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Outcomes of the Multimodal Treatment of Malignant Pleural Mesiothelioma: The Role of Surgery

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Background: The treatment of malignant pleural mesothelioma (MPM) is challenging, and multimodal treatment including surgery is recommended; however, the role of surgery is debated. The treatment outcomes of MPM in Korea have not been reported. We analyzed the outcomes of MPM in the context of multimodal treatment, including surgery. **Methods:** The records of 29 patients with pathologically proven MPM from April 1998 to July 2015 were retrospectively reviewed. The treatment outcomes of the surgery and non-surgery groups were compared. **Results:** The overall median survival time was 10.6 months, and the overall 3-year survival rate was 25%. No postoperative 30-day or in-hospital mortality occurred in the surgery group. Postoperative complications included tachyarrhythmia (n=4), pulmonary thromboembolism (n=1), pneumonia (n=1), chylothorax (n=1), and wound complications (n=3). The treatment outcomes between the surgery and non-surgery groups were not significantly different (3-year survival rate: 31.3% vs. 16.7%, respectively; p=0.47). In a subgroup analysis, there was no significant difference in the treatment outcomes between the extrapleural pneumonectomy group and the non-surgery group (3-year survival rate: 45.5% vs. 16.7%, respectively; p=0.23). **Conclusion:** Multimodal treatment incorporating surgery did not show better outcomes than non-surgical treatment. A nationwide multicenter data registry and prospective randomized controlled studies are necessary to optimize the treatment of MPM.

Key words: 1. Mesothelioma
2. Surgery
3. Prognosis

Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive malignancy. The crude incidence rate and crude prevalence rate in Korea were 0.3 per 100,000 and 0.5 per 100,000, respectively, in 2014 [1]. The incidence of MPM, however, is expected to increase until 2024, and the management of MPM is a concerning issue. MPM is challenging to treat and should be managed by a multidisciplinary approach [2]. The reported median survival time (MST) is less than 2 years with multimodal treatment, which consists of surgery, chemotherapy, and radiotherapy. The aim of surgery in the treatment of MPM is to achieve maximal cytoreduction through the macroscopic complete resection of the tumor. Adjuvant chemotherapy and radiotherapy are required to control the residual microscopic disease. Several studies have showed

Table 1. Characteristics of the patients

Characteristic	All patients (n=28)	Non-surgical group (n=12)	Surgical group (n=16)	p-value
Age (yr)	58.9±11.2	59.5±11.1	58.1±11.9	0.53
Sex (male)	24 (85.7)	11 (91.7)	13 (81.3)	0.61
Biopsy method				0.10
Surgical biopsy	16 (57.1)	9 (75)	7 (43.8)	
Needle biopsy	12 (42.9)	3 (25)	9 (56.3)	
Pathology				0.013
Epithelioid	15 (53.6)	4 (33.3)	11 (68.8)	
Sarcomatoid	3 (10.7)	1 (8.3)	2 (12.5)	
Biphasic	2 (7.1)	0	2 (12.5)	
Undetermined	8 (28.6)	7 (58.3)	1 (6.3)	
Clinical stage				0.001
I	3 (10.7)	0	3 (18.8)	
II	5 (17.9)	0	5 (31.3)	
III	10 (35.7)	2 (16.7)	8 (50.0)	
IV	10 (35.7)	10 (83.3)	0	
Asbestosis exposure	7 (25)	2 (16.7)	5 (31.3)	0.66
Forced expiratory volume in 1 second (%)	79±19	72.2±19.8	82.7±18.5	0.18
Diffusing capacity of the lung for carbon monoxide (%)	83±19	73.6±17.4	87.8±18.9	0.12

Values are presented as mean±standard deviation or number (%). All p-values were derived from the Mann-Whitney test, Fisher exact test, or linear-by-linear association comparing 2 groups.

promising outcomes of neoadjuvant treatment with pemetrexed followed by surgery and adjuvant treatment, and this trimodal treatment strategy is recommended as the standard treatment for MPM. However, the role of surgery in the treatment of MPM and the most suitable surgical method remain unclear. In the Mesothelioma and Radical Surgery (MARS) randomized feasibility study, the surgery group that underwent extrapleural pneumonectomy (EPP) showed significantly poorer prognoses than the non-surgery group [3]. The MARS-2 trial, investigating the effectiveness of pleurectomy/decortication (P/D), is ongoing. Whether EPP or P/D is a better surgical option is still being debated [4,5]. No report has analyzed the treatment outcomes of MPM in the Korean population. We analyzed the outcomes of MPM in the context of multimodal treatment including surgery.

Methods

We retrospectively reviewed the data of 29 patients with pathologically proven MPM who were treated from April 1998 to July 2015. The demographic and clinicopathologic data were obtained by reviewing the medical records. The last follow-up date was April 30, 2017. Complete follow-up was possible in 13 patients, and 15 patients were deemed dead at the time of discharge due to unresectable tumors or the failure of therapy. In patients who were diagnosed with MPM by video-assisted thoracoscopic biopsy or percutaneous needle biopsy, surgery was performed when the mass was resectable. The main operative procedure was EPP, which consisted of en bloc resection of the parietal and visceral pleura, ipsilateral lung, pericardium, and diaphragm. If the pulmonary function of a patient was not suitable for EPP, P/D was performed. Cisplatin-based chemotherapy was the standard chemotherapeutic approach throughout the study period. Pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) administered every 3 weeks have been the standard chemotherapy regimen since 2007.

The patients were divided into the surgery group and non-surgery group. In the surgery group, patients who underwent EPP were further classified as the EPP subgroup. The prognoses were compared between the surgery and non-surgery group and between the EPP and non-surgery group. One patient who refused treatment after an exploratory thoracotomy was excluded from the analysis. The Mann-
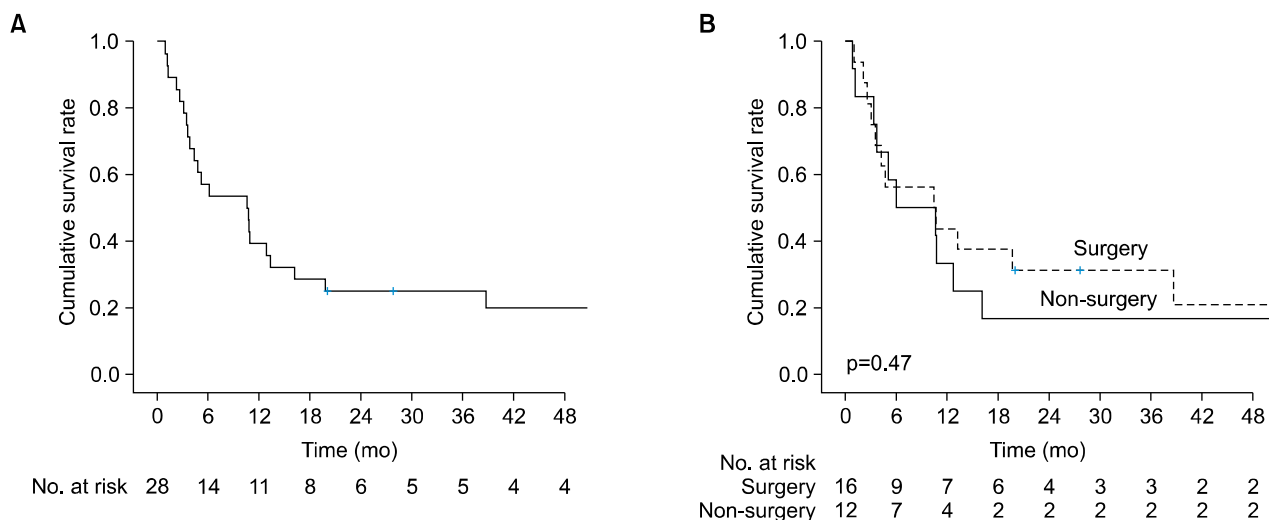
Fig. 1. (A) The Kaplan-Meier survival curves of all MPM patients. (B) Kaplan-Meier survival curves comparing the surgery group and non-surgery group. MPM, malignant pleural mesothelioma.

Whitney test, Fisher exact test, and linear-by-linear association were used for the univariable analysis comparing 2 groups. The overall survival (OS) rates were estimated using Kaplan-Meier curves and compared using the log-rank test. All p-values of 0.05 or less were considered to indicate statistical significance. Statistical analyses were performed using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA). This study was approved by the Institutional Review Board of Seoul National University Hospital and complied with the principles of the Declaration of Helsinki (#1704-011-842).

Results

The characteristics of the patients are summarized in Table 1. Among the 28 patients with MPM, 16 underwent surgery with curative intent and 12 inoperable patients underwent definitive chemotherapy. One patient with superior vena cava syndrome received additional palliative radiotherapy after the definitive chemotherapy. The epithelioid type (n=11, 68.8%) was the most common pathologic type in the surgery group. In contrast, the epithelioid type was seen in only 4 patients (33.3%) in the non-surgery group. Half of the surgery group patients were in clinical stages I and II, whereas no patients had clinical stage I or II disease in the non-surgery group. The clinical stages of the patients in the non-surgery group were stage III (n=2, 16.7%) and stage IV

(n=10, 83.3%).

In the surgery group, 11 patients underwent EPP (7 right-sided, 4 left-sided) and 1 patient underwent P/D. Four patients who were preoperatively misdiagnosed with non-small cell lung cancer underwent lobectomy with chest wall resection. Neoadjuvant chemotherapy was administered to 7 patients. The combination of pemetrexed and cisplatin combination was administered to 5 patients. Four patients showed partial remission or stable disease, and 1 patient showed progressive disease after neoadjuvant chemotherapy according to the modified version of Response Evaluation Criteria in Solid Tumors [6]. Adjuvant chemotherapy was administered to 7 patients and postoperative radiotherapy (51.9±8.34 Gy) was administered to 10 patients.

The median duration of the hospital stay in the surgery group was 18 days (range, 5 to 153 days). The postoperative morbidities included tachyarrhythmia (n=4), pulmonary thromboembolism (n=1), pneumonia (n=1), chylothorax (n=1), and wound complications (n=1). Pathologic stage II, III, and IV disease was found in 6, 8, and 2 patients, respectively. There were no cases of 30-day postoperative mortality or in-hospital mortality in the surgery group.

The median follow-up duration was 10.6 months (range, 1.0 to 78 months). The MST was 10.6 months, and the 3-year OS rate was 25% (Fig. 1A). In the surgery group, the MST was 10.6 months and the
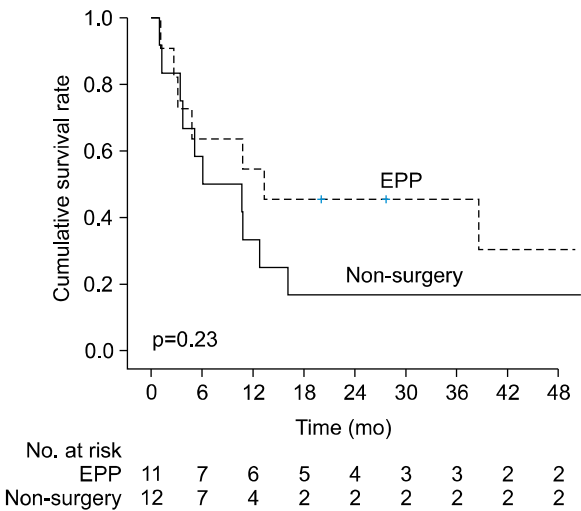
Fig. 2. Kaplan-Meier survival curves comparing the EPP group and the non-surgery group. EPP, extrapleural pneumonectomy.

3-year OS rate was 31.3%. In the non-surgery group, the MST was 8.4 months and the 3-year OS rate was 16.7%. However, there was no statistically significant difference in the survival rate between these 2 groups (p=0.47) (Fig. 1B). As the types of surgical procedures were heterogeneous, we further compared the EPP group with the non-surgery group. The trend of survival was better in the EPP group, but without statistical significance (MST: 13.3 versus 8.4 months; 3-year OS rate: 45.5% versus 16.7%; p=0.23) (Fig. 2).

Discussion

This study analyzed the outcomes of MPM treatment with a focus on a multimodal approach including surgery. The primary finding of this study is that multimodal treatment involving surgery was not superior to non-surgical treatment. A secondary finding is that EPP, one of the surgical treatments, did not show a survival advantage over non-surgical treatment. According to the latest National Comprehensive Cancer Network guidelines for MPM, patients with clinical stage I–III disease with epithelial or mixed histology are recommended to undergo surgical treatment if the tumor is medically operable. The surgical options are EPP, which is en bloc resection of the pleura, lung, ipsilateral diaphragm, and often the pericardium, or P/D, which refers to the com-

plete removal of the pleura and gross tumor mass [7]. EPP was first introduced by Butchart et al. [8] in 1976 for the management of MPM. In its early days, EPP was abandoned due to high morbidity and mortality. With the advent of multimodal treatment, improved results were reported in the treatment of MPM incorporating EPP [9,10]. EPP offers maximal cytoreduction and enables a more efficient delivery of postoperative radiotherapy. Apart from the high morbidity and mortality, other disadvantages of EPP include impaired postoperative cardiopulmonary function, reduced quality of life, and tolerance to adjuvant chemotherapy. The MARS trial was the first randomized feasibility study to compare multimodal treatment with or without EPP in MPM. The MSTs were 14.4 months (range, 5.3 to 18.7 months) in the EPP group and 19.5 months (range, 13.4 months to time not yet reached) in the non-EPP group, and the difference was statistically significant (hazard ratio, 2.75; p=0.016) [3]. The results of our study are similar to those of the MARS study. The prognoses of the surgery group and non-surgery group were not significantly different in the present study. The MST of the EPP group in our study (13.3 months) was similar that of the MARS study (14.3 months). This finding underscores that the quality of multimodal treatment performed in the present study was adequate. The short-term outcomes of EPP in our study were relatively favorable. There were no cases of operative mortality or severe complications. In a single-center report from Italy by Infante et al. [11], EPP was performed in 91 patients in the context of trimodal regimens. The 30-day mortality was 3.3% (n=3), and pleural sepsis was observed in 22 patients (24%) [11]. The Japan Mesothelioma Interest Group 0601 Trial, a prospective multi-institutional study, included 30 patients who underwent EPP. There were 4 treatment-related deaths due to bronchopleural fistula, hemothorax, and acute respiratory distress syndrome [12]. The good short-term outcomes in our EPP group may have been due to the sophisticated selection of patients and postoperative care. Considering the lower preoperative stages and the higher prevalence of epithelioid-type pathology in the non-surgery group, it would be difficult to argue that EPP had an advantage over non-surgical treatment in multimodal treatment within the same clinical conditions. P/D was first introduced as a pallia-

tive treatment for malignant pleural effusions and trapped lung [13]. Recent studies have suggested that P/D can be considered as an appropriate surgical option with intention to treat in the context of the multimodal treatment of MPM, especially in patients who cannot tolerate EPP. In a large study of 663 patients, the P/D group showed a better prognosis than the EPP group. In that study, the operative mortality rates were 7% in the EPP group and 4% in the P/D group, and the MSTs were 12 months in the EPP group and 16 months in the P/D group [4]. In a meta-analysis, the extended P/D group had a significantly lower perioperative mortality rate (2.9% versus 6.8%, p=0.02) and morbidity rate (27.9% versus 62.0%, p<0.0001) than the EPP group. The MSTs ranged between 13 and 29 months in the extended P/D group and 12 and 22 months in the EPP group, with a trend favoring extended P/D [14]. In an international database developed by the International Association for the Study of Lung Cancer, the MST of stage I patients was 40 months in the P/D group and 23 months in the EPP group [15]. P/D can preserve lung function and is suitable for patients with marginal cardiopulmonary function. Considering the possibility of postoperative recurrence, adjuvant chemotherapy is more suitable following P/D than after EPP. The disadvantages of P/D include a lower cytoreductive effect and a higher frequency of radiation-induced pneumonitis after adjuvant radiotherapy [16]. Considering the available data regarding the surgical treatment of MPM, it might be best to consider P/D as the first surgical option for MPM, with EPP reserved for carefully selected patients. The MARS 2 trial (ClinicalTrials.gov, NCT02040272) that intended to demonstrate the safety of adding P/D to cisplatin/pemetrexed chemotherapy in resectable MPM is nearing completion [17]. The MARS 2 trial and the following phase III study will determine the role of P/D in MPM.

The mainstay of chemotherapy in MPM has been a combination of pemetrexed and cisplatin ever since the results of a phase III trial were published in 2003 [18]. We adopted this regimen in 2007. However, we could not find any prognostic difference between the old regimen and the new regimen, possibly because the sample size was too small.

Adjuvant hemithoracic radiotherapy is indicated after EPP in patients with good pulmonary and renal

function [7]. The effect of adjuvant radiotherapy is controversial. In the SAKK 17/4 trial, patients were randomly assigned to the non-radiotherapy group or radiotherapy group following neoadjuvant chemotherapy and EPP. The MSTs were 20.8 months in those without adjuvant radiotherapy and 19.3 months in those with adjuvant radiotherapy [19]. Intensity-modulated radiation therapy (IMRT) is a good option because it allows better dose distribution to regions at risk of recurrence as well as reduced radiation to the surrounding organs. A phase II study using chemotherapy with or without P/D followed by IMRT in patients with MPM is currently ongoing [20].

The limitations of the present study are the small number of patients and the long study period. These limitations are difficult to overcome because of the rarity of the disease. For that reason, there has been no study of MPM in Koreans thus far. We hope that our study will promote research on MPM in Korea and lead to nationwide multi-institutional studies. Another limitation is our limited experience with P/D. The current trend of surgery for MPM favors P/D over EPP, and we believe that P/D should be considered as the first option in the multimodal approach, followed by EPP.

In conclusion, the survival benefit of EPP in the multimodal approach is unclear. A nationwide multi-center data registry and further prospective randomized controlled studies are necessary to clarify the effects of surgical treatment in patients with MPM in Korea.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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