



Does size matter? – a population-based analysis of malignant pleural mesothelioma

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Background: The 8th edition staging system for malignant pleural mesothelioma (MPM) has been proposed. The size of tumor is not taken into consideration. We intend to elucidate the prognostic value of the size of MPM and evaluate the current staging system via the data of SEER database.

Methods: All cases of primary MPM were identified and extracted from the SEER database during the period of 2004–2016. The endpoints were overall survival (OS) and cancer-specific survival (CSS) which were analyzed using Kaplan-Meier method. Log-rank test and Cox regression were utilized to identify the prognostic factors.

Results: A total of 2,138 patients were included in the primary cohort. The 1-, 3- and 5-year survival rates of MPM were 39.4%, 11.8% and 3.8%. Older, male and advanced stage patients accounted for larger proportion of the cohort. Besides tumor extension, lymph node involvement and metastatic status, tumor size, pathological type and differentiation grade were significant prognostic factors. In the stratified analysis of tumor extension, size is a significant prognostic factor in T2 patients and indicates inferior survival outcomes. Surgery, chemotherapy and radiation can increase both OS and CSS in MPM patients. Triple combination treatments showed a superiority to other treatments.

Conclusions: Tumor size matters in the prognosis of MPM especially in the early stage of MPM patients. The adjusted TNM staging system incorporating tumor size has better accuracy than the 8th edition IMIG system. However, some stages had not been fully identified. More cases of early stages are warranted for essential revision.

Keywords: Malignant pleural mesothelioma (MPM); tumor size; prognosis; SEER; outcomes; stage

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Introduction

The malignant pleural mesothelioma (MPM) is a rare and aggressive type of pleural malignancies. The incidence of MPM is proved to be highly related to the exposure to asbestos which accounts for more than 80% cases (1).

The symptoms of MPM are concealed. As a result, large proportion of patients are diagnosed as advanced diseases with only 8% of 5-year survival rate (2,3). A validated staging system is crucial for disease evaluation, treatment selection and follow-up strategy. A number of staging systems of MPM had been previously proposed and utilized

in some clinical retrospective studies regionally until 1990s (4). However, few of them were population-based or established as TNM (tumor, lymph node and metastasis) system. The most generally used staging system is the 7th edition TNM stage which is developed by the International Association for the Study of Lung Cancer (IASLC) and the International Mesothelioma Interest Group (IMIG) (5). However, it has not been widely accepted due to the absence of large-cohort validation.

The IASLC Staging Committee has performed a validation study using the data from multiple centers and proposed the 8th edition of MPM staging system (6-8). The result reports some essential revisions in T/N categories and the new groupings. Unlike other solid tumor staging system, tumor size of MPM is not taken into consideration in T category. Therefore, we intend to perform a study on the Surveillance, Epidemiology, and End Results Database (SEER) to analyze the prognostic factors of MPM and evaluate the prognostic effect of size.

Methods

Data Source

This study was performed using the data from SEER database, which was sponsored by National Cancer Institute and covered approximately 28% of US population (9). The database we used in the study was the SEER 18 Registry Custom Data (with additional treatment fields), Nov 2018 Sub and (2000–2016). The patients diagnosed as malignant mesothelioma including the pathological types of fibrous, epithelial, biphasic and non-other specific mesothelioma (ICD-0-3=9050-9053) in the primary site of pleural (SEER primary site code =38.4) were identified. The identified cases included the data of age at diagnosis, sex, race, surgery, radiation, chemotherapy, tumor size, tumor extension, lymph node involvement, metastasis status, histology, grade, vital status, overall survival interval and cancer-specific survival interval. Cases without data of tumor features were excluded after discussion. The selection process of primary cohort was demonstrated in *Figure 1*.

Definitions of data in SEER

The tumor features recorded in SEER were defined by CS coding system (CS Extension of Pleural) (10). We categorized the primary cohort by a general tumor extension classification based on the descriptions of coding

system and IMIG staging system. We defined E1-E4 as the same tumor involvement as T1-T4 in the 8th IMIG staging system.

In accordance to the current staging system, the pathological lymph node involvement was categorized as follow: Nx, lymph node involvement unknown; N0, no regional lymph node involvement; N1, intrathoracic lymph node involvements including ipsilateral bronchopulmonary and/or hilar lymph node; N2, subcarinal, ipsilateral internal mammary, mediastinal lymph nodes, or the peri-diaphragmatic lymph nodes; N3, distant lymph node involvement including contralateral mediastinal, contralateral internal mammary, or hilar area, and/or the ipsilateral supraclavicular or scalene area. Metastasis status were defined as M0 (metastasis-free) and M1 (distant metastasis).

Statistical analysis

Overall survival (OS) and cancer-specific survival (CSS) were estimated and analyzed by the Kaplan-Meier (KM) method and the log-rank test. Univariate and multivariate survival analyses were conducted using the Cox proportional hazards model. A Cox multivariate model was made including variables which were statistically significant in univariate analysis or considered as clinically significant. The prognostic effect of tumor size was analyzed in different tumor extension groups.

Treatments were categorized as surgery, chemotherapy and radiation groups. Besides, those who had received more than single treatment were classified in the double or triple combination groups.

The Kaplan-Meier and Cox regression were performed using the software of SPSS 25.0 and GraphPad Prism 5. The concordance to the actual survival of each stage model was evaluated by concordance index (C-index) using R (Version 3.4.1, R Core Team) (11). The comparison between two staging systems was performed using “rccorrp.cens” method and likelihood ratio test via “Hmisc” and “lmtest” packages in R (12,13). The statistical difference was considered as significant when $P < 0.05$. All tests were two-sided.

Result

Clinical characteristics of MPM

A total of 12,516 patients with pleural malignancies

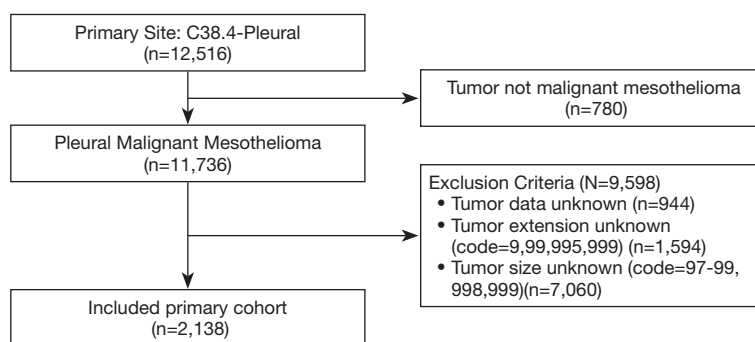


Figure 1 The diagram of primary cohort selection process.

were identified from SEER database. Among them, 11,736 patients diagnosed as malignant pleural mesothelioma were included in the original cohort. After the selection process, 2,138 patients were finally included in the primary cohort (Figure 1). According to the 8th edition IMIG staging system, 224 patients was stage IA, 313 in stage IB, 140 in stage II, 53 in stage IIIA, 908 in stage IIIB and 291 in stage IV. The mean age of the primary cohort was 69.02 ± 11.56 -year-old ranging from 24 to 96. No difference of age was observed among the stages. More patients were in the advance stages at the diagnosis. More patients were diagnosed as poorly and undifferentiated grades. More male patients were diagnosed MPM than female patients in each stage ($P < 0.05$). Referring to human race, the number of white patients which was 91.1% of primary cohort outweighed other races. T4 and N0 patients accounted for the largest proportion in T and N categories, respectively (Table 1).

Frequency and survival of MPM

Based on SEER data, the frequency of MPM patients increased smoothly from 0.5% in 1973 and reached the highest of 1.0% in 1993. Since then, it fluctuated in the range of 0.7% to 1.0% from 1994 to 2013 (Figure S1).

In order to elucidate the prognosis of MPM, we performed the overall survival (OS) and cancer-specific survival (CSS) analyses both in original cohort and the primary cohort. The median survival of both cohort in OS and CSS were 9 and 10 months. The 1-, 3- and 5-year survival rates of OS in primary cohort were 39.4%, 11.8% and 3.8%, which were consistent with the original cohort (36.7%, 9.6% and 4.8%) (Figure 2). The 1-, 3- and 5-year survival rate of CSS in primary cohort were 42.3%, 14.2% and 8.7%, which were also similar to the original cohort (43.2%, 12.1% and 6.6%) (Figure 2).

Prognostic factors of MPM

In the univariate analysis, the results indicated that some clinical characteristics were significant prognostic factors of MPM including age, sex. Older patients had worse prognosis than the younger patients (HR =1.027, 95% CI: 1.023–1.032, $P < 0.001$). On the other hand, female patients had better survival outcomes than male (HR =0.724, 95% CI: 0.647–0.81, $P < 0.001$). However, the human race showed no effect on the prognosis (Table 2).

Referring to the tumor features, the outcomes of epithelial histology was the best in four histology subtypes. The biphasic was slightly worse than the epithelial type. The sarcomatoid histology and mesothelioma no other specific type (NOS) were associated with poor prognosis, of which the median survivals were 7 and 8 months. The sarcomatoid histology showed superiority of survival to NOS after 14 months (HR =0.849, 95% CI: 0.736–0.979, $P = 0.024$) (Table 2).

Besides, tumor differentiation grade, size, extension, lymph node involvement and metastasis status were negative prognostic factors. Among them, undifferentiated grade (HR =2.75, 95% CI: 1.682–4.497, $P < 0.001$), N2 (HR =1.608, 95% CI: 1.227–2.108, $P = 0.001$) and metastasis (HR =1.472, 95% CI: 1.29–1.679, $P < 0.001$) were associated with the worst prognosis with only 6, 5 and 6 months of median survival, respectively. The median survival of T4 was 8 months, which was worse than T1 with 11 months (HR =1.375, 95% CI: 1.215–1.557, $P < 0.001$).

Chemotherapy, radiation and surgical treatments were able to improve the prognosis of MPM patients (Table 2). In the surgical treatment analysis, we noticed that both local destruction (HR =0.48, 95% CI: 0.422–0.546, $P < 0.001$) and radical surgery (HR =0.487, 95% CI: 0.425–0.558, $P < 0.001$) were significantly better than non-surgery groups, which

Table 1 The characteristics of patients with malignant pleural mesothelioma in different stages

Clinical features	Stage							Total
	IA	IB	II	IIIA	IIIB	IV	Unknown	
Cases	224	313	140	53	908	291	209	2,138
Age (year)								
Mean	71.14±11.8	68.29±12.03	68.57±11.46	66.30±9.49	68.52±11.41	70.27±11.5	69.28±11.58	69.02±11.56
Median	72 (35–96)	70 (24–94)	69 (25–92)	67 (47–89)	70 (26–96)	72 (33–95)	71 (37–91)	70 (24–96)
Sex								
Male	173	242	105	41	732	220	168	1,681
Female	51	71	35	12	176	71	41	457
Race								
White	210	286	124	48	823	261	195	1,947
Black	9	9	12	1	47	19	9	106
Other	4	18	4	4	36	11	5	82
Unknown	1	0	0	0	2	0	0	3
Histology								
NOS	100	140	61	9	536	170	125	1,141
Sarcomatoid	57	35	19	3	91	40	27	272
Epithelioid	54	98	55	31	227	68	43	576
Biphasic	13	40	5	10	54	13	14	149
Grade								
Well	5	5	1	0	13	0	4	28
Moderate	3	3	1	0	10	3	5	25
Poor	11	20	11	2	75	27	6	152
Undifferentiated	5	7	3	2	26	14	1	58
Unknown	200	278	124	49	784	247	193	1,875
Size (mm)								
Mean	58±44.31	58.21±41.95	59.41±57.32	98.66±99.64	72.36±43.61	63.37±46.28	72.79±37.61	67.02±47.1
Median	45 (1–250)	50 (2–300)	44.5 (3–440)	60 (10–420)	70 (1–460)	53 (3–300)	97 (1–250)	60 (1–460)
Tumor								
T1	224	0	59	0	5	30	83	401
T2	0	222	81	0	9	42	118	472
T3	0	91	0	53	3	23	8	178
T4	0	0	0	0	891	196	0	1087
Node								
N0	224	313	0	0	348	100	0	985
N1	0	0	140	53	135	92	0	420
N2	0	0	0	0	42	20	0	62
Nx	0	0	0	0	383	79	209	671

Table 1 (continued)

Table 1 (continued)

Clinical features	Stage							Total
	IA	IB	II	IIIA	IIIB	IV	Unknown	
Surgery								
No	118	125	81	19	380	234	70	1,027
Local destruction	56	92	27	11	147	42	26	401
Radical	29	66	22	23	141	14	37	332
Unknown	21	30	10	0	240	1	76	378
Radiation								
No	186	237	115	29	655	217	160	1,599
Yes	34	73	24	20	230	71	39	491
Unknown	4	3	1	4	23	3	10	48
Chemo-therapy								
No/Unknown	152	167	72	19	571	149	153	1,283
Yes	72	146	68	34	337	142	56	855

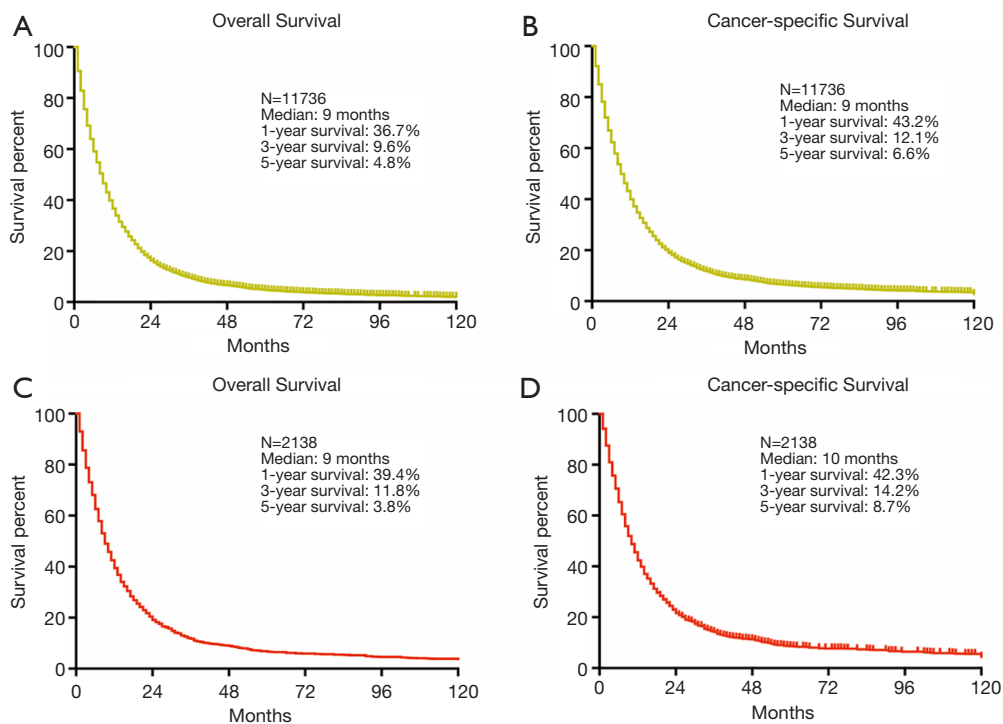


Figure 2 The frequency of malignant pleural mesothelioma in SEER database The survival outcomes of original and primary cohorts. (A) Overall survival of original cohort; (B) cancer-specific survival of original cohort; (C) overall survival of primary cohort; (D) cancer-specific survival of primary cohort.

Table 2 The univariate and multivariate analysis of prognostic factors in MPM patients

Clinical features	N	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Age (year)	2,138	1.027 (1.023–1.032)	<0.001	1.022 (1.017–1.026)	<0.001
Sex					
Male	1,681	1	–	1	–
Female	457	0.724 (0.647–0.810)	<0.001	0.767 (0.684–0.859)	<0.001
Race					
White	1,947	1	–	–	–
Black	106	1.025 (0.834–1.259)	0.814		
Other	82	0.867 (0.685–1.098)	0.236		
Unknown	3	0.83 (0.207–3.324)	0.793		
Histology					
Mesothelioma, NOS	1,141	1	–	1	–
Fibrous (Sarcomatoid)	272	0.849 (0.736–0.979)	0.024	1.018 (0.878–1.181)	0.809
Epithelioid	576	0.689 (0.619–0.767)	<0.001	0.82 (0.732–0.918)	0.001
Biphasic	149	0.814 (0.676–0.979)	0.029	1.047 (0.865–1.267)	0.639
Grade					
Well differentiated	28	1	–	1	–
Moderately differentiated	25	2.052 (1.143–3.684)	0.016	2.075 (1.152–3.737)	0.015
Poorly differentiated	152	2.163 (1.389–3.366)	0.001	1.958 (1.252–3.064)	0.003
Undifferentiated	58	2.750 (1.682–4.497)	<0.001	2.313 (1.406–3.807)	0.001
Unknown	1,857	2.190 (1.450–3.309)	<0.001	1.747 (1.153–2.648)	0.009
Size (mm)	2,138	1.001 (1.000–1.002)	0.021	1.002 (1.001–1.003)	<0.001
Extension					
E1	401	1	–	1	–
E2	472	1.190 (1.031–1.374)	0.018	1.354 (1.168–1.571)	<0.001
E3	178	1.115 (0.915–1.359)	0.282	1.385 (1.126–1.701)	0.002
E4	1,087	1.375 (1.215–1.557)	<0.001	1.323 (1.161–1.508)	<0.001
Node					
N0	985	1	–	1	–
N1	420	1.146 (1.013–1.297)	0.031	1.173 (1.030–1.337)	0.016
N2	62	1.608 (1.227–2.108)	0.001	1.725 (1.304–2.282)	<0.001
Nx	671	1.328 (1.199–1.471)	<0.001	1.112 (0.994–1.244)	0.063
Metastasis					
No	1,847	1	–	1	–
Yes	291	1.472 (1.290–1.679)	<0.001	1.255 (1.089–1.447)	0.002

Table 2 (continued)

Table 2 (continued)

Clinical features	N	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Surgery					
No	1,027	1	–	1	–
Local destruction	401	0.48 (0.422–0.546)	<0.001	0.558 (0.486–0.641)	<0.001
Radical	332	0.487 (0.425–0.558)	<0.001	0.507 (0.437–0.588)	<0.001
Unknown	378	0.966 (0.857–1.089)	0.575	0.92 (0.8–1.059)	0.248
Radiation					
No	1,599	1	–	1	–
Yes	491	0.88 (0.791–0.979)	0.019	0.966 (0.864–1.079)	0.537
Unknown	48	1.009 (0.747–1.362)	0.955	1.101 (0.812–1.492)	0.537
Chemotherapy					
No/Unknown	1,283	1	–	1	–
Yes	855	0.799 (0.728–0.876)	<0.001	0.781 (0.706–0.864)	<0.001

had median survival of 14, 16 and 7 months, respectively. The triple combination treatment provided the best survival outcomes while patients received no treatment had the worst (23 *vs.* 5 months, HR =2.216, 95% CI: 1.845–2.662, $P<0.001$). However, no significant difference of OS was observed between surgery and combined treatment group (HR =1.059, 95% CI: 0.823–1.362, $P=0.656$) (Figure S2).

The results of multivariate analysis showed that age, gender, histology, differentiation grade, tumor size, T category, N category, metastasis status, surgery and chemotherapy were independent prognostic factors, except radiation (Table 2).

Prognostic effect of tumor size

In the univariate and multivariate analysis, it showed that tumor size was an independent negatively prognostic factor. Therefore, the prognostic effect of size was evaluated in each tumor extension subgroups. The results showed tumor size had no significant prognostic effect in E1, E3 and E4 subgroups. Nevertheless, it had significant effect on survival in E2 (Data not shown).

Staging systems of MPM

The curve of hazard ratio (HR) of each size intervals in E2 were fitted by using Lowess smoother (Figure S3). It showed

that the cutpoint was at the 3rd subgroup (≤ 3 cm) and the HR rose remarkably from the 7th subgroup (>7 cm). On the other hand, the tertiles points of sizes in E2 which were 3 and 69.5 cm, which were consistent with the cutpoints. The KM curves showed the median survival of three groups were 19, 12 and 8 months, respectively ($P=0.015$) (Figure 3A). The E1 and E2 ≤ 3 cm patients had no difference in clinical outcomes, the same phenomenon was observed in the comparison between E2 >7 cm and E3 patients. After verifying the breaking point position in 5, 6 and 7 cm, the largest difference was observed at 7 cm. Therefore, the new T category was proposed as T1: E1, E2 ≤ 3 cm; T2: E2 3–7 cm; T3: E2 >7 cm, E3; T4: E4 (Figure 3B).

In the N category, we noticed N1 and N2 had no difference in OS. Therefore, we collapsed N1 and N2 into new N1 and reclassified N3 as new N2 in concordance to the 8th IMIG staging system. According to the upcoming system, despite of any other tumor features, T4 or N2 patients were categorized as Stage IIIB. In the survival analysis of Stage IIIB, it indicated that T4N0-1M0 had better outcomes than TanyN2M0 and M1 ($P<0.001$). Therefore, any N2 patients should be reclassified to Stage IV. In Stage II, no difference of survival outcome was observed among T1-2N1M0 and T3N0M0 of which the median survival were 11 months. As a result, the staging system was adjusted as follow: Stage IA (T1N0M0), Stage IB (T2N0M0), Stage II (T1-2N1M0, T3N0M0), Stage IIIA

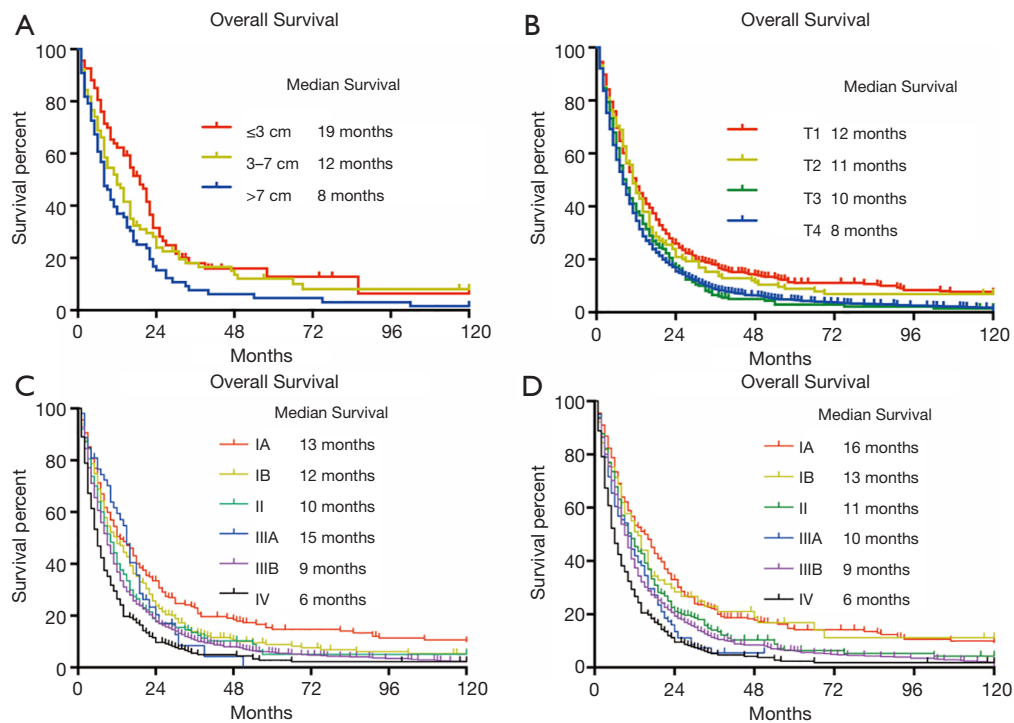


Figure 3 The survival outcomes of different stages. (A) Overall survival of different size cutpoints interval in T2; (B) overall Survival of the adjusted T category; (C) overall survival of primary cohort classified by the 8th edition IMIG system; (D) overall survival of primary cohort classified by the adjusted staging system.

(T3N1M0), Stage IIIB (T4N0-1M0) and Stage IV (any N2, M1). The prognosis of each previous and adjusted stages was shown in *Figure 3C,D*, respectively.

The detail of adjusted staging system was shown in *Table S1*. The C-indexes of the adjusted staging system, 7th and 8th edition of IMIG staging systems were 0.61, 0.54 and 0.58, respectively. The tests results indicated the adjusted system was more concordant to the actual survival than other system (0.61, 0.58 and 0.54, $P < 0.0001$).

Discussion

MPM is one of the rare malignancies of pleura, its frequency has elevated significantly in the past 40 years. Although numbers of treatments for MPM have been developed (14-22), the prognosis of MPM is still unsatisfied with only 40% of 1-year survival rate and no more than 10% of 3-year survival rate. The lack of accurate evaluation scales in both clinical and pathological aspects accounts for the difficulty of treatment selection and prognosis estimation. Therefore, we performed the current study to illustrate the clinical characteristics and tumor features of MPM. Additionally,

prognostic factors were identified and an adjusted staging system was proposed for better evaluation (23-26).

In the previous studies of MPM staging system, few has investigated the tumor size prognostic effect (27-32). A study has reported the thickness of tumor had impact on the survival of MPM. However, it is used to evaluate the effect of radical surgery or radiation rather than stage grouping (33). In the staging system of other solid tumors, T categories usually contains tumor involvement and size. IASLC recently has reported some alterations in T and N categories for the forthcoming 8th edition MPM staging system (6,7). The revision in T category is the collapsing of T1a and T1b. Although it mentions that tumor thickness is associated with survival, tumor size is still not taken into consideration in grouping (7). In our primary cohort, we notice that only tumor extension is not powerful enough to discriminate the T1-T3 patients. The similar result is reported by the IASLC study (7,27). We therefore explored the weight of size in different tumor extension strata and we realized it was significant prognostic factor especially in T2 category of 8th MPM staging system. In order to identify the cut-off value of sizes, we used two methods including

tertiles and breakpoints of regression curve. The results of both methods showed a high consistency that sizes of 3cm and 7cm turned were significant determinants. The adjusted T category incorporating tumor size showed a better power of discrimination in early stage patients.

An exploratory study of adjusted staging system was also performed after the prognostic effect of tumor size had been identified. The previous N category of IMIG staging system is very similar to the TNM staging system of lung cancer (34). Rusch *et.al.* have indicated the grouping of N1-N2 was empirical, since the lymphatic drainage pattern from N1 to N2 resembled lung cancer (8,34,35). Some studies suggest the sequence of N2 lymphatic drainage in MPM is inconsistent with lung cancer (36-38). A large-scale study performed by the IASLC committee suggests the previous N1 and N2 categories have no survival difference and they should be collapsed into a single N category (6). In our cohort, we observed the same results as the previous studies. The adjusted N1 and N2 curves have clear separation. N0 has a better median survival, but shows no significant result in this study. Along with metastasis, the 8th edition system categorizes any T4 or N2 patients as Stage IV regardless of other tumor features (8). Our data shows that only N2 shared the same survival outcome of M1 patients (*Figure S4*). In order to evaluate the prediction accuracy of models, C-index and two methods (39,40) were used to compare the performance of each staging system. Although the C-indexes of three models were not impressive, the 8th edition model was more accurate than the 7th, while the adjusted model was the most concordant to the actual survival.

Limitations have to be admitted in the current study. Firstly, 18F-fluorodeoxyglucose (18F-FDG) PET/CT and PET/MRI have also been proved to be determined and very helpful in diagnosing and evaluating MPM (41-43). Some researchers indicated that the metabolism of 18F-FDG could be used as assessment or predictive factor for responses of chemotherapy regimens (44,45). Moreover, serum biomarkers also play remarkable roles in monitoring MPM. Among them, mesothelin is highly associated with the disease status (46-48). Other inflammatory cytokines and miRNA also show some effects in diagnosis (49,50). However, SEER database fails to provide any radiographic or serological data. Neither clinical staging system nor further assessment of radiographic image was able to be studied in this research. Secondly, a large amount of incomplete data is eliminated during the process. Besides, the early stage patients only accounts for a small proportion of the cohort. The analysis of early stage patients might

be insignificant and inconclusive owing to a small sample size. Besides, some cases of multifocal lesions could not be identified in this study. The prognosis of these cases could not be clarified with incomplete data. Thirdly, preoperative evaluation of MPM is not as easy as other solid tumor. Given the pathological features and proliferation pattern, the conventional TNM staging even incorporating tumor size is not conclusive or accurate for prognosis prediction. In addition, the current study also suggests that tumor histology subtype and differentiation grade have crucial effects in survival of MPM. A novel prediction model is warranted. Finally, surgical treatments have a predominant status in the early stages of MPM, though adverse events might happen (51-55). Multimodality treatments favor better outcomes, which are consistent with other studies (56-60). Lacking of surgical approaches or comorbidities data lead to unclear superiority of P/D or EPP.

In summary, MPM is a rare malignancy with poor prognosis. Besides tumor extension, lymph node involvement and metastasis status, the tumor size matters in clinical outcomes especially in early stage of MPM. The adjusted pathological TNM staging system incorporating tumor size in T category shows a better accuracy in survival prediction. A larger cohort with complete data is warranted to further investigate and verify the prognostic effect of tumor size in early stage of MPM.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tlcr-19-488>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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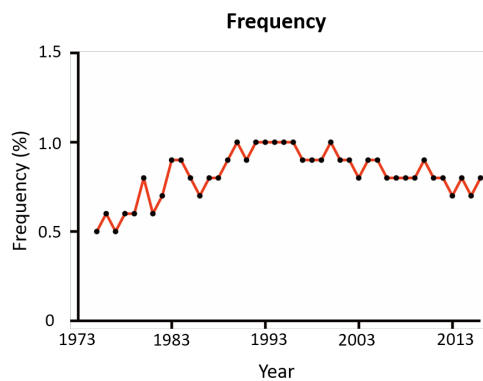


Figure S1 The frequency of malignant pleural mesothelioma in SEER database.

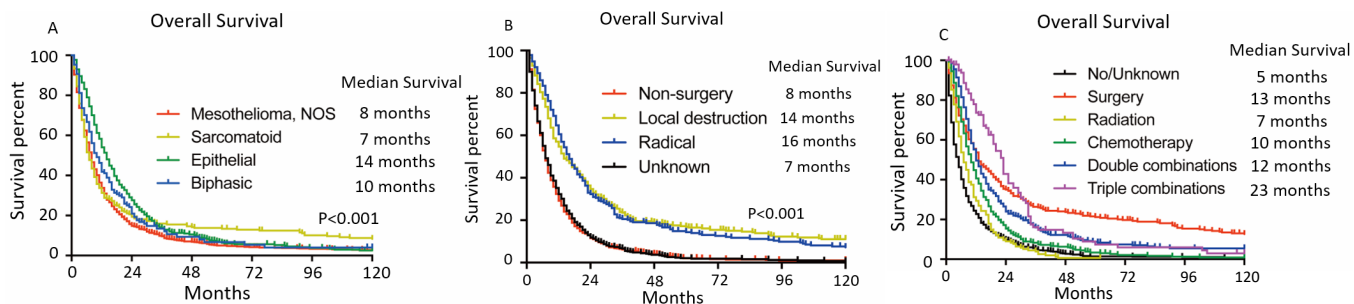


Figure S2 The survival outcomes of each subgroups. (A) Overall survival of pathology subtypes; (B) overall survival of surgery subgroup; (C) overall survival of treatments including multimodality treatments.

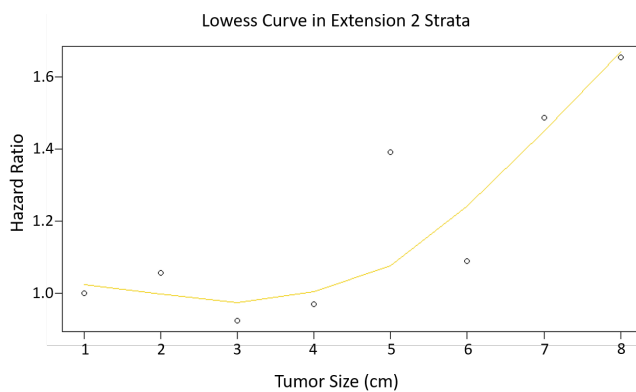


Figure S3 The smooth regression curve of HRs and size intervals in T2.

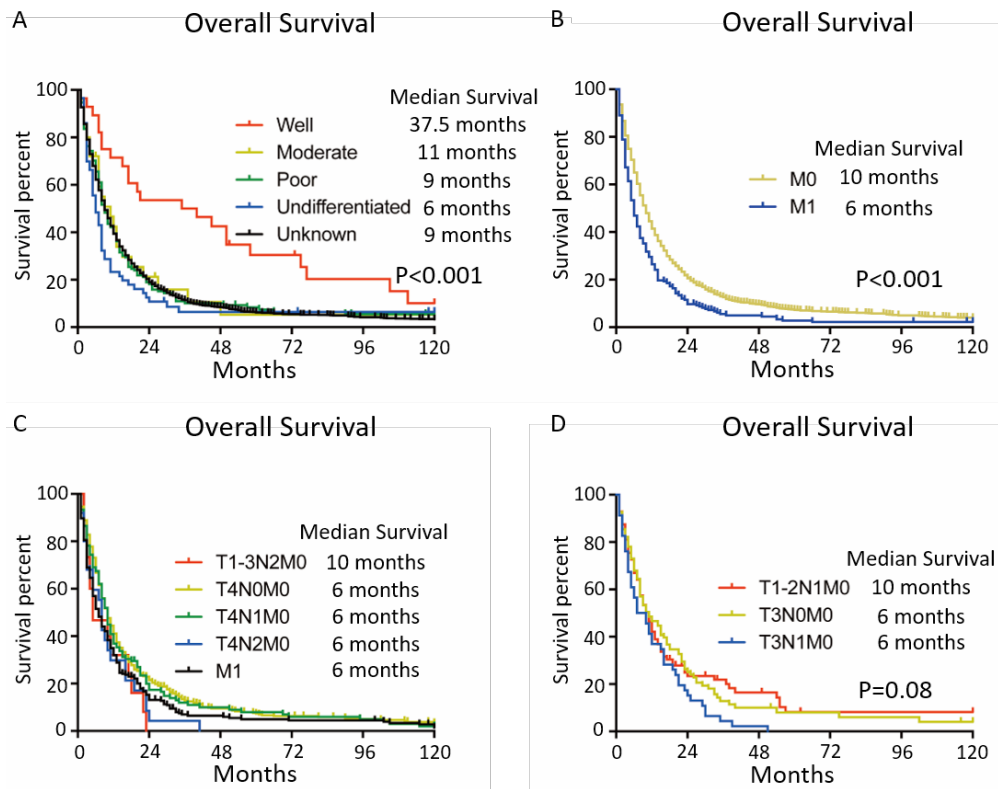


Figure S4 The survival outcomes of different subgroups in the primary cohort. (A) Overall survival of differentiation grade; (B) overall survival of non-metastatic and metastatic patients; (C) overall survival of patients in adjusted Stage IV; (D) overall survival of patients in adjusted Stage III.

Table S1 The new proposed TNM staging for malignant pleural mesothelioma

Stage	Definitions of each stage subgroup
T	
T1	Ipsilateral parietal pleural including mediastinal or diaphragmatic pleural, with or without involvement of visceral pleural, confined to pleural; lung tissue involved but size no more than 3 cm
T2	Mesothelioma nodule(s) broke through the visceral pleural surface to lung surface; lung parenchyma or diaphragm; tumor size 3–7 cm
T3	Adjacent connective tissue involvement: pericardium (non-transmural), endothoracic fascia, chest wall, solitary focus of tumor, mediastinal tissue, mediastinal fat; lung tissue involved and tumor size >7 cm
T4	Diffuse or multifocal invasion of soft tissues of chest wall, heart muscle, myocardium, mediastinal organs, rib, internal surface of pericardium, contralateral pleural; further contiguous extension: brachial plexus, cervical tissues, intra-abdominal organs, peritoneum, spine; pericardium effusion with positive cytology
N	
N0	No regional lymph node involvement
N1	Intrathoracic regional lymph node, ipsilater hilar, intrapulmonary; Ipsilateral mediastinal or internal mammary lymph nodes, subcarinal or subcardial
N2	Contralateral or bilateral mediastinal lymph node; Ipsilateral, contralateral or bilateral scalene or subclavicular lymph nodes
Nx	Unknown status
M	
M0	No distant metastasis
M1	Distant metastasis including cervical lymph node involvement, discontinuous involvement of contralateral pleural/chest wall
Stage	
IA	T1N0M0
IB	T2N0M0
II	T1-2N1M0, T3N0M0
IIIA	T3N1M0
IIIB	T4N0-1M0
IV	TanyN2M0, TanyNanyM1