dockers	6	(2.2)
Railway coach construction	6	(2.2)
Laboratory and research	7	(2.6)
Navy seamen	3	(1.1)
Other	14	(5.9)
Possible non-occupational exposure:		
Relative of occupationally exposed worker (one husband, one father)	2	(0.7)
Cut asbestos board for home refit	1	(0.4)
Lived near an asbestos factory	1	(0.4)
No exposure:		
Office and school	8	(2.9)
Housework and domestic cleaning	4	(1.5)
Mail sorting and delivery	2	(0.7)
Factory and craft work	12	(4.4)
Other	4	(1.5)
Unclassified	2	(0.7)
Total	272	(100)

mesotheliomas (7 (4) months). Smoking habits were not analysed because smoking is not a risk factor for mesothelioma.[6]

OCCUPATIONAL EXPOSURE TO ASBESTOS

Occupational details were obtained in all but two cases. In 10 cases, although asbestos exposure was denied or could not be identified, numerous asbestos bodies were seen and these were classified as asbestos exposed.

Occupational exposure to asbestos was noted in 86.8% of cases (212 certain and 24 probable exposures; table 1). There were 30 cases where no history of asbestos exposure could be elicited, and no asbestos bodies were identified. Four cases (two relatives of asbestos workers, one who cut asbestos board during kitchen alterations at his home, and one living near an asbestos factory) were accepted by the coroner as having possible non-occupational exposure although no asbestos bodies were identified (table 2). No definite categorisation could be made in two cases due to insufficient information.

There were 168 cases (61.8%) where the dates of first exposure had been fully verified – that is, exact date of first exposure had been verified from objective records such as employment records rather than by recall of dates by patients, relatives or colleagues. The mean (SD) latency (defined as interval from first exposure to death) for all cases was 41.4 (11.7) years (range 15–67). Latency was longer in the peritoneal cases at 46.7 (11.3) years ($p<0.05$). The frequency distribution for latency is shown in fig 2. Reliable information on duration of exposure was available in 166 cases (61%). It was not possible to identify asbestos type, but mixed exposure was usual in the UK. The mean duration of exposure for the whole group was 19 (13) years, ranging from three months to 53 years. Duration of exposure for peritoneal cases was not significantly different from that of pleural cases (17.3 (14) versus 19 (13) years), although the reliability of these figures is questionable as information on exposure duration was available in only nine peritoneal cases. In 34 cases there was no history of occupational exposure to asbestos and no asbestos bodies were identified.

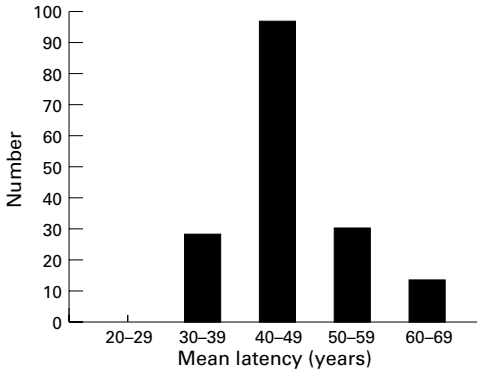

Figure 2 Frequency distribution of malignant mesothelioma by latency (n=168 where dates of occupational exposure to asbestos had been verified).

SITE OF TUMOUR

The site of the tumour was determined from clinical, radiographic, and necropsy data. When pleural tumours were bilateral, the site was classified according to the side of first onset of symptoms or first radiographic abnormality. Similarly, where there were both peritoneal and pleural tumours, the primary site was judged from the presenting clinical features.

Pleural tumours occurred in 257 cases with a right sided predominance (157 right sided, 99 left sided; ratio 1.6:1). In one case the original side of the pleural tumour could not be determined. Peritoneal tumours occurred in 14 cases (5.1%), with one pericardial malignant mesothelioma.

PATHOLOGY

Necropsies were conducted in 267 cases (98.1%) and mesothelioma was confirmed histologically in 265 (97.4%). In two cases the histological findings were equivocal despite special staining but the diagnosis was accepted on clinical and radiological grounds. In the remaining five cases histological confirmation was obtained from stored biopsy material.

Metastases (defined as secondary spread to the other lung, the peritoneum or more distant) were present in 150 cases (55.1%). Asbestosis

Table 3 Survival and metastases according to cell type (n=250)

Histological type	Number (%)	Metastases n (%)	Survival (months)
Epithelial	81 (32)	50 (62)	16.2 (13)
Mixed	84 (34)	48 (57)	14.7 (13.5)
Sarcomatous	83 (33)	43 (52)	10.1 (7.5)
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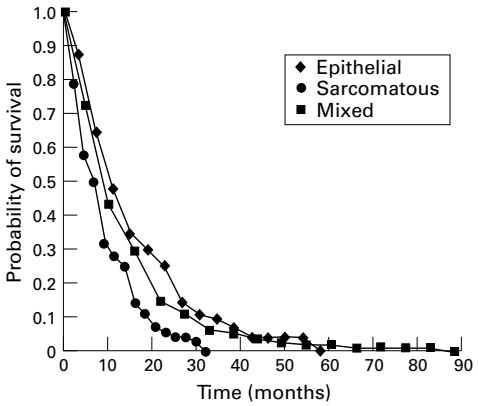

Figure 3 Survival curve for different subtypes of malignant mesothelioma (n=250). p<0.05 for median survival between sarcomatous and other subtypes.

was more common in peritoneal than in pleural cases, although numbers were small – five (35.7%) versus 10 (3.9%), respectively (p<0.01). Asbestos bodies were present in 125 cases (46%), plaques were found either at necropsy or radiologically in 78 (28.7%).

Classification of malignant mesothelioma into histological subtypes is shown in table 3. Although necropsies had been performed on 267 cases, histological subtyping was only available in 250 cases due to technical factors such as insufficient tissue or poor state of preservation. There were 83 sarcomatous mesotheliomas, 81 epithelial, 84 mixed, and two where the histological pattern could not be determined. A mixed pattern was diagnosed whenever both sarcomatous and epithelial components were evident, no matter how small the minor component. The mean survival time for epithelial cases was 16.2 (13) months, 14.7 (13.5) for mixed type and 10.1 (7.5) for sarcomatous cases, the latter being significantly shorter (p<0.05; fig 3). The median (interquartile range) survival times for epithelial, mixed and sarcomatous types were 12.5 (18) months, 11 (14) months, and 9.4 (10) months, respectively. When histological type was compared with frequency of metastasis no significant difference was seen between histological subtypes.

CLINICAL FEATURES

Most patients presented with chest pain and breathlessness. Other features included lassitude, weight loss, night sweats, pneumothorax, and a chest wall mass. Pleural effusion accompanied by breathlessness but without pain were the presenting features in 90 cases (33%). Chest pain initially unaccompanied by pleural effusion was present in 104 cases (38%). Fifty five cases (20%) presented with other symptoms including peritoneal malignant mesotheliomas (abdominal discomfort, swelling and ascites), those who were picked up incidentally (n=10), and those who presented with a chest wall mass (n=11). In 23 cases the presenting symptoms were unknown.

The mean (SD) survival time in those presenting with an effusion was no different in those with a pleural effusion (15 (11) months) and those with chest pain (13 (9) months). In 10 cases the diagnosis had been reached after a routine chest radiograph for some other reason; none of these had any chest symptoms. Their median survival was significantly longer at 21 (4) months (p<0.05). In these, a pleural abnormality was followed by an effusion in six cases and chest pain was a later development, on average about 12 months after the effusion.

MESOTHELIOMAS WITH NO OCCUPATIONAL EXPOSURE

Thirty four cases with no occupational exposure were identified. In these the male to female ratio was 1.35:1, significantly different from that of the group as a whole (12.6:1). This confirms the findings of Hirsch *et al*,[7] Peto *et al*,[8] and Law *et al*[9] in their reports of non-asbestos related cases. The mean age at death was lower than in those with asbestos related mesotheliomas (63.0 (10.2) years versus 65.4 years), and their survival time was shorter than in the main group (13 (12) months), but these differences were not statistically significant. There were 33 pleural mesotheliomas (20 right sided) and one peritoneal.

Although no asbestos exposure had been recalled in life and no asbestos bodies were seen at necropsy, the occupations of six patients could possibly have entailed some exposure. If these were removed from the series, however, the mean age and survival were not significantly changed.

Discussion

The continuing increase in death rate from malignant mesothelioma among workers exposed to asbestos implies that this rare tumour will become increasingly common.[1] Our study reports the largest number of cases of malignant mesothelioma from the UK since 1976,[3] and clarifies the clinical and occupational features which may prove useful for the early diagnosis of this tumour. The system of routine referral of every suspected asbestos related death to MBCs which was in operation in 1987 should have diminished the occupational selection bias which usually occurs in reports from pneumoconiosis units, although such a bias cannot be discounted. The high availability of necropsy tissue allowed verification of the diagnosis on histological grounds, and occupational histories were obtained from a wide variety of sources and carefully screened for possible exposure by a number of methods.

We found exposure to asbestos to be present in 87% of cases, of which 96% were oc-

cupational in origin. This is similar to previous studies,[10–13] but is likely to reflect some selection at source as a history of asbestos exposure may result in a greater likelihood of necropsy and also of a pathological diagnosis of malignant mesothelioma.[10] The high proportion of cases exposed in the ship building industry is typical of past exposure under conditions of poor hygiene, but it is notable that 37% of our cases were carpenters, electricians, research workers, or workers in the construction or naval industries where exposure precautions may not have been optimal. A high index of suspicion of asbestos exposure and a careful occupational history is therefore still of primary importance for the appropriate diagnosis of malignant mesothelioma.

Malignant mesothelioma is usually a disease of late middle age and the mean age seen in our series (65 years) is somewhat higher than in earlier series.[3 4] This could reflect an improvement in dust levels, but the frequency distribution for age demonstrates a wide range of age of onset (patients in their 30s to 90s). The mean latency was approximately 40 years, again comparable to other reports,[14] as was the least latency period at 15 years. Latency was longer in cases of peritoneal mesothelioma as has been shown in one previous study.[15]

The high proportion of pleural mesotheliomas is similar to that of most UK series, although the reverse has been documented in some cohort studies, mainly from the USA.[4] One interesting finding was the clear predominance of right sided mesotheliomas, with a right:left ratio of 1.6:1. This has been noted in a previous review[16] and described in one previous series from Germany,[17] but small case numbers have limited the certainty of such observations. Possible explanations could include differences in fibre deposition between the two lungs, the larger pleural surface area of the right lung, or differences in lymphatic drainage.

Clinical features in our study allowed a comparison between asbestos and non-asbestos related tumours. Presenting features of chest pain, dyspnoea, and breathlessness are well recognised,[3 16] but did not differentiate between those with and without exposure to asbestos. Although chest pain is commonly a presenting feature of mesothelioma, 38% of our cases presented with pleural effusion, often accompanied by minor chest pain only, which suggests that mesothelioma should be considered in every case of pleural effusion.

In our study necropsies were available in a very high proportion of cases (98%), allowing adequate histological samples and accurate documentation of the site of the primary tumour and of metastases. We were able to determine histological type in 248 (91%) of our cases, and to correlate this with clinical behaviour. Previously, there have been conflicting reports regarding frequency of histological type, some finding a preponderance of epithelial tumours[2 18 19] and others showing no difference in frequency,[4 15 20] possibly reflecting the limited numbers reported and the variable sampling methods employed. Our series, which was based on necropsy cases, afforded wide sampling of the tumour. It confirms the equal occurrence of all histological types and demonstrates a shortening of survival with sarcomatous cell type. No survival difference was observed between mixed and epithelial cell types, nor was there a difference in metastatic potential between types.

We were particularly interested to examine non-occupationally related mesotheliomas because these have been reported to have a different survival in previous studies.[7–9] Criteria for classification as non-exposed in our study were more rigid than for cases of exposure to asbestos and the different sex ratio (1.35:1) tends to confirm that these were probably genuinely non-occupational in origin. Cases were, on average, slightly younger than the whole group, similar to other studies,[7 8] but not significantly so. Although some previous reports have shown a shorter survival with non-asbestos related malignant mesothelioma,[7 9] our study did not confirm this. Similarly, no difference in site or side of malignant mesothelioma was shown, nor any difference in clinical behaviour. Thus, no differentiating features were found to separate asbestos related from non-asbestos related cases of mesothelioma.

Our study was not designed to evaluate treatment. Although new modes of prevention and treatment are currently under development, one major difficulty is the usual late presentation of malignant mesothelioma. In our series 10 patients had abnormalities incidentally discovered during routine chest radiographs for investigation of other diseases. The survival in these patients was longer than in the group as a whole, and a small pleural abnormality preceded either effusion or chest pain, suggesting that malignant mesothelioma may occasionally be present for up to a year before presentation. These findings raise the question as to whether early detection – for example, by screening of high risk groups – could alter disease outcome in the future by appropriate treatment of limited disease.

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