RESEARCH COMMUNICATION

Malignant Pleural Mesothelioma in Singapore

C SP Yip[1], HN Koong[2], CM Loo[3], KW Fong[1*]

Abstract

Aim: To examine the clinical characteristics and outcomes of malignant pleural mesothelioma (MPM) in Singapore. Methods and Materials: A retrospective case note review of patients diagnosed with MPM between 1997 and 2007. Overall survival (OS), locoregional recurrence-free survival (LRS) and metastasis-free survival (MFS) were estimated using Kaplan Meier method and comparison were done using log rank test. Multivariate analysis was not done due to the small number of patients. Results: There were 39 patients diagnosed with MPM. Fifty-nine percent of patients presented with Stage III and IV disease. Eight (21%) patients had surgery with 2 patients receiving trimodality treatment and adjuvant chemotherapy respectively. Three patients received adjuvant RT and one patient had no adjuvant therapy. Twelve patients received palliative RT or chemotherapy. Median follow-up was 27.0 weeks. Median overall survival (OS) for all patients was 8.0 months (95% CI 6.3-9.7). One-year and 2-year OS were 25.6% and 6.4% respectively. Thirty-eight patients died of progressive disease and one patient died of other cause. Locoregional recurrences and distant metastases occurred in 3/8 and 5/8 surgically treated patients respectively. Overall, distant metastases occurred in 44% of patients. Surgery did not affect survival outcomes although patients with dual modality treatment showed a trend towards improved survival. Epithelioid tumours had better prognosis (median OS 10.2 months) compared to biphasic (median OS 8.0 months) and sarcomatoid tumours (median OS 1.4 months). Conclusion: Future management of MPM will need to emphasize on both locoregional and systemic control and hence, inclusion of patients in clinical trials for multimodality treatment should be encouraged.

Keywords: Malignant pleural mesothelioma - outcomes - Asia

Asian Pacific J Cancer Prev, **12**, 1155-1159

Introduction

Malignant mesothelioma is an aggressive and rare tumour that arises from mesothelial surfaces of the pleura and peritoneum, pericardium or tunica vaginalis. Although these variants of mesothelioma are strongly associated with asbestos exposure, it is still not known if these diseases are indeed similar in biology. Malignant pleural mesothelioma (MPM) although rare, is commoner than the other types of mesothelioma. This disease is usually fatal with median survival ranging from 9 to 17 months. The most common risk factor associated with the development of MPM is inhalation of asbestos, which led to widespread legislative ruling in many countries to reduce exposure to asbestos in the general population. However, the peak of incidence of MPM is only expected in the future due to the long latent interval from asbestos exposure to development of MPM. Other possible risks of MPM include previous radiation exposure and simian virus 40 (SV-40). According to the Singapore Cancer Registry, there were 62 new MPM cases diagnosed from 1993 to 2002 and 11 new cases of peritoneal mesothelioma during the same period. Although the numbers might be small and accounted for only a small proportion of cancer patients seen in our population, nonetheless, management of this group of patients remains a challenge. A previous retrospective study of malignant mesothelioma in the Singapore General Hospital in 2003 had 16 patients, of which 13 patients had MPM and three patients had peritoneal mesothelioma. This study confirmed the dismal prognosis of this disease with a median survival of 6 months. Majority of the patients received basic supportive care and none of the patients had curative treatment (Chan et al., 2003). This current study aims to review the characteristics and outcomes of patients with MPM treated in our centre.

Materials and Methods

This was a retrospective study of all patients who were diagnosed with MPM and received treatment in our centre between 1997 and 2007. Patients who did not have histological confirmation of MPM and foreign patients (due to the lack of follow-up) were excluded from this study. Case notes were reviewed for patient characteristics, treatment modalities and clinical outcomes. Tumours were staged according the American Joint Committee of Cancer

*[1]Radiation Oncology, National Cancer Centre Singapore, [2]Surgical Oncology, National Cancer Centre, [3]Respiratory & Critical Care Medicine, Singapore General Hospital *For correspondence : trdfkw@nccs.com.sg*

(AJCC) 6th edition system. Our local Institutional Review Board committee approved this study.

Overall survival (OS), locoregional recurrence-free survival (LRS) and metastasis-free survival (MFS) were estimated using Kaplan Meier method and comparison between groups were done using log rank test. Multivariate analysis was not done due to the small number of patients. Overall survival and MFS were calculated from the date of diagnosis to the time of death from any cause and time of distant relapse respectively. Patients who were alive at the time of analysis were censored on 23rd March 2010 when the local death registry was queried. Locoregional recurrence-free survival was calculated from the date of definitive treatment to time of locoregional relapse. Patients who had residual disease were deemed to have LRS of 0 week. A p value of less than 0.05 was deemed as significant. Statistical analysis was performed using SPSS version 16.0.

Results

Patient characteristics

A total of 57 patients were identified with possible histological diagnosis of mesothelioma. However, 18 patients were excluded from the analysis because they had the wrong diagnosis (e.g. metastatic lung adenocarcinoma to the pleura or peritoneal mesothelioma) or were foreigners (7 patients). Hence, 39 patients were included in this analysis over the 10-year period.

There were 32 males (82%) and 7 females (18%). Median age of all patients was 64 years old (range 36-86). The majority of patients were Chinese (87%) followed by Malays and Indians (5% for each group). Half of these patients were documented smokers (46%). Most patients presented with pleural effusions and dyspnoea while some had cough, chest pain and weight loss. A third of the patients (33%) had occupational exposure to asbestos but details of exposure were not known for 5 (13%) patients. See Table 1 for patient characteristics.

Tumour characteristics

About half of the patients had T3/4 tumours but T stage was not known for 31% of all patients. More than half (59%) of the patients had radiological (49%) or pathological (10%) N0 disease. Seven (18%) patients had metastatic disease at diagnosis. More patients presented with Stage 3 (23%) and Stage 4 (36%) disease but tumour stage was not known in 28% of patients. Histology was found to be epithelioid, sarcomatoid, biphasic and not specified in 28%, 15%, 18% and 39% of patients respectively.

Treatment

Eight (21%) patients had surgery of which seven had extrapleural pneumonectomy (EPP) and one had pneumonectomy. The patient who had pneumonectomy was a 69 years old female with T4N0M0 disease but it was unclear as to why she did not have EPP. Two patients had positive resection margins. Among those eight patients, two had trimodality treatment, three had adjuvant radiotherapy (RT) and two had adjuvant chemotherapy. One patient did not have any adjuvant therapy. Adjuvant RT was delivered by conventional RT (3 patients), conformal RT (1 patient) and intensity-modulated radiotherapy (1 patient). One patient died before completing the course of adjuvant RT (received 24Gy) due to progressive disease.

Two patients with T4N0M0 disease had their surgeries abandoned as they were found to have unresectable tumours intraoperatively. One patient proceeded to have palliative chemotherapy and the other patient had best supportive care.

Five (13%) patients had palliative RT and seven (18%) patients had palliative chemotherapy. Chemotherapy regime commonly used in the adjuvant setting was

Table 1. Patient and Treatment Characteristics

Patient characteristics		Numbers (%) N=39
Gender	Male	32 (82)
	Female	7 (18)
Age	31-40	1 (3)
	41-60	14 (36)
	61-80	21 (54)
	> 80	3 (7)
Race	Chinese	34 (87)
	Malay	2 (5)
	Indian	2 (5)
	Others	1 (3)
Smoker	Yes	18 (46)
	No	16 (41)
	Unknown	5 (13)
Occupational asbestos	Yes	13 (33)
	No	21 (54)
	Unknown	5 (13)
T stage	1	2 (5)
	2	6 (15)
	3	11 (28)
	4	8 (21)
	x	12 (31)
N stage	0	23 (59)
	1	4 (10)
	2	4 (10)
	3	1 (3)
	x	7 (18)
M stage	0	28 (72)
	1	7 (18)
	x	4 (10)
Tumour stage	1	2 (5)
	2	3 (8)
	3	9 (23)
	4	14 (36)
	Unknown	11 (28)
Tumour type	Epithelioid	11 (28)
	Sarcomatoid	6 (15)
	Biphasic	7 (18)
	Not specified	15 (39)
Surgery	Extrapleural pneumonectomy	7 (18)
	Pneumonectomy + rib resection	1 (3)
	None	31 (79)
Curative treatment (N=9)	Surgery	1 (3)
	Surgery + adjuvant RT and/or chemotherapy	7 (18)
	Radiotherapy	1 (3)
Palliative (N=30)	Radiotherapy	4 (10)
	Chemotherapy	7 (18)
	Supportive care	19 (48)

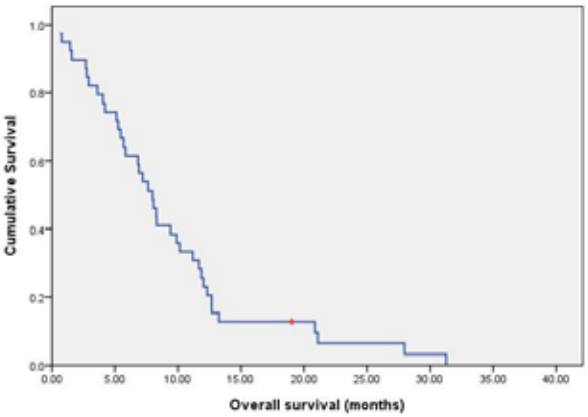

Figure 1. Overall Survival for All Patients

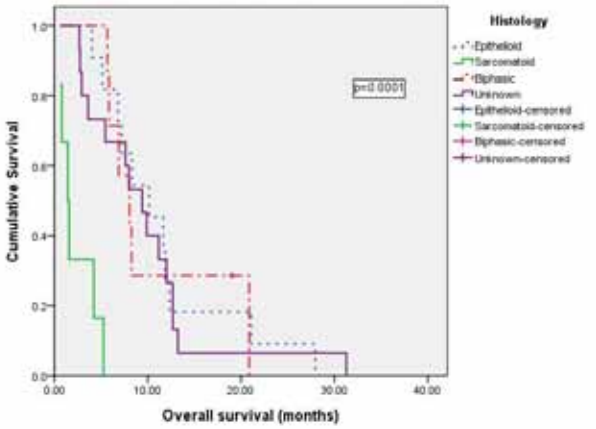

Figure 2. Overall Survival According to Histology

Pemetrexed and Cisplatin where as Gemcitabine and Carboplatin were used in the palliative setting. The remaining 19 (49%) patients were given best supportive care.

Median RT dose for all patients was 59.5Gy (range 20.0-64.0) and median RT duration was 28 days (range 8-47). Median RT dose for patients who had adjuvant RT was 60.0Gy (range 24.0-64.0Gy) where as median dose for patients treated palliatively was 38.0Gy (range 20.0-62.5Gy).

Outcomes

Median follow-up for all patients was 27.0 weeks (range 0-134.9). All patients died. Thirty-eight (97%) of them died of disease and one (3%) patient died of other cause. Median OS for all patients was 8.0 months (95% CI 6.3-9.7) with 1-year and 2-year OS of 25.6% and 6.4% respectively (Figure 1). Univariate analysis showed that histology of the tumour had a significant effect on overall survival with epithelioid subtype having the best prognosis (median OS = 10.2 months) followed by biphasic (median OS = 8.0 months) and sarcomatoid tumours (median OS = 1.4 months) (p=0.0001) (Figure 2). Age, gender, smoking status, previous asbestosis exposure, tumour stage and treatment modalities were not significant factors. Nonetheless, younger patients (less than 65 years old) and patients without previous asbestos exposure showed improved survival although these differences were not statistically significant.

Eight patients had surgical resection with seven patients undergoing EPP. One patient died within a week of EPP. Overall survival was not significantly different between patients who had surgery (median OS = 8.0 months) and those who did not (median OS = 7.6 months) (p=0.287). Patients who had dual modality treatment (surgery + RT or chemotherapy) had the best OS (median OS = 20.9 months) compared to patients who had trimodality treatment (median OS = 8.0 months) or surgery alone (median OS = 2.9 months) alone although this was not statistically significant. Patients who were given palliative RT or chemotherapy had median survival of 6.8 months. On the contrary, patients on supportive care had median survival of 8.0 months (p=0.181).

Three (38%) patients who underwent surgery had locoregional recurrences as well as distant failures. Six (75%) surgically treated patients developed distant metastases; of which 4 had prior chemotherapy. Time to locoregional recurrences were 5.9, 7.0 and 78.6 weeks respectively. Time to distant failure for the 6 patients were between 15.4 and 116.0 weeks. Distant metastases occurred in another 11 patients who did not have surgery. Sites of metastases included peritoneum (41%), lymph nodes (41%), lung (18%), liver (12%), bones (6%) and adrenal (6%). Median MFS was 26.7 months (95% CI 4.6-48.7).

Discussion

MPM is an aggressive disease with very poor prognosis and tends to affect older patients. Progress in the management of this group of patients has been limited by the rarity of the disease and hence, difficulty in conducting randomized trials. Surgical resection remains the mainstay of treatment although the high morbidity and mortality associated with surgery, in particular EPP, have limited its use in many patients with MPM.

Our study is one of the first comprehensive reviews of patients who were diagnosed with MPM in Singapore over a period of 10 years. Our study supports that males were affected more often than females. Although known as a disease affecting mainly older patients, more than half of our cohort was below 65 years old. A third of patients gave a history of occupational exposure to asbestos prior to diagnosis and more than half of the patients recorded no previous exposure. This figure of asbestos exposure is slightly lower than other published series (53%-87%) although reason for this is unclear (Ascoli et al., 1996; Yates et al., 1997).

This study also confirms that MPM remains a deadly disease with very poor prognosis regardless of treatment. All patients died with a short median survival of 8 months. Even among patients who received radical treatment, survival was not significantly different from those who were treated with palliative intent or basic supportive care. This could be due a number of factors. Firstly, EPP is associated with significant risk of morbidity and mortality. Several studies have recorded post-operative mortality rates of between 3.8-8.2% and morbidity rates ranging from 22-73% (Sugarbaker et al., 1996; Sugarbaker et al., 1999; Rice et al., 2007; Schipper et al., 2008). Furthermore, adjuvant RT or chemotherapy could also exert significant morbidity on these patients who

already had limited pulmonary reserve and frail physical condition, thus possibly negating the benefit of adjuvant treatment. Besides that, our study is also limited by the small number of patients. There were only 8 patients who were surgically treated and even fewer of them received dual or trimodality treatment to allow a meaningful comparison of survival between treatment groups. Hence, these results might not be reflective of the true treatment outcomes.

Our 1- and 2-year survival rates of 25.6% and 6.4% respectively were comparable to other studies. One retrospective study from Leicester with 142 patients recorded a median survival of 5.9 months with 1- and 2-year survival rates of 21.3% and 3.5% respectively. (Edwards et al., 2000) One Japanese study analysed the survival rates for patients who underwent surgery as well as unresectable patients. One- and 2-year OS for the resectable and unresectable groups were 67.9/35.0% and 40.5/10.8% respectively (Iyoda et al., 2008).

The only significant survival prognostic factor found in this study was that epithelioid subtype had improved survival. This was consistent with previous studies in which epithelioid tumours had the best prognosis where as sarcomatoid subtype conferred a worse outcome (Antman et al., 1988; Yates et al., 1997; Curran et al., 1998; Edwards et al., 2000; Balduyck et al., 2010) One of these study showed that surgically treated patients with sarcomatoid histology had the poorest prognosis regardless of the treatment received and it suggested that this group of patients should be treated with palliative intent from the start (Antman et al., 1988) This could be due to intrinsic molecular and biological differences between the subtypes. There has been evidence that epithelioid tumours express more Epidermal Growth Factor Receptor (EGFR) but how this influences survival is not clear at present.(Edwards et al., 2006)

Our study does have its limitations with the inherent problems of a retrospective study. The interpretation of the results and statistics of this study has to be done with caution due to the small number of patients. Furthermore, this was a heterogenous group of patients who received different types of treatment. Nonetheless, it provides vital information on patient characteristics and treatment outcomes in this rare but deadly disease in our local population. As this study was carried out on patients treated between 1997 and 2007, treatment of this disease shifted from surgery alone to the addition of adjuvant therapy and now, evidence are suggesting that trimodality treatment may confer better survival advantage in carefully selected group of patients (Krug et al., 2009; de Perrot et al., 2009). In our study, majority of the patients died of progressive locoregional disease rather than disseminated disease although metastases occurred in 44% of patients. Hence, combined emphasis on both locoregional and systemic control are important in this disease and more effort should be made to identify patients who are suitable for trimodality treatment as this strategy is not without toxicity. Patients will have to be medically and physically fit to undergo radical surgery, RT and chemotherapy. Previous studies also found that certain factors such as positive resection margins and positive nodes are associated with worse outcomes regardless of the addition of adjuvant treatment (Sugarbaker et al., 1999; de Perrot et al., 2009) Thus, patients who are more likely to benefit from combined modality treatment may be those who have disease confined to the hemithorax without invasion of vital structures and clinically node negative patients. Conformal RT and more recently, IMRT, have been increasingly used in the management of MPM. Intensity-Modulated Radiotherapy is a newer technique incorporating inverse planning and use of multiple beams for more conformal treatment and hence, decreasing toxicity to the normal tissues and improving therapeutic ratio. It remains to be confirmed if IMRT indeed improves outcomes and this will have to be investigated in future prospective trials.

In conclusion, MPM is an aggressive and deadly disease and survival remains poor. Improvement in the management of this disease has been slow but there are promising new developments. Multimodality treatment appears to be a viable option to control both local and systemic disease, although this was not confirmed in our study likely because of the small number of patients who received such treatment. However, multimodality treatment should be done in carefully selected patients and in centres with adequate experience, as it is associated with significant toxicities. Perhaps the outcomes for this group of patients will continue to improve in the future with newer RT techniques, improved systemic therapy and the use of molecular subtyping to guide patient management.

References

Antman K, Shemin R, Ryan L, et al (1988). Malignant mesothelioma: prognostic variables in a registry of 180 patients, the Dana-Farber Cancer Institute and Brigham and Women's Hospital experience over two decades, 1965-1985. *J Clin Oncol*, **6**, 147-53.

Ascoli V, Scalzo CC, Facciolo F, et al (1996). Malignant mesothelioma in Rome, Italy 1980-1995. A retrospective study of 79 patients. *Tumori*, **82**, 526-32.

Balduyck B, Trousse D, Nakas A, et al (2010). Therapeutic surgery for nonepithelioid malignant pleural mesothelioma: is it really worthwhile? *Ann Thorac Surg*, **89**, 907-11.

Chan K, Tan KL, Lee HS, et al (2003). Malignant mesothelioma: experience at the Singapore General Hospital. *Ann Acad Med Singapore*, **32**, 388-91.

Curran D, Sahmoud T, Therasse P, et al (1998). Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience. *J Clin Oncol*, **16**, 145-52.

de Perrot M, Feld R, Cho BC, et al (2009). Trimodality therapy with induction chemotherapy followed by extrapleural pneumonectomy and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. *J Clin Oncol*, **27**, 1413-8.

Edwards JG, Abrams KR, Leverment JN, et al (2000). Prognostic factors for malignant mesothelioma in 142 patients: validation of CALGB and EORTC prognostic scoring systems. *Thorax*, **55**, 731-5.

Edwards JG, Swinson DE, Jones JL, et al (2006). EGFR expression: associations with outcome and clinicopathological variables in malignant pleural mesothelioma. *Lung Cancer*, **54**, 399-407.

Iyoda A, Yusa T, Kadoyama C, et al (2008). Diffuse malignant pleural mesothelioma: a multi-institutional clinicopathological study. *Surg Today*, **38**, 993-8.

Krug LM, Pass HI, Rusch VW, et al (2009). Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. *J Clin Oncol*, **27**, 3007-13.

Rice DC, Stevens CW, Correa AM, et al (2007). Outcomes after extrapleural pneumonectomy and intensity-modulated radiation therapy for malignant pleural mesothelioma. *Ann Thorac Surg*, **84**, 1685-92; discussion 1692-3.

Schipper PH, Nichols FC, Thomse KM, et al (2008). Malignant pleural mesothelioma: surgical management in 285 patients. *Ann Thorac Surg*, **85**, 257-64; discussion 264.

Sugarbaker DJ, Flores RM, Jaklitsch MT, et al (1999). Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. J Thorac Cardiovasc Surg, 117, 54-63; discussion 63-5.

Sugarbaker, D. J., J. P. Garcia, W. G. Richards, et al (1996). Extrapleural pneumonectomy in the multimodality therapy of malignant pleural mesothelioma. Results in 120 consecutive patients. *Ann Surg*, **224**, 288-94; discussion 294-6.

Yates DH, Corrin B, Stidolph PN, et al (1997). Malignant mesothelioma in south east England: clinicopathological experience of 272 cases. *Thorax*, **52**, 507-12.