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Malignant Mesothelioma: A Clinical Study of 238 Cases

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Abstract: Malignant mesothelioma is a diffuse tumor arising in the pleura, peritoneum, or other serosal surface and is closely associated with asbestos exposure. An estimated 2,500 to 3,000 cases are diagnosed each year in the United States. Although there are individual case reports and small series detailing the clinical aspects of mesothelioma, few studies examine a large series of patients with malignant mesothelioma from the clinical perspective. This study reports on the findings of 238 cases of malignant mesothelioma from a private consultative medical practice. Most cases had a history of occupational asbestos exposure. The mean latency was 48.5 yr, with women having a longer latency than men. The mean age at diagnosis was 70. Survival overall was poor (mean 8.8 months), but treatment was beneficial (mean 11.3 versus 6.4 months). Epithelioid histology conferred a survival advantage over sarcomatoid and responded better to treatment. Our data support an inverse relationship between asbestos dose and latency.

Key words: Mesothelioma, Asbestos, Pleural cancer, Peritoneal cancer, Exposure, Latency, Diagnosis

Introduction

Malignant mesothelioma is a diffuse tumor arising in the pleura, peritoneum, or other serosal surface. The most frequent site of origin is the pleura (>90%), followed by peritoneum (6–10%), and only rarely other locations[1–4]. Mesothelioma is closely associated with asbestos exposure from a variety of occupational settings. Patients with non-occupational asbestos exposure, such as household contacts of asbestos workers and those residing near asbestos manufacturing plants or mining facilities also have experienced an increased risk of malignant mesothelioma. There is no apparent link between mesothelioma and tobacco.

There are an estimated 2,500 to 3,000 cases of malignant mesothelioma diagnosed each year in the United States[5–7]. These numbers, which were based on inaccurate coding, likely underestimate the true occurrence of this disease[8]. It has been estimated that about 27 million Americans had exposure to asbestos between the 1940s and 1970s[9]. Overall, malignant mesothelioma is much more common in men than in women, probably reflecting higher rates of occupational asbestos exposure in the male population.

Although there are individual mesothelioma case reports and small series detailing clinical aspects, few studies examine a large series of patients with malignant mesothelioma from the clinical perspective. Many of the larger series have focused on occupational information and pathological findings, rather than clinical data[1, 10, 11].

The present study examines the available clinical information and observations of 238 individuals diagnosed with malignant mesothelioma.

Materials and Methods

From within the medical and consultative files of Texas Occupational Medicine Institute (TOMI), a private pulmonary and occupational medicine practice in Houston, Texas, we were able to identify 286 individu-

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als diagnosed with malignant mesothelioma between 1977 and 2009. Over 80% of the cases were diagnosed in the 1990s and 2000s. Of these cases, sufficient information for inclusion in our analysis was available in 238. The diagnosis of malignant mesothelioma was confirmed by review of the pathology reports from the medical record in all cases included for analysis.

We obtained information on the sex, age, tumor histology and location, smoking history, clinical presentation, concomitant medical conditions, treatment (if any), and survival. The diagnosis of asbestosis required ILO reading ≥ 1/0, characteristic findings on CT scan, or pathological identification. The presence of pleural plaques (calcified or non-calcified) was identified by chest x-ray, CT scan (most cases), or at autopsy.

Cumulative asbestos dose is proportional to the intensity, frequency and duration of exposure. The nature of the exposure (direct, bystander or both) figures both in intensity and as a separate factor. Based on data from tissue analysis by others, given equal exposure durations, those working directly with asbestos products have greater lung burdens of asbestos than did workers with bystander exposure[1]. Patient exposure information was culled from the elicited lifetime work history, and specific physician query regarding their asbestos exposure, both occupational and non-occupational. From these data, the TOMI pulmonary or occupational physician categorized the individual's exposure as light, moderate, or heavy. While subjective, this classification method is found in the literature, as most workplaces lack sufficient quantitative exposure data for individuals, workers change jobsites throughout their careers, and there are vast inconsistencies in historical measurements.

In addition, we noted general information of occupation and industry setting and the decade(s) of exposure. We examined for a relationship between exposure and latency. We also analyzed survival data based upon parameters such as treatment modality, age at diagnosis, tumor location, and histological type.

Results

Of the cases specifying tumor location, there were 221 pleural (94.4%) and 13 peritoneal (5.6%) mesotheliomas. There was a right-sided predominance (63.4%) for pleural mesotheliomas. The 238 mesotheliomas consisted of 118 epithelial (50.2%), 40 sarcomatoid (17%), 30 biphasic (12.8%) and 47 cases where the histological type was not recorded (20%). The diagnosis was based upon tissue biopsy in most cases (92%), and 26% underwent post-mortem examination. There was no difference in histological type between pleural and peritoneal tumors. The most common other underlying medical conditions reported in the medical history were coronary artery disease (26.4%), diabetes mellitus (15.1%), and COPD (14.2%).

Demographic data

In the 217 men and 21 women, the mean age at diagnosis was 70.3 yr (range 34 to 92). The age at diagnosis for peritoneal mesotheliomas was slightly younger than for pleural cases (65.4 versus 70.6 yr), but this difference was not statistically significant. There was no significant sex difference regarding pleural or peritoneal tumor location. Of those with available smoking data, there were 94 non-smokers (42%) and 129 smokers or ex-smokers (58%), averaging 37.3 pack-years (n=119). Men were more likely smokers (60% versus 38%) and more likely to have COPD (15% versus 5%).

Occupation/Setting of exposure

Most patients had occupational asbestos exposure (91%). Pipefitter/plumber was the most commonly identified occupation (Table 1). All but two of the patients in the top six occupations were men. The exposure setting with the highest number of cases was petrochemical (possibly related to our location in Houston), followed by construction and shipyard (Table 2).

In the mesothelioma cases with a history of occupational asbestos exposure, there was a 35:1 male-to-female ratio. In those cases with non-occupational asbestos exposure, there was a female preponderance, with a female-to-male ratio of 8:1. Of all men, 97.8% had a history of occupational asbestos exposure, in contrast with only 23.8% of women.

Exposure data

Based upon the patient's lifetime occupational history and details of their asbestos exposure (including intensity, frequency, nature, and duration), the TOMI physician was able to categorize the exposure as heavy, moderate, or light in most cases.

Most individuals with mesothelioma in our series had heavy asbestos exposure (50%), followed by moderate (37.1%) and then light (12.9%). There was no statistical difference between intensity of exposure and histological type of mesothelioma. Of the pleural mesotheliomas, 49.2% had heavy exposure, as did 58.3% of the peritoneal mesotheliomas. There was, however, no statistical difference between intensity of exposure and location of mesothelioma. Those with a history of occupational asbestos exposure were far more likely to have had a heavy or moderate exposure rating compared to cases from non-occupational settings (96.1% versus 5.3%). The estimated exposure strongly correlated with

Table 1. Occupations in 202 cases of malignant mesothelioma

Occupation	Number of Cases	Percent of Total
Pipefitter/plumber	37	18.3%
Operator	24	11.9%
Laborer	20	9.9%
Insulator	19	9.4%
Electrician	15	7.4%
Boilermaker	13	6.4%
Machinist	8	4.0%
Engineer	8	4.0%
Carpenter	7	3.5%
Welder	7	3.5%
Merchant seaman	6	3.0%
Sheetmetal worker	3	1.5%
Brick worker	3	1.5%
Painter	3	1.5%
Other[1]	19	9.4%

[1]Occupations with 2 or fewer cases; including millright, railroad worker, mechanic, drywall worker, truck driver, safety inspector, policeman, civil engineer, printer, pumper, sandblaster, managerial.

Table 2. Exposure setting in 209 cases of malignant mesothelioma

Exposure Setting	Number of Cases[1]	Percentage Occurrence[1]
Petrochemical	117	56%
Construction	95	45.5%
Shipyard	50	23.9%
Marine	26	12.4%
Non-occupational	21	10%
Power Plant	15	7.2%
Transportation	7	3.3%

[1]In many cases, more than one exposure setting.

the presence of asbestosis (66.1% had heavy exposure, 32.1% moderate and only 1.8% light). The level of exposure also correlated with the presence of radiographic pleural plaquing. Those with heavy asbestos exposure had plaques in 57.4% of cases, moderate 37%, and light 5.6%. That these diseases are dose-responsive supports the rating of exposure by the clinician. Moreover, heavy exposure correlated with asbestos body count when performed.

Most individuals in our study with occupational exposure had daily (61.7%) rather than weekly (18.9%) or intermittent (19.4%) asbestos exposures. There was no trend toward decreasing exposure frequency based upon advancing decade of exposure. Those with daily exposures were more likely to have had a heavy exposure (70.2%) than those with weekly (31.6%) or intermittent (2.6%) exposure. As with degree of exposure, frequency correlated with the presence of asbestosis and pleural plaques. Exposure frequency does not appear to influence the histological type.

Table 3. Duration of asbestos exposure in 203 cases of malignant mesothelioma

Duration (yr)	Men	%	Women	%	Total	%
1–5	6	3.3	1	5.3	7	3.4
6–10	9	4.9	2	10.5	11	5.4
11–20	18	9.8	5	26.3	23	11.3
21–30	28	15.2	3	15.8	31	15.3
31–40	92	50.0	7	36.8	99	48.8
>40	31	16.8	1	5.3	32	15.8

Table 4. Latency[1] in 191 cases of malignant mesothelioma

Latency (yr)	Men	%	Women	%	Total	%
15–20	1	0.6	0	0	1	0.5
21–30	3	1.7	1	5.3	4	2.1
31–40	31	18.0	2	10.5	33	17.3
41–50	75	43.6	2	10.5	77	40.3
51–60	48	27.9	9	47.4	57	29.8
>60	14	8.2	5	26.3	19	10.0

[1]Based on cases with both date of first exposure and date of diagnosis.

Eighty-four percent of our cases had reported either direct or direct and bystander asbestos exposure. Seven percent had only bystander exposure and 9% had household or other non-occupational exposure. Men were far more likely to have some direct asbestos exposure (91.1%), whereas women were more likely to have only non-occupational exposure (76.2%). Those with direct exposure, as would be expected, had higher frequency of daily and heavy asbestos exposure rating. Direct exposure also correlated with the presence of asbestosis.

Duration of exposure, the actual number of years working with or exposed to asbestos, not inclusive of time between exposures, was calculated in 203 cases (Table 3). Based upon the provided occupational history, the mean duration of exposure was 31 yr. On average, women had a slightly shorter duration of exposure (25.5 versus 31.5 yr). There was no demonstrable difference in duration of exposure between those with pleural versus peritoneal mesothelioma.

Our series includes individuals with potential asbestos exposure from the 1920s through the 1980s. All but two cases had their first asbestos exposure before 1973. The mean age at first occupational exposure was 22.7 yr.

Latency

Latency, defined as the time interval between first exposure and diagnosis of malignant mesothelioma, was calculated in 191 cases (Table 4). In the present study, the mean latency was 48.5 yr (range 18–70). There was no statistical difference in the latency for pleural versus

peritoneal cases (48.6 versus 45.9 yr, respectively). The latency for insulators (generally presumed to be a more heavily exposed group) was not statistically different from other occupations. Furthermore, there was no statistical difference in latency comparing those with and without asbestosis. On the other hand, women, whom one might anticipate had lesser exposures on average, did have a longer latency period than men (53.3 versus 47.9 yr, $p<0.05$).

Clinical presentation

Of the cases of pleural mesothelioma, the most common presenting signs and symptoms were ipsilateral pleural effusion (90%), shortness of breath (79%), chest pain (64%), and cough (36%). With peritoneal tumors, ascites (77%) and abdominal pain (54%) were the most common presenting findings. Both tumor locations produced weight loss (pleural 30% and peritoneal 69%). A number of the study cohort had a prior malignancy, including skin (n=9), prostate (n=7), lung (n=4) and colon (n=4).

Asbestosis and pleural plaques

Pleural plaques (calcified and/or non-calcified) occurred in 124 of 224 cases (55.3%). Men more often had identified pleural plaques than did women (59.1% versus 19%), but there were too few women with plaques for statistical analysis. It is possible that overlying breast shadows clinically masked non-calcified plaques in women. In both men and women, pleural plaques were more often calcified, correlating with the long latencies involved.

In this series, asbestosis was noted in 63 of 223 (28.3%). All cases of asbestosis occurred in men. Of these, 90.2% had pleural plaques as well. To examine the hypothesis that peritoneal mesotheliomas are associated with higher asbestos exposures on average than are pleural mesotheliomas, we looked at the occurrence of asbestosis in relationship to tumor location. In this series, asbestosis was more often present in those with peritoneal than pleural mesothelioma (38.5% versus 27.6%), but this difference did not reach statistical significance.

Treatment

Treatment for malignant mesothelioma has consisted of surgery, chemotherapy, radiation therapy, or a combination. There has been definite progress in the systemic treatment of this disease over the past 5–8 yr.

Of the 238 cases of mesothelioma reviewed in this series, we have information on 219 regarding the treatment they received, if any. Of the 219, 53% underwent some sort of treatment, with chemotherapy alone the most likely choice (63.8% of those treated). The remaining 103 individuals had no treatment. Of note, the individuals diagnosed before 1993 were just as likely to undergo treatment as were those diagnosed in 2003 and beyond. Patients with peritoneal mesothelioma were somewhat more likely to undergo treatment than those with pleural mesothelioma (69.2% versus 51.9%). Despite recent innovations for surgery in peritoneal mesothelioma, none were performed in our group.

Survival

The overall survival from malignant mesothelioma has been poor. In our study, the trimmed mean survival was 8.8 months. There was a statistically significant difference comparing survival time with and without treatment (trimmed mean 11.3 versus 6.4 months, $p<0.001$). There was no statistical difference in survival between pleural mesotheliomas and peritoneal mesotheliomas.

We examined the hypothesis that a younger age at diagnosis conveys a survival advantage. In our study, we found a longer survival in those diagnosed with mesothelioma before age 60 compared to those 60 or older (13.7 versus 9.7 months), but the standard deviations were large and the difference not statistically significant.

In examining the three histological types for prognostic differences, we did find a significant survival benefit overall for epithelioid versus sarcomatoid tumors (mean 12.2 versus 7.3 months, $p<0.05$). Of those undergoing treatment, epithelioid histology conferred a survival advantage over sarcomatoid mesothelioma (trimmed mean 11.3 versus 7.8 months, $p<0.05$), despite no statistical differences in the provided therapy. Furthermore, treated epithelioid mesotheliomas faired better than non-treated tumors of the same histology (trimmed mean 11.3 versus 6.1 months, $p<0.001$). Although treatment of sarcomatoid tumors slightly prolonged survival (trimmed mean 7.8 versus 5.4 months), these values were not statistically different ($p=0.075$). Of note, untreated epithelioid mesotheliomas do just as poorly as untreated sarcomatoid varieties.

We compared the survival time of treated malignant mesotheliomas based upon the decade of diagnosis (1980s, 1990s, and 2000s). We were unable to detect a difference between those diagnosed in the former decade as compared to the latter.

Discussion

The majority of cases of malignant mesothelioma in the United States are caused by asbestos. An estimated 80% or more of patients with malignant mesothelioma

have a history of past asbestos exposure[12]. Given the long latency period involved, such exposure can be rather remote and involve poor recollection. The attribution to asbestos also depends on the degree of inquiry by the clinician. The proportion of mesothelioma cases recognized as asbestos-related seems to vary with the cohort and study[1, 13].

Out of concern for selection bias, as most of our cases were medicolegal, we compared our data to studies that surveyed all cases in an area, and therefore not involving selection bias. Our results are similar regarding occupational exposure, settings, and industry[14, 15]. As an example, in our study, 91% had worked with or around asbestos, consistent with other investigators[10, 11, 16].

Pleural plaques were seen radiographically in 55%, with evidence of dose-response. Asbestosis was seen half as frequently (28%), again with evidence of dose-response. This is consistent with observations that, in general, malignant mesothelioma and pleural plaques require a lower dose of asbestos than does asbestosis[17].

Chest pain, shortness of breath, and ipsilateral pleural effusion were the most common presenting signs and symptoms for the pleural mesotheliomas in our study. The peritoneal mesotheliomas usually had ascites, abdominal pain, and weight loss. These clinical findings are consistent with those of other investigators[18–20]. Of the pleural mesotheliomas, we found a distinct right-sided predominance (63.4%), similar to that reported by other investigators[11, 21–23]. No explanation for this predominance of right-sided disease has been identified, but some have postulated the less acute angle of the right main bronchus from the trachea as the cause[24].

Some have reported that women have a higher percentage of peritoneal versus pleural mesotheliomas than do men[25]. Mischaracterization of other peritoneal tumors or carcinomas metastatic to the peritoneum might be one explanation for this finding. In our study, we were unable to detect a sex difference in tumor location.

In most cases of mesothelioma reported in the literature, the latency (time from first exposure to diagnosis) is long, with a peak at 30–40 yr[26, 27]. In a review of 21 articles, encompassing 1,690 cases of malignant mesothelioma, Lanphear *et al*. found the median latency was 32 yr[28]. Other cohorts of malignant mesotheliomas reported mean latencies of 42[29] and 49 yr[30]. In the current study, we found a prolonged latency (48.5 yr), consistent with previous investigators. Furthermore, all cases in our study had sufficient latency for causation by asbestos.

We examined the latency for insulators compared to all other occupations and found no significant difference. Additionally, we found no statistical difference in latency between those with or without asbestosis. These findings would seem contrary to the opinion that the heavier the asbestos exposure, the shorter the latency[31]. One explanation is that since almost all of our cases had moderate to heavy asbestos exposure even the non-insulators and non-asbestotics had heavy enough asbestos exposures to prevent detection of differences in latencies. Given that women, on average, likely had lesser asbestos exposures than did men, our finding of a longer latency for women would support this inverse dose-latency hypothesis.

In previous studies, younger age and epithelioid histological type appeared to be beneficial prognostic factors[23, 32, 33]. Our study revealed a longer survival for those under the age of 60 at diagnosis, but this difference was not statistically significant. We were able to demonstrate improved survival with epithelioid histology, overall or with treatment, compared to sarcomatoid type. Epithelioid mesotheliomas also had a better response to therapy (as measured by survival) than sarcomatoid.

The survival from malignant mesothelioma has been poor, with a median reported at between 6–9 months[34]. In our cohort, the median survival was 8.8 months. Some investigators have found no survival increase comparing those diagnosed in the 1980s to those diagnosed in the 1990s[35]. We examined this and found no improvement in survival comparing treated mesotheliomas diagnosed in the 1980s versus the 2000s.

Due to its poor response to treatment, for many years physicians have held a nihilistic attitude towards malignant mesothelioma. Many physicians have reported little in the way of effective treatment[36–39]. However, new and more effective chemotherapeutic agents, newer surgical techniques, and emerging new modalities (such as immunotherapy and gene therapy), may usher in new hope for sufferers of this disease[40]. For example, in the treatment of peritoneal mesothelioma, some centers have used Continuous Hyperthermic Peritoneal Perfusion plus chemotherapy and/or cytoreductive surgery with dramatically improved survivals[41–43]. Our data support a small but statistically significant prolongation of survival with treatment, but we were not able to detect a particular modality or combination as superior.

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