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Original Article

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Malignant Pleural Mesothelioma: Clinicopathologic and Survival Characteristic in a Consecutive Series of 40 Patients*

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Introduction: Pleural malignant mesothelioma is an uncommon but extremely invasive tumor which originates from mesothelial cells and usually occurs after prolonged exposure to asbestos. Different types of surgical and oncological therapeutic methods have been used resulting in various outcomes. The aim of this study was to evaluate, clinicopathologically, 40 patients with pleural malignant mesothelioma and the main factors influencing their prognosis.

Methods: In this study, 40 patients with a definitive diagnosis, who had been followed up for at least 3 years were studied according to these: epidemiologic factors, stage and pathological types, treatment method and complications, and by using factors that influence patients survival, we evaluated them statistically.

Results: The M/F ratio was l3/1 with an average age of 55 years. Chest pain was the most common symptom. In 55% of patients, the lesions were localized in the left site and most were in Buchart stage I or II. The epithelial form was the most common pathological pattern (62.5%). 47.5% of patients only received radiotherapy and chemotherapy. Of patients who underwent decortication and pleurectomy with adjuvant therapy, extrapleural was performed in 20% of patients, and pneumonectomy, in 17.5%; and 15% refused any type of treatment. One patient died from the surgery. The most common surgical complication was wound infection. The average survival was 10.5 months, and the main factors influencing the survival were physiologic status, pathological form of disease, stage of disease and the pattern of pleural involvement.

Conclusion: Because of the low survival after multimodality invasive treatments in mesothelioma, aggressive therapeutic methods were recommended in patients with good physiological status and early clinical stage with a good pathology type.

Key words: malignant mesthelioma, pleura, diagnosis, treatment

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Introduction

Malignant pleural mesothelioma (MPM) is a rare malignancy that originates from mesothelial cells. Chronic exposure with Asbestos is the main risk factor for malignant mesothelioma and in contrast to lung malignancy, smoking is not a risk factor for this malignancy. MPM is asymptomatic in its early stages, and early diagnosis and aggressive therapy have the major roles in the management of this malignancy.[1)]

Dyspnea, chest pain, and pleural effusion are common presentations of MPM. Pleural effusion and thickening can be detected by chest X-ray (CXR) and computed tomography (CT) scan and tissue diagnosis is almost obtained by fine needle biopsy, thoracoscopic sampling, or open pleural biopsy.[2)] Therapeutic options include agressive approaches such as extrapleural pneumonectomy, or less invasive methods such as decortication and pleurectomy or pleurodesis. Surgical interventions may accompanied with adjuvant therapy such as radiotherapy, systemic or intrapleural chemotherapy. The value of these options remain unclear and controversial.[3)]

This is a clinicopathological study of 40 malignant mesothelioma patients in order to evaluate the prognostic factors of this malignancy.

Method and Materials

In this retrograde descriptive case series study, 40 patients with malignant pleural mesothelioma were studied from 1996 to 2008 in Ghaem and Omid hospitals (Mashhad-IRAN) and Emam Khomeini hospital (Tehran-IRAN). All patients were followed for at least 3 year after therapies, except for those patients who died during this period. Patient characteristics such as age, sex and history of exposure to asbestos or smoking, clinical signs and symptoms, side of pleural involvement, abdominal involvement, diagnostic methods, pathological type, platelet count at the time of diagnosis, macroscopic feature of pleural disease, therapeutic approach and mean survival were also evaluated. Data were analyzed by SPSS (Ver 11.5). Patients were placed into one of two groups, according to survival (less than and more 12 months) and all variables were compared between two groups by the Fisher exact test. A P value less than 0.05 was considered significant with a confidence interval of 95%.

Results

Forty patients were enrolled in this study. 30 were male and 10 were female (M/F = 3). Mean age was 55.2 ± 0.34. The youngest patient was 40 and the oldest was 78 years old. Fifteen patients (37.5%) were smokers, and 10 patients (25%) were exposed to asbestos.

Duration between the start of symptoms and diagnosis was longer than 6 months in 25 patients (62.5%), and it was shorter than 6 months in 15 patients (37.5%). Chest pain was the most common symptom, observed in 34 patients (85%). Exceptional dyspnea was seen in 27 (67.5%) and fatigue and weight loss were observed in 18 (45%). Chest radiography and chest and abdominal CT scan were done for all cases routinely. Left pleural cavity involvement was seen in 22 (55%), right side disease was observed in 16 (40%) and 2 (5%) had bilateral involvement.

Pleural effusion was detected in 6 patients (15%), and pleural thickening and confluent pleural nodularity view were seen in 25 (62.5%). Mediastinal lymph adenopathy was detected in 2 (5%) and sub diaphragmatic involvement was seen in 6 (5 in right and one in the left side), and bilateral lung disease was seen in 2 patients (5%).

All patients underwent diagnostic pleural tapping and biopsy, but a diagnosis was made in only two cases by these methods (5%). Diagnostic thoracoscopy was performed for 10 (25%), and in the others (70%), thoracoscopic evaluation had failed because of severe pleural thickening and obliteration of pleural cavity, so open pleural biopsy was inevitable in these patients.

Platelet count at the time of diagnosis was lower than 400 000 in 25 patients (62.5%) while in 15, the platelet count was over 400 000 (37.5%). Pleural cavity involvement was also assessed, and 7 patients had severe inflammation in pleural cavity (17.5%), and severe fibrosis of the pleural cavity was seen in 26 patients (65%), so even open pleural cavity exploration was problematic. Severe fibrosis with several visceral pleural nodules was reported in 6 patients (15%) Tissue diagnosis was made by needle biopsy in 2 patients (5%), and they were referred for neoadjuvant therapy because of unfavorable medical conditions, so the pleural cavity was not assessed in these two patients.

Staging was done by Butchart system, and 16 patients were in stage I (40%), 12, in stage II (30%), 3 c in stage III (7.5%), 7 in stage IV (17.5%) and 2 in stage V (5%).

Different therapeutic approaches were used. Six patients (15%) refused the treatment course, so palliative modality (pain control and bronchodilatory medications) were used. 19 patients were referred to oncologists and underwent chemoradiotherapy, and surgery was not recommended after the diagnostic evaluations. Among these

patients, 5 were unwilling to have surgery, 6 did not have sufficient cardiopulmonary reserve or were too old to tolerate the operation, 2 had bilateral pulmonary disease, 6 had both sides of diaphragmatic levels involved, so they were excluded from the surgical approach and 7 underwent decortication and pleurectomy because of limited cardiopulmonary reserve and extrapleural pneumonectomy intolerance. These 7 patients were referred for adjuvant chemoradiotherapy after the surgery (17.5%).

Extrapleural Pneumonectomy was performed in 8 patients (20%) who were younger than 60, had a FEV1>1.5 lit, favorable ejection fraction, unilateral pleural involvement without underdiaphragmatic involvement, and were free of hillar lymphadenopathy. Neoadjuvant therapy was performed before extrapleural pneumonectomy for 3 patients, and then they underwent adjuvant therapy (7.5%). Primary surgical intervention was done in 5 patients and then they underwent adjuvant therapy (12/5%).

One patient was missing from the adjuvant therapy protocol (2.5%), and the operation was performed in the right side in 5 patients (12.5%) and in the left side in 3 (7.5%).

The technique of extrapleural pneumonectomy compirses parietal plura, diaphragm and pericardium excision in the side of involvement and reconstruction of diaphragm and pericardium by prosthesis (Pericardium needs reconstruction only in the right side).

Extrapleural pneumonectomy is conducted via a postrolateral incision (thoracotomy in 5th and 8th intercostal spaces).

All patients remained in ICU at least for 48 hours after the operation. Six patients were extubated at the end of the operation and 2 were transferred to ICU with an orotracheal tube, who were extubated 24 hours later.

Postoperative death was reported only in one case; therefore, the mortality rate was 1/8 = 12.5% among those who underwent operation. The cause of mortality was massive bleeding from branches of aortic spinal arteries in a patient who underwent left extrapleural pneumonectomy. Death was not reported for 7 patients, who wre subsequently discharged.

Postoperative complications included cardiac herniation in one case (12.5%) related to malposition of pericardial prosthesis and its displacement of that. This complication was corrected by reoperation and reconstruction and patient was managed perfectly.

Wound dehiscence was seen in 1 patient (12.5%) 1 month after surgery, and we repaired it again. Wound infection also was observed in 2 patients (25%), who were managed conservatively.

Pathologic studies reported epithelial type in 25 patients (62.5%), sarcomatous type in 5 (12.5%) and Mixed type in 10 (25%).

Mean survival was 10.5 months (min, 7 months; maximum, 2.5 years).

In order to assess prognostic survival factors, we placed the patients into one of two groups: less than 12 months of survival or greater than 12 months.. Thirty-three patients survived less than 12 months, and 7 patients, longer than 12 months (17.5%)

Table 1 shows the relation between different variables and patients survival.

Our findings showed a significant relation between survival versus age, pathological type, pleural involvement type, bilateral involvement and presence of disease in both sides of diaphragm; however, there was no relation between survival and sex, history of smoking or asbestos exposure, therapeutic plan and platelet count before treatment and side of pleural involvement.

Discussion

Malignant mesothelioma is an invasive serosal malignancy that may invade pleura or peritoneum. This tumor was rare in the past but now there is an increasing rate of this malignancy in Africa, Europe and America and Australia because of increased exposure to risk factors such as asbestos.[4)]

Our study also showed that most of the cases have been diagnosed in recent 7–10 years that indicate increasing rate of disease and improvement of diagnostic methods.

Asbestosis is the most common and known etiology of malignant mesothelioma. Wagner and his colleagues first reported the relation between mesothelioma and asbestos exposure in the south of Africa.[5)] Chronic asbestos exposure may lead to mesothelioma. Parietal pleura involvement is more common due to chronic and recurrent extraction of amphibolic fibers from lung alveoli, which leads to excoriation and recurrent irritation of parietal pleura.[6)] In our trial, 25% of patients with mesothelioma had a positive history of asbestos exposure.

Recent articles suggest a role for a DNA virus named Simian virus 40 as another predisposing factor for mesothelioma.[7)]

Patients are mostly male (80%), and the age range is between 50 to 60 years. Primary symptoms include dyspnea and pleural effusion that leads to chest pain in 60% of

Table 1 Relation between different variables and survival in malignant mesothelioma

Variables	Dead patients after 12 months (N = 33)	Alive patients after 12 months (N = 7)	P value
Fisher exact test			
Age (younger than 60)	12	7	P <0.01
Sex (male/female)	25/8	5/2	P = 0.008
Smoking	13	2	P = 0.419
Asbest exposure	8	2	P <0.298
Pretreatment Plt >400.000	10	2	P = 0.844
Side of involvement (left:right:bilateral)	18/13/2	4/3/0	P = 0.556
Pleural involvement (inflammatory:fibrosan:fibronodular)	1/25/6	6/1/0	P <0.001
Bilateral diaphragmatic involvement	6	0	P <0.05
Therapeutic plan			P = 0.079
A) Chemoradiotherapy	17	2	
B) Chemo therapy + pleurectomy	5	2	
C) Chemo therapy + Pleuro Pneumonectomy	5	3	
D) Without treatment	6	0	
Pathologic type			P <0.05
A) Epithelial	19	6	
B) Sarcomatous	5	0	
C) Mixed	9	1	

cases, so coexistence of pleural effusion and chest pain is suspected for this disease. Other symptoms are fatigue and weight loss are reported in 30% of patients and clubbing is seen in 10% of cases.[8] The majority of our patients were male, and their most common symptoms were chest pain (67%), exertional dyspnea (67%) and chronic fatigue (45%).

The interval between the presence of pleural effusion or dyspnea and the patient receiving an exact diagnosis was a mean of 2–3 months; however, for some patients, mesothelioma may be accidentally found in a routine chest X ray.[8] Mean time from symptoms to exact diagnosis in our trial was often more than 6 months (62.5%).

Imaging evaluations such as CXR or CT scan show pleural effusion in 74% (as a single symptom). Pulmonary nodule with confluent pleural rid may be reported in 92% that may be together with intralobular groove infiltration in 86%. Chest wall invasion may be observed in 18%.[9] Radiological findings in our study included pleural effusion in 20% and confluent pleural rid in 62.5% and mediastinal lymph adenopathy in 5%.

The first step in disease diagnosis is pleural fluid sampling and analysis. Pleural fluid in mesothelioma is yellow mostly, although this in not diagnostic (it is reported in 20%–30% of cases). Biomarkers such as Corlertinin or tumor I antigen wilms are more accurate than other epithelial markers such as CA 15-3, Mucin-1; nevertheless, the latter are also useful.[10] Pleural fluid analysis was not a useful diagnostic tool for any of our patients, so parietal pleural biopsy was inevitable in all cases. Close biopsy by Abram's needle is the first supplementary diagnostic intervention after pleural fluid analysis; however, this method also has a low diagnostic value and requires immunohistochemical studies on the tissue sample or larger tissue specimens.[11] Routine use of thoracoscopy as the main diagnostic tool is become acceptable recently that is more accurate and sensitive but in advanced stages of disease, thoracoscopy may be impossible due to the pleural space obliteration, so in these cases, open pleural biopsy would be the last step in order to obtain tissue diagnosis.[12] Needle biopsy was a diagnostic procedure for only 2 patients (5%) and a diagnosis was made by thoracoscopy in 25%; the other patients (70%) required an open pleural biopsy for the tissue diagnosis.

Diagnosis of mesothelioma from other tumors such as metastatic adenocarcinoma is difficult and needs specific stainings (Vimentin and Citokeratin), and even electron microscopic studies may be necessary for making a definite diagnosis. Pathological classification of mesothelioma includes epithelial type (the most common), sarcomas and mixed type.[11] Frequency of different subtypes in our study observed as: epithelial type (62.5%), mixed (25%) and sarcomas (12.5%).

Mesothelioma is a tumor, but standard staging of

Table 2 Batchart staging system

Stage	Description
I	Unilateral involvement (Pleura, Pericardium and diaphragm)
II	Invasion to chest wall or mediastinum (esophagus or heart)
III	Mediastinal lymph node involvement
IV	Invasion to abdominal cavity trough diaphragm
V	Hematogen metastasis

tumor has remained unclear and few studies have been performed in this field. A standard and perfect staging method should be capable to predict the patient survival and guide the physician in management.[13] **Table 2** shows the staging system.

Although other staging methods such as tumor node metastasis (TNM) have been introduced recently; the tumor stage (T) is underestimated in these methods, and the role of lymphadenopathy (N) defining a lung malignancy in the TNM system as it spreads, as well as the routes of mesothelioma metastasis routes are unknown; this is because lymphatic metastasis is uncommon for a mesothelial histological type of tumor. Finally many centers prefer the old butchart system[14] we also used butchart staging system. The reason of using butchart staging system as mentioned before was the inability of clinical staging by TNM staging system to determine T and M correctly. The most accurate staging by TNM system is pathological staging with is based on reseated specimen. Regarding our study, 20% of the patients underwent extrapleural pneumonectomy and 80% received other treatment modalities because the determination of T and M was inaccurate in these patients. Therefore, we did not use the TNM system for staging and in its place, we decided to use the simple method of butchart that is being used in many centers. 40% of our patients were in stage I, (30%) were in stage II (7.5%) were in stage III (17.5%) were in stage IV and (5%) were in stage V.

Chamberlain et al. performed a study in 2008 to suggest a new method of N (Lymph node) evaluation by sampling through cervical mediastinotomy in right sided disease. Benefits of this method include little pain, low rate of tumor seeding in the biopsy site and rapid diagnosis for management.[15]

Vast spectrum of multimodality treatments is introduced for these tumors. Invasive extrapleural pneumonectomy was the only therapeutic option in the past. However, less invasive methods and chemoradiotherapy have been introduced recently, and successful results are reported for these modalities. Sugarbaker and his colleagues conducted a study about the role of radical surgery in the treatment of mesothelioma in 1991. They studied 31 patients, over 11 years, who had tolerated radical operations and underwent extrapleural pneumonectomy. They also used chemoradiotherapy as adjuvant therapy, and they reported acceptable results with a low complication and mortality rate and favorable effects on the survival of patients.[16] Shipper et al. also reported similar results in 2008. They suggested extrapleural pneumonectomy and adjuvant chemoradiotherapy as an effective treatment for malignant mesothelioma with low mortality and morbidity. They reported longer survival for patients who were treated by this method compared to other therapies such as pleurectomy, decortication or biopsy only.

However, they mentioned that extrapleural pneumonectomy should be performed in special centers with enough experience to achieve acceptable morbidity and mortality. Finally, survival is low in these patients, and 3 years survival had been estimated as 14% in previous research reports.[14] Okada et al. compared extrapleural pneumonectomy and pleurectomy with decortication in 2007. They reported better results for extrapleural pneumonectomy.[17] Aigner et al. (2008) also suggested extrapleural pneumonectomy as a preferred therapeutic method.[18] Other studies reported similar results for less invasive treatments such as pleurectomy and decortication, and Phillips et al. also reported a similar outcome and survival for decortication with pleurectomy and extrapleural pneumonectomy. So they limited the indications of extrapleural pneumonectomy to special situations because of high morbidity risk.[19] Flores et al. (2008) reported longer survival for patients who were treated with pleurectomy and decortication compared to extrapleural pneumonectomy although expeditious patient selection has an important role.[20]

Martin-Ucar et al. (2007) also compared the results and survival after extrapleural pneumonectomy and pleurectomy with decortication among N2 positive malignant mesothelioma cases. They insisted on the role of mediastinoscopy in management to achieve longer survival.[21]

Aelony et al. (2005) suggested talk pleurodesis with chemoradiation for symptom control and treatment.[22)]

Several different therapeutic options have been suggested for malignant mesothelioma; however, almost all physicians have accepted the role of oncologic treatments, even though most of the articles report that chemotherapy benefits only 15%–20% of patients. The most common chemotherapy protocol for malignant mesothelioma is a cisplatin-based regimen.[23)] Recent articles suggested intrapleural chemotherapy and immunotherapy as adjuvant therapy after surgery in mesothelioma. Luechi et al. (2007) studied intrapleural chemotherapy and immunotherapy and systemic chemotherapy and radiotherapy after decortication and pleurectomy for patients with stage II, III of mesothelioma. They used intrapleural IL2 for neoadjuvant immunotherapy, a gemcitabine-cisplatin-based regimen for adjuvant chemotherapy, and 30-CGY radiotherapy plus long-term injection of IL2 after surgery. Mean survival time in their study was 28 months.[24)]

Sautere et al. (1995) studied multimodality adjuvant therapy for mesothelioma by the combination of intrapleural and systemic chemotherapy, but they reported high toxicity for this treatment and did not recommend it as standard treatment of mesothelioma.[25)] Our study also showed that the type of surgery (extrapleural pneumonectomy or pleurectomy and decortication) did not affect the survival significantly. We used adjuvant chemo radiotherapy for all patients.

Prognostic survival factors for malignant mesothelioma patients were discussed by Minea and his colleagues in 2008. They reported that positive surgical margin, involved mediastinal lymph nodes, tumor pathology, age and physiologic condition of patients are factors that affect the survival.[26)] Sugerbaker et al. (1999) also suggested that the physiological condition, surgical margin, mediastinal lymphadenopathy and primary platelet count and stage and pathological type of tumor are prognostic factors for survival.[27)] On the other hand, Okada reported that tumor pathology, stage, age and type of surgery did not affect the survival.[17)] Age and physiologic condition, pathological type and pleural involvement type and stage of mesothelioma significantly affected the survival in our study.

Conclusion

Malignant pleural mesothelioma is among the invasive pleural malignancies that have a short time of survival, in spite of radical invasive therapies, so we suggest radical surgery such as extrapleural pneumonectomy only in special cases for patients who are in good physiological condition and and have low-stage tumors with a favorable pathologic type. Otherwise, we recommended less invasive treatments such as pleurectomy or pleurodesis alone or in combination with oncologic adjuvant treatments. Adjuvant chemoradiotherapy has an important role in the treatment of malignant mesothelioma, as a supplementary treatment after surgery.

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